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ORIGINAL PAPER

Drug-coated balloon versus drug-eluting stent for treating de novo large vessel coronary artery disease: a systematic review and meta-analysis of 13 studies involving 2888 patients

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Abstract

Introduction Drug-coated balloon (DCB) is an established treatment option for in-stent restenosis and small vessel, de novo, coronary artery disease (CAD). Although the use of this tool is increasing in everyday practice, data regarding performance in the treatment of de novo, large vessel CAD (LV-CAD) is still lacking. A systematic review and meta-analysis were conducted to evaluate the efficacy and safety of DCB versus drug-eluting stent (DES) in this setting.

Methods A comprehensive literature search was performed including Medline, Embase, and Cochrane electronic databases up to January 24, 2024, for studies which compared the efficacy and safety of DCB versus DES in the treatment of de novo lesions in large vessels (≥2.5 mm), reporting at least one clinical outcome of interest (PROSPERO ID: CRD42023470417). The analyzed outcomes were cardiovascular death (CVD), myocardial infarction (MI), target lesion revascularization (TLR), all-cause death (ACD), and late lumen loss (LLL) at follow-up. The effect size was estimated using a random effects model as risk ratio (RR) and mean difference (MD) and relative 95% confidence interval (CI).

Results A total of 13 studies (6 randomized controlled trials and 7 observational studies) involving 2888 patients (DCB $n=1334$; DES $n=1533$) with de novo LV-CAD were included in this meta-analysis following our inclusion criteria. No differences were observed between DCB and DES in terms of CVD (RR 0.49; 95% CI [0.23–1.03]; $p=0.06$), MI (RR 0.48; 95% CI [0.16–1.45]; $p=0.89$), TLR (RR 0.73; 95% CI [0.40–1.34]; $p=0.32$), ACD (RR 0.78; 95% CI [0.57–1.07]; $p=0.12$), and LLL (MD −0.14; 95% CI [−0.30 to 0.02]; $p=0.10$) at follow-up. DES proved a higher mean acute gain versus DCB [1.94 (1.73, 2.14) vs 1.31 (1.02, 1.60); $p=0.0006$].

Conclusion Our meta-analysis showed that DCB PCI might provide a promising option for the management of selected, de novo LV-CAD compared to DES. However, more focused RCTs are needed to further prove the benefits of a "metal-free" strategy in this subset of CAD.

Rodolfo Caminiti and Giampiero Vizzari contributed equally to this manuscript as a first author.

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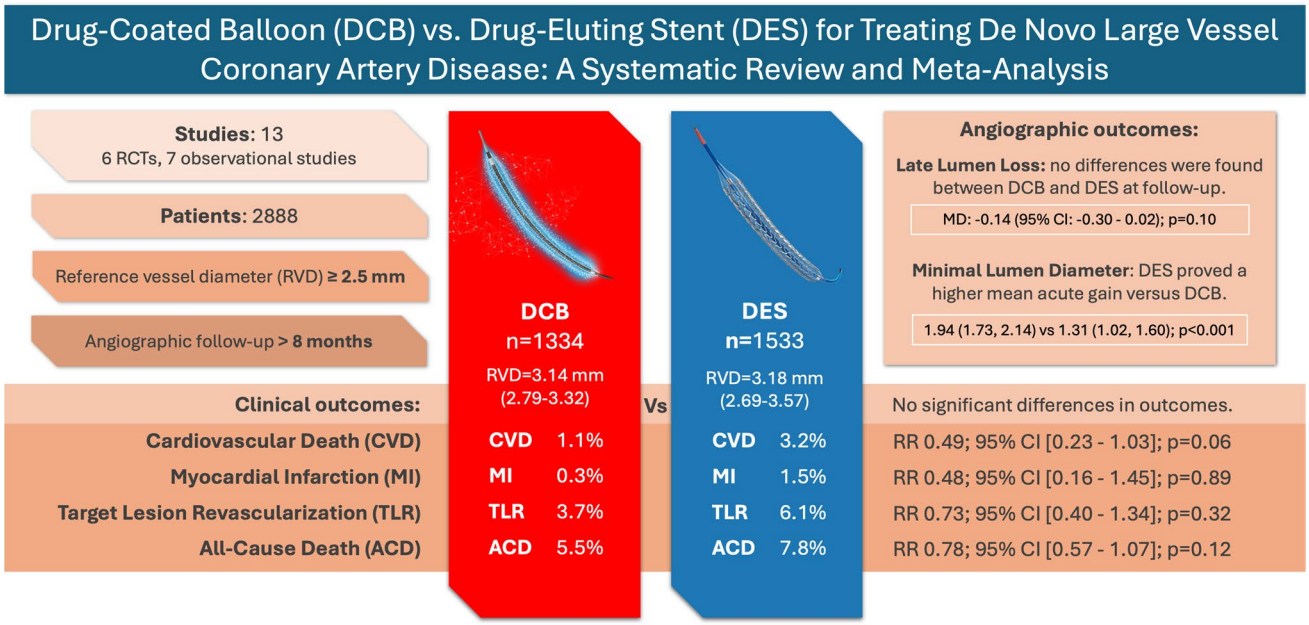
Graphical Abstract



Keywords Drug-coated balloon · Drug-eluting stent · De novo · Coronary artery disease · Large vessel disease · Angioplasty

Abbreviations

ACD	All-cause death
CAD	Coronary artery disease
CI	Confidence interval
CVD	Cardiovascular death
DAPT	Dual antiplatelet therapy
DCB	Drug-coated balloon
DES	Drug-eluting stent
ISR	In-stent restenosis
LLL	Late lumen loss
LV	Large vessel
MACE	Major adverse cardiovascular events
MD	Mean difference
MI	Myocardial infarction
MLD	Minimal lumen diameter
PCB	Paclitaxel-coated balloon
PCI	Percutaneous coronary intervention
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses
QCA	Quantitative coronary analysis
RR	Risk ratio
RVD	Reference vessel diameter
SCB	Sirolimus-coated balloon
SVD	Small vessel disease
TLF	Target lesion failure
TLR	Target lesion revascularization
ULM	Unprotected left main

Introduction

Drug-eluting stent (DES) implantation represents the gold standard treatment strategy for de novo CAD [1]. However, DES is still associated with a non-negligible rate of target lesion failure (TLF) at follow-up mainly due to device-related phenomena (e.g., polymer-associated inflammation of the vessel wall, poor/excessive endothelialization, incomplete stent expansion/apposition) [2–4]. In this scenario, a drug-coated balloon (DCB) is emerging as a fashionable alternative to lower total stent length during PCI while preserving the anatomy and physiology of the vessel wall. A proper lesion preparation is paramount to achieve an optimal DCB PCI in order to avoid acute recoil and favor the correct penetration of the drug inside the vessel wall [5]. Current European guidelines recommend DCB PCI for the treatment of in-stent restenosis (ISR) with a class IA recommendation, while many clinical trials, observational studies, and meta-analysis confirm its efficacy and safety in the treatment of de novo, small vessel disease (SVD) [6–8]. DCB PCI may also be considered a viable option in specific settings (e.g., high bleeding risk patients) or in association with DES in case of diffuse (e.g., long lesion/true bifurcation) CAD involving SVD [9–11].

