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CLINICAL RESEARCH **Interventional Cardiology**

A Randomized Comparison of Sirolimus-Eluting Stent With Balloon Angioplasty in Patients With In-Stent Restenosis

Results of the Restenosis Intrastent: Balloon Angioplasty Versus Elective Sirolimus-Eluting Stenting (RIBS-II) Trial

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OBJECTIVES We sought to assess the effectiveness of sirolimus-eluting stents (SES) in patients with in-stent restenosis (ISR).

BACKGROUND Treatment of patients with ISR remains a challenge.

METHODS The Restenosis Intrastent: Balloon Angioplasty Versus Elective Sirolimus-Eluting Stenting (RIBS-II) study is a multicenter randomized trial conducted in 150 patients with ISR (76 allocated to SES and 74 to balloon angioplasty [BA]). The primary end point was recurrent restenosis rate at nine months. Secondary end points included prespecified subgroup analysis, lumen volume on intravascular ultrasound (IVUS), and a composite of major clinical events at one year.

RESULTS Angiographic success was obtained in all patients. At 9-month angiographic follow-up (96% of eligible patients) minimal lumen diameter was larger (2.52 mm [interquartile range (IQR) 2.09 to 2.81] vs. 1.54 mm [IQR 0.91 to 2.05]; $p < 0.001$) and recurrent restenosis rate was lower (11% vs. 39%; $p < 0.001$) in the SES group. Prespecified subgroup analyses were consistent with the main outcome measure. Lumen volume on IVUS at 9 months was also larger (279 mm^3 [IQR 227 to 300] vs. 197 mm^3 [IQR 177 to 230]; $p < 0.001$) in the SES group. At one-year clinical follow-up (100% of patients), the event-free survival (freedom from death, myocardial infarction, and target vessel revascularization) was significantly improved in the SES group (88% vs. 69%; $p < 0.004$) as the result of a lower requirement for target vessel revascularization (11% vs. 30%; $p < 0.003$).

CONCLUSIONS In patients with ISR, the use of SES provides superior long-term clinical, angiographic, and IVUS outcome than BA treatment. (J Am Coll Cardiol 2006;47:2152–60) © 2006 by the American College of Cardiology Foundation

Coronary stents currently constitute the default strategy during percutaneous coronary interventions (PCI) (1–3). However, prevention and treatment of in-stent restenosis (ISR) remain among the most important challenges of interventional cardiology (1–3). Different therapeutic strategies have been used in patients with ISR, but all of them are shadowed by a high recurrence risk, especially in patients presenting diffuse ISR (4–8). As compared with balloon angioplasty, still the most frequently used therapy for ISR, repeated bare-metal stenting is able to guarantee optimal immediate results but exacerbates neointimal proliferation and, eventually, fails to significantly improve long-term clinical and angiographic outcome (9,10). In this context, the dramatic capacity of drug-eluting stents to inhibit neointimal proliferation has generated renewed expectations (2). Preliminary observational studies have demonstrated encouraging results with the use of these new stents in patients with ISR (11–14). Moreover, recent studies suggest that drug-eluting stents might even be superior to brachytherapy which, up to now, constitutes the only proven effective therapy in this challenging scenario (15–17).

The aim of this randomized study was to compare sirolimus-eluting stents with conventional balloon angioplasty in patients with ISR.

See page 2161

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Abbreviations and Acronyms

BA = balloon angioplasty
IQR = interquartile range
ISR = in-stent restenosis
IVUS = intravascular ultrasound
PCI = percutaneous coronary interventions
RIBS-II = Restenosis Intrastent: Balloon Angioplasty Versus Elective Sirolimus-Eluting Stenting study
SES = sirolimus-eluting stents

METHODS

Patient selection and study design. The Restenosis Intrastent: Balloon Angioplasty Versus Elective Sirolimus-Eluting Stenting (RIBS-II) study was designed as a prospective, multicenter, randomized clinical trial to compare these two therapeutic strategies in patients with ISR (Appendix). Inclusion and exclusion criteria were similar to those in the RIBS-I trial (a previous randomized study comparing balloon angioplasty with bare-metal stenting for ISR) (10).

Briefly, patients with a first ISR (>50% diameter stenosis) after bare-metal stenting were eligible if they presented with a clinical indication for repeat PCI (angina or documented ischemia) and had lesions amenable for both therapeutic strategies. Patients with ISR on small vessels (<2.5 mm in diameter on visual assessment), occluded arteries, or very diffuse ISR (>32 mm in length) were excluded. Patients with early (<4 weeks) ISR, those presenting with an acute myocardial infarction, and patients with a prior brachytherapy procedure were also excluded. Contraindications to aspirin or clopidogrel, and severe concomitant diseases interfering with follow-up, were additional prespecified exclusion criteria.

Randomization was centralized by telephone at the coordinating center (Clínico San Carlos University Hospital, Madrid) using a computer-generated code and was stratified according to lesion length. Eight university hospitals from Spain participated in the trial. All patients gave written informed consent. The study was performed according to the provisions of the Declaration of Helsinki regarding investigations with human subjects (18), was designed and conducted according to the CONSORT recommendations (19), and was approved by the corresponding institutional ethics committees. The trial was an investigators-driven initiative.

Coronary interventions. All patients were pretreated with aspirin. In elective cases clopidogrel was administered before the procedure. Patients undergoing "ad-hoc" procedures received a loading dose of 300 or 600 mg clopidogrel immediately after the procedure. During interventions heparin was given to maintain an activated clotting time >250 s.

