



Drug-eluting balloons versus new generation drug-eluting stents for the management of in-stent restenosis: an updated meta-analysis of randomized studies

Lei GAO, Ya-Bin WANG, Jing JING, Ming ZHANG, Yun-Dai CHEN[#]

Department of Cardiology, Chinese PLA General Hospital, Beijing, China

Abstract

Background New-generation drug-eluting stents (DES) was more effective in the treatment of in-stent restenosis (ISR) compared with the first-generation DES. Drug-eluting balloons (DEB) and new-generation DES had been available strategies in treatment of bare-metal stents/DES ISR (BMS/DES-ISR). Six new randomized trials have recently examined the angiographic outcomes and one-year clinical outcomes of DEB and new generation DES in BMS/DES-ISR. However, the optimal management for BMS/DES-ISR lesions remains controversial. **Methods** We searched the randomized clinical trials evaluating the angiographic outcomes and one-year clinical outcomes of DEB and new-generation DES in patients with BMS/DES-ISR. The primary endpoints were the angiographic outcomes, including the minimal luminal diameter (MLD), diameter stenosis % (DS%), late lumen loss (LLL), and binary restenosis (BR). **Results** A total of six randomized clinical trials with 1177 BMS/DES-ISR patients were included in our meta-analysis. For angiographic outcomes, there were significantly less MLD and more DS% with DEB compared to new-generation DES (MLD: MD = -0.18, 95% CI: -0.31–-0.04, $P < 0.001$; DS%: MD = 5.68, 95% CI: 1.00–10.37, $P < 0.001$). Moreover, for one-year clinical outcomes, DEB was associated with a significant increase risk in target lesion revascularization (TLR) (RR = 2.93, 95% CI: 1.50–5.72, $P = 0.002$). However, DEB was associated with higher risks of major adverse cardiac event, target vessel revascularization, TLR, BR, and more DS% only in DES-ISR group. **Conclusions** DEB and new-generation DES have the similar clinical efficacy for the treatment of BMS-ISR. However, DES showed more MLD, less DS%, and a decreased risk of TLR for the treatment of DES-ISR.

J Geriatr Cardiol 2019; 16: 448–457. doi:10.11909/j.issn.1671-5411.2019.06.002

Keywords: Drug-eluting balloons; Drug-eluting stents; In-stent restenosis; Meta-analysis

1 Introduction

Percutaneous coronary intervention is the most effective nonsurgical method for myocardial revascularization in patients with coronary artery disease.^[1] However, the phenomenon of restenosis has been plagued clinicians.^[2,3] To date, several medical techniques, from balloon angioplasty and bare-metal stents (BMS) to first- and second-generation drug eluting stents (DES), have been invented and dramatically declined the rate of in-stent restenosis (ISR).^[4] For example, the rate of ISR is more than 40% for balloon angioplasty alone.^[5] The use of BMS has been associated with one third incidence of ISR.^[6] DES is an exciting medical technique which could significantly decrease the ISR rate to 5%–15% with first-generation DES, and even lower ISR

incidence for second-generation DES.^[7,8] Quite a few meta-analysis have confirmed that new-generation of DES dramatically reduced the rate of ISR compared with balloon angioplasty and BMS.^[9–11]

Currently, there are several therapeutic strategies for ISR. Many previous researches had reported clinical efficacy of balloon angioplasty, BMS, and DES.^[12,13] Although, DES could significantly reduce the rate of restenosis in ISR patients, there are several limitations for DES. For example, exotic metal layers on the vessel wall. Lately, a newly introduced drug-eluting balloon (DEB) is also used to treat ISR. DEB is a remarkable treatment method for ISR, which can deliver anti-proliferative agents to a restenotic arterial segment and do not need to use additional extra layers of metal stents.^[14,15] So far, many randomized controlled trials have compared the clinical efficacy between DEB and new-generation DES.^[16–21] However, the results are different and the ideal treatment of ISR remains debatable.

Therefore, we enrolled the randomized control studies

[#]Correspondence to: Yun-Dai CHEN, Department of Cardiology, Chinese PLA General Hospital, Beijing, China. E-mail: cyundai@vip.163.com

Received: January 31, 2019

Revised: March 21, 2019

Accepted: May 15, 2019

Published online: June 28, 2019

and conducted a meta-analysis to evaluate the clinical efficiency between DEB and new-generation DES in treating BMS/DES-ISR patients. We also performed subgroup analysis to examine the clinical efficacy of DEB in the treatment of BMS-ISR and DES-ISR in comparison with new-generation DES.

2 Methods

2.1 Literature search

PubMed and the Excerpta Medica Database, Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov were searched for all publications evaluating the clinical efficacy of DEB compared with new-generation DES for the treatment of BMS/DES-ISR that had been published through March 1, 2018. The search strategy was based on combinations of the following terms: “drug eluting balloon or DEB”, “drug coated balloon or DCB”, “drug-eluting stent or DES”, and “in-stent restenosis or ISR”. To retrieve the most eligible studies, we manually screened all relevant publications and their reference lists. Language was restricted to English.

2.2 Inclusion and exclusion criteria

The following eligible studies were included in the meta-analysis: (1) randomized controlled clinical trials; (2) studies whose patients had BMS/DES-ISR; (3) studies making comparisons of clinical outcomes and angiographic outcomes between DEB and new-generation DES; and (4) studies including the angiographic outcomes [the minimal luminal diameter (MLD), diameter stenosis % (DS%), late lumen loss (LLL), and binary restenosis (BR)] and the one-year clinical outcomes [all-cause death or major adverse cardiac event (MACE) or myocardial infarction (MI) or target vascular revascularization (TVR) or target lesion revascularization (TLR)]. The following studies were excluded from the analysis: (1) duplicates of previous publications; (2) abstracts, reviews, commentaries and editorials; (3) animal studies; (4) studies without sufficient available original data, even after we had contacted their corresponding authors; (5) studies only comparing the clinical outcomes between two strategies without angiographic results; and (6) studies aiming to compare DEB with first-generation DES.

2.3 Outcomes of interest and definitions

Clinical outcomes of interest were all-cause death, MACE, MI, TVR and TLR; Angiographic outcomes of interest were the MLD, DS%, LLL, and BR. ISR was de-

defined as > 50% diameter stenosis on visual assessment. All-cause death was defined as death from any cause. MACE was defined as cardiac death, MI, and stent thrombus. MI was defined as the documentation of a new abnormal Q-wave after the index revascularization. Other outcomes were defined according to the study definition.

