JACC: CARDIOVASCULAR INTERVENTIONS VOL. 2, NO. 9, 2009

ISSN 1936-8798/09/$36.00
PUBLISHED BY ELSEVIER INC. DOI: 10.1016/j.jcin.2009.05.024

Impact of Vessel Size on Angiographic and Clinical Outcomes of Revascularization With Biolimus-Eluting Stent With Biodegradable Polymer and Sirolimus-Eluting Stent With Durable Polymer

The LEADERS Trial Substudy

Joanna J. Wykrzykowska, MD,* Patrick W. Serruys, MD, PhD,* Yoshinobu Onuma, MD,* Ton de Vries, MA,† Gerrit-Anne van Es, PhD,† Pawel Buszman, MD,‡ Axel Linke, MD,§ Thomas Ischinger, MD,‖ Volker Klauss, MD,¶ Roberto Corti, MD,# Franz Eberli, MD, PhD,#¶¶ William Wijns, MD,** Marie-Claude Morice, MD,†† Carlo di Mario, MD, PhD,‡‡ Robert Jan van Geuns, MD, PhD,* Peter Juni, MD, PhD,§§ Stephan Windecker, MD, PhD‖‖

Rotterdam, the Netherlands; Katowice, Poland; Leipzig and Munich, Germany; Zurich and Bern, Switzerland; Aalst, Belgium; Paris-Sud, France; and London, United Kingdom

Objectives We assessed the impact of vessel size on outcomes of stenting with biolimus-eluting degradable polymer stent (BES) and sirolimus-eluting permanent polymer stent (SES) within a randomized multicenter trial (LEADERS).

Background Stenting of small vessels might be associated with higher rates of adverse events.

Methods "All-comer" patients (n = 1,707) were randomized to BES and SES. Post-hoc–stratified analysis of angiographic and clinical outcomes at 9 months and 1 year, respectively, was performed for vessels with reference diameter ≤2.75 mm versus >2.75 mm.

Results Of 1,707 patients, 429 patients in the BES group with 576 lesions and 434 patients in the SES group with 557 lesions had only small vessels treated (50.6% of the patient cohort). In patients with small vessels there was no significant difference in overall major adverse cardiac events (MACE) rate (12.1% vs. 11.8%; p = 0.89) or target lesion revascularization (TLR) rate (9.6% vs. 7.4%; p = 0.26) between BES and SES. The MACE and TLR rates in the small-vessel patient population were higher than in the large-vessel population. The TLR rate was 9.6% versus 2.6%, and MACE rate was 12.1% versus 7.1% for small versus large vessels in the BES arm (TLR: hazard ratio [HR] = 3.724, p = 0.0013; MACE: HR = 1.720, p = 0.0412). In the SES arm, TLR was 7.4% versus 5.1%, and MACE was 11.8% versus 10.3% in small versus large vessels (TLR: HR = 1.435, p = 0.2594; MACE: HR = 1.149, p = 0.5546).

Conclusions Prevalence of small vessel disease is high in an "all-comer" population with higher TLR and MACE rates. The BES and SES seem equivalent in treatment outcomes of small vessels in this "all-comer" patient population. (J Am Coll Cardiol Intv 2009;2:861–70) © 2009 by the American College of Cardiology Foundation

From the *Department of Interventional Cardiology Thoraxcenter, Erasmus Medical Center, Rotterdam, the Netherlands; †Cardialysis, Rotterdam, the Netherlands; ‡Medical University of Silesia, Katowice, Poland; §Herzzentrum Leipzig, Leipzig, Germany; ‖Department of Cardiology, Hospital Bogenhausen, Munich, Germany; ¶Department of Cardiology, University Hospital Munich (Innenstadt), Munich, Germany; #Department of Cardiology, University Hospital, Zurich, Switzerland; **Department of Cardiology, Onze Lieve Vrouw Ziekenhuis, Aalst, Belgium; ††Institut Cardiovasculaire, Paris-Sud, France; ‡‡Department of Cardiology, Royal Brompton Hospital, London, United Kingdom; §§Clinical Trials Unit Bern; ‖‖Department of Cardiology, Bern University Hospital, Bern, Switzerland; and the ¶¶Triemlispital, Zurich, Switzerland. This work was funded by Biosensors Europe SA, Morges, Switzerland.

Manuscript received May 4, 2009, accepted May 15, 2009.

The recently published "all-comers" European LEADERS (Biolimus-eluting stent with biodegradable polymer versus sirolimus-eluting stent with durable polymer for coronary revascularization) trial showed that the biolimus-eluting biodegradable polymer stent (BES) represents a safe and noninferior alternative to sirolimus-eluting durable polymer stent (SES) in the treatment of coronary artery disease (1). Biolimus is a highly lipophilic sirolimus analogue (2). It inhibits the mammalian target of rapamycin and cell-cycle transition in smooth muscle cells with similar potency as sirolimus. It is eluted from a polylactic acid biodegradable polymer solely applied on the abluminal surface. Unlike paclitaxel-eluting stents (PES), BES has similar potency as SES in the suppression of neoinitmal hyperplasia and therefore late luminal loss (0.13 vs. 0.19 mm; p = 0.34 at 9 months). The amount of late luminal loss is usually independent of vessel size (3–8), and therefore a greater degree of restenosis is observed in smaller vessels owing to a reduced ability to accommodate neointimal growth without causing hemodynamically significant flow compromise (9,10). In the RAVEL (Randomized Study With the Sirolimus-Eluting Bx Velocity Balloon-Expandable Stent) study it was first demonstrated that SES perform well in small vessels with low restenosis rates (11). At 6-month follow-up, the restenosis rate in the SES group was 0% versus 20% to 35% in the different vessel-size strata of the bare-metal stents group. We hypothesized that, given the non-inferior rate of late loss in the BES arm of the LEADERS trial, BES will perform equivalently in small vessels to SES, unlike PES.

Abbreviations and Acronyms

BES = biolimus-eluting stent(s)
MACE = major adverse cardiac events
MI = myocardial infarction
MLD = minimal lumen diameter
PES = paclitaxel-eluting stent(s)
RVD = reference vessel diameter
SES = sirolimus eluting stent(s)
TLR = target lesion revascularization
TVR = target vessel revascularization

Methods

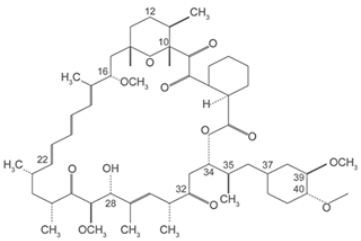
Device description. The BES, as used in this study and already described in the preceding text, elutes a highly lipophilic sirolimus analogue (2) (Fig. 1), which inhibits the mammalian target of rapamycin and cell-cycle transition in smooth muscle cells with similar potency as sirolimus. It is eluted from a polylactic acid biodegradable polymer applied to the abluminal surface (Fig. 1). This fully biodegradable polymer polylactic acid is metabolized to water and carbon dioxide and promises to cause less long-term inflammatory reaction. Full resorption occurs within 6 months. In the LEADERS trial the BES was found noninferior to the SES in terms of major adverse cardiac events (MACE) at 9 months as well as in-stent percent diameter stenosis (p = NS) (1).

