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Review

Polymer-free versus permanent polymer drug eluting stents in coronary artery disease: A meta-analysis of 10 RCTs with 6575 patients

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Abstract

Background: Permanent polymer drug eluting stents (PP-DES) may induce inflammation of the vessel wall due to the existence of the polymer, which may delay intimal healing. Polymer-free DES (PF-DES) that eliminate the polymeric carrier may potentially lead to safer DES. However, the safety and efficacy of PF-DES remains controversial.

Methods: Randomized controlled trials comparing PF-DES with PP-DES were searched in online database including MEDLINE, Excerpta Medica Database (EMBASE) and Cochrane Library. Studies reporting late lumen loss (LLL), all-cause death, myocardial infarction (MI), target lesion revascularization (TLR) and late stent thrombosis (LST) were enrolled and quantitatively analyzed.

Results: Ten studies enrolling 6575 patients were included in this meta-analysis. The PF-DES showed a benefit in reducing all-cause death ($OR = 0.77$, 95% *CI*: 0.61 to 0.98, $P = 0.03$) and long-term LLL (weighted mean difference (WMD) −0.16 mm, 95% *CI*: −0.22 to −0.11 mm, $P < 0.001$), while no superiority was found in reducing short-term LLL (WMD 0.03 mm, 95% *CI*: −0.07–0.13 mm, $P = 0.57$), MI ($OR = 1.12$, 95% *CI*: 0.19 to 23.18, $P = 0.39$), TLR ($OR = 1.19$, 95% *CI*: 0.42 to 3.38, $P = 0.83$) and LST ($OR = 0.92$, 95% *CI*: 0.05 to 5.71, $P = 0.74$).

Conclusion: PF-DES showed benefits in reducing long-term LLL and mortality compared with PP-DES, but no superiority was found in short-term LLL, MI, TLR and LST. These findings provide a sound basis for the wide application of PF-DES in the future.

Keywords: Drug eluting stent; Polymer-free DES; Meta-analysis

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Introduction

Drug eluting stents (DES) coated with anti-proliferative agents have been proven to reduce the incidence of restenosis and target lesion revascularization (TLR) by inhibition of neointimal hyperplasia.[1,2] However, DES are also associated with a higher rate of late stent thrombosis (LST) as compared with bare metal stents (BMS).[3,4]

A permanent polymer coating is used to bind the anti-proliferative drugs to the stent platform and control the drug release. The polymer stays *in situ* after the drug is released, which can cause chronic inflammation and can delay the endothelial healing.[5,6] Therefore, efforts have been made to develop stents with biodegradable polymers or with polymer-free surfaces. There have been several studies of whether polymer-free stents can produce a better clinical outcome compared with permanent polymer stents but there are conflicting results about the clinical outcomes.

This meta-analysis aims to summarize the data from randomized controlled trials (RCT) comparing permanent polymer DES (PP-DES) with polymer-free DES (PF-DES).

Methods

Search strategy

The meta-analysis was performed according to the Cochrane handbook for systematic reviews of interventions 5.1.0.[7] A systematic review was performed in MEDLINE, EMBASE, Cochrane Library, Scopus, Highwire Press and Google Scholar databases for publications until December, 2015. The search was conducted without language restriction by two independent investigators using the keywords “stent”, “drug eluting”, “polymer-free”, “nonpolymer”, “polymer” and “randomized”. Endnote X6 was used to build a library of references and to erase duplicated results. Meeting abstracts that provided sufficient data were also included. Studies with overlapping data were excluded.

Selection criteria

The citations were screened at the title and abstract level then retrieved as full reports. Inclusion criteria included the following: 1) RCTs comparing PF-DES with PP-DES; 2) studies reporting clinical outcomes as all-cause death and/or cardiac death and/or myocardial infarction (MI) and/or TLR and/or LST

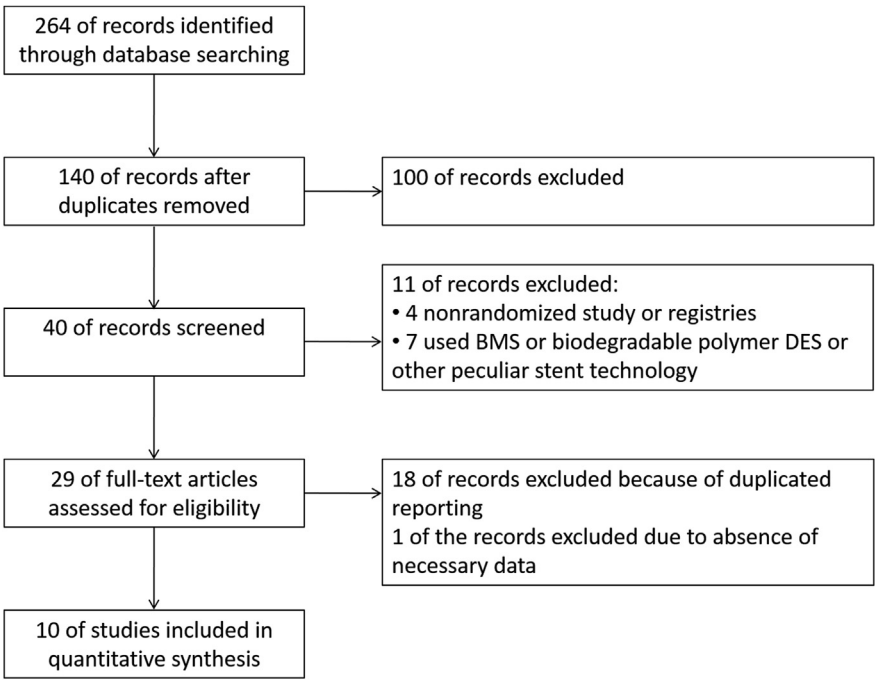

Fig. 1. Flow diagram of the review process.

