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Paclitaxel- Versus Sirolimus-Eluting Stents for Unprotected Left Main Coronary Artery Disease

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Objectives The aim of this trial was to compare the safety and efficacy of paclitaxel-eluting stents (PES) and sirolimus-eluting stents (SES) for treatment of unprotected left main coronary artery (uLMCA) disease.

Background Both PES and SES have reduced the risk of restenosis, particularly in high-risk patient and lesion subsets. However, their comparative performance in uLMCA lesions is not known.

Methods In this randomized study, 607 patients with symptomatic coronary artery disease undergoing percutaneous coronary intervention for uLMCA were enrolled: 302 were assigned to receive a PES (Taxus, Boston Scientific, Natick, Massachusetts) and 305 assigned to receive a SES (Cypher, Cordis, Johnson & Johnson, New Brunswick, New Jersey). The primary end point was the combined incidence of death, myocardial infarction, and target lesion revascularization (TLR) at 1 year. The secondary end point was angiographic restenosis on the basis of the LMCA area analysis at follow-up angiography.

Results At 1 year the cumulative incidence of death, myocardial infarction, or TLR was 13.6% in the PES and 15.8% in the SES group (relative risk [RR]: 0.85, 95% confidence interval [CI]: 0.56 to 1.29, p = 0.44). One patient in the PES group (0.3%) and 2 patients in the SES group (0.7%) experienced definite stent thrombosis (p = 0.57). Mortality at 2 years was 10.7% in the PES and 8.7% in the SES group (RR: 1.14, 95% CI: 0.66 to 1.95, p = 0.64). Angiographic restenosis was 16.0% with PES and 19.4% with SES (RR: 0.82, 95% CI: 0.57 to 1.19, p = 0.30).

Conclusions Implantation of either PES or SES in uLMCA lesions is safe and effective; both of these drug-eluting stents provide comparable clinical and angiographic outcomes. (Drug-Eluting-Stents for Unprotected Left Main Stem Disease [ISAR-LEFT-MAIN]; NCT00133237) (J Am Coll Cardiol 2009;53:1760–8) © 2009 by the American College of Cardiology Foundation

Up to 6% of patients with angiographically documented coronary artery disease present with significant left main coronary artery lesions (1). They represent a highly relevant therapeutic issue in view of the large amount of myocardium that is jeopardized if blood flow through the left main vessel is critically compromised. Although aorto-coronary artery bypass graft surgery (CABG) has been the preferred treatment approach, percutaneous coronary interventions (PCIs) are increasingly being used to treat unprotected left main coronary artery (uLMCA) lesions.

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Percutaneous intervention with plain balloon angioplasty in the left main coronary artery (LMCA) was performed on an infrequent basis in the past but was soon abandoned, due to suboptimal acute results and high rates of abrupt vessel closure after the procedure (2). The use of bare-metal stents (BMS) along with the evolution of dual antiplatelet therapy comprising aspirin and clopidogrel has increased the safety and the frequency of application of PCI for treatment of

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uLMCA lesions. However, the use of BMS for this type of lesion has been limited, because of high rates of restenosis and frequent need for reintervention (3). In a small randomized study comparing PCI (only 35% of stents implanted being drug-eluting stents [DES]) with CABG for treatment of uLMCA disease, the need for repeat revascularization at 1 year was 3 times higher for patients undergoing stenting compared with surgery (4).

DES have considerably reduced the risk of restenosis and are playing an increasing role in the treatment of various patient and lesion subsets. Recent evidence has shown that DES are at least as safe but much more effective in reducing the need for reintervention, as compared with BMS (5–8). With this potential, they might represent a reasonable treatment option for uLMCA lesions. Although superiority over BMS has been demonstrated for a variety of DES, currently available and approved DES might not necessarily be associated with equal performance efficacy (9–11). Potential differences in safety and efficacy between DES might be of particular import when treating uLMCA lesions. Despite the multitude of comparative DES studies for a variety of lesion characteristics, no such study has been performed for patients with uLMCA lesions. In fact, patients with uLMCA lesions have typically been excluded from any kind of randomized clinical trials focusing on the value of CABG or PCI for the management of coronary artery disease. There is increased interest in extending the remit of PCI with DES to the treatment of uLMCA and in comparing this method with CABG, which is the recommended treatment approach according to current guidelines (12–14). Whereas surgical methods have been well-standardized over the years (15,16), an accurate and comparative evaluation of the relative merits of currently available DES for this indication might help further optimization of a PCI-based strategy, a necessary step before launching dedicated randomized PCI versus CABG trials in patients with uLMCA disease.

