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Sirolimus-eluting stent is superior to paclitaxel--eluting stent for coronary intervention in patients with renal insufficiency: Long-term clinical outcomes

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Abstract

Background: *Renal insufficiency (RI) is an independent risk factor for the adverse cardiovascular events. Long-term clinical outcome of percutaneous coronary intervention (PCI) in patients with RI is unknown especially in the era of first generation drug-eluting stents (DES). This study aims at comparing clinical outcomes between sirolimus-eluting stents (SES) and paclitaxel-eluting stents (PES) based on large scaled registry.*

Methods: *Patients who underwent PCI with DES from January 2004 to December 2009 in the Catholic University of Korea-PCI (COACT) registry were prospectively enrolled. A group of 1,033 patients with RI, defined as estimated glomerular filtration rate under 60 mL/min, were analyzed. Major adverse cardiac events (MACE), including all-cause death, non-fatal myocardial infarction (MI), target lesion revascularization (TLR), and target vessel revascularization (TVR) according to the type of stents were compared.*

Results: *Median follow-up period was 810 days (interquartile range: from 361 to 1,354 days). A group of 612 (59.2%) patients were treated with SES and 421 (40.8%) patients were treated with PES. The PES vs. SES group had significantly higher rate of MACE (35.9% vs. 28.3%, p = = 0.01). In multivariate Cox hazard regression analysis, PES vs. SES group had significantly higher rate of MACE (adjusted hazard ratio [AHR] 1.29, 95% confidence interval [CI] 1.02––1.64, p = 0.033), particularly pronounced by all-cause death (AHR 1.34, 95% CI 1.008–1.770; p = 0.044). In further analysis with propensity score matching, overall findings were consistent.*

Conclusions: *In patients with RI, PCI using PES provides poorer clinical outcomes than SES in terms of MACE and all-cause death.* (Cardiol J 2016; 23, 6: 637–646)

Key words: renal insufficiency, percutaneous coronary intervention, sirolimus--eluting stent, paclitaxel-eluting stent

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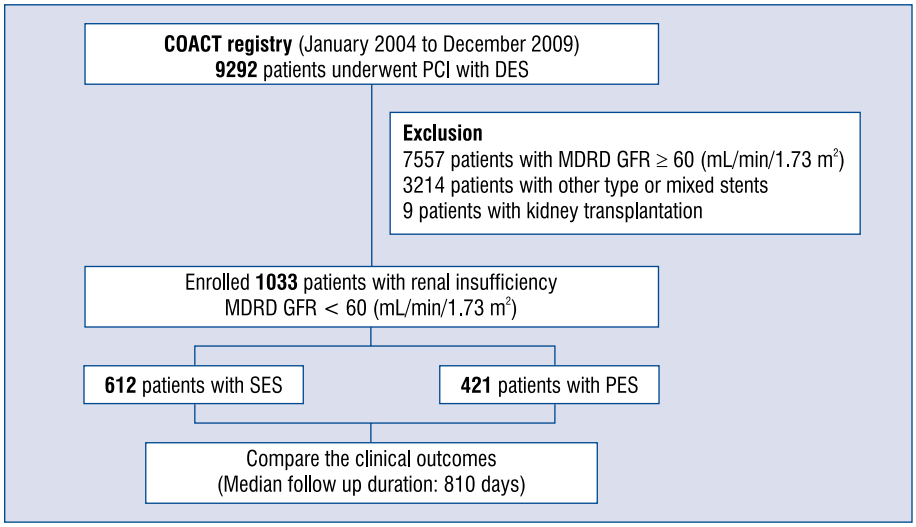

Figure 1. Study flow chart; COACT — CathOlic University of Korea: percutAneous Coronary inTervention; DES — drug eluting stents; GFR — estimated glomerular filtration rate; MDRD — Modification of Diet in Renal Disease; PCI — percutaneous coronary intervention; PES — paclitaxel-eluting stent; SES — sirolimus-eluting stent.

Introduction

Renal insufficiency (RI) is an independent risk factor for development of cardiovascular disease and death [1]. According to the clinical data in patients with RI, mild to severe degree of RI substantially increases the risk of major adverse cardiovascular events (MACE) after percutaneous coronary intervention (PCI) [2, 3]. While performing PCI in these patients, using the drug eluting stent (DES) is superior to using bare metal stent (BMS) in terms of mortality [4, 5] or in-stent restenosis [6]. However, there was paucity of data on the long-term efficacy and safety in performing PCI with different kinds of DES. Comparisons of clinical and angiographic outcomes concerning first generation DES performed in several randomized trials and meta-analyses [7] of 16 randomized trials report that sirolimus-eluting stents (SES) are superior to paclitaxel-eluting stents (PES) in terms of target vessel revascularization (TVR) and stent thrombosis. However, a recently published retrospective study [8] on moderate to severe RI suggests that the rates of MACE and all-cause death were similar in both stent groups. Controversy in these studies may result from different characteristics of enrolled subjects, especially decreased renal function and duration of follow-up suggesting that further studies are required in RI setting. Based on our large scaled registry containing "real-world" data of all-comers, we aimed to compare the long-term clinical outcomes between SES and PES in patients with RI.

