Original Article

Drug-eluting balloons with provisional bail-out or adjunctive stenting in *de novo* coronary artery lesions—a systematic review and meta-analysis

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Background: Efficacy of drug-eluting balloons (DEB) for treatment of *de novo* coronary lesions remains controversial. The present systematic review and meta-analysis of randomised controlled trials assessed DEB with bare-metal stents (BMS) and also DEB with provisional bail-out stents ('DEB-only' strategy), to other conventional options: plain-old balloon angioplasty (POBA), BMS and drug-eluting stents (DES).

Methods: A systematic literature search from January 2000 until May 2017 was conducted. Primary outcome measure, late lumen loss (LLL); and secondary outcomes; binary restenosis, major adverse cardiac events (MACE), target lesion revascularization (TLR), myocardial infarction (MI), cardiovascular death and stent thrombosis were analysed.

Results: Seventeen RCTs were included with 2,616 patients. Several comparative groups showed significant differences. DEB with BMS were inferior to DES for LLL [mean difference (MD) =0.12 mm; 95% confidence interval (CI), 0.03 to 0.22; P=0.01]; and binary restenosis [risk ratio (RR) =1.89; (CI, 1.13 to 3.18); P=0.02]. DEB with BMS was superior to BMS for LLL [MD =−0.27 mm; (−0.45 to −0.10); P=0.002]; and MACE [RR =0.64; (0.46 to 0.90); P=0.010]. Finally, DEB alone was superior to POBA for LLL [MD =−0.39 mm; (−0.67 to −0.11); P=0.006] and binary restenosis [RR =0.20; (0.05 to 0.85); P=0.03] in bifurcation lesions.

Conclusions: The results of this meta-analysis showed that whilst DEB with BMS is superior to BMS alone, the combination is inferior to DES for treatment of *de novo* coronary lesions. Thus, DEB + BMS should not be applied in *de novo* lesions unless in patients who have absolute contraindications to DES. DEB alone, however, should be considered for relative contraindications to DES such as small vessel disease and bifurcation lesions.

Keywords: Bare-metal stents (BMS); *de novo* lesions; drug-eluting balloons (DEB); drug-eluting stents (DES); plain-old balloon angioplasty (POBA)

Introduction

Percutaneous coronary intervention and stenting is the most commonly used treatment for coronary artery disease. Plain-old balloon angioplasty (POBA) was the first technique (1) which facilitated a minimally-invasive expansion of a stenosed coronary artery (2). The technique was limited

by acute complications including coronary dissection, which in some patients progressed to abrupt vessel closure requiring emergency bypass surgery; and acute elastic recoil, reducing the luminal gain following balloon dilatation. Post-procedure, restenosis due to neointimal proliferation of vascular smooth muscle cells represented another limiting factor most common in patients with diabetes and complex coronary artery disease (3-5).

Bare-metal stents (BMS) virtually solved the problem of dissection; acute vessel closure and the need for emergency bypass surgery (2), but did not reduce the risk of restenosis. The implantation of stents also led to a new problem of acute, late and very late stent thrombosis (6). However, treatment with dual antiplatelet therapy (DAPT) reduced this risk (7). The introduction of drug-eluting stents (DES) and its generational enhancements (i.e., thinner struts) partially resolved the problem of restenosis through release of anti-mitotic agents but concerns surrounding prolonged DAPT still remained (8,9).

To overcome the limitations of POBA, BMS and DES, the drug-eluting balloons (DEB) was developed. Initially introduced as a treatment for in-stent restenosis (ISR) in BMS and DES-lesions (10) they have emerged as a potential treatment for *de novo* coronary lesions. This is because the DEB intervention has several advantages over DES such as homogenous transfer of drug across vessel wall, lack of foreign body implantation, reduced bleeding risk (1 month DAPT versus 6–12 months of therapy for DES) and access to complex lesions (4,11). However, one disadvantage is that in a small proportion of DEB-treated patients, bail-out stenting is required, following recoil or dissections (12). Despite the promising characteristics of this intervention type, the indication for DEB use in *de novo* coronary lesions is still unclear.

Previous meta-analyses have failed to address the DEB-only strategy for *de novo* coronary artery disease (13,14). Moreover, analyses have not yet explored a DEB-only approach in bifurcation lesions. As initial studies suggest that DEB-alone show success for treatment of high-risk restenotic areas (15,16), we hypothesised that DEB will also provide superior results compared with other interventional treatments, for the treatment of small vessel disease and bifurcation lesions in *de novo* coronary disease. This study, which includes data from DEB and adjunctive BMS as well as DEB-only studies, therefore aims to provide the most up-to-date and comprehensive systematic review and meta-analysis for the treatment of

de novo coronary artery disease. The safety and efficacy of DEB (with or without BMS) will be compared to other conventional management options (POBA, BMS and DES) in treating *de novo* lesions.

Methods

This study was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Literature search

MEDLINE, Embase, PubMed and ClinicalTrials.gov were searched for RCTs published from 1st January 2000 through to 1st May 2017 using the key terms: 'drug eluting balloon', 'drug coated balloon', 'paclitaxel eluting balloon', '*de novo* coronary lesion', 'coronary stenosis', 'coronary disease', 'small vessel disease', 'bifurcation', 'complex long lesion', 'acute myocardial infarction', 'acute MI' and 'MI'. No filters were applied. Abstracts and conference proceedings of the American College of Cardiology and Transcatheter Cardiovascular Therapeutics Symposia were also screened. References included in literature reviews were searched manually to ensure all studies that complied with the inclusion criteria were identified. Two investigators (S Patel and T Svermova) independently reviewed the resulting articles. A qualitative risk of bias in seven domains (random sequence generation; allocation concealment; blinding of participants/personnel; outcome; incomplete outcome; selective reporting and other risk of bias) was conducted.

Study selection

We included all studies that compared angioplasty using the DEB-only strategy as well as DEB with adjunctive BMS to: POBA, BMS and DES. For analysis, data pertaining to the longest available follow up periods were used. Exclusion criteria were patients treated for ISR and use of interventions other than DEB, POBA, BMS or DES (e.g., endothelial progenitor capturing stents). Non-randomised controlled trials and non-observational studies were also excluded. The primary endpoint collected was in-segment or in-stent late lumen loss (LLL). Secondary angiographic and clinical endpoints were: binary restenosis (in-stent or in-segment), target lesion revascularization (TLR), major adverse cardiac events (MACE), myocardial infarction (MI)

and cardiac death.

Statistical analysis

Statistical analysis was performed using standard software packages (Review Manager version 5.3, The Nordic Cochrane Centre, The Cochrane Collaboration, 2014, Copenhagen, Norway; Comprehensive Meta-analysis version 3 software, Biostat Inc., Englewood, NJ, USA) with two-tailed P values <0.05 considered significant. Analyses are presented as forest plots—the conventional method for showing results from individual studies and meta-analysis. Risk ratios (RRs) with 95% confidence intervals (CIs) or mean differences (MDs) with standard deviations are presented as summary statistics. Subgroup analyses comparing DEB-only studies with DES were also performed. Heterogeneity between studies was compared by Q and I^2 statistics (respectively, P<0.1 indicates heterogeneity; <25%, 25–50% and >50% indicate low, medium and high levels). Studies were combined using the random effect model. Publication bias was assessed using funnel plots and Egger's test (P<0.05 indicates significant bias).