In the balloon arm, balloon size was selected to achieve a final balloon-to-artery ratio of 1.1:1. In the sirolimus-eluting stent arm the protocol mandated a careful lesion predilation. In particular, the use of undersized (1 mm below reference vessel diameter) and short balloons was strongly recommended. Likewise, the protocol emphasized the importance of full lesion coverage (including the predilated segment) with the sirolimus stent. If >1 stent was required a 2- to 3-mm overlap was advocated. Sirolimus-eluting stents (Cypher, Cordis Corp., Johnson & Johnson Co., Miami Lakes, Florida) were available in diameters of 2.5, 2.75, 3.0, and 3.5 mm and in lengths of 8, 13, 18, 23, and 33 mm. Relatively high pressures (>12 atm) were recommended in both arms. In the balloon arm, prolonged balloon inflations had to be performed before crossover to bare-metal stenting (residual stenosis >50% or major/ischemia-inducing dissections) (10).

Serum creatine kinase levels (with MB values if abnormal) and 12-lead electrocardiograms were obtained before, immediately after the procedure and then serially for 24 h. After the procedure all patients received aspirin indefinitely (100 to 300 mg daily) and clopidogrel (75 mg/day) for nine months.

Follow-up and definitions. Patients were followed up at one month, nine months, and one year. Angiographic follow-up was obtained routinely at nine months or earlier if clinically indicated. If restenosis was not demonstrated in an angiogram performed <3 months after the index procedure a second angiography was indicated at 9 months. An exercise test was recommended before the scheduled angiography. Case-report forms were completed at each site, submitted to the coordinating center, and entered into a dedicated database. Consistency checks were systematically performed, and, whenever needed, queries were sent back to the sites. All major events were verified against source documentation. Clinical events (death, myocardial infarction, target vessel revascularization) were adjudicated by an independent Clinical Events Committee blinded to the assigned treatment. Death was considered to be cardiac unless a noncardiac cause could be demonstrated. Myocardial infarction required two of the following: 1) prolonged (>30 min) chest pain; 2) creatine kinase rise above twice the upper normal value (with an abnormal MB fraction); and 3) appearance of new pathologic Q waves. The protocol mandated that repeated PCI at follow-up could only be performed in the presence of symptoms or ischemia.

Angiographic analysis. Coronary angiograms were carefully analyzed at the angiographic core laboratory, following standard morphologic criteria (9,10), by personnel blinded to treatment allocation. The Mehran classification was also used to assess the pattern of ISR (4).

Quantitative coronary angiographic analysis was performed with an automatic edge-detection system (CMS 4.0, Medis, Leiden, the Netherlands). Preselected matched angiographic views (after intracoronray nitroglycerin) were obtained and analyzed before and after intervention and at nine-month follow-up. The angiographic analysis included

"the segment" encompassing the lesion site, the treated region, and the adjacent vessel (5 mm) on each side (10). A second analysis, confined to the lesion site, was also made. Restenosis was defined as >50% diameter stenosis at follow-up.

Intravascular ultrasound (IVUS) analysis. As a substudy, IVUS imaging was performed before intervention, after the procedure, and at follow-up following administration of intracoronary nitroglycerin. A mechanical system, with a 40-MHz transducer was used (Boston Scientific, Sunnyvale, California). The imaging sequence started 1 cm distal to the distal edge of the stent and ended at the aortocoronary junction. The transducer was withdrawn at a constant speed of 0.5 mm/s using a motorized pullback device. Studies were recorded on a 0.5-inch s-VHS tape. Subsequently digitization was performed at a workstation designed for three-dimensional image reconstruction (Echoscan, Tomtec, Germany). A previously validated semiautomatic contour-detection program was used at the core-lab for volumetric analysis (9). Lumen volume was measured in stent and in segment (stent + 5-mm edges). Neointimal volume was analyzed within the stent. In the balloon arm neointimal proliferation was defined as neointimal volume at follow-up minus residual neointimal volume after the intervention.

Study end points. The primary end point was the recurrent restenosis rate at follow-up (in-segment analysis). Secondary angiographic end points were minimal lumen diameter and late loss at follow-up. Secondary IVUS end points included lumen volume and neointimal proliferation volume at follow-up. Finally, the rate of target vessel revascularization and the event-free survival at one year were also secondary clinical end points.

Statistical analysis. SAMPLE SIZE CALCULATION. Following the results of the RIBS-I study, we assumed a restenosis rate of 40% in the balloon arm (10). A restenosis rate of 15% was estimated for the sirolimus-eluting stent arm (11,12). Therefore, selecting a power of 90% and an alpha value of 0.05, and considering that it would be necessary to compensate for 10% loss in late angiography, a total number of 150 patients (75 in each arm) was eventually calculated.

Data are presented as values and percentages or mean ± SD. Median and interquartile range (IQR) were used when data was not normally distributed (Kolmogorov-Smirnov test). Categoric variables were compared with the chi-squared test or Fisher exact test (expected n of <5). The Student *t* test, the median test, or the sign test (paired sample) were used for the comparison of continuous variables. Event-free survival was estimated by Kaplan-Meier analysis and compared with the log rank test. Relative risks and 95% confidence intervals (CI) were calculated. A prespecified analysis of 10 relevant baseline variables (similar to RIBS-I) (10) was also performed. All analyses were performed according to the intention-to-treat principle (SPSS package, version 12.0, SPSS Inc., Chicago, Illinois). A p value of <0.05 was considered statistically significant.

