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Comparison of Zotarolimus- Versus Everolimus-Eluting Stents in the Treatment of Coronary Bifurcation Lesions

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Objectives: To compare zotarolimus-eluting stent (Endeavor Sprint®; ZES-S) and the everolimus-eluting stent (Xience V®; EES) in the treatment of coronary bifurcation lesions Background: Both these stents have demonstrated good outcomes in the treatment of coronary lesions. However, the outcomes with respect to treatment of bifurcation lesions have yet to be conclusively demonstrated. Methods: In this single centered, nonrandomized, open label study, we treated, between August 2006 and December 2008, 110 bifurcations with ZES-S and, in a second stage of the study, 129 bifurcations with EES. The primary end point was to compare the rate of major adverse cardiac events (MACE) (death, myocardial infarction, and new target lesion revascularization) in-hospital and at 12 months of follow-up. Provisional T stenting was the strategy used in the majority of cases. Angiographic follow-up was performed only in patients who presented signs or symptoms suggestive of angina or ischemia. Results: There were no significant differences in in-hospital MACE between the groups (ZES-S: 8.1%; EES: 6.2%; $P = 0.5$). At 12 months, the ZES-S group had significantly more MACE than the EES group (23.1% vs. 4.5%; $P < 0.001$) and an elevated index of new revascularization of the bifurcation (17.5% vs. 3.2%; $P < 0.001$). There were no significant differences in mortality (four patients in ZES-S vs. one in EES; $P = 0.14$). Conclusion: The treatment of coronary bifurcation lesions using everolimus-eluting stents results in better outcomes at 12 months of follow-up than zotarolimus-eluting stents.

Key words: zotarolimus eluting stent; everolimus eluting stent; coronary bifurcations

INTRODUCTION

Historically, the treatment of coronary bifurcation lesions has been difficult for the interventional cardiologist because of the complexity of the technique and the long-term outcomes. With the advent of the first-generation drug-eluting stents (DES) the results improved in the treatment of these coronary lesions, compared with those with bare metal stents [1,2]. Some studies had shown better results with the sirolimus-eluting stent (SES) compared with the paclitaxel-eluting stent (PES) in the treatment of coronary bifurcation lesions [3,4].

The second-generation DES, the zotarolimus-eluting stent (the Endeavor Sprint®; ZES-S), and the everolimus-eluting stent (the Xience stent V®; EES), have demonstrated similar excellent results in the treatment of coronary lesions [5–7]. A recent study of the efficacy of the new zotarolimus-eluting stent (the Endeavor Resolute®; ZES-R) versus EES showed no significant differences in terms of adverse events at 12 months of follow-up (ZES was not inferior to EES) [8]. However, the efficacy of ZES-R was not the objective of our current study. In a study we published recently [9], we highlighted that the treatment of coronary bifurcation lesions with ZES-S had poorer medium-term outcomes than other previous studies with SES [10,11].

In the present study we compare the results of our series of patients with coronary bifurcation lesions treated with ZES-S, with another series of similar patients treated with EES.

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Conflict of interest: Nothing to report.

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METHODS

This is a single-center, retrospective, nonrandomized, clinical trial. All patients had coronary bifurcation lesions (defined as stenosis $\geq$50% in one or both branches, with a diameter of both branches >2 mm) treated with ZES-S (Medtronic Vascular, Santa Rosa, CA) or with EES (Abbott Vascular, IL). In the first phase of the study, the patients who fulfilled the inclusion criteria were treated with ZES-S (the results of the study have been published recently) [9] and, in a subsequent phase, another similar series of consecutive patients were treated with EES.

The type of bifurcation was defined according to the classification of Medina et al. [12]. The exclusion criteria were: cardiogenic shock, acute myocardial infarct (AMI) with ST segment elevation within the previous 12 hr, severe noncardiac disease with a life expectancy of <1 year, and a contraindication or other circumstance that would impede compliance with double antiaggregation treatment over a period of 1 year.

Objectives

The primary end-point of the study was to compare the major adverse cardiac events (MACE) in-hospital and at 12 months of follow-up between the two groups. MACE included death from whatever cause, AMI, and new target lesion revascularization (TLR).

