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ORIGINAL ARTICLE

Five-Year Outcomes of Biodegradable Polymer Drug-Eluting Stents Versus Second-Generation Durable Polymer Drug-Eluting Stents: a Meta-Analysis of Randomized Controlled Trials

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Abstract

Purpose We investigated the safety and efficacy of biodegradable polymer drug-eluting stents (BP-DES) versus second-generation durable polymer drug-eluting stents (DP-DES) in a follow-up period of 5 years.

Methods A meta-analysis was performed using data from the PubMed, EMBASE, and Cochrane Library databases. The primary endpoint was target lesion failure (TLF), a composite endpoint of safety and efficacy, which included cardiac death, target vessel myocardial infarction (MI), and clinically indicated target lesion revascularization (TLR). Secondary endpoints were all-cause death, MI, TLR, definite or probable stent thrombosis (ST), and definite or probable very late ST. In addition, we performed subgroup analyses based on patient and stent characteristics.

Results Nine randomized controlled trials (RCTs) in 11,817 patients were included in the meta-analysis. Compared with second-generation DP-DES, BP-DES was not associated with increased risk of TLF (odds ratio (OR) 1.06, 95 % confidence interval [CI] 0.94–1.20; $p = 0.33$), all-cause death (OR 1.04, [0.92–1.18], $p = 0.49$), myocardial infarction (OR 0.97, [0.83–1.13], $p = 0.67$), target lesion revascularization (OR 1.08, [0.94–1.23], $p = 0.27$), definite or probable stent thrombosis (OR 0.85, [0.66–1.11], $p = 0.24$), or definite or probable very late stent thrombosis (OR 0.86, [0.58–1.26],$p = 0.43$). Furthermore, the subgroup analyses did not reveal any statistically significant differences between the stent groups.

Conclusion At 5 years of follow-up, the safety and efficacy of BP-DES are clinically comparable to those of second-generation DP-DES.

Keywords Drug-eluting stents · Biodegradable polymer · Durable polymer · Meta-analysis · Everolimus · Zotarolimus

Introduction

Since their emergence, drug-eluting stents (DES) have been widely used for their ability to reduce the rate of repeat revascularization in patients undergoing percutaneous coronary intervention (PCI) compared with the use of bare-metal stents (BMS) [1, 2]. However, safety concerns persist with DES used, particularly the incidence of very late stent thrombosis (VLST), which can in part be attributed to delayed healing and re-endothelialization [3]. Newer DES such as biodegradable polymer drug-eluting stents (BP-DES) have therefore been developed to provide improved long-term safety and maintain the early efficacy of durable polymer drug-eluting stents (DP-DES) after implantation [4]. Following polymer resorption, the surface of BP-DES resembles that of BMS and may lead to a reduction in VLST risk and an overall improved safety profile [5]. Against this background, it is important to compare the safety and efficacy of BP-DES with second-generation DP-DES. Some studies reported to date have performed such a comparison, but most included follow-up periods of only 1–3 years [6–8]. However, some important outcomes such as VLST have a low incidence or

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occur a long time after PCI [9]. We therefore sought to compare the safety and efficacy of BP-DES with second-generation DP-DES over a follow-up of 5 years in patients undergoing PCI.

Methods

Search Strategy

The keywords "biodegradable," "absorbable," "degradable," "bioabsorbable," "polymer," "biolimus," "everolimus," "zotarolimus," "biocompatible," "endeavor," "resolute," "xience," and "promus" were used to search the PubMed, Embase, and Cochrane Central Register of Controlled Trials (CENTRAL) databases to identify randomized controlled trials (RCTs) comparing BP-DES with second-generation DP-DES up to November 26, 2018 (further details are available in the Supplementary material). All references searched were published in English.

Eligibility Criteria

Studies with the following criteria were eligible for inclusion: RCTs, follow-up period ≥ 5 years, and intervention group of BP-DES versus control group of second-generation DP-DES.

Studies conducted in animals, retrospective studies, and trials that included fewer than 50 patients were not eligible.

Data Extraction and Quality Assessment

The titles and abstracts of candidate studies were examined to determine whether they met the eligibility criteria by two authors (Xi, Gao, and Nie). Disagreements were resolved by consultation with another author (Liu). The full text of identified studies was further analyzed, and the baseline characteristics, stents characteristics, and outcome data were extracted by two authors (Nie and Xi). The risk of bias for each study was subsequently evaluated in accordance with the Cochrane Handbook for Systematic Reviews of Interventions (version 5.1.0).

Efficacy and Safety Endpoints

The primary endpoint of this meta-analysis was target lesion failure (TLF), a composite endpoint including cardiac death, target vessel myocardial infarction (MI), and clinically indicated target lesion revascularization (TLR). Secondary endpoints were TLR, MI, all-cause death, definite or probable stent thrombosis (ST), and definite or probable VLST, defined according to the Academic Research Consortium [10].