Although DCBs use for the treatment of de novo CAD is rapidly increasing, limited data is known about the performance of a "metal-free" approach for treating de novo large vessel CAD (LV-CAD). The aim of this meta-analysis is

to evaluate the efficacy and safety of DCBs compared with DES in this setting of CAD.

Methods

Data sources and searches

We systematically searched the Medline, Embase, and Scopus electronic databases for studies published until 24 January 2024, focusing on those comparing the efficacy and safety of DCB and DES in the treatment of de novo LV-CAD with a reference vessel diameter (RVD) ≥ 2.5 mm and reporting at least one clinical outcome of interest. Two investigators (R.C. and G.V.) independently conducted searches using the following terms: "drug eluting stent", "drug coated balloon", "myocardial infarction". Detailed information on our literature search strategy is available in the Supplementary Appendix in the Expanded Methods.

Study selection

The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement for reporting systematic reviews and meta-analyses was used in this study. The predefined protocol was registered to the international prospective registry of systematic reviews (POSPERO ID: CRD42023470417). Studies had to meet the following criteria in order to be included in the analysis: (1) adult (≥ 18 years) population, (2) head-to-head (randomized or propensity match) comparison between DCB and DES, (3) ≥ 6 months clinical and/or angiographic follow-up available, and (4) one or more clinical outcomes of interest reported (e.g., cardiovascular death, myocardial infarction, all-cause death). Case reports, editorials, reviews, expert opinions, and studies not published in English language were excluded.

Data extraction and quality appraisal

Two investigators (R.C and G.V) extracted data from each trial using standardized protocol and reporting forms. Two reviewers (R.C and G.V) independently assessed quality items, and disagreements were resolved by consensus. The Newcastle–Ottawa Quality Assessment Scale for cohort studies and the Cochrane Risk of Bias tool for randomized clinical trials (RCTs) were used by two investigators (R.C and G.V) to assess the quality of each study.

Study endpoints

Cardiovascular death (CVD) was defined as death resulting from cardiovascular causes. Myocardial infarction (MI) was defined based on the World Health Organization definition [12]. Target lesion revascularization (TLR) was defined as a repeat PCI within the stented or DCB-treated segment or bypass surgery of the target vessel performed for restenosis or other complication of the target lesion. All-cause death (ACD) was defined as death resulting from cardiovascular and other causes. The angiographic endpoint was late lumen loss (LLL) obtained by quantitative coronary angiography (QCA) and defined as minimal lumen diameter (MLD) immediately after PCI minus MLD at follow-up angiography. All endpoints were commonly defined according to the Academic Research Consortium definitions [13].

Statistical analysis

Descriptive statistics are presented as mean and standard deviation (SD) for continuous variables, or number of cases (*n*) and percentage (%) for dichotomous and categorical variables. The Mantel–Haenszel risk ratio (RR) model was used to summarize the data for binary outcomes between treatment arms. For continuous variables, summary estimates and 95% confidence intervals (CI) were reported as the standardized mean difference. Heterogeneity between studies was assessed using the Chi2, Tau2, and Higgins-I2 statistics, and random effects models by DerSimonian and Laird were used. Subgroup analyses were performed including only RCT studies recruiting only patients with acute coronary syndrome and with SeQuent Please/SeQuent Please NEO balloon.

Publication bias was assessed using funnel plots. Statistical analysis was performed with ReviewManager (RevMan) (computer program) version 5.4.1, Copenhagen, Denmark: Nordic Cochrane Centre, The Cochrane Collaboration, 2020.

Results

Study selection and baseline characteristics

Among 597 screened articles, 53 full texts were retrieved and reviewed for possible inclusion; a total of 13 studies fulfilled the selection criteria and were included in the final analysis (Fig. 1).

The studies enrolled $n = 2888$ patients (Group DCB, $n = 1334$ patients; Group DES, $n = 1533$ patients). Overall, 75.3% (95% CI, 71.3–79.4%) of patients were male with an average age of 63.2 years (95% CI, 57.3–70.5). The indication for revascularization was in 60.2% (95% CI, 38.7–85.1%) of cases of acute coronary syndrome (ACS). The left anterior descending (LAD) artery was treated in the majority of cases (47.1%; 95% CI, 35.8–57.9%), followed by the right coronary artery (25.5%; 95% CI, 19.9–33.7%), left circumflex artery (18.1%; 95% CI, 11.5–23.3%), and unprotected left main (ULM) (9.3%; 95% CI, 6.1–23.2%).

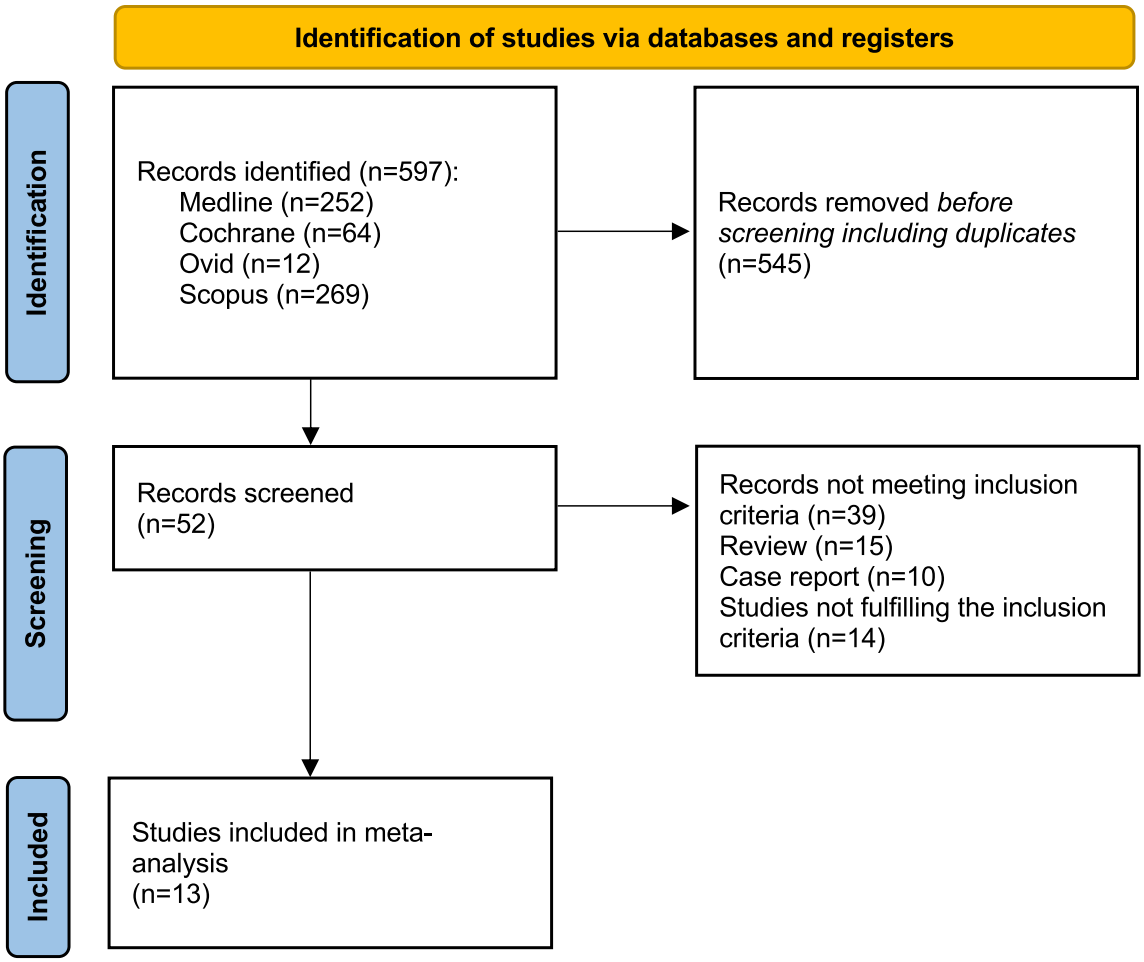


Fig. 1 Evidence search and selection of Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA)