We therefore designed this randomized study to investigate the value of DES in the treatment of uLMCA lesions by comparing 2 commonly available DES—a paclitaxel-eluting stent (PES) with a sirolimus-eluting stent (SES).

Methods

Patient population, randomization, and treatment protocol. We included patients older than age 18 years with ischemic symptoms or evidence of myocardial ischemia in the presence of ≥50% de novo stenosis located in the left main stem, provided that written informed consent for participation in the study was obtained from the patient or her/his legally-authorized representative. Exclusion criteria were ST-segment elevation myocardial infarction (MI) within 48 h of symptom onset; prior bypass graft surgery; in-stent restenosis; cardiogenic shock; malignancies or other comorbid conditions with life expectancy <1 year or that might result in protocol noncompliance; left main size >4.5 mm; planned staged PCI procedure within 30 days from index PCI; planned elective surgical procedure necessitating interruption of clopidogrel during the first 6 months after enrollment; known allergy to the study medications: clopidogrel, rapamycin, paclitaxel, stainless steel, or cobalt alloy; pregnancy; or previous enrollment in this trial. The study was conducted in accordance with the provisions of the Declaration of Helsinki and with the International Conference on Harmonization Good Clinical Practices, and protocol approval was obtained from the medical Ethics Committee for both participating centers, the Deutsches Herzzentrum and Medizinische Klinik I, Klinikum rechts der Isar, Munich, Germany. All eligible patients were informed that CABG is the currently recommended revascularization strategy and that DES are a new treatment option under investigation for LMCA disease. Patients not suitable for or unwilling to undergo CABG were considered for participation in this study.

Abbreviations and Acronyms

BMS = bare-metal stent(s)
CABG = aorto-coronary artery bypass graft surgery
CI = confidence interval
CK = creatine kinase
DES = drug-eluting stent(s)
MI = myocardial infarction
PCI = percutaneous coronary intervention
PES = paclitaxel-eluting stents(s)
RR = relative risk
SES = sirolimus-eluting stent(s)
TLR = target lesion revascularization
uLMCA = unprotected left main coronary artery

In each participating center, allocation to treatment, either with a PES (TAXUS, Boston Scientific, Natick, Massachusetts) or a SES (Cypher, Cordis, Johnson & Johnson, New Brunswick, New Jersey), was performed by means of sealed opaque envelopes containing a computer-generated sequence; this was done immediately after the decision to proceed with PCI. Patients who met all of the inclusion criteria and none of the exclusion criteria were randomized in the order they qualified. Patients were allocated to each of the 2 treatment groups in equal proportions. The treatment groups were studied concurrently. Patients were considered enrolled in the study and eligible for the final intention to treat analysis at the time of randomization.

Immediately after the decision to perform the intervention, patients were given 500-mg aspirin intravenously and intra-arterial or intravenous heparin up to a total amount of 140 U/kg body weight or bivalirudin (intravenous bolus of 0.75 mg/kg before the start of the intervention, followed by infusion of 1.75 mg/kg/h for the duration of the procedure). Glycoprotein IIb/IIIa inhibitors were given at the discretion of the operators. The SES was available in sizes 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; the PES was available in sizes of 2.25, 2.5, 2.75, 3.0, 3.5, 4.0, 4.5, and 5.0 mm and in lengths of 8, 12, 16, 20, 24, 28, and 32 mm.

After the intervention, all patients received 150 mg clopidogrel for the first 3 days. Thereafter they received 75 mg/day clopidogrel and 200 mg/day aspirin indefinitely

along with other cardiac medications according to the judgment of the patient's physician.

Stenting technique to be used was left to the discretion of the operators. However, use of 2 stents in "culotte" with final kissing balloon inflation was the preferred technique for distal bifurcation lesions.

Follow-up protocol, data management, study end points, and definitions. Blood samples were drawn every 8 h for the first 24 h after randomization and daily thereafter for the determination of cardiac markers (creatine kinase [CK], CK-myocardial band, troponin T or I) and blood cell counts (hemoglobin, hematocrit, platelet count, white blood cell count). Daily electrocardiographic recordings were performed until discharge. All patients were evaluated at 30 days and 12 months as well as yearly thereafter either by phone or office visit and were monitored throughout the study period for the occurrence of the following clinical events: death, MI, stroke, stent thrombosis, and target lesion revascularization (TLR). Repeat coronary angiography was scheduled at 6 to 9 months after enrollment in the study. Relevant data were collected and entered into a specialized computer database by specialized personnel of the Clinical Data Management Center. An events committee blinded to treatment allocation adjudicated all adverse clinical events.