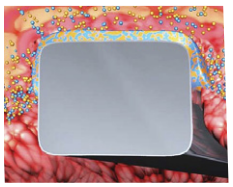
Study population. The LEADERS trial was a multicenter European non-inferiority trial comparing the safety and efficacy of BES with SES in 1,707 "all-comers" patients. Patients over the age of 18 with chronic stable coronary artery disease or acute coronary syndromes including ST-segment elevation myocardial infarction (MI) were eligible if they had at least 1 lesion with >50% diameter stenosis and reference vessel diameter 2.25 to 3.5 mm. The aim was for the patient population to reflect real world clinical practice, and thus no limits were set on the number or complexity of the lesions stented. The only exclusion criteria were: known allergy to acetylsalicylic acid, clopidogrel, heparin, stainless steel, sirolimus, biolimus, or contrast material that cannot be pre-medicated; planned surgery within 6 months of percutaneous coronary intervention unless the dual anti-platelet therapy could be maintained throughout the perisurgical period; pregnancy or participation in another trial before reaching the primary end point; and lastly, inability to give informed consent. The study complied with the Declaration of Helsinki and was approved by all institutional ethics committees. All patients provided written informed consent for participation in the trial.

Randomization and procedures. Randomization was done centrally after diagnostic cardiac catheterization and before percutaneous coronary intervention (PCI) by use of a telephone allocation service (Limburgia telefonische Antwoord Service, Rotterdam, the Netherlands). The allocation sequence was computer-generated, stratified according to center, and blocked with block sizes of 8 and 16, which varied randomly. We randomly allocated patients on a 1:1 basis to treatment with a BES (Biomatrix Flex, Biosensors, Inc., Newport Beach, California) or an SES (Cypher Select, Cordis, Miami Lakes, Florida) and to active angiographic follow-up at 9 months or clinical follow-up only on a 1:3 basis with a factorial design.

The BES were available in diameters of 2.25, 2.5, 3.0, and 3.5 mm and in lengths of 8, 11, 14, 18, 24, and 28 mm. The SES were available in diameters of 2.25, 2.5, 2.75, 3.0, and 3.5 mm and in lengths of 8, 13, 18, 23, 28, and 33 mm. We performed balloon angioplasty and stent implantation according to standard technique, and direct stenting was allowed. No mixture of drug-eluting stents was permitted within a given patient, unless the operator was unable to insert the study stent, in which case crossover to another device of the operator's choice was possible. Before or at the time of the procedure, patients were given at least 75 mg of acetylsalicylic acid, 300 to 600 mg loading dose of clopidogrel, and unfractionated heparin at a dose at least 70 IU/kg. After the procedure, all patients were advised to take aspirin indefinitely and clopidogrel for at least 12 months. In case of intercurrent revascularization procedures requiring stent implantation, treating cardiologists were encour-

- Biolimus is a semi-synthetic sirolimus analogue with 10x higher lipophilicity and similar potency as sirolimus.
- Biolimus is immersed at a concentration of 15.6 μg/mm into a biodegradable polymer, polylactic acid, and applied solely to the abluminal stent surface by a fully automated process.
- Polylactic acid is co-released with biolimus and completely desolves into carbon dioxide and water during a 6-9 months period.
- The stainless steel stent platform has a strut thickness of 112 μm with a quadrature link design.





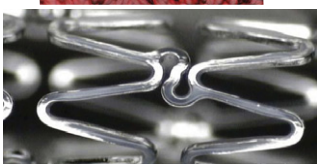


Figure 1. Structure of Biolimus and Scanning Electron Micrograph of the Biolimus Biodegradable Polymer Stent

aged to use the study stent. For other details we refer to the primary end point article (1).

Study end points. Adverse events were assessed in the hospital and at 1, 6, 9, and 12 months. An independent clinical events committee unaware of the patient's treatment assignments adjudicated all end points. One in four patients was asked to return for angiographic follow-up at 9 months. Definitions of all end points are provided elsewhere (1). Briefly, the pre-specified primary end point was the composite of cardiac death, MI, and clinically indicated target vessel revascularization (TVR) within 9 months. Secondary end points were any target lesion revascularization (TLR) (both clinically and nonclinically indicated), which was defined as repeat revascularization due to a stenosis within the stent or within a 5-mm border proximal or distal to the stent; any TVR, cardiac death, death from any cause, MI, stent thrombosis (defined according to the Academic Research Consortium) (12); device success (defined as achievement of a final residual diameter stenosis of <50% during the initial procedure); and lesion success (achievement of <50% stenosis with any approach for PCI).

The pre-specified principal outcome of the angiographic substudy was in-stent percent diameter stenosis. Secondary angiographic outcomes were in-segment percent diameter stenosis, minimal lumen diameter (MLD), late lumen loss, and binary restenosis. We obtained angiographic measurements within the stented segment (in-stent) and over the entire segment consisting of the stent and 5-mm proximal and distal margins (in-segment). We defined percent diameter stenosis as: ([reference vessel diameter − MLD]/reference vessel diameter) × 100%; late lumen loss as the difference between MLD after the procedure and MLD at follow-up; and binary restenosis as percentage diameter stenosis of 50% or greater in the target lesion.

Independent study monitors (D-Target, Montagny-pres-Yverdon, Switzerland) verified all case reports from data on-site. Data were stored in a database (KIKA Medical, Paris, France), which was maintained by a contract research organization (Cardialysis, Rotterdam, the Netherlands) in collaboration with an academic clinical trials unit (CTU Bern, Bern University Hospital, Bern, Switzerland). Clinical follow-up was done at 1, 6, 9, and 12 months. The operators were by necessity aware of the assigned study stent during PCI and angiographic follow-up, but patients and staff involved in follow-up assessment were blinded to the allocated stent type. Angiographies were centrally assessed at 1 angiographic core laboratory (Cardialysis) with assessors unaware of the allocated stent.