The mean lesion length was 22.8 mm (95% CI, 15.3–40.2 mm) in the DCB and 27.9 mm (95% CI, 18.1–45.6 mm) in the DES group. The mean reference vessel diameter (RVD) was 3.14 mm (95% CI, 2.79–3.32 mm) in the DCB and 3.18 mm (95% CI, 2.69–3.57 mm) in the DES group.

All studies used paclitaxel-coated balloons (PCB) except one in which a sirolimus-coated balloon (SCB) was also used.

Further details on baseline characteristics and clinical and angiographic follow-up time of the study population are reported in Table 1.

Endpoints

Twelve studies reported clinical follow-up data on CVD, MI, and TLR [14–25]. No differences were found between DCB and DES for the risk of CVD [1.1% vs 3.2%; RR, 0.49; 95% CI, 0.23–1.03; $p=0.06$; $I^2=0\%$] (Fig. 2); MI [0.3% vs 1.5%; RR, 0.48; 95% CI, 0.16–1.45; $p=0.89$; $I^2=0\%$] (Fig. 3), and TLR [3.7% vs 6.1%; RR, 0.73; 95% CI, 0.40–1.34; $p=0.32$; $I^2=27\%$] (Fig. 4).

Eight studies reported data on ACD [15, 17–21, 25, 26]. At follow-up, no differences were found between DCB and DES for the risk of ACD [5.5% vs 7.8%; RR, 0.78; 95% CI, 0.57–1.07; $p=0.12$; $I^2=0\%$] (Fig. 5).

In terms of angiographic results, nine studies reported data on LLL [14, 16–20, 22–24]. No differences were found between DCB and DES for LLL at follow-up [MD, − 0.14; 95% CI, − 0.30 to 0.02; $p=0.10$; $I^2=91\%$] (Fig. 6). Finally, six studies reported data on MLD before and after PCI [16–20, 24]. DES proved a higher mean acute gain versus DCB [1.94 (1.73, 2.14) vs 1.31 (1.02, 1.60); $p=0.0006$; $I^2=91.6\%$] (Fig. 7).

Subgroup analysis including only RCTs

Six RCTs reported data on CVD, MI, and TLR [14, 20–24]. At follow-up, no differences were found between DCB and DES for

Table 1 Main features of the studies included in the meta-analysis

Author			Nijhoff et al	Nishiyama et al	Gobic et al	Her et al	Vos et al	Scheller et al	Iwasaki et al	Xue Yu et al	Xiaojiao Hao et al	Merino-poulos et al	Nakamura et al	Gunawardena T.D. et al	Gitto et al
Year			2015	2016	2017	2018	2019	2019	2020	2021	2021	2022	2023	2023	2023
Study type			Nonrandomized, single-center (arm of the randomized DEB-AMI trial)	A simple randomization, open-label, single-center	RCT	Prospective, observational registry, single-center	RCT (the REVELATION)	RCT (the PEPCAD NSTEMI)	Retrospective, single-center, nonrandomized	RCT	RCT	Retrospective, single-center, nonrandomized	Retrospective, single-center, nonrandomized	Retrospective, single-center, nonrandomized	Retrospective, 2-center, nonrandomized
Total patients, *n*			40	60	75	151	120	210	165	170	80	1237	154	148	278
DCB patients, *n*			40	27	38	78	59	104	69	84	38	544	73	41	139
DES patients, *n*			49	33	37	73	61	51	88	79	42	693	81	107	139
Primary endpoint			LLL	MLD, LLL	MACE, LLL	LLL	MLD, LLL	TLF (cardiac death, unknown death, MI, TLR)	MACE	LLL, MACE	LLL	All-cause death	Cardiac death, MI, TLR	All-cause death	TLF (cardiac death, MI, TLR)
Definition of MACE			Cardiac death, MI, TLR	Cardiac death, MI, TLR	Cardiac death, MI, TLR	Cardiac death, MI, TLR, TVR	Cardiac death, MI, TLR	Cardiac death, non-cardiac death, MI, TLR, stroke, PCI at other vessels	Cardiac death, non-cardiac death, MI, TLR, major bleeding	Cardiac death, MI, TLR	Cardiac death, MI, TLR	Cardiac death, MI, TLR	Cardiac death, MI, TLR	Cardiac death, MI, TLR	Cardiac death, non-cardiac death, MI, TLR
Age (years)		DCB	57.9 + 10.0	67.30 + 11.12	54.3 ± 10.6	58.6 ± 8.6	57.4 + 9.2	66 ± 11.4	76 ± 7.2	62.6 ± 8.8	59 ± 11	69 (61–75)	67.1 ± 11.4	73.8 ± 11.7	69.32 ± 10.22
		DES	55.9 + 9.7	70.63 + 8.97	57.2 ± 13.1	59.0 ± 8.7	57.3 + 8.3	67 ± 13.1	74 ± 8.4	64.0 ± 10.5	56 ± 11	69 (61–75)	69.0 ± 10.4	69.8 ± 1.1	69.13 ± 11.72
Clinical presentation ACS/CCS, *n* (%)		DCB	40 (100)/0	27 (100)/0	38 (100)/0	40 (51.3)/38 (48.7)	59 (100)/0	104 (100)/0	2 (2)/67 (98)	76 (90.5)/8 (9.5)	38 (100)/0	0/544 (100)	0/73 (100)	28 (68.3)/13 (31.7)	0/139 (100)
		DES	49 (100)/0	33 (100)/0	37 (100)/0	44 (60.3)/29 (39.7)	61 (100)/0	51 (100)/0	2 (2)/86 (98)	69 (87.4)/10 (12.7)	42 (100)/0	0/693 (100)	0/81 (100)	57 (53.2)/50 (46.7)	0/139 (100)
Diabetes mellitus, *n* (%)		DCB	5 (12.5)	12 (40.0)	4 (10.8)	25 (32.1)	8 (13)	28 (26.9)	37 (54)	16 (19.0)	10 (28)	125 (23)	36 (49.3)	13 (31.7)	44 (31.65)
		DES	2 (4.1)	13 (43.3)	2 (5.3)	16 (21.9)	4 (7)	38 (35.8)	41 (47)	23 (29.1)	15 (35)	153 (22)	40 (49.4)	24 (22.4)	32 (23.02)
CKD		DCB	N/A	2 (6.7)	0	N/A	N/A	N/A	17 (19)	N/A	N/A	N/A	11 (15.1)	N/A	14 (10.07)
		DES	N/A	4 (13.3)	2 (5.3)	N/A	N/A	N/A	6 (9)	N/A	N/A	N/A	13 (16.0)	N/A	8 (5.76)
Target lesion	LM	DCB	N/A	N/A	N/A	N/A	N/A	N/A	2 (2)	N/A	N/A	15 (2.8)	1 (1.8)	148 (100)	0
		DES	N/A	N/A	N/A	N/A	N/A	N/A	3 (3)	N/A	N/A	27 (3.9)	3 (3.8)	0	0
	LAD	DCB	18 (45)	12 (44)	N/A	35 (44.9)	19 (32)	51 (41.5)	47 (59)	48 (57.1)	19 (52)	309 (57)	23 (32.1)	0	139 (100)
		DES	18 (37)	17 (51.5)	N/A	42 (57.5)	24 (40)	46 (38.3)	62 (60)	35 (44.3)	22 (50)	376 (54)	29 (35.8)	0	139 (100)