Results

A PRISMA diagram of the literature search and the subsequent selection is presented in *Figure 1*. In total, 606 articles were retrieved. Following screening for replicates, 405 remained; and after screening abstracts for relevance, a further 371 studies were removed. Finally, full text of the remaining 34 studies were screened, of which 17 randomised controlled trials (17-34) fulfilled the inclusion criteria and were qualitatively and quantitatively analysed.

Characteristics of the patients and study designs

A summary of the included studies is provided in *Table 1* and this table also documents: (I) interventions compared; (II) DEB, DES and BMS type; (III) indication; (IV) primary endpoint; (V) percent bare metal stenting; and (VI) angiographic follow-up time.

A total of 2,616 patients, ranging from 30 to 637 per study, were enrolled in the meta-analysis. There were 1,218 patients treated with DEB + BMS; whereas, 347 were treated with BMS; 1,028 with DES; and 32 with POBA. The mean age of patients recruited was 65 years; and all of the studies had a majority of male patients. Studies recruited from different patient populations. In the trial by Ali and colleagues (31), all

patients were diabetic; whereas, in trials conducted by Besic *et al.* (23) and Poerner *et al.* (25) all patients were hypertensive. Data for each trial are detailed in *Table 2*.

Risk of bias analysis revealed high-risk bias in open-label studies (17,22,27) and incomplete outcome data (25,27,30) where greater than 15% of patients were lost to follow-up (*Table 3*).

LLL

In subset analyses, DEB + BMS compared more favourably to POBA with a statistically significant difference observed for LLL [MD =–0.39; (–0.67 to –0.11); P=0.006]. DEB + BMS also had a significantly lower rate of LLL compared to the BMS group [MD =–0.27; (–0.45 to –0.10); P=0.002]. When compared to the DES group, the DEB + BMS group had an increased LLL and therefore was significantly less effective than DES [MD =0.12; (0.03 to 0.22); P=0.01] (*Figure 2*).

Binary restenosis

In subset analyses, risk of binary restenosis in the DEB + BMS group was significantly lower compared to the POBA group [RR =0.20; (0.05 to 0.85); P=0.03]. This was also seen in the DEB + BMS and DES groups, where binary restenosis was significantly lower in the former mode of intervention [RR =1.89; (1.13 to 3.18); P=0.02]. There was no statistically significant difference in binary restenosis, however, between the DEB + BMS and BMS groups [RR =0.44; (0.18 to 1.06); P=0.07] (*Figure 3*).

TLR

Compared to the BMS group, the DEB + BMS group had a significantly lower need for TLR [RR =0.65; (0.44 to 0.97); P=0.04]. The need for TLR, on the other hand, was higher in the DEB + BMS group compared to the DES group although this did not reach statistical significance [RR =1.57; (0.94 to 2.62); P=0.08] (*Figure 4*).

MACE

Definitions of MACE had slight variations across the 17 studies within this review. However, they were still interpreted under one global outcome. When compared to the BMS alone group, DEB + BMS had a significantly more favourable outcome (lower rate of MACE) [RR =0.64;

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│  Records identified     │        │  Additional records     │
│  through EMBASE,        │        │  identified through      │
│  MEDLINE & PubMed       │        │  other sources           │
│  searching              │        │  (n=8)                   │
│  (n=598)                │        │                          │
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              │  Records after          │
              │  duplicates removed     │
              │  (n=405)                │
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              │  Records screened       │
              │  (n=405)                │
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Records excluded
(n=371)

- ❖ Observational (n=133) (case-control, cohort, registry)
- ❖ Irrelevant (n=141)
- ❖ Review (n=56)
- ❖ Systematic review (n=2)
- ❖ Meta-analysis (n=10)
- ❖ Case Report (n=12)
- ❖ Animal model (n=9)
- ❖ Study protocol (n=2)
- ❖ Non-randomised (n=5)
- ❖ Commentary (n=1)

34 trials were included after review of title and abstract

Records excluded
(n=17)

- ❖ Sequential-order studies (n=2)
- ❖ Study design (n=1)
- ❖ Irrelevant (n=1)
- ❖ Study Protocol (n=1)
- ❖ Use of EPC stents (n=4)
- ❖ Follow-up studies (n=4)
- ❖ Sub-studies (n=4)

17 trials were included after review of full text

Figure 1 Study selection process. EPC, endothelial progenitor cell-capturing stent.

(0.46 to 0.90); P=0.010]. However, even though the rate of MACE was higher in the DEB + BMS group compared to the DES group, there was no statistically significant difference [RR =1.39; (0.96 to 2.01); P=0.08] (*Figure 5*).

MI

There was no significant differences reported between

the DEB + BMS groups and BMS or DES groups for MI [RR =0.66; (0.19 to 2.29); P=0.51]; [RR =1.30; (0.60 to 2.84, 95% CI); P=0.51] (*Figure 6*).

Death

There was also no significant differences reported between the DEB + BMS groups and BMS or DES groups for death

Table 1 Study characteristics

Study	Publication year	Comparators	Randomisation	Device type DEB	Device type Control(s)	Indication	Primary endpoint	Bare metal stenting (%)	Follow up (months) Angiographic	Follow up (months) Clinical
Chae et al. (17)	2017	(DEB + BMS) vs. DES	1:1	SeQuent Please	Coroflex blue BMS, Resolute Integrity DES	Acute coronary syndrome	LLL	100	9	12
PEPCAD-BIF (18)	2016	DEB vs. POBA	1:1	SeQuent Please	POBA	Bifurcation	LLL	15.6	9	NR
BELLO (19, 20)	2012/2015	DEB vs. DES	1:1	IN.PACT Falcon	Taxus DES	Small vessel disease	LLL	20.2	6	24
Żurakowski et al. (21)	2015	(BMS + DEB) vs. DES	1:1	SeQuent Please	Coroflex BMS, Coroflex Please DES	Symptomatic heart disease	LLL	100	9	9
IN.PACT CORO (22)	2015	BMS vs. (DEB + BMS)	1:2	IN.PACT Falcon	Skylor BMS	De novo simple lesions	Neointimal hyperplasia	100	6	12
Besic et al. (23)	2015	(BMS + DEB) vs. BMS	1:1	Elutax + SeQuent Please	NR	NSTEMI	LLL and ISR	100	6	6
Touchard et al. (24)	2015	(DEB + BMS) vs. DES	1:1	NR	NR	STEMI	LLL	100	9	12
Poerner et al. (25)	2014	(BMS + DEB) vs. DES	1:1	SeQuent Please	Coroflex blue BMS, Xience V DES	Native coronary lesion	LLL	100	6	6
BABILON (26)	2014	(DEB + BMS) vs. DES	1:1	SeQuent Please	Coroflex blue BMS, Xience V DES	Bifurcation	LLL	100	9	24
Liistro et al. (27)	2013	(DEB + BMS) vs. DES	1:1	Elutax-II	Xience DES, Prokinetic BMS	De novo coronary artery stenosis	Binary angiographic restenosis	100	9	9
Clever et al. (28)	2013	BMS vs. (DEB + BMS) vs. DES	1:1:1	NR	Coroflex blue BMS, Cypher DES	De novo lesions	Endothelial function, coronary flow reserve & velocity	100	9	9
Stella et al. (29)	2012	(DEB + BMS) vs. BMS DES	1:1:1	Dior-I	Taxus Liberté DES, Liberté BMS	Bifurcation	LLL	100	6	12

