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Drug-coated balloons versus drug-eluting stents in patients with small coronary artery disease: an updated meta-analysis

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Abstract

Background Drug-coated balloons (DCB) have promising results in the management of large coronary artery lesions (CAD), still their role in treating small CAD is not well established. We aimed to provide a comprehensive appraisal of the efficacy and safety of DCBs in patients with small CAD.

Methods We searched PubMed, Scopus, web of science, Ovid, and Cochrane Central from inception until 30 March, 2023. We included all relevant studies that compared DCB versus drug-eluting stents (DES) in small CAD patients undergoing PCI. We reported clinical outcomes as MACE, all-cause death, cardiac death, MI, TLR, TVR, and stent thrombosis, while angiographic outcomes were late lumen loss (LLL), mean lumen diameter (MLD), net luminal gain (NLG), and in-segment binary restenosis.

Results Twenty studies comprising 18,469 patients were included in this meta-analysis. The incidence rate of MACE was 9.4% in the DCB group compared to 9.9% in the DES group, without a significant difference in the risk of MACE (OR = 0.97, 95% CI: 0.77 to 1.22, $p = 0.78$). Moreover, DCB significantly decreased MLD and NLG compared to DES, with the following values, respectively (MD= -0.19, 95% CI: -0.32 to -0.06, $p < 0.001$, and MD -0.21, 95% CI: -0.40 to -0.01, $p = 0.04$). On the other hand, DCB was associated with higher odds in the risk of in-segment binary restenosis (OR 1.66, 95% CI: 1.03 to 2.68, $p = 0.04$).

Conclusion DCB is an alternative approach to DES in the management of small CAD and should be validated in daily clinical practice.

Prospero registration CRD42023413068.

Keywords Drug-coated balloon, Drug-eluting stent, Small coronary artery disease, Meta-analysis

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Introduction

The primary approach for treating coronary artery disease (CAD) involves drug-eluting stents (DESs) of second generations. However, drug-coated balloons (DCBs) offer a new and innovative alternative for certain patients, such as those with in-stent restenosis, a higher risk of bleeding, or large vessel CAD [1, 2].

DCBs consist of balloons coated with a specific drug in a specific matrix. Once the balloon is inflated, the drug is quickly embedded into the vessel wall, providing its anti-proliferative effect. DCBs can be used, also, in the coronary vasculature as long as the preparation of lesion does not lead to major complications as leaving residual stenosis greater than 30% or lead to flow-limiting dissections, and there is no inhibition of drug transfer due to the presence of a large intravascular thrombus [3, 4]. The primary drawback of the DCB-only strategy is the lack of intravascular foreign material, which could lead to severe complications as stent thrombosis. Other advantages include the need for only short-term dual antiplatelet therapy (DAPT) of four weeks after DCB and the potential long-term positive remodeling effect on the treated vessel associated with paclitaxel [3, 4].

Regarding DCB's role concerning different coronary artery disease diameters, Yu and colleagues found that treating large coronary de novo lesions using DCB alone was safe and effective [5]. For small vessel disease, both the Balloon Elution and Late Loss Optimization (BELLO) study and the Basel Kosten Effektivitäts Trial-Drug-Coated Balloons versus Drug-eluting Stents in Small Vessel Interventions (BASKET-SMALL) trial showed low rates of major adverse cardiac events (MACE) at the one-year follow-up [6, 7]. Additionally, a previous report from the RESTORE small vessel disease (SVD) China study indicated that DCBs were non-inferior to DES [8].

DES is associated with an improvement in clinical outcomes of patients with large CAD, despite the improved rates of clinical outcomes, the amount of stent length remains unchanged with higher rates of late adverse events [4, 5]. Moreover, the use of DES in patients with small de novo CAD lesions was associated with higher risk of restenosis and stent thrombus. Conflict data between the role of DCB and DES in small lesions were reported.

Li et al., in their meta-analysis, found that the use of DCB is comparable to the DES in achieving favorable outcomes, including a reduced risk of nonfatal myocardial infarction [9]. As such, it may be considered a highly recommended treatment approach for patients with de novo small coronary artery vessel disease.

From the aforementioned literature, DCB showed promising results in CAD, but their role in de novo small CAD needs stronger evidence to be established in our everyday clinical practice, and yet no comprehensive pooled analysis was established. So, We aimed to provide a more comprehensive and quantitative assessment of the efficacy and safety of DCB compared with DES in de novo small vessel CAD.

Methods

We adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines in the current meta-analysis [10], and followed the guidelines of the Cochrane Handbook of Systematic Reviews and Meta-analysis of Interventions. The study was registered on PROSPERO CRD42023413068.

Eligibility criteria

We included all the relevant studies, RCTs or observational studies, addressing patients of de novo small coronary artery disease undergoing PCI treated with DCB as the intervention group and the DES as the control group, and reported the outcomes of interest in an intention-to-treat analysis. we excluded the animal studies, conference abstracts, and unpublished data. We did not use the English filter, so any foreign language was considered in our inclusion criteria.

Primary and secondary outcomes

The primary outcome of interest was the incidence of MACE. The definitions reported by each author are illustrated in supplementary Table 1. While the secondary outcomes of interest were the incidence of myocardial infarction (MI), target lesion revascularization (TLR), cardiac death, all-cause death, target vessel revascularization (TVR), stent thrombosis, in-segment binary restenosis, and angiographic assessment as minimum lumen diameter (MLD), late lumen loss (LLL), and net lumen gain (NLG).

Literature search and screening

An electronic search on Scopus, PubMed, Web of Science, Ovid, and Cochrane Central from inception until March 30th, 2023, was carried out using the following search strategy: ("drug-coated balloon" OR "DCBs" OR "drug coated balloons") AND ("drug-eluting stent" OR "DES" OR "drug eluting stents" OR "stent") AND ("small-vessel coronary artery" OR "de novo small coronary vessel disease*" OR "de novo small coronary artery lesion*") AND ("PCI" OR "Percutaneous Coronary Intervention"). Any duplicates were removed using EndNote. Moreover, all included studies were retrieved manually for additional studies. The results were screened in a two-step wise; the first was title and abstract screening then a full-text screening of the relevant studies was done.

Data extraction

We used a specified data extraction sheet to include the following items: (1) Characteristics of the population of included studies, (2) Characteristics of the included studies, (3) Assessment of Risk of bias domains, (4) Outcomes of interests.

