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Prospective Randomized Comparison of Sirolimus- or Everolimus-Eluting Stent to Treat Bifurcated Lesions by Provisional Approach

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Objectives This study sought to compare the procedural performance and the acute angiographic result on side-branch ostium obtained using 2 different drug-eluting stents (DES) to treat patients with bifurcated coronary lesions.

Background Drug-eluting stents are routinely used in percutaneous coronary interventions (PCI) of bifurcated coronary lesions. Different DES types have major technical differences that may influence the procedural and clinical performance in bifurcation PCI.

Methods Consecutive patients with bifurcated lesions undergoing DES implantation using a systematic provisional-stenting strategy were randomized to sirolimus-eluting stent (SES) or everolimus-eluting stent (EES) before intervention. The procedural details for PCI were prospectively recorded to assess the occurrence of any trouble in the side-branch (SB) management (primary end point). Post-PCI angiographic result (primary end point: minimal lumen diameter at SB ostium) was evaluated offline by 3-dimensional reconstruction and quantitative coronary analysis. Clinical outcome was prospectively recorded up to 18 months to assess the occurrence of target bifurcation failure.

Results A total of 150 patients were enrolled in the study (29% diabetics, 17% unprotected left main). The stent was successfully implanted according to randomization in all cases. Procedural performance was not significantly different between the 2 kinds of DES. Three-dimensional reconstruction and quantitative coronary analysis showed similar post-PCI results in the main vessel and better results in the SB with EES than with SES (minimal lumen diameter at SB ostium: 1.94 $\pm$ 0.72 mm vs. 1.64 $\pm$ 0.62 mm; $p = 0.013$). At 18 months, target bifurcation failure occurred in 7 (9.0%) of SES-treated patients versus 8 (10.7%) of EES patients ($p = 0.57$).

Conclusions In patients with bifurcated lesions treated by provisional stenting technique, EES compared with SES is associated with similar procedural performance and better 3-dimensional reconstruction and quantitative coronary analysis result in the SB. Both DES are associated with low rates of major adverse events and angiographic failure. (Sirolimus Versus Everolimus-Eluting Stent Randomized Assessment in Bifurcated Lesions and Clinical Significance of Residual Side-Branch Stenosis [SEA-SIDE]; NCT00697372) (J Am Coll Cardiol Intv 2011;4:327–35) © 2011 by the American College of Cardiology Foundation

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JACC: CARDIOVASCULAR INTERVENTIONS, VOL. 4, NO. 3, 2011
MARCH 2011:327–35

Bifurcated lesions are challenging target lesions in percutaneous coronary interventions (PCI) that may specifically benefit from drug-eluting stents (DES) (1). Since the introduction of sirolimus-eluting stent (SES), various other DES have been developed and tested in clinical practice in different settings. Bifurcated lesions represent a particular subset of lesions in which tubular stents are usually implanted by modifying their struts' shape to take care of both the main vessel (MV) and the side-branch (SB) using various techniques (2). Accumulating clinical data suggest that the best technique to treat most bifurcated lesions is the "provisional" T-stenting approach, which is based on the implantation of DES in the MV followed, if deemed necessary, by kissing balloon inflation and side-branch (SB) stenting (2). As different types of DES have remarkable differences of metallic stent platform, drug used, and technology for drug-release, the procedural and clinical performance in bifurcation interventions may not be similar. In keeping with this hypothesis, a small randomized study (3) and a recent large registry (4) suggested that, when treating bifurcated lesions with first-generation DES, SES might offer some advantages over the paclitaxel-eluting stent. Recently, a last-generation everolimus-eluting stent (EES) characterized by an evolved stent platform (thin struts, large side cells) has been shown to provide promising results when compared with a first-generation (paclitaxel-eluting) DES (5) and has entered the market.

Thus, we designed the present single-center trial assessing the procedural performance, the angiographic result, and the long-term clinical outcome obtained by a first-generation DES (i.e., SES) compared with a last-generation DES (i.e., EES) in unselected bifurcated lesions.

Abbreviations and Acronyms

CK-MB = creatine kinase-myocardial band
DES = drug-eluting stent(s)
EES = everolimus-eluting stent(s)
MACE = major adverse coronary event(s)
MI = myocardial infarction
MLA = minimal lumen area
MLD = minimal lumen diameter
MV = main vessel
PCI = percutaneous coronary intervention
SB = side branch
SES = sirolimus-eluting stent(s)
TAP-stenting = T-stenting and small protrusion technique
TBF = target bifurcation failure
3DQCA = 3-dimensional reconstruction and quantitative coronary analysis

Methods

Study registration and inclusion/exclusion criteria. The study protocol design has been previously described and registered in the ClinicalTrial.gov registry as the SEA-SIDE (Sirolimus Versus Everolimus-Eluting Stent Randomized Assessment in Bifurcated Lesions and Clinical Significance of Residual Side-Branch Stenosis) trial. The Ethical Committee of the Catholic University of the Sacred Heart approved the study protocol.

From September 2007 to October 2008, consecutive patients with documented coronary artery disease undergoing PCI on a bifurcated lesion at our institution have been screened to enter the study. To enter the study, patients had to be >18 years of age; have no ascertained or suspected contraindications to prolonged double antiplatelet therapy; have no known hypersensitivity to sirolimus, everolimus, cobalt, chromium, nickel, tungsten acrylic, and fluoropolymers; and have no acute (within 48 h) ST-segment elevation acute myocardial infarction.