Table 1 (*continued*)

Table 1 (*continued*)

Study	Publication year	Comparators	Randomisation	Device type DEB	Device type Control(s)	Indication	Primary endpoint	Bare metal stenting (%)	Follow up (months) Angiographic	Follow up (months) Clinical
DEB-AMI (30)	2012	(DEB + BMS) vs. BMS vs. DES	1:1:1	Dior-II	Taxus DES, Genius Magic BMS	STEMI	LLL	100	6	6
Ali et al. (31)	2011	(DEB + BMS) vs. DES	1:1	SeQuent Please	Coroflex Blue BMS, Taxus DES	De novo lesions in diabetics	LLL	100	9	9
PICCOLETO (32)	2010	DEB vs. DES	1:1	Dior-I	Taxus DES	Small vessel disease	Diameter stenosis	36.0	6	9
Herdeg et al. (33)	2009	(BMS + DEB) vs. BMS vs. DES	1:1:1	GENIE Acrostak	Taxus Des, Multi-Link BMS	De novo lesions	LLL	100	6	6
Hamm et al. (34)	2009	(DEB + BMS) vs. DES	1:1	Coroflex DEBlue	CoCr BMS, Cypher DES	Stable/unstable angina	LLL	100	9	9

BMS, bare-metal stent; DEB, drug-eluting balloon; DES, drug-eluting stents; ISR, in-stent restenosis; LLL, late lumen loss; NR, not reported; NSTEMI, non ST-elevated myocardial infarction; POBA, plain-old balloon angioplasty; STEMI, ST-elevated myocardial infarction.

[RR =0.20; (0.02 to 1.70); P=0.14]; [RR =1.43; (0.45 to 4.52); P=0.54] (*Figure 7*).

Stent thrombosis

Stent thrombosis out of all the outcomes had the lowest incident rate. No statistically significant difference was reported in the DEB + BMS group versus control [RR =1.85; (0.84 to 4.08); P=0.13]. This was also the case for DEB + BMS compared with BMS alone and DES alone [RR =4.10; (0.46 to 36.40); P=0.21]; [RR =1.64; (0.70 to 3.83); P=0.26] (*Figure 8*).

Subgroup analysis

As part of the subgroup analysis, 'DEB-only' interventions were compared with DES. In terms of LLL, DEB-only had no statistically significant difference to DES [MD =–0.12; (–0.25 to 0.01); P=0.06]. This was also seen in binary restenosis, MACE, TLR, MI and death; binary restenosis— [RR =1.36; (0.31 to 6.04); P=0.69], MACE—[RR =1.15; (0.27 to 4.98); P=0.85], TLR—[RR =1.26; (0.24 to 6.79); P=0.78], MI—[RR =0.65; (0.11 to 3.86); P=0.64] and death—[RR =0.69; (0.12 to 4.17); P=0.69].

Publication bias

Egger's test revealed no evidence of significant publication bias within this meta-analysis (P>0.05). This lack of bias was also substantiated by the symmetrical funnel plot for our primary angiographic endpoint of LLL (*Figure 9*).

Discussion

This is the first meta-analysis to compare DEB with and without BMS to all three management options: POBA, BMS alone and DES for treatment of *de novo* coronary lesions. Of the 17 RCTs included in the study, 14 studies compared DEB + BMS with DES and/or BMS, two studies compared DEB-only to DES and one, DEB alone to POBA.

Findings

The significant findings of this study can be summarised as follows: (I) DES was superior to DEB + BMS in angiographic (LLL) and clinical (binary restenosis) outcomes; (II) DEB + BMS was superior to BMS in LLL and clinical outcomes (MACE, TLR); and (III) DEB-

Table 2 Main trial-level clinical characteristics

Study	Total number of patients and treatment type (N=2,616)				Total randomised	Age	Males, n (%)	DM, n (%)	Smokers, n (%)	HTN, n (%)	DLM, n (%)	Stable angina, n (%)	Unstable angina, n (%)
	DEB + BMS (N=1,218)	BMS (N=347)	DES (N=1,028)	POBA (N=32)									
Chae et al. (17)	90	–	90	–	180	62	132 (73.3)	54 (30.0)	46 (25.6)	65 (36.1)	33 (18.3)	85 (47.2)	48 (26.7)
PEPCAD-BIF (18)	32	–	–	32	64	67	47 (73.4)	23 (35.9)	16 (25.0)	NR	NR	41 (64.1)	15 (23.4)
BELLO (19,20)	90	–	92	–	182	66	143 (78.6)	74 (40.7)	25 (13.7)	147 (80.8)	144 (79.1)	NR	42 (23.1)
Żurakowski et al. (21)	102	–	100	–	202	64	138 (68.3)	45 (22.2)	39 (19.3)	169 (83.7)	108 (53.5)	108 (53.5)	94 (46.5)
IN-PACT CORO (22)	20	10	–	–	30	67	26 (86.7)	0 (0.0)	7 (23.3)	23 (76.7)	24 (80.0)	30 (100.0)	NR
Besic et al. (23)	41	44	–	–	85	66	68 (80.0)	25 (29.4)	27 (31.8)	85 (100.0)	75 (88.2)	NR	33 (38.8)
Touchard et al. (24)	111	112	–	–	223	NR	NR	NR	NR	NR	NR	NR	NR
Poerner et al. (25)	51	–	48	–	90*	69	72 (72.7)	47 (47.5)	NR	99 (100.0)	73 (73.7)	NR	NR
BABILON (26)	52	–	56	–	108	65	70 (64.8)	34 (31.5)	54 (50.0)	67 (62.0)	69 (63.9)	NR	NR
Liistro et al. (27)	59	–	66	–	125	66	107 (85.6)	17 (13.6)	38 (30.4)	50 (40.0)	16 (12.8)	NR	NR
Clever et al. (28)	27	25	25	–	77	66	57 (74.0)	19 (24.7)	13 (16.9)	70 (90.9)	59 (76.6)	NR	15 (19.5)
Stella et al. (29)	40	37	40	–	117	64	85 (72.6)	13 (11.1)	69 (59.0)	67 (57.2)	65 (55.6)	NR	NR
DEB-AMI (30)	50	51	49	–	150	59	124 (82.7)	11 (7.3)	76 (65.0)	50 (33.3)	40 (26.7)	NR	NR
Ali et al. (31)	45	–	39	–	84	61	64 (76.2)	84 (100.0)	22 (26.3)	71 (84.5)	63 (75.0)	NR	10 (11.9)
PICCOLETO (32)	29	–	31	–	60**	68	44 (77.1)	24 (42.1)	NR	41 (71.9)	30 (52.6)	26 (45.6)	NR
Herdeg et al. (33)	67	68	67	–	202	65	157 (77.7)	72 (35.6)	27 (13.4)	176 (87.1)	146 (72.2)	24 (11.9)	NR
Hamm et al. (34)	312	–	325	–	637	66	478 (75.1)	174 (27.4)	381 (56.6)	493 (77.5)	424 (66.6)	471 (74.0)	NR

