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A Randomized Comparison of Sirolimus- Versus Paclitaxel-Eluting Stent Implantation in Patients With Diabetes Mellitus

4-Year Clinical Outcomes of DES-DIABETES (Drug-Eluting Stent in patients with DIABETES mellitus) Trial

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Objectives We compared 4-year efficacy and safety of sirolimus-eluting stents (SES) and paclitaxel-eluting stents (PES) in patients with diabetes mellitus (DM).

Background Four-year comparison of SES with PES in diabetic patients has not been evaluated in a randomized manner.

Methods This prospective, multicenter, randomized study compared SES (n = 200) and PES (n = 200) implantation in diabetic patients. We evaluated 4-year major adverse cardiac events (MACE) including death, myocardial infarction (MI), and target lesion revascularization (TLR).

Results The 2 groups had similar baseline characteristics. At 2 years, TLR (3.5% vs. 11.0%, log-rank, $p < 0.01$) and MACE (3.5% vs. 12.5%, log-rank, $p < 0.01$) were significantly lower in SES versus PES group with no difference of death or MI. At 4 years there were no differences in death (3.0% vs. 5.0%, $p = 0.45$) or MI (1.5% vs. 1.0%, $p = 0.99$) between SES and PES group. The TLR (7.5% vs. 12.0%, log-rank, $p = 0.10$) and MACE (11.0% vs. 16.0%, log-rank, $p = 0.10$) were statistically not different between SES and PES group. At multivariate Cox regression, post-procedural minimal lumen diameter (hazard ratio [HR]: 0.44, 95% confidence interval [CI]: 0.24 to 0.81, $p < 0.01$), hypercholesterolemia (HR: 2.21, 95% CI: 1.29 to 3.79, $p < 0.01$), and use of intravascular ultrasound (HR: 0.51, 95% CI: 0.26 to 0.99, $p = 0.049$) were independent predictors of 4-year MACE.

Conclusions Superiority of SES over PES during 2 years was attenuated between 2 years and 4 years in diabetic patients. Use of intravascular ultrasound and larger post-procedural minimal lumen diameter were independent predictors of the improved long-term clinical outcomes. (J Am Coll Cardiol Intv 2011;4:310–6) © 2011 by the American College of Cardiology Foundation

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Diabetic patients are known to have poor long-term outcomes after bare-metal stent (BMS) implantation compared with nondiabetic subjects because of unfavorable coronary anatomy with small and diffusely diseased vessels and exaggerated neointimal hyperplasia after BMS implantation (1–4). Recently, a randomized study and registry showed that drug-eluting stent (DES) implantation significantly reduced angiographic restenosis and 2-year clinical cardiac events compared with BMS in diabetic patients (5–7); however, presence of diabetes mellitus (DM) has still been associated with an increased risk of restenosis and unfavorable clinical outcomes in the era of BMS or DES (8–12). Recently, the relative efficacies of sirolimus-eluting stents (SES) and paclitaxel-eluting stents (PES) in patients with DM have been evaluated in randomized and registry studies (13–18). Previous studies found SES to have greater efficacy than PES in diabetic patients for limited follow-up duration (16,17), and we also previously performed a randomized, multicenter, prospective study showing that SES is superior to PES in reducing angiographic restenosis and 9-month and 2-year cardiac events, mainly driven by reduction in need of repeat revascularization (DES-DIABETES [Drug-Eluting Stent in patients with DIABETES mellitus] trial) (18,19). However, the longer-term (>2 year) efficacy and safety of SES over PES remain controversial. Therefore, to compare longer-term (>2 year) efficacy and safety of 2 DES (SES and PES) in patients with DM, we report the 4-year clinical results of the patients included in the DES-DIABETES trial.