Methods

Study population and COACT registry

The COACT (**C**ath**O**lic university of Korea — percut**A**neous **C**oronary in**T**ervention) registry is a large, prospective observational registry of demographic, clinical and procedural data, and short-term and long-term clinical outcome data of all patients undergoing PCI with the use of DES from 8 affiliated hospitals of The Catholic University of Korea between January 2004 and December 2009 [9]. All the hospitals perform high-volume PCI (> 500 PCI/year) and are located throughout the country. There was no industry involvement in the design, conduct, or analysis of the study. The institutional review boards at each hospital approved the study.

For the present study, 1,033 out of total 9,293 registered patients who had RI and underwent PCI with first generation DES (only SES or PES) were analyzed. Exclusion criteria were as follows: patients with normal renal function; patients underwent PCI by other type of DES except SES or PES; patients underwent PCI by mixed SES and PES; patients with kidney transplantation (Fig. 1).

PCI procedure and medical treatment

All patients except for those who previously received aspirin or thienopyridines were administered a loading dose of aspirin (300 mg), and clopidogrel 600 mg before PCI. The standard protocol for renoprotective regimens was pre-hydration with intravenous 0.9% NaCl saline infusion at

0.5–1 mL/kg/h according to the patients' condition (left ventricular ejection fraction, renal replacement therapy) the day before and after PCI procedure. Nephrotoxic agents including non-steroidal anti-inflammatory drugs, metformin, and diuretics were avoided before the procedure. N-acetylcysteine was not used routinely.

The procedure was performed through femoral or radial artery after administration of unfractionated heparin (100 U/kg). During the procedure, patients received unfractionated heparin to maintain an activated clotting time between 250 s and 300 s. The choice of stent was at each physician's discretion and the stent was deployed after balloon angioplasty. A successful PCI procedure was defined as decrease in minimum stenosis diameter to < 30% with thrombolysis in myocardial Infarction (TIMI) grade III flow on coronary angiogram. After discharge, patients continued receiving the same medications except for some intravenous or temporary medications.

Study definition and clinical follow-up

Renal insufficiency was defined as estimated glomerular filtration rate (GFR) < 60 mL/min/1.73 m^2 according to Modification of Diet in Renal Disease (MDRD) formula. The serum creatinine as a necessary laboratory finding for GFR by MDRD formula was obtained before index PCI. Clinical and laboratory data were collected by independent research personnel using electronic medical records. During study periods, the initial DES implanted date was defined as index PCI date, and the following clinical outcome was reviewed by local events committee of the Cardiovascular Center of Seoul St. Mary's Hospital, Seoul, Korea. For the complete data, censored data on survival were additionally obtained from telephone interviews and from the database of the National Health Insurance Corporation, Korea using a unique personal identification number.

The endpoints of the present study were the composite of MACE including all-cause death, non-fatal myocardial infarction (MI), TVR including target lesion revascularization (TLR). MI was defined as ischemic symptom with new ST segment change in electrocardiogram and elevated cardiac markers at least twice the upper limit of normal value. TLR was defined as ischemia-driven PCI of the target lesion resulting from restenosis or reocclusion within the stent or in the adjacent 5 mm of the distal or proximal segments [10]. TVR was also defined as ischemia-driven PCI or bypass of any segment of the epicardial coronary artery containing the target lesion [10]. Stent thrombosis was defined as the occurrence of a thrombotic event classified as definite, probable, or possible, according to the Academic Research Consortium definition [10]. All clinical outcomes of interest were confined by source document and centrally adjudicated at the Cardiovascular Center of Seoul St. Mary's Hospital, Seoul, Korea, by an independent group of clinicians who were unaware of patient's status. Clinical, angiographic, procedural, operative, or outcome data were collected in the dedicated PCI and surgical databases by independent research personnel. For validation of complete follow-up data, information on censored survival data was obtained to 31 December, 2010 from the database of the National Health Insurance Corporation, Korea, with the use of a unique personal identification number.

Statistical analysis

Continuous variables were presented as mean ± standard deviation and compared using independent t-test or Mann-Whitney U test. Categorical variables were presented as frequency with percentages (%) and compared by χ^2 test or Fisher's exact test. Kaplan-Meier survival curves for cumulative survival were drawn and compared by log-rank test.

To reduce the impact of treatment selection bias and potential confounding in an observational study, we performed propensity score (PS) matching. We estimated PS for the type of DES using a non-parsimonious multivariable logistic regression model. In this model, age above 65-year-old, gender, hypertension, diabetes, dyslipidemia, smoking, family history of coronary artery disease, previous history of MI, acute coronary syndrome (ACS), ejection fraction, dialysis, number of lesion, location of lesion, complex lesion, number of stent, total length of stent, stent diameter, and type of DES were included as covariates. The model was well-calibrated (Hosmer-Lemeshow test: $p = 0.13$) with reasonable discrimination (c statistic = 0.68) [11]. We then applied PS, the single composite variable, to match each SES implanted patient with PES implanted patient with a very similar PS, thus matching 351 pairs (57.4% of the 612 were treated with SES and 83.4% of the 421 were treated with PES) with similar PS. In our matching algorithm, we performed 1:1 match iteration by similar PS from initial 8 to 1 digit. After all of the PS matches were performed, we assessed the balance in baseline covariates between the two intervention groups with the paired t-test or the Wilcoxon signed rank test for continuous variables, and McNemar's test or the marginal homogeneity test for categorical variables. Comparisons were

completed with Cox regression models with robust standard errors that accounted for clustering of the matched pairs.

