Comparison of Limus-Eluting and Paclitaxel-Eluting Stents for Coronary Intervention in Patients with Chronic Kidney Disease

A Meta-Analysis

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Summary

Chronic kidney disease (CKD) patients have worse adverse cardiovascular outcomes after percutaneous coronary intervention (PCI). Clinical outcomes comparing a limus-eluting stent (LES) to a paclitaxel-eluting stent (PES) in patients with CKD remain controversial.

A systematic search was conducted using PubMed, EMBASE, and Cochrane Library. A pooled odds ratio (OR) and 95% confidence interval (CI) were used to calculate original data. We conducted heterogeneity, quality assessment, and publication bias analyses.

A total of 17 trials involving 10,724 patients were included. No significant differences were found regarding target vessel revascularization, target lesion revascularization (TLR), stent thrombosis (ST), myocardial infarction (MI), all-cause mortality, and major adverse cardiac events (MACE) between first-generation LES implantation and PES implantation. Second-generation LES implantation was associated with lower rates of all-cause mortality (OR, 0.56; 95% CI, 0.39-0.82; $P = 0.003$), MACE (OR, 0.61; 95% CI, 0.38-0.97; $P = 0.04$), and ST (OR, 0.45; 95% CI, 0.26-0.77; $P = 0.004$) compared with PES implantation. In all, the long-term all-cause mortality rate was significantly lower after LES implantation than after PES implantation in patients with CKD (OR, 0.78; 95% CI, 0.66-0.93; $P = 0.004$). However, second-generation LES implantation resulted in a higher rate of TLR (OR, 2.23; 95% CI, 1.53-3.25; $P < 0.001$) than PES implantation in dialysis patients.

In patients with CKD, first-generation LES and PES implantation had comparable mortality and morbidity. Second-generation LES implantation was superior to PES in reducing long-term mortality, MACE, and ST. However, PES may be more effective than LES in dialysis patients.

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Key words: Percutaneous coronary intervention, Outcomes

Renal insufficiency has been independently associated with increased risk of cardiovascular morbidity and mortality in patients with coronary artery disease.^{1,2} Moreover, after percutaneous coronary intervention (PCI), patients with chronic kidney disease (CKD) have higher rates of adverse outcomes than patients without CKD.³⁻⁵ While performing PCI in these patients using first-generation drug-eluting stents (DES), paclitaxel-eluting stents (PES) and sirolimus-eluting stents (SES) have been reported to reduce restenosis or mortality when compared with bare metal stents (BMS).⁶⁻⁸ Although everolimus-eluting stents (EES), zotarolimus-eluting stents (ZES), and sirolimus-eluting stents (SES) are limus-eluting stents (LES) that share similar underlying pharmacological mechanisms, different effects on clinical outcomes after LES versus PES implantation may result from differences in drugs, pharmacokinetics, and polymers.

Previous studies have shown conflicting results in terms of major cardiac adverse events comparing SES to PES in patients with chronic kidney disease.⁹⁻¹² Newer-

generation DES, such as ZES, showed better preserved endothelial-dependent vasomotion and biocompatibility compared to first-generation DES.^{13,14} However, even if a second-generation DES is expected to be associated with better clinical outcomes in patients with CKD, data regarding the long-term adverse clinical outcomes treated with either EES/ZES or PES are still controversial.¹⁵⁻¹⁷

To the best of our knowledge, no meta-analysis thus far has been attempted to investigate whether limus-eluting stents or newer-generation DES reduce the risk of mortality and morbidity in patients with CKD compared with PES. Therefore, we performed such a meta-analysis with the aim of comparing clinical events of SES versus PES implantation, or of EES/ZES versus PES implantation in patients with CKD.