Methods

Patient selection. The design, exclusion and inclusion criteria, and the data collection of the DES-DIABETES trial have been previously described (18). In brief, this randomized study included 400 patients ≥18 years of age with angina pectoris and/or a positive stress test and a native coronary lesion. The study involved 5 cardiac centers in Korea between May 2005 and March 2006. Patients were considered eligible if they had DM, presented with angina pectoris or had a positive stress test, or met both criteria and had clinically significant angiographic stenosis in a native coronary vessel with a diameter stenosis ≥50% and visual reference diameter ≥2.5 mm. Patients were excluded if they had contraindication to aspirin, clopidogrel, or cilostazol; left main disease (diameter stenosis ≥50% by visual estimate); graft vessel disease; left ventricular ejection fraction <30%; recent history of hematologic disease or leukocyte count <3,000/mm^3 and/or platelet count <100,000/mm^3; hepatic dysfunction with aspartate aminotransferase or alanine aminotransferase ≥3× the upper normal reference limit; history of renal dysfunction or serum creatinine level ≥2.0 mg/dl; serious noncardiac comorbid disease with a life expectancy <1 year; planned bifurcation stenting in the side branch; primary angioplasty for acute myocardial infarction (MI) within 24 h; or inability to follow the protocol. In patients with multiple lesions fulfilling the inclusion and exclusion criteria, the first stented lesion was considered as target lesion. The institutional review board at each participating center approved the protocol. All patients provided written informed consent.

Randomization and procedures. Once the guidewire had crossed the target lesion, patients were randomly assigned in a 1:1 ratio to SES or PES implantation. After DES randomization, patients were randomly allocated in a 1:1 ratio to the triple antiplatelet group (aspirin, clopidogrel, and cilostazol [triple group], n = 200) or the dual antiplatelet therapy (aspirin and clopidogrel [standard group], n = 200) (antiplatelet arm) on the basis of a 2 × 2 factorial design with a computer-generated randomization sequence. Random assignments were stratified according to participation sites and blocked, with block size of 4 or 6, and were distributed in sealed envelopes to each participating center. The block size was concealed. From at least 24 h before the procedure and thereafter, all patients received aspirin (200 mg daily) and clopidogrel (loading dose of 300 mg, followed by 75 mg daily for at least 6 months). Patients in the triple group received a loading dose of 200 mg cilostazol immediately after the procedure and 100 mg twice/day for 6 months.

Abbreviations and Acronyms

BMS = bare-metal stent(s)
CI = confidence interval
DES = drug-eluting stent(s)
DM = diabetes mellitus
HR = hazard ratio
MACE = major adverse cardiac event(s)
MI = myocardial infarction
MLD = minimal lumen diameter
PES = paclitaxel-eluting stent(s)
SES = sirolimus-eluting stent(s)
TLR = target lesion revascularization
TVR = target vessel revascularization

Coronary stenting was performed with the standard technique. The decision of predilation or direct stenting was made by the operator. The use of intravenous glycoprotein IIb/IIIa inhibitors was at the discretion of the operators. A 12-lead electrocardiogram was obtained after the procedure and before discharge. Serum levels of creatine kinase, its myocardial band isoenzyme was assessed 8, 12, and 24 h after the procedure and thereafter if considered necessary.

Study end point and definitions. We evaluated 4-year clinical outcomes, including stent thrombosis, target vessel revascularization (TVR), and major adverse cardiac events (MACE) including death, MI, and target lesion revascularization (TLR). Q-wave MI was defined by the postprocedural presence of new Q waves of >0.04 s in 2 contiguous leads. Non–Q-wave MI was defined as a creatine kinase-myocardial band fraction >3× the upper limit of normal. Target lesion revascularization was defined as a repeat intervention (surgical or percutaneous) within the stent or in the 5-mm proximal or distal segments adjacent to the stent. Target vessel revascularization was defined as a

