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

José M. de la Torre-Hernández, Fermín Sainz-Laso, Miguel Llano-Cardenal, Marta Ruiz-Lera, Leticia Rodríguez-Friera, Virginia Burgos, Javier Zueco, Álvaro Figueroa, and Thierry Colman

Unidad de Hemodinámica y Cardiología Intervencionista, Hospital Universitario Marqués de Valdecilla, Santander, Spain.

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 planteamos 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%, 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 cardiacas; 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.[1-12]

Nevertheless, the studies and registries described in the literature typically report on clinical follow-up periods of 1 year,[1-12] with only 2 studies providing much longer term information, namely the FIM study (30 patients for 4 years)[13] and the RAVEL study (120 patients for 3 years).[14] 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.[14-17]

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.
6. Bifurcations.
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-percutaneous transluminal coronary angioplasty (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-segment 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

TABLE 1. Clinical Characteristics of the 200 Patients*

Age, mean±SD, years	60±11
Men, n (%)	170 (85)
Diabetics, n (%)	44 (22)
Hypertension, n (%)	105 (52.5)
Prior infarction, n (%)	108 (54)
Prior angioplasty, n (%)	52 (26)
Prior surgery, n (%)	19 (9.5)
Statins, n (%)	116 (58)
Ejection fraction, mean±SD, %	51±10
Stable angina, n (%)	91 (45.5)
Unstable angina, n (%)	86 (43)
Acute infarction, n (%)	23 (11.5)

*SD indicates standard deviation.

TABLE 2. Angiographic Characteristics of the 309 Lesions Treated*

Right coronary, n (%)	76 (24.6)
Left anterior descending, n (%)	174 (55)
Circumflex, n (%)	45 (14)
Trunk, n (%)	9 (2.9)
Mammary, n (%)	2 (0.65)
Saphenous, n (%)	3 (1)
Morphology and lesion severity	
Total occlusions, n (%)	50 (16)
Recent	16
Chronic (>3 months)	34
In-stent restenosis, n (%)	52 (16.8)
Occlusive	10
Diffuse (>10 mm)	20
Focal (<10 mm)	22
Diffuse (>20 mm), n (%)	86 (28)
Small vessel (≤2.5 mm), n (%)	93 (30)
Bifurcations, n (%)	17 (5.5)
Ostial, n (%)	8 (2.6)
Lesion length, mean±SD, mm	18.5±9
Reference diameter, mean±SD, mm	2.7±0.27
Baseline stenosis, mean±SD, %	67±10%

*SD indicates standard deviation.

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 untreatable 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

TABLE 3. Procedure Characteristics*

Treated vessels/patient, mean±SD	1.28±0.5
Treated lesions/patient, mean±SD	1.5±0.6
Stents/patient, mean±SD	1.56±0.6
Stent length, mean±SD, mm	20±8
Stent diameter, mean±SD, mm	2.78±0.27
Total stent length/patient, mean±SD, mm	29±16
Direct stent, n (%)	117 (38)
Abciximab, n (%)	28 (14)
Triple-vessel treatment, n (%)	5 (2.5)
Successful procedure	98%

*SD indicates standard deviation.

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

Hospitalization	
Non-Q wave infarction	3 (1.5%)
Transient ischemic attack	1 (0.5%)
Clinical follow-up	
Total deaths	4 (2%)
Nonfatal infarction	4 (2%)
Stent thrombosis	4 (2%)
Revascularization of treated lesion*	4 (2%)
Revascularization of other lesion	6 (3%)
Nonfatal stroke	2 (1%)

*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-basal aneurysm treated with 2 stents in the circumflex) and another at 15 days (60-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.[1-12] Nevertheless, the published studies and registries had clinical follow-up periods of less than 1 year, except for the FIM[13] and RAVEL[14] 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 stent and the time (7 months), it could also be explained by a complication of the distal lesion and the resulting retrograde thrombosis. The third case was unequivocally late and, based on the final angiographic results, could have been a severe focal restenosis that progressed to rupture and acute occlusion. In fact, after thrombus aspiration and dilatation, an image of in-stent dissection persisted—a finding that is extremely rare for thrombi alone—which improved only after successive expansions with a larger balloon. This mechanism of very late restenosis and rupture of in-stent plaque was previously proposed for any case of non-drug-eluting stent that showed acute occlusion years after implantation.[18] The described case of infarction at 11 months and no subsequent angiographic anomalies indicates the possibility of thrombosis; however, we should remember that about 5% of infarction cases show no significant lesions on angiography; hence, any lesion not angiographically significant over the vessel length could have caused the symptoms.

