Systematic Review and Meta-Analysis

Medicine®

OPEN

Polymer-free drug-eluting stents versus permanent polymer drug-eluting stents

An updated meta-analysis

Yun-lin Chen, PhD, Jinqi Fan, PhD, Guozhu Chen, PhD, Li Cao, PhD, Li Lu, PhD, Yanping Xu, PhD, Yuehui Yin, MD*

Abstract

Background: Polymer-free drug-eluting stents (PF-DES) have been demonstrated comparable to permanent polymer drug-eluting stents (PP-DES) during long-term follow-up. As a critical component of drug-eluting stents, antiproliferative drugs may be a confounding factor for the results. Thus, we sought to compare the outcomes of these stents during long-term follow-up, especially in consideration of different stent platforms with the same drugs.

Methods: A systemic search was performed to identify the related randomized controlled trials comparing PF-DES with PP-DES. Primary outcomes included short (≤1 year) and long-term (>1 year) target lesion revascularization (TLR), short-term in-stent late luminal loss (LLL) and diameter stenosis (DS). Subgroup analyses stratified by the different platforms with the same proliferative drugs were conducted in TLR, LLL, and DS. Standardized mean differences (SMDs) and risk ratios (RRs) were estimated using fixed /random effects models

Results: A total of 6927 patients extracted from 12 RCTs were enrolled in the meta-analysis. No differences were observed in clinical outcomes of short-term and long-term overall mortality, myocardial infarction and stent thrombosis and angiographic outcomes of short-term in-stent LLL and DS between PF-DES and PP-DES for patients with coronary artery lesions. Nevertheless, compared with PP-DES coated with the same proliferative drugs, PF-DES had significantly increased risks of in-stent LLL (SMD, 0.49; 95% confidence interval [CI], 0.25–0.72) and DS (SMD, 0.67; 95% CI, 0.27–1.07), and long-term TLR (RR, 1.64; 95% CI 1.13–2.39). There were no significant differences in other outcomes.

Conclusions: Under the condition of using same antiproliferative drugs (paclitaxel or sirolimus) in different stent systems, PF-DES are associated with the increased risk of restenosis compared to PP-DES.

Abbreviations: BMS = bare metal stents, CAD = coronary artery disease, CIs = confidence intervals, DES = drug-eluting stents, DS = diameter stenosis, LLL = late luminal loss, PES = paclitaxel-eluting stents, PF-DES = polymer-free drug-eluting stents, PP-DES = permanent polymer drug-eluting stents, PRISMA = preferred reporting items for systematic reviews and meta-analyses, RCTs = randomized controlled trials, RRs = risk ratios, SES = sirolimus-eluting stents, SMDs = standardized mean differences, ST = stent thrombosis, STEMI = ST-segment elevation myocardial infarction, TLR = target lesion revascularization.

Keywords: antiproliferative drug, meta-analysis, permanent polymer drug-eluting stent, polymer-free drug-eluting stent

1. Introduction

Drug-eluting stents (DES) composed of metal stent platforms, antiproliferative drugs, and polymer coatings reduce the risk of in-stent restenosis compared to bare metal stents.[1] However, serious concerns also arise from late complications of DES such as late or very late stent thrombosis (ST).[2] Polymer residue has been demonstrated as a leading cause of the late complications. So, polymer-free DES (PF-DES) have been developed and widely used in clinical practice to prevent restenosis after stent implantation.

Since the introduction of PF-DES, several randomized controlled trials (RCTs) and meta-analyses have shown little difference between PF-DES and permanent polymer DES (PP-DES) for the treatment of coronary artery disease (CAD).[3] Of note, plenty of evidence demonstrates that antiproliferative drugs have significant impacts on the efficacy and safety of DES, in addition to stent coating strategies and platforms.[4] Previous studies often compared polymer-free platforms to polymer-based platforms coated with different antiproliferative drugs, which may bring bias to outcomes. Recently, we noticed that some

Editor: Danny Chu.

Y-lC and JF contributed equally to the work.

This study was partly supported by grants from the National Natural Science Foundation of China (grant no. 81570302, no. 81500250).

The authors have no conflicts of interest to disclose.

Supplemental Digital Content is available for this article.

Department of Cardiology, The 2nd Affiliated Hospital of Chongqing Medical University, Chongqing, China.

* Correspondence: Yuehui Yin, Department of Cardiology, The 2nd Affiliated Hospital of Chongqing Medical University, Chongqing, China (e-mail: yinyh63@163.com).

Medicine (2019) 98:15(e15217)

Received: 29 October 2018 / Received in final form: 18 January 2019 / Accepted: 19 February 2019

http://dx.doi.org/10.1097/MD.0000000000015217

studies aimed to explore the difference between the distinct polymer platforms coated with the same antiproliferative drugs, and acquired valuable data.

Therefore, we performed an updated meta-analysis comparing the safety and efficacy profiles of PF-DES vs. PP-DES in patients with CAD and especially analyzed the data of different polymer platforms with the same antiproliferative drugs to gather better insight of this issue.

2. Methods

This study was not conducted directly on humans and ethical approval was therefore not necessary.