Table 1. Baseline Clinical and Characteristics

Variable	SES (n = 200)	PES (n = 200)	p Value
Age, yrs	61.1 ± 8.9	60.7 ± 8.8	0.62
Men	122 (61.0%)	110 (55.0%)	0.22
Hypertension	114 (57.0%)	124 (62.0%)	0.31
Treatment of diabetes mellitus			0.97
Dietary therapy alone	18 (9.0%)	19 (9.5%)	
Oral hypoglycemic agent	150 (75.0%)	148 (74.0%)	
Insulin	32 (16.0%)	33 (16.5%)	
Glycosylated hemoglobin	7.7 ± 1.8%	7.8 ± 1.6%	0.68
Total cholesterol ≥200 mg/dl	55 (27.5%)	63 (31.5%)	0.38
Current smoker	54 (27.0%)	57 (28.5%)	0.74
Previous PCI	25 (12.5%)	25 (12.5%)	0.99
Previous CABG	4 (2.0%)	3 (1.5%)	0.99
Clinical diagnosis			0.10
Stable angina	86 (43.0%)	82 (41.0%)	
Unstable angina	80 (40.0%)	67 (33.5%)	
Acute myocardial infarction	34 (17.0%)	51 (25.5%)	
Left ventricular ejection fraction, %	59 ± 10	58 ± 10	0.37
Multivessel disease	119 (59.5%)	137 (68.5%)	0.17

Values are expressed as mean ± SD or n (%).
CABG = coronary artery bypass surgery; PCI = percutaneous coronary intervention; SES = sirolimus-eluting stent(s).

reintervention of a lesion in the same epicardial vessel. Target lesion revascularization or TVR was considered clinically driven if prompted by symptoms consistent with myocardial ischemia, preceded by an abnormal stress test result consistent with myocardial ischemia, if there were other electrocardiographic changes consistent with myocardial ischemia, or if the lesion diameter stenosis was more than 70% at follow-up (20). Stent thrombosis was defined as any of the following after the procedure: angiographic documentation of stent occlusion with or without the presence of thrombus associated with an acute ischemic event, unexplained sudden death, or MI not clearly attributable to another coronary lesion (21,22).

Coronary angiograms were obtained after intracoronary nitroglycerin administration. Procedure (baseline), post-procedure, and follow-up angiograms were submitted to the angiographic core analysis center (Asan Medical Center, Seoul, Korea). Digital angiograms were analyzed with an automated edge detection system (CASS II, Pie Medical, Maastricht, the Netherlands). The core laboratory was blinded to the treatment assignment.

Follow-up. Repeat coronary angiography was mandatory at 6 months after stenting or earlier if indicated by clinical symptoms or evidence of myocardial ischemia. Clinical follow-up visits were scheduled at 30, 90, 180, and 270 days after procedure and every 3 months thereafter. At every visit, physical examination, electrocardiogram, cardiac events, angina recurrence, and medication were monitored. At each participating center, patient data were recorded prospectively on standard case report forms and gathered in the central data management center (Asan Medical Center). All adverse clinical events were adjudicated by an independent events committee blinded to the treatment groups.

Statistical analysis. Analyses of 2 groups were performed according to the intention-to-treat principle. Continuous variables are presented as mean ± SD and compared with Student unpaired *t* or Mann–Whitney *U* tests. Categorical variables are presented as numbers or percentages and were compared with chi-square or Fisher exact tests. The rate of cardiac events during 4-year follow-up period was analyzed with the Kaplan-Meier analyses, and the difference between rates was assessed by the log-rank, test. Cox proportional hazards models were used to examine the association of stent type with the risks of clinical events. The proportional-hazards assumptions of the models were violated, because TLR and MACE rate were exactly opposite before and after the 2-year time point. Thus, to evaluate the events of the first 2 years (<2 years after implantation) and of the second 2 years (≥2 years after implantation), time-dependent Cox model were performed with interaction of stent type and I (time ≥2 years), where I(·) is indicator function. Furthermore, to evaluate very late-occurring events (≥2 years after implantation), a landmark analysis was performed with a pre-specified landmark time point at 24 months. Patients who survived without MI or revascularization during the initial 24 months were included in this analysis. Univariate and multivariable Cox proportional hazards models were used to examine the predictor of cardiac event. All variables in Tables 1 and 2 were tested, and variables with a p value