2.4 Data extraction

Two reviewers independently extracted the following information from the eligible trials using a standardized data collection form: the trial’s name, publication year, location, numbers of patients, previous stent, the type of DEB and DES, clinical and angiographic follow-up durations, characteristics of the subjects (age, gender, and underlying diseases, such as hypertension, diabetes mellitus, dyslipidemia), clinical characteristics of the patients [previous MI, previous coronary artery bypass grafting, left ventricular ejection fraction, unstable angina, stable angina or silent ischemia, ISR lesions, quantitative findings before the procedure (reference vessel diameter, MLD, DS%, lesion length, previous stent diameter and length)] in the DEB and DES groups, clinical outcomes and angiographic data.

2.5 Statistical analysis

The data regarding the one-year clinical outcomes were categorical, and pooled risk ratios (RRs) and their corresponding 95% confidence intervals (CIs) were performed. The data regarding the angiographic outcomes were continuous, and pooled mean differences (MDs) and their corresponding 95% CIs were performed. The chi-square-based Cochran Q test and I^2 statistic were employed to assess between-study heterogeneity.^[22,23] Subgroup analyses were conducted to assess differences by ISR type (BMS-ISR and DES-ISR) for clinical and angiographic outcomes. Funnel plots, Begg’s rank test, and Egger’s linear regression test were performed to examine potential publication bias.^[24] Studies were combined using fixed effect model. However, a random-effects model was performed to calculate the risk estimation if a significant heterogeneity was detected. A two-sided $P < 0.05$ was considered statistically significant. All statistical analyses were conducted using STATA statistical software (Version 11.0, Stata Corp, College Station, Texas, USA).

3 Results

3.1 Characteristics of the included studies

The flow chart in Figure 1 displays information of comprehensive literature search and selection of studies assess-

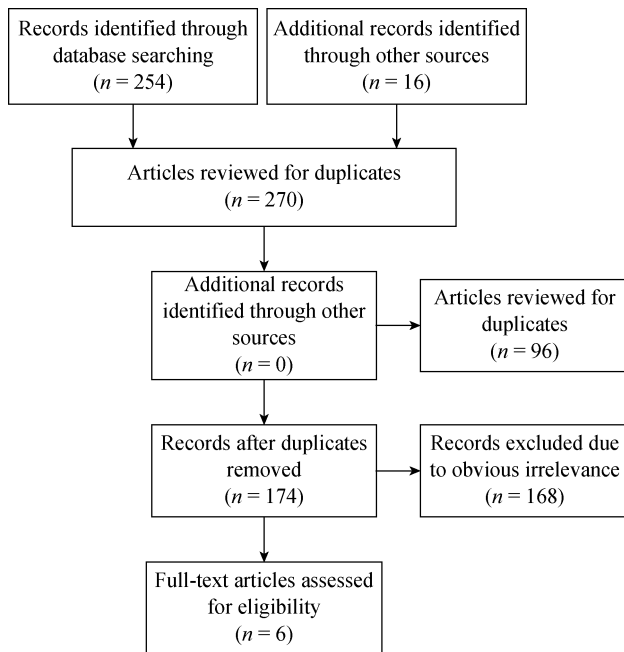


Figure 1. Flow diagram of the study selection process.

ing the clinical efficacy of DEB with DES in patients with BMS/DES-ISR. As a result of deduplication, screening of titles and abstracts, and full text review, six randomized clinical trials with 1177 BMS/DES-ISR patients were included in our meta-analysis. The characteristics of included studies are showed in Table 1. The baseline clinical and lesion characteristics of the patients are summarized in Tables 2 & 3. Among the 1177 BMS/DES-ISR patients, 596 patients accepted DEB treatment and 581 received new-generation DES treatment. Among the six trials, five were from western countries and one from Asia. Regarding type of ISR, three studies focused on BMS-ISR, two studies were about DES-ISR, and one study was about BMS/DES-ISR. Between the two groups, there were no significant differences in baseline characteristics and lesion characteristics, excepted age and smoking in Restenosis Intra-stent of Bare Metal Stents: paclitaxel-eluting balloon vs. everolimus-eluting stent (RIBS) V study,^[17] male in Drug-Eluting Balloon for In-Stent Restenosis (DARE) study,^[20] diabetes mellitus in Safety and Efficacy of a Drug eluting balloon in Coronary artery rEstenosis (SEDUCE) study.^[16]

Table 1. Characteristics of eligible studies enrolled in the meta-analysis.

Study	Year	Location	Patient size		Previous stent	DEB type	DES type	Follow-up	
			DEB	DES				Clinical	Angiographic
Alfonso F, <i>et al.</i> ^[17]	2014	Spain	95	94	BMS	PEB	EES	1 yr	9 months
Alfonso F, <i>et al.</i> ^[18]	2015	Spain	154	155	DES	PEB	EES	1 yr	9 months
Pleva L, <i>et al.</i> ^[19]	2016	Czech Republic	95	84	BMS	PEB	EES	1 yr	12 months
Adriaenssens T, <i>et al.</i> ^[16]	2014	Belgium	25	25	BMS	PEB	EES	1 yr	9 months
Baan J Jr., <i>et al.</i> ^[20]	2018	Netherlands	141	137	BMS/DES	PEB	EES	1 yr	6 months
Wong YTA, <i>et al.</i> ^[21]	2017	Korea	86	86	DES	PEB	EES	1 yr	9 months

BMS: bare-metal stent; DEB: drug-eluting balloon; DES: drug-eluting stent; EES: everolimus-eluting stent; PEB: paclitaxel-eluting balloon.

Table 2. Patient characteristics of the included studies.

Study	Group	Age, yrs	Male	HTN	DM	Dyslipidemia	Smoking	Previous MI	Previous CABG	LVEF	UA	SA/SI
Alfonso F, <i>et al.</i> ^[17]	DEB	67 ± 11	86%	72%	32%	73%	59%	60%	4%	58% ± 13%	40%	60%
	DES	64 ± 12*	87%	72%	20%	66%	75%*	60%	7%	59% ± 12%	45%	56%
Alfonso F, <i>et al.</i> ^[18]	DEB	66 ± 10	82%	71%	49%	71%	58%	47%	10%	58% ± 12%	52%	48%
	DES	66 ± 10	84%	78%	43%	78%	56%	50%	11%	59% ± 11%	51%	49%
Pleva L, <i>et al.</i> ^[19]	DEB	65.6 ± 10.9	63.2%	-	25%	-	45.6%	63.2%	4.4%	49.7% ± 12.0%	-	64.7%
	DES	65.5 ± 10.6	67.7%	-	26.5%	-	42.7%	60.3%	8.8%	49.6% ± 11.4%	-	63.2%
Adriaenssens T, <i>et al.</i> ^[16]	DEB	67.6 ± 7.7	72%	64%	24%	96%	20.8%	48%	-	-	20%	76%
	DES	64.2 ± 11.0	100%	60%	4%*	96%	12%	40%	-	-	20%	76%
Baan J Jr., <i>et al.</i> ^[20]	DEB	66 ± 11	72%	64%	31%	59%	17%	53%	14%	-	44%	-
	DES	65 ± 10	84%*	67%	33%	60%	13%	52%	16%	-	42%	-
Wong YTA, <i>et al.</i> ^[21]	DEB	67 ± 10	70.9%	69.8%	50%	-	46.5%	30.2%	-	59.4% ± 8.4%	45.3%	41.8%
	DES	66 ± 9	72.1%	75.6%	44.2%	-	43%	25.6%	-	59.9% ± 7.8%	38.4%	45.4%