Synthesis of results

In case of multiple time points reported by each study, we considered the outcomes of the last follow-up point as our long-term follow-up. The number of events and the total of sample size included were pooled as odds ratio (OR) and its 95% confidence interval (CI) for dichotomous outcomes using the DerSimonian-Laird random-effect model. Moreover, the mean difference (MD) and its 95% CI were pooled for continuous outcomes in the DerSimonian-Laird random-effect model. All analyses were computed using Stata MP 17 for Mac.

Assessment of heterogeneity

We used the chi-square test using the following equation: $I^2 = Q\text{-}dfQx100\%$ to assess the statistical heterogeneity reported among studies. The *P*-value of less than 0.05 was considered a significant heterogeneity. High heterogeneity was defined as I-square values ≥ 50%. When there is significant heterogeneity, the leave-one-out sensitivity analysis model was used to resolve reported heterogeneity. Galbraith plot was used to detect any heterogeneity across studies.

Quality assessment

The quality of included clinical trials was assessed according to the Cochrane Risk of Bias 2 (ROB-2) tool for RCTs that involves the following five domains: selection bias via the randomization process, performance bias via the deviation from the intended interventions, detection bias via the outcome measurement, attrition bias via any missing outcome data, reporting bias via the selection of reported results and any other potential source of bias.

The authors' decision is classified as Low risk of bias", 'Some concerns", or 'High risk of bias". We used funnel plots to detect the publication bias. Moreover, evidence of publication bias was assessed by Egger's regression test.

We performed a Trial Sequential Analysis (TSA) to assess the robustness of the pooled evidence from studied outcomes as to the cumulative analysis of the included trials; there is an increased possibility of multiple statistical errors as type 1 and type 2 errors. When the pooled Z-line on the curve crosses the reference boundary and boundary of pooled analysis, this is an indication of no further trials are required, and the evidence is conclusive and sufficient. However, if the pooled Z-line on the curve does not cross any boundary, then the evidence is not sufficient to draw a conclusion and more studies are still needed. In the current meta-analysis, we declared a 0.05 value as our alpha error, and a beta error of 0.2 corresponding to 80% power. We calculated the mean difference in this meta-analysis to obtain the sample size needed for TSA.

Results

Literature search

Our literature search included 318 records. After title and abstract screening, 30 articles were eligible for consideration as full-text screening. A total of 20 studies with 4 extended studies were included in the study. The process of study selection is shown in the PRISMA flow diagram, as shown in Fig. 1.

Characteristics of included studies

All studies enrolled 18,469 patients from 20 studies and 4 extended studies [5–7], [11–27]. Of the 20 included studies of which 13 studies were RCTs and 7 studies were observational. The summary and baseline of the included studies are summarized in Table 1.

Risk of bias assessment

Regarding risk of bias assessment of RCTs, seven studies showed an overall some concerns, mainly due to lack of information of the randomization process, as shown in Fig. 2.

As for risk of bias assessment of observational studies, All the seven studies were truly representative of the included patients. In addition, the control group was selected from the same community. Also, the two groups included in all studies were comparable in all studies. Some studies (Tasai 2022, Silverio 2020, and Giannini 2017) achieved comparability through a propensity matching model. The follow-up periods were adequate in all studies. In conclusion, the overall quality of all the studies is good. The risk of bias summary is illustrated in Table 2.

Clinical outcomes

MACE

The incidence of MACE was reported in 16 studies, of which the event rate in the DCB group was 9.4% (158 of 1,677), while it was 9.9% (185 of 1855) in the DES group. The pooled OR did not favour DCB over DES in MACE (OR = 0.97, 95% CI [0.77 to 1.22], $p = 0.78$; $I^2 = 0\%$, $p = 0.43$), as shown in Fig. 3. A pooled analysis of a composite of cardiac death, MI, and TLR showed that the pooled OR did not favour DCB over DES (OR = 1.11, 95% CI [0.76 to 1.63], $p = 0.60$), as shown in Supplementary Fig. 1.

A subgroup analysis was performed on study designs, of which the pooled analysis showed no significant