Angiographic criteria to define bifurcated lesions eligible for the study were:

1. Lesions: >50% located in a major bifurcation point regardless of length, morphology, and angulation;
2. TIMI (Thrombolysis In Myocardial Infarction) flow grade: ≥2 on both MV and SB;
3. MV visual diameter: ≥2.5 mm; and
4. SB visual diameter: ≥2.0 mm.

Patients fulfilling these clinical and angiographic characteristics and providing written informed consent entered the trial and were randomized to the SES (Cypher Select, Cordis, Warren, New Jersey) or the EES (Xience V, Abbott Vascular, Santa Clara, California) stent (Fig. 1). To highlight the major differences between the stent platforms of EES and SES that may potentially influence the procedural outcome during bifurcation interventions with provisional approach, the pictures of stent design and bench testing of MV stenting followed by kissing balloon inflation are reported for both stents in Figure 2.

PCI. Percutaneous coronary interventions were performed by radial or femoral approach according to the physician's preference. After confirmation of the presence of the criteria for enrollment, patients were randomized to the type of stent to be implanted (Fig. 1) according to a computer-generated random series of numbers. Then, PCI has been performed according to the previously reported "provisional TAP-stenting strategy" (6). This means that all patients were treated by MV stenting first under SB protection with jailed guidewire technique, then SB rewiring was attempted with a BMW Universal (Abbott Vascular), "workhorse wire." Furthermore, the kissing balloon technique was performed if considered necessary by the operator (kissing balloon being systematically attempted in cases of large territories supplied by the SB or when SB exhibited flow impairment after MV stenting). Then, if judged necessary by the operator, a second stent was implanted in the SB according to the T-stenting and small protrusion technique (TAP-stenting) (7). Further details on the technical aspects of the provisional TAP-stenting approach have been previously reported (6). In the case of occurrence of protocol

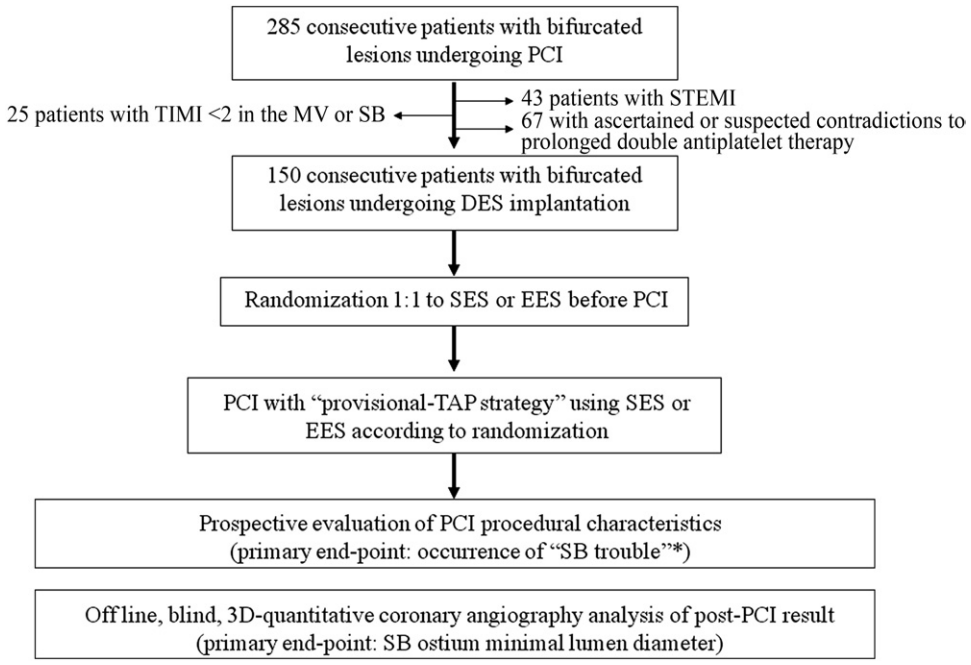


Figure 1. Study Flow Chart

The chart shows how patients were selected and randomized for this study. *See text for detailed end point definitions. DES = drug-eluting stent(s); EES = everolimus-eluting stent(s); MV = main vessel; PCI = percutaneous coronary intervention; SB = side branch; SES = sirolimus-eluting stent(s); STEMI = ST-segment elevation myocardial infarction; TAP = T-stenting and small protrusion technique; TIMI = Thrombolysis In Myocardial Infarction; 3D = 3-dimensional.

violations, patients were not excluded from the study and operators had to justify the reason for the adoption of other techniques.

The type of materials used and the sequence of their usage was prospectively collected including: the occurrence of SB flow impairment after MV stenting, the attempt to rewire the SB after MV stenting, the type and number of wires used for SB rewiring, the occurrence of failure to rewire or to dilate the SB after MV stenting.

Procedural duration (from sheath insertion to sheath removal or fixation with suture [in the case of decision to delay sheath removal]), fluoroscopy time, and total radiation exposure were prospectively recorded.

Procedural success was defined as TIMI flow grade 3 in both MV and SB, as well as visual residual stenosis <20% in MV.