Statistical analysis. A stratified post-hoc analysis of clinical and angiographic outcomes, which was specified after completion of patient recruitment, was performed according to vessel size. Methodology similar to the previously published SIRTAX (Sirolimus-Eluting Versus Paclitaxel-Eluting Stents for Coronary Revascularization) trial was used (9). Quantitative coronary angiography served to determine the reference vessel diameter (RVD). Patients who underwent stent implantation in lesions with an RVD ≤2.75 mm were categorized as having undergone treatment of small vessels. Conversely, patients who underwent stent implantation in lesions with RVD >2.75 mm were classified as having had treatment of large vessels. Patients with stent implantations in both small and large vessels were classified as "mixed". All

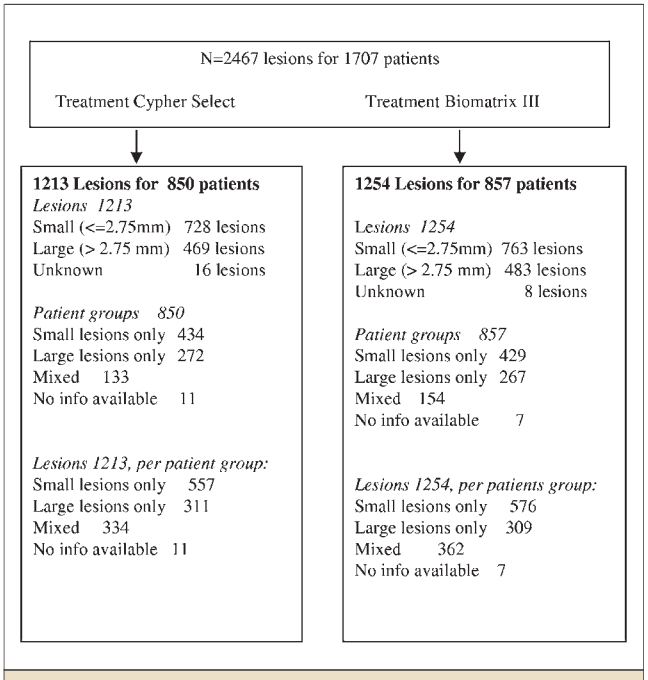


Figure 2. Study Flow Chart

randomized patients were included in the analysis of primary and secondary clinical end points in the groups that they were originally assigned to (intention-to-treat analysis). Analyses of the angiographic substudy were restricted to lesions from patients who attended follow-up angiography. Angiographic outcomes were analyzed with SAS version 8 Proc Mixed (SAS Institute, Cary, North Carolina) for continuous and Proc Genmod for binominal outcomes, taking into account the within-patient correlation structure of these data. We used a Cox proportional hazards model to compare clinical outcomes between the groups. All analyses were performed with SAS version 8.02 by a dedicated statistician. All p values and confidence intervals were 2-sided.

Results

Baseline clinical, angiographic, and procedural data. A total of 1,707 patients with 2,467 lesions were randomly assigned to treatment with either BES (857 patients, 1,254 lesions) or SES (850 patients, 1,213 lesions). Four hundred twenty-nine patients in the BES group with 576 lesions and 434 patients in the SES group with 557 lesions had only small vessels treated (863 of 1,707 [50.6%] of the entire patient population); 267 patients in the BES arm with 309 lesions and 272 patients in the SES arm with 311 lesions had only large vessels treated (RVD >2.75); and 154 patients in the BES group with 362 lesions and 133 patients with 334 lesions in the SES group had "mixed" disease (Fig. 2).

Baseline clinical and angiographic characteristics are summarized in Tables 1 and 2. There were no significant differences in the numbers of patients with diabetes, hypertension, hypercholesterolemia, smoking history, prior history of MI, stroke, or peripheral vascular disease between the SES and BES groups. These patient characteristics differed, however, when compared for vessel size. There was a higher proportion of women with small vessels (29% vs. 25% overall; $p < 0.001$), whereas no significant difference in the numbers of diabetic patients across vessel sizes was found. Smokers were more frequently found in the large vessel group ($p < 0.001$), whereas patients with small vessel disease had a higher frequency of previous MIs ($p = 0.007$) and past history of PCI ($p < 0.001$). A high proportion of patients in the entire cohort had presented with acute coronary syndromes (between 51% and 61%) and 13% to 21% of the cases were ST-segment elevation MIs. Lastly, patients with mixed vessel disease had a higher proportion of multivessel disease ($p < 0.001$).

Mean reference vessel diameters in the BES and SES group were 2.21 ± 0.34 mm and 2.24 ± 0.33 mm for small vessels, respectively, 3.21 ± 0.47 mm and 3.18 ± 0.37 mm for large vessels, and 2.69 ± 0.57 mm and 2.66 ± 0.59 mm for mixed lesions (Table 1). The lesion length did not differ between the 2 treatment groups but differed slightly over the range of 12 to 16 mm between vessel sizes. Percent diameter stenosis was 63 ± 18% in small vessels in both treatment arms, 66 ± 18% in large vessels treated with BES, 69 ± 18% in large vessels treated with SES, 62 ± 18% in the mixed vessels treated with BES, and 61 ± 18% in the mixed vessels treated with SES. The MLD amounted to 0.80 and 0.84 mm in small vessels treated with BES and SES and 1.01 and 1.07 mm in large vessels treated with BES and SES, respectively.

Procedural results are shown in Table 2. Post-stenting MLD in small vessels treated with BES and SES was 2.09 ± 0.35 mm and 2.13 ± 0.35 mm, respectively (p = NS); it was 2.76 ± 0.41 mm and 2.67 ± 0.38 mm in large vessels treated with BES and SES, respectively. There were no significant differences in acute gain after stenting with BES or SES, the acute gain being 1.29 ± 0.45 mm for small vessels, 1.74 ± 0.62 mm for large vessels treated with BES, and 1.59 ± 0.59 mm for large vessels treated with SES. This translated also in equivalent diameter stenosis after PCI in both stent groups.