It is worth considering whether the 2 cases of sudden death were due to stent thrombosis. This etiology is possible, but not to the same extent for the 2 cases described. In the one that occurred at 20 months, it is less likely, given the characteristics mentioned (previous infarction with a large aneurysm). The probability is higher in the case that occurred at 15 days, although the severe, very diffuse existing disease could have led to a new infarction. Sudden deaths occur in all series of heart disease patients, particularly those with major coronary disease, as was the case of our patients. Although it is prudent and advisable to consider the possibility of thrombosis when sudden death occurs in a revascularized patient, the presence of a drug-eluting stent should not become the main cause of sudden death at any follow-up time or in any kind of patient; ventricular function, scar from a previous infarction, ventricular aneurysm, new infarction or other causes continue to be important factors that should be taken into account. With regard to the subgroup of treated cases with total occlusions, some late thromboses may have gone unnoticed, although it is true that 2 of the cases described pertained to this subgroup, in which the occlusion was clinically evident even with excellent collateral circulation.

The incidence of 2% for thrombosis is higher than the rate reported in clinical trials (<1%), a finding that is logical in view of the types of lesions studied, given the higher associated risk for this complication. In fact, the incidence is comparable to the one described in large clinical studies, such as the 1.3% reported by a German-Italian group in 2229 patients followed for 9 months.[19] A finding of even greater interest in our series is that all thromboses were late; there has been several cases published where, as in several of our patients, the thrombosis occurred late (>1 year).[15-17] It can be speculated that late thrombosis may be favored by a potentially incomplete intimal coat or a hypersensitivity reaction to the polymer,[15] 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.[6]

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 RAVEL study,[1] 3 months in the SIRIUS study,[2] and 6 months in the Rotterdam group experience.[5,6] 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 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 RAVEL study[14] 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,

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 revascularization 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 revascularization 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 revascularizations for restenosis with 3% of patients with Class I-II 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 revascularization are routinely reported in our setting, namely, clinical follow-up rather than clinical and angiographic, and the characteristics of the clinical setting.[22] In this study, we observed that nonreferred 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 revascularization with conventional stents, even with a less adverse lesion profile, are significantly higher than those obtained with drug-eluting stents.[22]

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 revascularization 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