Procedure

Vascular access was via the femoral artery in all patients. A ventriculography was performed to determine the left ventricular ejection fraction. The severity of the stenosis of the bifurcation was determined initially by visual inspection in two orthogonal projections, and the grades of stenosis of the main vessel (MV) and of the side branch (SB) were calculated using a system of automatic measuring of borders and size (software Automatic Contour Detection, ACA/DCI-S R4.1.2, Philips, Best, Holland). All the patients were treated with aspirin (100 mg) and clopidogrel (75 mg). The double antiaggregation was maintained for at least 12 months following the intervention. The technique used for the treatment of the bifurcation (using one or two stents, kissing balloon) was at the discretion of the attending physician, although the strategy of provisional T stenting (PTS) is the technique of choice in our Center. In our laboratory, we perform kissing balloon in three situations: (1) when two stents needed to be used in both arms because of inadequate angiographic outcome in the SB; (2) in cases in which there was clear disproportion in the lumen cross-section of the MV between the segments proximal and distal to the exit of the SB; (3) when, after having implanted a stent in the MV, a simple balloon in the SB produced an angiographically evident deformation of the stent in the MV. The use of GP IIb/IIIa inhibitors was also at the discretion of the attending physician.

The patients had a scheduled check-up in the outpatients' clinic at 12 months postprocedure. Those who did not attend the scheduled appointment were contacted by telephone. All events occurring during this period were recorded in detail. At this visit, a transthoracic echocardiogram was performed in all patients. If the patient was observed to be asymptomatic, no further assessments to identify ischemia were conducted and the patient was managed with conservative treatment. If the patient presented with clinical recurrence with clear signs or symptoms suggestive of angina or ischemia, a new coronary angiography was indicated. Equally, catheterization was indicated if, during the period of follow-up, the patient was readmitted to hospital with unstable angina or AMI. The patients who presented with nonspecific chest pain had further assessment to detect ischemia which, if positive or if the results were doubtful, a new coronary angiography was recommended.

Definitions

AMI with periprocedural Q wave was defined as the presence of a new Q wave in the electrocardiogram with elevations of markers of myocardial injury following the revascularization. AMI without periprocedural Q wave was defined as an asymptomatic increase in troponin I $> 3 \times$ ULN (upper limit of normal) following the procedure. Stent thrombosis (definitive, probable, or possible) was defined according to the Academic Research Criteria [13]. Stent thrombosis was assigned as acute (<24 hr), subacute (1–30 days), and late (30 days to 1 year). Success of the procedure was defined as a residual stenosis <30% in MV and <50% in SB with TIMI III flow in both branches. TLR was defined as a new revascularization (percutaneous or surgical) of the stenosis of luminal diameter >50% within the stent, or 5 mm of the proximal and distal border of the stent. This re-intervention was performed when there was clinical evidence of angina or objective evidence of ischemia. Death from cardiac cause was defined as death due to AMI, sudden death, cardiac failure, or cardiac complications of surgery.

Statistical Analysis

Statistical description of the quantitative variables included mean and standard deviation (SD). Differences between means were assessed with the Student *t*-test. Qualitative variables are expressed as absolute

TABLE I. Baseline Characteristics of the Patients in the Study

Characteristic	ZES-S ($n = 107$) n (%)	EES ($n = 117$) n (%)	P
Age; years, mean (range)	63 (34–82)	64 (34–83)	0.37
Males	82 (76)	99 (83.9)	0.18
Risk factors			
Diabetes	28 (26.2)	47 (39.8)	**0.03**
Hypertension	54 (50.5)	76 (64.4)	**0.04**
Hypercholesterolemia	48 (44.9)	64 (54.2)	0.18
Smoking habit	56 (52.3)	61 (51.7)	0.92
Previous AMI	22 (20.6)	24 (20.3)	0.96
Previous PCI	12 (11.2)	22 (18.6)	0.09
Indication for intervention			0.29
Stable angina	31 (29)	36 (30.5)	
UA/NSTEMI	64 (59.8)	58 (49.1)	
STEMI	12 (11.2)	24 (20.3)	
Multivessel disease	67 (72.6)	96 (81.3)	**0.002**
LVEF (%), mean ± SD	63.01 ± 13.68	64.86 ± 13.95	0.32
LVEF < 50%	18 (16.8)	20 (17)	0.90

AMI, acute myocardial infarction; EES, everolimus-eluting stent; PCI, percutaneous coronary intervention; LVEF, left ventricular ejection fraction; STEMI, ST elevated myocardial infarction >12 hr; UA/NSTEMI, unstable angina/non-ST elevated myocardial infarction; ZES-S, zotarolimus-eluting stent (Endeavor Sprint®). Bold type indicates statistical significance ($P < 0.05$).

values or percentages. Comparisons were with the χ^2 test or Fisher's exact test. Analysis of event-free survival was performed using Kaplan-Meier survival curves. The data were analyzed with the SPSS version 15.0. Statistical significance was set at $P < 0.05$.