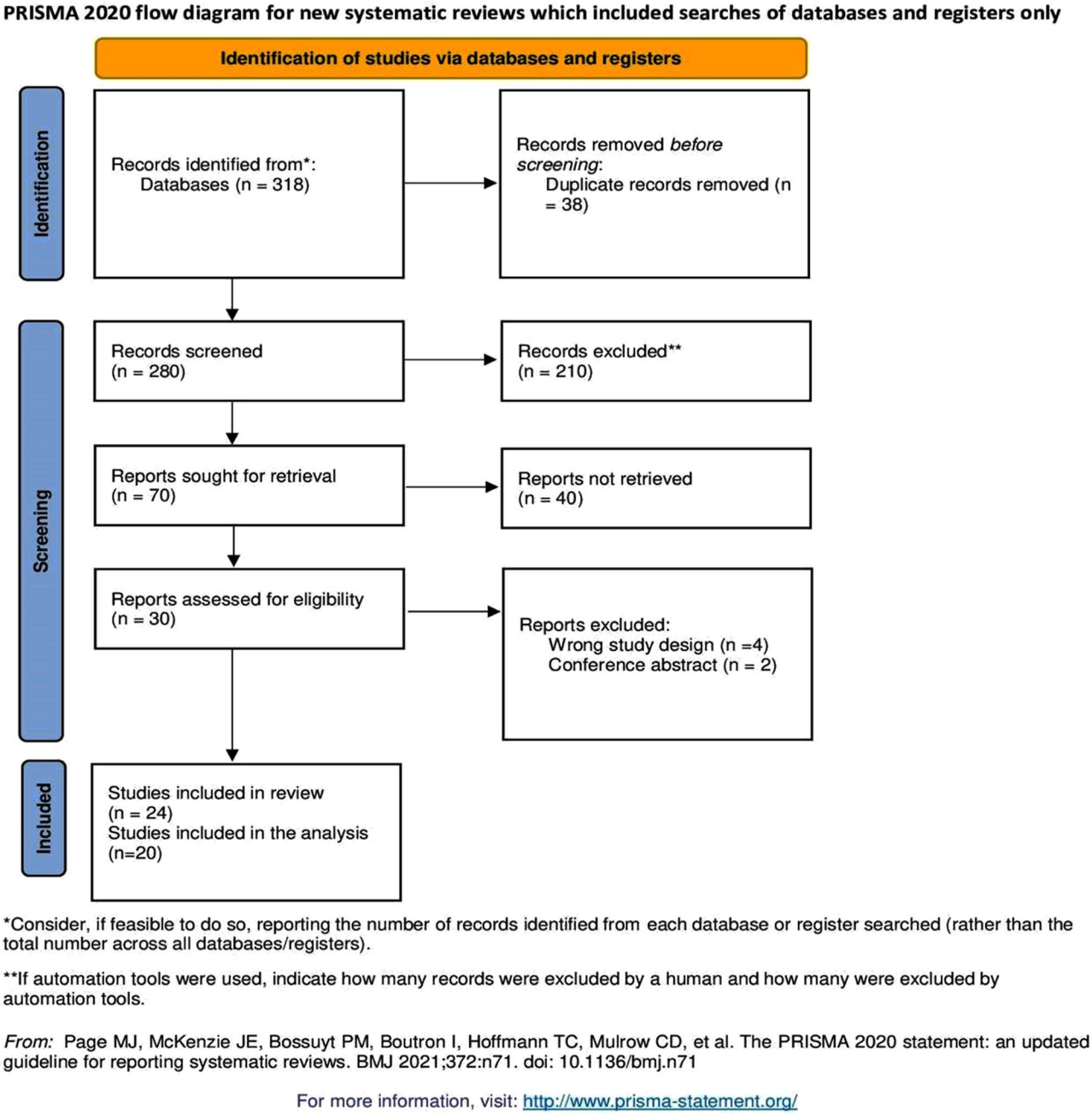

Fig. 1 PRISMA flow diagram

difference in the two subgroups (OR = 0.94, 95% CI [0.65 to 1.37], $p = 0.75$; $I^2 = 0\%$, $p = 0.99$ for observational studies, and (OR = 0.99, 95% CI [0.70 to 1.39], $p = 0.93$; $I^2 = 0\%$, $p = 0.14$ for RCTs), as shown in Supplementary Fig. 2.

We further performed another subgroup analysis on the intervention, in which the pooled analysis did not favour any of the two interventions in studies subgroups (OR = 1.78, 95% CI [0.70 to 4.50], $p = 0.22$, 0.88, 95% CI [0.69 to 1.13], $p = 0.32$) for the DCB plus BMS vs. DES, and DCB vs. DES, respectively, as shown in Supplementary Fig. 3.

Galbraith plot and funnel plot were assessed, and by inspection, only one study was visualized out of the 95% CI of the precision are, indicating their heterogeneity from other studies, however the funnel plot was symmetry and no other studies were need to achieve stability suggesting that no possible publication bias found, as shown in Figs. 4 and 5.

We performed a trial sequential analysis (TSA) on 16 studies that assessment MACE of which the cumulative Z-line on the curve did not cross either the conventional boundaries of benefit nor the trial sequential monitoring

Table 1 The summary and baseline of all included studies

Characteristics of All included Studies																			
Author, year	Type of Study	Country	Patients (n) (DCB/stent)	Criteria of Small vessel	Procedural success (%) (DCB/stent)	Age (mean) (DCB/stent)	male, n (DCB/stent)	mean follow up (months)	Outcomes reported	DCB type	Stent type	Bail-out stenting rate (%)	Medical Conditions, n (DCB/ stent)						
													History of stroke	History of MI	DM	HTN	Hyperlipidaemia	Current smoker	PAD
Latib, 2012, Naganuma, 2015 and Latib, 2015	RCT	italy	90/92	2.41/2.41	92/95	64.8/66.8	72/71	6	MLD/%DS/ acute gain/ MACE/MI/ TLR/TVR/ death/Peri-procedural MI/binary stenosis/ late lumen loss/net gain	IN.PACT Falcon paclitaxel DEB (Medtronic, Inc., Santa Rosa, California) dilation and provisional BMS;	PES (Taxus Libertè, Boston Scientific, Boston, Massachusetts)	20	NA	46/33	39/35	72/75	71/73	15/10	NA
Iiistro, 2013	RCT	italy	66/59	2.77/2.85	100/100	65/66	58/49	9	IDTLR/ death/MI/ TLR/binary stenosis/ RVD/MLD/ late loss/ restenosis pattern	second-generation Elutax PEB,	Xience V drug-eluting stent	NA	NA	6/7	10/7	28/22	10/6	23/15	NA
Nishiyama, 2016	RCT	japan	30/30	2.88/2.72	100/100	67.3/70.63	20/24	8	MLD/%DS/ Late lumen loss/Acute gain	paclitaxel-coated balloon catheter (paclitaxel at a dose of 3 µg/ mm2 balloon surface; SeQuent Please; B Braun Melsungen, Germany).	everolimus-eluting stents (EES: Xience Prime/ Xpedition; Abbott Vascular, Santa Clara, CA, USA).	N/A	N/A	N/A	12/13	23/27	24/23	17/19	NA

Table 1 (continued)

Characteristics of All included Studies																			
Author, year	Type of Study	Country	Patients (n) (DCB/stent)	Criteria of Small vessel	Procedural success (%) (DCB/stent)	Age (mean) (DCB/stent)	male, n (DCB/stent)	mean follow up (months)	Outcomes reported	DCB type	Stent type	Bail-out stenting rate (%)	Medical Conditions, n (DCB/ stent)						
													History of stroke	History of MI	DM	HTN	Hyperlipidaemia	Current smoker	PAD
Shin, 2016	observational	South Korea.	44/22	2.69/2.92	100/100	60.6/58.7	34/16	12.4 Median	major adverse cardiac events including cardiac death, MI, target lesion revascularization (TLR), and arterial thrombosis was recorded/ MLD/FFR	(SeQuent Please paclitaxel-coated balloon catheter, B. Braun, Melsungen, Germany)	DES, ei-ther zotarolimus- or everolimus-eluting stent (Resolute IntegrityVR or Xience primeVR) and BMS (VisionVR)	0	NA	3/0	13/5	24/8	19/8	20/5	NA
Silverio, 2020	observational	Sweden	1154/13,634	N/A	98.4/98.2	68/69	809/9054	36	The primary outcomes were restenosis and definite target lesion thrombosis at 3-year follow-up. The secondary outcomes were the occurrence of all-cause death and myocardial infarction.	N/A	N/A	0	NA	365/3386	310/3243	791/8779	680/6899	143/2302	NA
Sinaga, 2016	observational	Singapore	172/163	2.22/2.44	NA	132/117	61/61.2	12	Composite MACE - Death - MI - TLR - cerebrovascular accident	SeQuent Please pacli-tax-el-coated balloon, B-Braun, Melsungen, Germany)	NA	NA	NA	134/107	88/80	125/113	120/118	52/73	NA

Table 1 (continued)