2.1. Literature search strategy

This meta-analysis was conducted based on the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement.[5] An electronic search was conducted independently by 2 authors (C.Y.L. and F.J.Q.) from inception to March 5, 2018, first in PubMed, EMBASE, Web of Science, CENTRAL databases, and then in the relevant websites. Relevant reviews and editorials from major medical journals published within the last year were identified and assessed for possible information on the trials of interest. Keywords included "drug-eluting stent," "polymer free," "non-polymer," "permanent polymer," and "randomized controlled trials." No language restriction was applied. In addition, the reference lists of eligible articles were checked manually to include other potentially eligible trials.

2.2. Study selection

The following inclusive criteria were proposed for all included trials: population: patients with ischemic symptoms or evidence of myocardial ischemia due to de novo native coronary artery lesions who underwent percutaneous coronary interventions; intervention: PF-DES; comparison: PP-DES; outcomes: clinical and angiographic outcomes; study design: RCTs; titles and abstracts of records were screened independently by 2 authors (C.Y.L. and F.J.Q.). Those meeting inclusion criteria were selected for more detailed evaluation. Disagreement on trial selection was settled by discussion.

2.3. Study outcomes

The short ($\leq$1 year) and long-term (>1 year) clinical outcomes of this meta-analysis were overall mortality, myocardial infarction (MI), stent thrombosis (ST), and target lesion revascularization (TLR). The short-term angiographic outcomes were in-stent late luminal loss (LLL) and diameter stenosis (DS). The primary outcomes included TLR and short-term in-stent LLL and DS.

2.4. Data extraction and assessment of quality

Two responsible investigators independently extracted following prespecified data elements from each trial: trial name, first author, year of publication, study design, stent type, the number of patients, patient characteristics, primary endpoint, follow-up duration, clinical outcomes, angiographic outcomes, and other study characteristics. The quality of eligible studies was measured using the Cochrane Collaborations tool for assessing the risk of bias for RCTs. The disagreement was resolved by discussion and consensus. The kappa statistic was calculated to quantify the agreement between the 2 investigators on selection and quality assessment of the studies.

2.5. Statistical analysis

Outcomes were analyzed based on the intention-to-treat principle. All analyses were performed according to the Cochrane handbook for systematic reviews of interventions.[6] Differences were expressed as relative risk ratios (RRs) with 95% confidence intervals (CIs) for dichotomous outcomes, and standardized mean differences (SMDs) were with 95% CIs for continuous outcomes. I^2 statistic was used to assess statistical heterogeneity across studies, with I^2 statistic values <25%, 25% to 50%, and >50% considered a low, moderate, and a high degree of heterogeneity, respectively. Fixed and random effect models were used to calculate summary RRs with the Mantel–Haenszel or DerSimonian and Laird method, respectively. In the case of high heterogeneity (>50%), the random effects model was used.[7] Subgroup analyses were performed to assess the primary outcomes of PF-DS compared to PP-DES after controlling the effect of antiproliferative drugs. Sensitivity analyses for every outcome of interest were performed to assess the influence of each of the studies on the pooled effects. Potential publication bias was examined by constructing funnel plots. Where significant bias was detected, a trim-and-fill analysis was applied.[8] Statistical significance was set at 2 side $P < .05$. All CIs were calculated at the 95% level for the overall effect estimates. Statistical analyses were performed with R 3.4 statistical software (R Core Team, Auckland, New Zealand).

3. Results

3.1. Literature search and quality assessment

Twelve RCTs (17 publications) were eventually selected for data extraction [9–25] (Fig. 1). Agreement between investigators on study selection was good (kappa = 0.95). Among them, 5 trials showed various risks of bias across the domains [13,14,22,24,25] (Fig. 2). Agreement between investigators on the quality assessment of studies was completed (kappa = 1).

3.2. Characteristics of the studies and patients included

The main characteristics of the included trials are shown in Table 1. Twelve RCTs enrolled 6927 patients in which 3825 with PF-DES and 3102 with PP-DES. Only 7 trials enrolled patients with MI,[9,11,13,14,16–18,22,24,25] of which 2 trials exclusively enrolled patients with ST-segment elevation MI.[14,24] And, 16.8% to 100% of the candidates were diabetics, and 67.8% to 79.3% were men; the duration of consuming thienopyridines was >6 months. Paclitaxel or sirolimus was used in most trials. The duration of follow-up 12 months in 11 of the trials, 24 months in 5 of the trials, 60 months in the other 5 trials. Only 1 trial was a single-center RCT,[14] and the rest included were multicenter RCTs.[9–13,15–25]

3.3. Primary outcomes

Results at short-term follow-up were available in 9 studies demonstrating the similar performance of both PP-DES and PF-DES in TLR (RR = 0.95, 95% CI 0.8–1.12, $P = .50$; $I^2 = 0\%$, $P = .50$) (Table 2). A subgroup analysis stratified by different