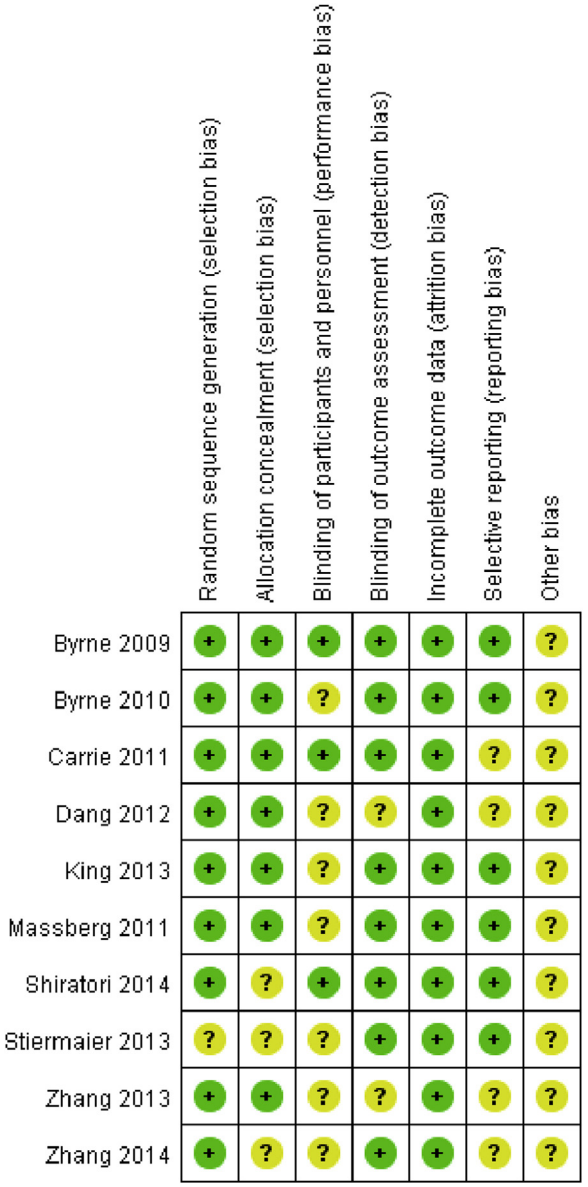

Fig. 2. Risk of bias judgment.

consistent with Academy Research Consortium (ARC) definition[8] and/or in-stent late lumen loss (LLL) and 3) a follow-up period longer than six months with or without quantitative coronary angiography reexamination. Exclusion criteria were: 1) duplicated reporting (in which studies with the longest follow-up time were selected); 2) using BMS or biodegradable polymer DES (BP-DES) or bioabsorbable scaffold stents or other peculiar stents. Data were abstracted on prespecified forms by two unblinded reviewers and divergences of opinion were resolved by consensus.

Quality assessment

The quality assessment was performed according to the Cochrane handbook for systematic reviews of interventions 5.1.0.[7] The quality of the studies included was appraised by two unblinded investigators. The risk of selection, performance, detection, attrition, reporting and other bias was qualified as a low risk of bias, an unclear risk of bias or a high risk of bias as recommended. The initial protocols registered in clinicaltrial.gov (https://clinicaltrials.gov/) were screened when qualifying a reporting bias.

Date extraction

Two blinded reviewers independently performed data extraction. Disagreements between the reviewers were resolved through discussion or by the third reviewer. The extracted data included: (1) first author's last name, the publication year; (2) characteristics of the study population, (3) stent types, duration of follow-up, (4) study design, and (5) study endpoints.

Endpoints and definitions

The composite endpoint of major adverse cardiovascular events (MACEs) was defined as the composite of all-cause death, MI, or ischemia-driven TLR. Definite or probable stent thrombosis was adjudicated using the Academic Research Consortium definite or probable criteria.[8]

Data analysis

Review manager 5.2.6 was used for all analyses. Odds ratios (ORs) were computed from individual studies and pooled according to a fixed effect or random effect model in case of statistical heterogeneity. Outcomes appraised were all-cause death, MI, TLR, MACEs, LST, and in-stent LLL. We used the Mantel-Haenszel method for combining ORs of binary outcomes. The mean difference of followed-up LLL compared with baseline was used for the in-stent LLL outcomes, and the overall weighted mean difference (WMD) was built with the inverse variance method, as recommended.[7]

We assessed the heterogeneity between eligible studies by the Cochrane Q test. We considered P values less than 0.10 as an indicator of significant heterogeneity because of the low statistical power. We also used the inconsistency index I^2 to quantify heterogeneity. Funnel plots were constructed to assess publication bias.