All analyses were two-tailed, p-value < 0.05 was considered to indicate the statistical significance. Statistical analyses were performed by SAS software, version 9.1 (SAS Institute, Cary, North Carolina) and R programming language.

Results

Characteristics of study populations

Of all the 1,033 patients, 612 patients were implanted with SES for 752 lesions and 421 patients were implanted with PES for 530 lesions. The baseline demographic, clinical, laboratory, and angiographic characteristics between the two groups are shown in Tables 1–3. Baseline clinical characteristics were comparable, except proportion of current smoking, previous MI, previous PCI, and ACS, which factors were more in PES group. SES group had higher proportion of dyslipidemia. In angiographic findings, PES group had more right coronary artery lesion and complex lesion, however, the number of stents per patient was lower in PES group than SES group (1.3 ± 0.8 vs. 1.5 ± ± 0.8, p = 0.001, respectively). The medication at discharge showed significant differences in statin, angiotensin converting enzyme inhibitors/angiotensin receptor blockers, β-blockers, and calcium channel blockers, which were more frequently prescribed in SES group (Table 4). In the propensity matched population, there was no longer any significant difference for any covariate including dyslipidemia, history of current smoking, previous MI and previous PCI, clinical presentation, location of lesion, number of B2/C lesion, number of stent, and medication (Tables 1–4).

Follow-up and clinical outcomes

The median follow-up duration was 810 days (interquartile range [IQR] 361–1,354) for overall patient, 851 days (IQR 366–1356) in the SES group, and 772 days (IQR 357–1,363) in the PES group, which was not significantly different (p = 0.443). Complete follow-up data for major clinical events was obtained in 97.2% patients. During follow-up, 173 (28.3%) patients had the composite of MACE in SES group and 151 (35.9%) patients in PES group (Table 5). A composite of MACE are higher in PES group compared with SES group (adjusted hazard ratio [HR] 1.29, 95% confidence interval [CI] 1.02–1.64; p = 0.03). All- cause death was significantly higher in PES group than SES group (adjusted HR 1.34, 95% CI 1.008–1.770; p = = 0.044). There was no significant difference in cardiac death, MI, repeat revascularization, and stent thrombosis between the groups. The incidence of definite or probable stent thrombosis was 10 (1.6%) in SES group and 8 (1.9%) in PES group. On the other hand, TVR including TLR was occurred more frequently in PES group than SES group before adjustment of baseline covariate, but there was no significant difference after rigorous adjustment of baseline covariates with multivariate Cox proportional hazard regression model and PS matching. Survival analysis by Kaplan-Meier curve showed higher event rate for PES group in a composite of MACE, all-cause death, TLR, and TVR, respectively (Fig. 2). The trends of higher event rate for PES group in composite of MACE and all-cause death were consistent, as shown in Table 5. Kaplan-Meier survival curve derived from propensity-matched population showed higher event rates in composite of MACE and it was pronounced by all-cause death (Fig. 3).

Subgroup analysis

We calculated the unadjusted HR for MACE in various subgroups (Fig. 4). The rate of MACE was numerically higher in the PES group than in the SES group in all subgroups, although statistical significance was not found in patients with age under 65, female gender, and non-ACS presentation. There were no significant interactions between the stent type and MACE among the six subgroups. The subgroup analysis in propensity-matched population had similar findings except that statistical significance was found in patients with age upper 65, male gender, ACS presentation, and non-dialysis.

Discussion

In the present study, compared to SES, PES implantation was an independent risk factor for the composite of MACE in patients with RI at long-term clinical follow-up. This difference in primary object was originated from the higher event rates on all-cause death in PES group than SES group. To validate the predisposing baseline clinical characteristics and angiographic findings which were favorable for SES group, we used Cox hazard regression analysis and propensity score matching [12]. Statistical analysis also showed consistent gap in the composite of MACE and all-cause death between the SES and PES groups.

To date, this has been one of the largest prospective observational study comparing SES with

Table 1. Baseline clinical characteristics and medication at discharge between the SES and PES groups.