Table 1 (continued)

Author		Nijhoff et al	Nishiyama et al	Gobic et al	Her et al	Vos et al	Scheller et al	Iwasaki et al	Xue Yu et al	Xiaojiao Hao et al	Merino-poulos et al	Nakamura et al	Gunawardena T.D. et al	Gitto et al
RVD, mm	DCB	2.83 ± 0.51	2.88 ± 0.57	3.04 ± 0.46	2.6 ± 0.5	3.28 ± 0.52	N/A	2.97 ± 0.45	2.77 (2.50 to 3.25)	N/A	3.00 (2.75–3.50)	2.97 ± 0.42	3.84 ± 0.26	3.12 (0.48)
	DES	2.78 ± 0.53	2.72 ± 0.64	2.61 ± 0.49	3.1 ± 0.5	3.20 ± 0.48	N/A	3.03 ± 0.36	3.01 (2.65 to 3.39)	N/A	3.50 (3.00–3.75)	3.32 ± 0.42	4.33 ± 0.60	3.09 (0.35)
Lesion length, mm	DCB	13.0 ± 5.7	16.13 ± 5.25	N/A	20.0 ± 5.4	N/A	N/A	14.3 ± 7.3	18.2 (16.0 to 20.1)	N/A	20 (20–30)	N/A	21.71 ± 7.80	65 (40–82)
	DES	16.8 ± 8.7	18.14 ± 7.41	N/A	21.7 ± 6.4	N/A	N/A	19 ± 10	20.0 (15.0 to 25.0)	N/A	24 (18–38)	N/A	24.72 ± 14.32	53 (45–62)
DCB drug		Paclitaxel	Paclitaxel	Paclitaxel	Paclitaxel	Paclitaxel	Paclitaxel	Paclitaxel	Paclitaxel	Paclitaxel	Paclitaxel	Paclitaxel	Paclitaxel	Paclitaxel and sirolimus
DCB brand		Dior	SeQuent Please	SeQuent Please	SeQuent Please	Pantera Lux	SeQuent Please	SeQuent Please	SeQuent Please	Biotech Bingo	N/A	SeQuent Please	SeQuent Please NEO	MagicTouch, SELUTION, In-Pact/Pre-vail, Restore
DES brand		N/A	XIENCE PRIME, XIENCE Xpedition	Cobalt-chro-mium sirolimus Bio-Mime	Resolute Integrity, XIENCE PRIME	Orsiro	N/A	N/A	Resolute, Synergy, XIENCE	N/A	N/A	Ultimaster, Synergy, Ulti-master Tansei, XIENCE Alpine/ Sierra, Promus PRE-MIER, Resolute Integrity	Resolute Onyx, Promus PREMIER, Synergy, XIENCE, PROMUS Element, Ultimaster	N/A
Lesion preparation strategy		Thrombus aspira-tion and SC balloon pre-dilatation	Scoring bal-loon pre-dilatation	Thrombus aspira-tion and SC balloon pre-dilation or both	SC balloon pre-dila-tation	Thrombus aspira-tion and SC balloon pre-dila-tation	According to the DCB consensus group	Mandatory rotabla-tion, accord-ing to the study design and SC balloon pre-dila-tation	According to the recom-menda-tions of the Ger-man and Chinese con-sensus group. NC, cutting, scoring, or NSE balloons	SC bal-loon pre-dil-atation	SC bal-loon pre-dil-atation	SC or scoring balloon pre-dilation	According to the third DCB consensus group	Balloons with a balloon-to-vessel ratio of 1:1, cutting balloons, or atherectomy devices
Clinical follow-up, months		12	8	6	12	9	9	12	12	12	42	14	33	24
Angiographic follow-up, months		12	8	6	9	9	N/A	12	9	12	N/A	14	N/A	N/A

RCT randomized controlled trial, *DCB* drug-coated balloon, *DES* drug-eluting stent, *RVD* reference vessel diameter, *LLL* late lumen loss, *MLD* minimum lumen diameter, *MACE* major adverse cardiovascular events, *MI* myocardial infarction, *NC* non-compliant, *SC* semi-compliant, *NSE* non-slip element, *TLF* target lesion failure, *TLR* target lesion revascularization, *ACS* acute coronary syndrome, *CCS* chronic coronary syndrome, *CKD* chronic kidney disease, *LM* left main, *LAD* left anterior descending, *LCX* left circumflex, *RCA* right coronary artery

the risk of CVD [1.2% vs 0.9%; RR, 0.84; 95% CI, 0.21–3.40; $p=0.80$; $I^2=0\%$] (Fig. 8A), MI [0.9% vs 1.6%; RR, 0.64; 95% CI, 0.18–2.30; $p=0.49$; $I^2=0\%$] (Fig. 8B), and TLR [1.5% vs 2.3%; RR, 0.77; 95% CI, 0.24–2.50; $p=0.67$; $I^2=0\%$] (Fig. 8C).

Two RCTs reported data on ACD [20, 21]. No differences were found between DCB and DES for the risk of ACD at follow-up [3.5% vs 4.7%; RR, 0.60; 95% CI, 0.16–2.30; $p=0.46$; $I^2=0\%$] (Fig. 8D).

Six RCT studies reported data on LLL [14, 20, 22–24]. No differences were observed between DCB and DES for LLL at follow-up [MD, −0.08; 95% CI, −0.27 to 0.12; $p=0.44$; $I^2=91\%$] (Fig. 8E).

Two RCT studies reported data on MLD before and after the procedure [20, 24]. DES proved a higher MLD mean difference before and after PCI [1.79 (1.67, 1.91) vs 1.06 (0.94, 1.18); $p<0.00001$; $I^2=98.6\%$] (Fig. 9).

Subgroup analysis including only acute coronary syndrome

Six studies reported data on CVD, MI, and TLR [14, 19–23]. At follow-up, no differences were found between DCB and DES for the risk of CVD [1.3% vs 1.0%; RR, 0.84; 95% CI, 0.21–3.40; $p=0.80$; $I^2=0\%$] (Supplemental Fig. 3A), MI [0.6% vs 1.4%; RR, 0.57; 95% CI, 0.13–2.44; $p=0.45$; $I^2=0\%$] (Supplemental Fig. 3B), and TLR [3.1% vs 1.8%; RR, 1.83; 95% CI, 0.58–5.83; $p=0.31$; $I^2=0\%$] (Supplemental Fig. 3C).

