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ORIGINAL ARTICLE
Cardiovascular Intervention

Efficacy of Paclitaxel-Eluting Stent in Patients With Impaired Glucose Tolerance

– Comparison With Sirolimus-Eluting Stent –

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Background: Experimental and clinical studies have shown that paclitaxel-eluting stent (PES) attenuates the effect of diabetes on re-stenosis after percutaneous coronary intervention. Although impaired glucose tolerance (IGT) is a pre-diabetic phase characterized as post-prandial hyperglycemia and hyperinsulinemia, the efficacy of PES in these pre-diabetic patients remains unknown. The purpose of the present study was therefore to compare the efficacy of PES in IGT patients with that of sirolimus-eluting stent (SES).

Methods and Results: A total of 370 IGT patients with coronary artery disease were examined (SES, n=229; PES, n=141). The incidence of major adverse cardiovascular events (MACE; all-cause death, non-fatal myocardial infarction or repeat revascularization) was compared between the 2 groups. The PES group had lower body mass index, total cholesterol and low-density lipoprotein cholesterol levels and higher prevalence of previous myocardial infarction than the SES group. The incidence of repeat revascularization in the PES group was similar to that in the SES group (22% vs. 19%, P=0.71). The incidence of hard cardiac events such as all-cause death and non-fatal myocardial infarction were also similar between the 2 groups. Finally, there were no significant differences in MACE between the SES and PES groups (23% vs. 21%, P=0.76).

Conclusions: In patients with IGT, the efficacy of PES was similar to that of SES, and any advantage of PES over SES was not observed in these pre-diabetic patients. (*Circ J* 2011; **75:** 868–873)

Key Words: Coronary artery disease; Impaired glucose tolerance; Paclitaxel-eluting stent; Percutaneous coronary intervention; Sirolimus-eluting stent

The sirolimus-eluting stent (SES) and paclitaxel-eluting stent (PES) are the first 2 drug-eluting stents (DES) to be approved by the Food and Drug Administration. These 2 DES have revolutionized interventional cardiology dramatically by the reduction of re-stenosis after percutaneous coronary intervention (PCI).[1,2] In addition, there is growing evidence for the usage of DES in various patient subsets including those with small vessel, diffuse lesion and diabetes.[3–8] A recent experimental study has shown that paclitaxel effectively inhibits smooth muscle cell proliferation and migration in hyperglycemic and insulin resistance conditions more than does rapamycin.[9] Some clinical studies also showed that PES attenuated the effect of diabetes on re-stenosis after PCI.[10,11] Thus, PES seems to have a more effective anti-restenotic effect in diabetic patients than SES.

Impaired glucose tolerance (IGT) is a pre-diabetic phase characterized as post-prandial hyperglycemia and insulin resistance. Previous studies have shown that IGT is an independent risk factor for cardiovascular disease, and IGT patients have more advanced coronary artery disease (CAD) such as small vessel and diffuse coronary narrowing compared with normoglycemic patients.[12–15] Considering the potential biologically and pharmacologically superior effect of paclitaxel over sirolimus in diabetic patients, PES may be a more effective DES even in patients with IGT than SES. There are few data, however, on the long-term efficacy of SES and PES in IGT patients with CAD. The purpose of the present study was therefore to compare the clinical efficacy of PES with SES in IGT patients.

Methods

Study Population

From August 2004 to December 2007, a total of 3,105 patients with CAD were treated with DES in the Department of Cardiology, National Cardiovascular Center, Osaka, and these

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Table 1. Baseline Characteristics

	SES (n=229)	PES (n=141)	P value
Age (years)	68±10	73±8	0.0003
Male, n (%)	199 (87)	113 (80)	0.09
BMI (kg/m²)	24.5±3.1	22.5±4.0	<0.0001
Stable AP, n (%)	131 (57)	72 (51)	0.04
Unstable AP, n (%)	98 (43)	69 (49)	0.003
Previous MI, n (%)	69 (29)	54 (38)	<0.0001
Coronary risk factors			
Hypertension, n (%)	179 (78)	125 (89)	0.06
Hyperlipidemia, n (%)	156 (68)	104 (74)	0.19
Smoking, n (%)	89 (39)	37 (26)	0.11
Family history of CAD, n (%)	60 (26)	31 (22)	0.28
Peripheral vessel disease, n (%)	21 (9)	17 (12)	0.74
Stroke, n (%)	32 (14)	8 (6)	0.24
Serum creatinine, n (%)	1.1±1.5	1.2±1.4	0.15
Glycemic profile			
Fasting plasma glucose (mg/dl)	95±11	92±9	0.09
2-h plasma glucose (mg/dl)	167±16	164±17	0.30
Fasting IRI (mg/dl)	6.2±3.4	8.4±11.8	0.09
2-h IRI (mg/dl)	99±68	89±30	0.51
HbA_{1c} (%)	5.5±0.4	5.5±0.3	0.20
Lipid profile			
Total cholesterol (mg/dl)	187±39	170±29	0.0005
Triglyceride (mg/dl)	152±83	148±86	0.01
HDL cholesterol (mg/dl)	43±12	45±10	0.59
LDL cholesterol (mg/dl)	116±33	101±27	<0.0001
Medical treatment			
β-blocker, n (%)	163 (71)	110 (78)	0.41
Calcium-channel antagonist, n (%)	124 (54)	59 (42)	0.12
ACE inhibitor, n (%)	55 (24)	32 (23)	0.84
ARB, n (%)	87 (38)	42 (30)	0.10
Statin, n (%)	147 (64)	97 (69)	0.09