Angiographic results. Angiographic follow-up at 9 months were obtained in 168 patient in the BES group and 167 patients in the SES group (Table 2). One hundred nine small vessel lesions, 62 large vessel lesions, and 82 mixed vessel lesions were evaluated angiographically at 9 months in the group treated with BES. One hundred fourteen small vessel lesions, 58 large vessel lesions, and 59 mixed lesions were evaluated angiographically in the SES group. In small, large, and mixed vessels there was no significant difference

Table 1. Baseline Clinical and Angiographic Characteristics for Small, Large, and "Mixed" Vessel Groups

	BES, Small	SES, Small	BES, Large	SES, Large	BES, Mixed	SES, Mixed	p Value*
Patient demographic data							
Number of patients	429	434	267	272	154	133	†
Age >65 yrs	225 (52)	209 (48)	125 (47)	134 (49)	78 (51)	73 (55)	0.44
Male	295 (69)	314 (72)	217 (81)	207 (76)	125 (81)	105 (79)	<0.001
Diabetes	104 (24)	105 (24)	63 (24)	56 (21)	51 (33)	29 (22)	0.18
Hypertension	315 (73)	319 (74)	193 (72)	205 (75)	117 (76)	88 (66)	0.74
Hyperlipidemia	291 (68)	299 (69)	170 (64)	177 (65)	95 (62)	101 (76)	0.27
Current smoking	85 (20)	96 (22)	76 (29)	82 (30)	41 (27)	33 (25)	0.002
Previous MI	151 (35)	146 (34)	64 (24)	84 (31)	59 (38)	46 (35)	0.007
Previous PCI	184 (43)	180 (42)	77 (29)	88 (32)	48 (31)	44 (33)	<0.001
Previous stroke	24 (6)	16 (4)	7 (3)	6 (2)	9 (6)	6 (4.5)	0.06
Previous PVD	39 (9)	35 (8)	13 (5)	19 (7)	18 (12)	9 (7)	0.12
Multivessel disease	83 (19)	58 (13)	22 (8)	22 (8)	103 (67)	96 (72)	<0.001
Clinical presentation							
Stable angina	160 (37)	156 (36)	79 (30)	78 (29)	55 (36)	53 (40)	0.03
Acute coronary syndromes	224 (52)	233 (54)	156 (58)	166 (61)	87 (56.5)	68 (51)	0.042
Unstable angina	99 (23)	92 (21)	58 (22)	61 (22)	33 (21)	27 (20)	
STEMI	54 (13)	61 (14)	56 (21)	56 (21)	22 (14)	18 (13.5)	
Non-STEMI	71 (17)	80 (18)	42 (16)	49 (18)	32 (21)	23 (17)	
Angiographic parameters							
Number of lesions	576	557	309	311	363	334	‡
Lesion length	15 ± 13	14 ± 11	17 ± 11	16 ± 12	14 ± 10	13 ± 9	<0.001
Reference vessel diameter	2.21 ± 0.34	2.24 ± 0.33	3.21 ± 0.47	3.18 ± 0.37	2.69 ± 0.57	2.66 ± 0.59	<0.001
MLD	0.80 ± 0.40	0.84 ± 0.43	1.01 ± 0.63	1.08 ± 0.58	1.02 ± 0.48	1.05 ± 0.53	<0.001
% diameter stenosis	63 ± 18	63 ± 18	69 ± 18	66 ± 18	62 ± 17	61 ± 17	<0.001

Values are n, n (%), and mean ± SD. *The p value is given for the difference among the 3 groups (small, large, and mixed) rather than biolimus-eluting degradable polymer stent (BES) versus sirolimus-eluting permanent polymer stent (SES). †Tested: equal distribution in the 3 groups. ‡Tested: equal mean in the 3 groups.
MI = myocardial infarction; MLD = minimal lumen diameter; PCI = percutaneous coronary intervention; PVD = peripheral vascular disease; STEMI = ST-segment elevation myocardial infarction.

in late luminal loss, MLD, percent diameter stenosis, or binary restenosis between BES and SES groups. In small vessels late loss was 0.17 ± 0.47 mm in the BES group and 0.22 ± 0.51 mm in the SES group (p = NS). Corresponding percent diameter stenosis was 24.9 ± 20.7% and 23.8 ± 21.3% in the BES and SES stent groups, respectively. In the large lesion population, in-stent late luminal loss was 0.14 ± 0.51 in the BES arm and 0.05 ± 0.37 in the SES group (p = NS). The percent diameter stenosis in the large vessel group was 18.2 ± 14.6% in the BES group and 19.2 ± 14.5% in the SES group (p = NS). Late loss, percent diameter stenosis, and binary in-stent restenosis were lower in the "mixed" lesion group treated with BES compared with SES.

Clinical outcomes. Clinical events at 1-year follow-up stratified by vessel size are listed in Table 3 and summarized in Figures 3 and 4. Vessel size seemed to influence the TLR rates in both SES and BES groups. Within the BES treatment arm TLR rate was 9.6% in the small vessel group (41 events) versus 2.6% in the large vessel group (7 events). Within the SES treatment arm TLR rate was 7.4% in the small vessel group (32 events) versus 5.1% in the large vessel group (14 events). There were no differences in the overall rate of MACE or TLR/TVR in patients with small vessels and large vessels treated with BES versus SES stents. There was no significant difference in overall MACE rate between BES- and SES-treated patients with "mixed" vessel disease, although rates of overall percutaneous TLR (7 [4.5%] patients vs. 15 [11.3%] patients; p = 0.037) were lower. Tests for interaction between treatment and vessel size reached statistical significance for TLR and TVR rates in the mixed disease group.

There were 13 definite stent thrombosis events in small vessels in the BES arm (3.0%) and 9 definite stent thrombosis events in the SES arm (2.1%) (p = 0.38).

Discussion

We present here a novel stent technology now commercially available in Europe that combines the biodegradable polymer technology with solely abluminal elution of biolimus and performs well in complex lesions such as small vessels in an "all-comer" patient population. The main finding of this substudy of the LEADERS multicenter randomized trial focusing on the effect of vessel size on angiographic and clinical outcomes is that BES seems noninferior to the

Table 2. Baseline Angiographic Characteristics, Procedural Outcomes, and Angiographic Follow-Up Results at 9 Months