Three studies reported data on ACD [19–21]. No differences were found between DCB and DES for the risk of ACD at follow-up [3.3% vs 3.0%; RR, 0.82; 95% CI, 0.21–3.20; $p=0.78$; $I^2=7\%$] (Supplemental Fig. 3D).

Two studies reported data on MLD before and after the procedure [19, 20]. DES proved a higher MLD mean difference before and after PCI [2.11 (1.95, 2.27) vs 1.78 (1.49, 2.08); $p<0.00001$; $I^2=46\%$] (Supplemental Fig. 3E).

Five studies reported data on LLL [14, 19, 20, 22, 23]. No differences were observed between DCB and DES for LLL at follow-up [MD, −0.04; 95% CI, −0.20 to 0.13; $p=0.66$; $I^2=88\%$] (Supplemental Fig. 3F).

Subgroup analysis including only studies with SeQuent Please/SeQuent Please NEO DCB

Eight studies reported data on CVD, MI, and TLR [14–18, 20, 21, 24]. At follow-up, no differences were found between DCB and DES for the risk of CVD [1.6% vs 3.6%; RR, 0.50; 95% CI, 0.23–1.12; $p=0.09$; $I^2=0\%$] (Supplemental Fig. 4A), MI [0.6% vs 2.0%; RR, 0.54; 95% CI, 0.15–1.89; $p=0.33$; $I^2=0\%$] (Supplemental Fig. 4B), and TLR [3.4% vs 6.0%; RR, 0.71; 95% CI, 0.40–1.28; $p=0.25$; $I^2=0\%$] (Supplemental Fig. 4C).

Five studies reported data on ACD [15, 17, 18, 20, 21]. No differences were found between DCB and DES for the risk of ACD at follow-up [5.4% vs 8.8%; RR, 0.72; 95% CI, 0.32–1.64; $p=0.44$; $I^2=47\%$] (Supplemental Fig. 4D).

Five studies reported data on MLD before and after the procedure [16–18, 20, 24]. DES proved a higher MLD mean difference before and after PCI [1.88 (1.67, 2.10) vs 1.19 (0.95, 1.43); $p<0.00001$; $I^2=91\%$] (Supplemental Fig. 4E).

Six studies reported data on LLL [14, 16–18, 20, 24]. No differences were observed between DCB and DES for LLL at follow-up [MD, −0.16; 95% CI, −0.41 to 0.89; $p=0.20$; $I^2=94\%$] (Supplemental Fig. 4F).

Publication bias

A graph and summary of the Cochrane Risk of Bias tool for RCTs and Newcastle–Ottawa Quality Assessment Scale

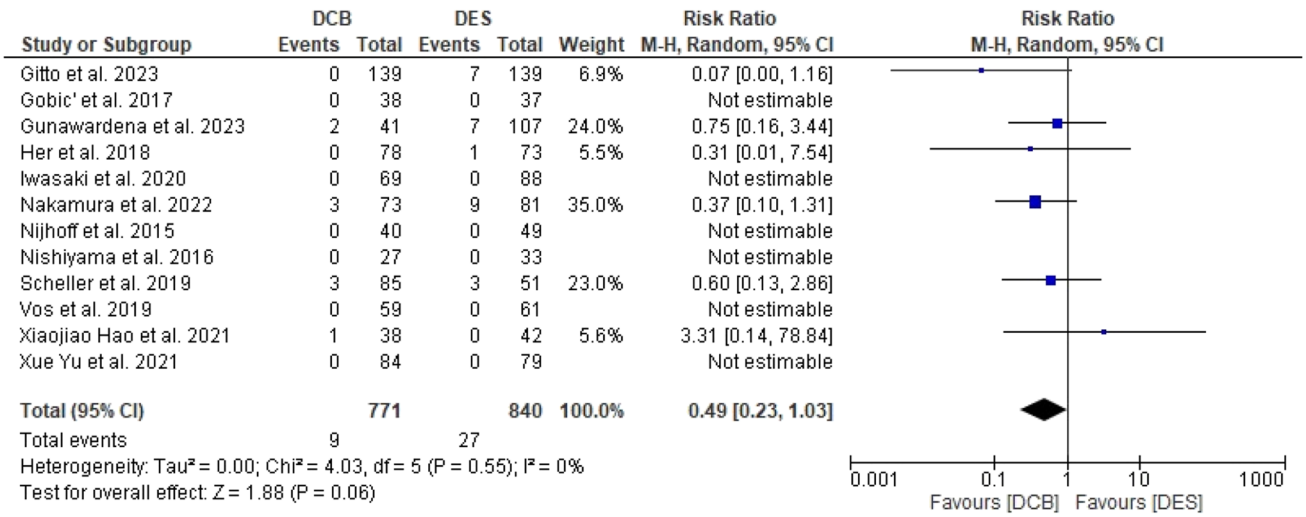


Fig. 2 Forest plots comparing cardiovascular death between drug-coated balloon and drug-eluting stent

for cohort studies are reported in Supplemental Fig. 1. The funnel plots for visual inspection of the bias showed no bias (Supplemental Fig. 2).

Discussion

In this meta-analysis, we evaluated the role of a "metal-free" approach with DCB for the treatment of de novo LV-CAD in both acute and elective settings.

In summary, our results suggest that the usage of the DCB-only strategy in this scenario is safe and effective with similar clinical and angiographic results compared to DES.

Note that the studies included in this meta-analysis are mainly related to selected lesions (length in both arms less than 28 mm) in specific subsets (e.g., calcified, ULM, and ACSs), which are currently considered "off-label" for DCBs usage.

Pre-dilation was performed in all treatment groups. This maneuver is a key step for a successful PCI, particularly in the case of DCB usage. According to the DCB consensus group, an optimal lesion preparation (e.g., residual % diameter stenosis less than 30) is required prior to DCB inflation [27]. An "aggressive" (e.g., non-compliant—NC—balloon escalation to super high-pressure NC balloons, scoring/cutting balloons, intravascular lithotripsy, debulking devices) pre-dilatation strategy could facilitate plaque incision and drug transfer to the vessel wall, reducing elastic recoil and influencing a good clinical outcome [5].

