

Efficacy of Sirolimus-Eluting Stent Implantation in Diabetic Patients With Very Small Vessels (≤ 2.25 mm). Insights From the DIABETES Trial

Pilar Jiménez-Quevedo,^a Manel Sabaté,^a Dominick J. Angiolillo,^a Fernando Alfonso,^a Rosanna Hernández-Antolín,^a José A. Gómez-Hospital,^b Marcelo Sanmartín,^c Camino Bañuelos,^a Raúl Moreno,^a Javier Escaned,^a Cristina Fernández,^a Marco A Costa,^d Francisco Fernández-Avilés,^e and Carlos Macaya^a

^aInstituto Cardiovascular, Hospital Clínico San Carlos, Madrid, Spain.

^bUnidad de Hemodinámica, Hospital Prínceps d'Espanya, L'Hospitalet de Llobregat, Barcelona, Spain.

^cUnidad de Hemodinámica, Hospital Do Meixoeiro, Vigo, Pontevedra, Spain.

^dUniversity of Florida, Cardiovascular Imaging Core Laboratories, Jacksonville, Florida, USA.

^eServicio de Cardiología, Hospital Clínico de Valladolid, Valladolid, Spain.

Introduction and objectives. Diabetic patients frequently have small-diameter vessels, which increases their risk of restenosis. The aim of this study was to determine the efficacy of sirolimus-eluting stent implantation in these high-risk patients following percutaneous coronary intervention.

Methods. Our study population comprised a subset of 85 diabetic patients from the DIABETES (DIABETes and sirolimus Eluting Stent) trial who had very small vessels, defined as those with a reference diameter ≤ 2.25 mm. In the 100 lesions treated, 49 sirolimus-eluting stents and 51 bare-metal stents were used. Glycoprotein IIb/IIIa inhibitors were used as recommended by the protocol and dual antiplatelet therapy was administered for 1 year.

Results. Baseline clinical and angiographic characteristics were comparable in the 2 groups. The patients' mean age was 66 (9) years, 42% were women, and 37% were insulin-dependent. On average, the lesion length was 15.0 (9.0) mm and the reference diameter was 1.9 (0.2) mm. At 9-month follow-up, both late lumen loss and the restenosis rate were significantly lower in the sirolimus-eluting stent group than in the bare-metal stent group, at -0.03 (0.3) mm vs 0.44 (0.5) mm ($P < .001$), and 9.1% vs 39.1% ($P = .001$), respectively. These differences were also observed in the subgroup of insulin-dependent patients. At 1-year follow-up, the stent thrombosis rate was 0% in the sirolimus-eluting stent group, whereas 2 patients in the bare-metal stent group presented with stent thrombosis.

Conclusions. Sirolimus-eluting stent implantation in diabetics with very small vessels is safe and effective, even in insulin-dependent patients.

Key words: *Diabetes mellitus. Drug eluting stent. Coronary angioplasty. Small vessels.*

SEE EDITORIAL ON PAGES 991-3

Correspondence: Dr. M. Sabaté.
Unidad de Hemodinámica. Hospital de la Santa Creu i Sant Pau.
Sant Antoni Maria Claret, 167. 08025 Barcelona. España.
E-mail: msabatet@santpau.es

Manuscript received March 13, 2006.
Accepted for publication June 22, 2006.

Eficacia de la implantación del *stent* recubierto de rapamicina en pacientes diabéticos con vasos muy pequeños ($\leq 2,25$ mm). Subanálisis del estudio DIABETES

Introducción y objetivos. La presencia de vasos de pequeño calibre en pacientes diabéticos es una combinación frecuente que confiere un riesgo elevado de reestenosis. El objetivo de este estudio fue evaluar la eficacia del *stent* recubierto de rapamicina en esta situación de riesgo tras intervencionismo percutáneo.

Métodos. La población incluida en este estudio consistió en un subgrupo de 85 diabéticos (100 lesiones: *stent* recubierto de rapamicina = 49, *stent* convencional = 51) incluidos en el estudio DIABETES (DIABETes and sirolimus Eluting Stent) con vasos muy pequeños, definido como un diámetro de referencia $\leq 2,25$ mm. El uso de inhibidores de la glucoproteína IIb/IIIa fue recomendado por protocolo y se administró doble antiagregación durante un año.

