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Comparison of biodegradable and durable polymer drug-eluting stents in acute coronary syndrome

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Abstract

Purpose: To compare the safety and effectiveness between biodegradable (BP-DES) and durable polymer drug-eluting stents (DP-DES) in acute coronary syndrome (ACS) patients.

Methods: We searched PubMed, Medline, Embase, and the Cochrane Controlled Register of Trials (CENTRAL) for comparative studies of BP-DES versus DP-DES in patients with ACS, from January 2000 to July 2021. Statistical pooling was performed for estimating incidence, using a random-effects model with generic inverse-variance weighting. Risk estimates were computed with 95% confidence intervals (CIs), using RevMan 5.3.

Results: Nine articles that compared BP-DES and DP-DES in ACS patients were identified and included in qualitative and quantitative analyses. There was no difference in the baseline characteristics, except for the total stent length, which was longer in the BP-DES group. A pooled analysis demonstrated that major cardiac adverse events, efficacy endpoints, and safety endpoints were similar between the 2 groups at 1 year. However, the total stent thrombosis (ST) incidence was significantly different between the BP-DES and DP-DES groups in the follow-up period. Subgroup analysis showed a statistically significant difference in the total ST, MACE , TLR, TVR and ST incidence over 2 years.

Conclusion: This meta-analysis revealed that the 2 stent types showed excellent safety and efficacy profiles at 12 months. However, there was a slightly increased MACE, TLR, TVR and ST incidence in the DP-DES group over the 2-year follow-up period, suggesting that BP-DES may be more favourable for treating patients with ACS.

Keywords: acute coronary syndrome, biodegradable drug-eluting stent, durable polymer

drug-eluting stent, major adverse cardiac event, stent thrombosis, target lesion revascularization, target vessel revascularization

Strengths and limitations of this study

1)This is the first meta analysis comparing the clinical outcomes of the two polymer in the patients with acute coronary syndrome. 2) In this meta-analysis, the research rolling in are all RCT and the follow up are all over 1 year even for 5 years, so the result mybe convincing. 3)According to the data,we sugest that both polymer types showed excellent safety and efficacy profiles at 1 year and BP-DES may be more favourable for treating patients with ACS due to a slightly increased incidence of MACE, TLR, TVR and ST in the DP-DES group in the follow-up period over 2 years.

However, the analysis mybe has some limitations.he present study had several limitations,which maybe introduce some bias. First, this study included RCTs and shares the limitations of original studies. Second, Biodegradable polymer DES are a heterogeneous group of stents differing with regards to stent platform thickness, time to complete degradation of the polymer, and drug-elution kinetics.The comparator group of durable polymer DES is an equally heterogeneous group. We were unable to match the stents in regards to the strut thickness and drug. As a consequence, the reported results may not be generalizable to all stents from the respective group. Third, Over 6 month dual antiplatelet therapy was given to the patients rolling in our including RCT trails, the difference of the duration of dual antiplatelet therapy that may influence the clinical outcomes.

No additional data available

Patient and public involvement

We do not need the patient and public involvement, as this is a meta anlysis and no new patients were rolled in it.

Contributorship Statement

Can Huang, Zhongshi Wu, and Haoyong Yuan developed the idea of the study, participated in its design and coordination and helped to draft the manuscript. Ting Lu and Tingting Wei contributed to the acquisition and interpretation of data. Yifan Zeng and Yalin Liu provided critical review and substantially revised the manuscript. All authors read and approved the final manuscript.

Ethics approval

This study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and the protocol was registered with PROSPERO (CRD42021253412). This study was approved by the institutional review board of the Second Xiangya Hospital, Central South University.

Funding

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Introduction

Percutaneous coronary intervention (PCI) is the current standard of care for patients with coronary artery disease, particularly acute coronary syndrome (ACS)(1, 2). Unlike bare-mental stents (BMS), drug-eluting stents (DES) use antiproliferative agents embedded in a polymer coating on the stent's surface, which inhibit neointimal hyperplasia to reduce the risk of restenosis(3). Although DES have substantially improved clinical outcomes, the first-generation durable polymer DES (DP-DES) released sirolimus or paclitaxel, and were associated with similar risks of death and myocardial infarction as BMS beyond 1 year after implantation(4). Later, the second-generation DP-DES were confirmed to have lower restenosis rates than first-generation devices and showed reduced rates of stent thrombosis (ST)(5). Recently, very late ST and neoatherosclerosis, with adverse clinical outcomes, have been observed with second-generation DP-DES, which has improved the biocompatibility of the polymer(6). Late stent failure has been attributed to delayed endothelial healing secondary to a hypersensitivity reaction to the durable polymer(7).

To address this potential limitation of DP-DES, biodegradable polymer DES (BP-DES) have been developed. Theoretically, BP-DES would lead to a reduction in vascular inflammation and a decreased risk of late stent-related complications due to the advantage of leaving behind only the BMS after complete drug elution and polymer degradation. BP-DES have been observed to reduce the rate of major adverse cardiac events (MACEs) compared to BMS(8) and first-generation DP-DES(9). Studies of all-comes who underwent PCI showed that the device-related outcomes were comparable between BP-DES and second-generation DP-DES(10-13). Thus, BP-DES would be expected to reduce the risk of ST-related MACEs

beyond the first year, as compared to DP-DES. However, previous studies enrolled a significant proportion of stable angina patients. ACS confers an increased risk of adverse outcome due to plaque characteristics, including culprit lesions, thrombus burden, and persistent inflammation, compared to stable coronary artery diseases. ACS would also increase the risk of delayed arterial healing and vessel remodelling(14), reflected by higher rates of incomplete stent strut coverage(15, 16) and malpositioning(17).

Recently, the randomized trials have been performed to compare the efficacy and safety of DP-DES and BP-DES in an ACS population who underwent PCI. In this meta-analysis, we aimed to summarize studies comparing the 2 polymer technologies in ACS patients and to analyse the safety and effectiveness of these therapeutic options.

Methods

Search strategy and registration

This study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. This study was approved by the institutional review board of the Second Xiangya Hospital, Central South University and the protocol was registered with PROSPERO (CRD42021253412).

Based on the PRISMA statement, PubMed, Medline, Embase, and the Cochrane Controlled Register of Trials (CENTRAL) databases were searched for comparative studies of BP-DES versus DP-DES in the treatment of ACS patients who underwent PCI. The following search terms were used: ‘BP-DES’, ‘DP-DES’, ‘Acute coronary syndrome’, ‘Acute myocardial infarction’, ‘biodegradable’, ‘bioabsorbable’, ‘polymer’, ‘everolimus’,

‘zotarolimus’, ‘endeavor’, ‘Resolute’, ‘Xience’, and ‘drug-eluting stent’. We also reviewed prior meta-analyses and the reference lists of the original trials and review articles to identify further studies. Only English language articles published in peer-reviewed journals from January 2000 to July 2021 were selected. Analyses were conducted by 2 independent reviewers.

Eligibility criteria

The inclusion criteria for this meta-analysis were as follows: 1) randomized controlled trials (RCTs) comparing BP-DES and DP-DES in the treatment of ACS patients who underwent PCI; 2) studies that reported data on patients’ baseline characteristics, follow-up duration, outcomes at the primary, safety, and efficacy endpoints; 3) studies where the mean follow-up time was over 12 months; and 4) full-text articles.

The exclusion criteria for the meta-analysis were the following: 1) duplicate of the sample size and reports evaluated by 2 independent reviewers; 2) case reports/series; 3) studies involving data from a national database.

Data extraction and outcome measurement

Two authors (Haoyong Yuan and Tingting Wei) systematically screened the titles and abstracts of publications retrieved using the search strategy to select studies that met the above inclusion criteria. Any disagreement between them over the eligibility of particular studies was resolved through discussion and involvement of a third author (Zhongshi Wu), when necessary. First, baseline characteristics, including the name of the first author, year of publication, study design, country of origin, number of patients, mean age of subjects, and

mean duration of follow-up were gathered from each included article. In addition, sex; body mass index; the presence of hypertension, diabetes, dyslipidaemia, chronic kidney disease, peripheral vessel disease, or smoking; left ventricular ejection fraction (LVEF), number of stents per person, and total stent length were collected for evaluation of procedure risk. MACEs were considered as the primary endpoint. The efficacy endpoint included target vessel revascularization (TVR) and target lesion revascularization (TLR). In addition, all-cause death, cardiac death, target vessel myocardial infarction (TVMI), and ST were employed as the safety endpoints to evaluate the safety of BP-DES and DP-DES.

Quality assessment of RCTs was based on sequence generation; randomized group allocation; concealment; blinding of participants, personnel, and outcome assessors; incomplete data; selectivity; outcome reporting, and other sources of bias

Data analysis and synthesis

Continuous variables are reported as the mean (standard deviation) and categorical variables are expressed as number. Statistical pooling was performed to estimate incidence, according to a random-effects model with generic inverse-variance weighting. We computed risk estimates with 95% confidence intervals (CIs), using RevMan 5.3 (The Cochrane Collaboration, The NordicCochrane Centre, Copenhagen, Denmark). Hypothesis testing for superiority was set at the two-tailed 0.05 level. Hypothesis testing for statistical homogeneity was set at the two-tailed 0.10 level and was based on the Cochran Q test, with I^2 values of 25%, 50%, and 75% representing mild, moderate, and severe heterogeneity, respectively.

Results

Search results

A total of 895 articles, written in English, were identified through the literature search. After an initial screening of the titles and abstracts, articles were eliminated, as they were not related to the topic of this study. 92 clinical studies and RCT articles of the two polymers remained. After further reading the full text, 28 articles about acute coronary syndromes were left and the patients of the 20 articles include the chronic and acute coronary syndrome. Finally, 8 articles of randomized controlled trials comparing BP-DES and DP-DES in patients with ACS were identified and were included in the qualitative and quantitative analyses (18-25). The follow-up duration ranged from 1 year to 5 years (Table 1).

General features of the trials

A total number of 8089 patients (3898 patients who were treated with BP-DES and 4191 patients who were treated with the DP-DES were included in this analysis. Further details about the total number of patients retrieved from each trial, the publication year, the country of origin of the publication, the centre in which trials were performed, the follow-up duration, the risk factors, primary, efficacy, and safety endpoints are listed in Table 1 to Table 3.

Patient characteristics

The baseline features of the patients are summarized in Tables 2 The mean age of the patients who were treated by BP-DES ranged from 61.3 to 64 years old, whereas the mean age of the patients who were treated by DP-DES ranged from 61.7 to 64.1 years. The number of male patients were above 70% in all the included trials. There was no difference in age

(mean difference [MD]: 0.14, 95%CI: -0.66–0.38; P = 0.60, I^2 = 0%), sex (male) (odds ratio [OR]: 1.10, 95%CI: 0.99–1.23; P = 0.07, I^2 = 0%), hypertension (OR: 1.03, 95%CI: 0.94–1.13; P = 0.57, I^2 = 37%), dyslipidaemia (OR: 0.92, 95%CI: 0.83–1.02; P = 0.10, I^2 = 36%), LVEF (MD: 0.00, 95%CI: 0.00–0.01; P = 0.12 I^2 = 12%), body mass index (MD:0.07, 95%CI: -0.11 to 0.25; P = 0.44, I^2 = 0%), diabetes (OR: 0.92, 95%CI: 0.83–1.02; P = 0.13, I^2 = 21%) , total stent length (MD: -0.72, 95%CI: -2.30 to -0.85; P = 0.37, I^2 = 40%) , and number of stents per person (MD: -0.00, 95%CI: -0.05 to 0.04; P = 0.84, I^2 = 0%) among patients who were implanted with BP-DES or DP-DES. A pooled analysis demonstrated that thes number of smoking patients (OR: 1.13, 95%CI: 1.03–1.24; P = 0.008 I^2 = 29%) is significantly lower in the BP-DES group than in the DP-DES group (Fig. 1 A–C).

Primary endpoint: MACEs reported during a follow-up period of 1–5 years, 1 year, and over 2 years

MACEs, including all-cause death, recurrent MI, or any coronary repeat revascularization involving TLR, TVR, and non-TVR, were considered as the primary endpoint of the trials. A pooled analysis indicated no statistically significant difference in MACEs in a follow-up period ranging from 1 to 5 years between the 2 groups (OR: 0.87, 95%CI: 0.75–1.01; P = 0.07, I^2 = 50%). Of the 5 studies that published 1-year outcomes, MACEs were not significantly different between the BP-DES and DP-DES groups, with OR: 0.97, 95%CI: 0.81–1.16; P = 0.74, I^2 = 44%. However, the over 2-year MACE is significant lower in the BP-DES group with OR: 0.71, 95%CI: 0.57–0.88; P = 0.002, I^2 = 0 % (Fig. 2).

Efficacy endpoint: TVR and TLR reported during a follow-up period of 1–5 years, 1 year, and over 2 years

TLR and TVR were considered as the efficacy endpoints of the trials. A pooled analysis indicated no statistically significant difference in TLR in a follow-up period ranging from 1 to 5 years between the 2 groups (OR: 0.78, 95%CI: 0.61–1.00; P = 0.05, I^2 = 48%). Among the 5 studies that published 1-year data, TLR was not significantly different between the BP-DES and DP-DES groups with OR: 0.72, 95%CI: 0.40–1.31; P = 0.29, I^2 = 65%. A pooled analysis indicated no statistically significant difference in TVR over a follow-up period ranging from 1 to 5 years, with OR: 1.01, 95%CI: 0.79–1.28; P = 0.96, I^2 = 46%, 1 year in 3 publications, with OR: 0.98, 95%CI: 0.40–2.38; P = 0.96, I^2 = 76%, However, the over 2-year TLR in 4 RCT studies, with OR: 0.71, 95%CI: 0.51–1.01; P = 0.05, I^2 = 0% and over 2-year TVR in 3 studies, with OR: 0.70, 95%CI: 0.52–0.94; P = 0.002, I^2 = 15% are much lower in BP group (Figs. 3, 4).