Statistical Analysis

All analyses were performed using Review Manager (RevMan) version 5.3 (The Cochrane Collaboration, Copenhagen, Denmark) and Stata 15.1 (StataCorp, College Station, TX,

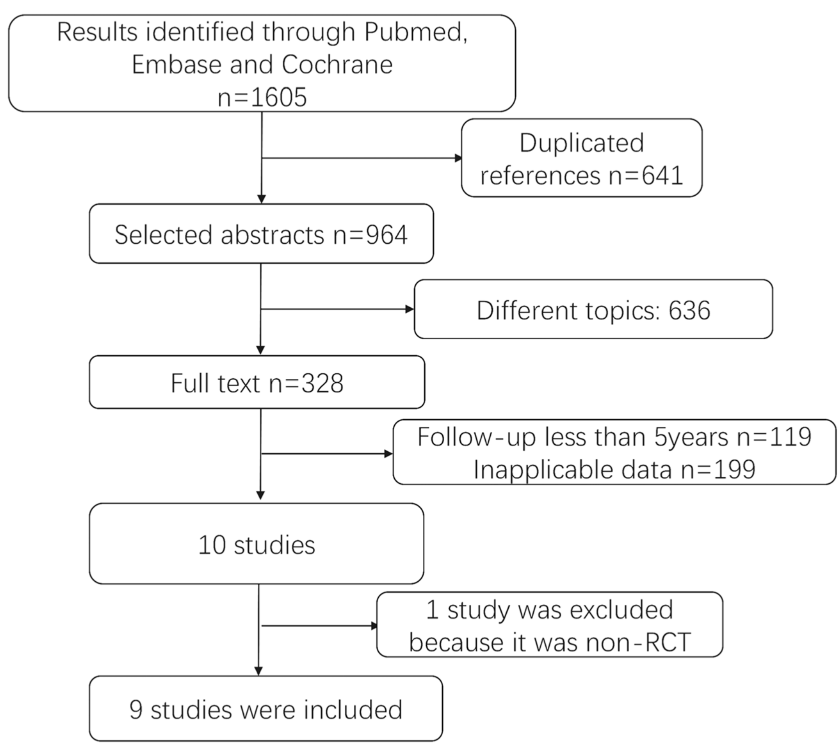

Fig. 1 Flowchart of study selection

Table 1 Main characteristics of stents included in the study

Trial name	Stent name	Characteristics of the stents					
		Drug	DAPT duration (months)	DAPT medication	Polymer biodegradation (months)	Drug release (months)	Strut thickness (μm)
BIOSCIENCE 2018	Orsiro/Xience Prime	Sirolimus/everolimus	12	According to local practice	14	12	60/81
BIOFLOW-II 2018	Orsiro/Xience Prime	Sirolimus/everolimus	≥ 6	Aspirin (100 mg) + clopidogrel (75 mg)	14	12	60/81
EVOLVE 2017	Synergy/Promus Element	Everolimus/everolimus	≥ 6	Aspirin (≥ 75 mg) + clopidogrel (75 mg)/prasugrel (unknown)	4	3	74/81
NEXT 2018	Nobori/Xience/Promus	Biolimus/everolimus	≥ 3	Aspirin (≥ 81 mg) + clopidogrel (75 mg)/ticlopidine (200 mg)	12	6–9	120/81
CENTURY II 2018	Ultimaster/Xience V	Sirolimus/everolimus	≥ 6	According to local practice	4	4	80/81
DESSOLVE II 2018	MiStent/Endeavor	Sirolimus/zotarolimus	6–12	According to local practice	3	9	64/91
TARGET I 2017	Firehawk/Xience V	Sirolimus/everolimus	≥ 12	Aspirin (100 mg) + clopidogrel (75 mg)	6–9	1	86/81
ISAR-TEST-42014	Yukon choice PC/Xience V	Sirolimus/everolimus	≥ 6	Aspirin (200 mg) + clopidogrel (75 mg)	2–3	1	87/81
COMPARE II 2017	Nobori/Xience V, Prime	Biolimus/everolimus	≥ 12	Aspirin (100 mg) + clopidogrel (75 mg)/prasugrel (10 mg)	12	6–9	120/81

USA) software. The study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and was registered in the PROSPERO database (NO. 42019118828) [11].

Heterogeneity across trials was calculated using the I^2 statistic and evaluated using the chi-squared test. We considered $I^2 > 50$ % to represent a substantial level of heterogeneity [12]. The odds ratio (OR) was calculated to compare the safety and efficacy outcomes. The Mantel–Haenszel-fixed effects model was used where $I^2 < 50$ %; otherwise, the Mantel–Haenszel random effects model was used. We performed a sensitivity analysis by sequentially omitting one trial. Publication bias was evaluated using a visual funnel plot and Begg's test.

We also performed a subgroup analysis using OR and 95 % confidence interval (CI) for diabetes status, polymer biodegradation duration > 1 year versus < 1 year, dual antiplatelet therapy (DAPT) > 12 months versus > 6 months, and strut thickness > 70 μm versus < 70 μm.

Results

Study Selection

Our keyword search of the PubMed, Embase, and Cochrane Library databases identified 1605 potential studies. After excluding 641 duplicates and 636 manuscripts on irrelevant topics, we searched the full text of 328 studies. Of these 328 studies, we excluded 119 with follow-up < 5 years, 199 with inapplicable data, and 1 non-RCT study. The remaining 9 studies in 11,817 patients were included in our meta-analysis (see flowchart in Fig. 1 and detailed search strategy in the Supplementary material) [9, 13–20].

Characteristics of Eligible Studies

Of the 11,817 included patients, 6826 (57.8 %) received BP-DES and 4991 (42.2 %) received second-generation DP-DES. All studies had a follow-up period of 5 years, and the number of patients in each study ranged from 178 to 2707. Five studies compared BP-DES-releasing sirolimus with second-generation DP-DES-releasing everolimus [13, 14, 18–20]. One study compared BP-DES-releasing everolimus with second-generation DP-DES-releasing everolimus [15]. Two studies compared BP-DES-releasing biolimus with second-generation DP-DES-releasing everolimus [9, 16]. One study compared BP-DES-releasing sirolimus with second-generation DP-DES-releasing zotarolimus [17].

Table 1 shows the stent characteristics and Table 2 shows the patient characteristics in each study, including diabetes status, strut thickness, duration of polymer biodegradation, drug release, and DAPT.