Methods

Literature search: This meta-analysis was performed and reported according to the PRISMA guidelines.¹⁸ We con-

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ducted a search of PubMed, EMBASE and Cochrane Library databases from their date of inception up to March 2017, using key words and/or medical subject heading terms: “sirolimus or everolimus or zotarolimus-eluting stent”, “paclitaxel-eluting stent”, “percutaneous coronary intervention”, “chronic kidney disease”, “chronic renal failure” and “dialysis”. No language or publication date restrictions were imposed. We also searched the reference lists of all retrieved articles to identify additional eligible studies.

Study inclusion and exclusion criteria: Studies were considered eligible for inclusion if the following criteria were met: (1) randomized controlled trials (RCTs) or observational trials, (2) comparisons of SES versus PES implantation, or of second generation LES (EES or ZES) versus PES implantation in patients with CKD undergoing PCI, and (3) at least 1 outcome as follows: major cardiovascular events (MACEs), all-cause mortality, myocardial infarction (MI), target lesion revascularization (TLR), target vessel revascularization (TVR), and stent thrombosis (ST, including definite and probable) should be reported. Exclusion criteria were (1) animal studies, reviews, case reports, letters, and conferences and (2) a follow-up period of less than 6 months. Two independent investigators (XY and QL) screened the titles and abstracts of all electronic citations. Any inconsistency was settled by discussion with a senior author (QX).

Data extraction and quality assessment: Two investigators (QL and XY) independently reviewed titles and abstracts generated by the search, and the third investigator adjudicated any discrepancies. Data was collected, including the outcomes of interest, general characteristics of the included studies, and study participants. CKD was defined as an estimated glomerular filtration rate (eGFR) of < 60 mL/minute/1.73 m². A duration of follow-up of more than one year was regarded as the long-term outcome. Outcomes were assessed at maximum available follow-up. Our primary outcome was long-term all-cause mortality. Secondary outcomes were major cardiovascular events, myocardial infarction, target lesion revascularization, target vessel revascularization, and stent thrombosis.

The methodological quality of the studies was assessed by means of the Jadad scale for quality of randomized controlled studies (RCTs)¹⁹ and the 9-item Newcastle-Ottawa Quality scale²⁰ for quality of observational studies in our meta-analysis. In the current study, we considered a study awarded a Jadad score of ≥ 2 , or a Newcastle-Ottawa score of ≥ 6 as a high-quality study.

Statistical analysis: Summary OR estimates and 95% CI (CIs) were calculated for the outcomes of interest. The fixed-effect model was used to calculate pooled ORs among studies. When statistically significant heterogeneity existed, a random-effect model (DerSimonian and Laird) was used to combine the results.²¹ Statistical heterogeneity was assessed using Cochran's Q test and I² statistic and a value of $> 50\%$ was considered to indicate significant heterogeneity among studies. Sensitivity analysis by removing one study at a time to evaluate that study's effects on the overall results was performed. Subgroup analyses were conducted according to the type of PCI: SES versus PES implantation or second generation LES (EES or ZES) ver-

sus PES. We also carried out subgroup analysis for each end point restricted to patients on chronic dialysis to compare the efficacy and safety of LES versus PES. Publication bias was assessed using a funnel plot and Egger's regression test for the outcome of all-cause mortality.²² If publication bias exists, the funnel plot is asymmetric or the Egger's test *P* value is < 0.05 . All statistical analyses were carried out with RevMan 5.3 and Stata 12.0 software. We considered a *P* value < 0.05 as significant.

Results

Study selection: The study selection process is shown in Figure 1. Of the 983 articles retrieved during the initial search, 647 were excluded at the title/abstract level. After full-text review of the remaining 98 articles, we excluded 12 articles that were reviews, letters, case reports, or abstracts, 28 articles that did not have comparison groups between limus-eluting and paclitaxel-eluting stents, 14 articles that did not report adverse clinical outcomes, and 27 articles that did not enroll patients with CKD. Finally, a total of 17 studies including 10,724 patients that met our predefined inclusion criteria were included in this study.^{9,12,15-17,23-32}