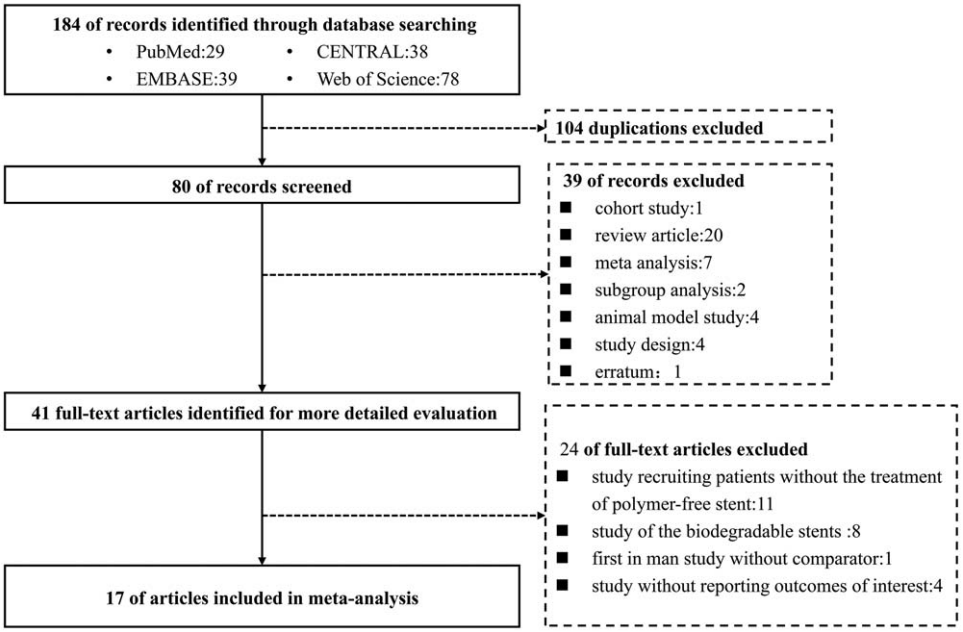

Figure 1. Flow diagram indicating the process of selecting literature for meta-analysis.

coating platform with the same antiproliferative drugs showed no statistical significance in short-term TLR (RR = 0.90, 95% CI 0.76–1.07, $P = .24$; $I^2 = 0\%$, $P = 0.80$; RR = 1.63, 95% CI 0.9–2.5, $P = .10$) (Fig. 3). Eight trials yielded data on long-term TLR showed no significant difference between PF-DES and PP-DES (RR = 1.07, 95% CI 0.83–1.39, $P = .58$; $I^2 = 55\%$, $P = .03$) (Table 2). However, the subgroup analysis including 3 trials showed significantly increased risk of TLR in PF-DES compared to PP-DES coated with the same antiproliferative drugs (RR = 1.64, 95% CI 1.13–2.39, $P < .01$; $I^2 = 40\%$, $P = .19$) (Fig. 3). The interaction test yielded chi-squared test = 7.44, $P < .01$, showing significant difference between the subgroups (Fig. 3). No publication bias was detected by the funnel plots (See Supplemental Figure 1, Supplemental Content, http://links.lww.com/MD/C917). The sensitivity analyses showed that no trial significantly affected the above results (See Supplemental Figure 2, Supplemental Content, http://links.lww.com/MD/C917).

The enough data on in-stent LLL and in-stent DS were only reported at short-term follow-up by 10 studies (6391 patients) and showed in-stent LLL (SMD = 0.08, 95% CI, −0.13 to 0.28, $P = .48$) and DS (SMD = 0.16, 95% CI, −0.15 to 0.47, $P = .30$) did not differ significantly across the treatment groups (Table 2). High heterogeneity across studies were noted ($I^2 = 92\%$, $P < .01$; $I^2 = 94\%$, $P < .01$) (Table 2). The significantly higher late loss (SMD = 0.49; 95% CI, 0.25–0.72, $P < .01$) and worsen diameter stenosis (SMD = 0.67; 95% CI, 0.27–1.07, $P < .01$) were observed in the PF-DES than those in the PP-DES with the same drugs (Fig. 3). Subgroup interaction test showed a significant difference between the subgroups (chi-squared test = 11.08, $P < .01$) (Fig. 3). No publication bias was reflected in the funnel plots (See Supplemental Figure 1, Supplemental Content, http://links.lww.com/MD/C917). The sensitivity analyses showed that no trial significantly affected the above results (See Supplemental Figure 2, Supplemental Content, http://links.lww.com/MD/C917).

3.4. Secondary outcomes

For short-term clinical outcomes, the combination of results from these trials indicated no significant effects of PF-DES on overall mortality (RR = 0.81; 95% CI, 0.6–1.09, $P = .17$), MI (RR = 1.12; 95% CI, 0.84–1.5, $P = .45$), ST (RR = 1.16; 95% CI, 0.75–1.80, $P = .50$) (Table 2). There was no evidence of heterogeneity (Table 2) and the indication of publication bias in each short-term clinical outcome (See Supplemental Figure 1, Supplemental Content, http://links.lww.com/MD/C917). Sensitivity analyses confirmed that no trial significantly affected the pooled results of each short-term clinical outcome (See Supplemental Figure 2, Supplemental Content, http://links.lww.com/MD/C917).

With respect to long-term clinical outcomes, PF-DES were not associated with any decrease in the risk of MI (RR = 1.07; 95% CI, 0.84–1.37; $P = .58$), and ST (RR = 0.87; 95% CI, 0.56–1.34, $P = .52$); there was no evidence of heterogeneity (Table 2). PF-DES had a similar risk of overall mortality compared with PP-DES (RR = 0.87; 95% CI, 0.75–1, $P = .05$) (Table 2). Of note, the trim-and-fill analysis with adding 2 studies yield a significant difference between PF-DES and PP-DES in long-term overall mortality (adjusted RR = 0.85, 95% CI, 0.74–0.97, $P = .97$) (See Supplemental Figure 1, Supplemental Content, http://links.lww.com/MD/C917). Besides, the sensitivity analysis, performed by removing each of the studies one at a time, demonstrated that a single study influenced the overall result (See Supplemental Figure 2, Supplemental Content, http://links.lww.com/MD/C917). Indeed, this result should be interpreted with caution.