	Total population			Propensity-matched population		
	SES (n = 612)	PES (n = 421)	P	SES (n = 351)	PES (n = 351)	P
Age	68.2 ± 9.2	68.8 ± 10.7	0.33	68.4 ± 9.4	68.8 ± 10.8	0.87
Age ≥ 65	422 (69.0%)	294 (69.8%)	0.76	242 (69.0%)	244 (69.5%)	0.93
Male	284 (46.4%)	208 (49.4%)	0.34	169 (48.3%)	172 (49.0%)	0.88
Body mass index [kg/m^2]	24.5 ± 3.3	24.3 ± 3.3	0.30	24.2 ± 3.1	24.3 ± 3.3	0.69
Hypertension	453 (74.0%)	310 (73.6%)	0.89	250 (71.2%)	250 (71.2%)	1.00
Diabetes	322 (52.6%)	238 (56.5%)	0.21	185 (52.7%)	192 (54.7%)	0.63
Dyslipidemia	154 (25.2%)	83 (19.7%)	**0.04**	70 (19.9%)	71 (20.2%)	1.00
Current smoker	111 (18.1%)	100 (23.8%)	**0.03**	85 (24.2%)	79 (22.5%)	0.59
Family history of CAD	25 (4.1%)	9 (2.1%)	0.09	11 (3.1%)	6 (1.7%)	0.27
Previous MI	30 (4.9%)	34 (8.1%)	**0.04**	23 (6.6%)	18 (5.1%)	0.52
Previous PCI	42 (6.9%)	51 (12.1%)	**< 0.01**	37 (10.5%)	29 (8.3%)	0.29
Previous CABG	5 (0.8%)	7 (1.7%)	0.26	3 (0.9%)	6 (1.7%)	0.51
Clinical presentation:			**< 0.01**			0.18
Stable angina	273 (44.6%)	133 (31.6%)		132 (37.6%)	117 (33.3%)	
ACS	339 (55.4%)	288 (68.4%)		219 (62.4%)	234 (66.7%)	
LVEF [%]*	56.7 ± 12.0	54.2 ± 12.3	**< 0.01**	55.9 ± 12.2	54.4 ± 11.9	0.09
LVEF < 45%	90 (14.7%)	87 (20.7%)	**0.04**	56 (16.0%)	65 (18.5%)	0.47
LVEF < 40%	56 (9.2%)	54 (12.8%)	0.16	35 (10.0%)	41 (11.7%)	0.68
LVEF < 35%	37 (6.1%)	31 (7.4%)	0.69	24 (6.8%)	23 (6.6%)	0.58
RI status:			0.13			0.20
Non-dialysis	562 (91.8%)	375 (89.1%)		328 (93.5%)	318 (90.6%)	
Dialysis	50 (8.2%)	46 (10.9%)		23 (6.6%)	33 (9.4%)	

Data are presented as mean ± standard deviation or n (%). *Left ventricular ejection fraction (LVEF) was available for 931 patients (90.1%); ACS — acute coronary syndrome; CABG — coronary artery bypass graft; CAD — coronary artery disease; MI — myocardial infarction; PCI — percutaneous coronary intervention; PES — paclitaxel-eluting stent; RI — renal insufficiency; SES — sirolimus-eluting stent

Table 2. Laboratory findings at index percutaneous coronary intervention and at follow-up according to follow-up HDL-C level.

	Total population			Propensity-matched population		
	SES (n = 612)	PES (n = 421)	P	SES (n = 351)	PES (n = 351)	P
Glucose [mg/dL]	140.7 ± 83.0	150.0 ± 86.6	0.081	142.7 ± 87.1	147.4 ± 85.1	0.471
Hemoglobin [g/dL]	12.1 ± 2.0	12.0 ± 2.2	0.510	12.0 ± 2.0	12.0 ± 2.2	0.771
Creatinine [mg/dL]	1.97 ± 1.82	2.24 ± 2.30	0.043	2.03 ± 1.94	2.11 ± 2.14	0.600
MDRD [mL/min/1.73 m^2]	43.9 ± 15.5	42.3 ± 17.0	0.325	43.6 ± 15.4	43.6 ± 16.4	0.991
MDRD < 30	107 (17.5%)	88 (20.9%)	0.172	59 (16.8%)	67 (19.1%)	0.491
Total cholesterol [mg/dL]	169.0 ± 54.6	158.0 ± 55.9	0.002	163.0 ± 54.8	158.0 ± 57.4	0.236
Triglyceride [mg/dL]	140.2 ± 107.0	117.8 ± 74.7	<0.001	131.7± 107.3	129.2 ± 74.2	0.776
LDL-C [mg/dL]	92.5 ± 54.0	86.2 ± 49.3	0.058	89.4 ± 52.6	86.4 ± 50.0	0.441
HDL-C [mg/dL]	37.8 ± 14.4	37.0 ± 14.7	0.364	37.5 ± 14.6	37.4 ± 14.9	0.893
Hs-CRP [mg/L]	1.65 ± 3.76	1.74 ± 3.87	0.716	1.83 ± 4.00	1.57 ± 3.70	0.366

Data are presented as mean ± standard deviation. HDL-C — high-density lipoprotein cholesterol; Hs-CRP — high-sensitivity C-reactive protein; LDL-C — low-density lipoprotein cholesterol; MDRD — Modification of Diet in Renal Disease; PES — paclitaxel-eluting stent; SES — sirolimus-eluting stent

Table 3. Angiographic characteristics according to the type of stent.