Table 2 Baseline characteristics of patients included in the study

BP-DES/DP-DES	Age (years)	Male (%)	Diabetes (%)	Hypertension (%)	Hyperlipidemia (%)	Previous MI (%)	Previous PCI (%)
BIOSCIENCE 2018	66.1 (11.6)/65.9 (11.4)	77.0/77.3	24.2/21.7	68.5/66.9	67.0/67.8	21.0/19.3	30.6/27.7
BIOFLOW-II 2018	62.7 (10.4)/64.8 (9.2)	78.2/74.7	28.2/28.6	77.5/77.3	67.8/73.4	30.2/20.1	43.0/35.7
EVOLVE 2017	62.1 (10.0)/64 (11.0)	79.6/69.9	22.4/17.2	69.4/61.3	70.4/68.5	34.4/32.3	32.7/33.3
NEXT 2018	69.2 (9.8)/69.5 (9.7)	77/76	48/46	81/81	81/80	29/29	50/50
CENTURY II 2018	65.2 (10.5)/65.5 (10.6)	78.6/82.4	31.9/30.9	73.3/67.8	70.3/69.6	28.3/27.6	37.2/35.0
DESSOLVE II 2018	65.0 (10.4)/65.1 (10.5)	69.1/73.8	19.0/19.7	70.5/68.9	72.7/81.7	23.1/16.4	30.9/22.9
TARGET I 2017	58.7 (9.4)/59.6 (9.4)	69.2/68.4	13.7/16.9	57.7/59.7	26.9/22.9	19.8/21.2	4.8/5.6
ISAR-TEST 42014	66.7 (11.1)/66.7 (10.3)	75.3/77.8	28.9/28.2	69.1/67.8	66.8/64.9	28.6/29.3	
COMPARE II 2017	63.0 (11.1)/62.7 (11.0)	74.4/74.3	21.8/21.6	54.8/56.3		20.3/18.8	17.8/17.0

Primary Endpoint of TLF

TLF was an endpoint in 8 studies including 9866 patients in the ultralong follow-up. As shown in Fig. 2, there was no significant difference in risk of TLF between BP-DES and second-generation DP-DES (OR 1.06, 95 % CI 0.94–1.20, $p = 0.33$, $I^2 = 0$). For the subgroup analysis of TLF rate by diabetes status, data from four studies of 4129 patients were used to compare BP-DES with second-generation DP-DES (OR 1.24 [0.90–1.71], $p = 0.19$ versus 0.93 [0.74–1.15], $p = 0.49$). No notable differences were observed between the other subgroups (Figs. 3, 4, 5, and 6).

Secondary Endpoints

Six studies in 10,898 patients were included in the efficacy analysis of TLR. There were 6218 (57.1 %) patients in the BP-DES group, of whom 600 were diagnosed with TLR (9.6 %), and 4680 (42.9 %) patients in the second-generation DP-DES group, of whom 417 were diagnosed with TLR (8.9 %). No statistically significant difference was observed between the groups (OR 1.08, 95 % CI 0.94–1.23, $p = 0.27$) (Fig. 7).

For the safety analysis, the rate of MI was evaluated in all 9 studies. In 6826 individuals (57.8 %) in the BP-DES group, 421 had MI (6.2 %), while in 4991 individuals (42.2 %) in the second-generation DP-DES, 318 had MI (6.4 %). The rates of MI were similar between the two groups (OR 0.97, 95 % CI 0.83–1.13, $p = 0.67$). Furthermore, there was no significant difference in the risk of all-cause death and definite or probable stent thrombosis between the BP-DES and second-generation DP-DES groups (OR 1.04, 95 % CI 0.92–1.18, $p = 0.49$; $I^2 = 35$ % and OR 0.85, 95 % CI 0.66–1.11, $p = 0.24$; $I^2 = 0$, respectively) (Fig. 7). Furthermore, we perform a landmark analysis of stent thrombosis and the rate of VLST performed 1 year after stent implantation did not differ between the two groups (OR 0.86, [0.58, 1.26], $p = 0.43$) (Fig. 8).

Publication Bias and Quality Assessment

The funnel plot and Begg's test did not show any obvious publication bias in the selected studies. Publican bias test and quality assessment are shown in the Supplementary material.

Sensitivity Analysis

We performed a sensitivity analysis by sequentially omitting one trial at a time and found that heterogeneity decreased from 35 to 4 % when the BIOSCIENCE trial was excluded.

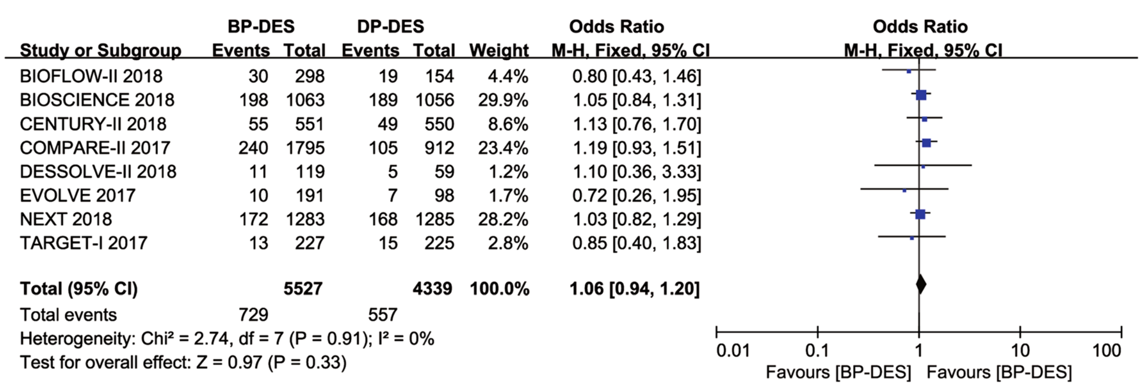

Fig. 2 Forest plot of rate of target lesion failure (TLF) between BP-BES and DP-DES. OR, odds ratio; CI, confidence interval