4. Discussion

To our knowledge, this is an updated meta-analysis which focuses on efficacy and safety of PF-DES compared to PP-DES after controlling the confounding effect of antiproliferative drugs. In contrast with previous studies, we found that PF-DES had a higher risk of clinical and angiographic restenosis, as compared

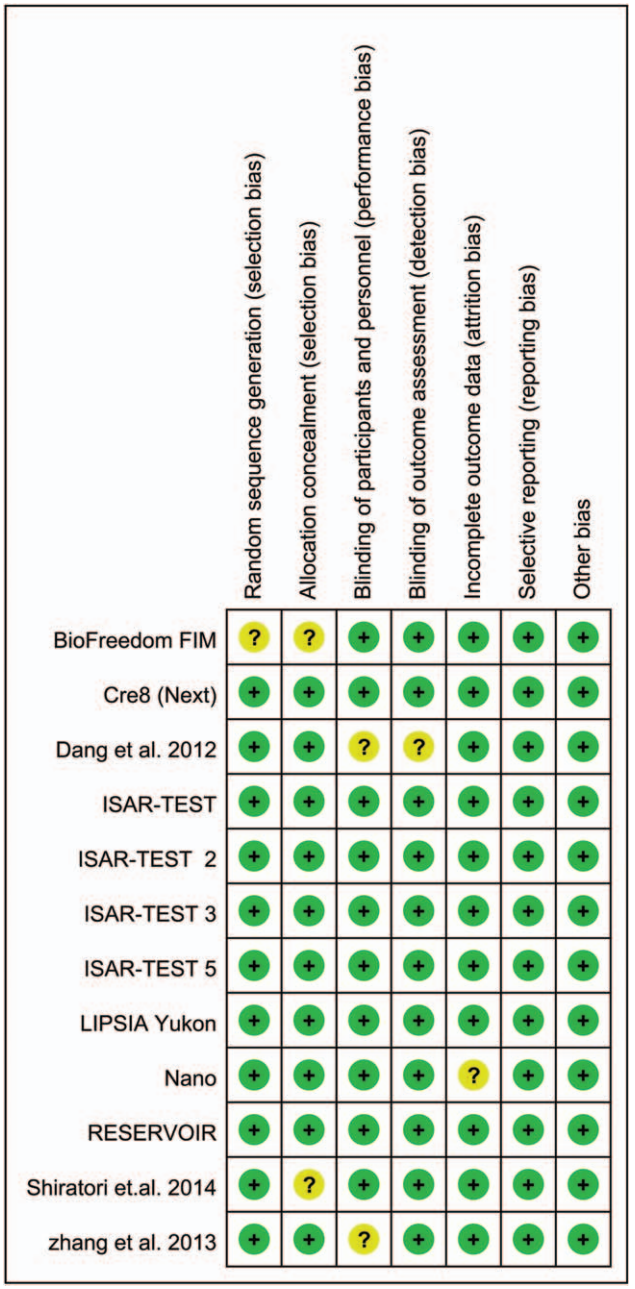

Figure 2. Risk of bias summary.

to the PP-DES coated with the same first generation antiproliferative drugs such as paclitaxel and sirolimus.

As a critical component of DES, antiproliferative drugs may be a confounder for comparing efficacy and safety between PF-DES and PP-DES for patients with CAD. More and more evidence suggests that sirolimus-eluting stents (SES) are superior to paclitaxel-eluting stents (PES) in terms of a significant reduction in the risk of reintervention and ST.[26] A recent network meta-analysis has confirmed that second-generation DES outperform first-generation DES for long-term safety and efficacy outcomes.[27] In this study, we pooled results from the studies that compared different stent platforms coated with different antiproliferative drugs and showed that the PF-DES had similar anti-restenotic efficacy as compared with PP-DES. Although this result is consistent with previous studies, it is not an impeccable data from the Intracoronary Stenting and Angiographic Restenosis - Test Equivalence Between Drug-Eluting Stents (ISAR-TEST) (PF-SES vs. PP-PES) suggested that the PF-DES exerted an equivalent anti-restenotic efficacy as PP-DES,[20] but the ISAR-TEST 3 (PF-SES vs. PP-SES) showed that PF-DES were inferior to PP-DES in anti-restenotic efficacy.[19] Of note, the same PF-DES (Yukon stents coated with sirolimus) were employed in the ISAR-TEST and ISAR-TEST 3 trials, and the LLL and TLR in the PF-DES of these 2 trials were almost identical. Therefore, those differences could be attributed to the different antiproliferative drugs. Antiproliferative drugs used in the PF-DES were better than in the PP-DES, which likely hid the real effect of different drug carrier vehicles on the anti-restenotic performance of stents.