*, nine patients with >1 suitable lesion were sequentially included in both device groups; **, three patients lost to follow-up straight after randomisation. BMS, bare-metal stent; DEB, drug-eluting balloon; DES, drug-eluting stents; DLM, dyslipidaemia; HTN, hypertension; NR, not reported; POBA, plain-old balloon angioplasty.

Table 3 Risk of bias

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Chae *et al*. (17)	L	0	H	L	L	L	L
PEPCAD-BIF (18)	L	L	L	L	L	L	H
BELLO (19,20)	L	L	L	L	L	L	0
Żurakowski *et al*. (21)	0	L	L	L	L	0	L
IN-PACT CORO (22)	0	0	H	L	L	L	L
Besic *et al*. (23)	0	0	L	0	L	0	0
Touchard *et al*. (24)	0	0	L	0	0	0	0
Poerner *et al*. (25)	0	0	L	L	H	L	0
BABILON (26)	L	0	L	L	L	L	L
Liistro *et al*. (27)	L	L	H	L	H	0	L
Clever *et al*. (28)	0	0	L	L	L	0	H
Stella *et al*. (29)	L	L	L	L	L	0	H
DEB-AMI (30)	L	L	L	L	H	L	H
Ali *et al*. (31)	0	0	L	L	L	L	H
PICCOLETO (32)	L	L	L	L	L	0	0
Herdeg *et al*. (33)	L	L	L	L	L	0	H
Hamm *et al*. (34)	0	0	L	L	L	L	H

Table highlights the various risks of biases present in the seven assessed domains. L, low risk of bias; H, high risk of bias; 0, insufficient/unreported bias.

only approach was superior to POBA for LLL and binary restenosis in bifurcation lesions.