Study or Subgroup	BP-DES Events	BP-DES Total	DP-DES Events	DP-DES Total	Weight	Odds Ratio M-H, Fixed, 95% CI
5.1.1 Diabetes mellitus						
BIOFLOW-II 2018	13	88	5	44	2.4%	1.35 [0.45, 4.07]
BIOSCIENCE 2018	74	257	57	229	18.4%	1.22 [0.82, 1.83]
CENTURY-II 2018	24	176	20	170	7.5%	1.18 [0.63, 2.23]
TARGET-I 2017	3	31	2	39	0.7%	1.98 [0.31, 12.67]
Subtotal (95% CI)		**552**		**482**	**29.0%**	**1.24 [0.90, 1.71]**
Total events	114		84			
Heterogeneity: Chi² = 0.30, df = 3 (P = 0.96); I² = 0%						
Test for overall effect: Z = 1.32 (P = 0.19)						
5.1.2 Non-diabetes						
BIOFLOW-II 2018	17	210	14	110	7.2%	0.60 [0.29, 1.28]
BIOSCIENCE 2018	124	806	132	827	47.1%	0.96 [0.73, 1.25]
CENTURY-II 2018	31	375	29	380	11.3%	1.09 [0.64, 1.85]
TARGET-I 2017	10	196	13	191	5.3%	0.74 [0.31, 1.72]
Subtotal (95% CI)		**1587**		**1508**	**71.0%**	**0.93 [0.74, 1.15]**
Total events	182		188			
Heterogeneity: Chi² = 1.96, df = 3 (P = 0.58); I² = 0%						
Test for overall effect: Z = 0.69 (P = 0.49)						
Total (95% CI)		**2139**		**1990**	**100.0%**	**1.02 [0.85, 1.22]**
Total events	296		272			
Heterogeneity: Chi² = 4.44, df = 7 (P = 0.73); I² = 0%						
Test for overall effect: Z = 0.18 (P = 0.86)						
Test for subgroup differences: Chi² = 2.18, df = 1 (P = 0.14), I² = 54.0%						

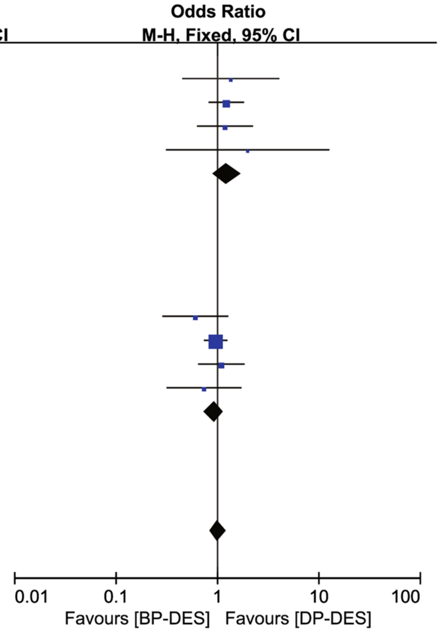

Fig. 3 Subgroup analysis of the rate of TLF between BP-DES and DP-DES by diabetes status

Discussion

To the best of our knowledge, the present meta-analysis is first to compare 5-year outcomes of the use of BP-DES with that of second-generation DP-DES. In our analysis of data from 9 RCTs, the key finding is that the long-term safety and efficacy of BP-DES and DP-DES were similar. Of note, the incidence of definite or probable VLST was also similar between the two groups, and in patients with diabetes, the risk of TLF was similar for BP-DES and DP-DES.

TLF is a composite endpoint of cardiac death, target vessel MI, and clinically indicated TLR, and thus represents a safety and efficacy outcome. With a follow-up period of up to 1 year, the BIOFLOW V study is the only study to demonstrate the superiority of BP-DES compared with second-generation DP-DES [21], with other studies indicating that both groups have similar short- and medium-term safety and efficacy [22–25]. Our meta-analysis showed that TLF rates in the two groups were similar at 5 years of follow-up, which is consistent with the findings of a previous meta-analysis with a mean follow-up

Study or Subgroup	BP-DES Events	BP-DES Total	DP-DES Events	DP-DES Total	Weight	Odds Ratio M-H, Fixed, 95% CI
3.1.1 polymer biodegradation duration longer than 12 months						
BIOFLOW-II 2018	30	298	19	154	4.4%	0.80 [0.43, 1.46]
BIOSCIENCE 2018	198	1063	189	1056	29.9%	1.05 [0.84, 1.31]
COMPARE-II 2017	240	1795	105	912	23.4%	1.19 [0.93, 1.51]
NEXT 2018	172	1283	168	1285	28.2%	1.03 [0.82, 1.29]
Subtotal (95% CI)		**4439**		**3407**	**85.8%**	**1.07 [0.94, 1.22]**
Total events	640		481			
Heterogeneity: Chi² = 1.73, df = 3 (P = 0.63); I² = 0%						
Test for overall effect: Z = 0.98 (P = 0.32)						
3.1.2 polymer biodegradation duration less than 12 months						
CENTURY-II 2018	55	551	49	550	8.6%	1.13 [0.76, 1.70]
DESSOLVE-II 2018	11	119	5	59	1.2%	1.10 [0.36, 3.33]
EVOLVE 2017	10	191	7	98	1.7%	0.72 [0.26, 1.95]
TARGET-I 2017	13	227	15	225	2.8%	0.85 [0.40, 1.83]
Subtotal (95% CI)		**1088**		**932**	**14.2%**	**1.03 [0.74, 1.42]**
Total events	89		76			
Heterogeneity: Chi² = 0.97, df = 3 (P = 0.81); I² = 0%						
Test for overall effect: Z = 0.16 (P = 0.87)						
Total (95% CI)		**5527**		**4339**	**100.0%**	**1.06 [0.94, 1.20]**
Total events	729		557			
Heterogeneity: Chi² = 2.74, df = 7 (P = 0.91); I² = 0%						
Test for overall effect: Z = 0.97 (P = 0.33)						
Test for subgroup differences: Chi² = 0.05, df = 1 (P = 0.82), I² = 0%						