Study characteristics and quality assessment: The characteristics and overall quality of the individual trials are shown in Table I. Of these 17 studies, 15 were observational retrospective studies^{9,12,15-17,23-32} and 2 were randomized controlled studies.^{10,11} The studies varied in sample size from 68 to 3,201 patients with a follow-up period ranging from 12 months to 47 months. Of these studies, 3 were conducted in the United States, 2 in European countries (1 in Netherlands and 1 in Switzerland), and 12 in Asian countries (8 in Japan and 4 in Korea). Most studies compared the clinical outcomes between SES and PES, while 5 investigated the clinical outcomes of second-generation drug eluting stents (ZES or EES) versus PES in CKD patients. The patients included were predominantly male and their mean ages ranged from 64 to 76 years. Seven out of 17 studies evaluated the efficacy and safety of limus-eluting versus paclitaxel-eluting stents for patients with end-stage renal disease on dialysis.^{11,16,24-26,28,29}

In addition, all studies included in our meta-analysis were considered as high quality (RCT with a Jadad score of ≥ 2 and observational studies with a Newcastle-Ottawa Quality Assessment Scale score of ≥ 6). The clinical characteristics of the included patients are shown in Table II.

Long-term all-cause mortality: A total of 12 studies (2,416 patients) reported long-term all-cause mortality. The long-term (> 1 year) all-cause mortality was significantly lower after LES implantation than after PES implantation (OR, 0.78; 95% CI, 0.66-0.93; *P* = 0.004), with low heterogeneity (I² = 8%) (Figure 2). In the subgroup analyses (Table III) by type of coronary stent, compared with PES, only secondary generation DES (SES or ZES) was associated with a significant reduction in risk for long-term all-cause mortality (OR, 0.56; 95% CI, 0.39-0.82; *P* = 0.003; I² = 18%).

MACE: Fifteen studies (9,884 patients) reported the MACE rate after coronary stent implantation. While PES (16.2%) had a higher MACE rate as compared to LES

Figure 1. Flow diagram of selection process.

Table 1. Key Characteristics of Included Studies on LES Versus PES in Patients with Chronic Kidney Disease

Study	Year	Country	Study design	Stents	Patients		Follow-up	Quality of study
					LES	PES		
Crimi ¹⁵⁾	2016	Switzerland	Post-hoc analysis of RCT	EES versus PES	87	98	24 months	^{N9}
Crimi ¹⁵⁾	2016	Switzerland	Post-hoc analysis of RCT	ZES versus PES	94	98	24 months	^{N9}
Ann ⁹⁾	2016	Korea	Prospective cohort	SES versus PES	351	351	26 months	^{N9}
Kitasato ²³⁾	2015	Japan	Retrospective cohort	EES versus PES	73	74	36 months	^{N8}
Otsuka ¹⁶⁾	2015	Japan	Retrospective cohort	EES versus PES	102	107	12 months	^{N8}
Otsuka ¹⁰⁾	2014	Japan	RCT	SES versus PES	613	593	12 months	^{J3}
Sardi ²⁴⁾	2014	USA	Prospective cohort	SES or EES versus PES	156	62	24 months	^{N9}
Kamoi ¹¹⁾	2013	Japan	RCT	SES versus PES	50	50	12 months	^{J5}
Tsujita ²⁶⁾	2013	Japan	Retrospective cohort	SES versus PES	41	38	12 months	^{N8}
Yano ²⁵⁾	2013	Japan	Retrospective cohort	SES versus PES	32	36	12 months	^{N6}
Hachinohe ¹⁷⁾	2012	Korea	Prospective cohort	SES versus PES	1845	1356	12 months	^{N8}
Hachinohe ¹⁷⁾	2012	Korea	Prospective cohort	ZES versus PES	365	1356	12 months	^{N8}
Simsek ¹²⁾	2012	Netherlands	Retrospective cohort	SES versus PES	290	260	72 months	^{N8}
Ahmed ²⁷⁾	2012	Korea	Prospective cohort	SES versus PES	420	381	12 months	^{N6}
Ahmed ²⁷⁾	2012	Korea	Prospective cohort	ZES versus PES	713	381	12 months	^{N6}
Ahmed ²⁷⁾	2012	Korea	Prospective cohort	EES versus PES	602	381	12 months	^{N6}
Higashitani ²⁹⁾	2011	Japan	Retrospective cohort	SES versus PES	49	54	12 months	^{N8}
Otsuka ²⁸⁾	2011	Japan	Retrospective cohort	SES versus PES	184	95	12 months	^{N7}
Syed ³¹⁾	2010	USA	Retrospective cohort	SES versus PES	346	224	12 months	^{N8}
Sukhija ³⁰⁾	2010	USA	Retrospective cohort	SES versus PES	141	287	47 months	^{N8}
Jeong ³²⁾	2007	Korea	Retrospective cohort	SES versus PES	76	28	12 months	^{N7}