Data are presented as means ± SD or %. * $P < 0.05$. CABG: coronary artery bypass grafting; DEB: drug-eluting balloon; DES: drug-eluting stent; DM: diabetes mellitus; HTN: hypertension; LVEF: left ventricular ejection fraction; MI: myocardial infarction; SA: stable angina; SI: silent ischemia; UA: unstable angina.

Table 3. Lesion characteristics of the included studies.

Study	Group	ISR lesions					RVD, mm	MLD, mm	DS%	Lesion length, mm	Previous stent	
		LM	LAD	LCA	RCA	VB					Diameter, mm	Length, mm
Alfonso F, <i>et al.</i> ^[17]	DEB	-	37%	22%	39%	2%	2.64 ± 0.60	1.02 ± 0.40	61 ± 14	13.7 ± 7.0	-	19 ± 6
	DES	-	39%	23%	34%	3%	2.64 ± 0.60	0.93 ± 0.40	65 ± 13	13.8 ± 6.0	-	18 ± 6
Alfonso F, <i>et al.</i> ^[18]	DEB	-	50%	18%	28%	4%	2.58 ± 0.50	0.79 ± 0.40	69 ± 17	10.4 ± 5.6	-	21 ± 7
	DES	-	46%	22%	29%	3%	2.55 ± 0.50	0.75 ± 0.40	72 ± 15	10.7 ± 5.4	-	21 ± 7
Pleva L, <i>et al.</i> ^[19]	DEB	-	47.3%	-	29.7%	1.4%	2.64 ± 0.47	0.92 ± 0.45	71.8 ± 13.9	-	3.18 ± 0.43	22.65 ± 11.70
	DES	-	54.1%	-	29.7%	2.7%	2.66 ± 0.45	0.79 ± 0.48	78.0 ± 13.4*	-	3.20 ± 0.41	19.39 ± 9.27
Adriaenssens T, <i>et al.</i> ^[16]	DEB	0%	24%	20%	52%	4%	3.00 ± 0.48	0.98 ± 0.60	67.7 ± 18.4	-	-	20 ± 10
	DES	4%	44%	28%	24%	0%	2.85 ± 0.44	0.57 ± 0.37	79.4 ± 13.5	-	-	18 ± 9
Baan J Jr., <i>et al.</i> ^[20]	DEB	-	41%	0%	37%	0.7%	2.56 ± 0.43	0.77 ± 0.33	69.7 ± 11.8	-	3.3 ± 0.9	22.4 ± 4.4
	DES	-	39%	0.7%	35%	1.4%	2.59 ± 0.54	0.79 ± 0.35	69.3 ± 12.5	-	2.9 ± 1.1	22.1 ± 8.6
Wong YTA, <i>et al.</i> ^[21]	DEB	0%	55.8%	15.1%	27.9%	1.2%	2.85 ± 0.50	0.63 ± 0.40	77 ± 17	18.1 ± 9.7	-	-
	DES	2.3%	60.5%	12.8%	24.4%	0%	3.06 ± 0.45*	0.63 ± 0.42	79 ± 13	17.4 ± 11.4	-	-

Data are presented as means ± SD or %. * $P < 0.05$. DEB: drug-eluting balloon; DES: drug-eluting stent; DS: diameter stenosis; ISR: in-stent restenosis; LAD: left anterior descending artery; LCA: left circumflex artery; LM: left main coronary artery; MLD: minimum lumen diameter; RCA: right coronary artery; RVD: reference vessel diameter; VB: vein bypass.

3.2 Angiographic outcomes

Six trials reported the angiographic follow-up of MLD, DS%, LLL, and BR. There were significantly less MLD and more DS% with DEB compared to DES (MLD: MD = -0.18, 95% CI: -0.31–-0.04, $P < 0.001$; DS%: MD = 5.68, 95% CI: 1.00–10.37, $P < 0.001$), with significant heterogeneity (MLD: $I^2 = 64.6\%$, $P = 0.015$; DS%: $I^2 = 71.8\%$, $P = 0.003$) across the studies (Figures 2 & 3, Table 4). However, there were no significant differences in angiographic outcomes of LLL and BR between DEB and DES for the

treatment of BMS/DES-ISR (LLL: MD = -0.07, 95% CI: -0.25–0.11, $P = 0.139$; BR: HR = 1.27, 95% CI: 0.73–2.22, $P = 0.229$), with significant heterogeneity (LLL: $I^2 = 86.1\%$, $P < 0.001$; BR: $I^2 = 53.9\%$, $P = 0.055$) among the trials (Figures 4 & 5, Table 4).

3.3 One-year clinical outcomes

Six trials reported the outcome of TVR, five trials showed the outcome of MI, and four trials presented one-year incidences of all-cause death, MACE and TLR. Overall, when all the studies were pooled in the meta-analysis, there were

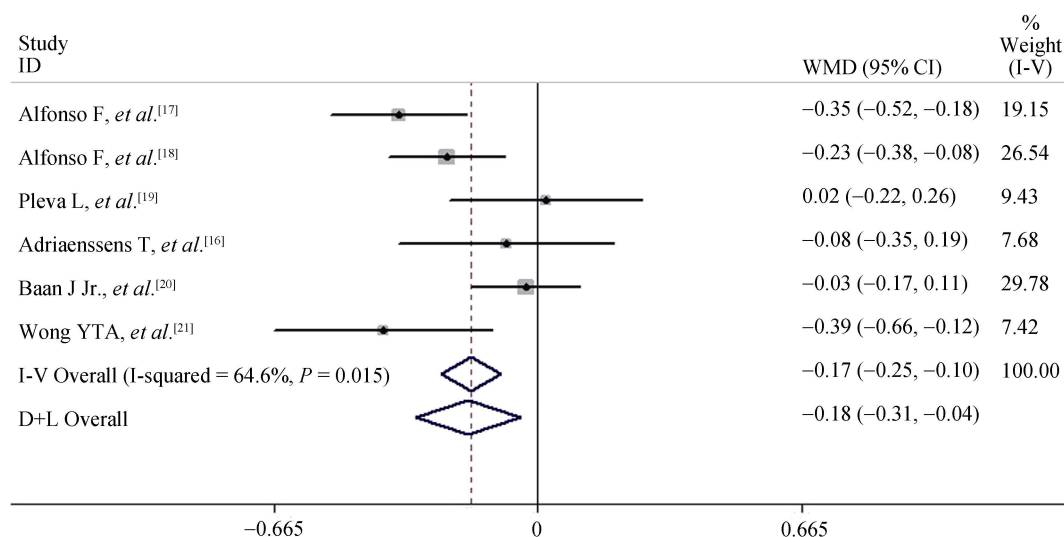


Figure 2. Forest plot for minimal luminal diameter of DEB and DES group (DEB vs. DES). DEB: drug-eluting balloon; DES: drug-eluting stent.