RESULTS

Between August 2006 and November 2007 there were 107 consecutive patients (110 bifurcations) who fulfilled the inclusion criteria, and were treated with the ZES-S. Between December 2007 and December 2008 there were 117 consecutive patients (129 bifurcations) treated with the EES. The clinical data of both groups are shown in Table I. The EES group had a higher percentage of patients with diabetes and hypertension, as well as a greater number with multivessel disease. There were no significant differences in the clinical indications between the groups; the most frequent being unstable angina and non-ST elevated myocardial infarction (NSTEMI).

Table II summarizes the angiographic characteristics of the bifurcations. The most frequent site in both groups was the anterior descending with the diagonal branch. There were more lesions located on previous restenosis in the EES group, with a tendency toward statistical significance relative to the ZES-S group. The proportions of true bifurcations (MV and SB affected) were similar in both groups. The percentage of basal stenosis of the MV and SB were greater in the ZES-S group, although the stenosis postprocedure was similar in both groups.

Table III summarizes the characteristics of the procedure. In the majority of cases in both groups, the strategy used was that of PTS with insertion of only one stent in the MV in 93% in the ZES-S group compared to 92% in the EES group. In three patients of each group a subsequent stent was inserted in the SB due to poor angiographic results following balloon dilatation. Initially, the T stenting strategy was planned in three patients in the ZES-S group and six in the EES group, and crush stenting in one patient of each group. Intra-vascular ultrasound (IVUS) application and kissing balloon strategy were similar in both groups. Prescription of GP IIb/IIIa inhibitors was significantly higher in the ZES-S group than the EES group (48% vs. 36%; $P = 0.04$). Since multivessel disease was more frequent in the EES group, so also was the need to treat more vessels apart from the bifurcation in these patients (50% vs. 76%; $P < 0.001$). Angiographic success was achieved in all MV of both groups, and in a high percentage of SB (97% vs. 96%). In three SB of the ZES-S group, the balloon could not be passed beyond the MV stent to dilate the SB and, as such, residual stenosis >50% remained, but with TIMI III flow. In the EES group, balloon dilatation could not be achieved in two patients following the implantation of the MV stent; in one patient following dilation of the SB there remained stenosis of >50% but with TIMI three flow and it was decided not to insert a second stent. In another patient, an acute closure of the SB was produced following the insertion of the MV stent, and the guide-wire could not cross the occlusion.

TABLE II. Angiographic Characteristics of the Lesions in the Study Subjects

Characteristic	ZES-S ($n = 110$) n (%)	EES ($n = 129$) n (%)	P
Site of the lesion			0.17
LAD/diagonal	69 (62.7)	81 (62.8)	
CX/OM	25 (22.7)	38 (29.5)	
PDA/PL	15 (13.6)	7 (5.4)	
Other	1 (0.9)	4 (3.1)	
Restenosis	3 (2.7)	11 (8.5)	0.06
Bifurcation type x,x,1	73 (66)	73 (56)	0.14
True bifurcation[a]	68 (61)	66 (51)	0.11
Main vessel lesion characteristics pre-PCI; mean ± SD			
Lesion length (mm)	14.59 ± 6.79	13.7 ± 5.94	0.3
Reference diameter (mm)	2.94 ± 0.45	2.92 ± 1.17	0.86
MLD (mm)	0.82 ± 0.46	0.93 ± 0.51	0.08
Stenosis (%)	72.16% ± 13.98	67.82% ± 15.28	**0.02**
Main vessel lesion characteristics post-PCI, mean ± SD			
MLD (mm)	2.57 ± 0.42	2.57 ± 0.40	0.96
Stenosis (%)	16.57% ± 7.17	17.47% ± 5.82	0.28
Side branch lesion pre-PCI, mean ± SD			
Lesion length (mm)	6.30 ± 3.39	6.71 ± 6.34	0.60
Reference diameter (mm)	2.34 ± 0.39	2.28 ± 0.36	0.30
MLD (mm)	1.01 ± 0.57	1.69 ± 5.63	0.21
Stenosis (% ±SD)	57.69% ± 21.50	48.45% ± 27.70	**0.005**
Side branch lesion characteristics, post-PCI, mean ± SD			
MLD (mm)	1.77 ± 0.42	1.71 ± 0.45	0.24
Stenosis (%)	25.71% ± 11.25	27.94% ± 14.21	0.17