Characteristics of All included Studies																			
Author, year	Type of Study	Country	Patients (n) (DCB/stent)	Criteria of Small vessel	Procedural success (%) (DCB/stent)	Age (mean) (DCB/stent)	male, n (DCB/stent)	mean follow up (months)	Outcomes reported	DCB type	Stent type	Bail-out stenting rate (%)	Medical Conditions, n (DCB/ stent)						
													History of stroke	History of MI	DM	HTN	Hyperlipidaemia	Current smoker	PAD
Tan, 2021	observational	china	56/212	2.64/2.65	NA	64.96/62.39	34/139	24	No. with angiographic follow- up / MLD/ Diameter stenosis/ Late lumen loss/All cause MACE/Cardiovascular death/ Non-fatal MI/TVR	(SeQuent® Please; B. Braun Melsungen, Germany)	the zotarolimus-eluting stent (Endeavor Resolute, Metronic company) or rapamycin-eluting stent (Firebird-2, Microport company)	NA	5/13	56/212	18/58	21/75	NA	29/94	NA
Chae 2017	RCT	Korea	90/90	2.2 –4 mm	100/100	61.2/62.4	68/63	9	the in-segment late loss (LL) at 9 months measured by quantitative coronary angiography (QCA).	paclitaxel-coated balloon	zotarolimus-eluting stent	NA	4/1	3/4	28/26	25/40	15/18	27/19	NA
Cortese 2010	RCT	Italy	28/29	less than of 2.75 mm	96.4/100	68/67	22/22	6	comparing the efficacy of the Dior PCB (Eurocor, Bonn, Germany) with Taxus Libertè DES	paclitaxe coated balloon	Taxus	NA	NA	5/6	13/11	21/20	17/13	NA	NA
Jeger 2018 and Jeger 2020	RCT	Switzerland and Germany	382/376	(< 3 mm in diameter)	96/98	67/68	295/262	12	non-inferiority of DCB versus DES regarding MACE after 12 months.	paclitaxel	everolimus	NA	16/32	160/133	122/130	324/332	262/259	82/72	27/26

Table 1 (continued)

Characteristics of All included Studies																			
Author, year	Type of Study	Country	Patients (n) (DCB/stent)	Criteria of Small vessel	Procedural success (%) (DCB/stent)	Age (mean) (DCB/stent)	male, n (DCB/stent)	mean follow up (months)	Outcomes reported	DCB type	Stent type	Bail-out stenting rate (%)	Medical Conditions, n (DCB/ stent)						
													History of stroke	History of MI	DM	HTN	Hyperlipidaemia	Current smoker	PAD
Tang 2018 and Tian 2019	RCT	China	116/114	> 2.25 mm and < 2.75 mm	99.1/99.1	60.1/60.5	77/88	9	DCB was non-inferior to the DES for the primary endpoint of 9-month angiographic in-segment %DS,	drug-eluting ammonium salt-paclitaxel	NA	5.2/1.8	8/14	26/28	58/71	78/86	61/55	34/36	NA
Yu 2022	RCT	China	84/79	2.25 –4 mm	97.6/98.7	62.6/64	62/56	12	lumen loss (LLL) of target lesions at the 9-month angiographic follow-up.	paclitaxel-coated	zotarolimus-eluting	2/0	NA	5/4	16/32	50/54	52/39	46/42	NA
Zurakowski 2015	RCT	Poland	100/102	2.25 mm to 3.5 mm.	NA	62.1/64	70/68	9	In-stent late lumen loss (LL) in coronary angiography,	paclitaxel-coated balloon	CoroflexTM	NA	NA	43/35	20/25	79/90	48/60	22/17	12-Dec
Tasi 2022	Observational	Taiwan.	47/59	from 2.0 to 2.25 mm)	NA	65.1/65.1	39/48	12	system. Angiographic, procedural, and clinical outcomes	SeQuent Please Neo	sirolimus-eluting Orsiro	NA	3 / 2	5/7	23/32	44/49	40/42	21/21	6/10

Table 1 (continued)

Characteristics of All included Studies																			
Author, year	Type of Study	Country	Patients (n) (DCB/stent)	Criteria of Small vessel	Procedural success (%) (DCB/stent)	Age (mean) (DCB/stent)	male, n (DCB/stent)	mean follow up (months)	Outcomes reported	DCB type	Stent type	Bail-out stenting rate (%)	Medical Conditions, n (DCB/ stent)						
													History of stroke	History of MI	DM	HTN	Hyperlipidaemia	Current smoker	PAD
Cortese 2020	RCT	Italy	118/114	2.23/2.18	98.3/98.2	64/66	83/87	12	MACE/ total death /cardiac death/MI/ TLR/BARC bleeds type 3 or 5/Vessel thrombosis/ RVD/MLD / acute gain / Stenosis, % of lumen diameter/Binary restenosis/ late loss/ lesion length/net luminal gain	Elutax SV/ Emperor	Xience EES	6.7/ NA	NA	45/34	45/40	77/76	72/63	23/19	NA
Zheng 2020	RCT	China	58/130	A vessel with a diameter between 2.25 and 2.80 mm	98.2/85.4	70.5/NA	44/NA	12	MI/TVR/ death/ procedural success/ LLL/MLD	paclitaxel drug-eluting balloon	everolimus-eluting stent	NA	NA	NA	NA	NA	NA	NA	NA
Tang 2019	RCT	China	36/62	A vessel with a diameter < 2.80 mm	94.4/94.2	65.8/71	25/48	9	MI/TLR/ death/ binary restenosis/ procedural success/ LLL/NLG/ MLD	paclitaxel drug-eluting balloon	paclitaxel-eluting stent	NA	NA	NA	NA	NA	NA	NA	NA
Zhou 2020	RCT	China	50/35	A vessel with a diameter < 2.80 mm	94/95.8	61.9/67.1	37/23	12	MI/TLR/ TVR/ procedural success/ LLL/NLG/ MLD	paclitaxel drug-eluting balloon	paclitaxel-eluting stent	NA	NA	NA	NA	NA	NA	NA	NA

Table 1 (continued)