SES indicates sirolimus-eluting stent; EES, everolimus-eluting stent; ZES, zotarolimus-eluting stent; LES, limus-eluting stent; PES, paclitaxel-eluting stent; CI, confidence interval; RCT, randomized controlled trials; ^J, Jadad quality-scoring scale for RCT, maximum score of 5; and ^N, Newcastle-Ottawa Quality Assessment Scale for non-RCT, maximum score of 9.

Table II. Key Clinical Characteristics of Included Patients

Study	Mean age (years)		Males (%)		Hypertension (%)		Diabetes mellitus (%)		Prior PCI (%)		Prior CABG (%)		Prior MI (%)	
	LES	PES	LES	PES	LES	PES	LES	PES	LES	PES	LES	PES	LES	PES
Crimi ¹⁵⁾	73	76	86	79	82	78	27	53	20	34	16	12	34	43
Crimi ¹⁵⁾	75	76	81	79	86	78	25	53	31	34	20	12	48	43
Ann ⁹⁾	68	69	48	49	71	71	53	55	11	8	1	2	7	5
Kitasato ²³⁾	69	70	81	82	83	82	60	55	NA	NA	NA	NA	NA	NA
Otsuka ¹⁶⁾	69	68	72	72	91	94	65	71	NA	NA	12	8	25	25
Otsuka ¹⁰⁾	73	73	72	68	85	88	51	50	26	27	5	5	17	16
Sardi ²⁴⁾	67	67	54	65	99	98	74	63	32	37	32	24	32	40
Tsujita ²⁶⁾	65	67	78	84	76	74	61	76	44	45	10	3	32	34
Yano ²⁵⁾	64	67	84	87	91	89	75	86	NA	NA	NA	NA	NA	NA
Kamoi ¹¹⁾	65	64	78	70	64	66	48	54	NA	NA	NA	NA	NA	NA
Hachinohe ¹⁷⁾	65	66	67	69	52	55	32	29	NA	NA	NA	NA	NA	NA
Hachinohe ¹⁷⁾	65	66	66	69	52	55	31	29	NA	NA	NA	NA	NA	NA
Simsek ¹²⁾	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Ahmed ²⁷⁾	65	67	82	80	52	54	28	30	NA	NA	NA	NA	NA	NA
Ahmed ²⁷⁾	67	67	80	80	53	54	26	30	NA	NA	NA	NA	NA	NA
Ahmed ²⁷⁾	64	67	81	80	54	54	30	30	NA	NA	NA	NA	NA	NA
Higashitani ²⁹⁾	65	64	41	41	43	48	32	41	17	24	12	14	19	21
Otsuka ²⁸⁾	67	66	74	69	84	80	62	59	NA	NA	13	4	35	27
Syed ³¹⁾	69	69	59	61	96	95	58	57	33	33	34	30	49	49
Sukhija ³⁰⁾	71	71	53	55	96	92	49	45	NA	NA	21	22	NA	NA
Jeong ³²⁾	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

LES indicates limus-eluting stent; PES, paclitaxel-eluting stent; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; and NA, not applicable.

Figure 2. Forest plots for long-term all-cause mortality in CKD patients with LES versus PES.