[a]True bifurcation: type 1-0-1, 0-1-1, or 1-1-1 of Medina. CX = circumflex artery; EES = everolimus-eluting stent; LAD = left anterior descending artery; MLD = minimum lumen diameter; MO = marginal obtuse; PCI = percutaneous coronary intervention; PD = posterior descending artery; PL = posterior-lateral branch of the right coronary artery; SD = standard deviation; ZES-S = zotarolimus-eluting stent (Endeavor Sprint®). Bold type indicates statistical significance ($P < 0.05$).

TABLE III. Characteristics of the Procedure

Characteristic	ZES-S, n (%)	EES, n (%)	P
Stent diameter (MV), mm, mean ± SD	3.08 ± 0.30	3.08 ± 0.36	0.91
Stent length (MV), mm, mean ± SD	22.46 ± 4.78	21.49 ± 4.57	0.11
Strategy employed			0.35
PTS (1 stent)	103 (93.6)	119 (92.2)	
PTS (2 stents)	3 (2.7)	3 (2.3)	
"T" stenting	3 (2.7)	6 (4.6)	
Crush stenting	1 (0.9)	1 (1.1)	
Kissing balloon	35 (31.8)	42 (32.6)	0.90
GP IIb/IIIa inhibitors	53 (48.2)	47 (36.4)	**0.04**
IVUS	11 (10)	19 (14.7)	0.27
Other artery treated	55 (50)	99 (76)	**<0.001**
Angiography success			
Main vessel	110 (100)	129 (100)	0.99
Side branch	107 (97.2)	125 (96)	0.52

EES = everolimus-eluting stent; GP = glycoprotein; IVUS = intra-vascular ultrasound; MV = main vessel; SD = standard deviation; PTS = provisional "T" stenting; ZES = zotarolimus-eluting stent (Endeavor Sprint®). Bold type indicates statistical significance ($P < 0.05$).

TABLE IV. In-Hospital Outcomes

Type	ZES-S, n (%)	EES, n (%)	P
Q-AMI	0	1 (0.7)	
NQ-AMI	9 (8.18)	7 (5.42)	
Cardiac deaths	0	0	
Total MACE	9 (8.18)	8 (6.2)	0.51

EES = everolimus-eluting stent; NQ-AMI = non-Q-wave myocardial infarction; Q-AMI = Q wave acute myocardial infarction; ZES-S = zotarolimus-eluting stent (Endeavor Sprint®).

In-hospital MACE are summarized in Table IV. There were no statistically significant differences between the two groups. There were no procedure-related deaths. There were nine patients with AMI in the ZES-S group and eight in the EES group ($P = 0.5$). AMI with Q wave in EES was due to a dissection in a segment proximal to the stent inserted in the bifurcation which produced an occlusion of the artery and which necessitated a reintervention 24 hr later.

Clinical follow-up for 12 months was achieved in 98% of the patients in the ZES-S group (105 patients, 108 bifurcations) and in 95.3% in the EES group (112 patients, 123 bifurcations). Reangiograph was performed because of symptoms in 33 patients (30.8%) in the ZES group and 17 (14.5%) in the EES group. MACE outcomes at 12 months of follow-up are summarized in Table V. The incidence of MACE in the ZES-S group was significantly higher compared with

TABLE V. Outcomes at 12 Months of Follow-Up[a]

Type	ZES-S, *n* (%)	EES, *n* (%)	*P*
Cardiac deaths	3 (2.85)	1 (0.8)	
Total deaths	4 (3.80)	1 (0.8)	0.14
Q-AMI	0	0	
NQ-AMI	2 (1.8)	1 (0.8)	0.50
TLR	19 (17.59)	4 (3.25)	**<0.001**
Total MACE	25 (23.1)	6 (4.87)	**<0.001**