Characteristics of All included Studies																			
Author, year	Type of Study	Country	Patients (n) (DCB/stent)	Criteria of Small vessel	Procedural success (%) (DCB/stent)	Age (mean) (DCB/stent)	male, n (DCB/stent)	mean follow up (months)	Outcomes reported	DCB type	Stent type	Bail-out stenting rate (%)	Medical Conditions, n (DCB/ stent)						
													History of stroke	History of MI	DM	HTN	Hyperlipidaemia	Current smoker	PAD
sim 2018	Observational	China	78/200	< 2.25 mm	97/96	58/61	70/154	12	target lesion and luminal stenosis	: Paclitaxel-coated balloon (SeQuent Please; B Braun Melsungen AG, Melsungen, Germany)	: Second-generation everolimus-eluting Xience stent (Abbott Vascular, Santa Clara, CA);	NA	NA	NA	55/108	69/136	70/153	42/59	NA
Giannini 2017	Observational	chinsese	90/91	< 2.8 mm	NA	65/66	72/71	12	target lesion and luminal stenosis	: Paclitaxel-coated balloon (SeQuent Please; B Braun Melsungen AG, Melsungen, Germany	Second-generation everolimus-eluting Xience stent (Abbott Vascular, Santa Clara, CA)	NA	NA	46/53	39/37	72/74	71/71	NA	NA

Fig. 2 Risk of bias assessment tool-2 (ROB-2) for RCTs

boundaries for any interventions, suggesting that DCB is not-inferior to DES, and further large volume RCTs should be carried out to validate our results, as shown in Fig. 6.

Secondary clinical outcomes

The pooled analysis of all-cause death reported by 16 studies ($n = 17{,}983$ patients) showed that DCB was non-inferior to DES (OR 0.98, 95% CI [0.69 to 1.40], $p = 0.93$; the pooled studies were homogenous ($p = 0.93$; $I^2 = 9\%$), as shown in Supplementary Fig. 4. Also, the pooled analysis of cardiac death reported by eight studies ($n = 1{,}108$ patients) showed that DCB was non-inferior to DES (OR 1.51, 95% CI [0.78 to 2.93], $p = 0.22$; the pooled studies were homogenous ($p = 0.92$; $I^2 = 0\%$), as shown in Supplementary Fig. 5.

Regarding MI, the pooled analysis of 19 studies ($n = 18{,}409$ patients) showed that DCB was non-inferior to DES (OR 1.07, 95% CI [0.89 to 1.30], $p = 0.47$; the pooled studies were homogenous ($p = 0.54$; $I^2 = 0\%$), as shown in Supplementary Fig. 6.

As to TLR and TVR, the pooled analysis of 18 studies ($n = 17{,}601$ patients) and 11 studies ($n = 2{,}346$ patients), respectively did not favor either of the two interventions (OR 1.04, 95% CI [0.74 to 1.48], $p = 0.82$; and OR 1.00, 95% CI [0.64 to 1.55], $p = 0.99$), respectively. The pooled studies were homogenous for TLR and little heterogenous for TVR with the following values, respectively ($p = 0.25$; $I^2 = 17.34\%$, and $p = 0.09$; $I^2 = 39.10\%$), as shown in Supplementary Figs. 7, 8.

We performed a sensitivity analysis called Leaveoneout for TVR, and no single study had a disproportional effect on the pooled OR, which varied from 0.86 by excluding Liistro et al. and by 1.11 when excluding Zheng et al., as shown in Supplementary Fig. 9.

Regarding stent thrombosis, the pooled analysis of 12 studies ($n = 2{,}788$ patients) showed that DCB was non-inferior to DES (OR 0.87, 95% CI [0.46 to 1.65], $p = 0.67$; the pooled studies were homogenous ($P = 0.96$; $I^2 = 0\%$), as shown in Supplementary Fig. 10.

Angiographic outcomes

As to MLD and NLG, the pooled analysis of 15 studies ($n = 2{,}195$ patients) and eight studies ($n = 2{,}195$ patients), respectively showed that DCB was superior to DES with the following values, respectively (MD -0.19, 95% CI [-0.32 to -0.06], $p < 0.001$, and MD -0.21, 95% CI [-0.40 to -0.01], $p = 0.04$), respectively, as shown in Figs. 7 and 8. The pooled studies for MLD and NLG were heterogenous with the following values ($p < 0.001$; $I^2 = 90.96\%$, and $p < 0.001$; $I^2 = 95.11\%$), respectively, as shown in Figs. 7 and 8.

We performed a sensitivity analysis called Leaveoneout for MLD, and no single study had a disproportional effect

Table 2 NOS scale for observational studies

Cohort studies															
Baseline							**Selection**			**Comparability**	**Outcome**				**Quality Score**
Study Title	**First Author**	**Year**	**Study Design (Prospective or retrospective)**	**mean follow up (months)**	**Sample (n) (DCB/stent)**	**Age at baseline mean (Year) (DCB/stent)**	**Representativeness of the exposed cohort**	**Selection of the non exposed cohort**	**Ascertainment of exposure**	**Demonstration that outcome of interest was not present at start of study**	**Comparability of cohorts on the basis of the design or analysis**	**Assessment of outcome**	**Was follow-up long enough for outcomes to occur**	**Adequacy of follow up of cohorts**	
Shin 2016	Eun-Seok Shin	2016	Retrospective cohort	12.4	44/22	60.6/58.7	*	*	*	*	**	*	*	*	Good (9)
Silverio 2020	Angelo Silverio	2022	Retrospective cohort	36	1154/13,634	68/69	*	*	*	*	*	*	*	*	Good (9)
SINAGA 2016	DASDO ANTONIUS SINAGA	2016	Retrospective cohort	12	172/163	61/61.2	*	*	*	*	*	*	*	*	Good (8)
Tan 2021	Qiang Tan	2021	Retrospective cohort	24	56/212	64.96/62.39	*	*	*	*	**	*	*	*	Good (9)
Tasi 2022	Cheng-Hsuan Tsai	2022	Retrospective cohort	12	47/59	65.1 / 65.1	*	*	*	*	**	*	*	*	Good (9)
Giannini 2017	Francesco Giannini	2017	Retrospective cohort	12	90/91	65/66	*	*	*	*	**	*	*	*	Good (9)
Sim 2018	Hui Wen Sim	2018	Retrospective cohort	12	87/200	58/61	*	*	*	*	**	*	*	*	Good (9)

on the overall MD. However, in NLG, only two studies Giannini et al., and Zhou et al., when excluded, the overall MD remains significant in favor of DCB, as shown in Supplementary Figs. 11, 12.

The pooled analysis of the LLL reported by 13 studies ($n = 1{,}936$ patients) did not favor either of the two interventions (MD -0.06, 95% CI [-0.22 to 0.09], $p = 0.43$; the pooled studies were heterogenous ($P = 0.01$; $I^2 = 96.82\%$), as shown in Supplementary Fig. 13.