SES, sirolimus-eluting stent; PES, paclitaxel-eluting stent; BMI, body mass index; AP, angina pectoris; MI, myocardial infarction; CAD, coronary artery disease; IRI, immunoreactive insulin; HbA_{1c}, hemoglobin A_{1c}; HDL, high-density lipoprotein; LDL, low-density lipoprotein; ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker.

patients were prospectively enrolled in the DES registry. We included only the first PCI performed during the study period. Of these, the following patients were excluded from the present study: patients with cardiogenic shock, severe congestive heart failure at the time of enrollment (class III or IV according to new York Heart Association), left main stenosis >50% in diameter, lesion located within a bypass graft conduit, acute ST-elevation myocardial infarction, any contraindication to PCI, intolerance or contraindication to ticlopidine or clopidogrel, serum creatinine >2.0 mg/dl, patients treated with both BMS and DES or both SES and PES, and patients treated with balloon angioplasty, rotational atherectomy or directional coronary atherectomy alone. Moreover, patients in whom a 75-g oral glucose tolerance test (75 g-OGTT) was refused or could not be performed were excluded, and patients who were already diagnosed with diabetes mellitus and treated with diet therapy, anti-diabetic drugs or insulin therapy were also excluded. Finally, 1,233 patients with CAD underwent a 75 g-OGTT. Of these, 370 patients were diagnosed with IGT and included in this analysis. IGT was defined as a fasting plasma glucose level <126 mg/dl and a 2-h plasma glucose level ≥140 mg/dl but <200 mg/dl.[16] Informed consent was obtained from every patient before the procedures. This study was approved by the Institutional Review Board of the National Cerebral and Cardiovascular Center, Suita, Japan.

PCI

PCI was performed by the implantation of SES (Cypher, Cordis, Johnson & Johnson, Miami Lakes, FL, USA) or PES (Taxus, Boston Scientific). All procedural decisions including device selection and adjunctive pharmacotherapy were made at the discretion of the individual PCI operator. There were no differences in recommendations for the usage of SES and PES. Intravenous unfractionated heparin (10,000 IU) and intracoronary nitroglycerin (0.5 mg) were administered before the PCI. After stent implantation, high-pressure dilatation was done to ensure an acceptable angiographic result. Intravascular ultrasound (IVUS) was used according to the operator's decision. Success was defined as a residual stenosis of <20% without major complications (ie, acute myocardial infarction, need for emergent coronary artery bypass graft or repeat PCI, or death). All patients received 324 mg/day of aspirin for at least 24 h before the procedure. Dual anti-platelet therapy (aspirin 200 mg and ticlopidine 200 mg) was prescribed in all patients treated with SES for at least 3 months and with PES for at least 6 months. For the assessment of re-stenosis, exer-

Table 2. Angiography and PCI Characteristics

	SES (n=229)	PES (n=141)	P value
No. diseased vessels, n (%)			
1-vessel disease	103 (45)	55 (39)	0.51
2-vessel disease	71 (31)	59 (42)	0.47
3-vessel disease	55 (24)	27 (19)	0.51
Reference diameter (mm)	2.8±0.6	2.8±0.6	0.91
Lesion length (mm)	23±17	21±10	0.91
Minimum lesion diameter (mm)	0.6±0.5	0.6±0.4	0.88
Percent diameter stenosis (%)	72±14	70±12	0.85
ACC/AHA type B2/C lesion, n (%)	156 (68)	92 (65)	0.83
Post-PCI percent diameter stenosis (%)	4.1±4.1	4.3±4.9	0.81
Post-PCI minimum lesion diameter (mm)	2.7±0.3	2.7±0.5	0.84
Acute gain (mm)	2.1±0.5	2.1±0.4	0.95
Averaged stent length (mm)	26±13	24±11	0.80
Total stent length (mm)	47±31	44±33	0.78
Stent diameter (mm)	2.9±0.4	2.9±0.3	0.92
No. used stents per patient, n	2.6±1.3	2.5±1.2	0.88
LVEF (%)	50±9	49±11	0.90
Chronic total occlusion, n (%)	27 (12)	16 (11)	0.91
IABP, n (%)	7 (3)	4 (3)	0.84
IVUS, n (%)	211 (92)	130 (92)	0.86
Rotablator, n (%)	11 (5)	7 (5)	0.92