Safety endpoint: All-cause death, cardiac-related death, target vessel myocardial infarction, and stent thrombosis over a follow-up period of 1–5 years, 1 year, and over 2 years

All-cause death, cardiac-related death, TVMI, and ST were considered as the efficacy endpoint of the trails. A pooled analysis indicated no statistically significant difference in all-cause death (OR: 0.88, 95%CI: 0.72–1.07; P = 0.20, I^2 = 0%), cardiac-related death (OR: 0.89, 95%CI: 0.71–1.12; P = 0.32, I^2 = 20%), and TVMI (OR: 0.73, 95%CI: 0.53–1.01; P = 0.05, I^2 = 0%) over a follow-up period ranging from 1 to 5 years, between the 2 groups. Of the 5 studies that published 1-year data, all-cause death, cardiac-related death, and TVMI

were not significantly different between the BP-DES and DP-DES groups (all-cause death OR: 0.91, 95%CI: 0.71–1.15; P = 0.42, I^2 = 0%, cardiac-related death OR: 0.96, 95%CI: 0.74–1.26; P = 0.79, I^2 = 35%, TVMI OR: 0.73, 95%CI: 0.53–1.01; P = 0.05, I^2 = 0%). Similar findings were observed for the over 2-year all-cause cardiac death, cardiac-related death, and TVMI in 5 studies (all-cause death OR: 0.85, 95%CI: 0.64–1.12; P = 0.25, I^2 = 0%, cardiac-related death OR: 0.77, 95%CI: 0.56–1.17; P = 0.12, I^2 = 0%, TVMI OR: 0.79, 95%CI: 0.51–1.22; P = 0.28, I^2 = 0%), respectively (Figs. 5–7). However, the total ST incidence, including the definite ST, probable ST, and definite or probable ST incidence, was significantly different between the BP-DES and DP-DES groups over the follow-up period (OR: 0.59, 95% CI: 0.46–0.77; P = 0.0001, I^2 = 48%). Subgroup analysis revealed no difference in total ST for a 1-year follow-up (OR: 0.61, 95%CI: 0.32–1.15; P = 0.13, I^2 = 72%), while pooled analysis indicated a statistically significant difference in the total ST for the over 2-year follow-up (OR: 0.63, 95%CI: 0.47–0.85; P = 0.002, I^2 = 0%) (Fig. 8).

Discussion

The choice of stent in patients undergoing PCI for ACS is debated. Coronary intervention with second-generation DP-DES generally reduces the need for revascularisation and improves mortality, as compared to BMS and first-generation DP-DES. Furthermore, the risk of late ST with DP-DES tends to off-set the benefit from reduction in the need for revascularisation in patients with ACS, as seen in real-world registries and clinical trials comparing them to BMS(15, 26). BP-DES was designed to leave only the BMS behind once the polymer has bio-degraded completely after drug elution, and may represent an attractive solution for patients with ACS(27). Prior meta-analyses have compared the clinical outcomes

among BMS, DP-DES, and BP-DES in patients with stable coronary artery disease, but no previous meta-analysis of RCTs and prospective trials directly comparing clinical outcomes between BP-DES and DP-DES for the treatment of ACS. To our knowledge, this meta-analysis exclusively compared BP-DES to DP-DES. It included 8 trials representing 8089 patients with a longer follow-up duration, ranging from 1 year to 5 years. Although BP-DES have been hypothesised to offer improved outcomes, mainly in the long term, several prior meta-analyses have demonstrated different outcomes with BP-DES as compared to DP- DES in patients undergoing PCI. Bangalore et al. found that BP-DES were associated with higher mortality than DP-DES beyond 1 year of follow-up(28). El-Hayek et al. demonstrated no significant difference in mortality between these types of stent(6). In our study, there was no significant differences in MACE, all-cause death, cardiac-related death, TVMI, TVR, or TLR at a follow-up of 1 year and all-cause death, cardiac death, TVMI at a follow-up of over 2 years. However, the over 2-year MACE, TVR and TLR are significant lower in the BP group comparing to the DP group. Pilgrim, T found that a higher all cause mortality among patients treat with BP-SES compared with DP-EES in the BIOSCIENCE trail, they also think comparable rates of all-cause motality between patients treated with BP-SES and DP-EES in the BIOSTEMI trail at 2 years(25).Taken together, this suggests that BP-DES share similar outcomes in terms of MACEs (all-cause death, cardiac-related death, TVMI, TVR, and TLR during a 1-year follow-up and mybe significant improve clincal outcomes over 2 years follow up.

ST is used to evaluate the safety of the stent. The risk of ST, particularly late ST occurring beyond 30 days, remains among the major concerns limiting the use of DES in the

treatment of ACS(29). Early-generation DP-DES were associated with increased rates of very late (> 1 year) ST, as compared with BMS. It was hypothesized that the mechanism underlying late ST with first DP-DES in ACS is related to adverse reactions to the durable polymer(30), and the use of more biocompatible polymer has been associated with a reduction in ST in high-risk patients(9). In the LEADERS trial, the rate of very late ST was lower with the use of the BP-DES than with DP-DES(31). Our data demonstrated that both BP-DES and DP-DES have similar risks of ST beyond 1 year. However, BP-DES are associated with a significantly reduced risk of ST at a follow-up of over 2 years as compared with DP-DES (OR: 0.64, 95%CI: 0.46–0.88; P = 0.006, I^2 = 0%). On the other hand, Kim et al. found that the incidence of ST by groups showed numerically lower rates in the DP-DES group (0.1%) than in the BP-DES group, and that all late ST cases occurred in those receiving thick-strut BP-DES stents. They proposed that no meaningful differences in terms of ST could be identified between the different polymer technologies by intravascular imaging and that the association of polymer technology and the risk of the ST was difficult to prove(19, 32, 33). It may therefore be hypothesized that the BP-DES result in improved arterial healing, which in turn not only minimizes the risk of ST, but also improves the long-term durability of the antirestenotic efficacy in the long term, even though the 2 groups have a similar risk of ST beyond 1 year.

Limitations

The present study had several limitations,which maybe introduce some bias. First, this study included RCTs and shares the limitations of original studies. Second, Biodegradable polymer DES are a heterogeneous group of stents differing with regards to stent platform

thickness, time to complete degradation of the polymer, and drug-elution kinetics.The comparator group of durable polymer DES is an equally heterogeneous group. We were unable to match the stents in regards to the strut thickness and drug. As a consequence, the reported results may not be generalizable to all stents from the respective group. Third, Over 6 month dual antiplatelet therapy was given to the patients rolling in our including RCT trails, the difference of the duration of dual antiplatelet therapy that may influence the clinical outcomes.

Conclusion

In this meta-analysis comparing BP-DES to DP-DES in ACS patients who underwent PCI, the data indicated that both polymer types showed excellent safety and efficacy profiles at 1 year. There was a slightly increased incidence of MACE, TLR, TVR and ST in the DP-DES group in the follow-up period over 2 years, suggesting that BP-DES may be more favourable for treating patients with ACS. These findings should be confirmed by the long-term follow-up in RCT trials.

Table Legends

Table 1. The characteristics of the included trials

Table 2. The baseline features of the patients

Figure Legends

Fig. 1 A. Baseline characteristics and stent information of patients with acute coronary syndrome

Fig. 1B. Baseline characteristics and stent information of patients with acute coronary syndrome

Fig. 1C. Baseline characteristics and stent information of patients with acute coronary syndrome

Fig. 2. Primary endpoint: major adverse cardiac events

Fig. 3. Target vessel revascularization

Fig. 4. Target lesion revascularization

Fig. 5. All-cause death

Fig. 6. Cardiac-related death

Fig. 7. Target vessel myocardial infarction

Fig. 8. Stent thrombosis

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Table 1. The characteristics of the included trails

Authors	Years	Journal	Study	Center	Country	Follow up	NO.patients	
							BP-DES	DP-DES
Hyo-Soo Kim	2021	Circulation	RCT	multicentre	Korea	12 month	1700	1713
Thomas Pilgrim	2021	JACC	RCT	multicentre	Switzerland	24month	649	651
Juan F Iglesias	2019	The Lancet	RCT	multicentre	Switzerland	12 month	649	651
Thomas Pilgrim	2016	EuroIntervention	RCT	multicentre	Switzerland	12 month	211	196
Yao-Jun Zhang	2015	Heart	RCT	multicentre	Netherlands	60month	280	293
Hyun Jong Lee	2015	International journal of cardiology	RCT	multicentre	Korea	24month	171	536
Antoinette de Waha	2015	EuroIntervention	RCT	multicentre	multicentre	48month	291	206
Antoinette de Waha	2015	EuroIntervention	RCT	multicentre	multicentre	12month	291	206
Qi Zhang	2014	Journal of Interventional Cardiology	RCT	multicentre	China	12 month	596	596

Table 2. The baseline features of the patients

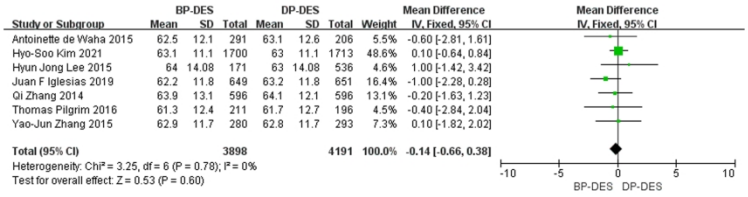
Authors	basic characters									
	Age		SEX(MALE)		Body mass index		Hypertension		Diabetes	
	BP-DES	DP-DES	BP-DES	DP-DES	BP-DES	DP-DES	BP-DES	DP-DES	BP-DES	DP-DES
Hyo-Soo Kim	63.1±11.1	63.0±11.1	1337	1351	25.0±3.2	24.9±3.1	1147	1092	747	789
Juan F Iglesias	62.2±11.8	63.2±11.8	513	477	26.9± 4.3	26.8± 4.3	281	297	73	82
Thomas Pilgrim	61.3±12.4	61.7±12.7	170	151	27.0±4.3	27.0±4.3	102	98	30	27
Yao-Jun Zhang	62.9±11.7	62.8±11.7	215	210	27.5±4.4	27.8±4.6	181	190	55	46
Hyun Jong Lee	64±14.08	63±14.08	128	400	/	/	102	308	82	269
Antoinette de Waha	62.5±12.1	63.1±12.6	214	149	/	/	142	110	56	34
Antoinette de Waha	62.5±12.1	63.1±12.6	214	149	/	/	142	110	56	34
Qi Zhang	63.9±13.1	64.1±12.1	475	467	/	/	360	376	129	113

Table2. The baseline features of the patients

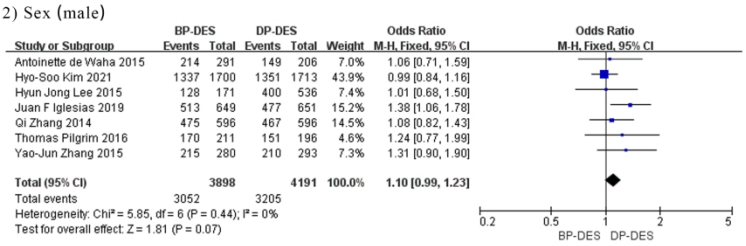
Authors	basic characters									
	Dyslipidemia		smoking		LVEF, %		Stent number per person		Total stent length, mm	
	BP-DES	DP-DES	BP-DES	DP-DES	BP-DES	DP-DES	BP-DES	DP-DES	BP-DES	DP-DES
Hyo-Soo Kim[	1,247	1,280	515	475	58.7±10.4	58.5±10.4	1.7±1.1	1.7±1.0	42.9±31.9	41.7±30.2
Juan F Iglesias	304	302	294	250	49.0 ± 11.0	48.4 ± 11.2	1.37 ± 0.64	1.39 ± 0.66	31.91± 18.21	33.92± 19.76
Thomas Pilgrim	110	101	93	77	49.5±10.9	48.3±11.1	1.42±0.71	1.39±0.71	29.49±17.83	30.52±18.99
Yao-Jun Zhang	152	176	107	115	51.5±10.1	51.4±11.8	2.2±0.5	2.2±0.6	26.6±15	27.9±15.2
Hyun Jong Lee	116	389	65	228	55 (45–65)	52 (43–62)	/	/	/	/
Antoinette de Waha[	119	109	120	90	47±10	48±12	/	/	25.9±12.6	27.7±14.2
Antoinette de Waha	119	109	120	90	47±10	48±12	/	/	25.9±12.6	27.7±14.2
Qi Zhang	87	76	257	223	50±12	49.0 ± 17.0	/	/	/	/

Fig1. A Baseline characteristics and stent information of patients with ACS

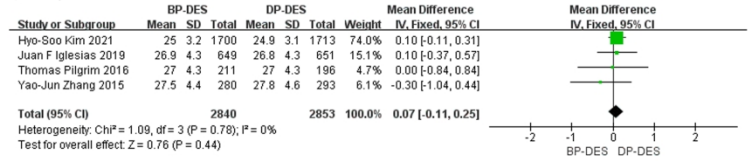
1) Age



2) Sex (male)