Only if antiproliferative drugs match perfectly with drug carrier vehicles, DES could have excellent anti-restenotic performance. Antiproliferative drugs have significant influences on the efficacy and safety profiles of DES, in addition to metal stent platforms and polymer coatings.[4] Previous meta-analyses did not compare PF-DES with PP-DES coated with the same antiproliferative drugs due to the lack of adequate original studies.[3] Recently, adequate data were available for the subgroup analysis stratified by the same antiproliferative drugs, in which the material of all stents was 316L stainless steel; PF-DES and PP-DES had similar strut thickness and drug kinetic profile; PF-DES had the higher dose of the antiproliferative drugs compared to PP-DES (Table S1).[11,22,24] Theoretically, the PF-DES could have better anti-restenotic performance. Interestingly, greater LLL and higher rates of long-term TLR were found in the PF-DES. One explanation could be more drug loss during the placement of PF-DES as compared with PP-DES. Pre-clinical studies estimate that up to 40% of drugs are lost during the delivery of PF-DES.[28] Another explanation could be a larger surface injury of stents during the placement of PF-DES than PP-DES. Numerous patients with complex coronary lesions (type B2/C) were enrolled in the ISAR-TEST 3 (Yukon) and the trial by Shiratori et al[22], (Axxion).[19] After analyzing the DES that failed to be implanted in tortuous and calcified vessels by scanning electron microscopy, Wiemer et al, found larger areas of stents surface injury in PF-DES (Yukon and Axxion) than in PP-DES. Larger surface injury means more antiproliferative drugs wiped off the surface of the PF-DES during stent delivery and deployment.[29] Hence the increased neointimal proliferation and subsequent restenosis were prone to occur in the PF-DES arms (Axxion or Yukon).

This meta-analysis has some limitations that should be addressed. Our study did not perform at the individual level, and also shared the limitations from the original studies. For long-term overall mortality, the pooled effect was influenced by any single trial. Nevertheless, this meta-analysis suggests that PF-DES are at least as safe as PP-DES. For primary outcomes, only 3 trials were included in the subgroup that stratified based on the different stent platforms coated with the same antiproliferative drugs, which may weaken the strength of outcomes. In addition, the antiproliferative drugs used in these DES systems merely were the first generation. To date, there are no trials comparing PF-DES with PP-DES coated with the same newest antiproliferative drugs such as zotarolimus and everolimus. More importantly, inflammation is closely associated with plaques that have caused acute CAD.[30] Inflammation also can induce the accelerated development of neoatherosclerosis that plays a critical role in the restenosis after stent implantation.[31] Hence, it is not hard to infer that patient selection (chronic or acute CAD) could influence

Table 1

Main characteristics of studies included.

Trial	Reference	Year	Stent type	Study design	Number of patients (n)	Patient characteristics	D.M (%)	Male (%)	Duration of thienopyridines (months)	Primary endpoint	Angiographic follow-up (months)	Clinical follow-up (months)	Maximum follow-up (months)
BioFreedom FIM	[13]	2016	PF -BA9 versus PP-PES	RCT, 4 centers	182	SA/UA/STEMI	27.5	69.8	≥6	LLL (in-stent)	4,12	12,60	60
Cre8 (NEXT)	[12]	2012	PF-AES versus PP-PES	RCT, 11 centers	323	SA/UA	26.9	72.1	≥6	LLL (in-stent)	6	12	60
Dang	[14]	2012	PF-PES versus PP-SES	RCT, 1 center	105	STEMI	25.7	69.5	–	angiographic outcomes	6	12	12
ISAR-TEST	[20]	2006	PF-SES versus PP-PES	RCT, 2 centers	450	SA/UA	29.1	76.9	≥6	LLL (in-stent)	6 to 9	9	60
	[16]	2012								MACEs		60	
ISAR-TEST-2	[11]	2009	PF-SPES versus PP-SES versus PP-ZES	RCT, 2 centers	1007	SA/UA/MI	27.4	76.7	≥6	BAR (in segment) MACEs	8	12	24
	[9]	2010								TLR	24	24	
ISAR-TEST-3	[19]	2008	PF-SES versus PP-SES	RCT, 3 centers	403	SA/UA	41.2	79.3	≥6	LLL (in-stent)	6 to 8	12	24
	[10]	2009								TLR	24	24	
ISAR-TEST-5	[18]	2011	PF-SPES versus PP-ZES	RCT, 2 centers	3002	SA/UA/STEMI	29	76.4	≥6	MACEs	6 to 8	12	60
	[17]	2016										60	
LIPSIA Yukon	[15]	2011	PF-SES versus PP-PES	RCT, 3 centers	240	SA/UA	100	68.6	12	LLL (in-stent)	9	9	60
	[23]	2013								MACEs		60	
Nano	[24]	2014	PF-SES versus PP-SES	RCT,19 centers	291	STEMI	16.8	76.63	≥24	LLL (in-stent)	9	24	24
RESE RVOIR	[21]	2016	PF-AES versus PP-EES	RCT, 5 centers	112	SA/UA	100	75	12	NVO	9	8,12	12
Shiratori	[22]	2014	PF-PES versus PP-PES	RCT, 20 centers	164	SA/UA/NSTEMI	32.3	72.6	≥6	LLL	9	24	24
Zhang	[25]	2013	PF-PES versus PP-SES	RCT, 5 centers	648	SA/UA/MI	43.5	67.8	≥12	MACEs	-	24	24

AES = Amphilimus-eluting stent, BA9 = Biolimus A9-eluting stent, BAR = Binary angiographic restenosis, EES = Everolimus-eluting stent, LLL = late luminal loss, MACE = major adverse cardiac event, MI = myocardial infarction, NSTEMI = non-ST-segment elevation myocardial infarction, NVO = neointimal volume obstruction, PES = paclitaxel-eluting stent, PF = polymer free, PP = permanent polymer, SA = stable angina, SES = sirolimus-eluting stent, SPES = sirolimus- and probucol-eluting stent, ST = stent thrombosis, STEMI = ST-segment elevation myocardial infarction, TLR = target lesion revascularization, TVR = target vessel revascularization, UA = unstable angina.