Results

Literature search and eligible studies

The review process is presented in Fig. 1. The literature search resulted in 140 relevant outcomes after duplicates removed. We excluded 100 reviews and irrelevant studies, and 11 studies were removed after closer inspection. The specific reasons for their exclusion were: 1) non-randomized studies or registries studies, 2) used BMS or BP-DES or other peculiar stent technologies. We excluded duplicated reports of the same studies. Finally, we considered 11 appropriate studies, one[9] of which did not provide necessary data and it was excluded from this meta-analysis.

The 10 studies[10–19] enrolling 6575 patients were included in the meta-analysis. Study follow-up duration ranged from 1 to 5 years. In ISAR-TEST-3,[11] Byrne et al compared the clinical outcomes of three different polymer coating strategies (PP-DES, BP-DES and PF-DES), and we only extracted data about PP-DES and PF-DES. In the ISAR-TEST-2,[10] Byrne et al compared PF-DES with two types of PP-DES, so we combined the data of the two types of PP-DES. The risk of bias assessment is presented in Fig. 2. There was no publication bias according to the funnel plot of each endpoint (Fig. 3). The main characteristics are presented in Table 1 and Table 2.

Outcome analysis

All-cause death

A fixed effect model was used to build up the quantitative analysis for all-cause death given that no heterogeneity was found. The 10 studies that enrolled 6539 patients were included in the analysis. Compared with PP-DES, PF-DES significantly decreased the all-cause death rate (*OR* = 0.77, 95% *CI*: 0.61 to 0.98, *P* = 0.03) (Fig. 4).

Myocardial infarction

A fixed effect model was used for the quantitative analysis as we found no heterogeneity. Compared with PP-DES, no significant benefit was found in the PF-DES group (*OR* = 1.12, 95% *CI*: 0.19 to 23.18, *P* = 0.39) (Fig. 5).

Target lesion revascularization

The result of TLR was available in 10 studies. We used a fixed effect model to perform the quantitative analysis as no heterogeneity was found. The PF-DES group showed no significant benefit compared with the PP-DES group (*OR* = 1.19, 95% *CI*: 0.42 to 3.38, *P* = 0.83) (Fig. 6).

MACEs

Three of the studies met the definition of MACEs in our analysis. In other studies, we calculated the MACEs according to the corresponding results. A

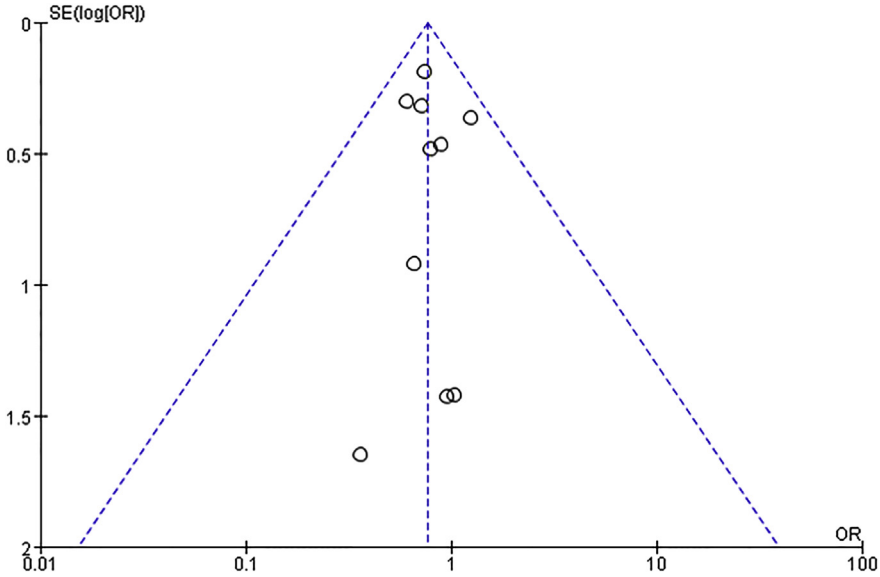

Fig. 3. Funnel plot of comparison Polymer-free drug eluting stents (PF-DES) vs. Permanent polymer drug eluting stents (PP-DES): outcome: in-stent late stent thrombosis. Funnel plot displays no publication bias about the end-point of late stent thrombosis (LST), as demonstrated by the absence of graphical asymmetrical distribution.

Table 1
Characteristics of included studies.

Author	Journal	Acronym	Patients	Total patients	PF-DES	PF-DES drug	PF-DES patients	PP-DES	PP-DES drug	PP-DES patients	Follow up time (year)
Byrne	Heart 2009	ISAR-TEST-3	CAD	403	2% rapamycin	Sirolimus	201	Cypher	Sirolimus	202	2
Byrne	JACC 2010	ISAR-TEST-2	CAD	1007	Dual-DES	Sirolimus, probucol	333	Cypher, Endeavor	Sirolimus, zotarolimus	674	2
Carrie	JACC 2011	–	CAD	296	Cre8	Amphilimus	148	Taxus Liberte	Paclitaxel	148	1
Dang	Chin Med J (Engl) 2012	–	STEMI	105	Yinyi	Paclitaxel	50	Partner	Sirolimus	55	1
Massberg	Circulation 2011	ISAR-TEST-5	CAD	450	Dual-DES	Sirolimus, probucol	225	Resolute	Zotarolimus	225	1
King	Catheter Cardiovasc Interv. 2013	ISAR-TEST	CAD	3002	Yukon	Sirolimus	2002	Taxus	Paclitaxel	1000	5
Shiratori	Catheter Cardiovasc Interv. 2014	–	CAD	164	Axxion	Paclitaxel	80	TAXUS Express	Paclitaxel	84	2
Stiermaier	Catheter Cardiovasc Interv. 2013	LIPSIA Yukon	CAD&DM	232	Yukon Choice	Sirolimus	118	Taxus Liberte	Paclitaxel	114	5
Zhang	Int J Cardiol 2013	–	CAD	648	Yinyi	Paclitaxel	327	Partner	Sirolimus	321	2
Zhang	Chin Med J (Engl) 2014	–	CAD	268	Nano	Sirolimus	132	Partner	Sirolimus	136	2