Even in an ACS setting and in the presence of a thrombus, which are not considered a good spot for a metal-free

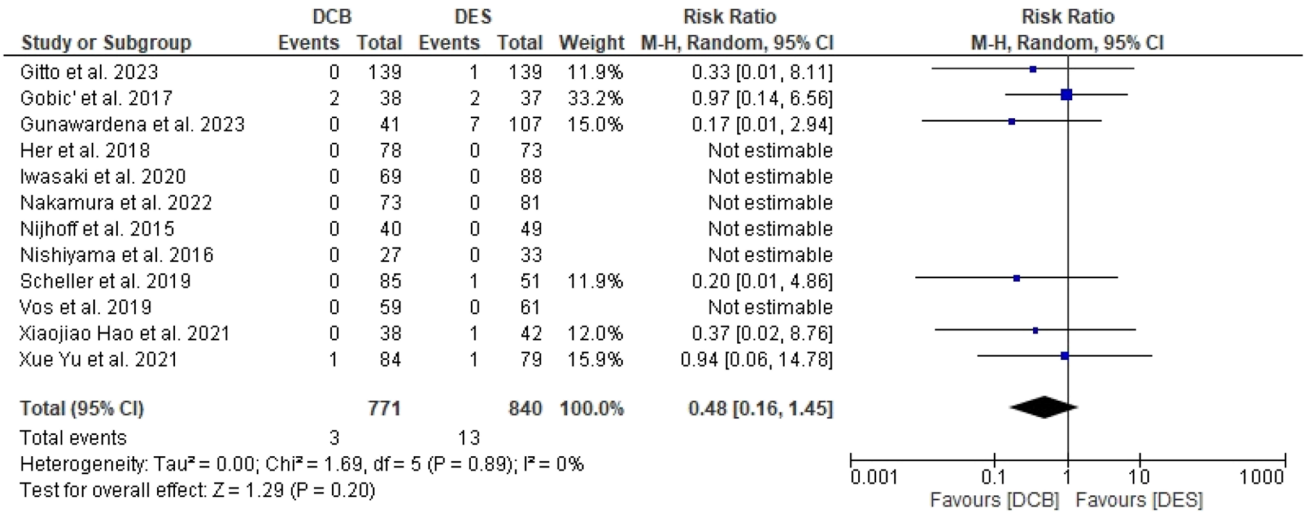


Fig. 3 Forest plots comparing myocardial infarction between drug-coated balloon and drug-eluting stent

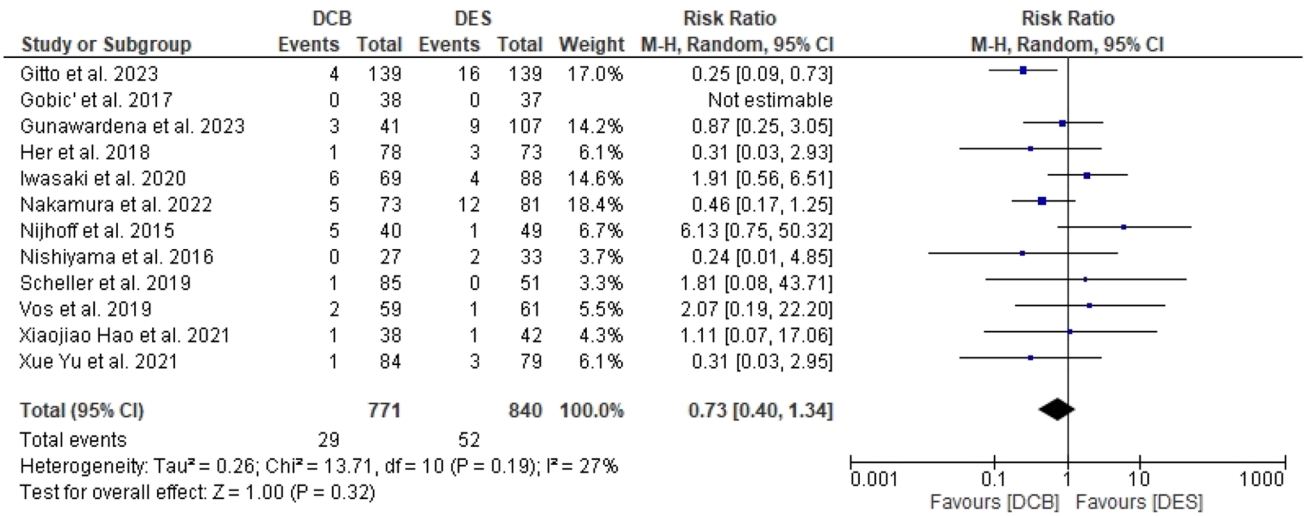


Fig. 4 Forest plots comparing target lesion revascularization between drug-coated balloon and drug-eluting stent

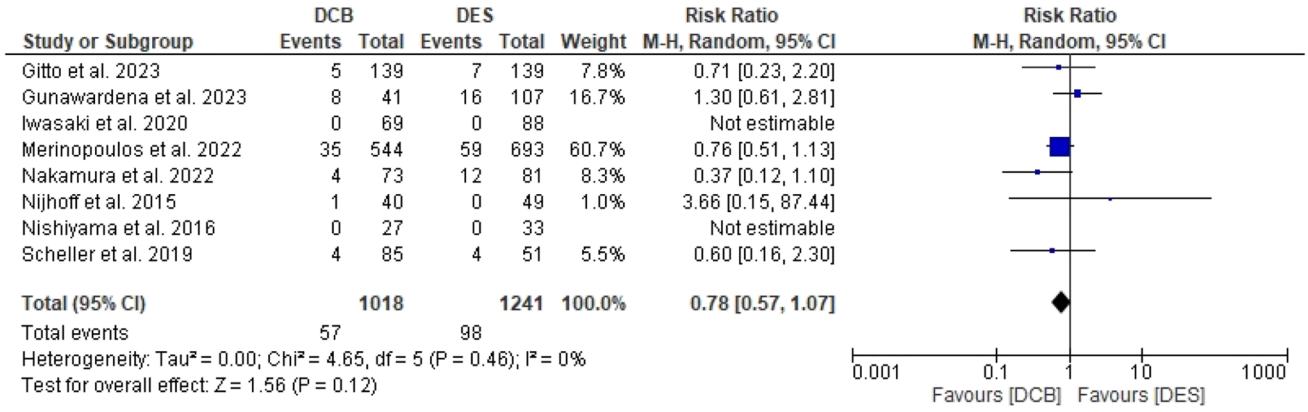


Fig. 5 Forest plots comparing all-cause death between drug-coated balloon and drug-eluting stent

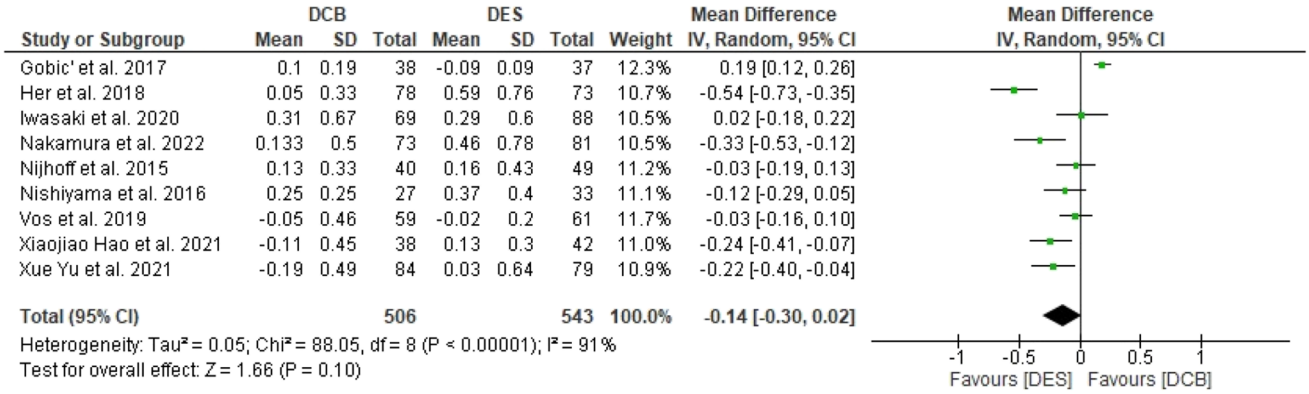


Fig. 6 Forest plots comparing late lumen loss between drug-coated balloon and drug-eluting stent