Baseline, post-procedural, and follow-up coronary angiograms were digitally recorded and assessed off-line in the quantitative angiographic core laboratory (ISAR Center, Munich, Germany) with an automated edge-detection system (CMS version 7.1, Medis Medical Imaging Systems, Leiden, the Netherlands) by 2 independent experienced operators unaware of the treatment allocation. Quantitative analysis was performed on the left main area, which was considered the anatomical coronary region from the left main stem ostium to the end of the 5-mm proximal segments of left anterior descending artery and left circumflex artery as well as of ramus intermedius if the latter had a vessel size of more than 2 mm in diameter. The LMCA stenosis were classified as ostial (stenosis located within 3 mm of LMCA ostium), midshaft (stenosis located in the medial part of LMCA having at least 3 mm of apparently nondiseased artery before LMCA bifurcation), and distal (stenosis involves the distal part of the LMCA and bifurcation/trifurcation with proximal left anterior descending artery, proximal left circumflex artery, and proximal ramus intermedius if the latter was present).

Patients with a Parsonnet score >15 or EuroSCORE ≥6 (17,18) were considered high-risk surgical candidates. The diagnosis of MI required the presence of new significant Q waves on the electrocardiogram and/or elevation of CK-myocardial band isoform (or CK if the latter was not available) at least 2 times the upper limit of normal in no fewer than 2 blood samples. The TLR was defined as any repeat PCI involving the left main area or CABG involving at least 1 of the main left coronary vessels due to luminal renarrowing in the presence of symptoms or objective signs of ischemia. Stent thrombosis was defined according to Academic Research Consortium criteria (19). Angiographic binary restenosis was defined as diameter stenosis ≥50%, measured by quantitative coronary angiography, in the left main area.

The primary end point of the study was the combined incidence of all-cause death, MI, and TLR at 1 year after randomization. The secondary end point was the incidence of binary angiographic restenosis at follow-up angiography in the left main area.

Sample size calculation and statistical methods. Sample size calculation was performed on the basis of the following assumption: 1-sided alpha level 0.05, power 80%, primary end point rate of 20% with SES on the basis of previously reported results for DES in similar patients (20), and a noninferiority threshold of 8% for the PES. Accordingly, 302 patients/group were needed. Two pre-specified analyses were planned to be performed in patients with diabetes and those with high surgical risk according to Parsonnet score and EuroSCORE. All analyses were planned on the basis of the intention-to-treat principle (i.e., analyses were based on treatment groups as randomized).

Baseline descriptive statistics are presented as frequencies and percentages for categorical variables and mean ± SD or median (interquartile range) for continuous variables. The differences between the groups were assessed with the chi-square test or Fisher exact test for categorical data and Student *t* test for continuous data. Survival analysis was made by applying the Kaplan-Meier method. Differences in survival parameters were assessed for significance, and relative risks (RRs) were calculated by means of the log-rank test. The noninferiority hypothesis was formally checked only for the primary end point in the overall population. In this respect, a 1-sided p value <0.05 was considered significant; otherwise, a 2-tailed p value <0.05 was considered to indicate statistical significance. Statistical software S-PLUS version 4.5 (S-PLUS, Insightful Corp., Seattle, Washington) was used for all analyses.

Results

Patient population. Between July 2005 and June 2007, a total of 607 patients undergoing PCI for uLMCA stenosis were enrolled and randomly assigned to receive either PES or SES (Fig. 1). Table 1 shows the baseline characteristics of patients, which were comparably distributed between the 2 treatment groups. One-fourth of the patients were women, and nearly 30% of them had diabetes. One-half of the patients in both groups presented with acute coronary syndrome. The proportion of high-risk surgical candidates was similar in both groups: Parsonnet score >15 in 35.0% of patients assigned to receive PES and 29.2% of patients assigned to receive SES (p = 0.12); EuroSCORE ≥6 in 37.0% and 31.8%, respectively (p = 0.17). Therapy at discharge was virtually the same for both groups, with