Resultados. Las características basales y angiográficas fueron comparables entre los grupos. La edad media fue 66 ± 9 años, el 42% fueron mujeres y el 37%, insulinodependientes. La longitud media de la lesión fue $15,0 \pm 9,0$ mm y el diámetro de referencia, $1,9 \pm 0,2$ mm. A los 9 meses de seguimiento, la pérdida luminal tardía y la tasa de reestenosis fueron significativamente menores en el grupo de *stent* recubierto de rapamicina comparado con el grupo de *stent* convencional ($-0,03 \pm 0,3$ frente a $0,44 \pm 0,5$ mm; $p < 0,001$ y el 9,1 frente al 39,1%; $p = 0,001$, respectivamente). Esta reducción se observó también en el subgrupo de pacientes insulinodependientes. Al año de seguimiento, la tasa de trombosis del *stent* en el grupo de *stent* recubierto de rapamicina fue del 0%, mientras que 2 pacientes presentaron trombosis del *stent* en el grupo de *stent* convencional.

Conclusiones. La implantación del *stent* recubierto de rapamicina en diabéticos con vasos muy pequeños es segura y eficaz al año de seguimiento, incluso en el subgrupo de pacientes insulinodependientes.

Palabras clave: *Diabetes mellitus. Stent recubierto. Angioplastia coronaria. Vasos pequeños.*

ABBREVIATIONS

DIABETES: DIABETes and sirolimus Eluting Stent.
 SES: sirolimus-eluting stent.
 BMS: bare metal stent.
 ICUS: intracoronary ultrasound.
 TLR: target lesion revascularization.

INTRODUCTION

The association between diabetes mellitus and coronary disease is widely recognized. Diabetic patients have an elevated incidence of ischemic heart disease characterized as being aggressive than in nondiabetic patients.^{1,2} Furthermore, the presence of diabetes after percutaneous coronary revascularization is an independent predictive factor of restenosis³ along with other factors such as lesion length and vessel size.⁴ There appears to be a cumulative effect between these factors, such that the incidence of restenosis following placement of a bare metal stent (BMS) in diabetic patients with small vessels is twice that of nondiabetic patients with the same vessel size.⁵

In randomized studies, sirolimus-eluting stents (SES) have been shown to be effective in lowering the incidence of restenosis and improving the prognosis of patients with coronary stenosis.^{6,7} In this regard, this type of stent has proven to be particularly effective in high-risk patients such as diabetic patients.⁸⁻¹⁰ Diabetic patients frequently present diffuse disease and small vessels.¹¹ A non-negligible percentage of these patients are seen for percutaneous revascularization, on the basis that the surgical option is ruled out due to the vessel size.¹² The purpose of the present study was to assess the safety and efficacy of sirolimus-eluting stent implantation in the subgroup of diabetic patients included in the DIABETES study with very small vessels, as well as to identify the predictive factors for restenosis at 9 months follow-up in this subgroup of high-risk patients.

METHODS**Study Design and Patient Selection**

The DIABETES study⁷ included 160 insulin- or noninsulin-dependent diabetic patients with 1 or more de novo coronary lesions randomized to receive an SES (Cypher™, Cordis, J&J) or an BMS (Velocity™, Cordis, J&J). The inclusion and exclusion criteria have been previously described.⁷ Briefly, diabetic patients were excluded if they were under dietary treatment or had severe renal or hepatic failure, acute coronary syndrome with persistent ST-elevation of less than 72 hours' evolution, lesions in the unprotected left main

coronary artery, bifurcation lesions, or saphenous or mammary graft.

For inclusion in this substudy, lesions with a baseline reference diameter ≤ 2.25 mm measured by quantitative coronary angiography were selected.

The DIABETES study was approved by the ethics committee at each site, and all patients gave written informed consent form prior to inclusion.

Procedure

The angioplasty was performed by following the standard procedure. Both direct stent implantation and predilatation were allowed, provided the entire damaged segment was covered with the balloon. The administration of glycoprotein IIb-IIIa inhibitors was recommended according to the protocol.

Angiographic and Intravascular Ultrasound Data Collection, Follow-Up, and Analysis

The clinical follow-up was done in months 9, 12, and 13 months (1 month after discontinuation of clopidogrel). Data collection was centralized at the coordinating center (Hospital Clínico San Carlos, Madrid, Spain). All patients received dual antiplatelet therapy with aspirin and clopidogrel for 1 year, unless there were contraindications.

The angiographic and intracoronary ultrasound (ICUS) study was performed after stent placement and 9 months follow-up. The angiographic and ICUS analysis was performed at an independent core laboratory, blinded to the type of treatment assigned, located at the University of Florida, USA. The segment with the stent itself was analyzed, along with 5 mm proximal and distal to the stent. Late luminal loss was defined as the difference between post-stenting lumen diameter and the diameter measured during follow-up. Binary restenosis was defined as stenosis greater than 50% of the lumen diameter in the target lesion on follow-up.