Table 2. Angiographic Characteristics and Procedural Results

Variable	SES (n = 200)	PES (n = 200)	p Value
Reference diameter, mm	2.80 ± 0.43	2.80 ± 0.43	0.96
Lesion length, mm	25.8 ± 12.9	27.2 ± 14.2	0.34
Stented length, mm	32.52 ± 13.9	33.2 ± 15.2	0.67
Target vessel			0.71
Left anterior descending artery	122 (61.0%)	118 (59.0)	
Left circumflex artery	28 (14.0%)	25 (12.5%)	
Right coronary artery	50 (25.0%)	57 (28.5%)	
Procedure-related non–Q MI	16 (8.0%)	18 (9.0%)	0.72
Maximal inflation pressure, atm	15.4 ± 3.6	14.6 ± 3.6	0.03
Use of intravascular ultrasound	67 (33.5%)	64 (32.0%)	0.75
Use of glycoprotein IIb/IIIa inhibitor	11 (5.5%)	7 (3.5%)	0.47
Pre-dilation before stenting	194 (97.0%)	190 (95.0%)	0.45
Post-stenting adjunctive balloon dilation	97 (48.5%)	87 (43.5%)	0.32
Largest balloon size for adjunctive dilation, mm	3.18 ± 0.43	3.25 ± 0.42	0.10
Multivessel stenting	64 (32.0%)	69 (34.5%)	0.60
Number of used stents at the target lesion	1.28 ± 0.49	1.28 ± 0.56	0.94

Values are expressed as mean ± SD or n (%).
MI = myocardial infarction; other abbreviations as in Table 1.

≤0.10 in univariate analyses were candidates for the multivariable Cox proportional hazards models. A backward elimination process was used to develop the final multivariable model, and adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated. Schoenfeld residuals test was used to verify that the proportional-hazards assumptions were not violated (23).

All p values were 2-sided, and $p < 0.05$ was considered significant. Statistical analysis was performed with SAS software (version 9.1, SAS Institute, Cary, North Carolina).

Results

Baseline characteristics of the patients. Table 1 shows the baseline clinical characteristics of the study groups. There were no significant differences between the 2 groups in baseline clinical characteristics or risk factors. Table 2 shows angiographic characteristics and procedural results. The 2 groups had similar anatomical and procedural characteristics.

Clinical outcomes. At 2 years, there was no difference in death or MI (Table 3). However, the rates of TLR (3.5% vs. 11.0%, log-rank, $p < 0.01$) and TVR (5.5% vs. 12.0%, log-rank, $p = 0.01$) were significantly lower in the SES than in the PES group. Clinically driven TLR (3.0% vs. 9.0%, log-rank, $p < 0.01$) and TVR (4.0% vs. 10.5%, log-rank, $p = 0.01$) rates were also significantly lower in the SES than in the PES group. The MACE rate was significantly lower in the SES than in the PES group (3.5% vs. 12.5%, log rank, $p < 0.01$), as was the composite of death, MI, or TVR (5.5% vs. 14.0%, $p < 0.01$). A 4-year clinical follow-up was performed in 97% of the study population (Table 3). Sixteen deaths (6 in SES patients and 10 in PES patients, $p = 0.45$) occurred. Myocardial infarction occurred in 3 SES and 2 PES patients ($p = 0.99$). During 4 years, 8 stent thromboses occurred in the SES group (1 acute, 7 very late) and 3 (3 very late) occurred in the PES group ($p = 0.22$). Of 10 very late stent thrombosis patients, 5 suffered from stent thrombosis during dual antiplatelet therapy. The rates of TLR (7.5% vs. 12.0%, log-rank, $p = 0.10$) and TVR (9.5% vs. 14.0%, log-rank, $p = 0.14$) were statistically not different between the SES and PES groups. Clinically driven TLR (7.0% vs. 9.5%, log-rank, $p = 0.29$) and TVR (8.0% vs. 12.0%, log-rank, $p = 0.15$) were also similar between the 2 groups. Incidence of MACE was also statistically not different between the SES and PES groups (11.0% vs. 16.0%, log-rank, $p = 0.10$), as was the composite of death, MI, or TVR (13.0% vs. 18.0%, log-rank, $p = 0.15$).

The Kaplan-Meier curves for TLR and MACE are depicted in Figure 1. The benefits of SES for reduction in TLR and MACE at 2 years were attenuated during long-term follow-up to 4 years. In landmark analysis from 2 years, the TLR and MACE rates tended to be higher in the SES group versus the PES group, but the difference did not reach statistical significance.