PF-DES: polymer-free drug eluting stents, PP-DES: permanent polymer drug eluting stents, CAD: coronary artery disease, STEMI: ST elevated myocardial infarction, DM: diabetes mellitus.

random effect model was used to perform the meta-analysis. The two kinds of stents showed similar results in MACEs (OR = 0.99, 95% CI: 0.79 to 1.24, P = 0.91) (Fig. 7).

Late stent thrombosis

We extracted definite or probable LST for further analysis. A fixed effect model was used to build up the quantitative analysis as no heterogeneity was found. The PF-DES and the PP-DES showed similar rates of LST (OR = 0.92, 95% CI: 0.05 to 5.71, P = 0.74) (Fig. 8).

Late lumen loss

A random effect model was used to perform the meta-analysis given the degree of heterogeneity found. Two of the studies[10,11] performed angiography twice during follow-up (once in 6−8 month, once in 2 years), while in three studies[12−14] it was performed once in 6−9 months. We built a meta-analysis for both short term LLL (6−9 months) and long term LLL (2 years). In the early phases, PF-DES showed no benefit in reducing LLL compared with PP-DES (WMD 0.03 mm 95% CI: −0.07 to 0.13 mm, P = 0.57). However, after reviewing the 2 years outcome, the PF-DES showed a significantly lower in-stent LLL (OR = 0.77, 95% CI: 0.61 to 0.98, P = 0.03) (Fig. 9).

Discussion

The main finding of this meta-analysis is that compared with PP-DES, PF-DES showed superiority in reducing long-term LLL and all-cause mortality, while showed no significant benefit on short-term LLL, MI, TLR and LST.

It has been demonstrated that vascular wall inflammation may be induced after PP-DES implanted in pigs[20,21] and humans.[22,23] This inflammation is considered to cause delayed intimal healing, late malapposition and LST,[24] and it may have an important etiological role in adverse events late after stent implantation. Permanent polymer can also aggravate neointimal atherosclerosis compared with BMS which could induce more adverse events.[25] Considering that, intimal inflammation and LST have become a bottleneck problem restricting the development of DES. As a consequence, both BP-DES and PF-DES have been the focus of and have been developed. BP-DES showed superiority in reducing TLR and LLL but without clear benefits for mortality, MI, and LST.[26] Nevertheless, studies also reported late inflammation after BP-DES implantation.[22,27]

Table 2
Features of clinical trials included after full-text inspection.

Study	Age (years)	Male (%)	Smoking (%)	HBP (%)	Dyslipidemia (%)	Diabetes (%)	ACS (%)	Prior MI	Prior PCI	Prior CABG	Type B2/C lesions (%)	Lesion length
Byrne 2009	66.0 ± 10.2	79.9	16.4	65.8	67.5	27.0	30.5	33.3	NA	10.4	NA	14.45 ± 6.14
Byrne 2010	66.9 ± 11.1	66.7	18.4	66.7	65.7	27.4	41.8	27.0	NA	8.83	72.5	14.46 ± 8.17
Carrie 2011	64.6 ± 10.3	72.1	24.5	64.4	61.9	26.9	NA	9.0	15.2	NA	31.3	15.28 ± 7.03
Dang 2012	66.2 ± 13.1	69.5	64.8	43.8	21.9	25.7	100	5.7	1.9	NA	56.7	NA
Massberg 2011	67.8 ± 11.1	76.4	17.4	66.7	63.5	29.0	41.0	29.5	NA	9.5	74.1	16.57 ± 9.74
King 2013	66.7 ± 10.3	76.9	18.2	66.0	74.4	29.1	42.9	31.8	NA	11.1	76.4	12.75 ± 6.47
Shiratori 2014	66.5 ± 9.3	72.6	18.9	73.2	61.6	32.3	42.7	31.1	28.9	6.1	73.8	15.91 ± 8.81
Stiermaier 2013	67.1 ± 9.3	68.6	25.0	97.5	NA	100	NA	22.0	30.1	7.6	36.4	16.74 ± 4.63
Zhang 2013	65.6 ± 10.8	67.0	40.0	64.8	NA	26.5	85.5	NA	NA	NA	87.7	NA
Zhang 2014	57.4 ± 10.4	76.8	51.6	53.5	31.1	16.8	NA	30.2	14.8	NA	NA	23.6 ± 13.5

HBP: high blood pressure, ACS: acute coronary syndrome, MI: myocardial infarction, PCI: percutaneous coronary intervention, CABG: coronary artery bypass grafting.