3) Body mass index



4) Hypertension

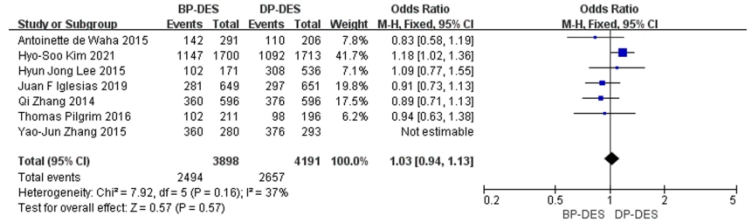


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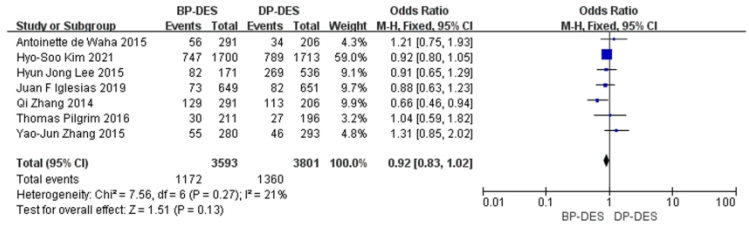
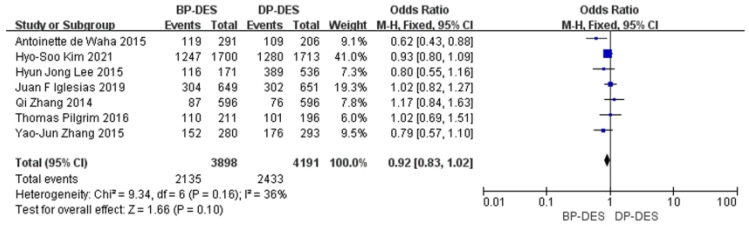
Fig1. B Baseline characteristics and stent information of patients with ACS

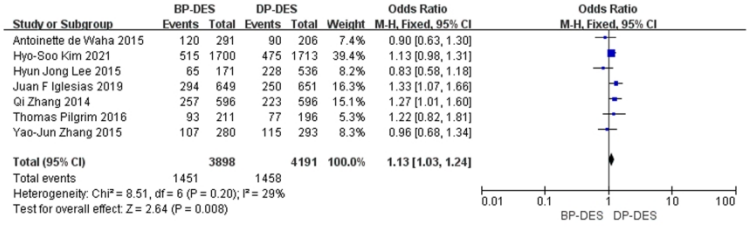
5) Diabetes



6) Dyslipidemia



7) Smoking



8) LVEF

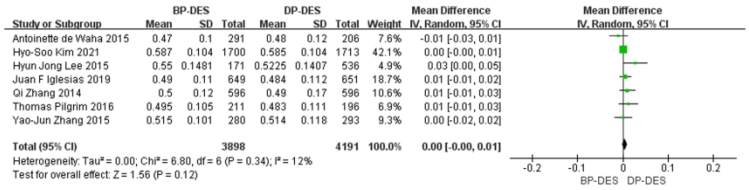


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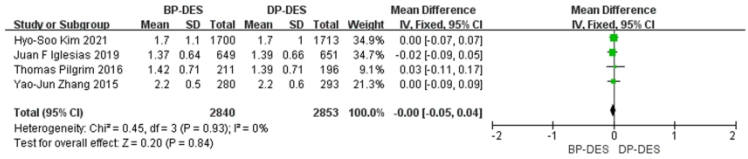
Fig1. C. Baseline characteristics and stent information of patients with ACS

9) Stent numerber per person



10) Total stent length

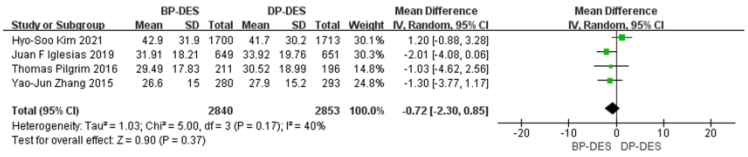


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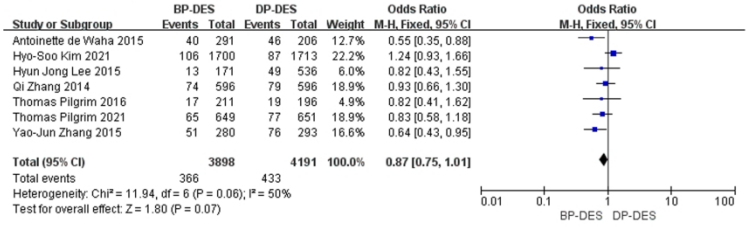
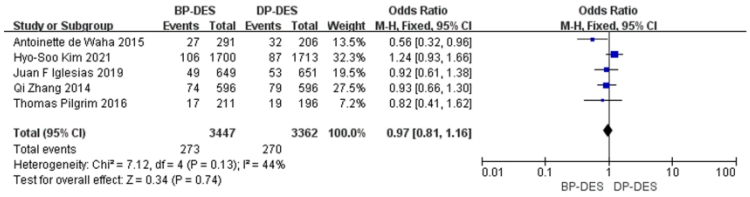
Fig2. Primary endpoint: MACE

2.1) MACE during follow up period



2.2) MACE at 1 year



2.3) MACE over 2 years

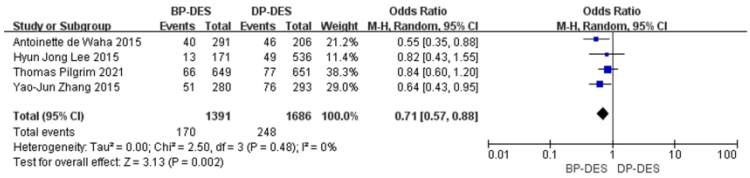


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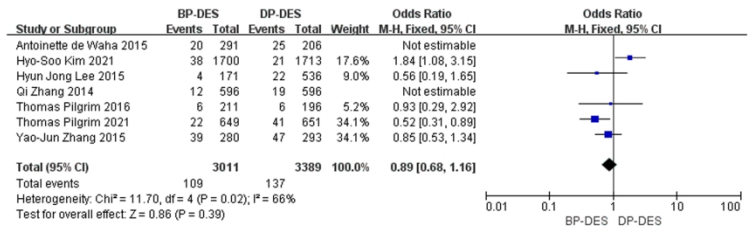
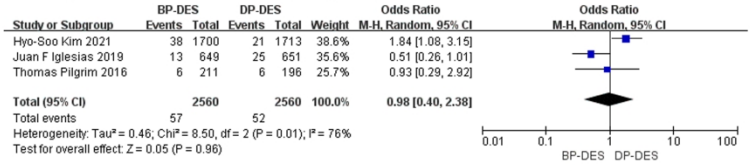
Fig3.Target vessel revascularization（TVR)

3.1) Target vessel revascularization（TVR) during follow up period



3.2) Target vessel revascularization（TVR) at 1 year



3.3) Target vessel revascularization（TVR) over 2 years

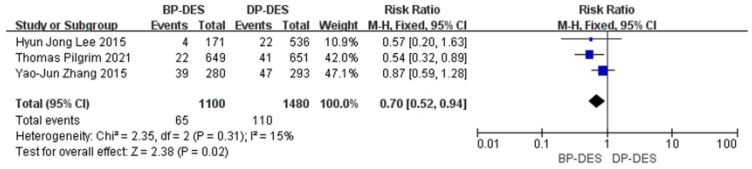


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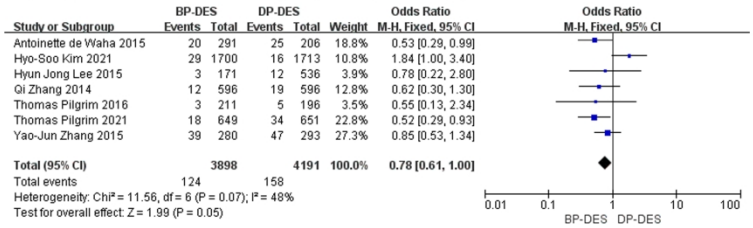
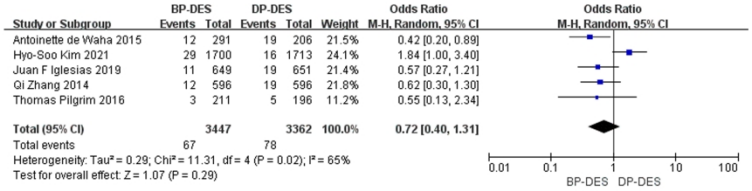
Fig4. Target lesion revascularization(TLR)

4.1) Target lesion revascularization(TLR) during follow up period



4.2)Target lesion revascularization(TLR) at 1 year



4.3) Target lesion revascularization(TLR) over 2 years

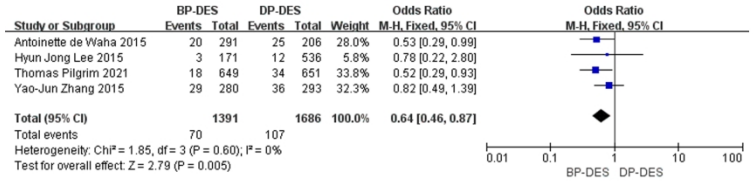


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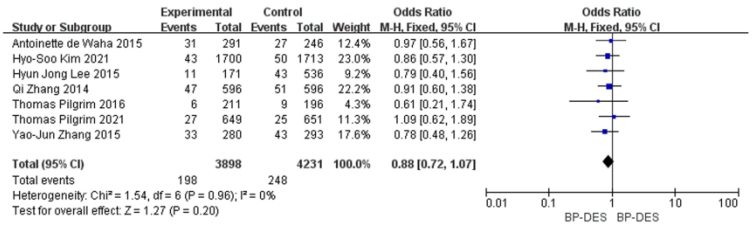
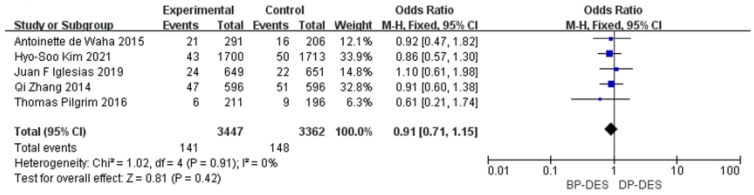
Fig 5. All cause death

5.1)All cause death during follow up period



5.2) All cause death at 1 year



5.3) All cause death over 2 years

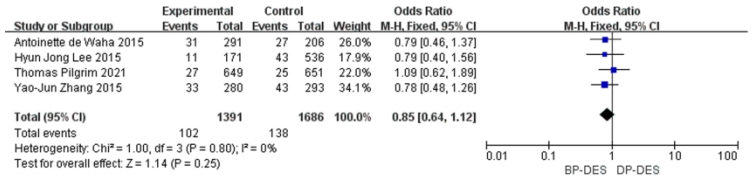


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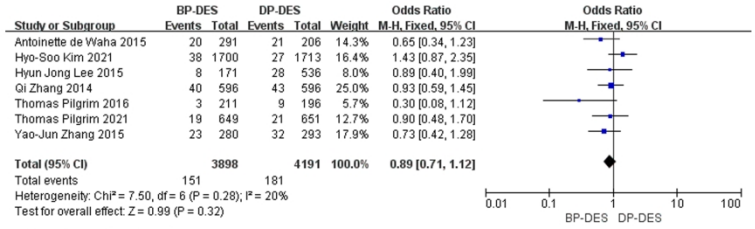
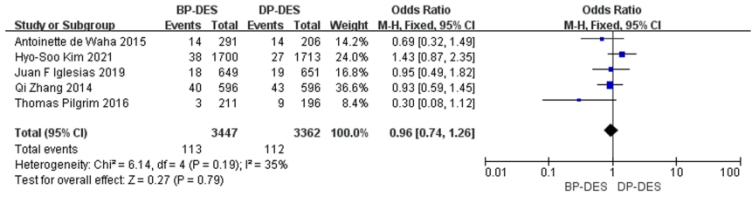
Fig 6. cardiac death

6.1) cardiac death during follow up period



6.2) cardiac death at 1 year



6.3) cardiac death over 2 years

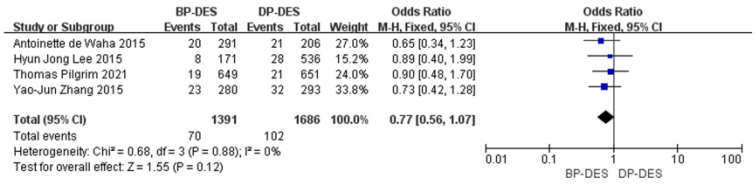


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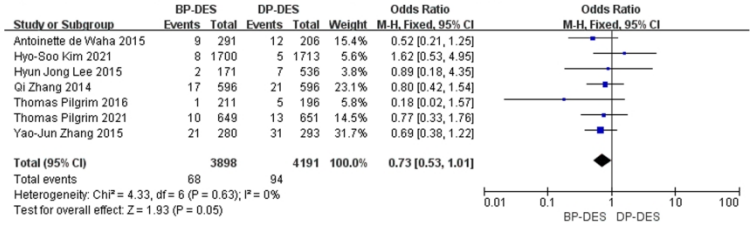
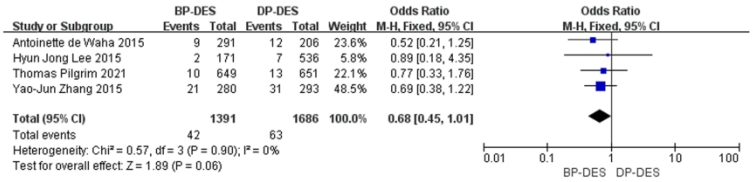
Fig 7.Target vessel myocardial infarction（MI)