Table 2

Intervention effects of PF-DES vs. PP-DES on all outcomes during long-term follow-up.

Outcomes	Studies (N)	Events/patients (N)		Methods	Test for overall effect				Heterogeneity				
		PF	PP		Effect size	95% CI	Z test	*P* value	Chi-square	df	*P* value	I^2	ζ
Clinical outcomes													
Overall mortality													
Short-term	9	95/3255	82/2534	M-H	RR: 0.81	0.60; 1.09	−1.37	.17	2.95	8	.94	0.00	0.00
Long-term	9	413/3544	299/2812	M-H	RR: 0.87	0.75;1.00	−1.97	.05	3.66	8	.89	0.00	0.00
Myocardial infarction													
Short-term	9	113/3255	76/2534	M-H	RR: 1.12	0.84;1.50	0.76	.45	2.93	8	.94	0.00	0.00
Long-term	9	149/3544	110/2812	M-H	RR: 1.07	0.84;1.37	0.55	.58	3.34	8	.91	0.00	0.00
Stent thrombosis													
Short-term	8	51/3255	34/2534	M-H	RR: 1.16	0.75;1.80	0.68	.50	2.15	7	.95	0.00	0.00
Long-term	7	33/1542	45/1812	M-H	RR: 0.87	0.56;1.34	−0.64	.52	1.60	6	.95	0.00	0.00
Target lesion revascularization													
Short-term	9	308/3255	259/2534	M-H	RR: 0.95	0.80;1.12	−0.67	.50	7.37	8	.50	0.00	0.00
Long-term	8	441/3217	337/2491	D+L	RR: 1.07	0.83;1.39	0.55	.58	15.53	7	.03	0.55	0.07
Angiographic outcomes													
In-stent diameter stenosis													
Short-term	9	1321	1709	D+L	SMD: 0.16	−0.15;0.47	1.03	.30	128.80	8	<.001	0.94	0.21
In-stent late luminal loss													
Short-term	10	3551	2840	D+L	SMD: 0.08	−0.13;0.28	0.71	.48	108.22	9	<.001	0.92	0.10

our results. We failed to conduct subgroup analyses to make clear if types of CAD can influence our results because limited information was provided in the included studies. We hope future studies could eventually clarify this issue.

5. Conclusions

In this meta-analysis, there were no differences observed in clinical outcomes of short-term and long-term overall mortality, MI and ST, and in angiographic outcomes of short-term in-stent