[a]At 12 months of follow-up in 105 patients (108 bifurcations) treated with ZES and 112 patients (123 bifurcations) treated with EES.
EES = everolimus-eluting stent; NQ-AMI = non-Q-wave myocardial infarction; Q-AMI = Q-wave acute myocardial infarction; Re-PCI = percutaneous coronary reintervention; TLR = target lesion revascularization; ZES-S = zotarolimus-eluting stent (Endeavor Sprint®). Bold type indicates statistical significance ($P < 0.05$).

the EES group (23.1% vs. 4.8%; $P < 0.001$) due, principally, to a higher index of new TLR of the bifurcation in the ZES-S group (17.5% vs. 3.2%; $P < 0.001$). There were four deaths in the follow-up period in the ZES-S group; one patient died at 6 months following protracted hospitalization due to congestive cardiac insufficiency. The angiographic reevaluation could not be performed due to poor general clinical status. Another patient suffered sudden death at 9 days post-procedure and was receiving double antiaggregation. Another patient died following admission to hospital at 6 months following an AMI without ST elevation and cardiogenic shock. Diffuse restenosis of the two previously treated bifurcations was observed, and the patient died 48 hr after new revascularization. The other death in the ZES-S group was due to leukemia at 10 months postcatheterization. The death in the EES group was due to AMI and cardiogenic shock at 11 months. There was severe restenosis in the distal segment of the left main coronary which had been treated with stents in both branches. Figure 1 shows the event-free survival curves at 12 months in the two treatment groups.

Table VI shows the types of restenosis documented in the MV in both groups. In the ZES-S group we observed not only focal but also diffuse restenosis. There was one occlusive restenosis in the EES group, located on the proximal border of the stent.

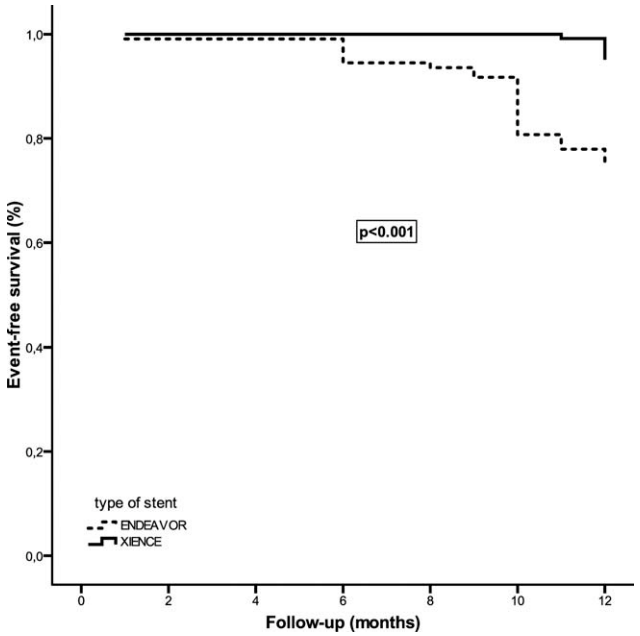

Fig. 1. Event-free survival curves at 12 months.

TABLE VI. Type of Restenosis in the Main Vessel (MV)

Type	ZES-S	EES
Focal	12	3
Diffuse	5	–
Diffuse-proliferative	2	–
Total occlusion	–	1
Total	19	4

EES = everolimus-eluting stent; ZES = zotarolimus-eluting stent (Endeavor Sprint®).

DISCUSSION

In this single center, retrospective, non-randomized, clinical trial, we compared the outcomes of two new generation drug-eluting stents (DES): the zotarolinus-eluting tent (Endeavor Sprint®; ZES-S) and the everolimus-eluting stent (Xience V®; EES) in the treatment of coronary bifurcation lesions. There have been several studies that compared the new DES with previous DES, but none had studied their specific application in coronary bifurcation lesions.

The ZES-S in the Endeavor III study [14] was compared with SES, and showed poorer late-loss and greater angiographic restenosis at 8 months of follow-up, but with similar proportion of MACE (12% ZES-S vs. 11.5% SES). In a 5-year follow-up study the results of which have been published recently [15], the ZES-S demonstrated a better safety profile than the SES (lower mortality/AMI index of 1.3% vs. 5.5%; $P < 0.02$) and a similar efficacy (overall MACE: 16.3% vs. 16.4%). However, in a recently published study under standard clinical practice conditions (SORT OUT 3) [16], ZES-S showed poorer outcomes at 18 months than SES (MACE: 9.7% vs. 4.5%; $P < 0.0001$). On the other hand, in comparison with the PES, the ENDEAVOR IV study showed that the ZES-S fulfilled the objective of noninferiority in terms of efficacy and safety in a follow-up of 9 months [17].