The ICUS images were acquired with an automatic pullback device at 0.5 mm/second, following the administration of intracoronary nitroglycerin. All ICUS studies were recorded on VHS video tapes. Three-dimensional IVUS for quantitative analysis was carried out using an analytical system (QIVA, Foot Medical Imaging)¹³ that allows both semiautomatic detection of the lumen, vessel, and stent, as well as quantitative analysis in the transverse and longitudinal slices. The volume was determined by summing the cross-sectional areas in all slices during pullback according to Simpson's rule.¹³ The volume of neointimal hyperplasia was calculated as the difference between stent volume and lumen volume at 9 months follow-up. The percent obstruction volume was defined as the volume of neointimal hyperplasia,

divided by the stent volume and multiplied by 100. The qualitative analysis included a study of stent malapposition, defined as at least 1 stent strut clearly separated from the vessel wall with evidence of blood speckles behind it,¹⁴ and classified into three categories: resolved, persistent, or acquired.¹⁵

Study Objective and Definitions

This substudy assessed the same parameters as the DIABETES study.⁸ The primary endpoint of the study was to assess late luminal loss by quantitative coronary analysis at 9 months follow-up. Additional endpoints included other angiographic parameters related to restenosis, intravascular ultrasound data, onset of major cardiac events such as cardiac death, acute myocardial infarction, need for target lesion revascularization (including in-stent and both edges), and stent thrombosis.⁷

Acute myocardial infarction was defined as the onset of prolonged chest pain and/or the development of pathological Q waves lasting at least 0.04 seconds in 2 or more adjacent leads with creatinine kinase-MB elevation, or in the absence of pathological Q waves, creatinine kinase elevation above twice the upper limit of normality with MB elevation.

Clinically driven target lesion revascularization (TLR) was defined as the need for new revascularization due to $\geq 50\%$ restenosis of the lumen diameter (considering the entire segment), along with objective evidence of myocardial ischemia in a functional study, or if the restenosis were at least 70%, associated with recurrent symptoms.

Stent thrombosis was considered as acute coronary syndrome with angiographic evidence of vessel occlusion or thrombus in or adjacent to the lesion previously treated with stent. In the absence of angiographic confirmation, both acute myocardial infarction in the distribution of the treated vessel and sudden death were considered as stent thrombosis.⁷

Statistical Analysis

The statistical analysis was performed using SPSS version 12.0 or STATA version 9.0. Continuous variables are shown as mean \pm standard deviation and the categorical variables, as a percentage. After using the normality test (Kolmogorov-Smirnov) to verify that the variable had a normal distribution, the continuous variables were compared by a Student *t* test. Categorical variables were compared by the χ^2 test or the Fisher's exact test when at least 25% of the values had an expected frequency of less than 5. A logistic regression model was used to identify restenosis predictors at 9 months follow-up. A stepwise model was used, in which variables that had $P < .1$ in the univariate analysis or were clinically

relevant have been included. To take into account the within-individual variability, the lesion analysis (repeated measures) was adjusted using a generalized estimation equation model. The survival curve was obtained by the Kaplan-Meier method. Statistical significance was defined as a two-tail *P*-value $< .05$.

RESULTS

Baseline Characteristics

Eighty-five patients (100 lesions) were included in this study, accounting for 53% of the patients (45% of the lesions) included in the DIABETES study. Forty-two patients (49 lesions) received an SES and 43 patients (51 lesions), a BMS; 90% of the lesions that were included had angiographic analysis at 9 months follow-up.

There were no significant differences between groups in the patients' baseline characteristics, nor were there any with regard to the rest of the population included in the DIABETES study except that the patients included in this study were more likely to present multivessel disease (74% vs 54.7%; $P = .01$). The mean age was 66 \pm 9 years, 42% were women, 37% had insulin-dependent diabetes mellitus, and 75% presented multivessel disease. The remaining baseline characteristics are shown in Table 1.

Angiographic and Procedure Data

Both groups were comparable in terms of angiographic and procedure data (Table 2). When comparing the characteristics of lesions included in this substudy to the remaining lesions included in the DIABETES study, lesions located in small vessels were more likely to be in the left anterior descending artery (49% vs 34.7%; $P = .03$) and circumflex artery (33% vs 14%; $P = .001$). Additionally, for reasons inherent to the study, vessel diameter and stent diameter were significantly smaller in this subgroup of patients (Table 2).

The success of stent placement was 100%. In general, the mean diameter of the vessels included was 1.9 \pm 0.2 mm and the length was 15.0 \pm 9.0mm; in addition, 12% of all chronic occlusions were included. The mean diameter of the implanted stent was 2.5 \pm 0.2 mm and the length was 23.0 \pm 12.9 mm; a stent was directly implanted in 25% of the cases.