7.1) Target vessel myocardial infarction（MI) during follow up period



7.2) Target vessel myocardial infarction（MI) at 1 year



7.3) Target vessel myocardial infarction（MI) over 2 year

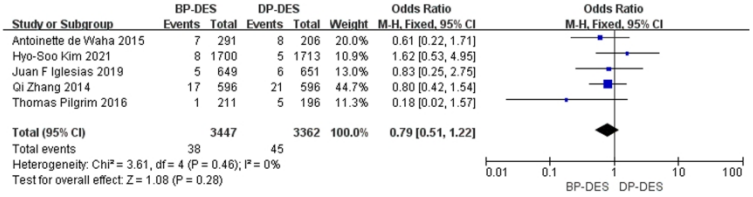


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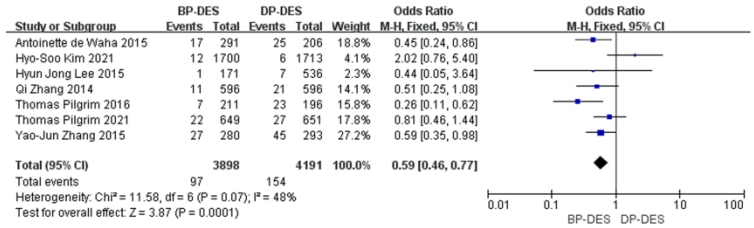
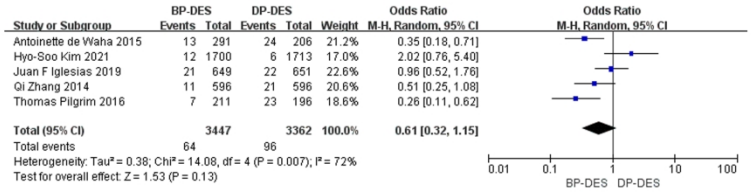
Fig 8. Stent thrombosis

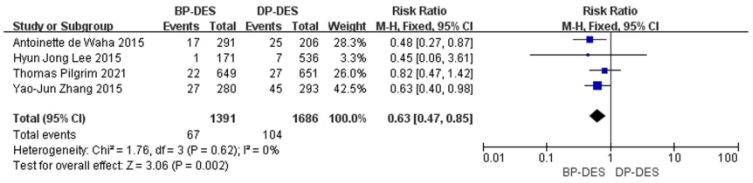
8.1) Stent thrombosis during follow up period



8.2) Stent thrombosis at 1 year



8.3) Stent thrombosis over 2 years



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PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Title page
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Abstract page
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 7-9
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 9-11
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	
Certainty	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
assessment			
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Page 11-15
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	
Study characteristics	17	Cite each included study and present its characteristics.	
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Page 15-17
	23b	Discuss any limitations of the evidence included in the review.	
	23c	Discuss any limitations of the review processes used.	
	23d	Discuss implications of the results for practice, policy, and future research.	
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Page 8
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	
Competing interests	26	Declare any competing interests of review authors.	
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi:

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Comparison of biodegradable and durable polymer drug-eluting stents in acute coronary syndrome: a meta-analysis

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Keywords:	Coronary heart disease < CARDIOLOGY, Coronary intervention < CARDIOLOGY, Myocardial infarction < CARDIOLOGY

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Comparison of biodegradable and durable polymer drug-eluting stents in acute coronary syndrome: a meta-analysis

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Word count: 2939

ABSTRACT

Objective: To compare the safety and effectiveness between biodegradable polymer drug-eluting stents (BP-DES) and durable polymer drug-eluting stents (DP-DES) in patients with acute coronary syndrome (ACS).

Design: Meta-analysis of randomized controlled trials (RTCs)

Primary and secondary outcome measures: Major adverse cardiovascular events (MACEs) were considered the primary endpoint. Efficacy endpoints included target vessel revascularization (TVR) and target lesion revascularization (TLR). Safety endpoints included all-cause death, cardiac death, target vessel myocardial infarction (TVMI), and ST.

Methods: We searched PubMed, Medline, Embase, and the Cochrane Controlled Register of Trials (CENTRAL) for comparative studies of BP-DES and DP-DES in patients with ACS from January 2000 to July 2021. Statistical pooling was performed for estimating incidence, using a random-effects model with generic inverse-variance weighting. Risk estimates were computed with 95% confidence intervals (CIs).

Results: Eight articles with 7 trails that compared BP-DES and DP-DES in patients with ACS were identified and included in qualitative and quantitative analyses. There was no difference in the baseline characteristics ($p>0.05$), except for the number of smoking patients ($p=0.008$), which was significantly lower in the BP-DES group. The meta-analysis demonstrated that MACEs, efficacy endpoints, and safety endpoints were similar between the groups at 1 year ($p>0.05$). However, the total stent thrombosis (ST) incidence was significantly different between the BP-DES and DP-DES groups in the follow-up period ($p=0.0001$). Further

analysis showed a statistically significant difference in MACEs (p=0.002), TLR (p=0.05), TVR (p=0.002), total ST incidence (p=0.0001), and ST incidence (p=0.002) over 2 years.

Conclusion: This meta-analysis revealed that both stent types showed excellent safety and efficacy profiles at 12 months. However, a slight increase in MACEs, TLR, TVR, and ST incidence was observed in the DP-DES group over the 2-year follow-up period, suggesting that BP-DES may be more favorable when treating patients with ACS. Long-term follow-ups are necessary to confirm these findings.

Keywords: acute coronary syndrome, biodegradable drug-eluting stent, durable polymer drug-eluting stent, major adverse cardiac event, stent thrombosis, target lesion revascularization, target vessel revascularization

Strengths and limitations of this study

- This meta-analysis includes randomized controlled trials with long-term follow-ups.
- The large sample size ensures adequate statistical power to detect even a small effect of interest.
- Heterogeneity among the BP-DES may distort the reported results.
- The differences in the durations of dual antiplatelet therapy may influence clinical outcomes.

Data availability statement

No additional data available.

Patient and public involvement

We did not require patient and public involvement, as this is a meta-analysis, and no new patients were enrolled in the study.

Ethics approval

This study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, and the protocol was registered with PROSPERO (CRD42021253412). This study was approved by the institutional review board of the Second Xiangya Hospital of Central South University.

Funding

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INTRODUCTION

Percutaneous coronary intervention (PCI) is the current standard of care for patients with coronary artery disease, particularly acute coronary syndrome (ACS)[1, 2].Unlike bare-mental stents (BMS), drug-eluting stents (DES) use antiproliferative agents embedded in a polymer coating on the stent's surface, which inhibit neointimal hyperplasia to reduce the risk of restenosis[3]. Although DES have substantially improved clinical outcomes, the first-generation durable polymer DES (DP-DES) released sirolimus or paclitaxel, and it was associated with similar risks of death and myocardial infarction to those of BMS beyond 1 year after implantation[4]. Later, the second-generation DP-DES were confirmed to have lower restenosis rates than first-generation devices and showed reduced rates of stent thrombosis (ST)[5]. Recently, very late ST and neoatherosclerosis, with adverse clinical outcomes, have been observed with second-generation DP-DES, which has improved the biocompatibility of the polymer[6]. Late stent failure has been attributed to delayed endothelial healing secondary to a hypersensitivity reaction to the durable polymer[7].

To address this potential limitation of DP-DES, biodegradable polymer DES (BP-DES) have been developed. Theoretically, BP-DES would lead to a reduction in vascular inflammation and a decreased risk of late stent-related complications due to the advantage of leaving only the BMS after complete drug elution and polymer degradation. BP-DES have been observed to reduce the rate of major adverse cardiac events (MACEs) compared to BMS[8] and first-generation DP-DES[9]. Studies of patients who underwent PCI showed that the device-related outcomes were comparable between BP-DES and second-generation DP-DES[10-13]. Thus, BP-DES would be expected to reduce the risk of ST-related MACEs beyond the first

year compared to that of DP-DES. However, previous studies enrolled a significant proportion of stable angina patients. ACS confers an increased risk of adverse outcomes due to plaque characteristics, including culprit lesions, thrombus burden, and persistent inflammation, compared to stable coronary artery diseases. ACS also increases the risk of delayed arterial healing and vessel remodeling[14], reflected by higher rates of incomplete stent strut coverage[15, 16] and malpositioning[17].

Recently, randomized trials have been performed to compare the efficacy and safety of DP-DES and BP-DES in patients with ACS who underwent PCI. In this meta-analysis, we aimed to summarize studies comparing the two polymer technologies in ACS patients and to analyze the safety and effectiveness of these therapeutic options.

METHODS

Search strategy and registration

This study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and was approved by the institutional review board of the Second Xiangya Hospital, Central South University. The protocol was registered with PROSPERO (CRD42021253412).

Based on the PRISMA statement, PubMed, Medline, Embase, and the Cochrane Controlled Register of Trials (CENTRAL) databases were searched for comparative studies of BP-DES and DP-DES in the treatment of patients with ACS who underwent PCI. The following search terms were used: “BP-DES,” “biodegradable,” “bioabsorbable,” “bioabsorbable polymer drug-eluting stent,” “biodegradable polymer drug-eluting stent,” “DP-

DES," "durable polymer," "durable polymer drug-eluting stent," "acute coronary syndrome," "ACS," "AMI," "Acute myocardial infarction," "Non ST segment elevation myocardial infarction," "ST segment elevation myocardial infarction," "NSTEMI," and "STEMI." We also reviewed prior meta-analyses and the reference lists of the original trials and review articles to identify further studies. Only English language articles published in peer-reviewed journals from January 2000 to July 2021 were selected. Analyses were conducted by two independent reviewers.

Eligibility criteria

The inclusion criteria for this meta-analysis were as follows: 1) randomized controlled trials (RCTs) comparing BP-DES and DP-DES in the treatment of patients with ACS who underwent PCI; 2) data reporting patients' baseline characteristics, follow-up durations, outcomes at the primary, safety, and efficacy endpoints; 3) mean follow-up time over 12 months; and 4) full-text articles.

The exclusion criteria for the meta-analysis were as follows: 1) duplications of samples and reports (evaluated by 2 independent reviewers); 2) case reports/series; and 3) studies involving data from a national database.

Data extraction and outcome measurement

Two authors (Haoyong Yuan and Tingting Wei) systematically screened the titles and abstracts of publications retrieved using the search strategy to select studies that met the above inclusion criteria. Any disagreement between them regarding the eligibility of particular studies was resolved through discussion and involvement of a third author (Zhongshi Wu), when

necessary. First, baseline characteristics, including the name of the first author, year of publication, study design, country of origin, number of patients, mean age of subjects, and mean duration of follow-up were gathered from each included article. In addition, sex; body mass index; presence of hypertension, diabetes, dyslipidemia, chronic kidney disease, peripheral vessel disease, or smoking; left ventricular ejection fraction (LVEF), number of stents per person; and total stent length were collected for evaluation of procedure risk. MACEs were considered the primary endpoint. The efficacy endpoints included target vessel revascularization (TVR) and target lesion revascularization (TLR). In addition, all-cause death, cardiac death, target vessel myocardial infarction (TVMI), and ST were employed as endpoints to evaluate the safety of BP-DESs and DP-DESs.

The Risk of Bias 2 (RoB2) tool was employed to assess the quality of RCTs based on sequence generation; randomized group allocation; concealment; blinding of participants, personnel, and outcome assessors; incomplete data; selectivity; outcome reporting; and other sources of bias(Supplementary Material 2)[18].

Data analysis and synthesis

Continuous variables are reported as the mean (standard deviation), and categorical variables are expressed as numbers. Statistical pooling was performed to estimate incidence, according to a random-effects model with generic inverse-variance weighting. We computed risk estimates with 95% confidence intervals (CIs), using RevMan 5.3 (The Cochrane Collaboration, The NordicCochrane Centre, Copenhagen, Denmark). Hypothesis testing for superiority was set at the two-tailed 0.05 level. Hypothesis testing for statistical homogeneity

was set at the two-tailed 0.10 level and was based on the Cochran Q test, with I^2 values of 25%, 50%, and 75% representing mild, moderate, and severe heterogeneity, respectively.

RESULTS

Search results

A total of 895 articles, written in English, were identified through the literature search. After an initial screening of the titles and abstracts, 803 articles were eliminated, as they were not related to the topic of this study. Following the removal of these articles, 92 clinical studies and RCT articles of the two polymers remained. After reading the full texts, 28 articles about acute coronary syndromes remained, with 20 articles including chronic and acute coronary syndrome. Finally, 8 articles, with 7 randomized controlled trials, comparing BP-DES and DP-DES in patients with ACS were identified and included in the qualitative and quantitative analyses[19-26]. The follow-up duration ranged from 1 year to 5 years (Supplementary Table 1 and Supplementary Material 1).

General features of the trials

A total number of 8089 patients (3898 patients who were treated with BP-DES and 4191 patients who were treated with the DP-DES) were included in this analysis. Further details about the the quality of RCTs, total number of patients retrieved from each trial, publication years, countries of origin of the publications, centers in which trials were performed, follow-up durations, risk factors, and primary, efficacy, and safety endpoints are listed in Supplementary Table 2 and Supplementary Material 2.

Patient characteristics

The baseline features of the patients are summarized in Tables 2. The mean age of the patients who were treated by BP-DES ranged from 61.3 to 64 years old, whereas the mean age of the patients who were treated by DP-DES ranged from 61.7 to 64.1 years. The proportions of male patients were above 70% in all included trials. There was no difference in age (mean difference [MD]: 0.14, 95%CI: -0.66–0.38; p=0.60, I^2=0%), sex (male) (odds ratio [OR]: 1.10, 95%CI: 0.99–1.23; p=0.07, I^2=0%), hypertension (OR: 1.03, 95%CI: 0.94–1.13; p=0.57, I^2=37%), dyslipidemia (OR: 0.92, 95% CI: 0.83–1.02; p=0.10, I^2=36%), LVEF (MD: 0.00, 95%CI: 0.00–0.01; p=0.12, I^2=12%), body mass index (MD:0.07, 95%CI: -0.11 to 0.25; p=0.44, I^2=0%), diabetes (OR: 0.92, 95%CI: 0.83–1.02; p=0.13, I^2=21%), total stent length (MD: -0.72, 95%CI: -2.30 to -0.85; p=0.37, I^2=40%), and number of stents per person (MD: -0.00, 95%CI: -0.05 to 0.04; p=0.84, I^2=0%) among patients who were implanted with BP-DES or DP-DES. The meta-analysis demonstrated that the number of smoking patients (OR: 1.13, 95%CI: 1.03–1.24; p=0.008, I^2=29%) was significantly lower in the BP-DES group than that in the DP-DES group (Figure 1-3).