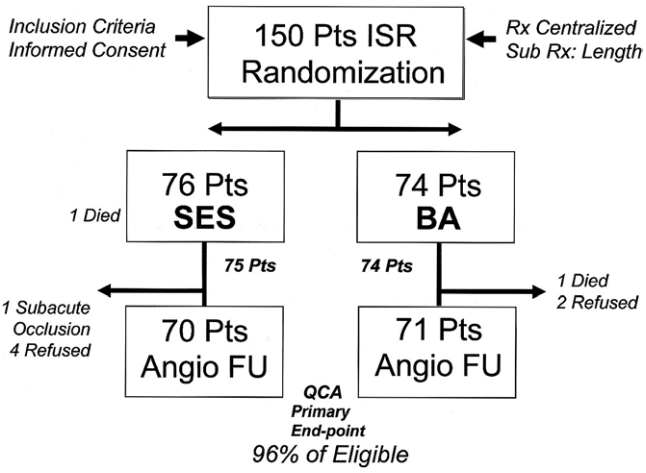

Figure 1. Flow chart of patients included in the trial and patients with final angiographic follow-up. BA = balloon angioplasty; FU = follow-up; ISR = in-stent restenosis; Pts = patients; QCA = quantitative coronary angiography; Rx = randomization; SES = sirolimus-eluting stents.

RESULTS

From February 2003 to April 2004, 150 patients with ISR were enrolled and randomly assigned to sirolimus stenting (76 patients) or balloon angioplasty (74 patients) (Fig. 1). Baseline clinical and angiographic characteristics were similar in both groups (Table 1). Procedural characteristics were also similar in both groups although longer balloon inflation times were used in the balloon group (Table 1). Final pressures were higher than those used in the RIBS-I study (10). Angiographic success was obtained in all patients (100%). The sirolimus stent was successfully implanted in all patients (in 69 after predilation and as direct stenting in 7). Twelve patients required >1 sirolimus stent. One patient in the sirolimus stent group died 17 days after the procedure from sepsis (20), and no other major events occurred during hospitalization.

Results of the quantitative angiography analysis are shown in Table 2. Baseline findings were similar in both groups, although a diffuse pattern of ISR tended to be more frequent in the sirolimus stent group. After the procedure, however, better angiographic results were obtained in the sirolimus stent group (including minimal lumen diameter and % diameter stenosis). Late angiographic follow-up (260 ± 48 days, median 274 days) was obtained in 141 patients (96% of those eligible). Late angiographic results were significantly better in the sirolimus-eluting stent group (Table 2). The recurrent restenosis rate (primary study end point) was 11% in the sirolimus stent group and 39% in the balloon group ($p < 0.001$). In clinical terms, four patients with ISR need to be treated with sirolimus stents to prevent one episode of recurrent ISR. The Mehran classification (I, II, and III) was unable to predict late loss in the sirolimus stent group (0.02 [−0.15 to 0.28] mm, 0.16 [−0.13 to 0.44] mm, and 0.13 [−0.11 to 0.95] mm, respectively; $p = 0.44$), whereas it significantly influenced late loss in the balloon group (0.50

Table 1. Baseline Clinical, Angiographic, and Procedural Characteristics

Characteristic	SES Group (n = 76)	BA Group (n = 74)	p Value
Age, yrs	64 ± 11	64 ± 10	0.76
Female gender, n (%)	18 (24)	19 (26)	0.77
Risk factors, n (%)			
Diabetes mellitus	29 (38)	23 (31)	0.36
Hyperlipidemia	43 (57)	49 (66)	0.23
Hypertension	46 (61)	36 (49)	0.14
Ever smoked	44 (58)	44 (59)	0.85
Clinical features, n (%)			
Unstable angina	31 (41)	37 (50)	0.26
Stable angina	32 (42)	27 (37)	0.48
Silent ischemia	13 (17)	10 (14)	0.54
Previous myocardial infarction	44 (58)	38 (51)	0.42
Previous bypass surgery	5 (7)	3 (4)	0.72†
Time to restenosis, days (range)	194 (158–296)	209 (174–323)	0.63‡
Target artery, n (%)			0.72
Left anterior descending	41 (54)	38 (52)	
Left circumflex	11 (14)	12 (16)	
Right coronary	24 (32)	23 (31)	
Saphenous vein graft	0 (0)	1 (1)	
B2-C lesion, n (%)	62 (81)	58 (78)	0.62
Mehran I, II, III,* n (%)	15 (20), 51 (67), 10 (13)	25 (34), 41 (55), 8 (11)	0.15
Ejection fraction, %	65 ± 11	66 ± 10	0.38
Procedural characteristics			
Length of initial stent (mm)	20 ± 8	21 ± 9	0.55
Maximal pressure (atm)	15.8 ± 2.9	15.5 ± 3.1	0.64
Total inflation time (s)	90 ± 63	132 ± 109	0.005
Balloon/artery ratio	1.17 ± 0.1	1.14 ± 0.1	0.37
Cross-over	0 (0)	6 (8)	0.01†
Angiographic success	76 (100)	74 (100)	1

*Mehran IV was not included. †Fisher test. ‡Median test.
BA = balloon angioplasty; SES = sirolimus-eluting stent.

[0.05 to 0.78] mm, 0.93 [0.37 to 1.46] mm, and 1.06 [0.16 to 1.24] mm, respectively; p = 0.03).

In the sirolimus-eluting stent group, patients with recurrent ISR had similar baseline clinical, angiographic, and procedural characteristics as patients without recurrent ISR. Recurrence rate was similar in patients treated with high (≥16 atm) and lower pressures. However, patients with recurrences tended to have longer lesions (24 ± 14 mm vs. 16 ± 8 mm; p = 0.14) and were treated with longer sirolimus stents (29 ± 11 mm vs. 22 ± 7 mm; p < 0.05) compared with patients without recurrences. Recurrent ISR after sirolimus stenting tended to be relatively focal (11 ± 5 mm), with a significant reduction in length from the index procedure (reduction of 13 ± 13 mm; p < 0.05 vs. baseline). Figure 2 depicts cumulative frequency distribution curves of minimal lumen diameter at all time points. Figure 3 displays the subgroup analyses.