	Total population			Propensity-matched population		
	SES (n = 612)	PES (n = 421)	P	SES (n = 351)	PES (n = 351)	P
Number of lesion	1.2 ± 0.5	1.3 ± 0.5	0.342	1.3 ±0.6	1.2 ± 0.5	0.20
Location of lesion:						
LMCA	43 (7.0%)	32 (7.6%)	0.73	21 (6.0%)	23 (6.6%)	0.88
LAD	486 (79.4%)	318 (75.5%)	0.14	263 (74.9%)	259 (73.8%)	0.79
LCx	296 (48.5%)	229 (54.4%)	0.06	172 (49.0%)	189 (53.9%)	0.22
RCA	307 (50.2%)	271 (64.4%)	**< 0.01**	232 (66.1%)	213 (60.7%)	0.10
Number of B2/C lesion	0.9 ± 0.6	1.0 ± 0.7	**0.01**	0.9 ± 0.7	1.0 ± 0.7	0.26
Stent number per patient	1.5 ± 0.8	1.3 ± 0.8	**< 0.01**	1.4 ± 0.8	1.4 ± 0.7	0.25
Total stent length [mm]	36.3 ± 19.8	36.7 ± 22.3	0.78	35.9 ± 20.3	34.0 ± 20.8	0.16
Mean stent diameter [mm]	3.1 ± 0.3	3.1 ± 0.5	0.23	3.1 ± 0.3	3.1 ± 0.5	0.38

B2/C — complex lesion; LAD — left anterior descending artery; LCx — left circumflex artery; LMCA — left main coronary artery; PES — paclitaxel-eluting stent; RCA — right coronary artery; SES — sirolimus-eluting stent

Table 4. Medications according to the type of stent.

	Total population			Propensity-matched population		
	SES (n = 612)	PES (n = 421)	P	SES (n = 351)	PES (n = 351)	P
Aspirin	580 (94.8%)	391 (92.9%)	0.21	330 (94.3%)	328 (93.5%)	0.88
Clopidogrel	540 (88.2%)	383 (91.0%)	0.15	325 (92.6%)	313 (89.2%)	0.17
Statin	457 (74.7%)	282 (67.0%)	**< 0.01**	256 (72.9%)	236 (67.2%)	0.13
ACEI/ARB	413 (67.5%)	275 (65.3%)	**0.02**	237 (67.5%)	233 (66.4%)	0.13
Beta blocker	391 (63.9%)	268 (63.7%)	**0.01**	229 (65.2%)	219 (62.4%)	0.13
Calcium-channel blocker	175 (28.6%)	97 (23.0%)	**< 0.01**	89 (25.4%)	79 (22.5%)	0.18

ACEI — angiotensin converting enzyme inhibitor; ARB — angiotensin II receptor blocker; CCB — calcium channel blocker; PES — paclitaxel-eluting stent; SES — sirolimus-eluting stent

PES in patients with RI and these patients were excluded in large randomized controlled trial. In this regard, this study may provide invaluable long-term clinical outcome data for patients who underwent PCI using first generation DES with RI.

To the best of our knowledge, RI was significantly associated with poor clinical outcomes in patients who underwent PCI regardless of the type of stent, BMS or DES [13–15]. Moreover, a few retrospective studies have been published concerning clinical outcome of DES in RI. Lemos et al. [14] and Garg et al. [15] suggested that RI increased mortality after implantation of SES compared to the patients with normal kidney function, despite the clear antirestenotic effect of SES. The causes of these phenomena may be explained by several mechanisms. Firstly, vascular and atheroma calcification is more severe and much more frequent in patients with RI than without RI [2, 16, 17]. Secondly, patients with RI was prone to the development of endothelial dysfunction by excessive endothelin levels and diminished vascular nitric oxide production [18–20]. Besides, RI was associated with increased level of inflammatory factors, abnormal apolipoprotein levels, elevated plasma homocysteine, and enhanced coagulability [1]. For these reasons, MACEs occurred more frequently (SES 28.3%, PES 35.9%, respectively) in the present study compared with previous studies on first generation DES [3, 7, 21].

In a few studies that showed the mortality benefit of DES compared with BMS in patients

Table 5. Clinical events in patients undergoing PCI by PES compared with SES.

	SES	PES	Unadjusted HR (95% CI)	P	Adjusted HR* (95% CI)	P
Total population (n = 1033)	**N = 612**	**N = 421**				
Composite of MACE	173 (28.3%)	151 (35.9%)	1.51 (1.21–1.88)	< 0.01	1.29 (1.01–1.64%)	0.03
All-cause death	118 (19.3%)	111 (26.4%)	1.58 (1.22–2.05)	< 0.01	1.34 (1.01–1.77)	0.04
Cardiac death	43 (7.0%)	40 (9.5%)	0.99 (0.64–1.52)	0.96	0.91 (0.57–1.44)	0.68
MI	7 (1.1)	7 (1.7%)	1.92 (0.67–5.49)	0.23	1.33 (0.42–4.23)	0.63
TLR/TVR	64 (10.5%)	52 (12.4%)	1.46 (1.01–2.11)	0.04	1.28 (0.86–1.91)	0.22
Propensity-matched population (n = 702)	**N = 351**	**N = 351**				
Composite of MACE	108 (30.8%)	128 (36.5%)	1.48 (1.17–1.88)	< 0.01	1.37 (1.06–1.78)	0.02
All-cause death	74 (21.1%)	94 (26.8%)	1.57 (1.18–2.09)	< 0.01	1.43 (1.06–1.94)	0.02
Cardiac death	28 (8.0%)	32 (9.1%)	1.24 (0.75–2.06)	0.41	1.17(0.62–2.19)	0.63
MI	5 (1.4%)	6 (1.7%)	1.33 (0.46–3.89)	0.60	1.47 (0.45–4.82)	0.53
TLR/TVR	39 (11.1%)	44 (12.5%)	1.39 (0.94–2.04)	0.10	1.35 (0.88–2.09)	0.17