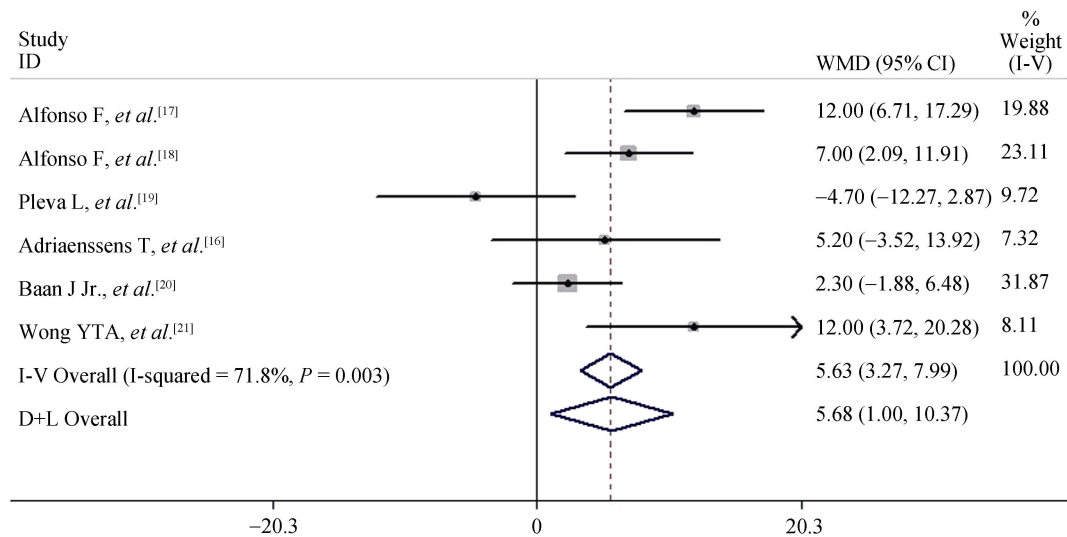


Figure 3. Forest plot for diameter stenosis of DEB and DES group (DEB vs. DES). DEB: drug-eluting balloon; DES: drug-eluting stent.

Table 4. Summary estimates for angiography outcomes of DEB and DES group (DEB vs. DES).

Outcome	n	Test of association				Heterogeneity analysis		
		MD (95% CI)	Z	P-value	Model	Q-value	P-value	I ²
Overall								
MLD	6	-0.18 (-0.31--0.04)	4.46	< 0.001	R	14.13	0.015	64.6%
DS%	6	5.68 (1.00-10.37)	4.68	< 0.001	R	17.75	0.003	71.8%
LLL	6	-0.07 (-0.25-0.11)	2.61	0.139	R	35.91	< 0.001	86.1%
BR*	6	1.27 (0.73-2.22)	1.20	0.229	R	10.84	0.055	53.9%
BMS								
MLD	3	-0.15 (-0.39--0.09)	3.10	0.002	R	6.84	0.033	70.7%
DS%	3	4.40 (-5.91-14.72)	3.16	0.002	R	12.64	0.002	84.2%
LLL	3	-0.06 (-0.35-0.24)	0.45	0.656	R	13.05	0.001	84.7%
BR*	3	1.02 (0.33-3.17)	0.40	0.689	R	4.40	0.111	54.5%
DES								
MLD	2	-0.27 (-0.39--0.14)	4.04	< 0.001	F	1.02	0.313	1.7%
DS%	2	8.30 (4.08-12.52)	3.85	< 0.001	F	1.04	0.309	3.5%
LLL	2	0.04 (-0.14-0.23)	1.13	0.261	R	2.26	0.133	55.7%
BR*	2	2.05 (1.19-3.54)	2.58	0.010	F	0.83	0.362	0.0%

*Risk ratio was used. BMS: bare-metal stent; BR: binary restenosis; DEB: drug-eluting balloon; DES: drug-eluting stent; DS: diameter stenosis; F: fixed; LLL: late lumen loss; MD: mean difference; MLD: minimum lumen diameter; R: random.

no significant differences in one-year outcomes of all-cause death, MACE, and MI between DEB and DES for the treatment of BMS/DES-ISR (all-cause death: RR = 1.28, 95% CI: 0.49-3.31, $P = 0.611$; MACCE: RR = 1.26, 95% CI: 0.85-1.87, $P = 0.255$; MI: RR = 1.01, 95% CI: 0.47-2.19, $P = 0.980$; TVR: RR = 1.36, 95% CI: 0.92-2.00, $P = 0.122$), with no significant heterogeneity (all-cause death: $I^2 = 0\%$, $P = 0.427$; MACE: $I^2 = 42.3\%$, $P = 0.158$; MI: $I^2 = 0\%$, $P = 0.745$; TVR: $I^2 = 48.0\%$, $P = 0.087$) for the outcomes across

the trials (Figure 6, Table 5). However, DEB was associated with a significant increase in TLR (RR = 2.93, 95% CI: 1.50-5.72, $P = 0.002$), with no heterogeneity ($I^2 = 0\%$, $P = 0.426$) across the studies (Figure 6, Table 5).