Primary endpoint: MACEs reported during follow-up periods of 1–5 years, 1 year, and over 2 years

MACEs, including all-cause death, recurrent MI, or any coronary repeat revascularization involving TLR, TVR, and non-TVR, were considered the primary endpoint of the trials. A meta-analysis indicated no statistically significant difference in MACEs in a follow-up period ranging from 1 to 5 years between the two groups (OR: 0.87, 95%CI: 0.75–1.01; p=0.07, I^2=50%). Of the 5 studies that published 1-year outcomes, MACEs were not significantly different between the BP-DES and DP-DES groups (OR: 0.97, 95%CI: 0.81–1.16; p=0.74,

I^2=44%). However, the MACEs with follow-up periods over 2-years are significant lower in the BP-DES group (OR: 0.71, 95%CI: 0.57–0.88; p=0.002, I^2=0 %) (Figure 4).

Efficacy endpoint: TVR and TLR reported during follow-up periods of 1–5 years, 1 year, and over 2 years

TLR and TVR were considered the efficacy endpoints of the trials. The meta-analysis indicated no statistically significant difference in TLR in follow-up periods ranging from 1 to 5 years between the two groups (OR: 0.78, 95%CI: 0.61–1.00; p=0.05, I^2=48%). Among the 5 studies that published 1-year data, TLR was not significantly different between the BP-DES and DP-DES groups (OR: 0.72, 95%CI: 0.40–1.31; p=0.29, I^2=65%). The meta-analysis indicated no statistically significant difference in TVR in follow-up periods ranging from 1 to 5 years (OR: 1.01, 95%CI: 0.79–1.28; p=0.96, I^2=46%) or in the 3 publications with 1 year follow-up periods (OR: 0.98, 95%CI: 0.40–2.38; p=0.96, I^2=76%). However, the difference in TLR was statistically significant in 4 RCT studies with follow-up periods over 2-years (OR: 0.71, 95%CI: 0.51–1.01; p=0.05, I^2=0%), and the difference in TVR was also statistically significant in 3 RCT studies with follow-up periods over 2-years (OR: 0.70, 95%CI: 0.52–0.94; p=0.002, I^2=15%), with values much lower in the BP-DES group (Figures 5, 6).

Safety endpoint: All-cause death, cardiac-related death, target vessel myocardial infarction, and stent thrombosis over follow-up periods of 1–5 years, 1 year, and over 2 years

All-cause death, cardiac-related death, TVMI, and ST were considered the efficacy endpoints. The meta-analysis indicated no statistically significant difference between the two

groups in all-cause death (OR: 0.88, 95%CI: 0.72–1.07; p=0.20, I^2=0%), cardiac-related death (OR: 0.89, 95%CI: 0.71–1.12; p=0.32, I^2=20%), and TVMI (OR: 0.73, 95%CI: 0.53–1.01; p=0.05, I^2=0%) over a follow-up period ranging from 1 to 5 years. Of the 5 studies that published 1-year data, all-cause death, cardiac-related death, and TVMI were also not significantly different between the BP-DES and DP-DES groups ([all-cause death, OR: 0.91, 95%CI: 0.71–1.15; p=0.42, I^2=0%], [cardiac-related death, OR: 0.96, 95%CI: 0.74–1.26; p=0.79, I^2=35%], [TVMI, OR: 0.73, 95%CI: 0.53–1.01; p=0.05, I^2=0%]). In the 5 studies with follow up periods of over 2-year, similar findings were observed for the all-cause cardiac death, cardiac-related death, and TVMI ([all-cause death, OR: 0.85, 95%CI: 0.64–1.12; p=0.25, I^2=0%], [cardiac-related death, OR: 0.77, 95%CI: 0.56–1.17; p=0.12, I^2=0%], [TVMI, OR: 0.79, 95%CI: 0.51–1.22; p=0.28, I^2=0%) (Figures 7–9). However, the total ST incidence, including the definite ST, probable ST, and definite or probable ST incidence, was significantly different between the BP-DES and DP-DES groups during the follow-up period (OR: 0.59, 95% CI: 0.46–0.77; p=0.0001, I^2=48%). Further analysis revealed no difference in total ST for a 1-year follow-up (OR: 0.61, 95%CI: 0.32–1.15; P=0.13, I^2=72%), while the meta-analysis indicated a statistically significant difference in the total ST for the follow-ups over 2-years (OR: 0.63, 95%CI: 0.47–0.85; p=0.002, I^2=0%) (Figure 10).

DISCUSSION

The choice of stent in patients undergoing PCI for ACS is debated. Coronary intervention with second-generation DP-DES generally reduces the need for revascularization and improves mortality compared to BMS and first-generation DP-DES. Furthermore, the risk of late ST with DP-DES tends to off-set these benefits, as seen in registries and clinical trials comparing DP-

DES to BMS[15, 27]. BP-DES was designed to leave only the BMS behind once the polymer completely bio-degraded after drug elution and may represent an attractive solution for patients with ACS[28]. Prior meta-analyses have compared the clinical outcomes among BMS, DP-DES, and BP-DES in patients with stable coronary artery disease, but no previous meta-analysis of RCTs and prospective trials directly compared clinical outcomes between BP-DES and DP-DES for the treatment of ACS. To our knowledge, this meta-analysis exclusively compared BP-DES to DP-DES. It included 7 trials representing 8089 patients with relatively long follow-up durations, ranging from 1 year to 5 years. Although BP-DES have been hypothesized to offer improved outcomes, mainly in the long term, several prior meta-analyses have demonstrated different outcomes with BP-DES compared to DP-DES in patients undergoing PCI. Bangalore et al. found that BP-DES were associated with higher mortality than DP-DES beyond 1 year of follow-up[29]. El-Hayek et al. demonstrated no significant difference in mortality between these types of stent[6]. In our study, there were no significant differences in MACEs, all-cause death, cardiac-related death, TVMI, TVR, or TLR at a follow-up period of 1 year and no significant differences in all-cause death, cardiac death, or TVMI at a follow-up period of over 2 years. However, at a follow-up of over 2-years, MACEs, TVR and TLR are significant lower in the BP group than those in the DP group. Pilgrim T et al. found a higher all-cause mortality among patients treated with BP-SES compared with DP-EES in the BIOSCIENCE trial; they also found comparable rates of all-cause mortality between patients treated with BP-SES and DP-EES in the BIOSTEMI trial with a 2-year follow-up[6]. Mario Iannaccone et al. found that BP-DES might potentially decrease the risk of ischemic events in selected high-risk subgroups of patients, although the two DES stents share the same safety

factors for patients in high-anatomical-risk settings like left main (LM) disease[30]. Together, these findings suggest that BP-DES share similar outcomes in terms of MACEs (all-cause death, cardiac-related death, TVMI, TVR, and TLR) during a 1-year follow-up and might significantly improve clinical outcomes over a 2-year follow-up.

ST is defined as a thrombotic occlusion of a coronary stent[31] and is a major complication. The risk of ST, particularly late ST (occurring beyond 30 days), remains among the major concerns limiting the use of DES in the treatment of ACS[32]. Early-generation DP-DES were associated with increased rates of very late (>1 year) ST compared with BMS. It was hypothesized that the mechanism underlying late ST with first DP-DES in ACS was related to adverse reactions with the durable polymer[33], and the use of more biocompatible polymers has been associated with a reduction in ST in high-risk patients[9]. In the LEADERS trial, the rate of very late ST was lower with the use of the BP-DES than that with DP-DES[34]. Our data demonstrated that both BP-DES and DP-DES have similar risks of ST beyond 1 year. However, BP-DES are associated with a significantly reduced risk of ST at a follow-up of over 2 years compared with DP-DES (OR: 0.64, 95%CI: 0.46–0.88; p=0.006, I^2=0%). In contrast, Kim et al. found that the incidence of ST by groups showed numerically lower rates in the DP-DES group (0.1%) than those in the BP-DES group and that all late ST cases occurred in those receiving thick-strut BP-DES stents. They proposed that no meaningful differences in terms of ST could be identified between the different polymer technologies by intravascular imaging and that the association of polymer technology and the risk of the ST was difficult to prove[20, 35, 36]. Therefore, it may be hypothesized that the BP-DES result in improved arterial healing, which not only minimizes the risk of ST, but also improves the long-term durability of the

antirestenotic efficacy in the long term, although the two groups have a similar risk of ST beyond 1 year.

Limitations

The present study had several limitations. First, this study included RCTs and shares the limitations of original studies. Second, BP-DES are a heterogeneous group of stents, differing with regards to stent platform thickness, time to complete degradation of the polymer, and drug-elution kinetics. DP-DES is an equally heterogeneous group. Innaccone et al. found that lower strut thickness would have a positive clinical outcome, reducing stent thrombosis and target lesion revascularizations[37]. We were unable to match the stents in regard to strut thickness. As a consequence, the reported results may not be generalizable to all stents from the respective group. Third, over-6-month dual antiplatelet therapy (DAPT) was given to the patients in our including RCT trials. D'Ascenzo et al. found a similar rate of MACEs between durable and biodegradable polymers, irrespective of DAPT length, and the DAPT duration seems to partially impact the risk of adverse events of different types of stents at follow-up[38]. Thus, we remain concerned that the duration differences of DAPT may influence the clinical outcomes.

CONCLUSION

In this meta-analysis comparing BP-DES to DP-DES in ACS patients who underwent PCI, the data indicated that both polymer types showed excellent safety and efficacy profiles at 1 year. There was a slightly increased incidence of MACEs, TLR, TVR, and ST in the DP-DES group in the follow-up period over 2 years, suggesting that BP-DES may be more favorable for

treating patients with ACS. These findings should be confirmed by long-term follow-up in RCT trials.

Author contributions

Can Huang, Zhongshi Wu, and Haoyong Yuan developed the idea of the study, participated in its design and coordination and helped to draft the manuscript. Ting Lu and Tingting Wei contributed to the acquisition and interpretation of data. Yifan Zeng and Yalin Liu provided critical review and substantially revised the manuscript. All authors read and approved the final manuscript.

SUPPLEMENTARY **TABLE LEGENDS**

Table 1. The characteristics of the included trials

Table 2. The baseline features of the patients

FIGURE LEGENDS

Figure 1 . Baseline characteristics and stent information of patients with acute coronary syndrome

Figure 2. Baseline characteristics and stent information of patients with acute coronary syndrome

Figure 3. Baseline characteristics and stent information of patients with acute coronary syndrome

Figure 4. Primary endpoint: major adverse cardiac events

Figure 5. Target vessel revascularization

Figure 6. Target lesion revascularization

Figure 7. All-cause death

Figure 8. Cardiac-related death

Figure 9. Target vessel myocardial infarction

Figure 10. Stent thrombosis

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Supplementary Material 1: search strategy and PRISMA flow chart for included studies

A. Search strategy

1. Pubmed (N=688)

Search date: from January 2000 to July 2021

Search terms:

1#. ("BP-DES"[MeSH Terms] OR "BP-DES"[All Fields] OR "biodegradable "[All Fields] OR "bioabsorbable "[All Fields] OR "bioabsorbable polymer drug-eluting stent"[All Fields] OR "biodegradable polymer drug-eluting stent"[All Fields]) AND ("acute coronary syndrome"[All Fields] OR "ACS"[All Fields] OR "AMI"[All Fields] OR "Acute myocardial infarction"[All Fields] OR "Non ST segment elevation myocardial infarction"[All Fields] OR "ST segment elevation myocardial infarction"[All Fields] OR "NSTEMI"[All Fields] OR "STEMI"[All Fields])

2#. ("DP-DES"[All Fields] OR "DP-DES"[MeSH Terms] OR "durable polymer"[All Fields] OR "durable polymer drug-eluting stent"[All Fields]) AND ("acute coronary syndrome"[All Fields] OR "ACS"[All Fields] OR "AMI"[All Fields] OR "Acute myocardial infarction"[All Fields] OR "Non ST segment elevation myocardial infarction"[All Fields] OR "ST segment elevation myocardial infarction"[All Fields] OR "NSTEMI"[All Fields] OR "STEMI"[All Fields])

3#. ("BP-DES"[MeSH Terms] OR "BP-DES"[All Fields] OR "biodegradable "[All Fields] OR "bioabsorbable "[All Fields] OR "bioabsorbable polymer drug-eluting stent"[All Fields] OR "biodegradable polymer drug-eluting stent"[All Fields]) and ("DP-DES"[All Fields] OR "DP-DES"[MeSH Terms] OR "durable polymer"[All Fields] OR "durable polymer drug-eluting stent"[All Fields]) AND ("acute coronary syndrome"[All Fields] OR "ACS"[All Fields] OR "AMI"[All Fields] OR "Acute myocardial infarction"[All Fields] OR "Non ST segment elevation myocardial infarction"[All Fields] OR "ST segment elevation myocardial infarction"[All Fields] OR "NSTEMI"[All Fields] OR "STEMI"[All Fields])