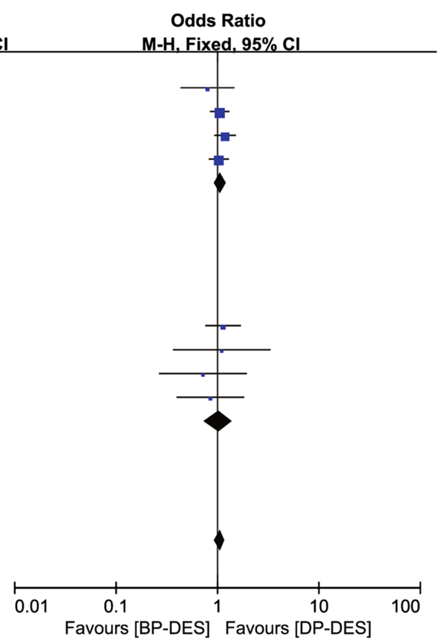

Fig. 4 Subgroup analysis of the rate of TLF between BP-DES and DP-DES by polymer biodegradation duration

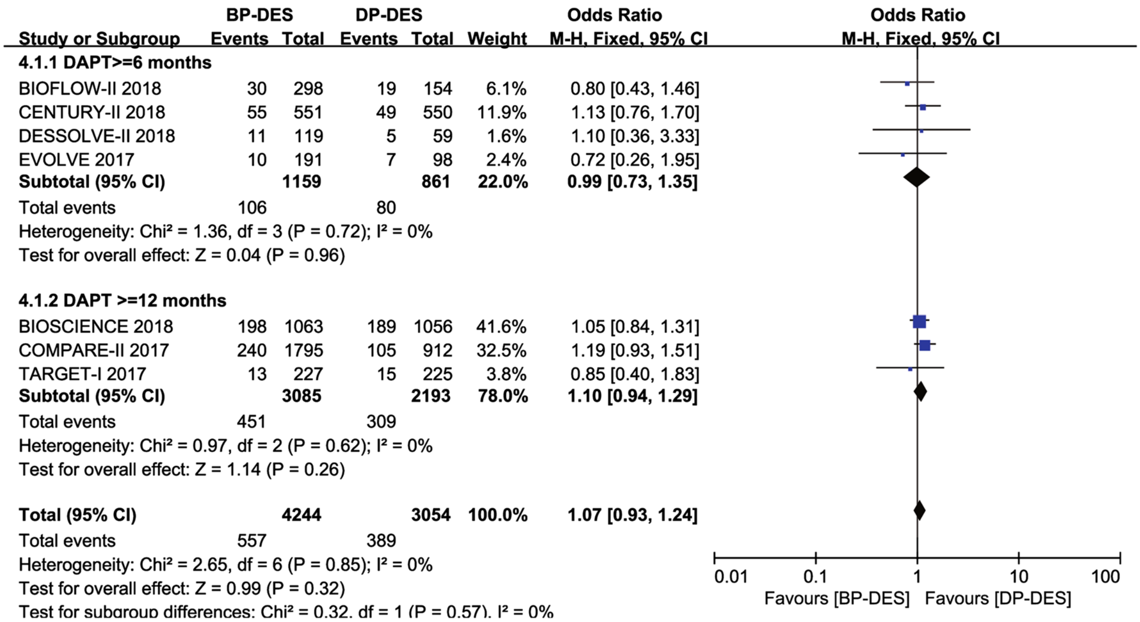

Fig. 5 Subgroup analysis of the rate of TLF between BP-DES and DP-DES by duration of DAPT

of 26 months [26]. In addition to RCTs, our safety and efficacy findings are supported by data from the recent large-scale real-world SCAAR study which followed 16,504 patients with BP-DES and 79,106 with DP-DES for 2 years. Regarding all-cause death, the BIOSCIENCE and EVOLVE trials showed a higher rate in patients treated with BP-DES than in those treated with second-generation DP-DES [15, 20]. The high all-cause mortality in the BIOSCIENCE trial has been attributed to its all-comer design [20], which may explain why the omission of this trial in our sensitivity analysis resulted in a decrease in overall heterogeneity from 35 to 4 %. However, when all the trials were synthesized, the advantage of DP-DES disappeared, with OR, 1.04; 95 % CI, [0.92–1.18]; $p = 0.49$.