PCI, percutaneous coronary intervention; ACC/AHA, American College of Cardiology/American Heart Association; LVEF, left ventricular ejection fraction; IABP, intra-aortic balloon pump; IVUS, intravascular ultrasound. Other abbreviations see in Table 1.

cise test or stress scintigraphy was routinely performed at 6–8 months after PCI. If myocardial ischemia or ischemic symptoms were noted in this initial non-invasive testing, follow-up coronary angiography was performed.

Clinical Follow-up

Follow-up information was obtained either at the outpatient clinic, by review of the medical records, or via telephone interview. Follow-up was completed for all patients (follow-up rate, 100%). The primary endpoint was defined as the occurrence of any of major adverse cardiovascular events (MACE; defined as death due to all-cause death, non-fatal myocardial infarction or repeat revascularization by PCI or bypass surgery). We assessed all clinical endpoints occurring within 3 years of the index PCI.

Myocardial infarction was defined as evidence of 2 or more of the following: (1) typical chest pain >20 min not relieved by nitroglycerin; (2) serial electrocardiogram recordings showing changes from baseline in ST-T and/or Q-waves in 2 or more contiguous leads; (3) total serum creatine phosphokinase greater than 2 times the upper limit of normal. Repeat revascularization was defined as repeated PCI or coronary bypass surgery, which was performed due to the occurrence of re-stenosis or a new stenotic lesion. The occurrence of stent thrombosis was assessed using the definitions of the Academic Research Consortium.[17]

Statistical Analysis

The clinical and angiographic characteristics and the incidence of MACE were compared between the 2 groups. Continuous data are expressed as mean±SD. Comparison between the 2 groups was performed using the chi-square test (or the Fisher exact test) for categorical data. Analysis of variance was performed for continuous data. Event-free survival was estimated using the Kaplan–Meier method, and differences were assessed using the log-rank test. To investigate the predictor for the occurrence of MACE, multivariate analyses were performed using a Cox proportional hazards model. All baseline clinical and angiographic characteristics (age, gender, coronary risk factor, glycemic and lipid profile, usage of each medication, multivessel disease, left ventricular ejection fraction, lesion complexity, reference diameter, lesion length, stent diameter, stent length and PCI to chronic total occlusion) were initially included for analysis. When verifying the analysis results with stepwise forward or backward Cox's regression, a P-value of 0.10 was used to exclude or include the variables. $P<0.05$ was considered to be statistically significant. All analyses were performed using SPSS 15.0 for Windows (SPSS, Chicago, IL, USA).

Results

Baseline Characteristics

Of the 370 patients with IGT, 229 patients were treated with SES, and 141 patients were treated with PES. The baseline clinical characteristics of these patients are summarized in Table 1. The PES group had lower body mass index and higher prevalence of previous myocardial infarction than the SES group. There were no significant differences in coronary risk factors and glycemic profile between the 2 groups. Total cholesterol and low-density lipoprotein cholesterol levels were significantly lower in the PES group compared with the SES group. The usage of each cardiovascular medication was similar between the 2 groups.

Angiography and PCI Characteristics

Table 2 lists the angiography and PCI characteristics in the 2 groups. There were no significant differences in these char-

Table 3. Cumulative Cardiovascular Events During 3-Year Follow-up

	SES (n=229)	PES (n=141)	P value
MACE, n (%)	48 (21)	32 (23)	0.76
All-cause death, n (%)	6 (3)	3 (2)	0.83
Non-fatal MI, n (%)	11 (5)	6 (4)	0.87
Repeat revascularization, n (%)	44 (19)	31 (22)	0.71
Target lesion revascularization, n (%)	18 (8)	17 (12)	0.70
New lesion revascularization, n (%)	27 (12)	23 (16)	0.89

MACE, major adverse cardiovascular event. Other abbreviations see in Table 1.