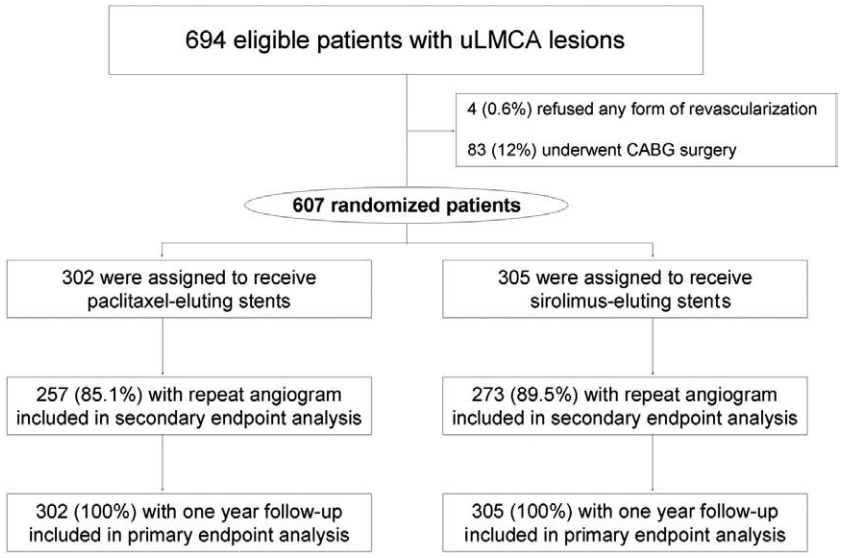

Figure 1 Study Flow Chart

CABG = coronary artery bypass graft; uLMCA = unprotected left main coronary artery.

approximately 95% of patients receiving statin and beta-blocker drugs, as shown in Table 1.

Two-thirds of the patients had 3-vessel disease, and in nearly 15% the dominant right coronary artery was occluded. The localization of stenosis within the LMCA area was virtually the same, with 63% of patients having distal stenosis in both groups. Implantation of the assigned stent was successful in all patients. Both groups were well-matched with regard to procedural characteristics as shown in Table 2. No differences were observed in the PCI technique used for uLMCA stenting: 50% of patients in both groups underwent single stenting, and 49% of patients

Table 1 Baseline Characteristics and Therapy at Discharge

Characteristics	PES (n = 302)	SES (n = 305)	p Value
Age, yrs	68.8 ± 10.1	69.3 ± 9.34	0.74
Women	77 (25)	62 (20)	0.13
Arterial hypertension	210 (70)	209 (69)	0.79
Hypercholesterolemia	237 (78)	229 (75)	0.32
Diabetes mellitus	90 (30)	86 (28)	0.66
Insulin-requiring	31 (10)	23 (8)	0.24
Oral drug-requiring	42 (14)	41 (13)	0.87
On diet only	17 (6)	22 (7)	0.43
Current smoker	31 (10)	30 (10)	0.86
Body mass index, kg/m^2	27.0 ± 4.1	27.1 ± 3.8	0.74
Acute coronary syndrome	132 (44)	121 (40)	0.31
History of myocardial infarction	77 (25)	84 (28)	0.57
History of percutaneous coronary intervention	139 (46)	153 (50)	0.31
Creatinine serum level, mg/dl	1.08 ± 0.81	1.06 ± 0.52	0.81
Malignancies	30 (9.9)	31 (10.2)	0.92
Parsonnet score	12.8 ± 9.8	12.0 ± 9.1	0.42
EuroSCORE	4.7 ± 3.4	4.4 ± 3.2	0.25
Therapy at hospital discharge			
Statins	288 (95)	291 (95)	0.99
ACE inhibitors	263 (87)	261 (86)	0.59
AT1 receptor blockers	33 (11)	39 (13)	0.48
Beta-blockers	296 (98)	298 (98)	0.79

Data are presented as n (%) or mean ± SD.
ACE = angiotensin-converting enzyme; AT1 = angiotensin II type 1; PES = paclitaxel-eluting stent(s); SES = sirolimus-eluting stent(s).

Table 2 Angiographic and Procedural Characteristics

	PES (n = 302)	SES (n = 305)	p Value
Left ventricular ejection fraction, %	53.4 ± 12.8	54.4 ± 12.5	0.68
Vessel size of left main artery, mm	3.83 ± 0.56	3.78 ± 0.55	0.20
Coronary artery dominance			0.56
Right	236 (78)	224 (80)	
Left	41 (14)	33 (11)	
Balanced	25 (8)	28 (9)	
Three-vessel disease	213 (71)	225 (74)	0.37
Occluded right coronary artery	41 (14)	46 (15)	0.60
Trifurcation morphology	75 (25)	74 (24)	0.85
Localization of left main lesion			0.82
Ostium	37 (12)	33 (11)	
Midshaft	74 (25)	79 (26)	
Distal	191 (63)	193 (63)	
Stenting technique			0.89
Single stenting	148 (49)	154 (51)	
T-stenting	5 (2)	4 (1)	
Culotte stenting	149 (49)	147 (48)	
Kissing balloon technique	152 (50)	151 (50)	0.84
Intra-aortic balloon pump	4 (1)	4 (1)	0.99
Abciximab administration	26 (9)	33 (11)	0.34
Bivalirudin administration	46 (15)	50 (16)	0.69

Data are presented as n (%) or mean ± SD.
Abbreviations as in Table 1.

assigned to receive PES versus 48% of patients assigned to receive SES underwent culotte-stenting (p = 0.89). Sixty-six percent of patients with distal lesions received 2 stents; 98% of them received implantation with the "culotte" technique. Final kissing balloon inflation was used in 50% of all patients but in 90% of those patients who received 2 stents. Rotational atherectomy was used in <1% of the cases. Intravascular ultrasound was not used in this study, either during the procedure or at follow-up. Additional PCI of at least 1 lesion outside the LMCA area was performed in 63 patients (21%) assigned to receive PES and in 65 patients (21%) assigned to receive SES (p = 0.89).