Data interpretation

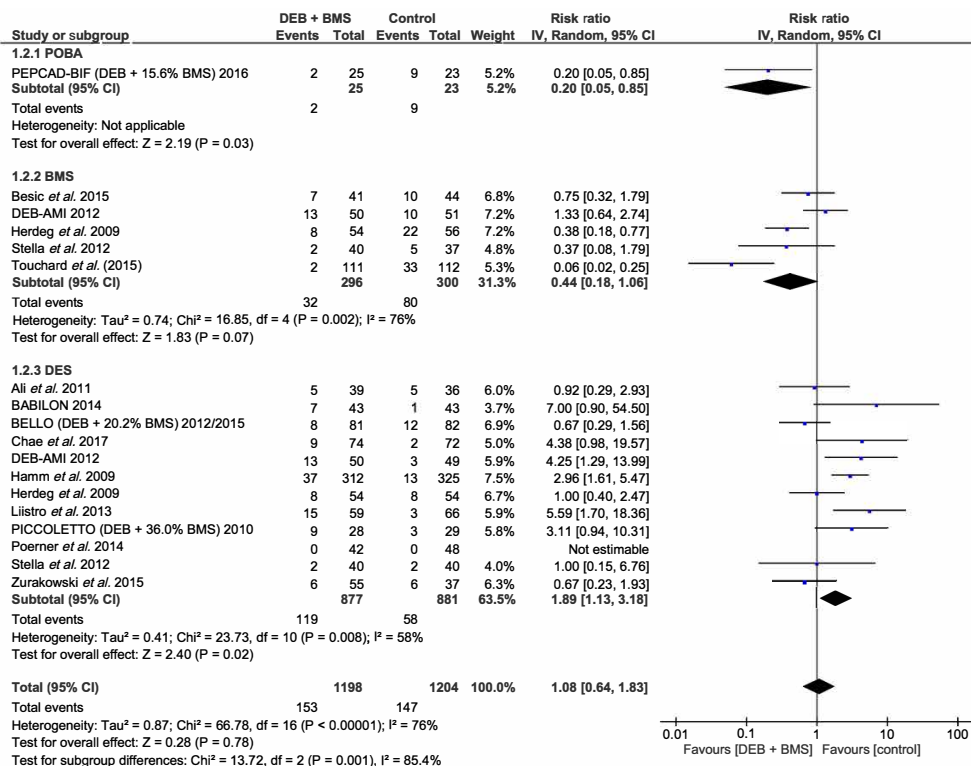The current standard of care for PCI treatment of *de novo* coronary lesions is implantation of a second generation DES (35). However, there is increasing concern about the longer term risk of DES, such as increased bleeding risk with prolonged antiplatelet therapy (10,36). Additional risks include development of ISR and late ST which remain a factor of concern for DES users despite a lower incidence of
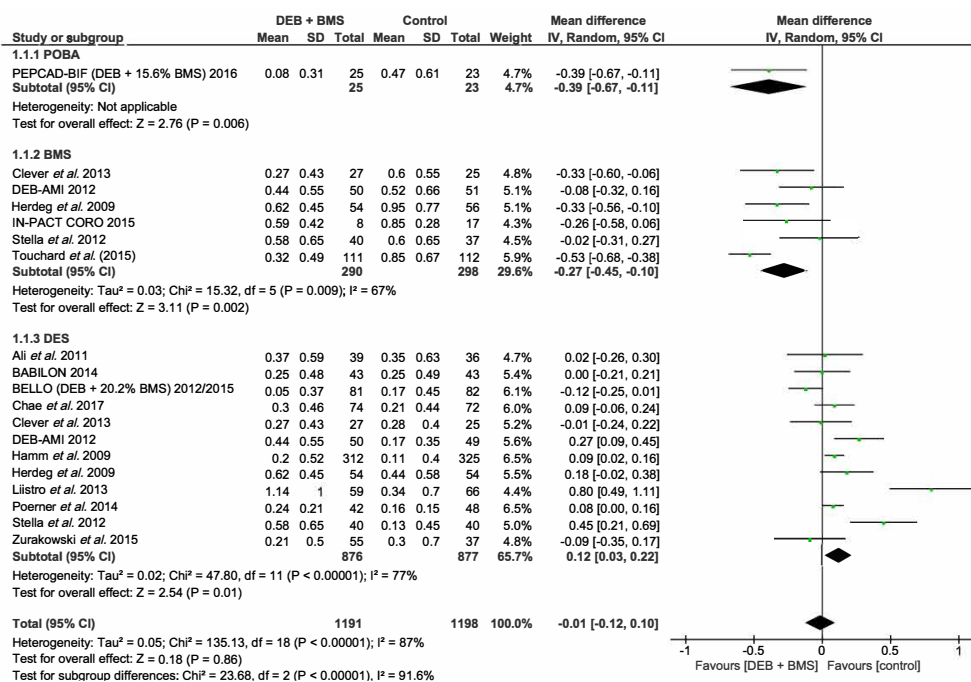
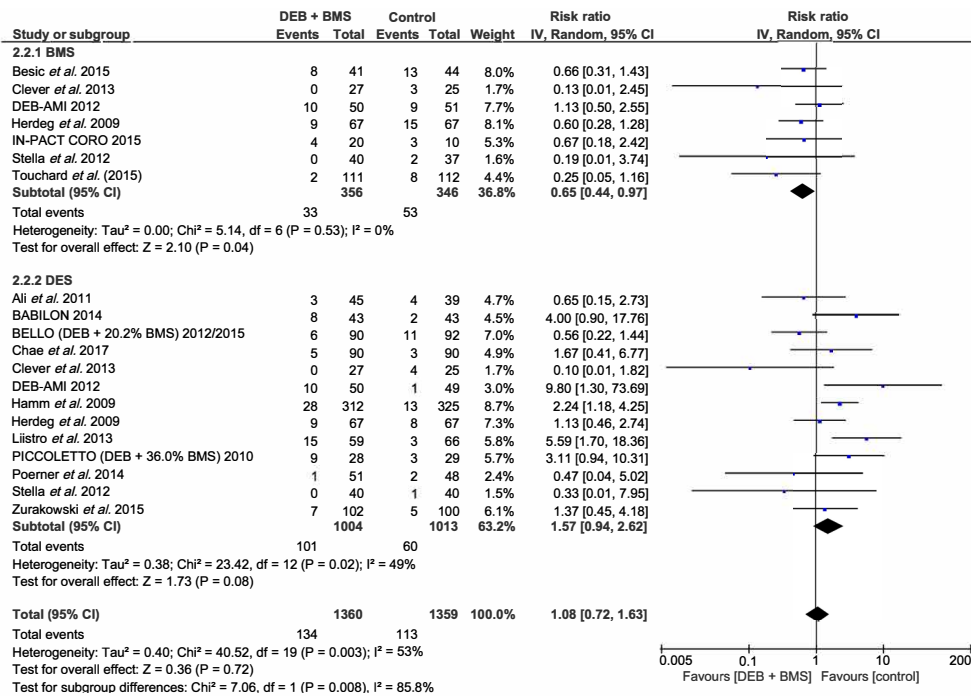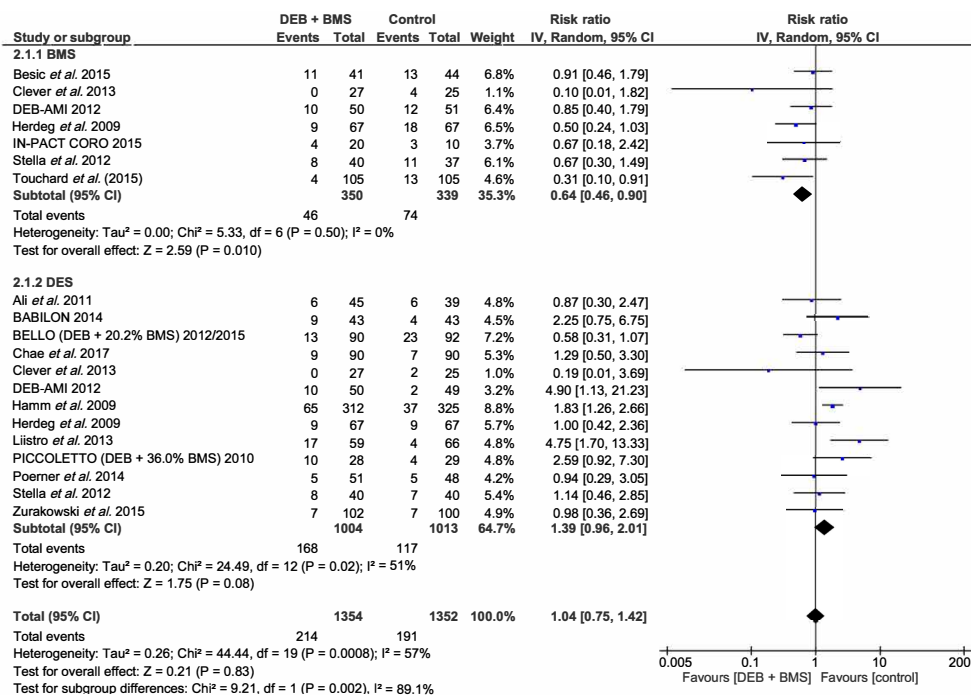**Figure 2** Forest plot of mean differences for late lumen loss. BMS, bare-metal stents; CI, confidence interval; DEB, drug-eluting balloons; DES, drug-eluting stents; POBA, plain-old balloon angioplasty.
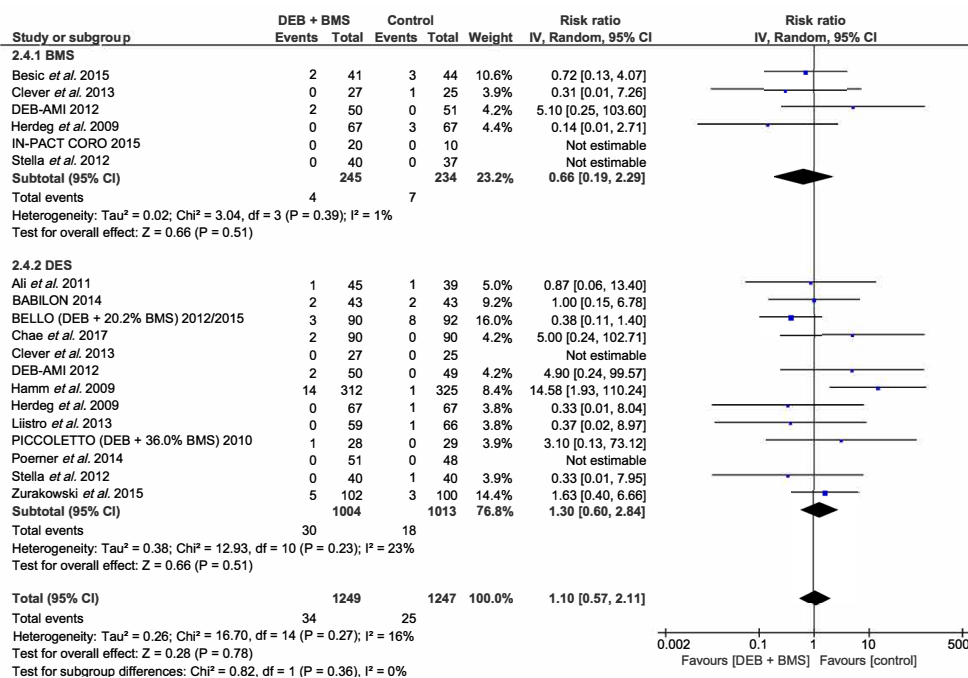

Figure 3 Forest plot of risk ratios (RR) for binary restenosis. BMS, bare-metal stents; CI, confidence interval; DEB, drug-eluting balloons; DES, drug-eluting stents; POBA, plain-old balloon angioplasty.