Intravascular ultrasound studies were obtained in 114 patients (76%). However, complete, serial studies of adequate quality for quantitative analysis were available in 82 patients (42 sirolimus stent and 40 balloon group). Baseline characteristics of these patients were similar to those found in the complete population. Ultrasound findings preintervention were similar in both groups. After the procedure, however, a larger lumen volume was obtained in the stent group. At late follow-up, lumen volume (both in-segment and in-stent analyses) was significantly larger in the sirolimus-eluting stent group (Fig. 4). The volume of neointimal proliferation was also significantly reduced in the sirolimus stent group (Fig. 4). At late follow-up, only 4% (IQR 3% to 7%) of the total sirolimus stent volume was occupied by neointima.

A complete one-year clinical follow-up was obtained in all 150 patients (100%). Table 3 summarizes all adverse clinical events documented during this time. Two patients suffered an abrupt vessel closure and developed a Q-wave myocardial infarction (one patient in each arm); hyperhomocysteinemia was found in an 80-year-old patient in the sirolimus stent arm in whom doubts emerged concerning the correct intake of the dual antiplatelet regimen.

Overall clinical events at nine-month and one-year follow-up were significantly reduced in the sirolimus stent group. This was largely due to a lower requirement for target vessel revascularization which, in some patients, was performed after nine months once ischemia was demonstrated (Table 3).

DISCUSSION

This randomized study demonstrates the superiority of sirolimus-eluting stents, compared with balloon angioplasty, in patients with ISR. Patients treated with sirolimus-eluting

Table 2. Initial and Follow-Up Angiographic Results

Variable	SES Group	BA Group	p Value
Before the procedure*	(n = 76)	(n = 74)	
Reference vessel diameter (mm)	2.66 ± 0.5	2.68 ± 0.4	0.80
Minimal lumen diameter (mm)	0.74 ± 0.3	0.70 ± 0.3	0.54
Stenosis (% of lumen diameter)	72 ± 13	74 ± 11	0.32
Lesion length (mm)	16.9 ± 9	15.7 ± 9	0.40
Diffuse lesions (>10 mm), n (%)	61 (80)	49 (66)	0.05
After the procedure*	(n = 76)	(n = 74)	
Reference vessel diameter (mm)	2.91 ± 0.4	2.80 ± 0.4	0.12
Minimal lumen diameter (mm)	2.69 ± 0.4	2.29 ± 0.4	<0.001
Stenosis (% of lumen diameter)	7 ± 6	18 ± 9	<0.001
Acute gain (mm)	1.95 ± 0.5	1.59 ± 0.4	<0.001
At follow-up (in-segment analysis)†	(n = 70)	(n = 71)	
Reference vessel diameter (mm)	2.87 (2.61–3.11)	2.70 (2.40–2.96)	0.03
Minimal lumen diameter (mm)	2.52 (2.09–2.81)	1.54 (0.91–2.05)	<0.001
Stenosis (% of lumen diameter)	8 (4–21)	40 (25–65)	<0.001
Restenosis, n (%)	8 (11)	28 (39)	<0.001
Late loss (mm)	0.13 (−0.13–0.43)	0.69 (0.15–1.28)	<0.001
Loss index	0.06 (−0.07–0.21)	0.43 (0.11–0.83)	<0.001
Net gain (mm)	1.81 (1.39–2.09)	0.89 (0.24–1.25)	<0.001
At follow-up (in-lesion analysis)†	(n = 70)	(n = 71)	
Reference vessel diameter (mm)	2.85 (2.60–3.10)	2.70 (2.40–2.96)	0.08
Minimal lumen diameter (mm)	2.56 (2.28–2.81)	1.54 (0.91–2.05)	<0.001
Stenosis (% of lumen diameter)	8 (4–17)	40 (25–65)	<0.001
Restenosis, n (%)	5 (7)	28 (39)	<0.001
Late loss (mm)	0.11 (−0.13–0.27)	0.69 (0.15–1.28)	<0.001
Loss index	0.06 (−0.07–0.15)	0.43 (0.11–0.83)	<0.001
Net gain (mm)	1.84 (1.47–2.10)	0.89 (0.24–1.25)	<0.001

*Values before and after the procedure followed a gaussian distribution (mean ± SD). †Angiographic data at follow-up, not normally distributed (median, interquartile range), were compared with the median test.
Abbreviations as in Table 1.

stents had a dramatic improvement in all angiographic parameters at follow-up, including recurrent restenosis rate, the primary end point of the study. This was the result not only of a better initial angiographic result, but also, more importantly, of a marked reduction in the angiographic late loss. Subgroup analyses were consistent with the main outcome measure. In addition, the use of sirolimus stents, associated with prolonged dual antiplatelet therapy, proved to be safe in this challenging setting with an incidence of abrupt vessel closure similar to that found in the balloon group. Moreover, our IVUS substudy provided further mechanistic insights and demonstrated the ability of sirolimus-eluting stents to virtually abolish recurrent neointimal proliferation. Finally, these excellent late angiographic and ultrasound findings translated into an improved clinical outcome, mainly as the result of a significant reduction in the need for target vessel revascularization.