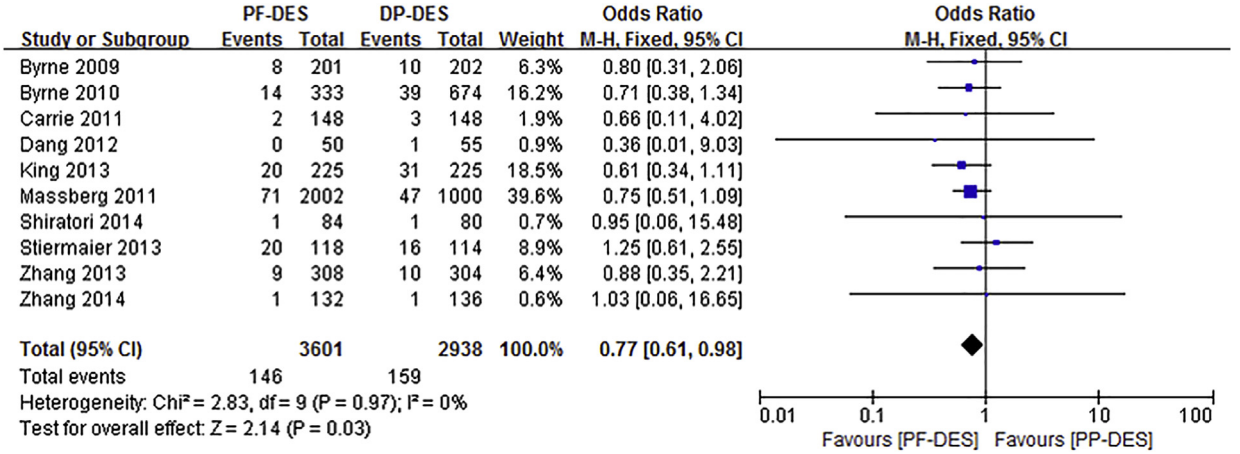

Fig. 4. Individual and summary odds ratios for all-causes death in patients treated by PF-DES and PP-DES implantation. PF-DES: polymer-free drug eluting stents, PP-DES: permanent polymer drug eluting stents, M−H: Mantel-Haenszel method.

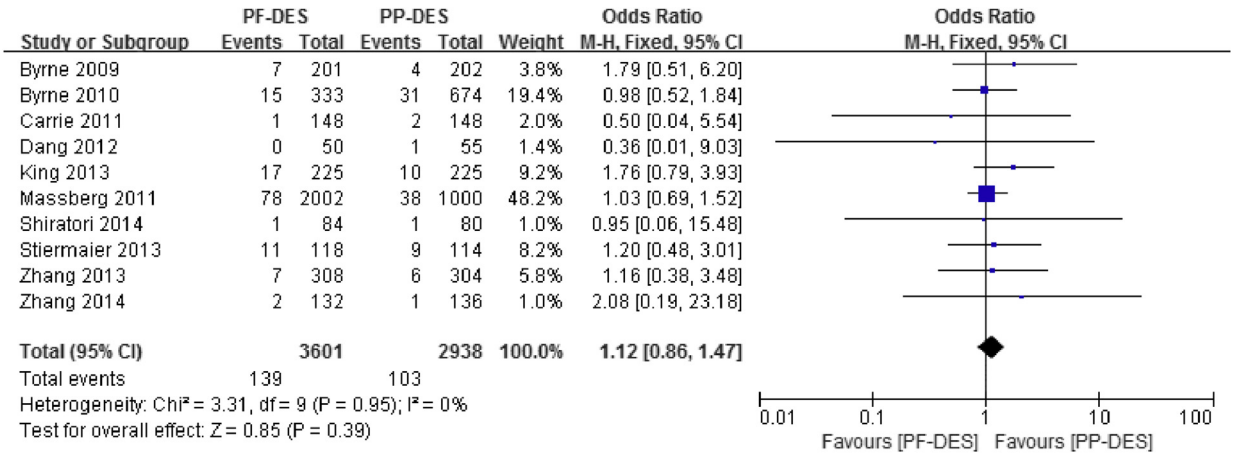

Fig. 5. Individual and summary odds ratios for myocardial infraction in patients treated by PF-DES and PP-DES implantation. PF-DES: polymer-free drug eluting stents, PP-DES: permanent polymer drug eluting stents, M−H: Mantel-Haenszel method.