2. OVID (N=207, EMBS=134, MEDLINE=54, Controlled Register of Trials=19)

Search date: from January 2000 to July 2021

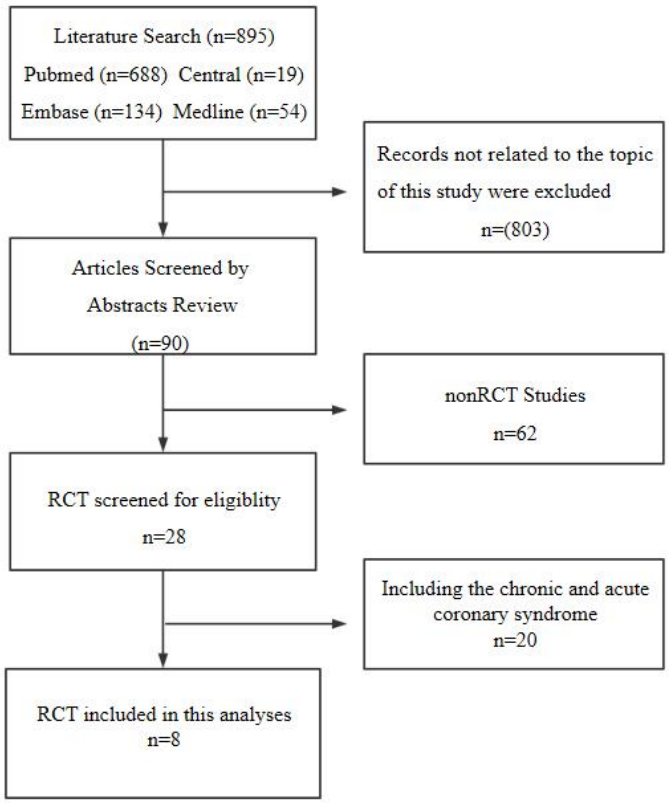
Search terms:

1#.("BP-DES" OR "bioabsorbable polymer drug-eluting stent" OR "biodegradable polymer drug-eluting stent") and ("acute coronary syndrome" OR "ACS" OR "AMI" OR "Acute myocardial infarction" OR "Non ST segment elevation myocardial infarction" OR "ST segment elevation myocardial infarction" OR "NSTEMI" OR "STEMI")

2#.("DP-DES" OR "durable polymer drug-eluting stent") and ("acute coronary syndrome" OR "ACS" OR "AMI" OR "Acute myocardial infarction" OR "Non ST segment elevation myocardial infarction" OR "ST segment elevation myocardial infarction" OR "NSTEMI" OR "STEMI")

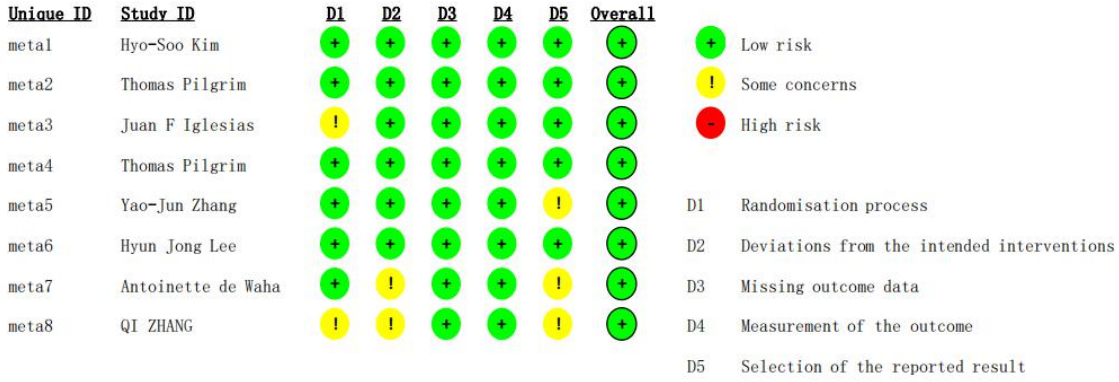
3#.("BP-DES" OR "bioabsorbable polymer drug-eluting stent" OR "biodegradable polymer drug-eluting stent") and ("DP-DES" OR "durable polymer drug-eluting stent") and ("acute coronary syndrome" OR "ACS" OR "AMI" OR "Acute myocardial infarction" OR "Non ST segment elevation myocardial infarction" OR "ST segment elevation myocardial infarction" OR "NSTEMI" OR "STEMI")

B. PRISMA flow chart for studies included in the meta-analysis



Supplementary Material 2. Risk-of-bias summary for included trials

A.



B.

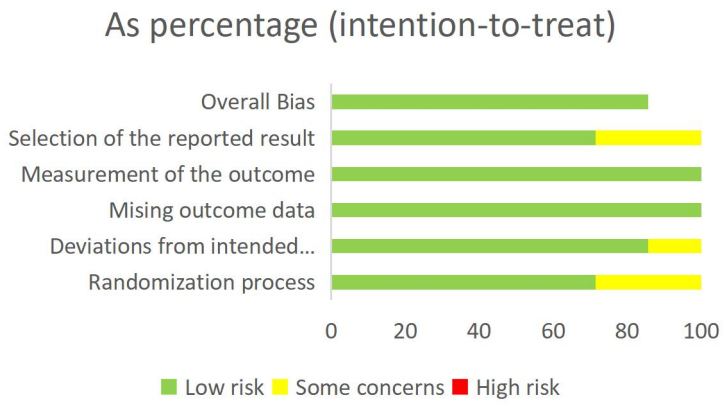


Table 1. The characteristics of the included trails

Authors	Years	Journal	Study	Center	Country	Follow up	NO.patients	
							BP-DES	DP-DES
Hyo-Soo Kim	2021	Circulation	RCT	multicentre	Korea	12 month	1700	1713
Thomas Pilgrim	2021	JACC	RCT	multicentre	Switzerland	24month	649	651
Juan F Iglesias	2019	The Lancet	RCT	multicentre	Switzerland	12 month	649	651
Thomas Pilgrim	2016	EuroIntervention	RCT	multicentre	Switzerland	12 month	211	196
Yao-Jun Zhang	2015	Heart	RCT	multicentre	Netherlands	60month	280	293
Hyun Jong Lee	2015	International journal of cardiology	RCT	multicentre	Korea	24month	171	536
Antoinette de Waha	2015	EuroIntervention	RCT	multicentre	multicentre	48month	291	206
Qi Zhang	2014	Journal of Interventional Cardiology	RCT	multicentre	China	12 month	596	596

Table 2. The baseline features of the patients

	basic characters									
Authors	Age		SEX(MALE)		Body mass index		Hypertension		Diabetes	
	BP-DES	DP-DES	BP-DES	DP-DES	BP-DES	DP-DES	BP-DES	DP-DES	BP-DES	DP-DES
Hyo-Soo Kim	63.1±11.1	63.0±11.1	1337	1351	25.0±3.2	24.9±3.1	1147	1092	747	789
Juan F Iglesias	62.2±11.8	63.2±11.8	513	477	26.9± 4.3	26.8± 4.3	281	297	73	82
Thomas Pilgrim	61.3±12.4	61.7±12.7	170	151	27.0±4.3	27.0±4.3	102	98	30	27
Yao-Jun Zhang	62.9±11.7	62.8±11.7	215	210	27.5±4.4	27.8±4.6	181	198	55	46
Hyun Jong Lee	64±14.08	63±14.08	128	400	/	/	102	308	82	269
Antoinette de Waha	62.5±12.1	63.1±12.6	214	149	/	/	142	110	56	34
Qi Zhang	63.9±13.1	64.1±12.1	475	467	/	/	360	376	129	113

Table 2. The baseline features of the patients

Authors	basic characters									
	Dyslipidemia		smoking		LVEF, %		Stent number per person		Total stent length, mm	
	BP-DES	DP-DES	BP-DES	DP-DES	BP-DES	DP-DES	BP-DES	DP-DES	BP-DES	DP-DES
Hyo-Soo Kim	1,247	1,280	515	475	58.7±10.4	58.5±10.4	1.7±1.1	1.7±1.0	42.9±31.9	41.7±30.2
Juan F Iglesias	304	302	294	250	49.0 ± 11.0	48.4 ± 11.2	1.37 ± 0.64	1.39 ± 0.66	31.91± 18.21	33.92± 19.76
Thomas Pilgrim	110	101	93	77	49.5±10.9	48.3±11.1	1.42±0.71	1.39±0.71	29.49±17.83	30.52±18.99
Yao-Jun Zhang	152	176	107	115	51.5±10.1	51.4±11.8	2.2±0.5	2.2±0.6	26.6±15	27.9±15.2
Hyun Jong Lee	116	389	65	228	55 (45–65)	52 (43–62)	/	/	/	/
Antoinette de Waha	119	109	120	90	47±10	48±12	/	/	25.9±12.6	27.7±14.2
Qi Zhang	87	76	257	223	50±12	49.0 ± 17.0	/	/	/	/

BMJ Open

Comparison of biodegradable and durable polymer drug-eluting stents in acute coronary syndrome: a meta-analysis

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Comparison of biodegradable and durable polymer drug-eluting stents in acute coronary syndrome: a meta-analysis

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ABSTRACT

Objective: To compare the safety and effectiveness between biodegradable polymer drug-eluting stents (BP-DES) and durable polymer drug-eluting stents (DP-DES) in patients with acute coronary syndrome (ACS)

Design: Meta-analysis of randomized controlled trials (RTCs)

Primary and secondary outcome measures: Major adverse cardiovascular events (MACEs) were considered the primary endpoint. Efficacy endpoints included target vessel revascularization (TVR) and target lesion revascularization (TLR). Safety endpoints included all-cause death, cardiac death, target vessel myocardial infarction (TVMI), and ST.

Methods: We searched PubMed, Medline, Embase, and the Cochrane Controlled Register of Trials (CENTRAL) for comparative studies of BP-DES and DP-DES in patients with ACS from January 2000 to July 2021. Statistical pooling was performed to estimate incidence using a random-effects model with generic inverse-variance weighting. Risk estimates were computed with 95% confidence intervals (CIs).

Results: Eight articles with seven RCTs that compared BP-DES and DP-DES in patients with ACS were identified and included in the qualitative and quantitative analyses. There was no difference in the baseline characteristics, except for the number of smoking patients (OR: 1.13, 95% CI: 1.03–1.24; p=0.008, I^2=29%), which was significantly lower in the BP-DES group. The meta-analysis demonstrated that MACEs, efficacy endpoints, and safety endpoints were similar between the groups at 1 year. However, the incidence of total stent thrombosis (ST) was significantly different between the BP-DES and DP-DES groups in the follow-up

period (p=0.0001). Further analysis showed a statistically significant difference in MACEs (OR: 0.71, 95% CI: 0.57–0.88; p=0.002, I^2=0 %) , TLR (OR: 0.71, 95% CI: 0.51–1.01; p=0.05, I^2=0%) , TVR (OR: 0.70, 95% CI: 0.52–0.94; p=0.002, I^2=15%), total ST incidence (OR: 0.59, 95% CI: 0.46–0.77; p=0.0001, I^2=48%), and ST incidence (OR: 0.63, 95% CI: 0.47–0.85; p=0.002, I^2=0%) over 2 years.

Conclusion: This meta-analysis revealed that both stent types demonstrated excellent safety and efficacy profiles at 12 months. However, a slight increase in MACEs, TLR, TVR, and ST incidence was observed in the DP-DES group over the 2-year follow-up period, suggesting that BP-DES may be more favorable when treating patients with ACS.

Keywords: acute coronary syndrome, biodegradable drug-eluting stent, durable polymer drug-eluting stent, major adverse cardiac event, stent thrombosis, target lesion revascularization, target vessel revascularization

Strengths and limitations of this study

- This meta-analysis included randomized controlled trials with long-term follow-ups.
- The large sample size ensures adequate statistical power to detect even a small effect of interest.
- Heterogeneity among the BP-DES may distort the reported results.
- The differences in the duration of dual antiplatelet therapy may influence clinical outcomes.

INTRODUCTION

Percutaneous coronary intervention (PCI) is the current standard of care for patients with coronary artery disease, particularly acute coronary syndrome (ACS)[1, 2]. Unlike bare-metal stents (BMS), drug-eluting stents (DES) use antiproliferative agents embedded in a polymer coating on the stent's surface, which inhibit neointimal hyperplasia to reduce the risk of restenosis[3]. DES have substantially improved clinical outcomes; however, the first-generation durable polymer DES (DP-DES) were known to release sirolimus or paclitaxel, and were associated with similar risks of death and myocardial infarction compared with those of BMS beyond 1 year after implantation[4]. Later, the second-generation DP-DES were confirmed to have lower restenosis rates than the first-generation devices and demonstrated reduced rates of stent thrombosis (ST)[5]. Recently, very late ST and neoatherosclerosis, with adverse clinical outcomes, have been observed with the second-generation DP-DES, which has improved the biocompatibility of the polymer[6]. Late stent failure has been attributed to delayed endothelial healing secondary to a hypersensitivity reaction due to the durable polymer[7].

To address this potential limitation of DP-DES, biodegradable polymer DES (BP-DES) have been developed. Theoretically, BP-DES would lead to a reduction in vascular inflammation and a decreased risk of late stent-related complications due to the advantage of leaving the BMS only after complete drug elution and polymer degradation. BP-DES have been observed to reduce the rate of major adverse cardiac events (MACEs) compared with BMS[8] and first-generation DP-DES[9]. Studies of patients who underwent PCI revealed that the device-related outcomes were comparable between BP-DES and second-generation DP-DES[10-13]. Thus, BP-DES would be expected to reduce the risk of ST-related MACEs beyond

the first year compared with that of DP-DES. However, previous studies enrolled a significant proportion of stable angina patients. ACS confers an increased risk of adverse outcomes due to plaque characteristics, including culprit lesions, thrombus burden, and persistent inflammation, compared with stable coronary artery diseases. ACS also increases the risk of delayed arterial healing and vessel remodeling[14], reflected by higher rates of incomplete stent strut coverage[15, 16] and malpositioning[17].

Recently, many randomized trials have been performed to compare the efficacy and safety of DP-DES and BP-DES in patients with ACS who underwent PCI. In this meta-analysis, we aimed to summarize the studies comparing the two polymer technologies in ACS patients and analyze the safety and effectiveness of these therapeutic options.