	BES, Small	SES, Small	BES, Large	SES, Large	BES, Mixed	SES, Mixed	p Value Interaction
Number at initial procedure (at 9-month follow-up)	561 (105)	539 (114)	308 (62)	309 (58)	360 (82)	326 (59)	
In-stent							
Reference vessel diameter							
After procedure	2.46 (0.36)	2.48 (0.35)	3.24 (0.42)	3.16 (0.40)	2.79 (0.52)	2.79 (0.52)	0.0192
9-month follow-up	2.55 (0.37)	2.45 (0.39)	3.25 (0.33)	3.21 (0.44)	2.84 (0.49)	2.81 (0.51)	0.7792
MLD							
After procedure	2.09 (0.35)	2.13 (0.35)	2.76 (0.41)	2.67 (0.38)	2.36 (0.51)	2.38 (0.50	0.0033
9-month follow-up	1.91 (0.59)	1.87 (0.62)	2.65 (0.53)	2.60 (0.59)	2.08 (0.51)	1.83 (0.62)	0.209
Acute gain	1.29 (0.46)	1.30 (0.45)	1,74 (0.62)	1.60 (0.59)	1.34 (0.55)	1.32 (0.53)	0.0169
Late loss	0.17 (0.47)	0.22 (0.51)	0.14 (0.51)	0.05 (0.37)	0.06 (0.40)	0.25 (0.56)	0.047
% diameter stenosis							
After procedure	14.8 (8.4)	14.1 (7.6)	14.6 (7.5)	15.2 (7.0)	15.0 (9.7)	14.7 (9.1)	0.3955
9-month follow-up	24.9 (20.7)	23.8 (21.3)	18.2 (14.6)	19.2 (14.5)	17.8 (13.7)	26.4 (20.0)	0.0236
Binary restenosis rate (%)	10.1	7.9	3.2	3.4	1.2	15.3	0.0144
In-segment							
Reference vessel diameter							
After procedure	2.37 (0.38)	2.39 (0.38)	3.14 (0.45)	3.06 (0.46)	2.69 (0.55)	2.71 (0.56)	0.0723
9-month follow-up	2.50 (0.38)	2.37 (0.40)	3.16 (0.36)	3.13 (0.46)	2.78 (0.52)	2.76 (0.52)	0.4379
MLD							
After procedure	1.78 (0.36)	1.84 (0.37)	2.48 (0.46)	2.44 (0.43)	2.07 (0.52)	2.07 (0.52)	0.0845
9-month follow-up	1.73 (0.55)	1.65 (0.56)	2.42 (0.50)	2.35 (0.56)	2.08 (0.51)	1.83 (0.62)	0.1293
Acute gain	0.99 (0.48)	1.00 (0.47)	1.45 (0.66)	1.36 (0.63)	1.04 (0.56)	1.02 (0.53)	0.2238
Late loss	0.09 (0.44)	0.19 (0.48)	0.10 (0.49)	0.04 (0.33)	0.04 (0.42)	0.19 (0.51)	0.079
% diameter stenosis							
After procedure	24.4 (10.1)	23.3 (9.3)	21.0 (8.6)	20.2 (8.8)	22.8 (10.6)	23.3 (10.5)	0.236
9-month follow-up	30.6 (19.2)	30.6 (19.7)	23.3 (14.0)	24.8 (14.7)	25.2 (12.7)	33.3 (18.7)	0.1105
Binary restenosis rate (%)	12.8	9.7	3.2	5.2	1.2	18.6	0.0052

Values are mean (SD), unless otherwise indicated.
Abbreviations as in Table 1.

"gold standard" SES in small vessels. To our knowledge this is the first report of another drug-eluting stent being noninferior to SES in the setting of small vessel disease. Angiographic outcomes at 9-month follow-up in a subset of patients show equivalent late luminal loss, percent diameter stenosis, and binary restenosis rates, which translate into similar rates of MACE and TLR at 1 year in both stent treatment groups in small vessel disease. This equivalent performance is achieved in a complex "all-comer" patient population that reflects "real world" clinical practice. These results in small vessel disease are unlike those reported in trials to date comparing SES and PES, where SES has shown a consistent advantage over PES in both angiographic and clinical outcomes (13–16).

Another important finding of our study is that the prevalence of small vessel lesions (defined as reference diameter <2.75 mm) is high (50.6%) in real world clinical practice, and the overall rate of MACE and TLR in small vessel lesions across stent types are higher than for large vessel lesions (Online Figures). This latter finding is at variance with recent findings of the BASKET (Basel Stent Cost-Effectiveness Trial) 3-year follow-up, where within the drug-eluting stent-treated group there seemed to be no difference in the MACE and TLR rates between small and large vessels (17). The increased event rate in the large stent group seemed to be a late rather than early phenomenon, with the curve diverging after 6 to 9 months, a phenomenon that might have been missed in the present study with only 1-year clinical follow-up. Conversely, failure to detect earlier higher event rates in the small vessel group in the BASKET study might have been due to the lower number of patients (187 patients with small vessels treated with DES compared with 863 patients in the present study).

The SES (Cypher Select) uses a poly-n-butyl methacrylate durable polymer technology for drug elution that has been shown to cause inflammation and fibrin deposition as well as endothelial dysfunction and delayed endothelialization (18). Poly-n-butyl methacrylate is hydrophobic and causes monocytes to adhere to its surface and

