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, CI = 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. However, serious concerns also arise from late complications of DES such as late or very late stent thrombosis (ST). 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). 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. 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
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 in 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 (<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. I² statistic was used to assess statistical heterogeneity across studies, with I² 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 and 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-DES 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; I² = 0%, P = .50) (Table 2). A subgroup analysis stratified by different
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; I² = 0%, P = .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; I² = 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; I² = 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 (I² = 92%, P < .01; I² = 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...
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 re-reintervention and ST.

A recent network meta-analysis has confirmed that second-generation DES outperform first-generation DES for long-term safety and efficacy outcomes. 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, but the ISAR-TEST 3 (PF-SES vs. PP-SES) showed that PF-DES were inferior to PP-DES in anti-restenotic efficacy. 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. 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. 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).

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. 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, (Axxion). 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. 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. Inflammation also can induce the accelerated development of neoatherosclerosis that plays a critical role in the restenosis after stent implantation. 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           | [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                  | STEMII                  | 25.7    | 69.5    | –                                  | angiographic outcomes | 6                            | 12                        | 12                        |
| ISAR-TEST            | [20]      | 2006       | PF-PES versus PP-PES | RCT, 2 centers | 450                  | SA/UA                   | 29.1    | 76.9    | ≥6                                 | LLL (in-stent)       | 6 to 9                        | 9                         | 60                        |
| ISAR-TEST-2          | [11]      | 2010       | PF-SPE vs PP-ZES    | RCT, 2 centers | 1007                 | SA/UA/MI                | 27.4    | 76.7    | ≥6                                 | BAR (in segment) MACEs | 8                            | 12                        | 24                        |
| ISAR-TEST-3          | [18]      | 2008       | PF-SPE vs PP-ZES    | RCT, 3 centers | 403                  | SA/UA                   | 41.2    | 79.3    | ≥6                                 | MACEs               | 24                           | 24                        | 24                        |
| ISAR-TEST-5          | [17]      | 2011       | PF-SPE vs PP-ZES    | RCT, 2 centers | 3002                 | SA/UA/STEMI             | 29      | 76.4    | ≥6                                 | MACEs               | 6 to 12                       | 12                        | 60                        |
| UPSA                 | [23]      | 2011       | PF-SPE vs PP-ZES    | RCT, 3 centers | 240                  | SA/UA                   | 100     | 68.6    | 12                                 | MACEs               | 9                            | 9                         | 60                        |
| Yukon                | [24]      | 2013       | PF-SPE vs PP-ZES    | RCT, 19 centers | 291                  | STMII                   | 16.8    | 76.63   | ≥24                                | LLL (in-stent)       | 9                            | 24                        | 24                        |
| Nano                 | [21]      | 2016       | PF-PES versus PP-PES | RCT, 5 centers | 112                  | SA/UA                   | 100     | 75      | 12                                 | NVO                 | 8                            | 12                        | 12                        |
| RESM                 | [20]      | 2014       | PF-PES versus PP-PES | RCT, 20 centers | 160                  | SA/UA/STEMI             | 32.3    | 72.6    | ≥6                                 | LLL                 | 9                            | 24                        | 24                        |
| Shiratori            | [22]      | 2013       | PF-PES versus PP-PES | RCT, 5 centers | 60                   | SA/UA/STEMI             | 32.3    | 72.6    | ≥6                                 | MACEs               | -                            | 24                        | 24                        |

AES = Amphiphilimus-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, STEMII = ST-segment elevation myocardial infarction, TLR = target lesion revascularization, TVR = target vessel revascularization, UA = unstable angina.
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
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.

Formal analysis: Yunlin Chen.

Investigation: Yunlin Chen.

Funding acquisition: 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.

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