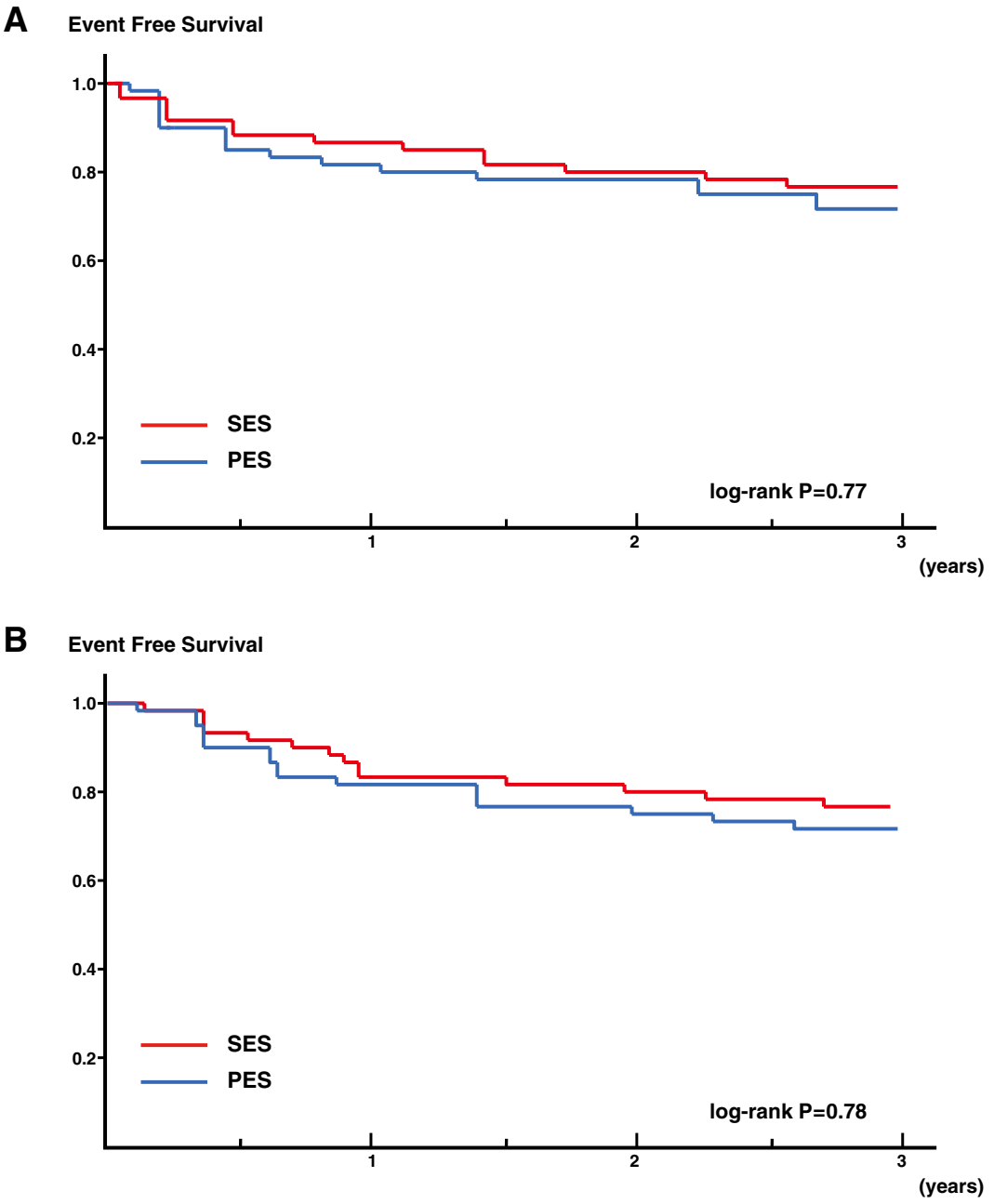

Figure. Kaplan–Meier curves for (**A**) freedom from repeat revascularization in patients treated with sirolimus-eluting stent (SES) and paclitaxel-eluting stent (PES); and (**B**) freedom from major adverse cardiovascular events in patients treated with SES and PES.

Table 4. Multivariate Analysis for Predictors of MACE

	HR (95%CI)	P value
Peripheral artery disease	1.446 (0.858–2.318)	0.28
Stroke	1.166 (0.746–1.756)	0.17
Triglyceride	0.996 (0.992–0.998)	0.04
LVEF	0.971 (0.965–0.984)	0.003
Multivessel disease	1.117 (1.069–1.358)	0.04

HR, hazard ratio; CI, confidence interval. Other abbreviations see in Tables 2,3.

acteristics between the SES and PES groups. In both groups, small reference diameter and long lesion length were observed. Due to these angiographic characteristics, long stents with a small stent diameter were used. The prevalence of AHA/ACC type B2/C lesion in the SES and PES groups was 68% and 65%, respectively. IVUS was frequently used (87–92%).