METHODS

Search strategy and registration

This study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and was approved by the institutional review board of the Second Xiangya Hospital, Central South University. The protocol was registered with PROSPERO (CRD42021253412).

Based on the PRISMA statement, PubMed, Medline, Embase, and the Cochrane Controlled Register of Trials (CENTRAL) databases were searched for comparative studies of BP-DES and DP-DES that were used in the treatment of patients with ACS who underwent PCI. The following search terms were used: “BP-DES,” “biodegradable,” “bioabsorbable,” “bioabsorbable polymer drug-eluting stent,” “biodegradable polymer drug-eluting stent,” “DP-

DES," "durable polymer," "durable polymer drug-eluting stent," "acute coronary syndrome," "ACS," "AMI," "Acute myocardial infarction," "Non ST segment elevation myocardial infarction," "ST segment elevation myocardial infarction," "NSTEMI," and "STEMI." We also reviewed prior meta-analyses and the reference lists of the original trials and reviewed articles to identify further studies. Only English language articles published in peer-reviewed journals from January 2000 to July 2021 were selected. Analyses were conducted by two independent reviewers.

Eligibility criteria

The inclusion criteria for this meta-analysis were as follows: 1) randomized controlled trials (RCTs) comparing BP-DES and DP-DES in the treatment of patients with ACS who underwent PCI; 2) data reporting patients' baseline characteristics, follow-up durations, outcomes at the primary, safety, and efficacy endpoints; 3) mean follow-up time over 12 months; and 4) full-text articles.

The exclusion criteria for the meta-analysis were as follows: 1) duplications of samples and reports (evaluated by two independent reviewers); 2) case reports/series; and 3) studies involving data from a national database.

Data extraction and outcome measurement

Two authors (Haoyong Yuan and Tingting Wei) systematically screened the titles and abstracts of publications retrieved using the search strategy to select studies that met the above inclusion criteria. Any disagreement regarding the eligibility of particular studies was resolved through discussion and involvement of a third author (Zhongshi Wu), when necessary. First,

baseline characteristics, including the name of the first author, year of publication, study design, country of origin, number of patients, mean age of participants, and mean duration of follow-up, were gathered from each included article. In addition, data on sex; body mass index; the presence of hypertension, diabetes, dyslipidemia, chronic kidney disease, peripheral vessel disease, or smoking; left ventricular ejection fraction (LVEF); number of stents per person; and total stent length were collected for evaluation of procedure-related risks. MACEs were considered the primary endpoint. The efficacy endpoints included target vessel revascularization (TVR) and target lesion revascularization (TLR). In addition, all-cause death, cardiac death, target vessel myocardial infarction (TVMI), and ST were used as endpoints to evaluate the safety of BP-DES and DP-DES.

The Risk of Bias 2 (RoB2) tool was utilized to assess the quality of RCTs based on sequence generation; randomized group allocation; concealment; blinding of participants, personnel, and outcome assessors; incomplete data; selectivity; outcome reporting; and other sources of bias (Supplementary Material 1)[18].

Data analysis and synthesis

Continuous variables were reported as the mean (standard deviation), and categorical variables were expressed as numbers. Statistical pooling was performed to estimate incidence, according to a random-effects model with generic inverse-variance weighting. We computed risk estimates with 95% confidence intervals (CIs), using RevMan 5.3 (The Cochrane Collaboration, The NordicCochrane Centre, Copenhagen, Denmark). Hypothesis testing for superiority was set at the two-tailed 0.05 level. Hypothesis testing for statistical homogeneity

was set at the two-tailed 0.10 level and was based on the Cochran Q test, with I^2 values of 25%, 50%, and 75% representing mild, moderate, and severe heterogeneity, respectively.

RESULTS

Search results

A total of 895 articles, written in English, were identified through the literature search. After an initial screening of the titles and abstracts, 803 articles were eliminated, as they were not related to the topic of this study. Following the removal of these articles, 92 clinical studies and RCTs of the two polymers remained. After reading the full texts, 28 articles about ACS remained, with 20 articles including chronic and ACS. Finally, eight articles, with seven RCTs, comparing BP-DES and DP-DES in patients with ACS were identified and included in the qualitative and quantitative analyses[19-26]. The follow-up duration ranged from 1 year to 5 years (Supplementary Table 1 and Supplementary Material 2).

General features of the trials

A total number of 8089 patients (3898 patients who were treated with BP-DES and 4191 patients who were treated with DP-DES) were included in this analysis. Further details about the quality of RCTs; total number of patients retrieved from each trial; publication years; countries of origin of the publications; centers in which the trials were performed; follow-up durations; risk factors; and primary, efficacy, and safety endpoints are listed in Supplementary Table 2 and Supplementary Material 2.

Patient characteristics

The baseline features of the patients are summarized in Supplementary Tables 2. The mean age of the patients who were treated by BP-DES ranged from 61.3 to 64 years, whereas the mean age of the patients who were treated by DP-DES ranged from 61.7 to 64.1 years. The proportions of male patients were above 70% in all included trials. There was no difference in age (mean difference [MD]: 0.14, 95% CI: -0.66–0.38; p=0.60, I^2=0%), sex (male) (odds ratio [OR]: 1.10, 95% CI: 0.99–1.23; p=0.07, I^2=0%), hypertension (OR: 1.03, 95% CI: 0.94–1.13; p=0.57, I^2=37%), dyslipidemia (OR: 0.92, 95% CI: 0.83–1.02; p=0.10, I^2=36%), LVEF (MD: 0.00, 95% CI: 0.00–0.01; p=0.12, I^2=12%), body mass index (MD: 0.07, 95% CI: -0.11 to 0.25; p=0.44, I^2=0%), diabetes (OR: 0.92, 95% CI: 0.83–1.02; p=0.13, I^2=21%), total stent length (MD: -0.72, 95% CI: -2.30 to -0.85; p=0.37, I^2=40%), and in the number of stents per person (MD: -0.00, 95% CI: -0.05 to 0.04; p=0.84, I^2=0%) among patients who were implanted with BP-DES or DP-DES. The meta-analysis demonstrated that the number of smoking patients (OR: 1.13, 95% CI: 1.03–1.24; p=0.008, I^2=29%) was significantly lower in the BP-DES group than that in the DP-DES group (Figure 1-3).

Primary endpoint: MACEs reported during follow-up periods of 1–5 years, 1 year, and over 2 years

MACEs, including all-cause death, recurrent MI, or any coronary repeat revascularization involving TLR, TVR, and non-TVR, were considered to be the primary endpoint of the trials. A meta-analysis indicated no statistically significant difference in the MACEs in a follow-up period ranging from 1 to 5 years between the two groups (OR: 0.87, 95% CI: 0.75–1.01; p=0.07, I^2=50%). Of the five studies that published 1-year outcomes, MACEs were not significantly different between the BP-DES and DP-DES groups (OR: 0.97, 95% CI: 0.81–1.16; p=0.74,

I^2=44%). However, MACEs with follow-up periods of over 2 years were significantly lower in the BP-DES group (OR: 0.71, 95% CI: 0.57–0.88; p=0.002, I^2=0 %) (Figure 4).

Efficacy endpoint: TVR and TLR reported during follow-up periods of 1–5 years, 1 year, and over 2 years

TLR and TVR were considered the efficacy endpoints of the trials. The meta-analysis indicated no statistically significant difference in TLR in the follow-up periods ranging from 1 to 5 years between the two groups (OR: 0.78, 95% CI: 0.61–1.00; p=0.05, I^2=48%). Among the five studies that published 1-year data, TLR was not significantly different between the BP-DES and DP-DES groups (OR: 0.72, 95% CI: 0.40–1.31; p=0.29, I^2=65%). The meta-analysis indicated no statistically significant difference in TVR in the follow-up periods ranging from 1 to 5 years (OR: 1.01, 95% CI: 0.79–1.28; p=0.96, I^2=46%) or in the three publications with 1-year follow-up periods (OR: 0.98, 95% CI: 0.40–2.38; p=0.96, I^2=76%). However, the difference in TLR was statistically significant in four RCT studies with follow-up periods of over 2 years (OR: 0.71, 95% CI: 0.51–1.01; p=0.05, I^2=0%), and the difference in TVR was also statistically significant in three RCT studies with follow-up periods of over 2 years (OR: 0.70, 95% CI: 0.52–0.94; p=0.002, I^2=15%), with values much lower in the BP-DES group (Figures 5 and 6).

Safety endpoint: All-cause death, cardiac-related death, target vessel myocardial infarction, and stent thrombosis over follow-up periods of 1–5 years, 1 year, and over 2 years

All-cause death, cardiac-related death, TVMI, and ST were considered the efficacy endpoints. The meta-analysis indicated no statistically significant difference between the two

groups in all-cause death (OR: 0.88, 95% CI: 0.72–1.07; p=0.20, I^2=0%), cardiac-related death (OR: 0.89, 95% CI: 0.71–1.12; p=0.32, I^2=20%), and TVMI (OR: 0.73, 95% CI: 0.53–1.01; p=0.05, I^2=0%) over a follow-up period ranging from 1 to 5 years. Of the five studies that published 1-year data, all-cause death, cardiac-related death, and TVMI were also not significantly different between the BP-DES and DP-DES groups ([all-cause death, OR: 0.91, 95% CI: 0.71–1.15; p=0.42, I^2=0%], [cardiac-related death, OR: 0.96, 95% CI: 0.74–1.26; p=0.79, I^2=35%], and [TVMI, OR: 0.73, 95% CI: 0.53–1.01; p=0.05, I^2=0%]). In the five studies with follow-up periods of over 2 years, similar findings were observed for the all-cause cardiac death, cardiac-related death, and TVMI ([all-cause death, OR: 0.85, 95% CI: 0.64–1.12; p=0.25, I^2=0%], [cardiac-related death, OR: 0.77, 95% CI: 0.56–1.17; p=0.12, I^2=0%], and [TVMI, OR: 0.79, 95% CI: 0.51–1.22; p=0.28, I^2=0%]) (Figures 7–9). However, the total ST incidence, including the definite ST, probable ST, and definite or probable ST incidence, was significantly different between the BP-DES and DP-DES groups during the follow-up period (OR: 0.59, 95% CI: 0.46–0.77; p=0.0001, I^2=48%). Further analysis revealed no difference in total ST for the 1-year follow-up (OR: 0.61, 95% CI: 0.32–1.15; P=0.13, I^2=72%), while the meta-analysis indicated a statistically significant difference in the total ST for the follow-up periods of over 2 years (OR: 0.63, 95% CI: 0.47–0.85; p=0.002, I^2=0%) (Figure 10).

DISCUSSION

The choice of stent in patients undergoing PCI for ACS is debated. Coronary intervention with second-generation DP-DES generally reduces the need for revascularization and improves mortality compared with BMS and first-generation DP-DES. Furthermore, the risk of late ST

with DP-DES tends to off-set these benefits, as seen in registries and clinical trials comparing DP-DES to BMS[15, 27]. BP-DES was designed to leave only the BMS behind once the polymer completely bio-degraded after drug elution and may represent an attractive solution for patients with ACS[28]. Prior meta-analyses have compared the clinical outcomes among BMS, DP-DES, and BP-DES in patients with stable coronary artery disease, but no previous meta-analysis of RCTs and prospective trials directly compared clinical outcomes between BP-DES and DP-DES for the treatment of ACS. To our knowledge, this meta-analysis exclusively compared BP-DES to DP-DES. It included seven trials representing 8089 patients with relatively long follow-up durations, ranging from 1 year to 5 years. BP-DES have been hypothesized to offer improved outcomes, mainly in the long term; however, several prior meta-analyses have demonstrated different outcomes with BP-DES compared with DP-DES in patients undergoing PCI. Bangalore et al. observed that BP-DES were associated with higher mortality than DP-DES beyond 1 year of follow-up[29]. El-Hayek et al. demonstrated no significant difference in mortality between these stent types [6]. In our study, there were no significant differences in MACEs, all-cause death, cardiac-related death, TVMI, TVR, or TLR at a follow-up period of 1 year and no significant differences in all-cause death, cardiac death, or TVMI at a follow-up period of over 2 years. However, at a follow-up of over 2 years, MACEs, TVR, and TLR were significantly lower in the BP group than those in the DP group. Pilgrim et al. observed higher all-cause mortality among patients treated with BP-DES than with DP-DES in the BIOSCIENCE trial; they also observed comparable all-cause mortality rates among patients treated with BP-DES and DP-DES in the BIOSTEMI trial with a 2-year follow-up[6]. Mario Iannaccone et al. observed that BP-DES might decrease the risk of ischemic events in selected

high-risk subgroups of patients, although the two DES stents share the same safety factors for patients in high-anatomical-risk settings like left main (LM) disease[30]. Together, these findings suggest that BP-DES share similar outcomes in terms of MACEs (all-cause death, cardiac-related death, TVMI, TVR, and TLR) during a 1-year follow-up and might show significantly improved clinical outcomes over a 2-year follow-up.

ST is defined as a thrombotic occlusion of a coronary stent[31] and is a major complication. The risk of ST, particularly late ST (occurring beyond 30 days), remains one of the major concerns limiting the use of DES in the treatment of ACS[32]. Early-generation DP-DES were associated with increased rates of very late (>1 year) ST compared with BMS. It was hypothesized that the mechanism underlying late ST with first DP-DES in ACS was related to adverse reactions with the durable polymer[33], and the use of more biocompatible polymers has been associated with a reduction in ST in high-risk patients[9]. In the LEADERS trial, the rate of very late ST was lower with the use of the BP-DES than that with DP-DES[34]. Our data demonstrated that both BP-DES and DP-DES have similar risks of ST beyond 1 year. However, BP-DES are associated with a significantly reduced risk of ST at a follow-up of over 2 years compared with DP-DES (OR: 0.64, 95% CI: 0.46–0.88; p=0.006, I^2=0%). In contrast, Kim et al. observed that the incidence of ST by groups demonstrated numerically lower rates in the DP-DES group (0.1%) than those in the BP-DES group and that all late ST cases occurred in those receiving thick-strut BP-DES stents. They proposed that no meaningful differences in terms of ST could be identified between the different polymer technologies by intravascular imaging and that the association of polymer technology and the risk of the ST was difficult to prove[20, 35, 36]. Therefore, it may be hypothesized that BP-DES result in improved arterial

healing, which not only minimizes the risk of ST, but also improves the long-term durability of the antirestenotic efficacy in the long term, although the two groups have a similar risk of ST beyond 1 year.