Table 3. Clinical Outcomes at 4 Years

Variable	SES (n = 200)	PES (n = 200)	p Value
2-yr outcomes			
Death	0	3 (1.5%)	0.25
Cardiac	0	2 (1.0%)	
Noncardiac	0	1 (0.5%)	
MI	1 (0.5%)	2 (1.0%)	0.99
Q-wave	0	2 (1.0%)	
Non–Q-wave	1 (0.5%)	0	
TLR	7 (3.5%)	22 (11.0%)	<0.01
Stent thrombosis	2 (1.0%)	0	0.50
Acute (<1 day)	1 (0.5%)	0	
Subacute (1 day–1 month)	0	0	
Late (1 month–12 months)	0	0	
Very late (>12 months)	1 (0.5%)	0	
TVR	11 (5.5%)	24 (12.0%)	0.01
Death/MI/TVR	11 (5.5%)	28 (14.0%)	<0.01
MACE (death/MI/TLR)	7 (3.5%)	25 (12.5%)	<0.01
>4-yr outcomes			
Death	6 (3.0%)	10 (5.0%)	0.45
Cardiac	5 (2.5%)	5 (2.5%)	
Noncardiac	1 (0.5%)	5 (2.5%)	
MI	3 (1.5%)	2 (1.0%)	0.99
Q-wave	0	2 (1.0%)	
Non–Q-wave	3 (1.5%)	0	
TLR	15 (7.5%)	24 (12.0%)	0.18
Stent thrombosis	8 (4.0%)	3 (1.5%)	0.22
Acute (<1 day)	1 (0.5%)	0	
Subacute (1 day–1 month)	0	0	
Late (1 month–12 months)	0	0	
Very late (>12 months)	7 (3.5%)	3 (1.5%)	
TVR	19 (9.5%)	28 (14.0%)	0.21
Death/MI/TVR	26 (13.0%)	36 (18.0%)	0.21
MACE (death/MI/TLR)	22 (11.0%)	32 (16.0%)	0.19

Cumulative incidence represents simple proportion of the events in the population.
MACE = major adverse cardiac event(s); TLR = target lesion revascularization; TVR = target vessel revascularization; other abbreviations as in Tables 1 and 2.

Predictor of clinical outcomes. Variables with a p value ≤0.10 in univariate analyses were candidates for the multivariable Cox proportional hazards models. In the final multivariable model, hypercholesterolemia, clinical diagnosis, post-procedural minimal lumen diameter (MLD), and use of intravascular ultrasound were tested. An independent predictor of 4-year TLR was post-procedural MLD (HR: 0.28, 95% CI: 0.14 to 0.57, $p < 0.01$). Post-procedural MLD (HR: 0.44, 95% CI: 0.24 to 0.81, $p < 0.01$), hypercholesterolemia (HR: 2.21, 95% CI: 1.29 to 3.79, $p < 0.01$), and use of intravascular ultrasound (HR: 0.51, 95% CI: 0.26 to 0.99, $p = 0.049$) were independent predictors of 4-year MACE.