Table 3. Clinical Outcomes at 1-Year Follow-Up

	BES, Small (n = 429)	SES, Small (n = 434)	HR (95% CI)	p Value	BES, Large (n = 267)	SES, Large (n = 272)	HR (95% CI)	p Value	BES, Mixed (n = 154)	SES, Mixed (n = 133)	HR (95% CI)	p Value	p Value Interaction
Death	12 (2.8)	10 (2.3)	1.21 (0.52–2.8)	0.65	10 (3.7)	12 (4.4)	0.85 (0.37–1.97)	0.71	4 (2.6)	5 (3.8)	0.68 (0.18–2.55)	0.57	0.73
Cardiac death	10 (2.3)	8 (1.8)	1.26 (0.50–3.20)	0.62	6 (2.2)	9 (3.3)	0.68 (0.24–1.91)	0.47	1 (0.6)	5 (3.8)	0.17 (0.02–1.47)	0.11	0.16
MI	24 (5.6)	20 (4.6)	1.21 (0.67–2.19)	0.52	10 (3.7)	11 (4.0)	0.92 (0.39–2.17)	0.85	16 (10.4)	7 (5.3)	2.02 (0.83–4.92)	0.12	0.43
All TLR	41 (9.6)	32 (7.4)	1.31 (0.82–2.08)	0.26	7 (2.6)	14 (5.1)	0.50 (0.20–1.25)	0.14	8 (5.2)	15 (11.3)	0.44 (0.19–1.04)	0.06	0.03
TLR percutaneous	40 (9.3)	31 (7.1)	1.32 (0.83–2.11)	0.25	5 (1.9)	12 (4.4)	0.42 (0.15–1.20)	0.10	7 (4.5)	15 (11.3)	0.39 (0.16–0.95)	0.037	0.014
TLR surgical	5 (1.2)	4 (0.9)	1.26 (0.34–4.68)	0.73	2 (0.7)	2 (0.7)	1.02 (0.14–7.23)	0.99	1 (0.6)	1 (0.8)	0.84 (0.05–13.46)	0.90	0.96
Clinically justified TLR	34 (7.9)	26 (6.0)	1.33 (0.80–2.21)	0.28	5 (1.9)	11 (4.0)	0.46 (0.16–1.32)	0.15	5 (3.2)	10 (97.5)	0.42 (0.14–1.23)	0.11	0.05
Clininally justified TLR percutaneous	33 (7.7)	25 (5.8)	1.34 (0.80–2.26)	0.27	4 (1.5)	10 (3.7)	0.40 (0.13–1.29)	0.13	5 (3.2)	10.75	0.42 (0.14–1.23)	0.11	0.041
Clininally justified TLR surgical	4 (0.9)	3 (0.7)	1.34 (0.30–6.00)	0.70	1 (0.4)	1 (0.4)	1.02 (0.06–16.33)	0.99	—	—			0.99
All TVR	46 (10.7)	43 (9.9)	1.08 (0.72–1.64)	0.7	10 (3.7)	21 (7.7)	0.48 (0.22–1.01)	0.054	10 (6.5)	18 (13.5)	0.45 (0.21–0.99)	0.046	0.048
TVR percutaneous	44 (10.3)	39 (9.0)	1.15 (0.75–1.77)	0.53	6 (2.2)	17 (6.3)	0.35 (0.14–0.90)	0.029	9 (5.8)	18 (13.5)	0.41 (0.18–0.91)	0.029	0.012
TVR surgical	6 (1.4)	7 (1.6)	0.86 (0.29–2.56)	0.79	4 (1.5)	4 (1.5)	1.02 (0.25–4.07)	0.98	1 (0.6)	1 (0.8)	0.84 (0.05–13.46)	0.90	0.98
Clininally justified TVR	36 (8.4)	32 (7.4)	1.14 (0.71–1.83)	0.59	7 (2.6)	14 (5.1)	0.50 (0.20–1.25)	0.14	6 (3.9)	12 (9.0)	0.42 (0.16–1.11)	0.08	0.08
Clininally justified TVR percutaneous	35 (8.2)	31 (7.1)	1.15 (0.71–1.86)	0.58	5 (1.9)	12 (4.4)	0.42 (0.15–1.19)	0.10	6 (3.9)	12 (9.0)	0.42 (0.16–1.11)	0.08	0.06
Clininally justified TVR surgical	4 (0.9)	3 (0.7)	1.34 (0.30–6.00)	0.70	2 (0.7)	2 (0.7)	1.02 (0.14–7.22)	0.99	—	1 (0.8)			0.42
Stent thrombosis	19 (4.4)	12 (2.8)	1.61 (0.78–3.32)	0.20	6 (2.2)	8 (2.9)	0.76 (0.26–2.19)	0.61	5 (3.2)	6 (4.5)	0.72 (0.22–2.34)	0.58	0.36
Definite stent thrombosis	13 (3.0)	9 (2.1)	1.47 (0.63–3.43)	0.38	1 (0.4)	4 (1.5)	0.25 (0.03–2.27)	0.22	3 (1.9)	4 (3.0)	0.65 (0.14–2.88)	0.57	0.22
Possible stent thrombosis	2 (0.5)	3 (0.7)	0.67 (0.11–4.02)	0.66	4 (1.5)	3 (1.1)	1.36 (0.30–6.09)	0.69	1 (0.6)	3 (2.3)	0.28 (0.03–2.73)	0.28	0.49
Probable stent thrombosis	5 (1.2)	1 (0.2)	5.05 (0.59–43.24)	0.14	1 (0.4)	1 (0.4)	1.02 (0.06–16.36)	0.99	—	1 (0.6)			0.53
MACE	52 (12.1)	51 (11.8)	1.03 (0.70–1.51)	0.89	19 (7.1)	28 (10.3)	0.68 (0.38–1.22)	0.20	18 (11.7)	19 (14.3)	0.83 (0.44–1.58)	0.57	0.50
Target vessel failure	58 (13.5)	57 (13.1)	1.03 (0.71–1.48)	0.88	17 (6.4)	30 (11.0)	0.57 (0.31–1.03)	0.06	18 (11.7)	24 (18)	0.63 (0.34–1.17)	0.14	0.16

CI =confidence interval; HR = hazard ratio; MACE = major adverse cardiac events; TLR = target lesion revascularization; TVR = target vessel revascularization; other abbreviations as in Table1.