Limitations

The present study had several limitations. First, this study included RCTs and shares the limitations of original studies. Second, BP-DES are a heterogeneous group of stents, differing in stent platform thickness, time to complete degradation of the polymer, and drug-elution kinetics. DP-DES is an equally heterogeneous group. Innaccone et al. observed that lower strut thickness would have a positive clinical outcome, thereby reducing stent thrombosis and target lesion revascularizations[37]. We were unable to match the stents with regards to the strut thickness. Consequently, the reported results may not be generalizable to all stents from the respective group. Third, over 6 months of dual antiplatelet therapy (DAPT) was provided to the patients in our study, including those in RCTs. D'Ascenzo et al. observed a similar rate of MACEs between durable and biodegradable polymers, irrespective of DAPT length, and the DAPT duration seems to partially impact the risk of adverse events of different types of stents during follow-up[38]. Thus, we remain concerned that the duration differences of DAPT may influence the clinical outcomes.

CONCLUSION

In this meta-analysis comparing BP-DES to DP-DES in ACS patients who underwent PCI, the data indicated that both polymer types demonstrated excellent safety and efficacy profiles at 1 year. There was a slightly increased incidence of MACEs, TLR, TVR, and ST in the DP-

DES group in the follow-up period of over 2 years, suggesting that BP-DES may be more favorable for treating patients with ACS. These findings should be confirmed by long-term follow-ups in RCT trials.

Data availability statement

No additional data is available.

Patient and public involvement

We did not require patient and public involvement, as this is a meta-analysis, and no new patients were enrolled in the study.

Ethics approval

This study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, and the protocol was registered with PROSPERO (CRD42021253412). This study was approved by the institutional review board of the Second Xiangya Hospital of Central South University.

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Competing interests And Acknowledgements

The authors report no conflicts of interest in this work. We would like to thank Editage (www.editage.com) for English language editing

Author contributions

Can Huang, Zhongshi Wu, and Haoyong Yuan developed the idea of the study, participated in its design and coordination, and helped draft the manuscript. Ting Lu and Tingting Wei contributed to the acquisition and interpretation of data. Yifan Zeng and Yalin Liu provided a critical review and substantially revised the manuscript. All authors read and approved the final

manuscript.

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SUPPLEMENTARY TABLE LEGENDS

Table 1. The characteristics of the included trials

Table 2. The baseline features of the patients

FIGURE LEGENDS

Figure 1. Baseline characteristics and stent information of patients with acute coronary syndrome

Figure 2. Baseline characteristics and stent information of patients with acute coronary syndrome

Figure 3. Baseline characteristics and stent information of patients with acute coronary syndrome

Figure 4. Primary endpoint: major adverse cardiac events

Figure 5. Target vessel revascularization

Figure 6. Target lesion revascularization

Figure 7. All-cause death

Figure 8. Cardiac-related death

Figure 9. Target vessel myocardial infarction

Figure 10. Stent thrombosis

Supplementary Material 2: search strategy and PRISMA flow chart for included studies

A. Search strategy

1. Pubmed (N=688)

Search date: from January 2000 to July 2021

Search terms:

1#. ("BP-DES"[MeSH Terms] OR "BP-DES"[All Fields] OR "biodegradable "[All Fields] OR "bioabsorbable "[All Fields] OR "bioabsorbable polymer drug-eluting stent"[All Fields] OR "biodegradable polymer drug-eluting stent"[All Fields]) AND ("acute coronary syndrome"[All Fields] OR "ACS"[All Fields] OR "AMI"[All Fields] OR "Acute myocardial infarction"[All Fields] OR "Non ST segment elevation myocardial infarction"[All Fields] OR "ST segment elevation myocardial infarction"[All Fields] OR "NSTEMI"[All Fields] OR "STEMI"[All Fields])

2#. ("DP-DES"[All Fields] OR "DP-DES"[MeSH Terms] OR "durable polymer"[All Fields] OR "durable polymer drug-eluting stent"[All Fields]) AND ("acute coronary syndrome"[All Fields] OR "ACS"[All Fields] OR "AMI"[All Fields] OR "Acute myocardial infarction"[All Fields] OR "Non ST segment elevation myocardial infarction"[All Fields] OR "ST segment elevation myocardial infarction"[All Fields] OR "NSTEMI"[All Fields] OR "STEMI"[All Fields])

3#. ("BP-DES"[MeSH Terms] OR "BP-DES"[All Fields] OR "biodegradable "[All Fields] OR "bioabsorbable "[All Fields] OR "bioabsorbable polymer drug-eluting stent"[All Fields] OR "biodegradable polymer drug-eluting stent"[All Fields]) and ("DP-DES"[All Fields] OR "DP-DES"[MeSH Terms] OR "durable polymer"[All Fields] OR "durable polymer drug-eluting stent"[All Fields]) AND ("acute coronary syndrome"[All Fields] OR "ACS"[All Fields] OR "AMI"[All Fields] OR "Acute myocardial infarction"[All Fields] OR "Non ST segment elevation myocardial infarction"[All Fields] OR "ST segment elevation myocardial infarction"[All Fields] OR "NSTEMI"[All Fields] OR "STEMI"[All Fields])

2. OVID (N=207, EMBS=134, MEDLINE=54, Controlled Register of Trials=19)

Search date: from January 2000 to July 2021

Search terms:

1#.("BP-DES" OR "bioabsorbable polymer drug-eluting stent" OR "biodegradable polymer drug-eluting stent") and ("acute coronary syndrome" OR "ACS" OR "AMI" OR "Acute myocardial infarction" OR "Non ST segment elevation myocardial infarction" OR "ST segment elevation myocardial infarction" OR "NSTEMI" OR "STEMI")

2#.("DP-DES" OR "durable polymer drug-eluting stent") and ("acute coronary syndrome" OR "ACS" OR "AMI" OR "Acute myocardial infarction" OR "Non ST segment elevation myocardial infarction" OR "ST segment elevation myocardial infarction" OR "NSTEMI" OR "STEMI")

3#.("BP-DES" OR "bioabsorbable polymer drug-eluting stent" OR "biodegradable polymer drug-eluting stent") and ("DP-DES" OR "durable polymer drug-eluting stent") and ("acute coronary syndrome" OR "ACS" OR "AMI" OR "Acute myocardial infarction" OR "Non ST segment elevation myocardial infarction" OR "ST segment elevation myocardial infarction" OR "NSTEMI" OR "STEMI")

B. PRISMA flow chart for studies included in the meta-analysis

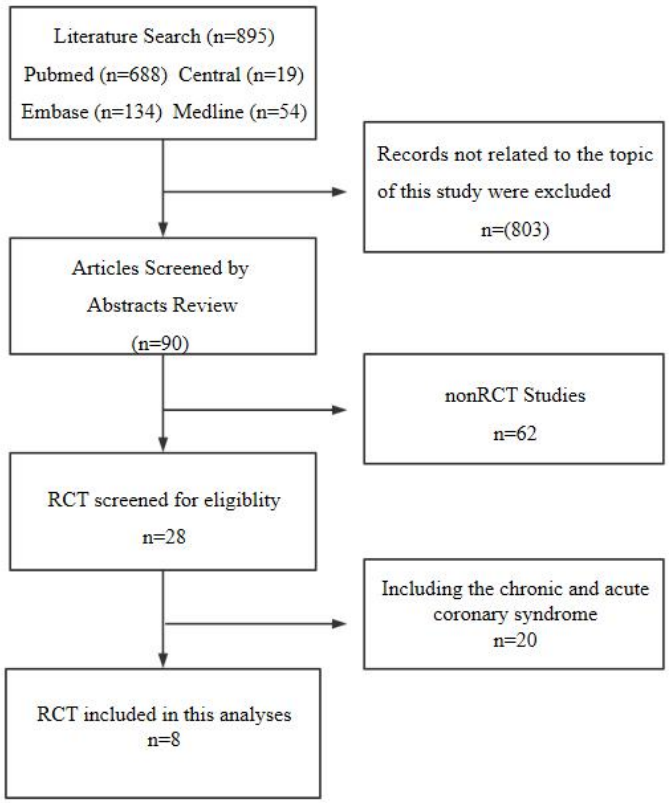


Table 1. The characteristics of the included trails

Authors	Years	Journal	Study	Center	Country	Follow up	NO.patients	
							BP-DES	DP-DES
Hyo-Soo Kim	2021	Circulation	RCT	multicentre	Korea	12 month	1700	1713
Thomas Pilgrim	2021	JACC	RCT	multicentre	Switzerland	24month	649	651
Juan F Iglesias	2019	The Lancet	RCT	multicentre	Switzerland	12 month	649	651
Thomas Pilgrim	2016	EuroIntervention	RCT	multicentre	Switzerland	12 month	211	196
Yao-Jun Zhang	2015	Heart	RCT	multicentre	Netherlands	60month	280	293
Hyun Jong Lee	2015	International journal of cardiology	RCT	multicentre	Korea	24month	171	536
Antoinette de Waha	2015	EuroIntervention	RCT	multicentre	multicentre	48month	291	206
Qi Zhang	2014	Journal of Interventional Cardiology	RCT	multicentre	China	12 month	596	596

Table 2. The baseline features of the patients

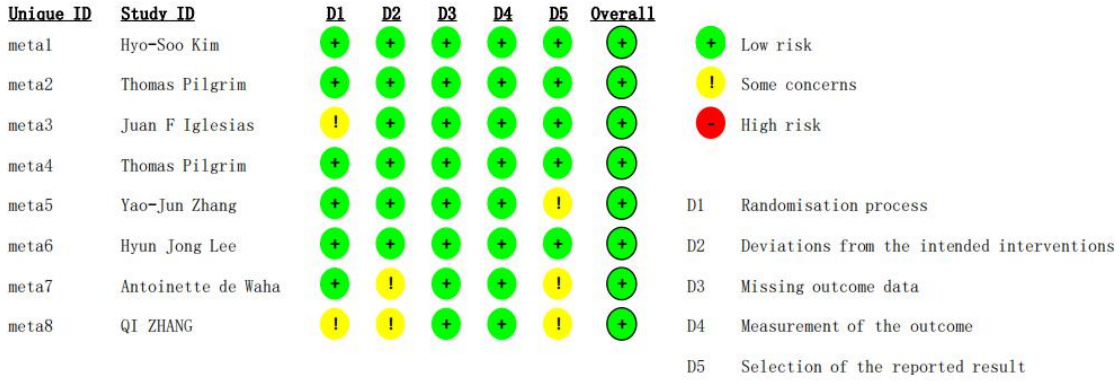
	basic characters									
Authors	Age		SEX(MALE)		Body mass index		Hypertension		Diabetes	
	BP-DES	DP-DES	BP-DES	DP-DES	BP-DES	DP-DES	BP-DES	DP-DES	BP-DES	DP-DES
Hyo-Soo Kim	63.1±11.1	63.0±11.1	1337	1351	25.0±3.2	24.9±3.1	1147	1092	747	789
Juan F Iglesias	62.2±11.8	63.2±11.8	513	477	26.9± 4.3	26.8± 4.3	281	297	73	82
Thomas Pilgrim	61.3±12.4	61.7±12.7	170	151	27.0±4.3	27.0±4.3	102	98	30	27
Yao-Jun Zhang	62.9±11.7	62.8±11.7	215	210	27.5±4.4	27.8±4.6	181	198	55	46
Hyun Jong Lee	64±14.08	63±14.08	128	400	/	/	102	308	82	269
Antoinette de Waha	62.5±12.1	63.1±12.6	214	149	/	/	142	110	56	34
Qi Zhang	63.9±13.1	64.1±12.1	475	467	/	/	360	376	129	113

Table 2. The baseline features of the patients

Authors	basic characters									
	Dyslipidemia		smoking		LVEF, %		Stent number per person		Total stent length, mm	
	BP-DES	DP-DES	BP-DES	DP-DES	BP-DES	DP-DES	BP-DES	DP-DES	BP-DES	DP-DES
Hyo-Soo Kim	1,247	1,280	515	475	58.7±10.4	58.5±10.4	1.7±1.1	1.7±1.0	42.9±31.9	41.7±30.2
Juan F Iglesias	304	302	294	250	49.0 ± 11.0	48.4 ± 11.2	1.37 ± 0.64	1.39 ± 0.66	31.91± 18.21	33.92± 19.76
Thomas Pilgrim	110	101	93	77	49.5±10.9	48.3±11.1	1.42±0.71	1.39±0.71	29.49±17.83	30.52±18.99
Yao-Jun Zhang	152	176	107	115	51.5±10.1	51.4±11.8	2.2±0.5	2.2±0.6	26.6±15	27.9±15.2
Hyun Jong Lee	116	389	65	228	55 (45–65)	52 (43–62)	/	/	/	/
Antoinette de Waha	119	109	120	90	47±10	48±12	/	/	25.9±12.6	27.7±14.2
Qi Zhang	87	76	257	223	50±12	49.0 ± 17.0	/	/	/	/

Supplementary Material 2. Risk-of-bias summary for included trials

A.



B.