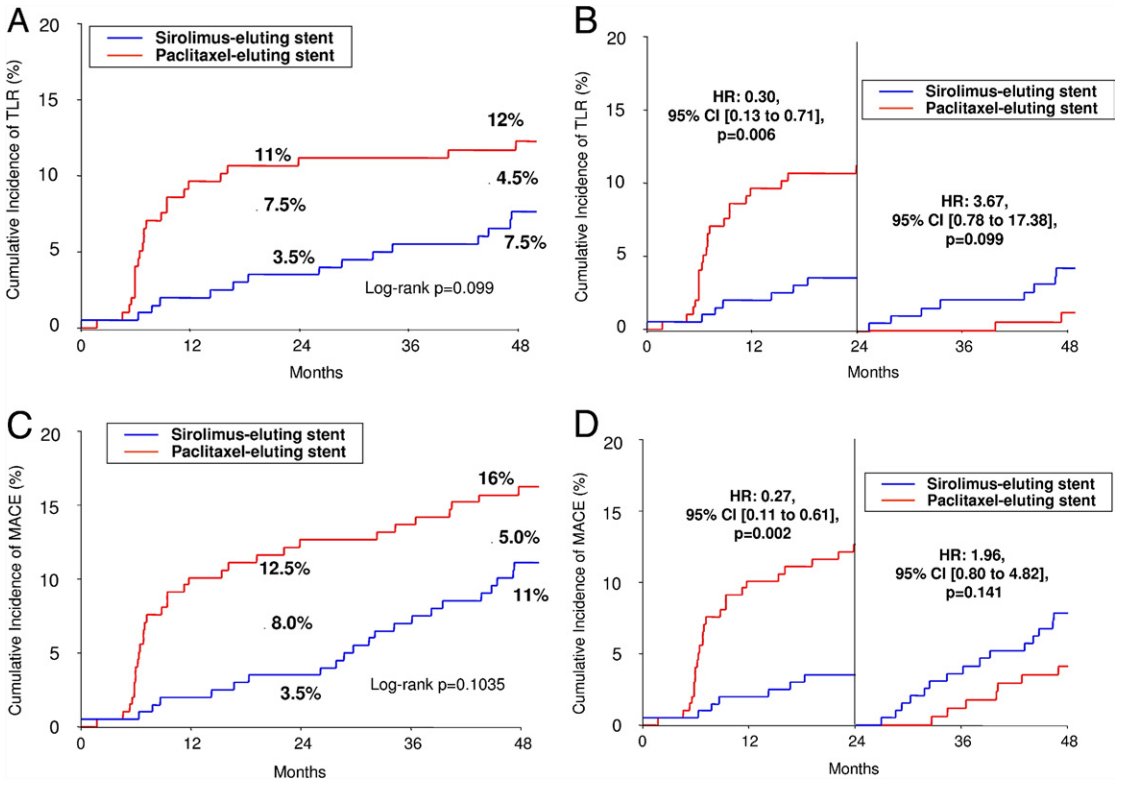

Figure 1. Kaplan-Meier Curves for Outcome According to Stent Type During 4-Year Follow-Up

(A) Cumulative incidence of 4-year target lesion revascularization (TLR). **(B)** Landmark analysis of TLR. Hazard ratios (HRs) of stent type were time-dependent before and after 2 years; p = 0.0054. **(C)** Cumulative incidence of major adverse cardiac events (MACE) (death, myocardial infarction, and TLR). **(D)** Landmark analysis of MACE (death, myocardial infarction, and TLR). The HRs of stent type were time-dependent before and after 2 years; p = 0.0013. CI = confidence interval.

Discussion

The major findings of this study are that: 1) the superiority of SES over PES in TLR and MACE at 2 years was attenuated during long-term follow-up to 4 years, with no differences in death or MI in diabetic patients; 2) use of intravascular ultrasound and larger post-procedural MLD were independent predictors of improved long-term clinical outcomes; and 3) 10 (2.5%) cases of very late stent thrombosis occurred, suggesting that more optimal stent implantation, DES with biocompatible polymer, bioabsorbable DES, or more effective antiplatelet therapy might be needed to improve long-term clinical outcomes.

Restenosis and subsequent TLR in diabetic patients are still important and persist, albeit to a lesser extent, with DES. Until recently, there have been heterogeneous results of clinical outcomes with SES versus PES in diabetic persons (13–18). Recently, we reported the results of the DES-DIABETES study (18), confirming the findings of the ISAR-DIABETES (Intracoronary Stenting and Angiographic Results: Do Diabetic Patients Derive Similar Benefit from Paclitaxel-Eluting and Sirolimus-Eluting Stents) study (16), which showed that SES significantly reduced restenosis with statistically insignificant reduction of repeat revascularization compared with PES in diabetic patients. The DES-DIABETES trial added the statistical significance in reduction of repeat revascularization as well as angiographic restenosis. We also reported that superiority of SES over PES in risks of TLR and MACE was maintained up to 2 years in the DES-DIABETES trial (19).