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Study or subgroup	DEB + BMS		Control		Weight	Risk ratio IV, Random, 95% CI	Risk ratio IV, Random, 95% CI
	Events	Total	Events	Total			
2.2.1 BMS							
Besic *et al.* 2015	8	41	13	44	8.0%	0.66 [0.31, 1.43]	
Clever *et al.* 2013	0	27	3	25	1.7%	0.13 [0.01, 2.45]	
DEB-AMI 2012	10	50	9	51	7.7%	1.13 [0.50, 2.55]	
Herdeg *et al.* 2009	9	67	15	67	8.1%	0.60 [0.28, 1.28]	
IN-PACT CORO 2015	4	20	3	10	5.3%	0.67 [0.18, 2.42]	
Stella *et al.* 2012	0	40	2	37	1.6%	0.19 [0.01, 3.74]	
Touchard *et al.* (2015)	2	111	8	112	4.4%	0.25 [0.05, 1.16]	
Subtotal (95% CI)		356		346	36.8%	0.65 [0.44, 0.97]	
Total events	33		53				
Heterogeneity: Tau² = 0.00; Chi² = 5.14, df = 6 (P = 0.53); I² = 0%							
Test for overall effect: Z = 2.10 (P = 0.04)							
2.2.2 DES							
Ali *et al.* 2011	3	45	4	39	4.7%	0.65 [0.15, 2.73]	
BABILON 2014	8	43	2	43	4.5%	4.00 [0.90, 17.76]	
BELLO (DEB + 20.2% BMS) 2012/2015	6	90	11	92	7.0%	0.56 [0.22, 1.44]	
Chae *et al.* 2017	5	90	3	90	4.9%	1.67 [0.41, 6.77]	
Clever *et al.* 2013	0	27	4	25	1.7%	0.10 [0.01, 1.82]	
DEB-AMI 2012	10	50	1	49	3.0%	9.80 [1.30, 73.69]	
Hamm *et al.* 2009	28	312	13	325	8.7%	2.24 [1.18, 4.25]	
Herdeg *et al.* 2009	9	67	8	67	7.3%	1.13 [0.46, 2.74]	
Liistro *et al.* 2013	15	59	3	66	5.8%	5.59 [1.70, 18.36]	
PICCOLETTO (DEB + 36.0% BMS) 2010	9	28	3	29	5.7%	3.11 [0.94, 10.31]	
Poerner *et al.* 2014	1	51	2	48	2.4%	0.47 [0.04, 5.02]	
Stella *et al.* 2012	0	40	1	40	1.5%	0.33 [0.01, 7.95]	
Zurakowski *et al.* 2015	7	102	5	100	6.1%	1.37 [0.45, 4.18]	
Subtotal (95% CI)		1004		1013	63.2%	1.57 [0.94, 2.62]	
Total events	101		60				
Heterogeneity: Tau² = 0.38; Chi² = 23.42, df = 12 (P = 0.02); I² = 49%							
Test for overall effect: Z = 1.73 (P = 0.08)							
Total (95% CI)		1360		1359	100.0%	1.08 [0.72, 1.63]	
Total events	134		113				
Heterogeneity: Tau² = 0.40; Chi² = 40.52, df = 19 (P = 0.003); I² = 53%							
Test for overall effect: Z = 0.36 (P = 0.72)							
Test for subgroup differences: Chi² = 7.06, df = 1 (P = 0.008), I² = 85.8%							

0.005 0.1 1 10 200
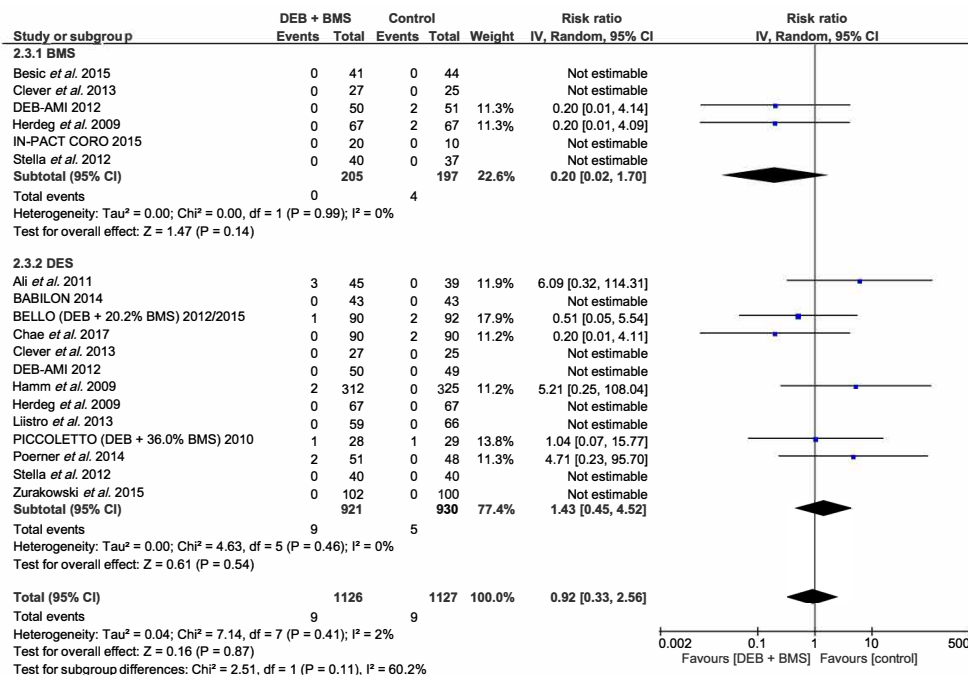Favours [DEB + BMS] Favours [control]

Figure 4 Forest plot of risk ratios (RR) for TLR. BMS, bare-metal stents; CI, confidence interval; DEB, drug-eluting balloons; DES, drug-eluting stents; POBA, plain-old balloon angioplasty; TLR, target lesion revascularization.