In the SPIRIT IV study [18] conducted in 3,687 patients, EES was compared with PES with a clinical follow-up of 1 year. The results indicated superiority of EES in terms of percentage MACE (4.2% vs. 6.8%; $P =$

0.001), a significant reduction in new revascularization of the treated lesion (2.5% vs. 4.6%; $P = 0.001$), and a lower rate of stent thrombosis (0.17% vs. 0.85%; $P = 0.004$), with the exception of diabetic patients in whom the events were similar in both treatment groups. Similarly, the EES also showed superiority to the PES in the COMPARE study [19] conducted in 1,800 patients with few exclusion criteria and in which the conclusion was that the EES significantly reduces the rate of MACE compared with PES (6.2% vs. 9.1%; $P = 0.02$).

Serruys et al. published the only randomized study which compared ZES-R versus EES [8]. It included >2,000 patients, of whom >65% had at least one off-label indication, and the study sample contained 17% of bifurcations in each treatment group. The ZES-R fulfilled the primary objective of noninferiority at 12 months of follow-up, compared with EES with respect to target-lesion failures (8.2% vs. 8.3%) and, as well, with respect to the secondary objective of in-stent stenosis in the patients randomized for angiographic re-evaluation (ZES-R: $21 \pm 14\%$ vs. EES: $19 \pm 14\%$; $P = 0.04$ for non-inferiority). This study is different from previous studies conducted with ZES and from our current study in that the stent used is the Endeavor Resolute® (Medtronic Vascular, Santa Rosa, CA). This stent has the same platform as the Endeavor Sprint®, but has a different polymer which is highly biocompatible and with a wide exposure of the drug in the vessel over a longer period of time [20].

With respect to the procedure in our study, in accord with the previous studies that did not show advantages of the complex strategy of two stents [21–23], we used the PTS strategy with implantation of only one stent in MV in the majority of cases (93% in the ZES group and 92% in the EES group) with 100% angiographic success in MV and >95% in the SB in both treatment groups. These outcomes have been confirmed recently in the BBC ONE study [24] which demonstrated significantly better results and less MACE at 9 months using the simpler, single stent, strategy (8% vs. 15%; $P = 0.009$). The EES group had a higher incidence of patients with diabetes, multivessel disease and artery revascularization other than the target bifurcation but, despite this, excellent results were recorded. In our study we had a high MACE index in the ZES-S group (23% vs. 4.8%) and a high TLR rate (17.5% vs. 3.2%). This suggests that the ZES-S has poorer antiproliferative efficacy; a consequence being an increase in the number of reinterventions in the follow-up when the ZES-S stent is used in coronary bifurcations. Another relevant observation is that 7 of the 19 restenosis of the MV (36%) were diffuse or diffusoproliferative. This differs from that observed in the study with EES, and which had been reported previously in studies with SES i.e. in great part these restenoses of the MV are of the focal type [25]. Another important point is the low incidence of stent thrombosis. There was only one probable thrombosis event in the ZES-S group (0.9%) i.e. in the patient who died suddenly at 9 days postprocedure. There were no episodes of thrombosis after 30 days postprocedure in either group. This suggests that both stents are quite safe in the medium-term for the treatment of coronary bifurcations. Previous studies had concluded that bifurcation lesions may predict stent thrombosis [26–28].

The low MACE incidence in the EES group was similar to the results obtained in previous studies [18,19]. In our study, however, all the lesions treated were off-label indication, suggesting that EES can indeed produce excellent results in the medium-term with respect to efficacy and safety in the treatment of coronary bifurcations.

Study Limitations

Our study has some limitations. First, it is not a randomized study and, as such, the statistical power is lower. Nevertheless, the differences recorded are considerable. Second, the follow-up was limited to 12 months and, as such, we cannot know whether the differences observed would be maintained over the longer term. Third, angiographic assessment had not been applied systematically in all the patients. In keeping with our standard practice, we only performed a new angiograph when there was a clinical indication for it. We believe that this avoids additional procedures in asymptomatic patients.

CONCLUSIONS

At a follow-up of 12 months, the everolimus-eluting stent had better outcomes, with a lower incidence of adverse events and lower rate of new revascularizations, than the zotarolimus-eluting stent in the treatment of coronary bifurcation lesions.

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