However, when we performed a sensitivity analysis upon excluding Liistro et al., the pooled analysis favored DCB group over DES group (MD -0.12, 95% CI [-0.23 to -0.01], $p = 0.03$), as shown in Supplementary Fig. 14.

On the other hand, the pooled analysis of the in-segment binary restenosis reported by eight studies ($n = 15{,}841$ patients) favored the DES group over the DCB group (OR 1.66, 95% CI [1.03 to 2.68], $p = 0.04$; the pooled studies were heterogenous ($p = 0.05$; $I^2 = 49.92\%$), as shown in Supplementary Fig. 15. However, when we performed a sensitivity analysis upon excluding Liistro et al., the pooled analysis did not show any significant difference between the two interventions (OR 1.49, 95% CI [0.95 to 2.33], $p = 0.08$), as shown in Supplementary Fig. 16.

Discussion

Our study systematically retrieved all studies comparing DCB intervention to DES intervention for the management of patients with small CAD including 20 trials entered the quantitative analysis comprising 18,469 patients. Our pooled analysis did not favor DCB, when compared to DES, regarding MACE, and further subgroup analyses based on the type of study, language, and the indication of the interventions, yet, did not favor DCB over DES. Moreover, there was no significant difference in terms of all-cause death, cardiac death, MI, TLR, stent thrombosis, or TVR between the two studied groups. In terms of in-segment binary restenosis, DCB had higher odds, however; when excluding Liistro et al. 2013, the pooled analysis showed non-inferiority with no superiority of DES over the DCB. As to angiographic outcomes, our pooled analysis favored DCB intervention compared to DES according to MLD and NLG. Regarding LLL, the pooled analysis did not favor DCB or DES, however; when excluding Liistro et al. 2013, the pooled analysis favored DCB.

PCI, for small CAD, is still challenging due to the increased risk of technical complications, acute vessel closure, and the necessity for multiple revascularization procedures [28, 29]. DES is still the standard treatment approach for PCI [30]. However, DES implantation can cause damage to the arterial wall, triggering a cascade of cellular proliferation and migration that leads to neointimal hyperplasia [31]. In contrast, DCB can