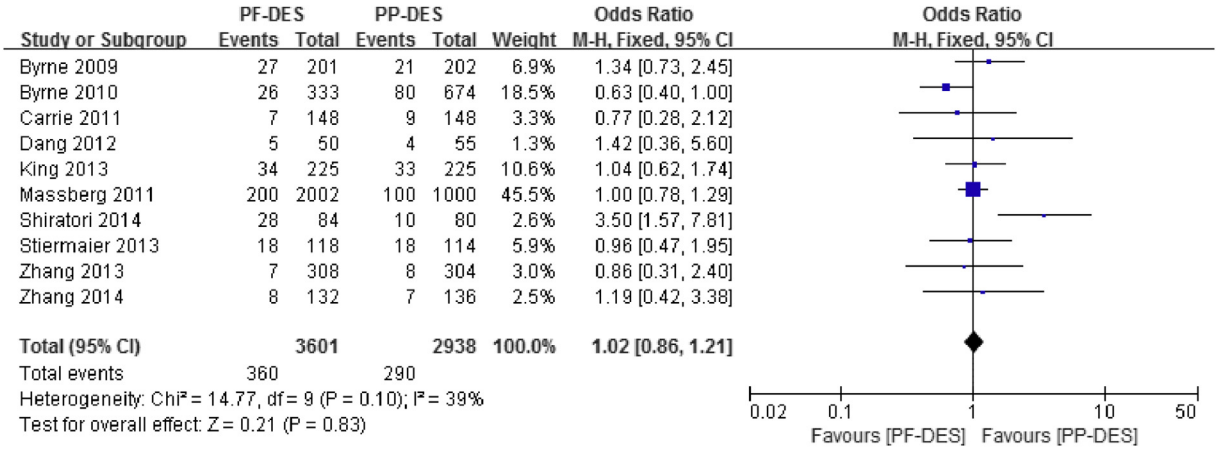

Fig. 6. Individual and summary odds ratios for target lesion revascularization in patients treated by PF-DES and PP-DES implantation. PF-DES: polymer-free drug eluting stents, PP-DES: permanent polymer drug eluting stents, M–H: Mantel-Haenszel method.

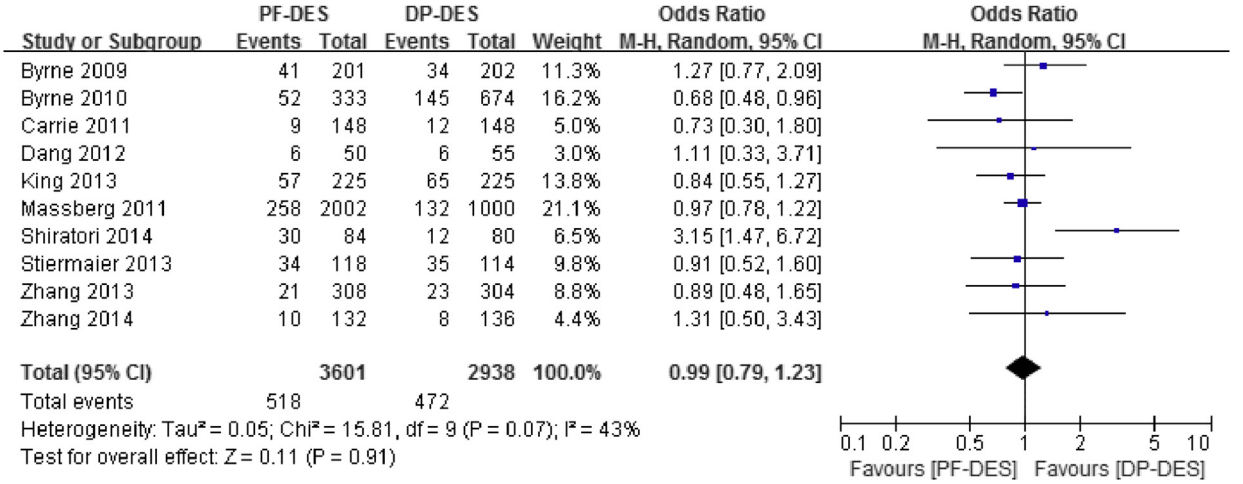

Fig. 7. Individual and summary odds ratios for major adverse cardiovascular events in patients treated by PF-DES and PP-DES implantation. PF-DES: polymer-free drug eluting stents, PP-DES: permanent polymer drug eluting stents, M–H: Mantel-Haenszel method.

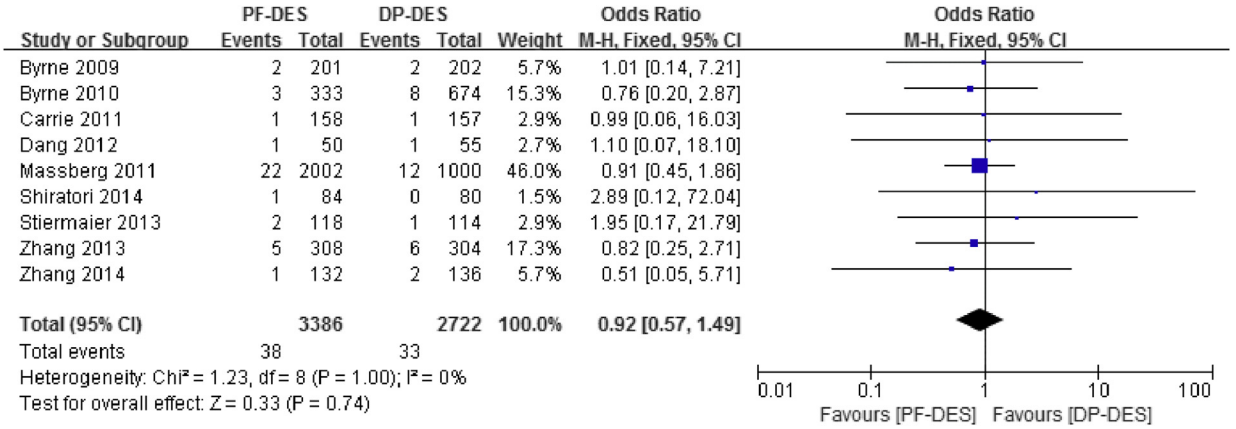

Fig. 8. Individual and summary odds ratios for definite or probable late stent thrombosis in patients treated by PF-DES and PP-DES implantation. PF-DES: polymer-free drug eluting stents, PP-DES: permanent polymer drug eluting stents, M–H: Mantel-Haenszel method.