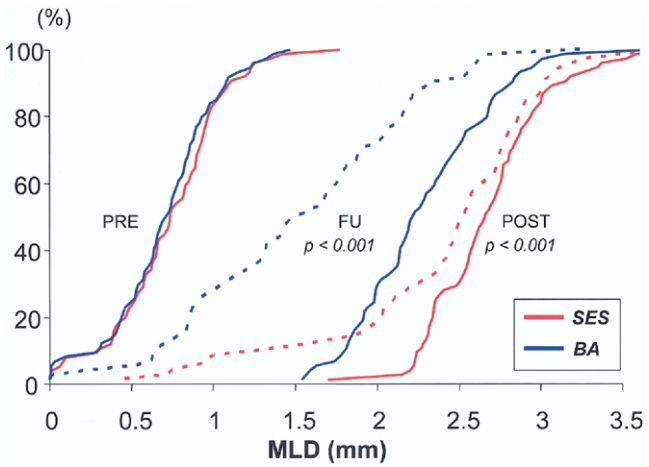

Figure 2. Cumulative frequency distribution curves of minimal lumen diameter (MLD) (in-segment analysis) before the procedure (PRE), after intervention (POST), and at follow-up (FU), in patients treated with balloon angioplasty (BA) and sirolimus-eluting stenting (SES).

Previous studies. Several observational studies have demonstrated the efficacy of drug-eluting stents in patients with ISR. In a pioneer study Sousa el al. (11) demonstrated excellent long-term clinical and angiographic results with the use of sirolimus stents in a relatively favorable patient cohort. Subsequently, the value of these stents was demonstrated in patients with more complex patterns of ISR, including those with occluded vessels and recurrences after brachytherapy (12). Although the results of that study compared favorably with historical series, the recurrent restenosis rate at 6 months was 20% (12). More recently Neumann et al. (13) reported the largest series (162 patients) treated with sirolimus stents for ISR. In that prospective registry the binary restenosis rate was 9.7% and the requirement for a new intervention in the target vessel 7.4%. On the other hand, the use of paclitaxel-eluting stents in patients with ISR has also generated considerable interest. In the In-Stent Restenosis Treated With Stent-Based

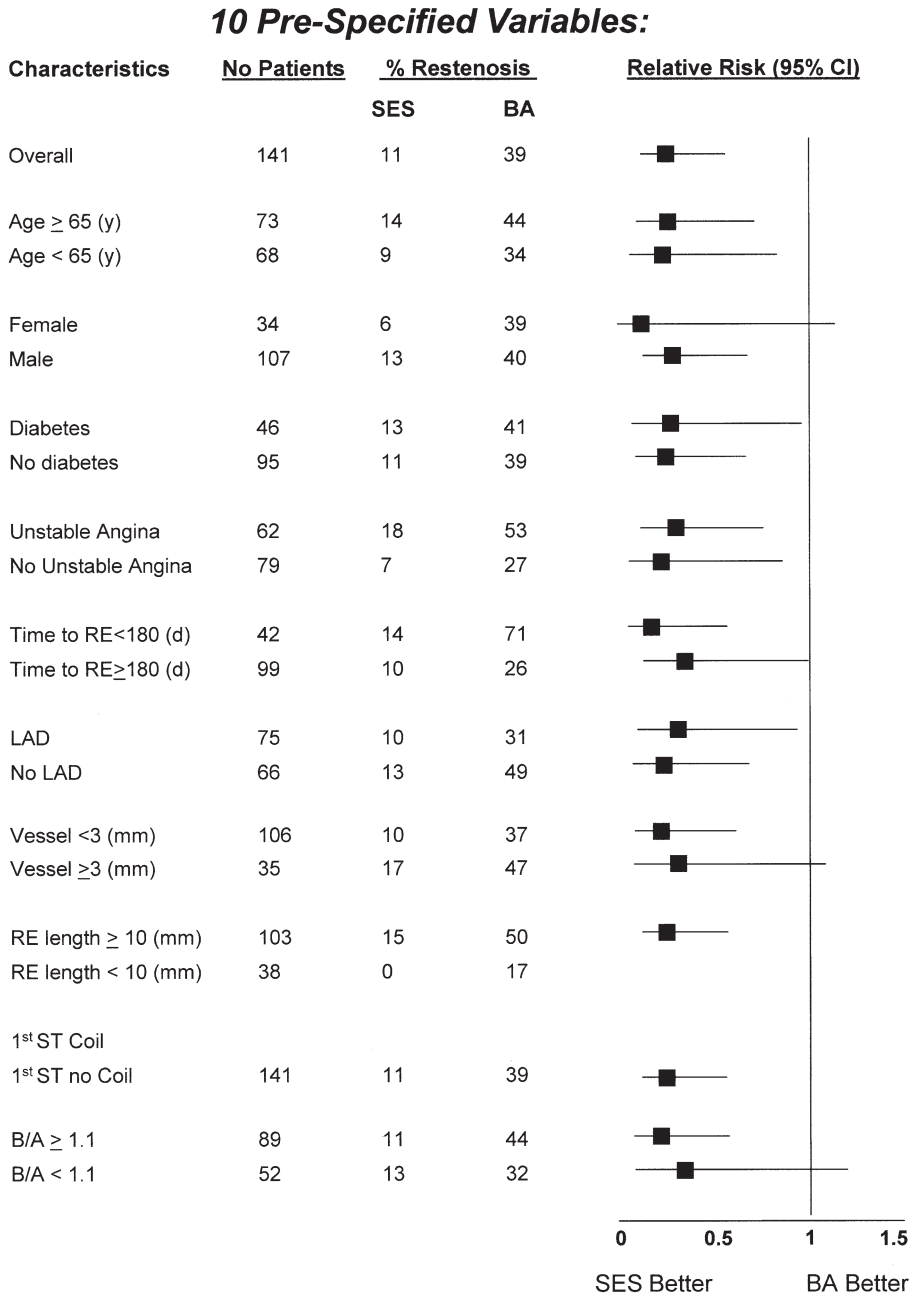

Figure 3. Restenosis risk according to treatment allocation and ten prespecified variables. The relative risk for short lesions was undefined, because 0% recurrence was found in the sirolimus-eluting stent (SES) group. No patient with in-stent restenosis of a coil stent (first ST Coil) was included. BA = balloon angioplasty; B/A = balloon/artery ratio; CI = confidence interval; LAD = left anterior descending coronary artery; RE = restenosis.