1. Morice MC, Serruys PW, Sousa JE, Fajadet J, Ban Hayashi E, Perin M, et al. for the RAVEL study group. A randomized comparison of a sirolimus eluting stent with a standard stent for coronary revascularization. N Engl J Med. 2002;346:1773-80.
2. Moses J, Leon MB, Popma JJ, Fitzgerald PJ, Holmes DR, O'Shaughnessy C, et al, for the SIRIUS investigators. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. N Engl J Med. 2003;349:1315-23.
3. Schofer J, Schluter M, Gershlick AH, Wijns W, García E, Schampaert E, et al. Sirolimus-eluting stents for treatment of patients with long atherosclerotic lesions in small coronary arteries: double-blind, randomised controlled trial (E-SIRIUS). Lancet. 2003;362:1093-9.
4. Schampaert E, Cohen EA, Schluter M, Reeves F, Traboulsi M, Title LM, et al. C-SIRIUS Investigators. The Canadian study of the sirolimus-eluting stent in the treatment of patients with long de novo lesions in small native coronary arteries (C-SIRIUS). J Am Coll Cardiol. 2004;43:1110-5.
5. Lemos PA, Serruys PW, van Domburg RT, Saia F, Arampatzis CA, Hoye A, et al. Unrestricted utilization of sirolimus eluting stents compared with conventional bare metal stent implantation in the «real world»: the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) registry. Circulation. 2004;109:190-5.
6. Ong AT, Serruys PW, Aoki J, Hoye A, van Mieghem CA, Rodríguez-Granillo GA, et al. The unrestricted use of paclitaxel- versus sirolimus-eluting stents for coronary artery disease in an unselected population: one-year results of the Taxus-Stent Evaluated at Rotterdam Cardiology Hospital (T-SEARCH) registry. J Am Coll Cardiol. 2005;45:1135-41.
7. Ruiz-Nodar JM, Frutos A, Carrillo P, Morillas P, Valero R, Rodríguez JA, et al. Utilización del stent recubierto de rapamicina en la revascularización de lesiones complejas: estudio con seguimiento clínico y angiográfico. Rev Esp Cardiol. 2004;57:123-9.
8. de la Torre Hernández JM, Burgos V, González-Enríquez S, Cobo M, Zueco J, Figueroa A, et al. Stent liberador de rapamicina en el tratamiento de lesiones coronarias con alto riesgo de reestenosis. Seguimiento clínico a 6 meses de los primeros 100 pacientes. Rev Esp Cardiol. 2004;57:116-22.
9. Lozano I, Herrera C, Morís C, Gómez-Hospital JA, Rondán J, Iráculis E, et al. Stent liberador de fármacos en lesiones de tronco coronario izquierdo en pacientes no candidatos a revascularización quirúrgica. Rev Esp Cardiol. 2005;58:145-52.
10. Hoye A, Tanabe K, Lemos PA, Aoki J, Saia F, Arampatzis C, et al. Significant reduction in restenosis after the use of sirolimus-eluting stents in the treatment of chronic total occlusions. J Am Coll Cardiol. 2004;43:1954-8.
11. Lemos PA, Arampatzis CA, Saia F, Hoye A, Degertekin M, Tanabe K, et al. Treatment of very small vessels with 2.25-mm diameter sirolimus-eluting stents (from the RESEARCH registry). Am J Cardiol. 2004;93:633-6.
12. Neumann FJ, Desmet W, Grube E, Brachmann J, Presbitero P, Rubartelli P, et al. Effectiveness and safety of sirolimus eluting stents in the treatment of restenosis after coronary stent placement. Circulation. 2005;111:2107-11.
13. Sousa JE, Costa MA, Abizaid A, Feres F, Seixas AC, Tanajura LF, et al. Four year angiographic and intravascular ultrasound follow up of patients treated with sirolimus eluting stents. Circulation. 2005;111:2326-9.

14. Fajadet J, Morice MC, Bode C, Parragan P, Serruys P, Wijns W, et al. Maintenance of long term clinical benefit with sirolimus eluting stents. Three year results of the RAVEL trial. Circulation. 2005;111:1040-4.
15. Virmani R, Guagliumi G, Farb A, Musumeci G, Grieco N, Motta T, et al. Localized hypersensitivity and late coronary thrombosis secondary to a sirolimus eluting stent. Should we be cautious? Circulation. 2004;109:701-5.
16. McFadden E, Stabile E, Regar E, Cheneau E, Ong ATL, Kinnaird T, et al. Late thrombosis in drug eluting coronary stents after discontinuation of antiplatelet therapy. Lancet. 2004;364:1519-21.
17. Karvouni E, Korovesis S, Katritsis DG. Very late thrombosis after implantation of sirolimus eluting stent. Heart. 2005;91:e45
18. Bertrand OF, Rodes-Cabau J, Poirier P. Very late in stent restenosis (five years) presenting as an ST elevation acute myocardial infarction. Can J Cardiol. 2004;20:1481-3.
19. Iakovou I, Schmidt T, Bonizzoni E, Ge L, Sangiorgi GM, Stankovic G, et al. Incidence, predictors and outcome of thrombosis after successful implantation of drug eluting stents. JAMA. 2005; 293:2126-30.
20. Wang F, Stouffer GA, Waxman S, Uretsky BF. Late coronary stent thrombosis: early vs late stent thrombosis in the stents era. Catheter Cardiovasc Interv. 2002;55:142-7.
21. Heller LI, Shemwell KC, Hug K. Late stent thrombosis in the absence of prior intracoronary brachytherapy. Catheter Cardiovasc Interv. 2001;53:23-8.
22. de la Torre Hernández JM, Sainz Laso F, Ruisánchez C, Zueco J, Figueroa A, Colman T. Tratamiento de lesiones con alto riesgo de reestenosis. Estudio comparativo en 300 pacientes del *stent* liberador de rapamicina, el *stent* con polímero liberador de paclitaxol y el *stent* convencional. Rev Esp Cardiol. 2005; 58:262-9.