Quantitative Coronary Analysis

At 9 months follow-up, a significantly lower late luminal loss was observed in the SES group than BMS group (Table 3). Nevertheless, no differences were found between the groups in late luminal loss at either edge. Consequently, the restenosis rate, regardless of

TABLE 1. Baseline Demographic Characteristics*

	Total Population of the DIABETES Study (n=160)	Diabetic With Small Vessel Substudy		P
		Sirolimus-Eluting Stent (n=42)	Bare Metal Stent (n=43)	
Age, y	66.5±9	65.1±8	68.3±9	.10
Male sex, n (%)	100 (62.5)	23 (54.8)	27 (62.8)	.45
IDDM, n (%)	53 (33.1)	15 (35.7)	17 (39.5)	.71
Dyslipidemia, n (%)	98 (61.3)	24 (57.1)	24 (55.8)	.90
Hypertension, n (%)	106 (66.3)	31 (73.8)	29 (67.4)	.52
Smokers, n (%)	76 (47.5)	15 (35.7)	20 (46.5)	.31
History of infarction, n (%)	59 (36.9)	13 (31.0)	17 (39.5)	.41
Prior revascularization, n (%)	30 (18.7)	10 (23.8)	5 (11.6)	.14
Unstable angina	92 (57.5)	18 (42.9)	22 (51.2)	.44
Glycated hemoglobin	7.3±1.4	7.4±1.5	7.4±1.7	.99
No. diseased vessels	1.9±0.8	1.9±0.8	2.1±0.6	.20
BMI	29.1±4	29.3±3.9	28.1±3.5	.16
LVEF	65.4±13	68.2±12.6	64.0±13.3	.14
GP IIb/IIIa inhibitors, n (%)	94 (58.8)	25 (59.5)	28 (65.1)	.59

TABLE 2. Baseline Angiographic and Procedure Characteristics

	Total Lesions of DIABETES Study (n=160)	Diabetic With Small Vessel Substudy		P
		Sirolimus-Eluting Stent (n=49)	Bare Metal Stent (n=46)	
Treated artery				
LAD	(41.2)*	25 (49.0)	24 (49.0)	.99
Cx	(22.6)*	17 (33.3)	16 (32.7)	.94
RCA	(36.2)*	9 (17.6)	9 (18.4)	.92
Lesion length, † mm	15.0±8	14.8±9.7	15.3±8.5	.76
Reference diameter, mm	2.34±0.6*	1.9±0.3	1.9±0.2	.55
Multivessel stent	37 (23.1)*	12 (28.6)	14 (32.6)	.69
No. stenosis/patient	1.4±0.6	1.5±0.6	1.5±0.6	.80
No. stent/patient	1.6±0.9*	1.8±1	2.0±0.9	.26
Stent length, § mm	22.6±11.9	22.7±11.0	23.4±14.8	.78
B2/C, n(%)‡	177 (80.1)	38 (74.5)	43 (87.8)	.91

Data are expressed as mean ± standard deviation or as the number of patients and percentage (%).

* $P < .05$ between the lesions included in this study and the remaining lesions included in the DIABETES study.

†Total occlusions were excluded in the analysis of lesion length.

‡According to the American College of Cardiology-American Heart Association (ACC/AHA) lesion classification.

§Length of stent analyzed by lesion

whether the in-stent and entire segment was analyzed (in-stent and both edges), was significantly reduced in the SES group compared to the BMS group. This significant decrease in the incidence of restenosis was also observed when analyzing the subgroup of patients with insulin-dependent diabetes. The incidence of restenosis according to type of diabetic treatment is shown in Figure 1. Finally, the incidence of occlusive restenosis was 0% in the SES group, compared to 8.2% in the control group ($P=.05$).

The multivariate analysis was performed by logistic regression and fitted using the generalized estimation equation method. The following variables have been included: sirolimus-eluting stent implantation, type of

diabetes, lesion length, stent length, post-stenting minimum lumen diameter, multivessel stent, number of lesions treated and number of stents implanted in each lesion. At 9 months follow-up, the only independent predictor of restenosis was SES implantation (odds ratio [OR] = 0.05; 95% confidence interval [CI], 0.004-0.4; $P=.008$).

Results of Intravascular Ultrasound

Fifty percent of the lesions included in the study (23 lesions in the SES group and 22 in the BMS group) were analyzed by ICUS. Of the 45 lesions studied, 42 lesions had a baseline and follow-up IVUS study; 3

TABLE 3. Results of Quantitative Coronary Analysis at 9 Months Follow-Up

	Sirolimus-Eluting Stent (n=44)	Bare Metal Stent (n=46)	P
Late luminal loss (in-segment), mm	-0.03±0.3	0.44±0.5	<.001
Late luminal loss (in-stent), mm	0.05±0.3	0.64±0.4	<.001
Late luminal loss (proximal reference), mm	-0.08±0.3	0.01±0.3	.23
Late luminal loss (distal reference), mm	-0.13±0.2	-0.11±0.3	.79
Restenosis (in-segment), n (%)	4 (9.1)	18 (39.1)	.001
Restenosis (in-stent), n (%)	2 (4.5)	17 (37)	<.001
Proximal reference restenosis, n (%)	1 (2.3)	1 (2.2)	1
Distal reference restenosis, n (%)	1 (2.3)	0 (0)	.49