Delivery of Paclitaxel Incorporated in a Slow-Release Polymer Formulation (TAXUS III) registry (14), including 28 patients, the mean late loss at 6 months was 0.54 mm and the rate of adverse clinical events at 1 year was 29%.

Recently the results of the Intracoronary Stenting with Antithrombotic Regimen-Drug-Eluting Stents for In-Stent Restenosis (ISAR-DESIRE) randomized study have been reported (21). This study allocated 300 patients with ISR to balloon therapy, sirolimus stent, or paclitaxel stent implantation. Both drug-eluting stents proved to be superior to balloon angioplasty. In a secondary analysis, however, the sirolimus stent had a trend to a lower rate of angiographic restenosis (14.3% vs. 21.7%) and significantly reduced late lumen loss (median 0.32 vs. 0.55 mm) and the rate of target vessel revascularization (8% vs. 19%) compared with the paclitaxel stent. Intravascular ultrasound studies, however, were not performed in this trial.

Multiple randomized trials have unequivocally demonstrated the superiority of brachytherapy over balloon angioplasty in this adverse anatomic setting. Brachytherapy, however, is limited by inherent logistics, cumbersome procedures, concern of edge effects, a prolonged risk of vessel

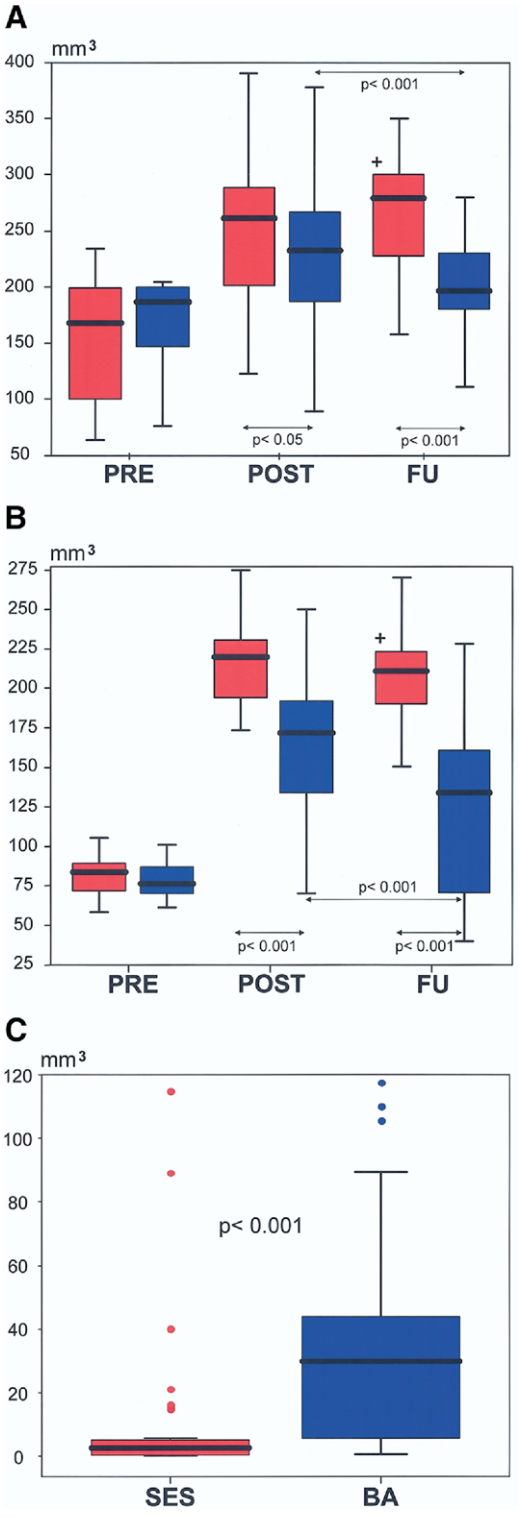

Figure 4. Box whisker plot (median and interquartile range) of intravascular ultrasound findings at follow-up. **(A)** In-segment lumen volume. **(B)** In-stent lumen volume. **(C)** Neointimal proliferation volume. The median test was used to compare results between the two arms. The paired sample sign test was used to assess changes within each arm. $+p < 0.05$ (stent group, post-procedure vs. follow-up [FU]). BA = balloon angioplasty **(blue)**; PRE = before the procedure; POST = after intervention; SES = sirolimus-eluting stents **(red)**.

occlusion and a decrease in benefit over time (22). In Spain, only 3% of all PCI performed for ISR in 2003 used brachytherapy (3), and since 2005 this therapy is no longer available. In this regard, recent studies in patients with ISR matched for clinical and angiographic variables (15–17) suggest the superiority of drug-eluting stents (both paclitaxel and sirolimus) over brachytherapy.