*Adjusted variables: age > 65, gender, family history of coronary artery disease, previous MI, previous PCI, previous coronary artery bypass grafting, diabetes, hypertension, hyperlipidemia, current smoking, acute coronary syndrome, ejection fraction < 35%, renal insufficiency state, location of lesion, number of lesion over B2C, number of stent, stent length, mean stent diameter; CI — confidence interval; HR — hazard ratio; MACE — major adverse cardiovascular events; MI — myocardial infarction; PCI — percutaneous coronary intervention; PES — paclitaxel-eluting stent; SES — sirolimus-eluting stent; TLR/TVR — target lesion revascularization/target vessel revascularization

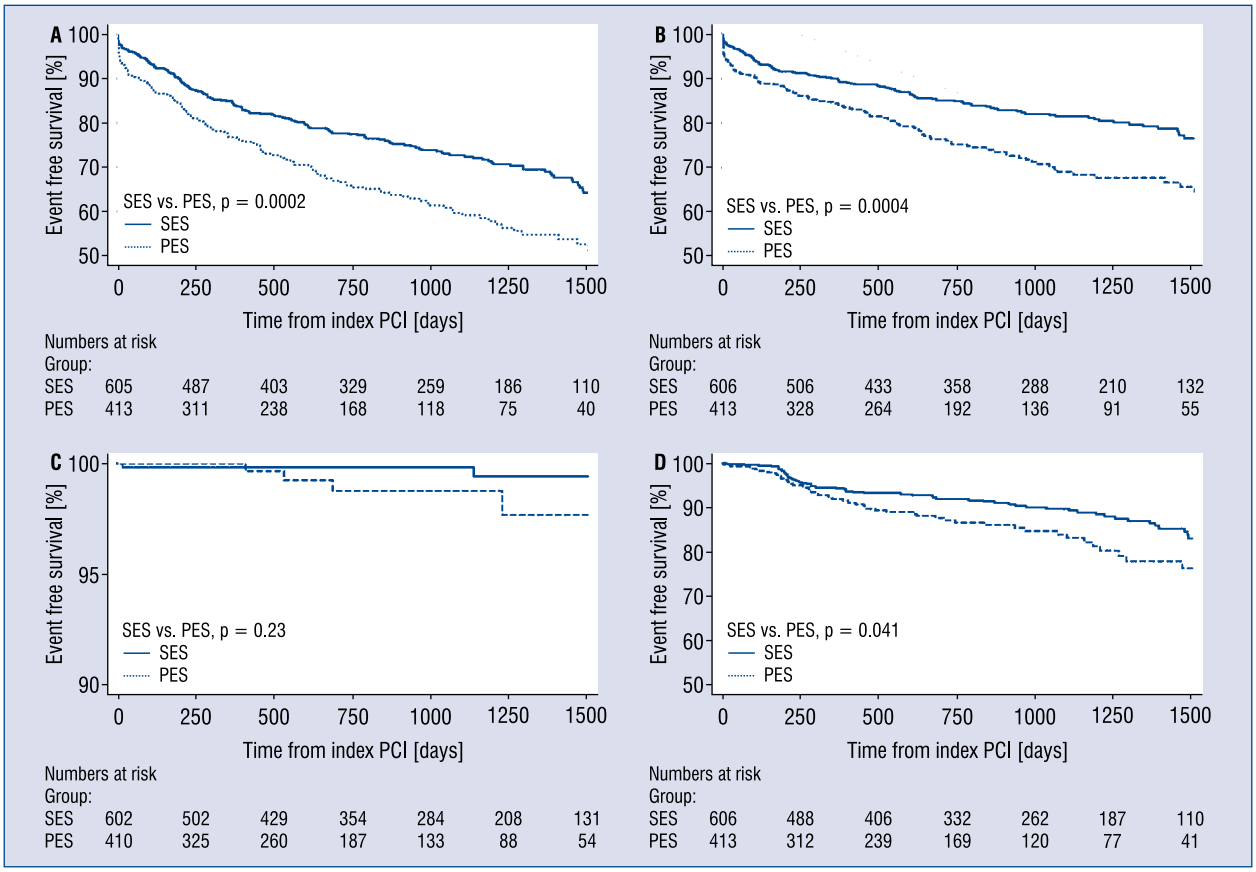

Figure 2. Kaplan-Meier curve for a composite of major adverse cardiac events (**A**), all-cause death (**B**), myocardial infarction (**C**), and target lesion revascularization/target vessel revascularization (**D**) between the SES and PES groups; PCI — percutaneous coronary intervention; PES — paclitaxel-eluting stent; SES — sirolimus-eluting stent.