Following the release of drugs after DES implantation, the residual polymer coating can lead to a persistent chronic inflammation reaction and platelet aggregation [5, 27], affect vascular endothelial repair, and lead to VLST. Biodegradable polymer coating, however, is completely degraded by approximately 3–14 months after stent implantation, and may lead to a reduced risk of adverse cardiovascular events associated with durable polymer coating. A pooled analysis based on patient data showed that BP-DES has superior safety and efficacy outcomes

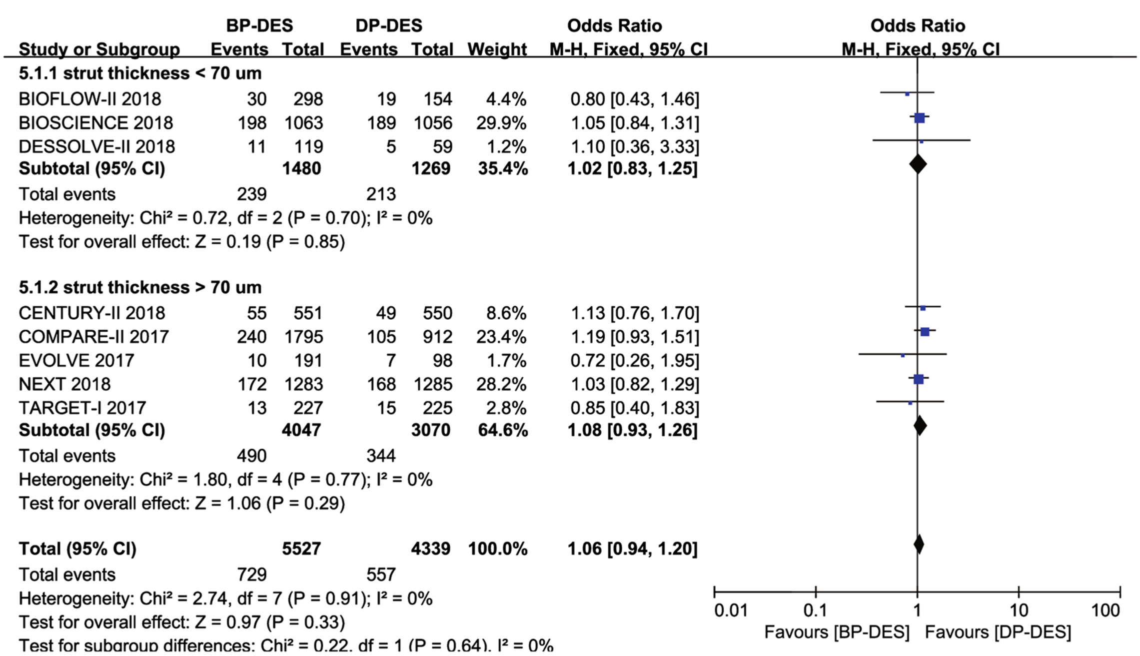

Fig. 6 Subgroup analysis of the rate of TLF between BP-DES and DP-DES by strut thickness

Study or Subgroup	BP-DES Events	BP-DES Total	DP-DES Events	DP-DES Total	Weight	Odds Ratio M-H, Fixed, 95% CI
6.1.1 Myocardial infarction						
BIOFLOW-II 2018	13	298	9	154	0.8%	0.73 [0.31, 1.76]
BIOSCIENCE 2018	99	1063	118	1056	7.9%	0.82 [0.62, 1.08]
CENTURY-II 2018	18	551	21	550	1.5%	0.85 [0.45, 1.61]
COMPARE-II 2017	137	1795	64	912	5.7%	1.09 [0.80, 1.49]
DESSOLVE-II 2018	7	119	3	59	0.3%	1.17 [0.29, 4.68]
EVOLVE 2017	8	191	2	98	0.2%	2.10 [0.44, 10.08]
ISAR-TEST-4 2014	70	1299	32	652	2.9%	1.10 [0.72, 1.70]
NEXT 2018	64	1283	60	1285	4.2%	1.07 [0.75, 1.54]
TARGET-I 2017	5	227	9	225	0.6%	0.54 [0.18, 1.64]
Subtotal (95% CI)		**6826**		**4991**	**24.1%**	**0.97 [0.83, 1.13]**
Total events	421		318			
Heterogeneity: Chi² = 5.28, df = 8 (P = 0.73); I² = 0%						
Test for overall effect: Z = 0.42 (P = 0.67)						
6.1.2 Target lesion revascularization						
BIOSCIENCE 2018	110	1063	106	1056	7.0%	1.03 [0.78, 1.37]
CENTURY-II 2018	52	551	45	550	3.0%	1.17 [0.77, 1.78]
COMPARE-II 2017	142	1795	65	912	5.8%	1.12 [0.83, 1.52]
ISAR-TEST-4 2014	170	1299	77	652	6.5%	1.12 [0.84, 1.50]
NEXT 2018	118	1283	114	1285	7.6%	1.04 [0.79, 1.36]
TARGET-I 2017	8	227	10	225	0.7%	0.79 [0.30, 2.03]
Subtotal (95% CI)		**6218**		**4680**	**30.6%**	**1.08 [0.94, 1.23]**
Total events	600		417			
Heterogeneity: Chi² = 0.86, df = 5 (P = 0.97); I² = 0%						
Test for overall effect: Z = 1.11 (P = 0.27)						
6.1.3 Definite or probable stent thrombosis						
BIOFLOW-II 2018	0	298	1	154	0.1%	0.17 [0.01, 4.23]
BIOSCIENCE 2018	62	1063	76	1056	5.3%	0.80 [0.56, 1.13]
CENTURY-II 2018	7	551	7	550	0.5%	1.00 [0.35, 2.86]
COMPARE-II 2017	30	1795	15	912	1.4%	1.02 [0.54, 1.90]
DESSOLVE-II 2018	1	119	1	59	0.1%	0.49 [0.03, 8.00]
EVOLVE 2017	0	191	0	98		Not estimable
ISAR-TEST-4 2014	15	1299	9	652	0.9%	0.83 [0.36, 1.92]
NEXT 2018	6	1283	4	1285	0.3%	1.50 [0.42, 5.34]
TARGET-I 2017	0	227	1	225	0.1%	0.33 [0.01, 8.12]
Subtotal (95% CI)		**6826**		**4991**	**8.7%**	**0.85 [0.66, 1.11]**
Total events	121		114			
Heterogeneity: Chi² = 2.75, df = 7 (P = 0.91); I² = 0%						
Test for overall effect: Z = 1.18 (P = 0.24)						
6.1.4 All-cause death						
BIOFLOW-II 2018	14	298	14	154	1.3%	0.49 [0.23, 1.06]
BIOSCIENCE 2018	139	1063	105	1056	6.7%	1.36 [1.04, 1.78]
CENTURY-II 2018	42	551	42	550	2.8%	1.00 [0.64, 1.56]
COMPARE-II 2017	155	1795	75	912	6.6%	1.05 [0.79, 1.41]
DESSOLVE-II 2018	11	119	6	59	0.5%	0.90 [0.32, 2.56]
EVOLVE 2017	13	191	1	98	0.1%	7.08 [0.91, 54.97]
ISAR-TEST-4 2014	182	1299	92	652	7.7%	0.99 [0.76, 1.30]
NEXT 2018	146	1283	158	1285	10.2%	0.92 [0.72, 1.16]
TARGET-I 2017	7	227	8	225	0.6%	0.86 [0.31, 2.42]
Subtotal (95% CI)		**6826**		**4991**	**36.6%**	**1.04 [0.92, 1.18]**
Total events	709		501			
Heterogeneity: Chi² = 12.32, df = 8 (P = 0.14); I² = 35%						
Test for overall effect: Z = 0.69 (P = 0.49)						
Total (95% CI)		**26696**		**19653**	**100.0%**	**1.02 [0.95, 1.10]**
Total events	1851		1350			
Heterogeneity: Chi² = 24.08, df = 31 (P = 0.81); I² = 0%						
Test for overall effect: Z = 0.51 (P = 0.61)						
Test for subgroup differences: Chi² = 3.02, df = 3 (P = 0.39), I² = 0.8%						