Clinical outcomes. The incidence of definite stent thrombosis was 0.3% in the PES group (1 patient had stent thrombosis 10 days after PCI while taking dual antiplatelet therapy) and 0.7% in SES group (1 patient had stent thrombosis 3 days and another 10 days after PCI, both while taking dual antiplatelet therapy) (p = 0.57). All 3 cases of stent thrombosis were associated with ST-segment elevation MI and death, shortly after successful recanalization in 2 and failed intervention in 1. There was only 1 probable stent thrombosis in the SES group. That consisted of 1 sudden death at day 19 after enrollment.

Clinical follow-up at 12 ± 1 month was available for all patients, and respective outcomes are shown in Table 3. No significant differences were observed between the 2 stent groups in terms of death, MI, stroke, or repeat revascularization within 30 days. The incidence of the primary end point of death, MI, and TLR was 13.6% (95% confidence interval [CI]: 12.2% to 20.4%) in the PES and 15.8% (95% CI: 10.2% to 18.1%) in the SES group. This corresponds to a difference of −2.2% with an upper 95% CI of +2.7%. Accordingly, the null inferiority hypothesis for the PES was rejected (p < 0.001). Assignment to the paclitaxel-eluting stent group was thus associated with an RR of the primary end point of 0.85 (95% CI: 0.56 to 1.29). The incidence of death, MI, and stroke within 1 year was 5.0%, 5.0%, and 1.7%, respectively, in patients assigned to receive PES and 6.6%, 4.6%, and 1.0%, respectively, in patients assigned to receive SES. The cumulative incidence of death, MI, and stroke was similar in both groups: 9.6% in the PES and 10.2% in the SES group (RR: 0.95; 95% CI: 0.57 to 1.57, p = 0.83).

The primary end point was also analyzed in the prespecified subgroups of patients defined by diabetes and surgical risk status (Fig. 2). Among diabetic patients, the incidence of the primary end point was 13.5% in the PES and 19.8% in the SES group (RR: 0.65; 95% CI: 0.31 to 1.36, p = 0.26); in patients with Parsonnet score >15 the incidence of the primary end point was 17.0% in the PES and 26.0% in the SES group (RR: 0.62; 95% CI: 0.27 to 1.40, p = 0.25); in patients with EuroSCORE ≥6 the primary end point rate was 21.5% in the PES and 24.8% in the SES group (RR: 0.81; 95% CI: 0.46 to 1.42, p = 0.47).

At 2 years no differences were observed regarding Kaplan-Meier estimates of mortality, MI, and stroke, with 10.4%, 5.4%, and 2.1%, respectively, in patients assigned to receive PES and 8.7%, 4.6%, and 1.5%, respectively, in patients assigned to receive SES. Four patients (1.3%) in each group experienced a Q-wave MI. The cumulative incidence of death or MI was 14.5% in the PES group and 11.7% in the SES group (RR: 1.20; 95% CI: 0.76 to 1.90,