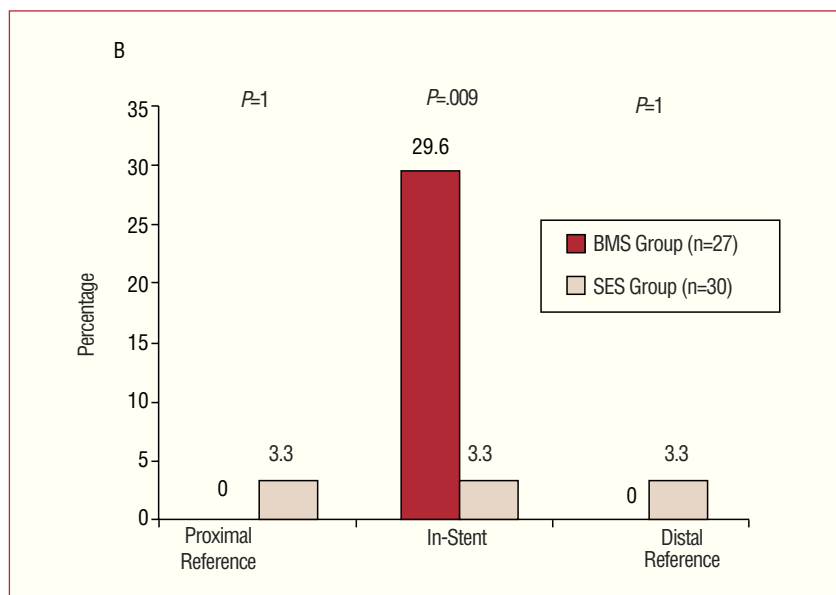
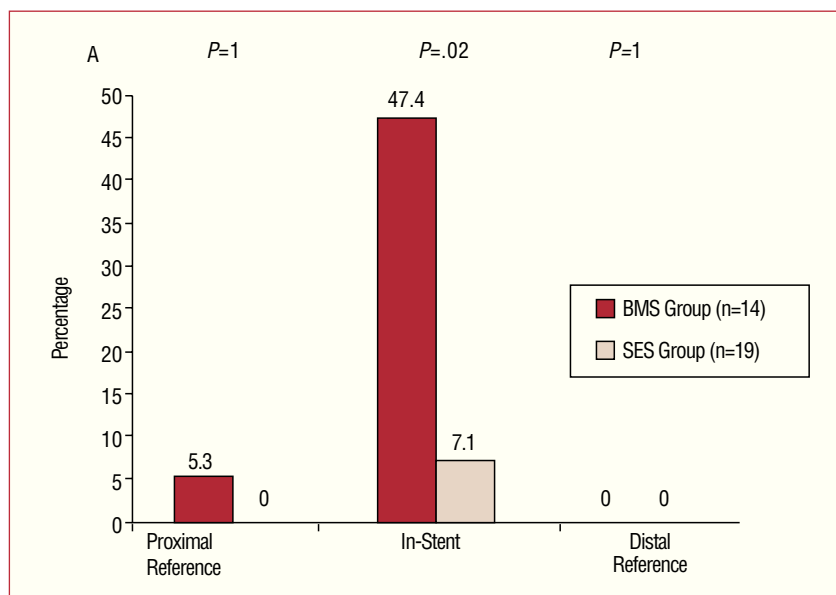


Figure 1. Incidence of restenosis in-stent and at both edges, according to type of anti-diabetic treatment at 9 months' follow-up. A: incidence of restenosis in the subgroup of patients with insulin-dependent diabetes. B: incidence of restenosis in the subgroup of patients treated with oral anti-diabetic therapy.

lesions had no baseline study. At 9 months follow-up, a significant decrease was observed in neointimal hyperplasia area and volume in the SES versus BMS group (mean area 0.05±0.7 mm² vs 2.3±1.5 mm²;

P<.001; volume 1.2±2.1 mm³ vs 69.1±78.5 mm³; P=.001), which represents a relative reduction in the percent obstruction volume, favoring the SES, of 98% (0.7%±1.0% vs 37.9%±24.5%; P<.001).