Current study. Some findings of the present study deserve further comments. The median late loss of 0.13 found in our study favorably compares with the 0.32 mm late loss found in the ISAR-DESIRE trial (21). In addition, in our study, in-stent and in-segment late loss were nearly identical (excluding the presence of significant edge effects), whereas in ISAR-DESIRE in-segment late loss was three times the in-stent late loss. Nevertheless, 11% of our patients developed recurrences. The reason for treatment failure in these patients remains unclear. We were unable to identify predictors of this complication other than sirolimus stent length. Similar findings have been reported by other investigators (13). However, Fujii et al. (23) suggested that severe stent underexpansion could represent a marker of patients with a higher risk for recurrences. In this regard the high implantation pressures used in our study were designed in an attempt to prevent this problem. Vessel size is yet another potentially important factor to explain recurrences. In the present study as well as in previous studies (13,21) patients treated for ISR had relatively small vessels which could facilitate the appearance of recurrences for any given angiographic late loss. Finally, 35% of patients in the current study were diabetic (38% in the sirolimus stent group). This number is higher than that found in other previous ISR trials (7,8,21), including the RIBS-I study (26% diabetic) (10).

The pattern of late angiographic findings was also of interest. Notably, at follow-up we found a skewed distribution of most late angiographic variables, mainly affecting the sirolimus stent group. The implications of this finding have been recently emphasized in some drug-eluting stent trials (24,25). It is important to keep in mind that at late follow-up most patients maintain excellent angiographic and ultrasound results, with findings difficult to differentiate from those seen immediately after the procedure. However, a small but sizable number of patients behave differently, experiencing significant neointimal proliferation and eventually developing severe recurrent ISR. This distinct bimodal distribution pattern explains late angiographic data not being normally distributed. Furthermore, as previously described (23) patients with recurrences after sirolimus stenting tend to present with a relatively "focal" pattern of ISR which, at least on theoretical grounds, could facilitate a benign outcome after subsequent treatment.

Finally, our IVUS substudy complements previous findings and confirms the value of sirolimus stents to markedly inhibit recurrent neointimal proliferation in patients with ISR. As a result, lumen volume at follow-up (both in-segment and in-stent analyses) was significantly larger in the

Table 3. In-Hospital and One-Year Clinical Events

Event	SES Group (n = 76)	BA Group (n = 74)	p Value	HR (95% CI)
Hospital events, n (%)				
Death	1 (1.3)	0 (0)	0.49	—
Myocardial infarction	0 (0)	0 (0)	1	1
Target vessel revascularization	0 (0)	0 (0)	1	1
Coronary angioplasty	0 (0)	0 (0)	1	1
Coronary surgery	0 (0)	0 (0)	1	1
Any major hospital event	1 (1.3)	0 (0)	0.49	—
Events at 9 months, n (%)				
Death	3 (3.9)	1 (1.4)	0.32	0.34 (0.03–3.27)
Myocardial infarction	2 (2.6)	1 (1.4)	0.57	0.51 (0.05–5.61)
Target vessel revascularization	3 (3.9)	10 (13.5)	0.03	3.56 (0.98–12.9)
Coronary angioplasty	2 (2.6)	7 (9.5)	0.08	3.65 (0.76–17.5)
Coronary surgery	1 (1.3)	3 (4.1)	0.54	2.06 (0.19–22.7)
Any major event at 9 months	4 (5.3)	11 (14.9)	0.05	2.93 (0.93–9.20)
Events at 1 year, n (%)				
Death	3 (3.9)	3 (4.1)	0.98	1.02 (0.21–5.05)
Myocardial infarction	2 (2.6)	2 (2.7)	0.99	1.01 (0.14–7.17)
Target vessel revascularization	8 (10.5)	22 (29.7)	0.003	3.16 (1.40–7.09)
Coronary angioplasty	7 (9.2)	18 (24.3)	0.01	2.83 (1.18–6.76)
Coronary surgery	1 (1.3)	4 (5.4)	0.16	4.12 (0.46–36.9)
Any major event at 1 year	9 (11.8)	23 (31.1)	0.004	2.90 (1.34–6.28)

Patients with more than one event are counted only once for the composite clinical end points, although each event is listed separately in the corresponding category. p values from Cox analysis.
CI = confidence intervals; HR = hazard ratio; — = undefined; other abbreviations as in Table 1.

sirolimus stent group. Of interest, in the sirolimus stent group lumen volume at follow-up increased in the in-segment analysis and decreased in the in-lesion (stent) analysis. Furthermore, although initial results were significantly better in the sirolimus stent arm the main factor accounting for the larger coronary lumen at follow-up in this arm was the striking inhibition of neointimal proliferation. This provides comprehensive mechanistic insights on the efficacy of these stents in this challenging scenario.

Study limitations. First, only patients with ISR after bare-metal stenting were included. Therefore, the efficacy of the studied strategies in patients with ISR after drug-eluting stenting would require additional investigation. Second, patients with occluded stents and very diffuse ISR were not included. Third, the lack of a brachytherapy arm prevents comparing the results of sirolimus-eluting stents with this well established therapy for ISR. Lastly, IVUS studies were not obtained in all patients. However, results of our IVUS substudy were consistent with the main findings of the study.

CONCLUSIONS

This randomized controlled clinical trial demonstrates that in patients with ISR the use of sirolimus-eluting stents provides superior long-term clinical, angiographic, and IVUS outcome compared with conventional balloon angioplasty and, therefore, should be recommended.