Table 3 Clinical Outcome

	PES (n = 302)	SES (n = 305)	RR (95% CI)	p Value
30 days				
Definite stent thrombosis	1 (0.3)	2 (0.7)	0.50 (0.04–5.29)	0.57
Probable stent thrombosis	0	1 (0.3)		0.32
Death	3 (1.0)	5 (1.6)	0.60 (0.14–2.49)	0.48
MI	13 (4.3)	11 (3.6)	1.19 (0.54–2.66)	0.66
Stroke	2 (0.6)	1 (0.3)	2.02 (0.19–21.27)	0.56
CABG	0	0		
Repeat PCI	1 (0.3)	2 (0.7)	0.50 (0.04–5.29)	0.57
TLR	1 (0.3)	2 (0.7)	0.50 (0.04–5.29)	0.57
Death or MI	15 (5.0)	14 (4.6)	1.08 (0.52–2.24)	0.83
Death, MI, or stroke	17 (5.6)	15 (4.9)	1.14 (0.57–2.29)	0.70
Death, MI, or TLR	15 (5.0)	14 (4.6)	1.08 (0.52–2.24)	0.83
1 yr				
Death	15 (5.0)	20 (6.6)	0.74 (0.38–1.45)	0.39
MI	15 (5.0)	14 (4.6)	1.08 (0.52–2.24)	0.83
Stroke	5 (1.7)	3 (1.0)	1.67 (0.40–6.90)	0.47
CABG	3 (1.0)	2 (0.7)	1.48 (0.25–8.78)	0.66
Repeat PCI	16 (5.5)	23 (7.8)	0.67 (0.36–1.27)	0.23
TLR	19 (6.5)	23 (7.8)	0.81 (0.44–1.47)	0.49
Death or MI	26 (8.7)	29 (9.5)	0.90 (0.53–1.53)	0.71
Death, MI, or stroke	29 (9.6)	31 (10.2)	0.95 (0.57–1.57)	0.83
Death, MI, or TLR	41 (13.6)	48 (15.8)	0.85 (0.56–1.28)	0.44
2 yrs				
Death	28 (10.4)	25 (8.7)	1.14 (0.66–1.95)	0.64
MI	16 (5.4)	14 (4.6)	1.15 (0.56–2.36)	0.69
Stroke	6 (2.1)	4 (1.5)	1.52 (0.43–5.34)	0.51
CABG	3 (1.0)	3 (1.0)	1.00 (0.20–4.97)	>0.99
Repeat PCI	22 (8.2)	30 (10.7)	0.68 (0.36–1.27)	0.23
TLR	25 (9.2)	30 (10.7)	0.82 (0.48–1.40)	0.47
Death or MI	40 (14.5)	34 (11.7)	1.20 (0.76–1.90)	0.43
Death, MI, or stroke	44 (15.9)	36 (12.3)	1.25 (0.81–1.94)	0.31
Death, MI, or TLR	59 (21.3)	60 (20.6)	0.98 (0.70–1.44)	0.96

Data are presented as n (%); percentages are Kaplan-Meier estimates.
CABG = coronary artery bypass graft surgery; CI = confidence interval; MI = myocardial infarction; PCI = percutaneous coronary intervention; RR = relative risk; TLR = target lesion revascularization; other abbreviations as in Table 1.

p = 0.43). The cumulative incidence of death, MI, or stroke was 15.9% in the PES group and 12.3% in the SES group (RR: 1.25; 95% CI: 0.81 to 1.94, p = 0.31) Moreover, no differences were observed in the combined incidence of death, MI, and TLR, with 21.3% in patients assigned to receive PES and 20.6% in patients assigned to receive SES (RR: 1.01; 95% CI: 0.70 to 1.44, p = 0.96) (Fig. 3). Three patients in each group (1.0%) underwent CABG for symptomatic restenosis. The incidence of TLR was also similar in the 2 groups: 9.2% for the PES group and 10.7% for the SES group (RR: 0.82; 95% CI: 0.48 to 1.40, p = 0.47). No new cases of stent thrombosis were observed over and above those that occurred during the first 30 days after randomization.

Angiographic restenosis. The median (interquartile range) interval to repeat coronary angiography was 196 (141 to 214) days. Follow-up angiography data were available for 257 (85.1%) patients in the PES group and 273 (89.5%) patients in the SES group (p = 0.10).

The incidence of binary angiographic restenosis—the secondary end point of the study—was not significantly different between the 2 stent groups: 16.0% (41 of the 257 patients) in the PES group and 19.4% (53 of the 273 patients) in the SES group (RR: 0.82; 95% CI: 0.57 to 1.19, p = 0.30). Restenosis was localized in the distal part of the left main area in all but 1 patient in the PES group and in all patients in the SES group. In the only patient without a distal restenosis, this complication was of ostial location.

Discussion

This study has 2 unique features: it is the largest specifically designed randomized study on the interventional treatment of uLMCA lesions and the first comparative evaluation in this lesion type of 2 different DES platforms that are commonly used in other types of coronary disease. The lack of an additional group treated with CABG obviously limits direct comparisons with this treatment option, which is currently the form of therapy with the most widespread use