Periprocedural medications. At the time of PCI, all patients were on double antiplatelet therapy with aspirin (100 to 160 mg daily) and clopidogrel (300-mg loading dose on the day before the PCI or 75 mg daily for more than 3 days before the procedure). Procedural anticoagulation was achieved with unfractionated heparin (70- to 100-U/kg intravenous bolus with further dose adjustment to maintain an activated clotting time of about 300 s). Use of glycoprotein IIb/IIIa inhibitors was per operator discretion. After the procedure, all patients received double antiplatelet therapy with aspirin 100 mg and clopidogrel 75 mg for 12 months with the indication to continue aspirin indefinitely. According to our internal guidelines on medical therapy of patients with documented coronary artery disease, patients were prescribed statins, beta-blockers, and angiotensin-converting

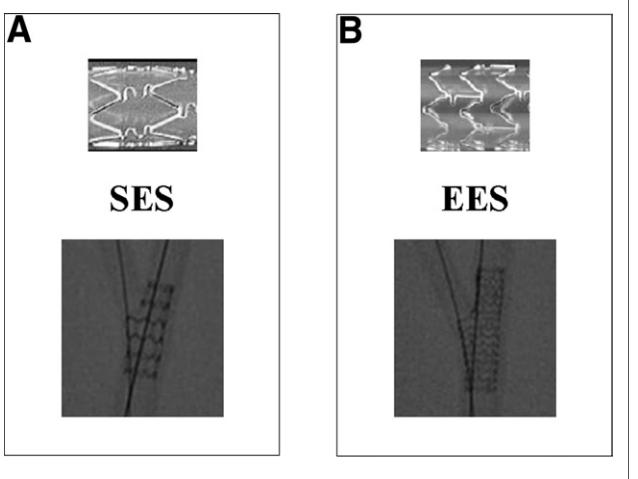


Figure 2. Aspect of SES and EES

Stent platform aspect **(top)** and fluoroscopic appearance in bench testing (main vessel stenting followed by kissing inflation **[bottom]**) of SES **(A)** and EES **(B)**. Abbreviations as in Figure 1.

JACC: CARDIOVASCULAR INTERVENTIONS, VOL. 4, NO. 3, 2011
MARCH 2011:327–35

enzyme inhibitors. Usage of nitrates was not recommended after interventions.

Laboratory testing and follow-up. After PCI, all patients underwent post-PCI electrocardiogram, and 6- and 24-h assessment of troponin T and creatine kinase-myocardial band (CK-MB) levels. Thereafter, further electrocardiogram and enzyme evaluations were performed if clinically indicated.

After PCI, the in-hospital clinical course was carefully monitored, whereas, after discharge, patients were followed-up by hospital visit or by phone interview at 6, 9, 12, and 18 months. Follow-up coronary angiography has not been planned in all patients. However, according to the clinical practice of our center, follow-up angiography was suggested to patients receiving double DES implantation at the bifurcation level. Furthermore, all patients with symptoms' recurrence and those with inducible ischemia at >4-month provocative tests have been recommended to undergo angiographic evaluation.

Patients' records and angiographic studies were carefully reviewed for all suspect adverse events before adjudication.

The clinical events were defined as follows:

- Death: the cause of death has been ascertained by reviewing the available clinical records and all deaths without clear noncardiac cause were considered as cardiac death.
- Myocardial infarction (MI): ST-segment elevation MI (>20 min lasting chest pain with >0.1 mV ST-segment elevation in at least 2 contiguous leads) or non–ST-segment elevation MI (typical chest pain with documentation of transient >0.1 mV ST-segment depression or T-wave modifications in at least 2 contiguous leads) with any increase in serum cardiac enzymes above the 99th percentile of the upper reference limit. Post-procedural MI was defined as CK-MB increase >3× the upper reference limit in patients with normal troponin T levels before PCI and CK-MB increase >5× the pre-PCI CK-MB levels in patients with abnormal troponin T levels before PCI.
- Target vessel revascularization: repeat PCI or coronary surgery on the target vessel owing to recurrent ischemia.
- Major adverse coronary events (MACE): death or MI or target vessel revascularization.
- Target bifurcation-related MACE: any MACE not clearly caused by another vessel.
- Target bifurcation angiographic failure: ≥50% restenosis on the main vessel or TIMI flow grade <3 on the SB at angiography performed during the follow-up.
- Stent thrombosis was defined according to the Academic Research Consortium criteria (8) as follows: "definite" = angiography- or autopsy-confirmed stent thrombosis; "probable" = any unexplained death within first 30 days or any MI in the territory of the stent and in the absence of any other obvious cause; "possible" = any unexplained death after 30 days.

Angiographic analyses. Pre-PCI, post-PCI, and follow-up angiography have been performed with the aim of allowing 3-dimensional reconstruction and quantitative coronary analysis (3DQCA). Accordingly, at least 2 views have been obtained at least 30° apart. In cases of suboptimal imaging, a third obtained view was used to improve the 3D reconstruction accuracy.

Offline 3DQCA analysis using the previously validated CardiOp-B system (9–11) was performed by a trained interventional cardiologist (D.T.) who was blinded to clinical and procedural characteristics, patients' statuses, and outcomes.

Using the 3DQCA reconstruction, the following parameters have been obtained for pre- and post-PCI angiography:

- Reference diameter of the MV
- Minimal lumen diameter (MLD) and area (MLA) of the MV
- Percentage area stenosis of the MV
- Reference diameter of the SB
- MLD and MLA of the SB
- Percentage area stenosis of the SB
- MLD and MLA of the SB ostium (using the software's scroll bar tool)
- Bifurcation proximal angle (angle between proximal MV and SB)
- Bifurcation distal angle (angle between SB and distal MV)

Study end points and sample size estimation. The study was primarily aimed at assessing the procedural characteristics and the acute angiographic results of patients with bifurcated lesions treated by the 2 types of DES.