(15.3%), no significant difference was found (OR, 0.88; 95% CI, 0.72-1.07; *P* = 0.20). Significant heterogeneity was observed (*I*² = 65%). Sensitivity analysis did not significantly alter the results. In the subgroup analyses (Table III) by type of coronary stent, only secondary generation DES (SES or ZES) was associated with a significantly lower rate of MACE as compared to PES (OR, 0.61; 95% CI, 0.38-0.97; *P* = 0.04). The incidence of MACE was comparable in SES and PES cohorts (OR, 1.03; 95% CI, 0.82-1.28; *P* = 0.81) (Figure 3).

MI: The incidence of myocardial infarction was comparable in both cohorts. MI was present in 2.8% and 2.9% patients in the LES and PES cohorts, respectively (OR, 1.14; 95% CI, 0.84-1.55; *P* = 0.41; *I*² = 0%) (Figure 3). Neither subgroup analysis by type of coronary stent nor sensitivity analysis significantly altered the results.

TLR and TVR: Seven studies (7,644 patients) reported the number of patients undergoing TLR after coronary stent implantation. TLR was performed in 4.6% and 4.1% patients in the LES and PES cohort, respectively. Both co-

Table III. Subgroup Analysis of Included Studies

End points	Studies	LES		PES		OR	Overall effect		Heterogeneity	
		Events	Total	Events	Total		95% CI	P value	I ²	P
SES versus PES										
Long-term all-cause mortality	9	265	2260	244	1948	0.88	0.73-1.07	0.21	0	0.72
Myocardial infarction	10	54	2121	46	1997	1.24	0.82-1.86	0.31	0	0.89
Target lesion revascularization	8	139	3156	105	2506	1.35	0.72-2.54	0.35	76	0.0001
Target vessel revascularization	5	118	1708	106	1632	1.21	0.65-2.25	0.54	73	0.005
MACE	11	680	4278	604	3570	1.03	0.82-1.28	0.81	58	0.008
Stent thrombosis	8	33	1897	18	1584	1.59	0.88-2.85	0.12	0	0.82
ZES or EES versus PES										
Long-term all-cause mortality	5	51	1136	80	871	0.56	0.39-0.82	0.003	18	0.30
Myocardial infarction	6	39	1209	36	945	1.14	0.70-1.85	0.59	0	0.43
Target lesion revascularization	7	57	1574	90	2301	0.77	0.41-1.44	0.42	63	0.01
Target vessel revascularization	4	30	1035	26	764	1.15	0.66-1.99	0.62	0	0.45
MACE	7	160	1574	321	2301	0.61	0.38-0.97	0.04	75	0.0004
Stent thrombosis	5	20	1136	42	871	0.45	0.26-0.77	0.004	10	0.35
Dialysis patients										
Long-term all-cause mortality	6	121	552	80	393	0.78	0.54-1.11	0.16	0	0.92
Myocardial infarction	6	16	508	8	380	1.42	0.62-3.26	0.41	29	0.22
Target lesion revascularization	7	122	550	45	416	2.23	1.53-3.25	< 0.001	0	0.51
Target vessel revascularization	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
MACE	5	176	507	89	345	1.30	0.94-1.81	0.11	45	0.12
Stent thrombosis	6	17	542	9	382	1.43	0.64-3.18	0.38	0	0.61

MACE indicates major adverse cardiac events; SES, sirolimus-eluting stent; EES, everolimus-eluting stent; ZES, zotarolimus-eluting stent; LES, limus-eluting stent; PES, paclitaxel-eluting stent; CI, confidence interval; OR, odds ratio; and NA, not applicable, only 1 study reported.

horts were similar (OR, 1.10; 95% CI, 0.73-1.67; $P = 0.65$; $I^2 = 69\%$). Moreover, both LES (6.4%) and PES (5.6%) had comparable TVR rates (OR, 1.27; 95% CI, 0.82-1.67; $P = 1.97$; $I^2 = 59\%$) (Figure 3). Subgroup analysis by type of coronary stent and sensitivity analysis yielded similar results.