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REFERENCES

1. Serruys PW, De Jaegere P, Kiemeneij F, et al. A comparison of balloon-expandable-stent implantation with balloon angioplasty in patients with coronary artery disease. N Engl J Med 1994;331:489–95.
2. Morice MC, Serruys PW, Sousa JE, et al. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. N Engl J Med 2002;346:1773–80.
3. López-Palop R, Moreu J, Fernández-Vazquez F, Hernández-Antolín R. Spanish Registry of Cardiac Catheterization and Coronary Interventions. Thirteenth Official Report of the Working Group on Cardiac Catheterization and Interventional Cardiology of the Spanish Society of Cardiology (1990–2003). Rev Esp Cardiol 2004;57;1076–89.
4. Mehran R, Dangas G, Abizaid AS, et al. Angiographic patterns of in-stent restenosis. Classification and implications for long-term outcome. Circulation 1999;100:1872–8.
5. Bauters C, Banos JL, Van Belle E, Fadden EP, Lablanche JM, Bertrand ME. Six-month angiographic outcome after successful repeat percutaneous intervention for in-stent restenosis. Circulation 1998;97:318–21.
6. Radke PW, Kaiser A, Frost C, Sigwart U. Outcome after treatment of coronary in-stent restenosis. Results from a systematic review using meta-analysis techniques. Eur Heart J 2002;24:266–73.
7. vom Dahl J, Dietz U, Haager PK, et al. Rotational atherectomy does not reduce recurrent in-stent restenosis. Results of the Angioplasty Versus Rotational Atherectomy for Treatment of Diffuse In-Stent Restenosis Trial (ARTIST). Circulation 2002;105:583–8.
8. Albiero R, Silber S, Di Mario C, et al. Cutting balloon versus conventional balloon angioplasty for the treatment of in-stent restenosis. Results of the Restenosis Cutting Balloon Evaluation Trial (RESCUT). J Am Coll Cardiol 2004;43:943–9.
9. Alfonso F, García P, Fleites H, et al. Repeat stenting for the prevention of the early lumen loss phenomenon in patients with in-stent restenosis: angiographic and intravascular ultrasound findings of a randomized study. Am Heart J 2005;149:e1–8.
10. Alfonso F, Zueco J, Cequier A, et al. A randomized comparison of repeat stenting with balloon angioplasty in patients with restenosis after coronary stenting. J Am Coll Cardiol 2003;42:796–805.
11. Sousa JE, Costa M, Abizaid A, et al. Sirolimus-eluting stent for the treatment of in-stent restenosis. A quantitative coronary angiography

and three-dimensional intravascular ultrasound study. Circulation 2003;107:24–7.
12. Degertekin M, Regar E, Tanabe K, et al. Sirolimus eluting stent for treatment of complex in-stent restenosis. The first clinical experience. J Am Coll Cardiol 2003;41:184–9.
13. Neumann FJ, Desmet W, Grube E, et al. Effectiveness and safety of sirolimus-eluting stents in the treatment of restenosis after coronary stent placement. Circulation 2005;111:2107–11.
14. Tanabe K, Serruys PW, Grube E, et al. TAXUS III trial: in-stent restenosis treated with stent-based delivery of paclitaxel incorporated in a slow-release polymer formulation. Circulation 2003;107:559–64.
15. Radke PW, Kobella S, Kaiser A, et al. Treatment of in-stent restenosis using a paclitaxel-eluting stent: acute results and long-term follow-up of a matched comparison with intracoronary beta-radiation therapy. Eur Heart J 2004;25:920–5.
16. Saia F, Lemonths PA, Hoye A, et al. Clinical outcomes for sirolimus-eluting stent implantation and vascular brachytherapy for the treatment of in-stent restenosis. Catheter Cardiovasc Interv 2004;62: 283–8.
17. Iofina E, Radke PW, Skurzewski P, et al. Superiority of sirolimus-eluting stent compared with intracoronary beta-radiation therapy for treatment of in-stent restenosis: a matched comparison. Heart 2005; 91:1584–9.
18. World Medical Association Declaration of Helsinki. Ethical Principles for Medical Research Involving Human Subjects. 52nd WMA General Assembly, Edinburgh, Scotland, October 2000. Available at: http://www.wma.net/e/policy/17c_e.html. Accessed March 17, 2005.
19. Altman DG, Schulz KF, Moher D, et al., CONSORT group. The revised CONSORT statement for reporting randomised trials: explanation and elaboration. Ann Intern Med 2001;134:663–94.
20. Alfonso F, Moreno R, Vergas J. Fatal infection following rapamycin eluting coronary stent implantation. Heart 2005;91:e51.
21. Kastrati A, Mehilli J, von Beckerath N, et al. Sirolimus-eluting stent or paclitaxel-eluting stent versus balloon angioplasty for prevention of recurrences in patients with coronary in-stent restenosis: a randomized controlled trial. JAMA 2005;293:165–71.
22. Waksman R, Ajani AE, White L, et al. Five-year follow-up after intracoronary gamma radiation therapy for in-stent restenosis. Circulation 2004;109:340–4.
23. Fujji K, Mintz GS, Kobayashi Y, et al. Contribution of stent underexpansion to recurrence after sirolimus-eluting stent implantation for in-stent restenosis. Circulation 2004;109:1085–8.
24. Mauri L, Orav EJ, O'Malley AJ, et al. Relationship of late loss in lumen diameter to coronary restenosis in sirolimus-eluting stents. Circulation 2005;111:321–7.
25. Ellis SG, Popma JJ, Lasala JM, et al. Relationship between angiographic late loss and target lesion revascularization after coronary stent implantation. Analysis from the TAXUS-IV trial. J Am Coll Cardiol 2005;45:1193–200.

APPENDIX

For a list of the RIBS-II Investigators, coordinators, and sites, please see the online version of this article.