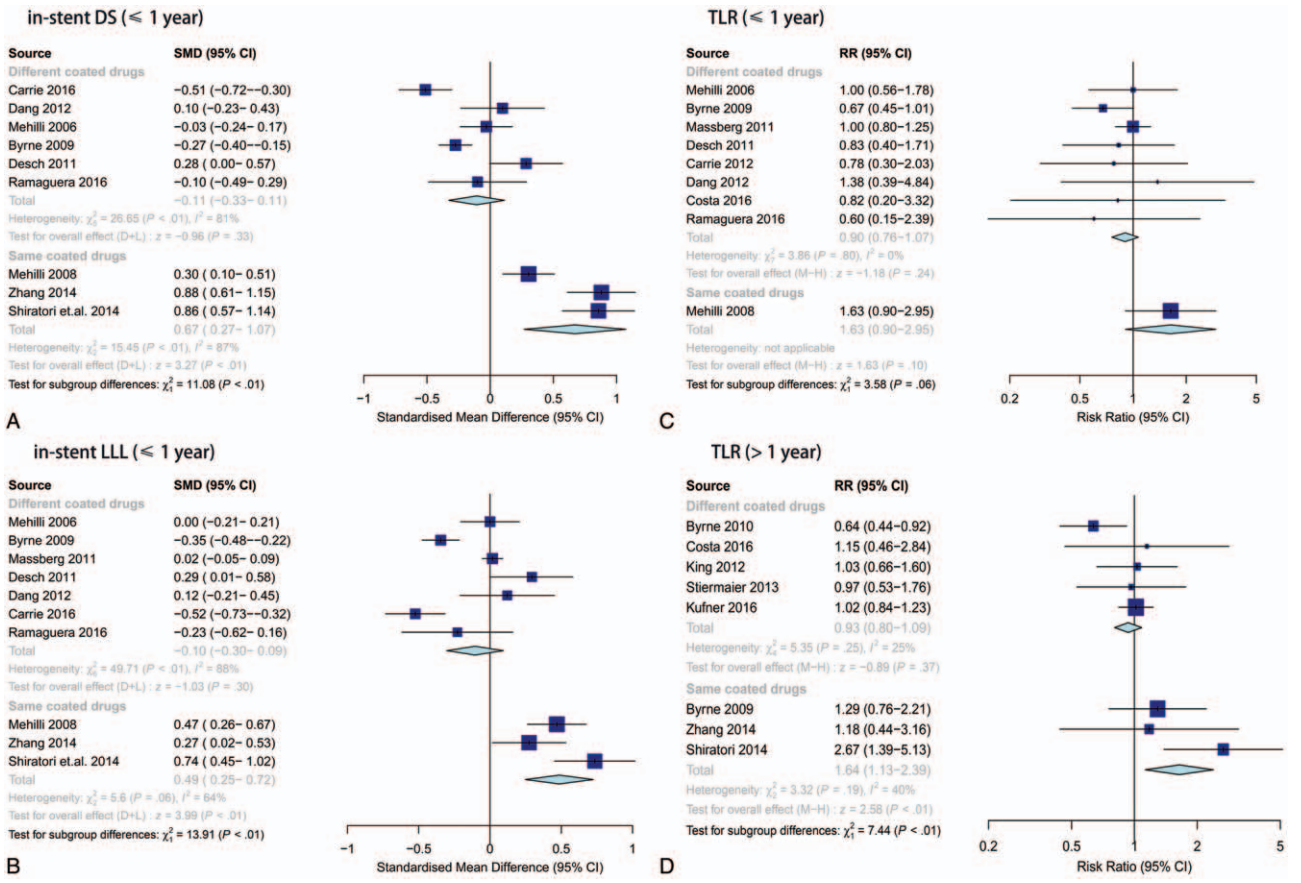

Figure 3. Subgroup analyses of primary outcomes comparing between PF-DES group and PP-DES group. PF-DES = polymer-free drug-eluting stents, PP-DES = permanent polymer drug-eluting stents.

LLL and DS between PF-DES and PP-DES for patients with coronary artery lesions. When stratified by different stent platforms with the same antiproliferative drugs (paclitaxel or sirolimus), PF-DES were associated with an increased risk of restenosis as compared to PP-DES. Polymer seems to play an important role in the anti-restenotic performance of DES.

Author contributions

Conceptualization: Yunlin Chen, Jinqi Fan, Yuehui Yin.
Data curation: Yunlin Chen, Jinqi Fan.
Formal analysis: Yunlin Chen.
Funding acquisition: Yuehui Yin.
Investigation: Yunlin Chen.
Methodology: Yunlin Chen.
Software: Yunlin Chen, Yanping Xu.
Visualization: Yunlin Chen.
Writing – original draft: Yunlin Chen, Jinqi Fan.
Writing – review & editing: Yunlin Chen, Jinqi Fan, Guozhu Chen, Li Cao, Li Lu, Yanping Xu, Yuehui Yin.