Study or subgroup	DEB + BMS		Control		Weight	Risk ratio IV, Random, 95% CI	Risk ratio IV, Random, 95% CI
	Events	Total	Events	Total			
2.1.1 BMS							
Besic *et al.* 2015	11	41	13	44	6.8%	0.91 [0.46, 1.79]	
Clever *et al.* 2013	0	27	4	25	1.1%	0.10 [0.01, 1.82]	
DEB-AMI 2012	10	50	12	51	6.4%	0.85 [0.40, 1.79]	
Herdeg *et al.* 2009	9	67	18	67	6.5%	0.50 [0.24, 1.03]	
IN-PACT CORO 2015	4	20	3	10	3.7%	0.67 [0.18, 2.42]	
Stella *et al.* 2012	8	40	11	37	6.1%	0.67 [0.30, 1.49]	
Touchard *et al.* (2015)	4	105	13	105	4.6%	0.31 [0.10, 0.91]	
Subtotal (95% CI)		350		339	35.3%	0.64 [0.46, 0.90]	
Total events	46		74				
Heterogeneity: Tau² = 0.00; Chi² = 5.33, df = 6 (P = 0.50); I² = 0%							
Test for overall effect: Z = 2.59 (P = 0.010)							
2.1.2 DES							
Ali *et al.* 2011	6	45	6	39	4.8%	0.87 [0.30, 2.47]	
BABILON 2014	9	43	4	43	4.5%	2.25 [0.75, 6.75]	
BELLO (DEB + 20.2% BMS) 2012/2015	13	90	23	92	7.2%	0.58 [0.31, 1.07]	
Chae *et al.* 2017	9	90	7	90	5.3%	1.29 [0.50, 3.30]	
Clever *et al.* 2013	0	27	2	25	1.0%	0.19 [0.01, 3.69]	
DEB-AMI 2012	10	50	2	49	3.2%	4.90 [1.13, 21.23]	
Hamm *et al.* 2009	65	312	37	325	8.8%	1.83 [1.26, 2.66]	
Herdeg *et al.* 2009	9	67	9	67	5.7%	1.00 [0.42, 2.36]	
Liistro *et al.* 2013	17	59	4	66	4.8%	4.75 [1.70, 13.33]	
PICCOLETTO (DEB + 36.0% BMS) 2010	10	28	4	29	4.8%	2.59 [0.92, 7.30]	
Poerner *et al.* 2014	5	51	5	48	4.2%	0.94 [0.29, 3.05]	
Stella *et al.* 2012	8	40	7	40	5.4%	1.14 [0.46, 2.85]	
Zurakowski *et al.* 2015	7	102	7	100	4.9%	0.98 [0.36, 2.69]	
Subtotal (95% CI)		1004		1013	64.7%	1.39 [0.96, 2.01]	
Total events	168		117				
Heterogeneity: Tau² = 0.20; Chi² = 24.49, df = 12 (P = 0.02); I² = 51%							
Test for overall effect: Z = 1.75 (P = 0.08)							
Total (95% CI)		1354		1352	100.0%	1.04 [0.75, 1.42]	
Total events	214		191				
Heterogeneity: Tau² = 0.26; Chi² = 44.44, df = 19 (P = 0.0008); I² = 57%							
Test for overall effect: Z = 0.21 (P = 0.83)							
Test for subgroup differences: Chi² = 9.21, df = 1 (P = 0.002), I² = 89.1%							

0.005 0.1 1 10 200
Favours [DEB + BMS] Favours [control]

Figure 5 Forest plot of risk ratios (RR) for MACE. BMS, bare-metal stents; CI, confidence interval; DEB, drug-eluting balloons; DES, drug-eluting stents; MACE, major adverse cardiac events; POBA, plain-old balloon angioplasty.

Figure 6 Forest plot of risk ratios (RR) for MI. BMS, bare-metal stents; CI, confidence interval; DEB, drug-eluting balloons; DES, drug-eluting stents; MI, myocardial infarction; POBA, plain-old balloon angioplasty.

Figure 7 Forest plot of risk ratios (RR) for death. BMS, bare-metal stents; CI, confidence interval; DEB, drug-eluting balloons; DES, drug-eluting stents; POBA, plain-old balloon angioplasty.

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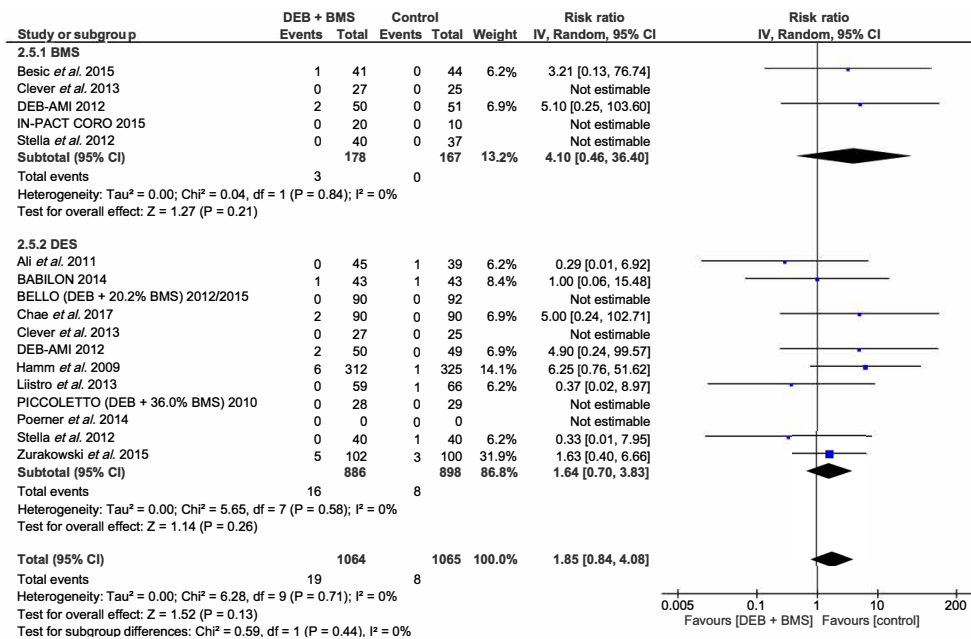
Figure 8 Forest plot of risk ratios (RR) for stent thrombosis. BMS, bare-metal stents; CI, confidence interval; DEB, drug-eluting balloons; DES, drug-eluting stents; POBA, plain-old balloon angioplasty.
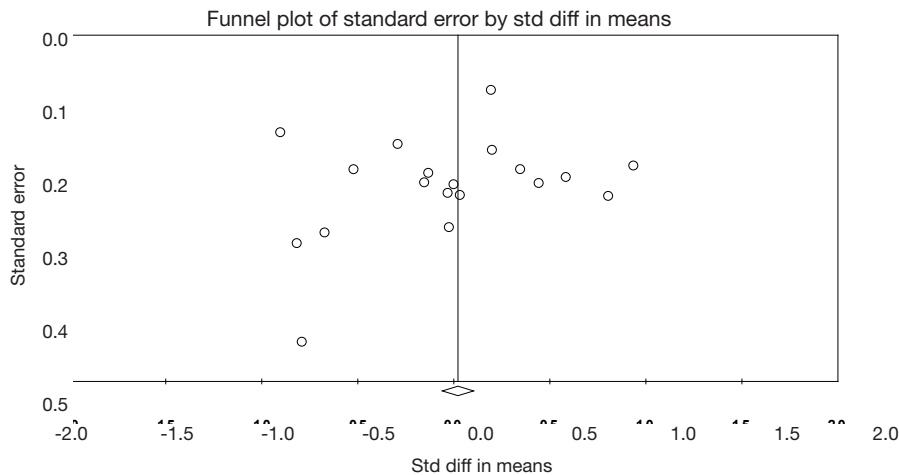
Figure 9 Funnel plot for publication bias using the primary angiographic endpoint of late lumen loss.

disease compared to BMS (37,38). DEB, advocated for their ability to reduce DAPT and promote homogeneous drug transfer have been proposed as an alternative to DES (39). However, drawbacks such as dissection and acute elastic recoil means that DEB treatment is often seen accompanied with BMS (39).