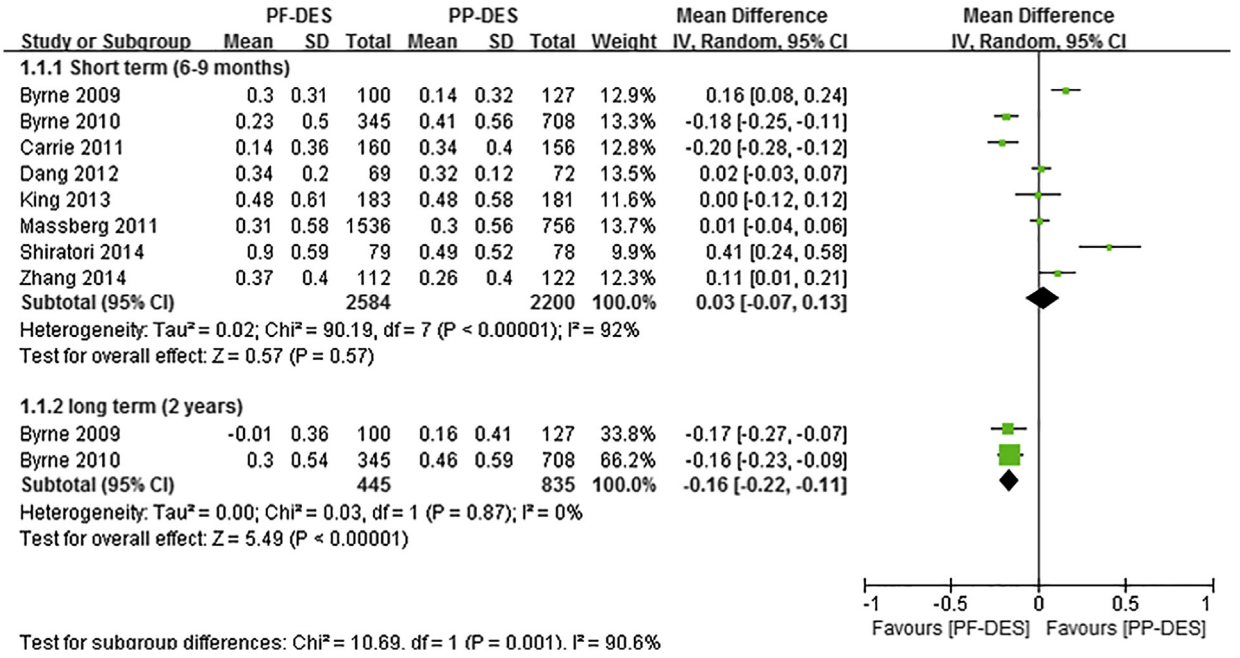

Fig. 9. Individual and summary odds ratios for in-stent lumen loss in patients treated by PF-DES and PP-DES implantation at short (6−9 months) or long (2 years) term. PF-DES: polymer-free drug eluting stents, PP-DES: permanent polymer drug eluting stents, IV: inverse variance method.

Several studies have evaluated the safety and efficiency of PF-DES involving different types of stent coating different agents including Paclitaxel,[16,28] sirolimus,[10,11,13−15] biolimus[29] and amphilimus.[12] This meta-analysis included 10 studies comparing polymer-free paclitaxel, sirolimus and amphilimus eluting stents with PP-DES with 1−5 years follow-up duration. PF-DES coated with biolimus were not included due to absence of the necessary data.

Given that two (2)[10,11] of the studies didn't provide data on cardiac death, we analyzed rates of all-cause death to evaluate the efficiency of PF-DES in reducing mortality. It showed that PF-DES could significantly reduce mortality without any detectable heterogeneity so that this may be convincing evidence in the evaluation of PF-DES.

Another noteworthy finding of this meta-analysis was that compared with PP-DES, PF-DES had a similar LLL 6−9 months after stent implantation, while it showed significant benefit in long-term follow-up. Because of a higher speed of drug release (~75% in the first 10 days), PF-DES may have relatively higher initial lumen loss in 6−9 months compared with PP-DES. However, it may consequently prompt earlier and more complete vessel healing than PP-DES. It has been demonstrated that additional lumen loss was found in PP-DES implanted vessels even beyond 6−9 months.[30,31] It might also be proposed that existence of a polymer induced more inflammation and higher lumen loss.[32]

No benefit in reducing TLR, MI and LST of PF-DES was found in this meta-analysis. Among the 10 studies, two (2) of them had a 5-year follow-up time while the other eight (8) studies followed up for 1 or 2 years. A short duration of follow-up might make it difficult to detect endpoints with low incidences even though we had a large sample size. Further studies with larger sample size and longer follow-up duration need to be performed in the future.

Limitations

We did not have access to the data of the Biofreedom FIM study,[9] even though we made a great effort, and it might have been important for this analysis. The coating agents and follow-up duration ranged among different studies, which lead to heterogeneity in the analysis. Finally, we could not get access to individual patient data which prevented us from making subgroup analysis; such as acute coronary syndrome, diabetes, and other meaningful clinical conditions.

Conclusion

In this meta-analysis, PF-DES showed benefit on reducing long-term LLL and all-cause mortality compared with PP-DES, but no superiority was found in short-term LLL, MI, TLR and LST. These findings provide a sound basis to wide application of PF-DES in the future.