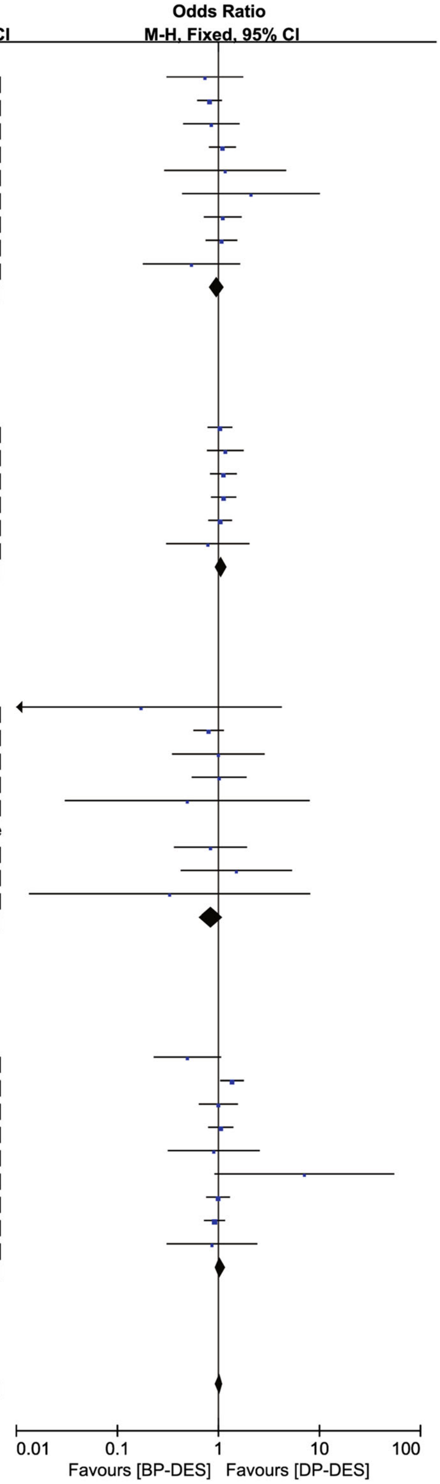

Fig. 7 Incidence of TLR, MI, all-cause death, and definite or probable stent thrombosis identified in the meta-analysis of 9 trials

other than VLST over DP-DES in a long-term follow-up of 4 years [28], and a previous meta-analysis also showed that BP-BES can significantly reduce the risk of adverse cardiovascular events after PCI at 5 years of follow-up [29]. However, a more recent study did not support this benefit and showed a tendency for higher risk of TVR [8], while a prior network meta-analysis showed that BP-DES was associated with a higher rate of ST compared with second-generation DP-DES [30]. The present meta-analysis did not show an obvious difference between the two groups. We observed that an advantage of BP-DES has been reported only in studies with first-generation DP-DES as a comparator, such as in the LEADERS trial [29,