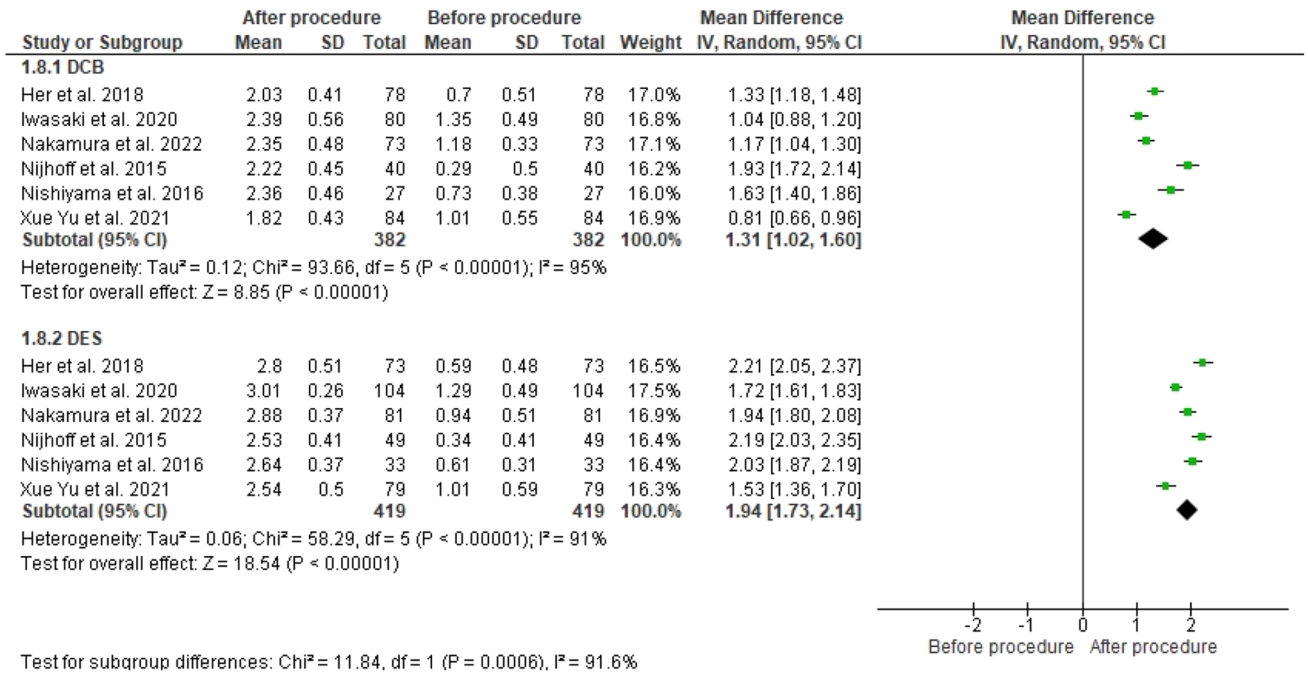


Fig. 7 Forest plots comparing minimal lumen diameter before and after procedure between drug-coated balloon and drug-eluting stent

approach because of the potentially lower dose of drug transferred to the vessel wall, optimal lesion preparation is mandatory before inflating a DCB. Proper thrombus aspiration, which was performed in many of the ACS patients enrolled in the included studies (78% in the DCB group of the REVELATION trial), could be crucial to reduce the number of pre-dilatation balloon inflations and the subsequent risk of distal embolization while facilitating drug penetration in the vessel wall. Indeed, the sub-analysis of the DEB-AMI trial showed a higher LLL in the DCB arm. However, this result might have been influenced by the DCB used (the first-generation DIOR delivers 25% only of the drug dose to the vessel wall) [28].

Although vessel preparation plays a key role in DCB PCI, on the other hand, it may be associated with vessel injuries. Indeed, a main concern associated with DCB PCI only in proximal LV-CAD is the occurrence of malignant dissections. Cortese et al. assessed the fate of leaving non-flow-limiting dissection (A-C) after DCB PCI. At 6-month angiographic follow-up, complete vessel healing was reported in 93.8% of cases, while a low incidence of major adverse events occurred at 9-month follow-up. The authors