The primary procedural and angiographic end points were respectively:

- "SB trouble" (at least 1 or a composite of more than 1 of the following procedural parameters: 1) SB TIMI flow grade <3 after MV stenting; 2) need of guidewire(s) different from the workhorse wire to rewire SB after MV stenting; 3) failure to rewire the SB after MV stenting; or 4) failure to dilate the SB after MV stenting and SB rewiring);
- "SB acute angiographic result" (comparison of the 3DQCA-estimated MLD in the SB ostium).

Such primary end points have been ideated and defined for the first time in the present study. Accordingly, no published data in the literature were available for any of the study end points, thus limiting the strength of sample size calculations. We hypothesized that the design of the EES platform, because of higher possibility to dilate the side cells and owing to smaller strut width compared with that of SES, could facilitate the provisional approach by reducing

the SB trouble and improving the angiographic result in the SB. Accordingly, double sample sizing was performed as follows. First, we observed that in the NORDIC I trial (12), in the provisional arm using the SES, an MLD of 1.5 ± 0.6 mm was observed after the procedure in the SB. Thus, we calculated that, hypothesizing that EES was associated with a 20% increase in the SB MLD, at least 64 patients for each arm should be enrolled in the study to have an alpha error of 0.05 and power of 0.8. Second, in a retrospective analysis of 30 cases of bifurcated lesions treated by SES at our institution, 7 patients (23.3%) were found to have SB trouble, thus we calculated that at least 69 patients for each arm should be enrolled to show a 50% reduction of SB trouble with use of EES, with an alpha error of 0.05 and power of 0.8. Finally, to compensate for any possible failure or dropout, we decided to enroll 75 patients for each arm.

The following angiographic and clinical end points were pre-defined secondary study end points:

- 3DQCA-estimated MLA in the SB ostium;
- "Target bifurcation failure" (TBF): defined as target bifurcation-related MACE or target bifurcation angiographic failure in the absence of MACE.

Statistical analysis. All analyses were performed according to the intention to treat. Continuous variables were tested for normality and for homogeneity of variance by Kolmogorov-Smirnov and Levene tests, respectively, and compared by unpaired Student *t* or Mann-Whitney *U* tests as appropriate. Chi-square tests (Fisher corrected when appropriate) were used to compare discrete variables (reported as raw numbers [%]). The incidence of TBF over time was studied using the Kaplan-Meier method and compared with log-rank tests.

Analyses were carried out using SPSS for Windows, version 11.0 (SPSS Inc., Chicago, Illinois). Statistical significance was defined by 2-tailed $p < 0.05$.

Results

Study population characteristics and procedural outcome. A total of 150 patients entered the study so that 75 patients were randomly assigned to the SES group and 75 to the EES group. The pre-intervention clinical and angiographic characteristics are reported in the Table 1. Briefly, 28% of the patients were diabetics; 37% presented with an acute coronary syndrome; and 82% had normal ejection fraction. The baseline characteristics were well balanced except for the smoking status, which was significantly different between the 2 study groups.

Regarding the pre-PCI angiographic features, the target bifurcation was located in an unprotected left main in 17% of patients, and in the left anterior descending/diagonal branch bifurcation in 62%; 30% of the bifurcated lesions were classified as Medina 1,1,1 and 43% had significant involvement of the SB ostium. As shown in Table 1, all the baseline clinical and angiographic characteristics were well balanced between the 2 study groups.

Table 1. Pre-PCI Clinical and Angiographic Characteristics of Patients Randomized to SES or EES

	SES (n = 75)	EES (n = 75)	p Value
Age, yrs	65 ± 9	64 ± 10	0.86
Male	56 (75%)	64 (85%)	0.10
Risk factors			
Family history of ischemic heart disease	25 (33%)	23 (31%)	0.73
Diabetes mellitus	25 (33%)	19 (25%)	0.28
Hypertension	52 (69%)	52 (69%)	1.00
Hypercholesterolemia	40 (53%)	47 (63%)	0.25
Active smoking	9 (12%)	19 (25%)	0.036
Clinical history			
Acute coronary syndrome at presentation	29 (39%)	37 (49%)	0.19
Previous myocardial infarction	10 (13%)	6 (8%)	0.29
Previous coronary surgery	4 (5%)	5 (7%)	0.73
Extent of coronary artery disease			
Single-vessel disease	32 (43%)	38 (51%)	0.33
2-vessel disease	20 (27%)	22 (29%)	0.72
3-vessel disease	23 (31%)	15 (20%)	0.13
Left main disease	10 (13%)	11 (15%)	0.81
Left ventricular function			
Ejection fraction ≥50%	52 (69%)	54 (72%)	0.72
Ejection fraction <50%	23 (31%)	21 (28%)	
Target bifurcation			
Distal left main	11 (15%)	15 (20%)	0.39
Left anterior descending—diagonal	48 (64%)	45 (60%)	0.62
Left circumflex-marginal	10 (13%)	13 (17%)	0.50
Right posterior descending—posterior lateral	6 (8%)	2 (3%)	0.15
ACC/AHA modified lesion classification			
Type B2	42 (56%)	43 (57%)	0.87
Type C	33 (44%)	32 (43%)	
Plaque distribution on the target bifurcation			
Proximal main vessel	51 (68%)	47 (63%)	0.50
Distal main vessel	62 (83%)	64 (85%)	0.66
Side branch ostium	30 (40%)	30 (40%)	1.00
Medina bifurcation classification			
1.1.1	18 (24%)	19 (25%)	0.87
1.1.0	20 (27%)	17 (23%)	
1.0.1	4 (5%)	2 (3%)	
0.1.1	8 (11%)	9 (12%)	
1.0.0	9 (12%)	9 (12%)	
0.1.0	16 (21%)	19 (25%)	
0.0.1	0	0	