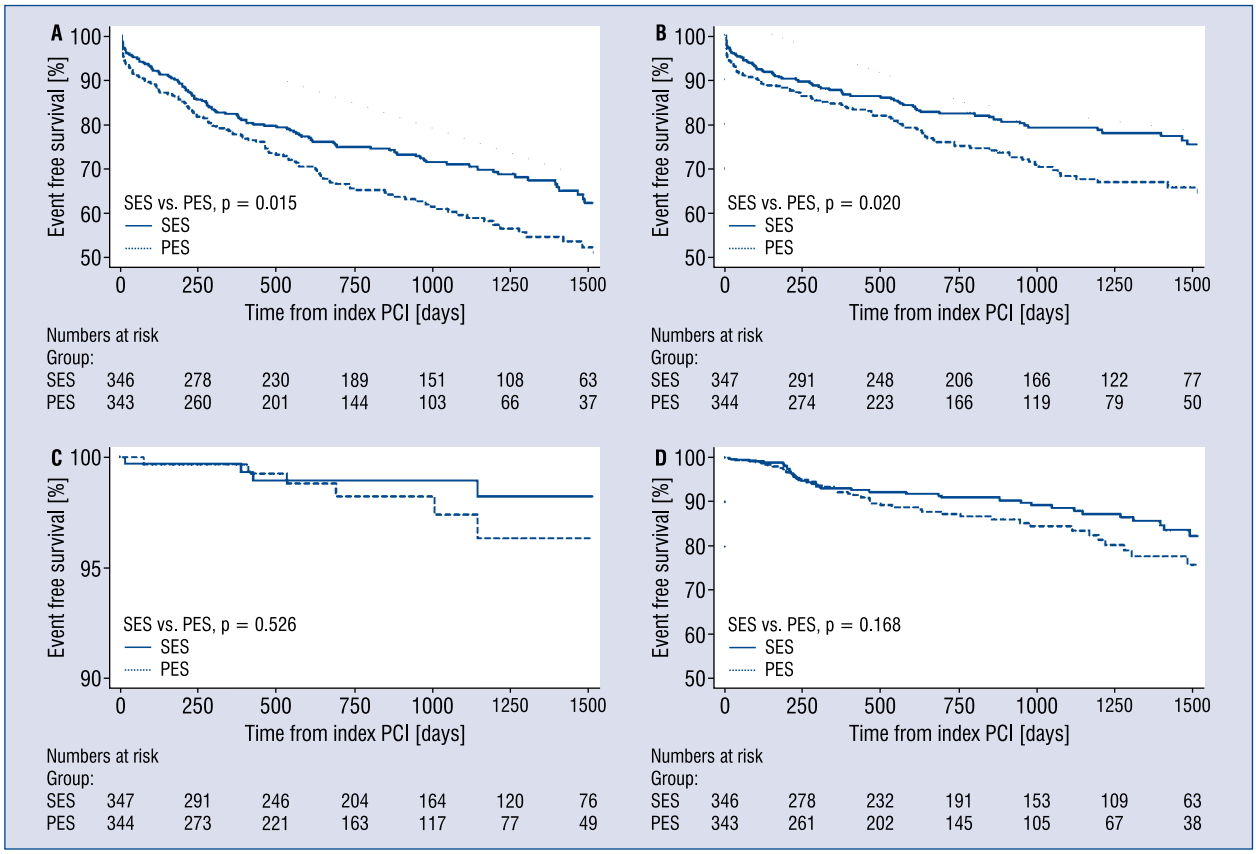

Figure 3. Kaplan-Meier Curve for a composite of major adverse cardiac events (**A**), all-cause death (**B**) myocardial infarction (**C**), and target lesion revascularization/target vessel revascularization (**D**), between the propensity score matched SES and PES groups; PCI — percutaneous coronary intervention; PES — paclitaxel-eluting stent; SES — sirolimus-eluting stent.

with RI, the presumed causes of this result were related with selection bias and reduced restenosis in patients who underwent PCI by DES [4, 5]. Meta-analysis [7] of 16 randomized trials comparing clinical outcome of SES and PES in general population has showed a better clinical outcome in SES than PES in the aspects of reintervention rate and stent thrombosis. Some random controlled trials report that SES has more beneficial impact on in-stent restenosis than PES [21–23]. Researchers suggested a few explanations based on the difference of pharmacological action, drug release kinetics, pattern of drug distribution in the arterial wall, and stent characteristics of SES and PES [24]. SES elutes nearly all of the loaded sirolimus in 1 month from non-erodable polymer and PES releases paclitaxel as an initial burst followed by a constant slow release up to 3 months. In autopsy data, PES showed greater inflammation consisting of lymphocytes, eosinophils, and macrophages at 4 months compared to SES [25].

In the present study, patients in PES group were more often current smokers, had previous MI, previous PCI, ACS, low ejection fraction, and number of B2/C lesions, and took less statins. In renal insufficiencies, calcified target lesion showed worse clinical outcome compared to non-calcified lesion in SES registry [26]. Even though we performed rigorous adjustments of these variables using multivariate Cox proportion hazards regression analysis and PS matching to minimize the bias of the registry data, we cannot rule out the possibility of overestimation of mortality benefit of SES compared to PES.