Stent thrombosis: Stent thrombosis was reported in 11 studies. Although PES (2.5%) had a higher stent thrombosis rate as compared to LES (1.8%), the difference was not statistically significant (OR, 0.80; 95% CI, 0.55-1.17; $P = 0.25$; $I^2 = 21\%$) (Figure 3). Examining first generation and secondary generation DES separately (Table III), we found only secondary generation DES (SES or ZES) had a significantly lower rate of stent thrombosis as compared with PES (OR, 0.45; 95% CI, 0.26-0.77; $P = 0.004$; $I^2 = 10\%$). Stent thrombosis was similar between the SES and PES groups (OR, 1.59; 95% CI, 0.88-2.85; $P = 0.12$).

Adverse outcomes in patients on chronic dialysis: Of note, when adverse clinical outcomes were specifically analyzed in patients with chronic dialysis, TLR significantly favored PES as compared to LES (OR, 2.23; 95% CI, 1.53-3.25; $P < 0.001$; $I^2 = 0\%$) (Table III). No significant differences were found regarding long-term all-cause mortality, MI, TVR, MACE, and ST between LES and PES. A low level of heterogeneity was observed when analyzing the adverse clinical outcomes between LES and PES in patients on chronic dialysis.

Publication bias: There was no indication of a publication bias in the reporting of results on long-term all-cause mortality, either from visualization of the funnel plot (Figure 4) or the Egger weighted regression method (P value = 0.51).

Discussion

In the present study, we performed a meta-analysis of 2 randomized trials and 15 cohort studies that had a total of 10,724 participants. The results of the analysis found significantly lower rates of all-cause mortality after LES implantation than after PES implantation. However, LES implantation offered similar MACE, MI, TVR, TLR, and stent thrombosis rates at follow-up compared with PES. Subgroup analyses further revealed that second-generation DES (ZES or EES) rather than first-generation DES (SES) were associated with lower risks of all-cause mortality, MACE and stent thrombosis compared with PES. Of note, in dialysis patients, TLR was significantly higher in LES implantation compared to PES implantation.

Despite the use of new interventional devices, patients with CKD have higher rates of cardiovascular events including dyslipidemia, increased inflammation, oxidative stress, and adverse clinical outcomes compared with those with normal renal function.^{33,34} Use of PCI is associated with improved long-term survival when compared with medical therapy alone in patients with severe CKD and acute coronary syndrome.³⁵

Although stent under-expansion, residual reference segment stenosis, and stent fracture after DES implantation have been associated with restenosis and stent thrombosis,^{36,37} DES implantation has markedly improved the safety and efficacy of percutaneous revascularization. Suzuki and colleagues confirmed the superiority of mid-term angiographic outcomes after the placement of EES over SES for *de novo* coronary stenosis.³⁸ Large randomized trials have shown improved clinical outcomes, such as reduced rates of death and MI, associated with EES

A MACE

B MI

C TVR

D TLR

E Stent thrombosis

Figure 3. Forest plots for secondary outcomes in CKD patients with LES versus PES, major adverse cardiac events (A); myocardial infarction (B); target vessel revascularization (C); target lesion revascularization (D); stent thrombosis (E).

Figure 4. Funnel plot assessing publication bias in the included studies.

and ZES as compared to PES and SES in unselected patients.³⁹⁻⁴¹⁾ By blocking the stimulatory effects of growth factors released after vascular injury and cytokines and inhibiting smooth muscle cell proliferation, EES with its thinner strut design, greater durability, lower risk of strut fracture due to the cobalt chromium platform, lower polymer mass, and limus-based anti-proliferative drugs may induce a lower local inflammatory response, which is associated with a lower incidence of arterial injury and stent thrombosis as compared to first generation DES.^{23,42)} In addition, more rapid endothelialization and preserved endothelial vasomotor response are seen after implantation of the ZES compared with first-generation DES.⁴³⁾