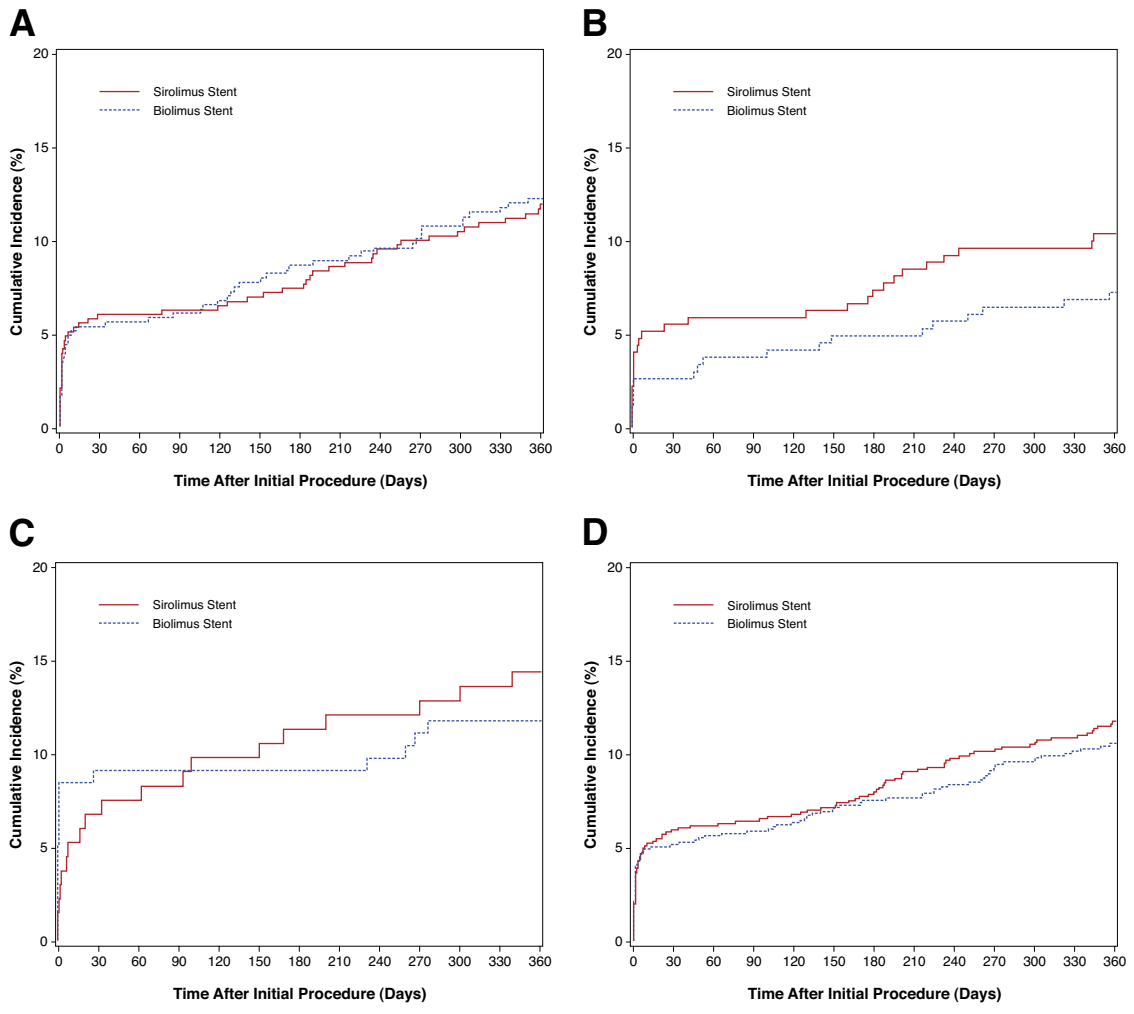


Figure 3. Kaplan-Meier Curves for Overall MACE Rate at 1 Year

Kaplan-Meier curves for overall major adverse cardiac events (MACE) rate at 1 year. **(A)** Small vessels; **(B)** large vessels; **(C)** mixed vessels; **(D)** all vessels.

produce cytokines such as monocyte chemotactic protein-1, plasminogen activator inhibitor-1, and tissue factor (19). Persistence of this pro-inflammatory polymer is hypothesized to be a potential major contributor to late stent thrombosis events. The BES in the present study uses, unlike SES, a biodegradable polymer made of polylactic acid, which completely disintegrates to water and carbon dioxide within 6 months. Therefore, it holds promise of a lower rate of late stent thrombosis or need for dual antiplatelet inhibition in the long term as well as equivalent performance in terms of efficacy in the short term. The drug is eluted on the abluminal surface and therefore might be hypothetically less likely to cause delayed endothelialization, while still preventing in-stent restenosis.

We noted a higher number of stent thrombosis cases than in on-label clinical trials, particularly in small vessels in both BES- and SES-treated groups of patients. Yet, the rate of stent thrombosis corresponds well to other all-comer trials such as SYNTAX (Synergy Between PCI With Taxus and Cardiac Surgery) (20). It might also be explained by a relatively high percentage of patients with acute coronary syndromes, including up to 21% with ST-segment elevation MI, because similar rates of stent thrombosis have been reported in TRITON–TIMI 38 (A Comparison of CS-747 and Clopidogrel in Acute Coronary Syndrome Subjects who are to Undergo Percutaneous Coronary Intervention–Thrombolysis In Myocardial Infarction 38) and HORIZON-AMI (Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction) trials (21,22). There seems to be overall similar rates of definite stent thrombosis in small, large, and "mixed" vessel groups. Longer-term follow-up will determine whether the biodegradable polymer adds any advantage over a durable polymer in terms of very late events.

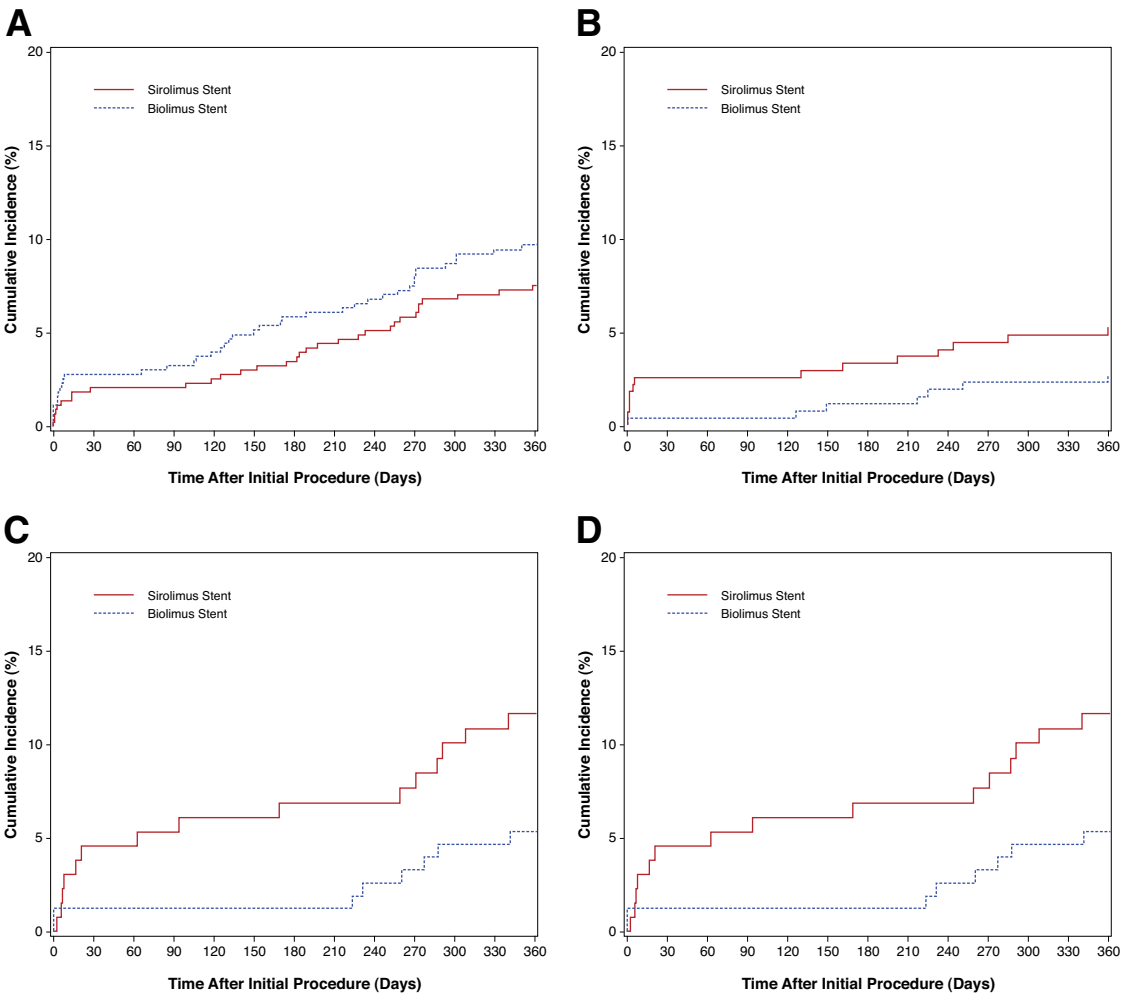


Figure 4. Kaplan-Meier Curves for TLR Rates at 1 Year

Kaplan-Meier curves for target lesion revascularization (TLR) rates at 1 year. **(A)** Small vessels; **(B)** large vessels; **(C)** mixed vessels (p = 0.05); **(D)** all vessels.