Recently, it has been reported that there were no differences in MACE, mortality, or revascularization between SES and PES in patients with RI in 2 papers [8, 27]. However, those papers contained smaller numbers of patients (141 in SES group, 287 in PES group in 1 paper, 346 in SES group, 224 in PES group in the other) than the present study. In large scaled registry data [28] on ST elevation MI, SES and PES showed no differences in clinical out-

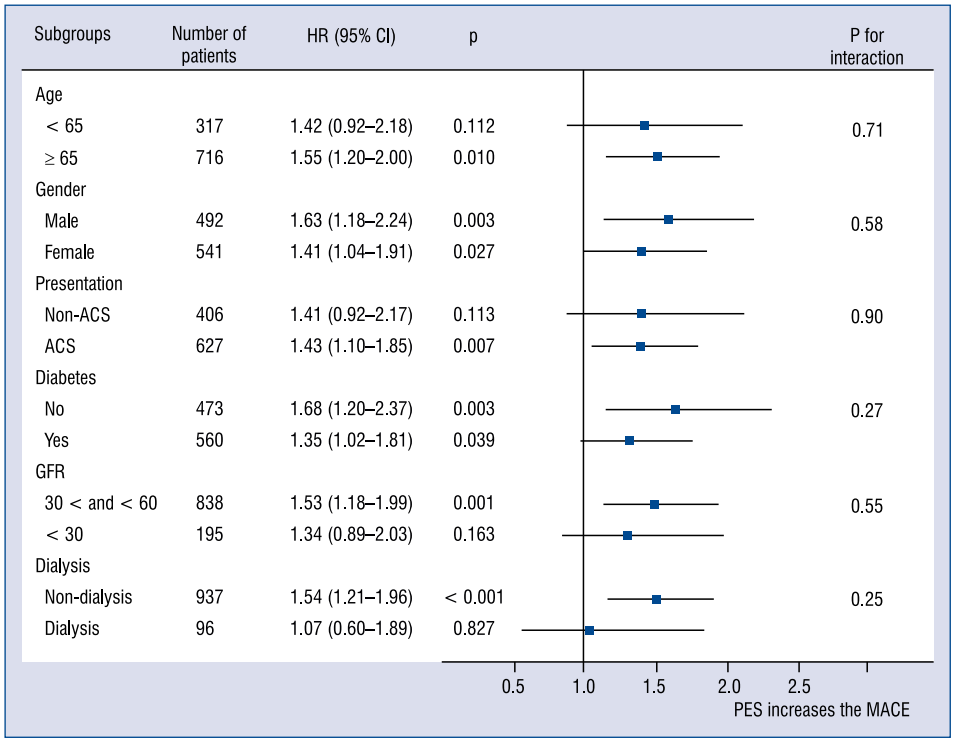

Figure 4. Comparative unadjusted hazard ratio (HR) of major adverse cardiac events (MACE) for subgroups; ACS — acute coronary syndrome; CI — confidence interval; GFR — glomerular filtration rate; PES — paclitaxel-eluting stents.

come during median follow-up of 342 days. In those papers, there were no rigorous adjustments such as PS matching different to our study. As presented in our results of subgroup analysis, renal function of study population might affect the comparison of clinical outcome between the SES and PES group.

Limitations of the study

Our study has some limitations. First, the first generation DES are already getting old fashioned. Thus, the analysis of difference between the first generation stents might be no more needed, however, many patients have been already treated with these stents. Therefore, we need to know the clinical outcomes of the first generation stents in various clinical situations. Second, selection bias and confounding factors might have affected the results, because this study has a non-randomized observational design. To minimize these biases, we performed propensity-score matching, but hidden bias may still remain because of the influence of unmeasured confounders. Third, we did not collect data on the development of contrast induced nephropathy, type of contrast, volume of contrast in this study. Because contrast-induced nephropathy is one of the important risk factors for worse clinical outcomes, we cannot exclude that this might affect the results. Fourth, detection of events and patient follow-up were less rigorous than in randomized controlled trials. Even though 97.2% of patients were followed and the data of the National Health Insurance Corporation were reviewed for survival, nonfatal events (e.g. MI or TVR) may have been underestimated. As the information on censored survival data was obtained from National Health Insurance Corporation as form of death or alive, classification of the cause of death was impossible in 94 patients (9.0% of total population). These 94 patients were classified as non-cardiac death and early interruption of antiplatelet agent or tachyarrhythmia after revascularization may be related to cardiovascular cause of death but underestimated in this study. Fifth, coronary angiography was analyzed qualitatively, not quantitatively. Detailed quantitative coronary analysis may be helpful in further interpreting our findings.

Conclusions

In patients with RI, PCI using PES provides poorer long-term clinical outcome than SES in terms of MACE and all-cause death. There was no

difference of repeat revascularization between the SES and PES groups during 2.2 years of follow-up.

Conflict of interest: None declared

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