TABLA 4. Clinical Events at 1 Year Follow-Up

	Sirolimus-Eluting Stent (n = 42)	Bare Metal Stent (n = 43)	p
Death, n (%)	1 (2.4)	1 (2.3)	1
AMI, n (%)			
ST elevation	0 (0)	0 (0)	
No ST elevation	0 (0)	4 (9.3)	.1
TLR, n (%)	2 (4.8)	16 (37.2)	< .001
MCE, n (%)	3 (7.1)	18 (41.9)	< .001
Stent thrombosis, n (%)	0 (0)	2 (4.6)	.49

AMI indicates acute myocardial infarction; MCE, major cardiac events; TLR, target lesion revascularization. Excluding events.

The qualitative analysis of lesions by ICUS generally showed incomplete stent apposition in 8 lesions (34.8%) in the SES group and 2 lesions (10%) in the BMS group ($P=.07$). No between-group differences were observed in either incidence of resolved malapposition (0 [0%] vs 2 [10%]; $P=.2$), as well as the incidence of persistent malapposition (2 [8.7%] vs 0 [0%]; $P=.2$). However, a significant increase in the incidence of late stent malapposition was observed in the SES group (6 [26.1%] vs 0 [0%]; $P=.02$). An acquired (and nonpersistent) malapposition can only be guaranteed in 3 of them, because a baseline ICUS study was not available for the other 3.

Clinical Follow-Up at 1 Year Follow-Up

The clinical follow-up at 1 year was done in 100% of the patients. During this period, a significant reduction in major cardiac events in the SES versus BMS groups was observed (Table 4). This fact was

mainly due to a significant reduction in the need for target lesion revascularization (TLR) in the SES group. Of the 18 patients who required TLR at 1 year follow-up, 3 patients were revascularized in 2 vessels, with only one of them being a small vessel; in the remaining patients (15 patients) the only vessel revascularized was a small-diameter vessel. No differences between the groups were observed in the incidence of death or myocardial infarction. The survival curve for patients with no need for new target lesion revascularization at 1 year follow-up is shown in Figure 2.

Regarding the safety data at 1 year follow-up, no stent thrombosis was reported in the SES group. In the BMS group, however, 1 patient suffered a subacute thrombosis that manifested as sudden death and another patient, a late thrombosis at 2 months from inclusion. Clopidogrel was discontinued in this patient for gastrointestinal surgery (Table 4). After 13 months follow-up (1 month after discontinuation of clopidogrel), no thrombotic event was observed in any patient enrolled in this study.

DISCUSSION

Our study is the first conducted among diabetic patients with a mean vessel size of less than 2 mm in which ICUS data are available for 50% of the lesions.

The most important findings of this study are: *a*) the decrease in the incidence of post-stenting restenosis is independent of vessel size, even in the subgroup of diabetic patients treated with insulin; *b*) this resulted in a significant reduction in major cardiac events at the expense of reducing the need for new revascularization, favoring the SES group, at 1 year

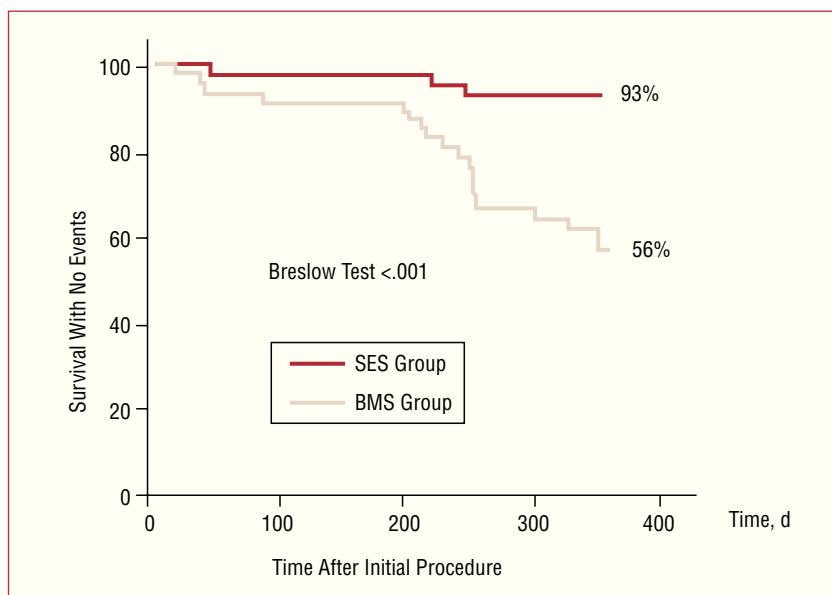


Figure 2. Survival curve (Kaplan-Meier) for patients with no need for new target lesion revascularization at 1 year follow-up.

follow-up; *c*) there is an elevated incidence of late malapposition in the SES group; and lastly *d*) SES implantation in diabetic patients with small vessels is safe, since no stent thrombosis has been observed at 1 year follow-up.