3.4 Subgroup analysis

In subgroup analyses performed by ISR type for angiographic outcomes, there were remained no differences between DEB and DES in terms of LLL (Table 4), DEB

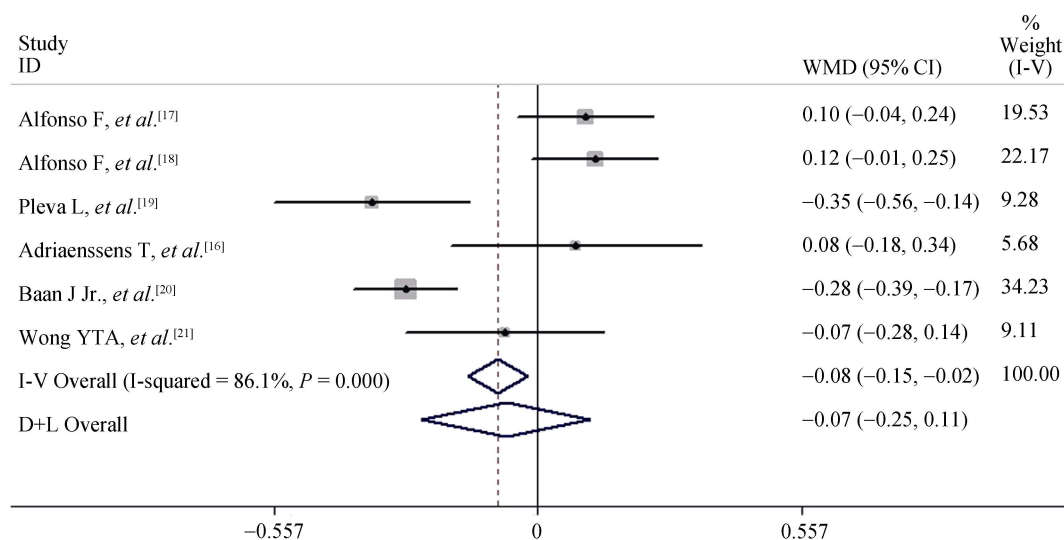


Figure 4. Forest plot for late lumen loss of DEB and DES group (DEB vs. DES). DEB: drug-eluting balloon; DES: drug-eluting stent.

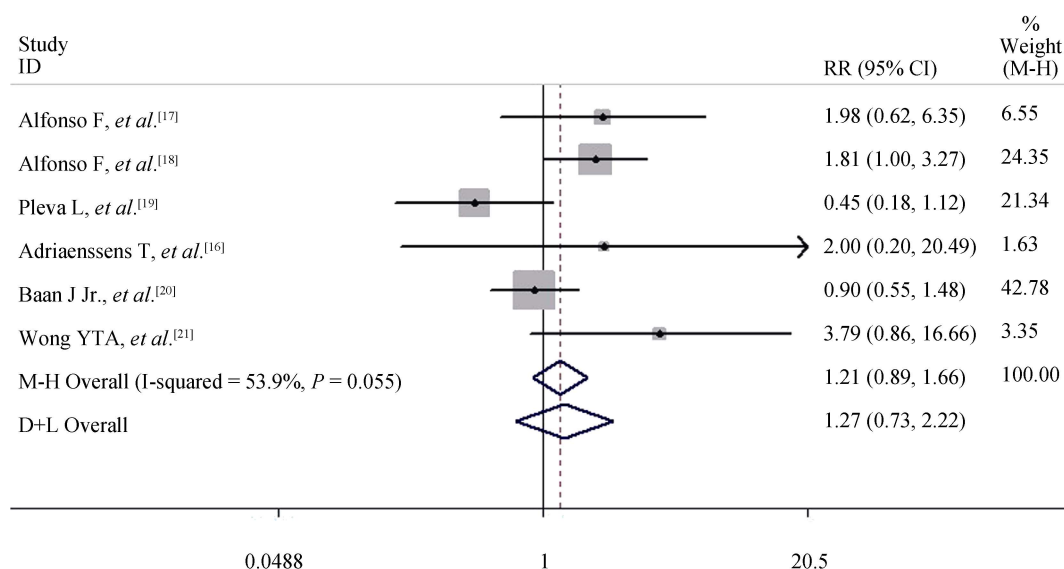


Figure 5. Forest plot for binary restenosis of DEB and DES group (DEB vs. DES). DEB: drug-eluting balloon; DES: drug-eluting stent.

continued to have a significantly less MLD, regardless of ISR type (Table 4). However, there were higher risk of BR and a significantly more DS% with DEB versus DES only in DES-ISR group (BR: RR = 2.05, 95% CI: 1.19–3.54, *P* = 0.010; DS%: MD = 8.30, 95% CI: 4.08–12.52, *P* < 0.001), and no significant difference in BMS-ISR group (BR: RR = 1.02, 95% CI: 0.33–3.17, *P* = 0.689; DS%: MD = 4.40, 95% CI: -5.91–14.72, *P* = 0.002) (Table 4). In subgroup analyses performed by ISR type for one-year clinical outcomes, there was no difference between DES and DEB for treatment of BMS-ISR in terms of all-cause death, MACE, MI, TVR and

TLR (Table 5). However, the results of our analysis showed that DEB were associated with higher risks of MACE, TVR, and TLR only in DES-ISR group (MACE: RR = 1.71, 95% CI: 1.02–2.87, *P* = 0.043; TVR: RR = 2.16, 95% CI: 1.18–3.94, *P* = 0.012; TLR: RR = 3.14, 95% CI: 1.45–6.80, *P* = 0.004) (Table 5).

3.5 Publication bias

We constructed funnel plots and carried out Begg's rank test and Egger's linear regression test to assess whether publication bias affected the results of the studies. We found