References

[1] Kang SH, Park KW, Kang DY, et al. Biodegradable-polymer drug-eluting stents vs. bare metal stents vs. durable-polymer drug-eluting stents: a systematic review and Bayesian approach network meta-analysis. Eur Heart J 2014;35:1147–58.
[2] Camenzind E, Steg PG, Wijns W. Stent thrombosis late after implantation of first-generation drug-eluting stents: a cause for concern. Circulation 2007;115:1440–55.
[3] Navarese EP, Kowalewski M, Cortese B, et al. Short and long-term safety and efficacy of polymer-free vs. durable polymer drug-eluting stents. A comprehensive meta-analysis of randomized trials including 6178 patients. Atherosclerosis 2014;233:224–31.
[4] Garg S, Bourantas C, Serruys PW. New concepts in the design of drug-eluting coronary stents. Nat Rev Cardiol 2013;10:248–60.
[5] Panic N, Leoncini E, de Belvis G, et al. Evaluation of the endorsement of the preferred reporting items for systematic reviews and meta-analysis (PRISMA) statement on the quality of published systematic review and meta-analyses. PLoS One 2013;8:e83138.
[6] Higgins JP, Green S. Cochrane handbook for systematic reviews of interventions version 5.1.0. The Cochrane Collaboration 2011;5:
[7] Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. BMJ 2003;327:557–60.
[8] Duval S, Tweedie R. Trim and fill: a simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. Biometrics 2000;56:455–63.
[9] Byrne RA, Kastrati A, Tiroch K, et al. 2-year clinical and angiographic outcomes from a randomized trial of polymer-free dual drug-eluting stents versus polymer-based Cypher and Endeavor [corrected] drug-eluting stents. J Am Coll Cardiol 2010;55:2536–43.
[10] Byrne RA, Kufner S, Tiroch K, et al. Randomised trial of three rapamycin-eluting stents with different coating strategies for the reduction of coronary restenosis: 2-year follow-up results. Heart 2009;95: 1489–94.
[11] Byrne RA, Mehilli J, Iijima R, et al. A polymer-free dual drug-eluting stent in patients with coronary artery disease: a randomized trial vs. polymer-based drug-eluting stents. Eur Heart J 2009;30:923–31.
[12] Carrie D, Berland J, Verheye S, et al. A multicenter randomized trial comparing amphilimus- with paclitaxel-eluting stents in de novo native coronary artery lesions. J Am Coll Cardiol 2012;59:1371–6.
[13] Costa RA, Abizaid A, Mehran R, et al. Polymer-free biolimus A9-coated stents in the treatment of de novo coronary lesions: 4- and 12-month angiographic follow-up and final 5-year clinical outcomes of the prospective, multicenter BioFreedom FIM Clinical Trial. JACC Cardiovasc Interv 2016;9:51–64.
[14] Dang Q, Li YJ, Gao L, et al. Six-month angiographic and one-year clinical outcomes of polymer free paclitaxel-eluting stent in patients with ST-segment elevation myocardial infarction: a comparison with permanent polymer sirolimus-eluting stent. Chin Med J (Engl) 2012;125:3393–7.
[15] Desch S, Schloma D, Mobius-Winkler S, et al. Randomized comparison of a polymer-free sirolimus-eluting stent versus a polymer-based paclitaxel-eluting stent in patients with diabetes mellitus: the LIPSIA Yukon trial. JACC Cardiovasc Interv 2011;4:452–9.
[16] King L, Byrne RA, Mehilli J, et al. Five-year clinical outcomes of a polymer-free sirolimus-eluting stent versus a permanent polymer paclitaxel-eluting stent: final results of the intracoronary stenting and angiographic restenosis: test equivalence between two drug-eluting stents (ISAR-TEST) trial. Catheter Cardiovasc Interv 2013;81:E23–28.
[17] Kufner S, Sorges J, Mehilli J, et al. Randomized trial of polymer-free sirolimus- and probucol-eluting stents versus durable polymer zotarolimus-eluting stents: 5-year results of the ISAR-TEST-5 Trial. JACC Cardiovasc Interv 2016;9:784–92.
[18] Massberg S, Byrne RA, Kastrati A, et al. Polymer-free sirolimus- and probucol-eluting versus new generation zotarolimus-eluting stents in coronary artery disease: the Intracoronary Stenting and Angiographic Results: Test Efficacy of Sirolimus- and Probucol-Eluting versus Zotarolimus-eluting Stents (ISAR-TEST 5) trial. Circulation 2011;124:624–32.
[19] Mehilli J, Byrne RA, Wieczorek A, et al. Randomized trial of three rapamycin-eluting stents with different coating strategies for the reduction of coronary restenosis. Eur Heart J 2008;29:1975–82.
[20] Mehilli J, Kastrati A, Wessely R, et al. Randomized trial of a nonpolymer-based rapamycin-eluting stent versus a polymer-based paclitaxel-eluting stent for the reduction of late lumen loss. Circulation 2006;113:273–9.
[21] Romaguera R, Gomez-Hospital JA, Gomez-Lara J, et al. A Randomized comparison of reservoir-based polymer-free amphilimus-eluting stents versus everolimus-eluting stents with durable polymer in patients with diabetes mellitus: the RESERVOIR Clinical Trial. JACC Cardiovasc Interv 2016;9:42–50.
[22] Shiratori Y, Cola C, Brugaletta S, et al. Randomized comparison between polymer-free versus polymer-based paclitaxel-eluting stent: two-year final clinical results. Circ Cardiovasc Interv 2014;7:312–21.
[23] Stiermaier T, Heinz A, Schloma D, et al. Five-year clinical follow-up of a randomized comparison of a polymer-free sirolimus-eluting stent versus a polymer-based paclitaxel-eluting stent in patients with diabetes mellitus (LIPSIA Yukon trial). Catheter Cardiovasc Interv 2014;83: 418–24.
[24] Zhang Y, Chen F, Muramatsu T, et al. Nine-month angiographic and two-year clinical follow-up of polymer-free sirolimus-eluting stent versus durable-polymer sirolimus-eluting stent for coronary artery disease: the Nano randomized trial. Chin Med J (Engl) 2014;127:2153–8.
[25] Zhang Y, Shen J, Li Z, et al. Two-year clinical outcomes of different drug-eluting stents with different polymer coating strategies in coronary artery heart disease: a multi-centre, randomised, controlled clinical trial. Int J Cardiol 2013;168:2646–52.
[26] Schomig A, Dibra A, Windecker S, et al. A meta-analysis of 16 randomized trials of sirolimus-eluting stents versus paclitaxel-eluting stents in patients with coronary artery disease. J Am Coll Cardiol 2007;50:1373–80.
[27] Palmerini T, Benedetto U, Biondi-Zoccai G, et al. Long-term safety of drug-eluting and bare-metal stents: evidence from a comprehensive network meta-analysis. J Am Coll Cardiol 2015;65:2496–507.
[28] Lansky AJ, Costa RA, Mintz GS, et al. Non-polymer-based paclitaxel-coated coronary stents for the treatment of patients with de novo coronary lesions: angiographic follow-up of the DELIVER clinical trial. Circulation 2004;109:1948–54.
[29] Wiemer M, Butz T, Schmidt W, et al. Scanning electron microscopic analysis of different drug eluting stents after failed implantation: from nearly undamaged to major damaged polymers. Catheter Cardiovasc Interv 2010;75:905–11.
[30] Libby P, Tabas I, Fredman G, et al. Inflammation and its resolution as determinants of acute coronary syndromes. Circ Res 2014;114:1867–79.
[31] Joner M, Finn AV, Farb A, et al. Pathology of drug-eluting stents in humans: delayed healing and late thrombotic risk. J Am Coll Cardiol 2006;48:193–202.