Values are mean ± SD or n (%).

ACC/AHA = American College of Cardiology/American Heart Association; EES = everolimus-eluting stent(s); PCI = percutaneous coronary intervention; SES = sirolimus-eluting stent(s).

JACC: CARDIOVASCULAR INTERVENTIONS, VOL. 4, NO. 3, 2011
MARCH 2011:327–35

Procedural outcome and 3-dimensional quantitative angiography results. Procedures were performed through radial access in most of the patients using 6-F guiding catheters (7- or 8-F guiding catheters were used only in 16% of patients) and glycoprotein IIb/IIIa inhibitors were administered in 16 patients (13% of EES vs. 8% of SES, p = 0.29). All patients received the SES or the EES according to randomization. The details of procedural characteristics are reported in Table 2. Direct stenting on the MV was successfully performed in 36% of the cases. Kissing balloon inflation was performed in 67% of the patients after MV stenting and was repeated at the end of procedure in all the 12 patients receiving a stent in the SB. All the main steps of provisional procedure were not significantly different between the 2 DES arms except for a smaller size of MV stent and higher rate of MV post-dilation in the SES group. These differences probably reflected the fact that a 4.0-mm stent diameter is not available for SES so that a 3.5-mm SES followed by post-dilation was used to treat large MV. Protocol deviations leading to adoption of techniques different from provisional TAP stenting occurred in 4 cases (3%) and consisted of 4 cases (2 SES and 2 EES) of simultaneous kissing stenting motivated by the presence of Medina 0,1,1 lesions with similar size of MV and SB.

Optimal result (visual residual stenosis <20%, TIMI flow grade 3) was achieved in all patients in the MV, but in 6 (4%) patients, the post-PCI SB flow was <3 (2 TIMI flow grade 2 and 4 TIMI flow grade 0 to 1).

The procedural performance of EES and SES was not significantly different as shown in Table 2. In particular, the "SB-trouble" end point occurred in 8 (11%) of EES patients compared with 12 (16%) of SES patients (p = 0.34). The numerically higher "SB-troubles" in SES, compared with EES, were mainly driven by a double number (although statistically not significant) of procedures in which guidewires different from BMW were needed to rewire the SB after MV stenting (Table 2).

The 3DQCA results are reported in detail in Table 3. Baseline angiographic characteristics were similar between patients treated by EES or SES (Table 3). As shown in Table 3, at post-PCI analysis, although MV results were similar, the lumen measures on the SB were significantly higher in the EES group than in the SES group (ostium SB MLD: 1.94 ± 0.72 mm in EES vs. 1.64 ± 0.62 mm in SES, p = 0.013; ostium SB MLA: 3.32 ± 2.34 mm^2 in EES vs. 2.37 ± 1.50 mm^2 in SES, p = 0.005).

Clinical outcome and angiographic follow-up data. The 18-month clinical follow-up rate was 100%. Overall, 10 patients had MACE during the follow-up: 2 cardiac deaths, 4 periprocedural non–ST-segment elevation MI (2 in patients with subsequent cardiac death, 1 in patient with subsequent re-PCI owing to in-stent restenosis), 4 non–ST-segment elevation MI (with documentation of in-stent restenosis that was treated by re-PCI), 10 repeated revascularizations owing to symptomatic restenosis of the target bifurcation (7 re-PCI, 3 coronary artery bypass graft, 1 in patient with periprocedural MI, and 2 in patients with MI during follow-up). No definite or probable stent thrombosis was observed, and the 2 deaths have been also classified as possible stent thrombosis according to the Academic Research Consortium criteria. A detailed report of MACE is in Table 4 and shows no difference between the EES and SES groups.

Table 2. Procedural Characteristics in the Bifurcation PCI of Patients Randomized to SES or EES