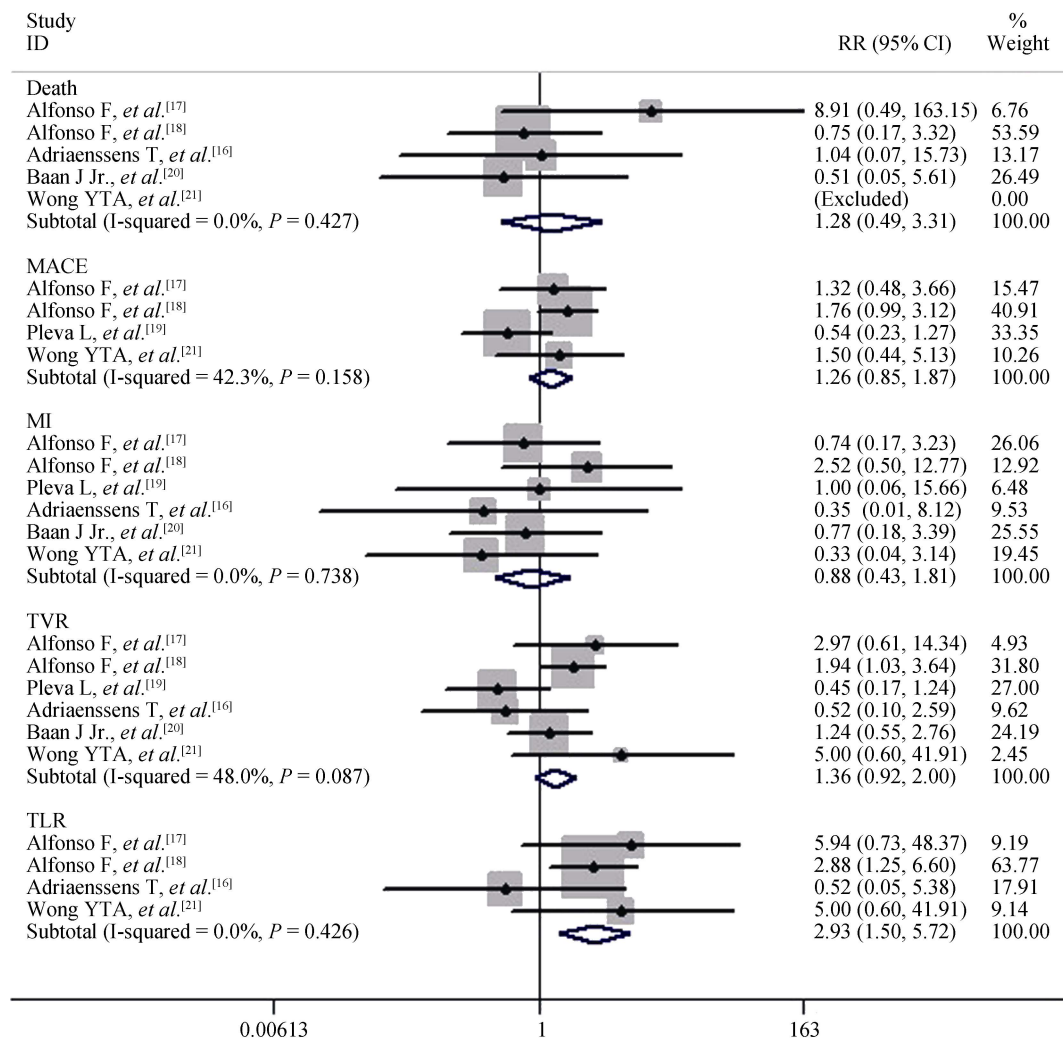


Figure 6. Forest plot for one-year clinical outcomes of DEB and DES group (DEB vs. DES). DEB: drug-eluting balloon; DES: drug-eluting stent; MACE: major adverse cardiac events; MI: myocardial infarction; RR: risk ratio; TLR: target lesion revascularization; TVR: target vascular revascularization.

no evidence of funnel plot asymmetry across the studies (Figure 7), and the Begg's rank test and Egger's linear regression test was not significant for the outcomes studied (not shown).

4 Discussion

To the best of our knowledge, this is the largest meta-analysis, as including a total of six randomized clinical trials with 1177 BMS/DES-ISR patients compared the clinical efficacy of DEB with new-generation DES in treatment of BMS/DES-ISR. The results of this analysis indicated that DEB was associated with a significant increase in TLR. Meanwhile, there were significantly less MLD and more DS% with DEB compared to those treated with new-generation DES. However, DEB was associated with higher risks of MACE, TVR, TLR, BR, and more DS% only in

DES-ISR group, not in BMS-ISR group. The results proved that DEB and new-generation DES have the similar clinical efficacy for the treatment of BMS-ISR. However, the new-generation DES showed better one-year clinical outcomes and angiographic results for the treatment of DES-ISR.

Numerous treatment technologies have been developed for ISR patients. These technologies included balloon angioplasty, BMS, cutting or scoring balloon, rotational atherectomy and intravascular brachy therapy. However, the re-ISR remains a major problem with unsatisfactory clinical outcomes. The underlying mechanical factors of ISR is far more complex, which not only including neointima, vessel and lesion factors, such as hypocellular neointima, neointimal disruptions, lipid-laden neointima, but also including procedural factors, such as inadequate stent expansion and stent malapposition.^[25-27] DES could significantly reduce

Table 5. Summary estimates for one-year clinical outcomes of DEB and DES group (DEB vs. DES).

Outcome	<i>n</i>	Test of association				Heterogeneity analysis		
		RR (95% CI)	Z	<i>P</i> -value	Model	<i>Q</i> -value	<i>P</i> -value	<i>I</i> ²
Overall								
Death	4	1.28 (0.49–3.31)	0.51	0.611	F	2.78	0.427	0.0%
MACE	4	1.26 (0.85–1.87)	1.14	0.255	F	5.20	0.158	42.3%
MI	5	1.01 (0.47–2.19)	0.03	0.980	F	1.95	0.745	0.0%
TVR	6	1.36 (0.92–2.00)	1.55	0.122	F	9.61	0.087	48.0%
TLR	4	2.93 (1.50–5.72)	3.15	0.002	F	2.78	0.426	0.0%
BMS								
Death	2	3.71 (0.61–22.43)	1.43	0.154	F	1.19	0.275	15.9%
MACE	2	0.79 (0.42–1.49)	0.74	0.460	F	1.74	0.187	42.6%
MI	3	0.69 (0.21–2.26)	0.61	0.543	F	0.26	0.877	0.0%
TVR	3	0.81 (0.26–2.52)	0.75	0.456	R	4.11	0.128	51.3%
TLR	2	1.86 (0.17–20.56)	1.25	0.210	R	2.35	0.125	57.5%
DES								
Death	1	0.76 (0.17–3.32)	0.37	0.710	-	-	-	-
MACE	2	1.71 (1.02–2.87)	2.02	0.043	F	0.05	0.816	0.0%
MI	1	2.52 (0.50–12.77)	1.11	0.266	-	-	-	-
TVR	2	2.16 (1.18–3.94)	2.50	0.012	F	0.71	0.398	0.0%
TLR	2	3.14 (1.45–6.80)	2.90	0.004	F	0.23	0.634	0.0%

BMS: bare-metal stent; DEB: drug-eluting balloon; DES: drug-eluting stent; F: fixed; MACE: major adverse cardiac events; MI: myocardial infarction; R: random; RR: risk ratio; TLR: target lesion revascularization; TVR: target vascular revascularization.