TLR has been demonstrated to be significantly reduced after SES or PES implantation in patients with chronic renal insufficiency compared with bare-metal stent (BMS) implantation.^{44,45)} However, when we compared first and second generation DES with PES, our study did not find any significant difference in terms of TLR or TVR in CKD patients. Otsuka and colleagues demonstrated that the PES group was associated with a lower incidence of 1-year MACE compared with the SES group in dialysis patients,²⁸⁾ and also reported that there was no significant difference with regard to MACE between PES and SES implantation in patients with moderate to severe renal insufficiency, and the differences between these reports might have been due to the differences in renal insufficiency severity and study population exclusion criteria.¹⁰⁾

Dialysis patients had more complex morphologies such as coronary calcified lesions, and higher incidences of MACE and clinical restenosis after SES implantation,

compared to non-dialysis patients.^{46,47)} Notably, our study indicated that PES implantation had lower TLR than LES implantation in dialysis patients. PES, which inhibits in-stent restenosis and cardiac events in hemodialysis patients, may play an important role in suppression of the chronic inflammatory response in target lesions as compared with SES.²⁵⁾ It is well known that patients on dialysis have more complex coronary lesions, and/or multivessel disease, compared with non-dialysis patients, and are at very high risk of death from coronary artery disease.^{48,49)} It has been shown that sirolimus effects are lacking or minimized in a significant number of HD patients, especially in severely calcified lesions.⁵⁰⁾ Severely calcified lesions may interfere with diffusion of the more hydrophilic anti-proliferative drugs such as sirolimus, but PES may be less influenced by the adverse lesion conditions than SES as paclitaxel is a hydrophobic potent anti-neoplastic agent and inhibits leptin.⁵¹⁾ Of note, TLR means the stenting site has stenosis progression, while no TLR does not mean the stenting site has no progression. Second generation DES (EES/ZES) have better crossability than PES with an improved platform (stent architecture/alloy/polymer, etc), so we can treat an in-stent restenosis lesion that we cannot treat with PES. This is another possibility for dialysis patients receiving PES to have lower risk of TLR. Thus, whether paclitaxel stents have favorable effects on dialysis patients requires further investigations.

Limitations: Several limitations in the present study must be carefully addressed. First, the pooled results of our review were derived from both randomized controlled trials and retrospective studies. Potential biases such as selec-

tion bias and treatment bias may exist in the original non-randomized studies. Second, our analyses of clinical outcomes after second-generation LES implantation combined data for EES and ZES implantation because separate analyses for EES and ZES were subject to limited studies. For example, in dialysis patients, the majority of studies compared SES and PES implantation, and only one study¹⁶⁾ included in our meta-analysis provided related data on ZES or EES versus PES in those patients, which prevented us from performing subgroup analysis of second-generation DES versus PES. Third, the outcomes of clinical adverse events could be associated with different stages of CKD, but we only restricted our analysis to dialysis patients. Other stages of CKD could not be stratified and analyzed from the data of the included studies. Fourth, the present study used summarized published event rates for each trial as opposed to individual patient data. Access to individual patient-level data would have enabled further subgroup analyses and propensity analyses to account for any differences in preprocedural risk thereby allowing a better stratification of patients and reduction in potential bias.

All of these limitations may explain the high level of heterogeneity between studies analyzing some adverse outcomes. Notwithstanding the limitations, this study is the first meta-analysis to perform head-to-head comparisons of LES versus PES implantation in patients with CKD as well as patients on chronic dialysis and has shed some light on the optimal stent choice in those patients. Large adequately-powered randomized controlled trials are warranted to confirm the results.

Conclusions

In patients with CKD, first-generation LES and PES implantation had comparable mortality and morbidity. Second-generation LES implantation was superior to PES in reducing long-term mortality, MACE, and stent thrombosis. However, PES may be more effective than LES in dialysis patients.

Disclosures

Availability of data and materials: All data and materials used in this research are freely available in electronic databases. References have been provided.

Conflicts of interest: None.

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