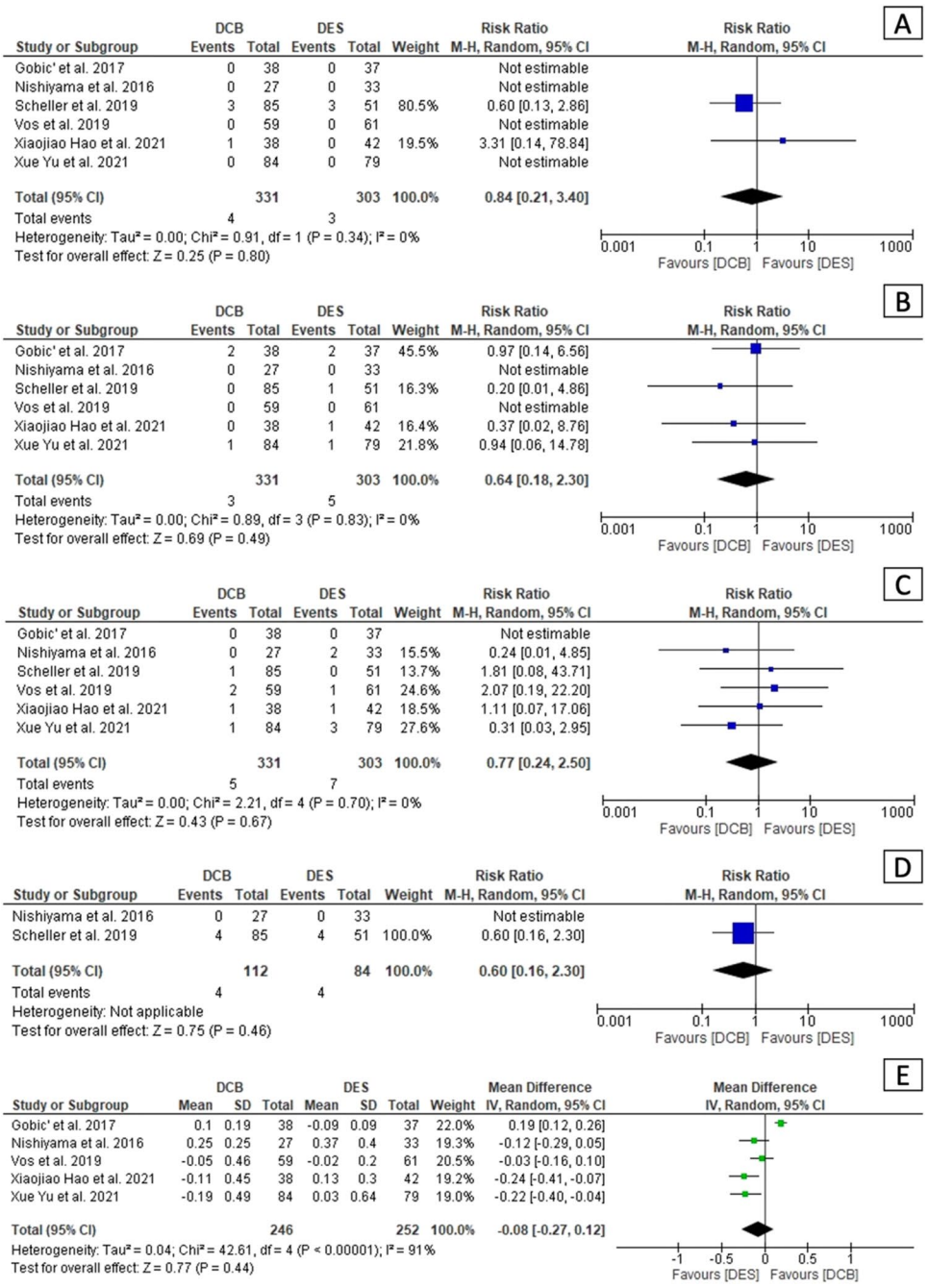


Fig. 8 Forest plots comparing cardiovascular death (**A**), myocardial infarction (**B**), target lesion revascularization (**C**), all-cause death (**D**), **a**nd late lumen loss (**E**) between drug-coated balloon and drug-eluting stent in randomized controlled trial subgroup

hypothesized that paclitaxel may play a role in facilitating coronary vessel healing when properly delivered at the target site [29]. Besides angiography, a functional evaluation could lead to the management of a dissection in the setting of DCB PCI. Especially in the case of type A-B dissection, a Pd/Pa threshold of more or equal than 0.90 may be used as a surrogate for optimal outcome (leaving the dissection), while a Pd/Pa less than 0.90 may lead to bail-out DES implantation reducing the risk of abrupt vessel closure and MI [30].

Most of the studies included in this meta-analysis assessed the performance of PCBs, with the most commonly used brand being SeQuent Please (B. Braun) in seven studies.

The main difference among PCBs is related to the formulation of the water-soluble excipient and the drug concentration, with the first aspect mostly influencing the final effect on the vessel wall, due to its sustained release properties [26]. Although a non-randomized, score-matched comparison (SIRPAC trial) of two large registries assessing the performance of a PCB (Elutax SV, Aachen Resonance, Lainate, Italy) versus a first-generation SCB (MagicTouch, Concept Medical, Tampa, FL, USA) reported similar clinical results at 12 months [31–33], a recent randomized study showed that the same SCB resulted inferior to SeQuent Please NEO PCB in terms of angiographic net lumen gain at 6 months [34]. These results deserve further attention particularly when choosing a DCB in the setting of LV-CAD.

Consistently with other studies, our analysis confirmed that, in LV-CAD PCI, DES is associated with a significantly higher acute gain as compared to DCB. However, LLL at follow-up was similar between the groups, claiming indirectly for a positive remodeling associated with DCB PCI [5, 6, 35, 36].

DCB PCI was also challenged vs DES in heavily calcified lesions requiring rotational atherectomy. Angiographic and clinical outcomes at 1-year follow-up were similar between the groups [17]. Even in de novo ULM disease, which is considered a high-risk subset, DCB PCI was associated with similar results as compared to DES, at a median of 33 months follow-up [15].

However, the data from these two studies on specific high-risk populations are from retrospective registries and should be interpreted with caution. More recently, a propensity score (PS) matching analysis of a DCB-alone or in combination with DES ("hybrid" strategy) versus a DES-alone strategy in the treatment of de novo long LAD lesions and large RVD (> 3 mm) resulted in a lower TLF rate (TLR, CVD, and target vessel—MI) at 2 years in the DCB group as compared to the DES group. Furthermore, a signal toward lower CVD risk was reported in the DCB group. This finding is consistent with the results of our meta-analysis, where this outcome is close to significance ($p = 0.06$), hypothesizing an advantage of the "metal-free" approach [25].

Data from ongoing RCTs comparing current generation DCBs vs DES in a large cohort of patients including those with LV-CAD are awaited [37, 38].

Limitations

Our meta-analysis has several limitations. We included not only RCTs but also observational studies, which could lead to bias in the results. However, our results were confirmed by the subgroup analysis of RCTs only. Furthermore, different methods of lesion preparation and different stent platforms were used in the studies, preventing a sub-analysis to investigate their impact on angiographic outcomes.

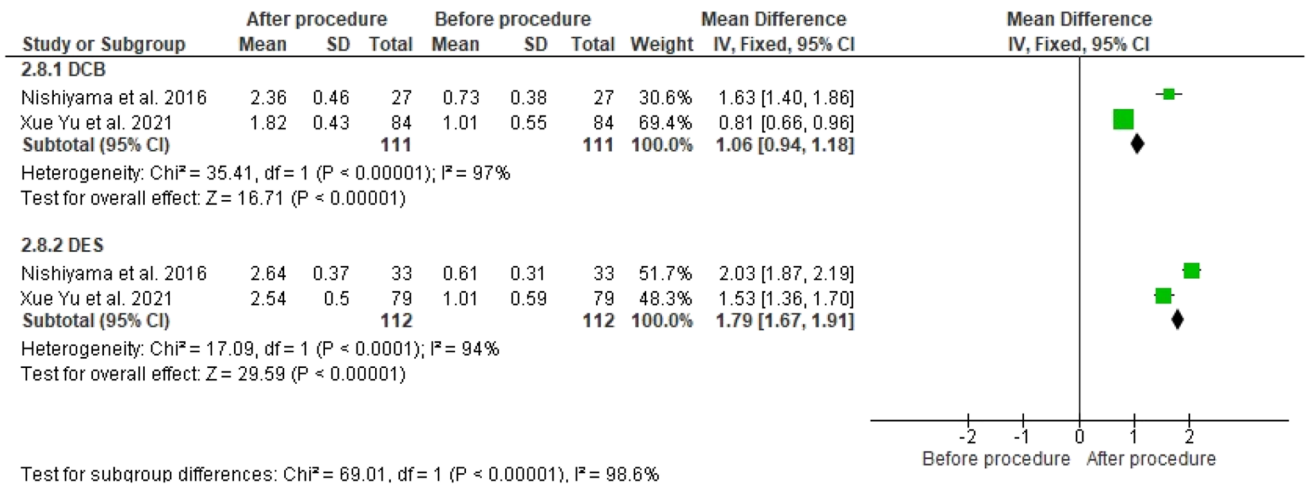


Fig. 9 Forest plots comparing minimal lumen diameter before and after the procedure between drug-coated balloon and drug-eluting stent in randomized controlled trial subgroup

Conclusions

DCBs are an attractive option for the treatment of de novo CAD. Our meta-analysis showed no significant clinical and angiographic differences between DCB and DES in treating LV-CAD in either acute or elective settings. Focused RCTs providing further evidence on the potential benefit of a metal-free approach in LV-CAD are strongly needed.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00392-024-02481-8.

Data availability The data underlying this article are available in the article and its online supplementary material.

Declarations

Conflict of interest The authors declare no competing interests.

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