	SES (n = 75)	EES (n = 75)	p Value
Vascular access			
Radial	62 (83%)	53 (72%)	0.08
Femoral	13 (17%)	22 (28%)	
Technical characteristics			
Stent implanted according to randomization	75 (100)	75 (100)	1.00
MV direct stenting	28 (37%)	23 (31%)	0.39
"SB trouble"	12 (16%)	8 (11%)	0.34
SB TIMI flow grade <3 after MV stenting	7 (9%)	8 (11%)	0.79
Need of guidewire(s) different from the workhorse wire to rewire SB after MV stenting	6 (8%)	3 (4%)	0.30
Failure to rewire the SB after MV stenting	2 (3%)	3 (4%)	0.65
Failure to dilate the SB after MV stenting and SB rewiring	1 (1%)	1 (1%)	1.00
Kissing balloon inflation after MV stent	50 (67%)	51 (68%)	0.86
SB stenting	6 (8%)	6 (8%)	1.00
Kissing balloon inflation after SB stent	6 (8%)	6 (8%)	1.00
MV stent post-dilation	51 (68%)	38 (51%)	0.031
MV stent			
Stent diameter	3.1 ± 0.4	3.4 ± 0.5	<0.001
Total stent length	30.3 ± 16.5	29.6 ± 13.7	0.78
SB stent			
Stent diameter	3.1 ± 0.5	2.9 ± 0.5	0.42
Total stent length	21.8 ± 10.3	18.9 ± 5.0	0.51
Procedural result			
Post-PCI TIMI flow grade 3 in the MV	75 (100%)	75 (100%)	1.00
Post-PCI TIMI flow grade 3 in the SB	72 (96%)	72 (96%)	1.00
Procedural success (TIMI flow grade 3 in both MV and SB, visual residual stenosis <20% in MV)	72 (96%)	72 (96%)	1.00
Resources consumption			
Contrast media, ml, mean ± SD	251 ± 108	246 ± 133	0.83
Procedural time, min, mean ± SD	70 ± 43	81 ± 32	0.50
Fluoroscopy time, min, mean ± SD	20 ± 13	20 ± 11	0.85

Values are n (%) or mean ± SD.
MV = main vessel, SB = side branch; TIMI = Thrombolysis In Myocardial Infarction; other abbreviations as in Table 1.

Table 3. 3DQCA Results in Patients Randomized to SES or EES

	SES (n = 75)	EES (n = 75)	p Value
3DQCA before PCI			
MV reference diameter, mm	2.37 ± 0.63	2.47 ± 0.73	0.38
MV minimal lumen diameter, mm	1.08 ± 0.42	1.20 ± 0.41	0.11
MV minimal lumen area, mm^2	0.94 ± 0.79	1.22 ± 1.04	0.08
MV percentage area stenosis	80.0 ± 13.7	75.9 ± 14.7	0.08
SB reference diameter, mm	2.08 ± 0.61	2.27 ± 0.74	0.11
SB minimal lumen diameter, mm	1.59 ± 0.66	1.67 ± 0.69	0.50
SB minimal lumen area, mm^2	1.71 ± 1.59	2.03 ± 1.86	0.29
Minimal lumen diameter at SB ostium, mm	1.72 ± 0.52	1.84 ± 0.73	0.26
Minimal lumen area at SB ostium, mm^2	2.63 ± 1.65	3.02 ± 2.53	0.29
SB percentage area stenosis	50.2 ± 24.1	54.6 ± 23.1	0.27
Bifurcation proximal angle, °	133.8 ± 19.0	132.9 ± 20.2	0.78
Bifurcation distal angle, °	65.0 ± 18.7	67.0 ± 17.7	0.51
3DQCA after PCI			
MV reference diameter, mm	3.10 ± 0.67	3.34 ± 0.687	0.08
MV minimal lumen diameter, mm	2.62 ± 0.51	2.76 ± 0.57	0.14
MV minimal lumen area, mm^2	5.22 ± 2.21	5.83 ± 2.89	0.16
MV percentage area stenosis	29.3 ± 14.1	30.8 ± 13.7	0.55
SB reference diameter, mm	1.92 ± 0.48	2.25 ± 0.70	0.002
SB minimal lumen diameter, mm	1.49 ± 0.65	1.81 ± 0.91	0.020
SB minimal lumen area, mm^2	1.77 ± 1.25	2.70 ± 2.33	0.004
Minimal lumen diameter at SB ostium, mm	1.64 ± 0.62	1.94 ± 0.72	0.013
Minimal lumen area at SB ostium, mm^2	2.37 ± 1.50	3.32 ± 2.34	0.005
SB percentage area stenosis	43.9 ± 23.9	39.4 ± 22.3	0.27
Bifurcation proximal angle, °	133.6 ± 16.3	134.6 ± 17.9	0.76
Bifurcation distal angle, °	58.5 ± 14.4	61.6 ± 16.9	0.25

Values are mean ± SD.
3DQCA = 3-dimensional reconstruction and quantitative coronary analysis; other abbreviations as in Tables 1 and 2.

During the follow-up, 62 patients (41%, 33 EES, 28 SES) had angiographic follow-up during the study. Among these, 11 patients had target bifurcation angiographic failure: 10 were treated by re-PCI or coronary artery bypass graft (as previously described) and 1 (treated by a single SES on left anterior descending/diagonal bifurcation) had documentation of collateralized occlusion of the SB in the absence of significant restenosis in the MV and was treated medically (Table 4).

As a consequence, TBF, the pre-defined study clinical end point, occurred in 7 (9.0%) SES patients versus 8 (11%) EES patients at 18 months. Figure 3 represents the rate of TBF in the 2 study groups at 6, 9, 12, and 18 months, showing that few late adverse events were observed during the study with both stents.

Finally, the low (41%) rate of angiographic follow-up, and the fact that angiographic follow-up was performed on clinical ground, did not to allow a reliable estimation of late loss for the 2 types of DES.

Discussion

The present single-center trial comparing EES and SES in unselected patients undergoing PCI on bifurcated lesions using a provisional TAP-stenting approach shows that:

- SB management is not significantly affected by the use of the (very different) SES or EES platforms;
- The 3-dimensional angiographic result is improved in the SB ostium using EES, compared with using SES.