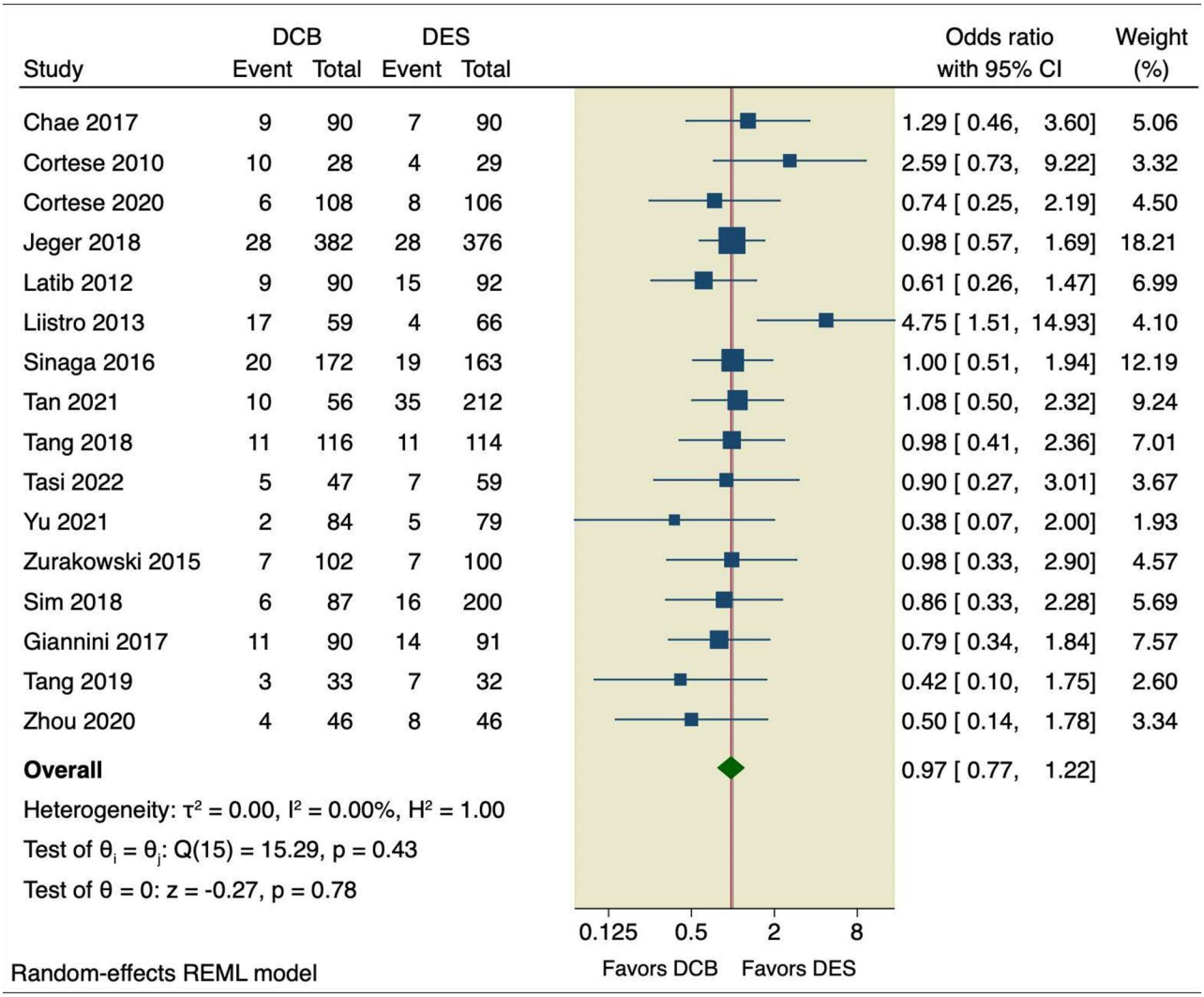

Fig. 3 Forest plot of MACE

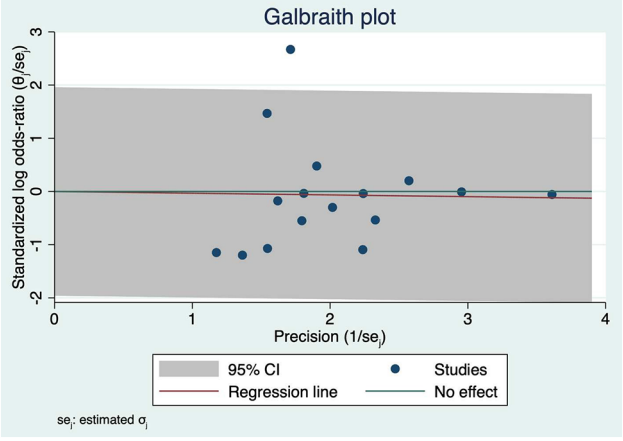

Fig. 4 Galbraith plot of MACE

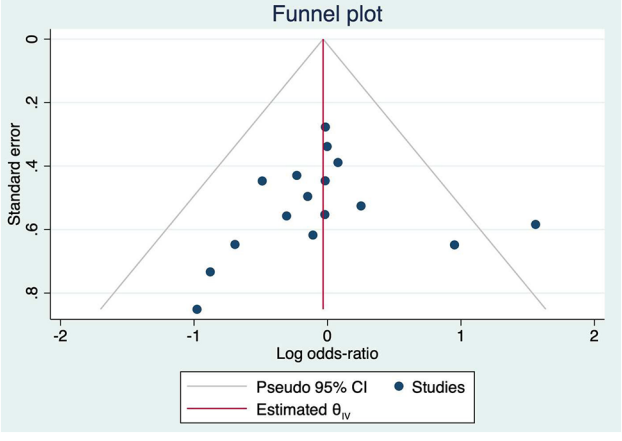

Fig. 5 Funnel plot of MACE ($p = 0.186$)

administer antiproliferative drugs directly into the vessel wall without the need for metal struts, which can

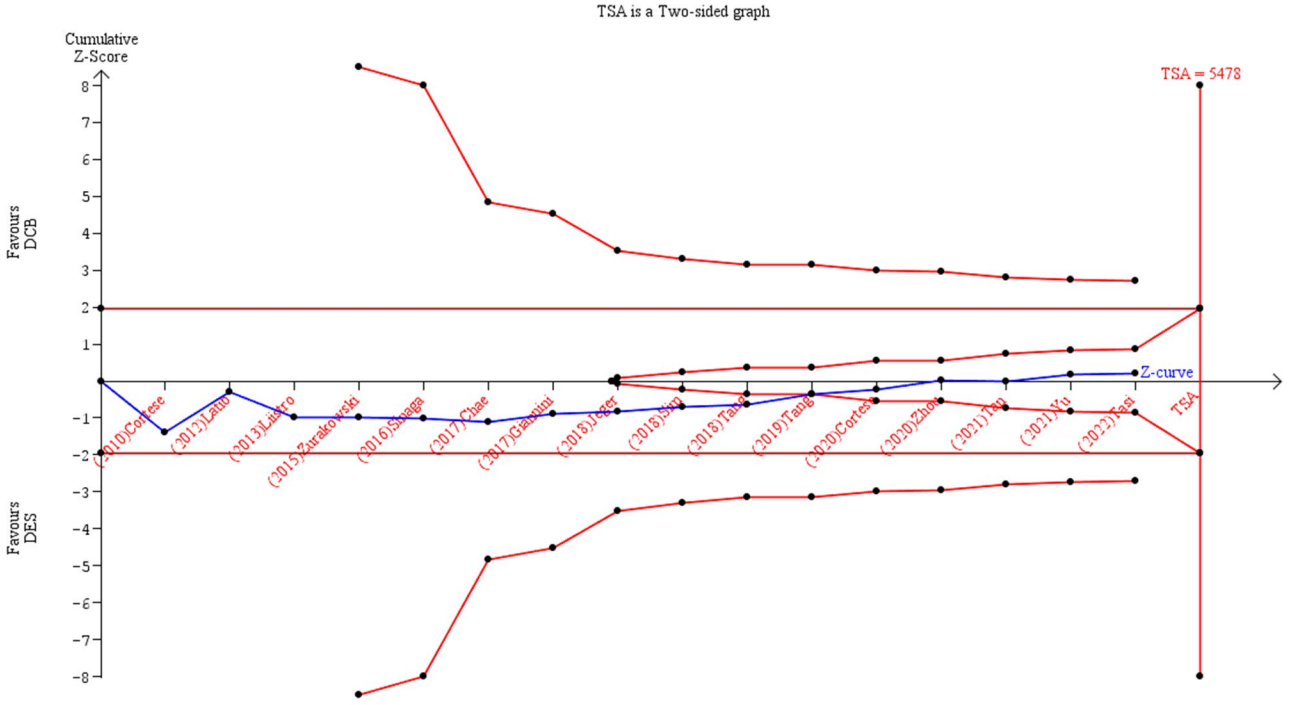

Fig. 6 A trial sequential analysis (TSA) for 16 studies assessing the incidence of MACE of which the cumulative Z-line on the curve did not cross either the conventional boundaries of benefit nor the trial sequential monitoring boundaries for any interventions, suggesting that DCB is not-inferior to DES, and further large volume RCTs should be carried out to validate our results. A diversity-adjusted required information size of 5,478 patients was calculated using an alpha error of 0.05, a beta error of 0.20 (power 80%), and a control event proportion of 9.9%, as calculated from the control group in this meta-analysis

inhibit endothelial proliferation and adverse remodeling [32]. Therefore, theoretically, DCB implantation is a more effective treatment option for small-vessel coronary artery lesions compared to DES.

The current disease guidelines and consensus do not offer an optimal treatment selection for patients with de novo CAD. One potential solution is the use of DCB, which has shown promising outcomes. However, it has certain drawbacks such as a shorter balloon inflation time and concerns about its impact on blood flow, which raises questions about whether it delivers enough medication to the vessel wall and if it can sustain drug concentration at levels comparable to those achieved with DES [33]. Furthermore, there are cases where bailout stenting is necessary, which is an important strategy in situations where angiography results are suboptimal, significant dissection occurs, or there is acute elastic recoil following DCB treatment, which in turn makes it difficult to directly compare the effectiveness of DCB versus DES. Several studies [9, 34]– [37] have recently used meta-analytic techniques to compare the safety and effectiveness of DCB versus DES for treating de novo lesions in small-vessel coronary disease.

One such meta-analysis by Li et al., [9] found that DCB was not inferior to DES and produced positive outcomes in terms of non-fatal MI, while being comparable to DES in terms of TLR. Therefore, it is suggested that DCB can be a recommended treatment strategy for patients with de novo small-vessel coronary artery disease. However, their results were in line with our results regarding TLR, but not for MI; also, they had numerous falls as (1) assessment of non-fetal MI, not all MI; this could be a source of bias due to the higher incidence of fetal MI in DCB compared to DES, (2) their included studies used different device types or generations that could impact the overall results, (3) the follow-up reported in their studies were short.