Clinical Outcomes

Table 3 lists the incidence of MACE and specific cardiovascular events during the 3-year follow-up period. The incidence of repeat revascularization in the PES group was similar to that in the SES group (Figure A). The incidence of target lesion revascularization, and the incidence of revascularization due to a development of new stenotic lesion were also comparable between the 2 groups. In the present study, 1 possible and 1 definite stent thrombosis could be observed. One patient was treated with multiple SES and in that patient sudden death occurred at 423 days despite the continuation of aspirin and ticlopidine. One patient treated with PES had a definite stent thrombosis after discontinuation of clopidogrel at 320 days. The incidence of stent thrombosis between the 2 groups was not statistically significant (SES, 0.4%; PES, 0.7%; P=0.258), and the incidence of hard cardiac events such as all-cause death or non-fatal myocardial infarction were also similar between the 2 groups. Finally, there was no significant difference in MACE between the SES and PES groups (Figure B).

Multivariate Analysis

We performed multivariate analyses to determine predictors for the occurrence of MACE (Table 4). Triglyceride level, multivessel disease and left ventricular ejection fraction were independent predictors for the occurrence of MACE, whereas stent type was not related to the occurrence of MACE.

Discussion

This is the first study with a 3-year follow-up that compares SES and PES in patients with IGT. In the present study, the efficacy of PES in patients with IGT was similar to that of SES, and any advantage of PES over SES could not be observed in these pre-diabetic patients.

Although some controversy may remain as regards which first-generation DES provides the greatest benefit in various patients, evidence has been accumulating that there is no major difference in safety and efficacy between SES and PES.[18–20] In contrast, in diabetic patients, some differences in biological and pharmacological effects of these 2 DES have been reported. Diabetes and insulin act via the PI3-kinase signal transduction pathway to upregulate the mammalian target of rapamycin (mTOR). Because rapamycin inhibits mTOR, thereby blocking cell division by interference of the cell cycle at the transition from G1 to S phase, the effects of rapamycin may be attenuated.[21,22] In contrast, paclitaxel, which acts via the microtubules, does not utilize mTOR or the PI3-kinase pathway to inhibit the cell cycle.[23] In addition, Patterson et al showed that mTOR blockade by rapamycin paradoxically induces AKT activation and enhances migration of vascular smooth muscle cells, and this phenomenon becomes even more striking under hyperglycemia and insulin resistance.[9] Considering these differences in the mechanism of action between rapamycin and paclitaxel, PES may have a theoretical advantage over SES in IGT patients. In the present study, PES was effective even in patients with IGT, similar to SES. There was, however, no clinical advantage of PES over SES. Other clinical studies also showed that these 2 DES had similar efficacy in diabetic patients.[24,25] In the pre-diabetic patients, the potential biological and pharmacological effects of paclitaxel may not produce any clinically superior effects compared with SES.

Recently there have been growing concerns about stent thrombosis after DES implantation. Hanna et al reported that the incidence of stent thrombosis for SES and PES at 3 years in a real-world population was 2.2% and 1.6%, respectively.[19] Although the incidence of stent thrombosis in the present study was relatively low (SES, 0.4%; PES, 0.7%) compared with that study, longer and careful follow-up is needed for confirmation of these results.

Study Limitations

This was a non-randomized, single-center retrospective analysis. This might have introduced a significant bias in patient and device selection. In the present study, baseline clinical, angiographic and PCI characteristics in the SES and PES groups were not associated with the occurrence of MACE. Therefore, that bias seems to be small in the present study.

The study population was relatively small compared with that in other clinical trials of DES, therefore use of a larger study population may have produced different results.

Because systematic angiographic follow-up was not performed, there is a possibility of underestimation of the clinical events such as the development of re-stenosis and/or new coronary artery stenosis. A recent study reported that routine angiographic follow-up increases oculostenotic revascularization of non-ischemic intermediate lesions without affecting the subsequent outcome.[26] Therefore, assessment of clinically driven repeat revascularization seems to be meaningful in the clinical setting.

Detailed data for various clinical parameters such as glucose and lipid profiles were not collected during the follow-up period. Therefore, the potential impact of those factors on clinical outcome could not be evaluated.

Conclusion

SES and PES are equally efficacious in patients with IGT, and any additional efficacy of PES over SES was not observed in the present study. With regard to efficacy, the present results indicate that SES and PES provide a similar favorable benefit in IGT patients.

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