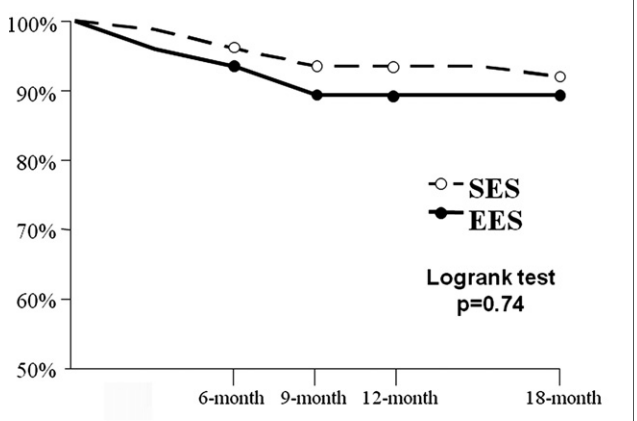
Bifurcated lesions constitute a challenging subset of coronary lesions. Albeit not specifically designed for this, DES may be implanted in bifurcated lesions using different techniques resulting in improved outcomes compared with bare-metal stents (1). Even if the optimal technique to treat all bifurcated lesions has not still been identified, the simple approach of implanting the DES in the MV (i.e., the "provisional stenting approach") is gradually emerging as the gold standard for the majority of bifurcated lesions (2). When the provisional approach with DES is adopted, another important issue is DES selection. Indeed, available DES exhibit profound differences of both platform and drug-coating technology; thus, prospective randomized trials in the specific field of bifurcated lesions are warranted. Previous studies comparing first-generation DES in patients with bifurcated lesions showed some potential angiographic and clinical advantages for SES over the paclitaxel-eluting stent (3,4). These data support the notion that in bifurcated lesions different DES may be associated with different outcomes, confirming the need of head-to-head comparisons in this field.

In this study, we compare SES, a first-generation DES with well-established efficacy, with an EES, a promising last-generation DES, in the challenging field of bifurcation PCI. We have focused our attention on the procedural and angiographic performances of these stents. Indeed, EES and SES probably represent 2 extremes of the possible

Table 4. Adverse Events and Angiographic Failures Observed During the Follow-Up Patients Randomized to SES or EES

	SES (n = 75)	EES (n = 75)	p Value
Any major adverse cardiac event	7 (9%)	9 (12%)	0.60
Cardiac death	1 (1%)	1 (1%)	0.56
Periprocedural myocardial infarction*	1 (1%)	3 (4%)	0.31
Myocardial infarction after discharge*	1 (1%)	3 (4%)	0.31
Target vessel revascularization	5 (7%)	5 (7%)	1.00
Target bifurcation angiographic failure	6 (8%)	5 (7%)	0.75
Associated to major adverse coronary events	5 (7%)	5 (7%)	1.00
Detected by angiography and not treated nor associated to major adverse coronary events	1 (1%)	0 (0%)	0.32
Target bifurcation failure	7 (9%)	8 (11%)	0.78

*All myocardial infarctions were non–ST-segment elevation.
Abbreviations as in Table 1.



Time (months)	0-month	6-month	9-month	12-month	18-month
SES	75	73	72	71	68
EES	75	68	68	68	67

Figure 3. Survival Free From TBF

Patients free from target bifurcation failure (TBF) during the study according to randomization (SES or EES). Abbreviations as in Figure 1.

evolution of stent technology regarding their adaptability to bifurcated lesions. On 1 hand, the SES platform is characterized by thick (0.0055-inch) stainless steel struts and by a cell design that has been associated with limited side-cell expansion (13). By contrast, the EES stent platform is based on a thin (0.0032-inch) cobalt chromium strut structure with a cell design that allows obtainment of larger side cells after SB balloon dilation (14). To assess the EES and SES procedural performance, we prospectively collected a detailed series of pre-defined procedural parameters (which should provide a detailed report of the bifurcation PCI complexity) and analyzed the acute angiographic outcome using a dedicated 3DQCA software. This approach should provide useful information to assess whether differences of DES design (previously well described in bench testing) may translate in different procedural outcomes. Although, some recent observations from substudies of larger trials not focused on bifurcated lesions have suggested that the angiographic outcome of small SBs may be influenced by the stent platform favoring last-generation DES designs compared with the first-generation paclitaxel-eluting stent (15,16), no published study has systematically and prospectively assessed the SB procedural and angiographic outcome on unselected bifurcated lesions (in which jailed wire protection, SB rewiring, kissing balloon dilation, and SB stenting were eventually performed). Theoretically, as the stent platform of EES is characterized by side cells, which may be deformed by SB ballooning up to larger diameters, it should both facilitate the performance of provisional stenting and provide better angiographic results in the SB than if an SES were used. Overall, the observed results seem to provide 2 different insights. Indeed, although the EES was associated with better angiographic results in the SB as evaluated by 3DQCA, it failed to facilitate the management of bifurcation when compared with SES use. This latter finding may have different explanations. First, the "SB trouble" may have not been adequately powered as the expected rate in SES group was 23.3% versus 16% observed in the study and the expected risk ratio was 50% versus 30% observed in the study. Second, the ideal stent characteristics for SB rewiring and ballooning are still unclear: both side-cell shape and area may be equally relevant for MV side-cell recrossing so that a more favorable shape may theoretically compensate for lower cell area. As a consequence, it is possible that the SES platform characteristics, although being theoretically somewhat inferior to EES, are sufficient to successfully manage most unselected bifurcated lesions.