Conflicts of interest

None.

References

1. Moses JW, Leon MB, Popma JJ, et al. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. *N Engl J Med*. 2003;349:1315−1323.
2. Stone GW, Ellis SG, Cox DA, et al. A polymer-based, paclitaxel-eluting stent in patients with coronary artery disease. *N Engl J Med*. 2004;350:221−231.
3. Grines CL, Bonow RO, Casey Jr DE, et al. Prevention of premature discontinuation of dual antiplatelet therapy in patients with coronary artery stents: a science advisory from the American Heart Association, American College of Cardiology, Society for Cardiovascular Angiography and Interventions, American College of Surgeons, and American Dental Association, with representation from the American College of Physicians. *Circulation*. 2007;115:813−818.
4. Luscher TF, Steffel J, Eberli FR, et al. Drug-eluting stent and coronary thrombosis: biological mechanisms and clinical implications. *Circulation*. 2007;115:1051−1058.
5. Finn AV, Joner M, Nakazawa G, et al. Pathological correlates of late drug-eluting stent thrombosis: strut coverage as a marker of endothelialization. *Circulation*. 2007;115:2435−2441.
6. 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.
7. Julian PT, Higgins SG. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (Updated March 2011)*. The Cochrane Collaboration; 2011. http://handbookcochraneorg2011.
8. Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation*. 2007;115:2344−2351.
9. Grube E, Mueller R, Schuler G, Hauptmann KE, Schofer J. Comparison of polymer-free biofreedom(trademark) stents with durable polymer taxus liberte(trademark) stents: 3-Year results from the biofreedom first-in-man trial. *J Am Coll Cardiol*. 2012;60:B14.
10. 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;55:2536−2543.
11. 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;95:1489−1494.
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;59:1371−1376.
13. King L, Byrne RA, Mehilli J, Schomig A, Kastrati A, Pache J. 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−E28.
14. 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;124:624−632.
15. 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;83:418−424.
16. Dang Q, Li YJ, Gao L, Jin Z, Gou LX. 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*. 2012;125:3393−3397.
17. 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*. 2014;127:2153−2158.
18. 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;7:312−321.
19. 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;168:2646−2652.
20. Carter AJ, Aggarwal M, Kopia GA, et al. Long-term effects of polymer-based, slow-release, sirolimus-eluting stents in a porcine coronary model. *Cardiovasc Res*. 2004;63:617−624.
21. Wilson GJ, Nakazawa G, Schwartz RS, et al. Comparison of inflammatory response after implantation of sirolimus- and paclitaxel-eluting stents in porcine coronary arteries. *Circulation*. 2009;120:141−149, 1−2.
22. Virmani R, Guagliumi G, Farb A, et al. Localized hypersensitivity and late coronary thrombosis secondary to a sirolimus-eluting stent: should we be cautious? *Circulation*. 2004;109:701−705.
23. Finn AV, Kolodgie FD, Harnek J, et al. Differential response of delayed healing and persistent inflammation at sites of overlapping sirolimus- or paclitaxel-eluting stents. *Circulation*. 2005;112:270−278.

24. Cook S, Ladich E, Nakazawa G, et al. Correlation of intravascular ultrasound findings with histopathological analysis of thrombus aspirates in patients with very late drug-eluting stent thrombosis. *Circulation*. 2009;120:391−399.
25. Nakazawa G, Otsuka F, Nakano M, et al. The pathology of neoatherosclerosis in human coronary implants bare-metal and drug-eluting stents. *J Am Coll Cardiol*. 2011;57:1314−1322.
26. Lupi A, Rognoni A, Secco GG, et al. Biodegradable versus durable polymer drug eluting stents in coronary artery disease: insights from a meta-analysis of 5834 patients. *Eur J Prev Cardiol*. 2014;21:411−424.
27. van der Giessen WJ, Lincoff AM, Schwartz RS, et al. Marked inflammatory sequelae to implantation of biodegradable and nonbiodegradable polymers in porcine coronary arteries. *Circulation*. 1996;94:1690−1697.
28. Zhang L, Yuan J, Liu G, et al. One-year clinical outcome of a randomized trial of polymer-free paclitaxel-eluting stents versus biodegradable polymer-based rapamycin-eluting stents in patients with coronary heart disease. *J Int Cardiol*. 2012;25:604−610.
29. Grube E, Mueller R, Schuler GC, et al. Comparison of polymer-free BioFreedom(trademark) stents with durable polymer Taxus Liberte(trademark) stents: 2-year results from the BioFreedom first-in-man trial. *J Am Coll Cardiol*. 2011;58:B68.
30. Byrne RA, Iijima R, Mehilli J, et al. Durability of antirestenotic efficacy in drug-eluting stents with and without permanent polymer. *JACC Cardiovasc Interv*. 2009;2:291−299.
31. Sousa JE, Costa MA, Abizaid A, et al. Four-year angiographic and intravascular ultrasound follow-up of patients treated with sirolimus-eluting stents. *Circulation*. 2005;111:2326−2329.
32. De Jong WH, Eelco Bergsma J, Robinson JE, Bos RR. Tissue response to partially in vitro predegraded poly-L-lactide implants. *Biomaterials*. 2005;26:1781−1791.

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