In the present study, we found that the superior clinical results of SES over PES at 2 years in terms of reduction in TLR and MACE were no longer apparent at 4 years, because late TLR increased more for SES than PES between 2 and 4 years. In the SIRTAX (Sirolimus-Eluting Versus Paclitaxel-Eluting Stents for Coronary Revascularization) LATE trial (24), clinical superiority of SES over PES at 1 year in TLR and MACE was lost during 5-year follow-up, mainly driven by insignificantly higher repeat revascularization in the SES group between 1 year and 5 years. These findings were explained by 5-year angiographic follow-up study of the SIRTAX LATE trial, in which superiority of 8-month in-stent late loss in SES versus PES

(0.12 ± 0.36 mm vs. 0.25 ± 0.49 mm, $p < 0.001$) was no longer apparent at 5-year follow-up angiography between SES and PES groups (0.30 ± 0.51 mm vs. 0.37 ± 0.51 mm, $p = 0.21$). Higher late loss between 8 months and 5 years in the SES versus PES groups of the SIRTAX LATE trial might explain our results of higher late TLR of the SES versus PES group between 2 and 4 years. These findings suggest that the restenosis process after DES implantation is delayed and late loss continuously increases.

By multivariate analysis, post-procedural MLD was identified as a predictor of 4-year TLR and MACE. Post-procedural MLD has been known as the predictor of angiographic restenosis (25) in diabetes and in real practice with different complex lesions (26). Because late restenosis (beyond 6 months) after DES implantation resulted mostly from neointimal hyperplasia (4,25,27), binary restenosis and need for revascularization might be more likely to occur in patients with smaller post-procedural MLD. Therefore, achievement of larger post-procedural MLD improved the 4-year clinical outcomes in diabetic patients.

In our study, there was no difference in the incidence of death (3.0% vs. 5.0%, $p = 0.45$) or MI (1.5% vs. 1.0%, $p = 0.99$) between the SES and PES groups. These findings are consistent with a network meta-analysis of 38 trials showing no differences in the risks of death or MI for SES, PES, and BMS patients for up to 4 years (28) and the SIRTAX LATE trial (24). However, stent thrombosis continuously occurred during the follow-up period. In our study, very late stent thrombosis occurred in 10 patients (2.5%). Of these, 5 patients suffered from stent thrombosis during dual antiplatelet therapy. Furthermore, 29% (10 of 34) of MACE between 1 year and 4 years of overall population was associated with very late stent thrombosis, which is consistent with the previous study (29). Recently, 1 study found that very late stent thrombosis after DES implantation was related to stent malapposition (73.9%), probably due to inflammatory response to the polymer and disease progression with neointimal rupture (43.5%) (30). These results underlie the importance of aggressive medical treatment, optimal stent implantation, development of DES with biocompatible or bioabsorbable polymers, or bioabsorbable DES (31–33).

Study limitations. First, stress tests to detect myocardial ischemia were not routinely performed during the 4-year follow-up. Considering that silent myocardial ischemia occurs in >1 in 5 asymptomatic patients with type 2 diabetes in the DIAD (Detection of Ischemia in Asymptomatic Diabetics) study (34), there might be a possible bias associated with clinical decisions related to TLR. Second, our study was initially designed to find the difference of angiographic restenosis between SES and PES at 6-month follow-up angiography. Therefore this study is underpowered to evaluate the differences in TLR, MACE, stent thrombosis, death, or MI. However, this study is a randomized and dedicated study for diabetic patients, and the results clearly showed that superiority of SES over PES up to 2 years in TLR and MACE was attenuated at 4-year follow-up. These findings give us the message that the 2 first-generation DES have a similar efficacy during long-term follow-up in diabetic patients. Third, our multivariable model might be overfitted on the basis of the small numbers of end point events.

Conclusions

The superiority of SES over PES in TLR and MACE at 2 years was attenuated during long-term follow-up to 4 years with no differences in death or MI in diabetic patients. Post-procedural MLD served as an independent predictor of 4-year TLR and MACE. A substantial number (29%) of MACE after first-generation DES was related to very late stent thrombosis during long-term follow-up.

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