Lastly, there seems to be an advantage of treatment with BES in patients with "mixed" lesions and multivessel disease. This difference in angiographic outcomes (late loss) and trend to a significant difference in TLR and TVR in patients with "mixed" disease must be explored further. Although late loss has been established as a discriminating factor in stent performance (3–5), it remains uncertain whether this translates into differences in long-term clinical outcomes. The interpretation of this result in this complex group with "mixed" lesions is difficult; nevertheless, given the prevalence of "mixed" lesion populations in our clinical practice, it is noteworthy.

Study limitations. The study suffers from the usual limitations of post hoc analyses and, for some subgroup analyses, might lack sufficient power to detect superiority of 1 treatment over the other. Some of the key differences in outcomes such as late stent thrombosis in a degradable versus permanent polymer stent might emerge at long-term follow-up.

Conclusions

Vessel size has been an important predictor of in-stent restenosis and clinical events. The SES have been thus far superior to PES and bare-metal stents in treatment of small vessels. We demonstrate for the first time the non-inferiority of BES to SES in angiographic late loss and percutaneous TLR rates.

Acknowledgments

The authors would like to thank Dr. Pedro Eerdmans, MD, MSc, and Marco Bressers, PhD, for their assistance with manuscript preparation and data analysis.

Reprint requests and correspondence: Dr. Patrick W. Serruys, Interventional Cardiology, Thoraxcenter, Erasmus Medical Center, 's Gravendijkwal 230, Bd 412, 3015CE Rotterdam, the Netherlands. E-mail: p.w.j.c.serruys@erasmusmc.nl.

REFERENCES

1. Windecker S, Serruys PW, Wandel S, et al. Biolimus-eluting stent with biodegradable polymer versus sirolimus-eluting stent with durable polymer for coronary revascularisation (LEADERS): a randomised non-inferiority trial. Lancet 2008;372:1163–73.
2. Grube E, Buellesfeld L. BioMatrix Biolimus A9-eluting coronary stent: a next-generation drug-eluting stent for coronary artery disease. Expert Rev Med Devices 2006;3:731–41.
3. Mauri L, Orav EJ, Candia SC, Cutlip DE, Kuntz RE. Robustness of late lumen loss in discriminating drug-eluting stents across variable observational and randomized trials. Circulation 2005;112:2833–9.
4. Mauri L, Orav EJ, Kuntz RE. Late loss in lumen diameter and binary restenosis for drug-eluting stent comparison. Circulation 2005;111: 3435–42.
5. Mauri L, Orav EJ, O'Malley AJ, et al. Relationship of late loss in lumen diameter to coronary restenosis in sirolimus-eluting stents. Circulation 2005;111:321–7.
6. Meier B, Sousa E, Guagliumi G, et al. Sirolimus-eluting coronary stents in small vessels. Am Heart J 2006;151:1019.e1–7.
7. Kuntz RE, Safian RD, Carrozza JP, Fishman RF, Mansour M, Baim DS. The importance of acute luminal diameter in determining restenosis after coronary atherectomy or stenting. Circulation 1992;86: 1827–35.
8. Kuntz RE, Safian RD, Levine MJ, Reis GJ, Diver DJ, Baim DS. Novel approach to the analysis of restenosis after the use of three new coronary devices. J Am Coll Cardiol 1992;19:1493–9.
9. Togni M, Eber S, Widmer J, et al. Impact of vessel size on outcome after implantation of sirolimus-eluting and paclitaxel-eluting stents: a subgroup analysis of the SIRTAX trial. J Am Coll Cardiol 2007;50: 1123–31.
10. Ellis SG, Popma JJ, Lasala JM, et al. Relationship between angiographic late loss and target lesion revascularization after coronary stent implantation: analysis from the TAXUS-IV trial. J Am Coll Cardiol 2005;45:1193–200.
11. Regar E, Serruys PW, Bode C, et al. Angiographic findings of the multicenter Randomized Study With the Sirolimus-Eluting Bx Velocity Balloon-Expandable Stent (RAVEL): sirolimus-eluting stents inhibit restenosis irrespective of the vessel size. Circulation 2002;106:1949–56.
12. Mauri L, Hsieh WH, Massaro JM, Ho KK, D'Agostino R, Cutlip DE. Stent thrombosis in randomized clinical trials of drug-eluting stents. N Engl J Med 2007;356:1020–9.
13. Windecker S, Remondino A, Eberli FR, et al. Sirolimus-eluting and paclitaxel-eluting stents for coronary revascularization. N Engl J Med 2005;353:653–62.
14. Kastrati A, Mehilli J, von Beckerath N, et al. Sirolimus-eluting stent or paclitaxel-eluting stent vs balloon angioplasty for prevention of recurrences in patients with coronary in-stent restenosis: a randomized controlled trial. JAMA 2005;293:165–71.
15. Elezi S, Dibra A, Mehilli J, et al. Vessel size and outcome after coronary drug-eluting stent placement: results from a large cohort of patients treated with sirolimus- or paclitaxel-eluting stents. J Am Coll Cardiol 2006;48:1304–9.
16. Tanimoto S, Daemen J, Tsuchida K, et al. Two-year clinical outcome after coronary stenting of small vessels using 2.25-mm sirolimus- and paclitaxel-eluting stents: insight into the RESEARCH and T-SEARCH registries. Catheter Cardiovasc Interv 2007;69:94–103.
17. Pfisterer M, Brunner-La Rocca HP, Rickenbacher P, et al. Long-term benefit-risk balance of drug-eluting vs. bare-metal stents in daily practice: does stent diameter matter? Three-year follow-up of BASKET. Eur Heart J 2009;30:16–24.
18. Joner M, Finn AV, Farb A, et al. Pathology of drug-eluting stents in humans: delayed healing and late thrombotic risk. J Am Coll Cardiol 2006;48:193–202.
19. Hezi-Yamit A, Sullivan C, Wong J, et al. Novel high throughput polymer biocompatibility screening designed for SAR (structure-activity relationship): application for evaluating polymer coatings for cardiovascular drug-eluting stents. Comb Chem High Throughput Screen 2009 Aug 1 [E-pub ahead of print].
20. Serruys PW, Morice MC, Kappetein AP, et al. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. N Engl J Med 2009;360:961–72.
21. Stone GW, Witzenbichler B, Guagliumi G, et al. Bivalirudin during primary PCI in acute myocardial infarction. N Engl J Med 2008;358: 2218–30.
22. Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2007;357:2001–15.

Key Words: biodegradable polymer ■ biolimus-eluting stent ■ long lesions ■ sirolimus-eluting stent ■ small vessels ■ target vessel revascularization.

APPENDIX

For supplementary figures and tables, please see the online version of this article.