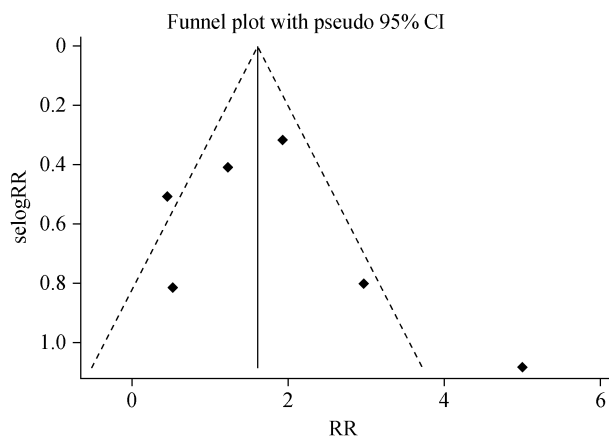


Figure 7. Publication bias by funnel plot. CI: confidence interval; RR: risk ratio.

the occurrence of restenosis in ISR patients, particularly DES-ISR patients, by the profound inhibitory effect on neointimal formation.^[28] DES, however, have several limitations as follows: (1) DES could increase the burden of multi-metal layers on the vessel wall, which may increase the risk of ST and bleeding; and (2) the stent exposed to previous stent may induce chronic inflammation, which can increase the risk of late stent thrombosis.^[16] Thus, another novel therapy of DEB is developed as an alternative treatment strategy in the treatment of ISR. The most common

DEB in clinical practice is paclitaxel eluting balloon, which can delivery anti-proliferative agents to a restenotic arterial segment and do not need to use additional extra layers of metal stents. There are also some advantages with DEB as follows: (1) it is more suited to a tortuous or calcified vessel where could not use stent; (2) it does not need to prolonged anti-platelet therapies; (3) it could avoid stent overlap; and (4) the absence of polymers in DEB could inhibit the chronic inflammation, and thus reduce the risk of late stent thrombosis.^[29,30]

Currently, several meta-analyses have been performed to compare the clinical efficacy between DEB and DES in the treatment of BMS/DES-ISR patients. One previous meta-analysis identified 2052 DES-ISR patients from three randomized clinical trials and four observational studies to determine the clinical efficacy of DEB compared with DES, and found that MACE, TLR, MI, stent thrombosis, and cardiac death were not different between patients treated with DEB and with DES.^[31] However, our meta-analysis indicated that DEB was associated with higher risks of MACE, TVR, TLR, BR, and more DS% in DES-ISR patients. The limitations of this previous meta-analysis should not be ignored. Firstly, the angiography outcomes (MLD, DS% and LLL) were continuous variables, but it extracted the data with categorical variables and used odds ratios (ORs) to represent the effects which might not reflect the real effects.

Secondly, this previous meta-analysis did not enroll the latest SEDUCE, RESTORE and DARE trials. Another meta-analysis also showed that there were no significant differences between DEB and DES in terms of TLR, MACE, MI and stent thrombosis.^[32] However, it did not include the latest studies, did not research the angiography outcomes, and did not perform the subgroups of BMS-ISR and DES-ISR. One meta-analysis by Liou, *et al.*^[30] reported that there were higher TLR and MACE rates with DEB, it also reported that DEB was associated with inferior in MLD, higher LLL and a higher BR rate, compared to DES. Our results indicated that DEB was associated with a significant increase in TLR, but there were no differences in death, MACE, MI and TVR. Our meta-analysis also showed that significantly less MLD and more DS% with DEB compared to those treated with new-generation DES. The results were consistent with the research of Liou, *et al.*^[30] The following reasons may explain these results: (1) the new-generation DES had the mechanical scaffolding, which contributed to the higher luminal gain and less DS% with DES; (2) the two methods had different pharmacologies, compared with everolimus, paclitaxel could induce a higher degree of inflammation and thus a greater neointimal thickness in the vessel;^[33] and (3) the follow-up time was only one year, which was too short to observe the different clinical outcomes, as the clinical outcomes, such as death, MACE and MI, might present in long-term follow-up. That is why there were different angiography outcomes, but no significantly different clinical outcomes were found between the two groups. Last but not least, DES showed better one-year clinical outcomes and angiographic results only for the treatment of DES-ISR. However, there were no significant differences in BMS-ISR patients between DEB and DES. The reason may be that different ISR type has different etiologies of ISR. For BMS-ISR, the important factors are neointimal hyperplasia and stent underexpansion. However, for DES-ISR, the dominant factor is neoatherosclerosis in vessel.^[34]

4.1 Limitations

There were several limitations in this meta-analysis. Firstly, the meta-analysis included only six studies enrolling 1177 BMS/DES-ISR patients, 596 patients received DEB treatment and 581 received DES. The sample size is so small, which may not have enough statistical power to properly compare the clinical efficacy of DEB and DES in BMS/DES-ISR patients. Moreover, the enrolled trials were stratified by the type of ISR, the sample sizes of the subgroups were much smaller, which greatly hampered our ability to explore effects in these subgroups. Secondly, we

could not obtain the information of individual data of the included studies, thus we could not assess the baseline, clinical and lesion characteristics which may influence clinical outcomes further. Thirdly, the data of this meta-analysis was based on unadjusted estimates, which could not eliminate various confounders. Fourthly, the post-procedural dual anti-platelet therapy and treatment time for patients were different. Last but not least, no later time follow-up results were available in the majority of the included trials, thus limited our analysis to only one-year clinical outcomes.

4.2 Conclusions

In summary, the results of our meta-analysis demonstrated that DEB and new-generation DES have the similar clinical efficacy for the treatment of BMS-ISR. However, new-generation DES showed more MLD, less DS%, and a decreased risk of TLR for the treatment of DES-ISR. Additional well-designed studies that are based on larger sample sizes and involve patients of different clinical characteristics are needed to validate these findings.

Acknowledgments

This study was supported by the National Natural Science Foundation of China (No. 81671731), and the Capital Clinical Feature Research Project (Z171100001017158). All authors had no conflicts of interest to disclose.

References

- 1 Henderson RA, Timmis AD. Almanac 2011: stable coronary artery disease. An editorial overview of selected research that has driven recent advances in clinical cardiology. *Heart* 2011; 97: 1552–1559.
- 2 Nicolais C, Lakhter V, Virk HUH, *et al.* Therapeutic options for in-stent restenosis. *Curr Cardiol Rep* 2018; 20: 7–7.
- 3 Kassimis G, Raina T. GuideLiner extension catheter-facilitated side strut stenting technique for the treatment of right coronary artery ostial in-stent restenosis. *Cardiovasc Revasc Med* 2018; 19: 133–136.
- 4 Alraies MC, Darmoch F, Tummala R, *et al.* Diagnosis and management challenges of in-stent restenosis in coronary arteries. *World J Cardiol* 2017; 9: 640–651.
- 5 Alfonso F, Zueco J, Cequier A, *et al.* A randomized comparison of repeat stenting with balloon angioplasty in patients with in-stent restenosis. *J Am Coll Cardiol* 2003; 42: 796–805.
- 6 Alfonso F, Byrne RA, Rivero F, *et al.* Current treatment of in-stent restenosis. *J Am Coll Cardiol* 2014; 63: 2659–2673.
- 7 Farooq V, Gogas BD, Serruys PW. Restenosis: delineating the numerous causes of drug-eluting stent restenosis. *Circ*