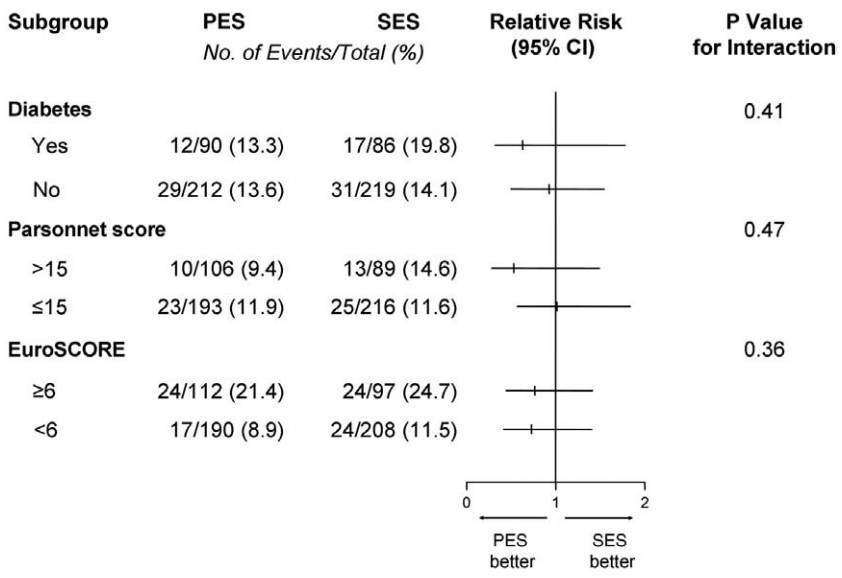

Figure 2 **1-Year Incidence and Relative Risk of the Primary End Point of Death, Myocardial Infarction, and Target Lesion Revascularization in Pre-Specified Subgroups**

Relative risks associated with the use of paclitaxel-eluting stents (PES) as compared with sirolimus-eluting stents (SES) are shown with their 95% confidence intervals (CIs).

among patients with uLMCA lesions. The main findings of the present study were that DES are associated with an excellent procedural success rate and are safe and efficacious in a large cohort of relatively nonselected patients with LMCA disease. In addition, there was no significant difference in outcomes achieved with the 2 DES types: the PES and the SES.

On the basis of results from a subgroup analysis confined to a subset of 91 patients with uLMCA disease from the randomized Veterans Administration Coronary Bypass Surgery Cooperative study (21) and 10-year follow-up data of 150 patients with uLMCA disease included in a meta-analysis of 7 randomized trials (22), CABG has been recommended as the standard treatment for such disease in contemporary guidelines (14).

The use of PCI has been limited to emergency or palliative indications in clinical situations considered unsuitable for surgery. Furthermore, the predilection of uLMCA disease for location in or close to the bifurcation makes PCI a real challenge for interventional cardiologists independent of the device type used (23). In our study, two-thirds of the patients presented with multivessel disease, more than 60% of them had distally localized lesions, and 50% of them underwent double stent implantation with culotte technique. Yet, stenting was successful in all patients, with a very infrequent use of intra-aortic balloon counterpulsation support. Usage of DES in bifurcation lesions has been reported to increase the rate of reduced coronary flow and peri-interventional thrombotic complications (24). This was not observed in our study cohort. Systematic use of 600-mg clopidogrel pre-treatment in our study might be 1 plausible explanation for this.

The low incidence of definite and probable stent thrombosis in our study and previous registries (25) supports the long-term safety of DES in uLMCA lesions. Moreover, the mortality rates of 1.3% at 30 days, 5.8% at 1 year, and 9.5% at 2 years compare very favorably with the ones observed in patients undergoing surgery for uLMCA disease. Old retrospective surgery studies have demonstrated mortality rates from 1.7% to 7.0% in-hospital and from 6% to 14% at 1 year (26–28). In the recently published MAIN-COMPARE (Revascularization for Unprotected Left Main Coronary Artery Stenosis: Comparison of Percutaneous Coronary Angioplasty versus Surgical Revascularization) registry, 3-year mortality was 8.3% among 1,138 consecutive patients who underwent CABG (13,29). Mortality findings from the present study compare well with these latter results, particularly when bearing in mind that the population of the MAIN-COMPARE registry was younger (62 years of age), presented less frequently with a history of MI (15%), had better left ventricular function (ejection fraction 62%), and had lower frequency of both multivessel disease (60%) and distal uLMCA lesion location (52%), as compared with the present study population. Moreover, the mortality rate at 1 year of 12.0% in high-risk surgical patients is also very similar to previously published data (30,31).