In this analysis, it was shown that DEB + BMS were significantly inferior to DES in clinical and angiographic

outcomes. Apparent lack of efficacy of DEB + BMS compared to DES could be explained in part by the high use of first-generation paclitaxel based DEB which are likely to be inferior to DES in terms of drug delivery. Also, the relatively short contact time between DEB and vessel wall could result in a greater 'wash-off' effect than with DES. A study investigating DEB techniques found optimal concentrations of paclitaxel in the vessel wall following

short inflation times of 30 to 45 seconds (40). The study which compared 1st and 2nd generation DIOR balloons in a porcine model also found higher tissue concentrations of drug and reduced arterial wall injury with 2nd generation DEBs (40). Coupling of 2nd generation DEBs with a shorter inflation time could therefore improve release kinetics and safety in future studies.

Different generation DES were also used. Eight trials used 1st generation DES, whilst five used 2nd generation devices. The TAXUS Liberté paclitaxel-eluting stent was the most common followed by the Xience V everolimus-eluting stent. A meta-analysis which compared 1st and 2nd generation DES found that 1st generation sirolimus-eluting stents compared well in efficacy to 2nd generation everolimus/zotarolimus eluting stents in TLR, MACE and restenosis (41,42); whereas, 2nd generation everolimus-based stents had better clinical outcomes (MI and ST rates) (41,42). Thus, it cannot be ruled out that some heterogeneity within results arose from a lack of uniformity in the DEB and DES employed.

Implications of DEB-only approach

DEB-only intervention is currently accepted in routine practice for treatment of ISR, re-restenosis or for side branch POBA. There may also be other niche indications including high-risk restenotic lesions such as bifurcations, long lesions, diffuse disease in diabetic patients and small vessel disease (43). The PEPCAD-BIF trial was the first randomised controlled trial to explore DEB-only use in side branch and/or distal main branch lesions (18). The trial showed that for bifurcations, DEB alone had a statistically significant reduction in LLL and binary restenosis (18). Whilst not having been directly compared to DES, the DEB-only approach is attractive for bifurcations owing to preservation of vessel patency and avoidance of carina shift—a phenomenon largely responsible for side branch occlusion following DES treatment (16,18). In addition, low rates of restenosis and TLR seen in the PEPCAD-BIF trial also suggested some promise for the DEB-only treatment of bifurcation lesions (18). However, more randomised controlled trials comparing DES and DEB alone are needed to determine whether these theoretical benefits translate to better angiographic and clinical outcomes.

Small vessel disease is another area where the DEB-only strategy has shown potential because short drug transfer time and lack of foreign body implantation reduces higher rates of neointimal proliferation and inflammatory response found in smaller-calibre vessels treated with BMS treatment (44). This was substantiated by our findings which suggested that DEB alone performed comparably to the current mainstay of treatment, DES, for both clinical and angiographic outcomes. It should be noted, however, that our meta-analysis only presented data from two studies comparing DES and DEB-alone (BELLO and PICCOLETO) since randomised controlled trials concerning this topic were scarce.

Despite these two trials portraying DEB-alone in a favourable light in small vessel disease, data from the study endpoints were rather heterogeneous. This could be explained by the use of IN.PACT Falcon, a 2nd generation DEB in the BELLO trial and DIOR I, a 1st generation DEB in the PICCOLETO trial. Furthermore, pre-dilatation rates were very low in the PICCOLETO trial compared with the BELLO trial (25% versus 96.8% respectively) (19,32). This is an important difference as pre-dilatation is a necessary prerequisite for optimal drug absorption through creation of micro-channels in the plaque and vessel wall (45). Importantly in this regard, studies did not also report the use of cutting or scoring balloon which may be important in improving drug access to the vessel wall. Experience has indicated that adequate and appropriate lesion preparation is essential when using DEB. It is important therefore that in future studies there is a standardised approach to lesion preparation, use of adjunctive technology such as cutting or scoring balloon and an adequate description of the methodology since it is possible that this will have an important effect on the efficacy of the DEB technique. Hence, the DEB-only approach with the right variant and preparation technique could show even more promise for small vessel lesions.

Limitations

This meta-analysis had several limitations. For example, a large majority of studies had a small sample size and results were moderately heterogeneous. However, this was likely the result of different generations of DEB and DES used as well as different study design comparators such as DES, POBA and BMS. For this reason, stratified and subgroup analyses were taken into account to further isolate sources of variability. Secondly, 14 trials reported clinical outcomes from relatively short follow-up periods (≤1 year) which may have failed to capture episodes of late stent thrombosis and thus influenced results. As already mentioned, the latest generations of DES and DEB were not universally studied

and therefore results should be interpreted with caution in the context of latest devices in current clinical use. Additionally, any future studies of DEB must be against the latest generation of DES so that a valid comparison can be made against the technology in current clinical use. Finally, some studies were susceptible to industry bias owing to author involvement in relevant device companies such as B. Braun, Boston Scientific Medtronic and Eurocor GmbH (18,21,22,28,29,31,33). Similarly, conflicts of interest may have arisen due to these companies funding studies which investigated their own products (18,21,26,28,30,31,33,34).

Conclusions

Overall, the results of this meta-analysis found that DEB in combination with BMS was not superior to DES in both clinical and angiographic outcomes for *de novo* coronary lesions. Compared to BMS alone, however, the combination of DEB and BMS was superior in LLL and MACE. The strategy of DEB alone has shown some promise. For example, DEB-only studies performed comparably to DES within the setting of small coronary vessels. In addition, the approach has shown early success in bifurcation lesions with DEB alone. These findings suggest that for major *de novo* coronary lesions, DEB + BMS should not be considered for treatment unless in patients who have significant contraindications to DES. Whilst the result from DEB-alone may be advantageous in cases of high-risk restenotic lesions such as small vessel disease following successful pre-dilatation and bifurcation lesions of certain classifications (Medina type 0, X, X) we conclude that DEB are still not a widely accepted modality of treatment.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: This study was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

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