- Cardiovasc Interv* 2011; 4: 195–205.
- 8 Cassese S, Byrne RA, Tada, *et al.* Incidence and predictors of restenosis after coronary stenting in 10004 patients with surveillance angiography. *Heart* 2014; 100: 153–159.
 - 9 Goel SS, Dilip Gajulapalli R, Athappan G, *et al.* Management of drug eluting stent in-stent restenosis: a systematic review and meta-analysis. *Catheter Cardiovasc Interv* 2016; 87: 1080–1091.
 - 10 Lee JM, Park J, Kang J, *et al.* Comparison among drug-eluting balloon, drug-eluting stent, and plain balloon angioplasty for the treatment of in-stent restenosis: a network meta-analysis of 11 randomized, controlled trials. *JACC Cardiovasc Interv* 2015; 8: 382–394.
 - 11 Sun Y, Li L, Su Q, *et al.* Comparative efficacy and safety of drug-eluting stent and conventional therapies in coronary heart disease patients with in-stent restenosis: a meta-analysis. *Cell Biochem Biophys* 2014; 68: 211–229.
 - 12 Kastrati A, Mehilli J, von Beckerath N, *et al.* Sirolimus-eluting stent or paclitaxel-eluting stent vs balloon angioplasty for prevention of recurrences in patients with coronary in-stent restenosis: a randomized controlled trial. *JAMA* 2005; 293: 165–171.
 - 13 Almalla M, Schroder JW, Pross V, *et al.* Three-year follow-up after treatment of bare-metal stent restenosis with first-generation or second-generation drug-eluting stents. *Coron Artery Dis* 2013; 24: 165–170.
 - 14 Gao S, Shen J, Mukku VK, *et al.* Efficacy of drug-eluting balloons for patients with in-stent restenosis: a meta-analysis of 8 randomized controlled trials. *Angiology* 2016; 67: 612–621.
 - 15 Indermuehle A, Bahl R, Lansky AJ, *et al.* Drug-eluting balloon angioplasty for in-stent restenosis: a systematic review and meta-analysis of randomised controlled trials. *Heart* 2013; 99: 327–333.
 - 16 Adriaenssens T, Dens J, Ughi G, *et al.* Optical coherence tomography study of healing characteristics of paclitaxel-eluting balloons vs. everolimus-eluting stents for in-stent restenosis: the SEDUCE (Safety and Efficacy of a Drug eluting balloon in Coronary artery rEstenosis) randomised clinical trial. *EuroIntervention* 2014; 10: 439–448.
 - 17 Alfonso F, Pérez-Vizcayno MJ, Cárdenas A, *et al.* A randomized comparison of drug-eluting balloon versus everolimus-eluting stent in patients with bare-metal stent-in-stent restenosis: the RIBS V Clinical Trial (Restenosis Intra-stent of Bare Metal Stents: paclitaxel-eluting balloon vs. everolimus-eluting stent). *J Am Coll Cardiol* 2014; 63: 1378–1386.
 - 18 Alfonso F, Pérez-Vizcayno MJ, Cárdenas A, *et al.* A prospective randomized trial of drug-eluting balloons versus everolimus-eluting stents in patients with in-stent restenosis of drug-eluting stents: the ribs iv randomized clinical trial. *J Am Coll Cardiol* 2015; 66: 23–33.
 - 19 Pleva L, Kukla P, Kusnierova P, *et al.* Comparison of the efficacy of paclitaxel-eluting balloon catheters and everolimus-eluting stents in the treatment of coronary in-stent restenosis: the treatment of in-stent restenosis study. *Circ Cardiovasc Interv* 2016; 9: e003316–e003316.
 - 20 Baan J Jr., Claessen BE, Dijk KB, *et al.* A randomized comparison of paclitaxel-eluting balloon versus everolimus-eluting stent for the treatment of any in-stent restenosis: the dare trial. *JACC Cardiovasc Interv* 2018; 11: 275–283.
 - 21 Wong YTA, Kang DY, Lee JB, *et al.* Comparison of drug-eluting stents and drug-coated balloon for the treatment of drug-eluting coronary stent restenosis: a randomized RESTORE trial. *Am Heart J* 2018; 197: 35–42.
 - 22 Higgins J, Thompson S, Deeks J, *et al.* Statistical heterogeneity in systematic reviews of clinical trials: a critical appraisal of guidelines and practice. *J Health Serv Res Policy* 2002; 7: 51–61.
 - 23 DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986; 7: 177–188.
 - 24 Egger M, Davey Smith G, Schneider M, *et al.* Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997; 315: 629–634.
 - 25 Dangas GD, Claessen BE, Caixeta A, *et al.* In-stent restenosis in the drug-eluting stent era. *J Am Coll Cardiol* 2010; 56: 1897–1907.
 - 26 Piraino D, Cimino G, Buccheri D, *et al.* Recurrent in-stent restenosis, certainty of its origin, uncertainty about treatment. *Int J Cardiol* 2017; 230: 91–96.
 - 27 Minha S, Pichard AD, Waksman R. In-stent restenosis of drug-eluting stents. *Future Cardiol* 2013; 9: 721–731.
 - 28 Ribamar Costa J, Sousa AG, Moreira A, *et al.* Comparison of the very long term (> 1 year) outcomes of drug-eluting stents for the treatment of bare-metal and drug-eluting stent restenosis. *EuroIntervention* 2009; 5: 448–453.
 - 29 Waksman R, Pakala R. Drug-eluting balloon: the comeback kid? *Circ Cardiovasc Interv* 2009; 2: 352–358.
 - 30 Liou K, Jepson N, Cao C, *et al.* Drug-eluting balloon versus second generation drug eluting stents in the treatment of in-stent restenosis: a systematic review and meta-analysis. *Heart Lung Circ* 2016; 25: 1184–1194.
 - 31 Bajraktari G, Jashari H, Ibrahim P, *et al.* Comparison of drug-eluting balloon versus drug-eluting stent treatment of drug-eluting stent in-stent restenosis: a meta-analysis of available evidence. *Int J Cardiol* 2016; 218: 126–135.
 - 32 Wang Y, Lou X, Xu X, *et al.* Drug-eluting balloons versus drug-eluting stents for the management of in-stent restenosis: a meta-analysis of randomized and observational studies. *J Cardiol* 2017; 70: 446–453.
 - 33 Buszman PP, Milewski K, Pajak J, *et al.* Differences in vessel healing following delivery of everolimus or paclitaxel: a comparative experimental study using identical stent and biodegradable polymer platforms. *EuroIntervention* 2014; 10: 724–731.
 - 34 Lee SY, Hong MK, Shin DH, *et al.* Mechanisms of postintervention and nine-month luminal enlargement after treatment of drug-eluting in-stent restenosis with a drug-eluting balloon. *Am J Cardiol* 2014; 113: 1468–1473.