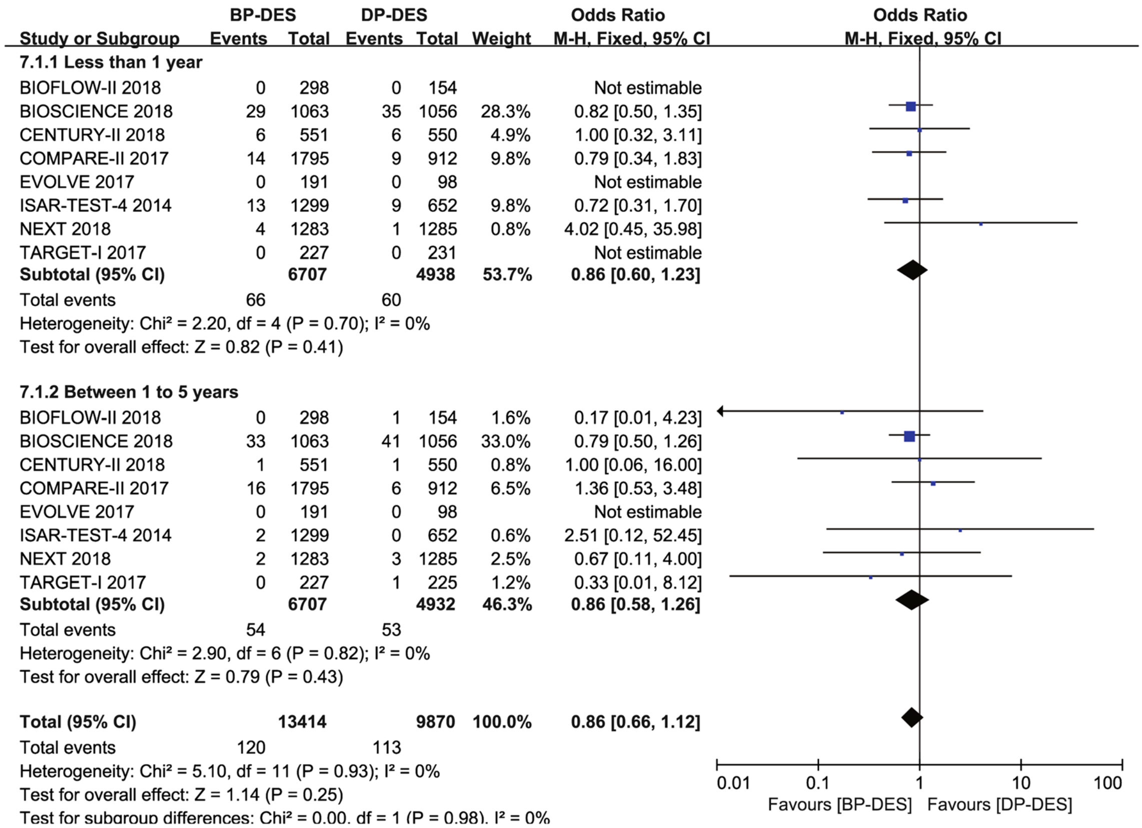

Fig. 8 Analysis of definite or probable stent thrombosis and landmark analysis

31, 32]. This discrepancy may be attributable to the biocompatible polymer used in second-generation DP-DES and subsequent improvements in safety and efficacy, which counteract the benefit of using biodegradable polymer [32–34]. In addition to the polymer coating, other components can influence the safety and efficacy of stents [7], and some studies have shown that ultrathin struts are associated with reduced platelet aggregation and inflammatory cell adhesion [35, 36]. For example, a previous study reported a 16 % reduction in TLF (RR, 0.84; 95 % CI, 0.72–0.99) associated with ultrathin struts compared with thick DP-DES after 12 months of follow-up [37]. To determine whether this benefit persists after 5 years, we performed a subgroup analysis of strut thickness but did not observe any difference between the groups. Our findings are not consistent with data from the recent BIO-RESORT study, which found that patients with small coronary vessel lesions had a lower risk for repeated target lesion revascularization if treated with ultrathin-strut stents rather than thin-strut stents [38]. This finding may be associated with the smaller size of vessels in the BIO-RESORT study and other characteristics of newer-generation stents such as stent geometry, polymer type, and eluting drug. Further studies of long follow-up duration are thus needed to confirm the real-world safety and efficacy of BP-DES. We also performed subgroup analysis of duration of polymer biodegradation, and no difference was found between BP-DES and DP-DES, even with different durations of DAPT.

Diabetes can affect the prognosis of patients undergoing PCI [39], and a previous study showed that diabetic patients had a higher risk of adverse cardiovascular events compared with nondiabetic patients but did not indicate which types of stents are best suited for use in this patient group [39, 40]. In the COMPARE II study, BP-DES was shown to increase the risk of MACE risk by 7 % (relative risk 1.53, 95 % CI 1.00–2.35, $p = 0.05$) compared with second-generation DP-DES in a follow-up of 3 years [41], although other trials with a 5-year follow-up did not show a difference [13, 18]. No meta-analysis to date has compared BP-DES with DP-DES in patients with diabetes, so we performed a subgroup analysis based on diabetes status and found no difference between the groups. Given the lack of clinical evidence for the safety and efficacy of BP-DES versus DP-DES in patients with diabetes, further studies in this population may be required.

Limitations

The current meta-analysis had some limitations apart from those inherent in the original trials. First, owing to our requirement for a long follow-up period, only 9 studies were included, and some subgroups were therefore not powered to determine the difference between groups. Second, we only included articles published in English, which may have caused selection bias. Third, since this meta-analysis is based on a study level instead of a patient level, baseline characteristics of patients may have differed between the trials. Fourth, the small number of included trials may have limited our ability to test for publication bias. Finally, although several studies have shown that ultrathin stents can improve safety and efficacy outcomes, our data do not support this finding, likely because of the limited number of patients included in our meta-analysis.

Conclusion

BP-DES displays a clinically comparable performance to that of second-generation DP-DES at 5 years of follow-up in patients undergoing PCI.

Impact on Clinical Practice Previous studies have shown that BP-DES has similar clinical effects to second-generation DES in a medium follow-up period. Our meta-analysis extends this result to 5 years of follow-up and confirms that both types of stent are safe, with a low rate of all-cause death, TLR, MI, and ST.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical Approval This article does not contain any studies with human participants performed by any of the authors.

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