Finally, the initial advantage associated with EES with regard to the angiographic measures of SB ostium did not translate into reduction of TBF when compared with SES use, thus reinforcing the perception of an overall limited clinical relevance for SB angiographic result during bifurcation PCI (17). The study, however, was by far underpowered to show differences in the clinical outcome so the described clinical findings should be regarded as explorative. In this view, it should be noted that, in the treatment of unselected bifurcated lesions, a systematic provisional-TAP approach with low rate of SB stenting is associated to low rates of major adverse events and clinically evident restenosis, so that very large numbers of patients are required to detect differences between various DES.

Study limitations. The results of the present study are based on a small study population so that reliable subgroup analyses according to the type and location of the target bifurcation has not been possible. Moreover, as no systematic angiographic follow-up has been planned in the study protocol, the low rate of angiographic follow-up obtained did not allow reliable comparison of late angiographic outcome measures.

Conclusions

The results of the present prospective study suggest that, in patients with coronary bifurcated lesions treated by provisional technique, EES, compared with SES, is associated with similar procedural performance and better 3DQCA results in the SB. Both stents are associated with low rates of major adverse events and angiographic failure.

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REFERENCES

1. Colombo A, Moses JW, Morice MC, et al. Randomized study to evaluate sirolimus-eluting stents implanted at coronary bifurcation lesions. Circulation 2004;109:1244–9.
2. Louvard Y, Thomas M, Dzavik V, et al. Classification of coronary artery bifurcation lesions and treatments: time for a consensus! Catheter Cardiovasc Interv 2008;71:175–83.
3. Pan M, Suárez de Lezo J, Medina A, et al. Drug-eluting stents for the treatment of bifurcation lesions: a randomized comparison between paclitaxel and sirolimus stents. Am Heart J 2007;153:15.e1–7.
4. Song YB, Hahn JY, Choi SH, et al. Sirolimus- versus paclitaxel-eluting stents for the treatment of coronary bifurcations results: from the COBIS (Coronary Bifurcation Stenting) Registry. J Am Coll Cardiol 2010;55:1743–50.
5. Stone GW, Rizvi A, Newman W, et al., for the SPIRIT IV Investigators. Everolimus-eluting versus paclitaxel-eluting stents in coronary artery disease. N Engl J Med 2010;362:1663–74.
6. Burzotta F, Sgueglia GA, Trani C, et al. Provisional TAP-stenting strategy to treat bifurcated lesions with drug-eluting stents: one-year clinical results of a prospective registry. J Invasive Cardiol 2009;21:532–7.
7. Burzotta F, Gwon HC, Hahn JY, et al. Modified T-stenting with intentional protrusion of the side-branch stent within the main vessel stent to ensure ostial coverage and facilitate final kissing balloon: the T-stenting and small protrusion technique (TAP-stenting). Report of bench testing and first clinical Italian-Korean two-centre experience. Catheter Cardiovasc Interv 2007;70:75–82.
8. Cutlip DE, Windecker S, Mehran R, et al. for Academic Research Consortium. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation 2007;115:2344–51.
9. Gradaus R, Mathies K, Breithardt G, Bocker D. Clinical assessment of a new real time 3D quantitative coronary angiography system: evaluation in stented vessel segments. Catheter Cardiovasc Interv 2006;68:44–9.
10. Dvir D, Marom H, Assali A, Kornowski R. Bifurcation lesions in the coronary arteries: early experience with a novel 3-dimensional imaging and quantitative analysis before and after stenting. EuroIntervention 2007;3:95–9.
11. Collingwood R, Bermudez E, Fischell TA. Comparison between three-dimensional angiographic reconstruction and intravascular ultrasound imaging for the measurement of cross-sectional luminal dimensions in intermediate coronary lesions. J Interv Cardiol 2009;22:277–81.
12. Steigen TK, Maeng M, Wiseth R, et al., for the NORDIC PCI Study Group. Randomized study on simple versus complex stenting of coronary artery bifurcation lesions: the Nordic bifurcation study. Circulation 2006;114:1955–61.
13. Ormiston JA, Webster MW, El Jack S, et al. Drug-eluting stents for coronary bifurcations: bench testing of provisional side-branch strategies. Catheter Cardiovasc Interv 2006;67:49–55.
14. Mortier P, Van Loo D, De Beule M, et al. Comparison of drug-eluting stent cell size using micro-CT: important data for bifurcation stent selection. EuroIntervention 2008;4:391–6.
15. Popma JJ, Mauri L, O'Shaughnessy C, et al. Frequency and clinical consequences associated with side branch occlusion during stent implantation using zotarolimus-eluting and paclitaxel-eluting coronary stents. Circ Cardiovasc Interv 2009;2:133–9.
16. Applegate R, Hermiller J, Williams J, et al. Evaluation of the effects of everolimus-eluting and paclitaxel-eluting stents on target lesions with jailed side branches: 2-year results from the SPIRIT III randomized trial. Catheter Cardiovasc Interv 2010;76:644–51.
17. Koo BK, Kang HJ, Youn TJ, et al. Physiologic assessment of jailed side branch lesions using fractional flow reserve. J Am Coll Cardiol 2005;46:633–7.

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