The superior efficacy of SES versus BMS implantation in the general population with small vessels has been previously demonstrated in randomized studies.^{13,16} In a study with 352 patients, Schofer et al (E-SIRIUS)¹³ showed that the implantation of SES compared to SC reduces both late luminal loss (0.19 ± 0.38 vs 0.80 ± 0.57 ; $P < .0001$) and the incidence of restenosis (5.9% vs 42.3%; $P < .0001$). Likewise, a study conducted by Ardissino et al (SES-SMART)¹⁶ showed that SES implantation reduced the incidence of restenosis in the SES group by 82%.

The efficacy of SES in diabetic patients with small vessels was analyzed in a subanalysis of diabetic patients included in the SES-SMART study.¹⁷ This substudy included 74 diabetics, of which 29 received SES and 45, BMS. At 8 months follow-up, a significant decrease was observed in the angiographic restenosis rate (primary endpoint of the study), both in-stent (11% vs 59%, $P < .001$), as well as in-segment within the SES group (25% vs 63%; $P = .003$). However, no clinical differences were observed in the incidence of major cardiac events during follow-up. As in the subanalysis of diabetics in the SIRIUS study,¹⁸ the SES SMART study observed an excessive incidence of restenosis in the edges among the subgroup of insulin-dependent diabetics. The design of the DIABETES study emphasized the need to avoid geographic miss¹⁹ by using in all cases shorter balloons of smaller diameter than the stent being implanted, covering the entire damaged segment in the predilatation.¹⁹ Our study did not observe any relevant edge effect in either group, not even in the subgroup of insulin-dependent patients.

In our study, although TLR is clinically driven, the incidence of TLR at 1 year follow-up in the BMS group is high for a study conducted with very small vessels.¹⁷ This high incidence is explained by the fact that 75% of the lesions with restenosis in the BMS group were located in the proximal and middle segment of the left anterior descending, circumflex, or right coronary artery, with 46% of the lesions with restenosis located in the proximal or middle segment of the left anterior descending artery. The fact that this study was performed among diabetics with diffusely diseased arteries means that the lumen diameter is smaller. Nevertheless, a lesion at this level can have a high repercussion due to the extent of myocardium at risk. This explains why ischemia has been detected in patients with restenosis in these small-diameter vessels.

Several studies have shown that the incidence of stent thrombosis is not increased following SES

implantation, in comparison with BMS.^{6,13,19-22} Although our series studied high-risk patients, the incidence of stent thrombosis in the SES group is 0% at 1 year follow-up, a finding that contrasts with the incidence (3%) of stent thrombosis observed in the subanalysis of diabetic patients in the SES-SMART study. Among the factors that could have contributed to the increased incidence of stent thrombosis in this study are the short period of dual antiplatelet therapy (2 months) and the low rate of glycoprotein IIb-IIIa inhibitors administration (10%).

Limitations

As limitations of this study, we should mention that this was not a randomized study, but rather a subanalysis of the DIABETES study and included only a few patients. As a result, the conclusions of this study must be confirmed in large randomized studies in diabetic patients with small vessels. In addition, this problem may be particularly relevant in the smallest study subgroups, for instance, among diabetics with lesions in small vessels.

Routine coronary angiography on follow-up could theoretically increase the incidence of TLR. As a result, in our study all revascularization was driven during follow-up by evidence of ischemia. Moreover, this potential bias would theoretically have affected both groups in an identical manner, in particular, the TLR of the sirolimus-eluting stent group was no higher than that obtained for larger vessels. Lastly, due to lesion size, an ICUS study has only been performed in 50%. Therefore, there is a potential selection bias, which may mean the results are not extrapolated to the general population of diabetic patients with small vessels. Nevertheless, this is the first study in the era of drug-eluting stents that presents ICUS data for a patient group at high risk of restenosis, namely, diabetics with a very small vessel size.

CONCLUSIONS

Sirolimus-eluting stents are effective in reducing the incidence of restenosis and the long-term clinical events in diabetic patients with very small vessels, without increasing the risk of stent thrombosis. Unlike other previously published studies, in our series this beneficial effect of SES is extended to the subgroup of patients with insulin-dependent diabetes mellitus, making it advisable to use this type of stent among these patients.