Notwithstanding the value of long-term outcomes after PCI, which are comparable to those shown for CABG in terms of hard safety end points such as mortality, death, and

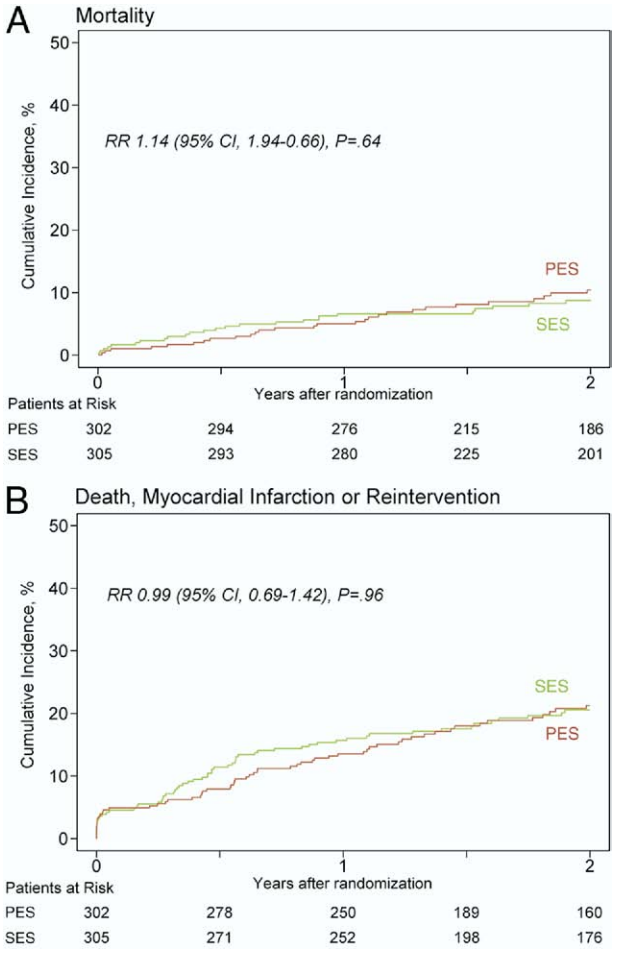

Figure 3 **2-Year Adverse Event Rates in the PES and SES Groups**

(A) Mortality. **(B)** Composite of death, myocardial infarction, and target lesion revascularization. RR = relative risk; other abbreviations as in Figure 2.

stroke, the frequency of need for repeat revascularization remains a constant concern with PCI techniques (2). Compelling evidence from large registries and randomized studies has demonstrated a consistent reduction in restenosis rates and need for repeat revascularization with PES and rapamycin-eluting stents (on the order of 70% to 80%) compared with BMS in lesions located outside the left main vessel (8,32). The only randomized study comparing paclitaxel-eluting stents with BMS in uLMCA lesions (33) showed a 2% revascularization rate with PES versus 16% with BMS. A systematic review of more than 1,200 patients with uLMCA lesions demonstrated a low revascularization rate of 6.5% with DES at a median of 10 months of follow-up (31). Other investigators have reported cumulative rates of TLR of 18.8% at 1 year and 20.7% at 3 years (34). The overall 2-year cumulative incidence of TLR of 10% (with CABG in only 1% of patients) observed in the present study emphasizes the efficacy of DES for uLMCA lesions. The impact of stenting technique in the subsequent risk of restenosis is not known for uLMCA lesions. However, the results achieved in this study might not be extrapolated to situations in which other stenting techniques are used to cover uLMCA lesions.

Interestingly, we did not see any significant difference in the risk of restenosis between the 2 DES used: PES and SES. This is in contrast with some previous studies and meta-analyses on lesions situated outside the left main coronary artery showing a higher risk of restenosis with PES (11,35). The difference might be explained by the larger size of the left main coronary artery, which might accommodate a larger degree of neointima formation without significant lumen obstruction (36). An additional factor might have been the availability of PES in sizes larger than SES, which is an advantage for large left main vessels. We should acknowledge that inclusion of protocol-mandated follow-up angiography might have exaggerated the TLR rates in both groups. Conversely, follow-up angiography should be regarded as an important precautionary measure to enable timely treatment of an asymptomatic left main artery restenosis in consideration of the still-limited experience with DES in uLMCA lesions. Importantly the overall adverse event rates observed in our study are comparable to those observed in the subgroup of patients with uLMCA lesions treated either with DES or CABG as part of a recent randomized trial comparing these 2 strategies in patients with left main or 3-vessel coronary artery disease (37). The lower-than-expected event rate in the present study inevitably reduces the power of the trial; yet, it still remains the largest randomized trial dedicated to the interventional treatment of LMCA disease.

Conclusions

The use of DES in uLMCA lesions in relatively unselected patients is feasible, safe, and effective. Two approved and commonly used DES platforms, the PES and SES, provide similar clinical and angiographic outcomes in this important patient group.

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Key Words: coronary artery disease ■ drug-eluting stents ■ left main coronary artery ■ paclitaxel ■ restenosis ■ sirolimus.

APPENDIX

For a list of participating centers and investigators, please see the online version of this article.