REFERENCES

1. Laakso M, Lehto S. Epidemiology of macrovascular disease in diabetes. *Diabetes Rev.* 1997;5:294-315.

2. Zueco Gil J. Importancia de los factores clínicos y anatómicos en el intervencionismo coronario. *Rev Esp Cardiol*. 2005;58:430-41.
3. Kastrati A, Schomig A, Elezi S, Schuhlen H, Dirschinger J, Hadamitzky M, et al. Predictive factors of restenosis after coronary stent placement. *J Am Coll Cardiol*. 1997;30:1428-36.
4. Bauters C, Hubert E, Prat A, Bougrimi K, van Belle E, McFadden EP, et al. Predictors of restenosis after coronary stent implantation. *J Am Coll Cardiol*. 1998;31:1291-8.
5. Suselbeck T, Latsch A, Siri H, Gonska B, Poerner T, Pflieger S, et al. Role of vessel size as a predictor for the occurrence of in-stent restenosis in patients with diabetes mellitus. *Am J Cardiol*. 2001;88:243-7.
6. Morice MC, Serruys PW, Sousa JE, Fajadet J, Ban Hayashi E, Perin M, 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.
7. Moses JW, Leon MB, Popma JJ, Fitzgerald PJ, Holmes DR, O'Shaughnessy C, et al. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. *N Engl J Med*. 2003;349:1315-23.
8. Sabaté M, Jiménez-Quevedo P, Angiolillo DJ, Gómez-Hospital JA, Alfonso F, Hernández-Antolín R, et al. Randomized comparison of sirolimus-eluting stent versus standard stent for percutaneous coronary revascularization in diabetic patients: the diabetes and sirolimus-eluting stent (DIABETES) trial. *Circulation*. 2005;112:2175-83.
9. Berenguer A, Mainar V, Bordes P, Valencia J, Gómez S. Utilidad de los stents recubiertos de rapamicina en pacientes diabéticos con lesiones coronarias complejas. *Rev Esp Cardiol*. 2006;59:117-24.
10. Sabaté M. Insulino dependencia, ¿rapamicina resistencia? *Rev Esp Cardiol*. 2006;59:91-3.
11. Kip KE, Faxon DP, Detre KM, Yeh W, Kelsey SF, Currier JW. Coronary angioplasty in diabetic patients. The National Heart, Lung, and Blood Institute Percutaneous Transluminal Coronary Angioplasty Registry. *Circulation*. 1996;94:1818-25.
12. Shah PJ, Gordon I, Fuller J, Seevanayagam S, Rosalion A, Tatoulis J, et al. Factors affecting saphenous vein graft patency: clinical and angiographic study in 1402 symptomatic patients operated on between 1977 and 1999. *J Thorac Cardiovasc Surg*. 2003;126:1972-7.
13. Schofer J, Schluter M, Gershlick AH, Wijns W, Garcia 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.
14. Degertekin M, Serruys PW, Tanabe K, Lee CH, Sousa JE, Colombo A, et al. Long-term follow-up of incomplete stent apposition in patients who received sirolimus-eluting stent for de novo coronary lesions: an intravascular ultrasound analysis. *Circulation*. 2003;108:2747-50.
15. Jimenez-Quevedo P, Sabate M, Angiolillo DJ, Costa MA, Alfonso F, Gomez-Hospital JA, et al. Vascular effects of sirolimus-eluting versus bare metal stents in diabetic patients: three-dimensional ultrasound results of the DIABETES trial. *J Am Coll Cardiol*. 2006;47:2172-9.
16. Ardissino D, Cavallini C, Bramucci E, Indolfi C, Marzocchi A, Manari A, et al. Sirolimus-eluting vs uncoated stents for prevention of restenosis in small coronary arteries: a randomized trial. *JAMA*. 2004;292:2727-34.
17. Ortolani P, Ardissino D, Cavallini C, Bramucci E, Indolfi C, Aquilina M, et al. Effect of sirolimus-eluting stent in diabetic patients with small coronary arteries (a SES-SMART substudy). *Am J Cardiol*. 2005;96:1393-8.
18. Moussa I, Leon MB, Baim DS, O'Neill WW, Popma JJ, Buchbinder M, et al. Impact of sirolimus-eluting stents on outcome in diabetic patients: a SIRIUS (SIROlimUS-coated Bx Velocity balloon-expandable stent in the treatment of patients with de novo coronary artery lesions) substudy. *Circulation*. 2004;109:2273-8.
19. Angiolillo DJ, Sabate M, Alfonso F, Macaya C. Candy wrapper effect after drug-eluting stent implantation: deja vu or stumbling over the same stone again? *Catheter Cardiovasc Interv*. 2004;61:387-91.
20. Moreno R, Fernandez C, Hernandez R, Alfonso F, Angiolillo DJ, Sabate M, et al. Drug-eluting stent thrombosis: results from a pooled analysis including 10 randomized studies. *J Am Coll Cardiol*. 2005;45:954-9.
21. Holmes DR Jr, Leon MB, Moses JW, Popma JJ, Cutlip D, Fitzgerald PJ, et al. Analysis of 1-year clinical outcomes in the SIRIUS trial: a randomized trial of a sirolimus-eluting stent versus a standard stent in patients at high risk for coronary restenosis. *Circulation*. 2004;109:634-40.
22. Schampaert E, Cohen EA, Schluter M, Reeves F, Traboulsi M, Title LM, et al. 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.