Another meta-analysis by Megaly et al., [38] found that DCB decreased LLL compared to DES and a comparable risk of MACE, death, TLR, and TVR in both interventions. Their results were in line with our results regarding LLL, and other clinical outcomes. Moreover, another meta-analysis by Abdelaziz et al., [39] found that DCB was not inferior to DES in terms of clinical and angiographic outcomes in patients with AMI, highlighting the necessity of DCB as an alternative feasibility strategy in AMI patients.

Morever, when Li et al., [35] compared DCB to DES in patients with DM and small vessel CAD, they found that DCB did not show superiority compared to DES in terms of MLD and NLG. Moreover, DCB had a lower probability of MACE, LLL, and binary restenosis. Additional

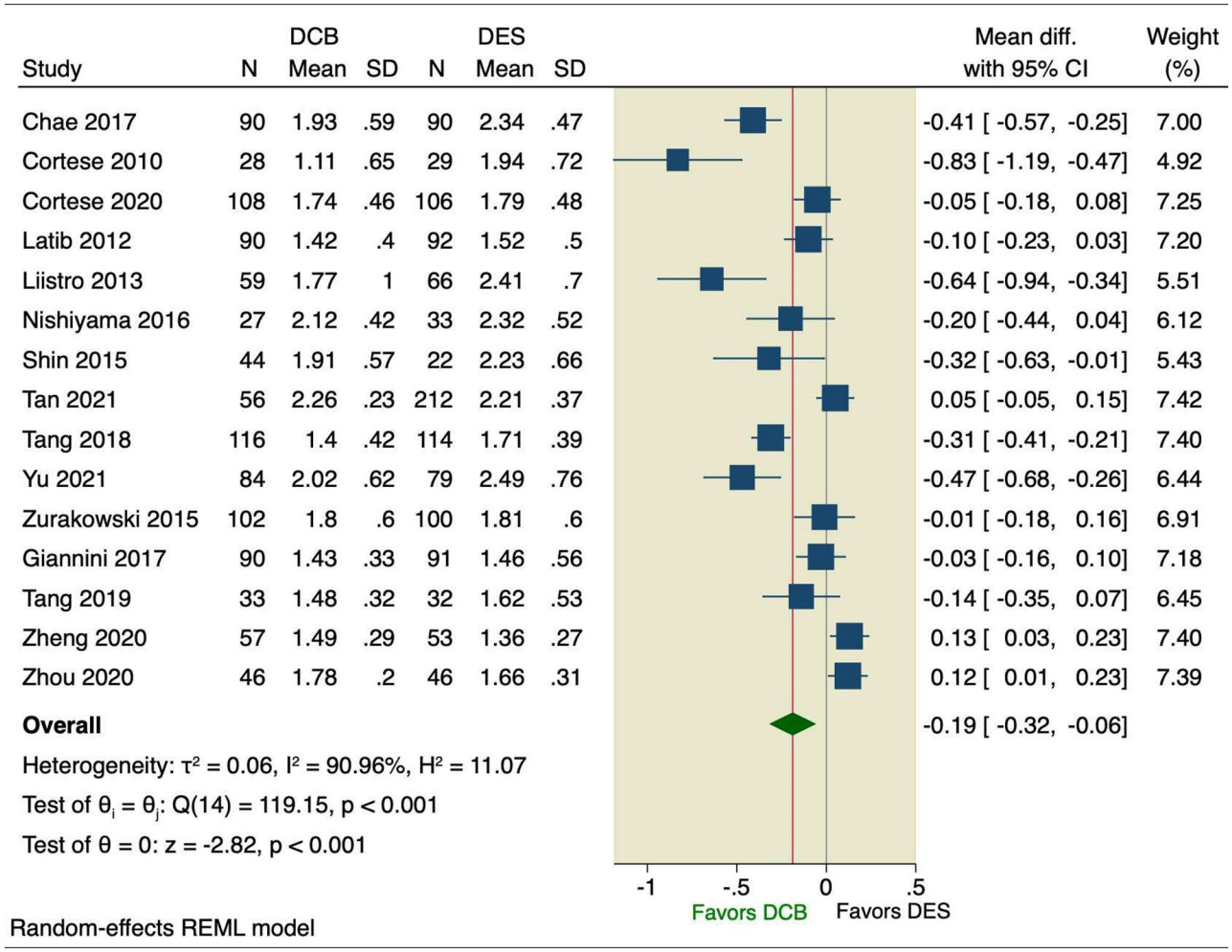

Fig. 7 Forest plot of MLD

analysis indicated that DCB resulted in fewer MI, TLR, and TVR occurrences than DES, while having a death rate comparable to DES. However, their results are in line with our results regarding LLL, we did not find a significant difference in terms of MACE, MI, TLR, and TVR, and on the other hand; we found DCB had higher odds, when compared to DES. Some limitations of their study should be addressed, such as the short follow-up periods reported in their included studies, the limited number of studies in each outcome reported, and the significant heterogeneity found in some reported outcomes, which was not solved via a sensitivity analysis restricting to the limited included studies.

Additionally, in align with our results, a recent network meta-analysis addressing the efficacy of endovascular approaches as DCB and DES in peripheral artery diseases as femoropopliteal (FP) and infrapopliteal (IP) lesions including 33 RCTs with a total of 5745 patients, found that in FP lesions, DCBs and DESs had comparable MAEs. However, in IP lesions, DESs had significantly lower rates of MAEs highlighting the beneficial effect of DES in IP lesions [40].

Our study, to the best of our knowledge, is the most comprehensive meta-analysis addressing the safety and effectiveness of DCB in patients with small CAD as it included 24 studies; also, it had many stratifications and sub-group analyses that previous meta-analyses had missed due to the limited amount of papers included: (1) we stratified the incidence of MACE according to the indication of intervention used, the type of study, either RCT and observational, and the language of the included studies, (2) the statistical power of our meta-analysis is substantially higher, leading to more reliable results, (3) the inclusion of 11 outcomes allowed comprehensive evaluation of the therapeutic efficacy and safety of DCB for small-vessel CAD, (4) we conducted a TSA analysis, so that we can assess if the evidence is conclusive.

There are some limitations to be addressed in our study. Firstly, the included studies in terms of MACE and small vessels definition have high statistical heterogeneity

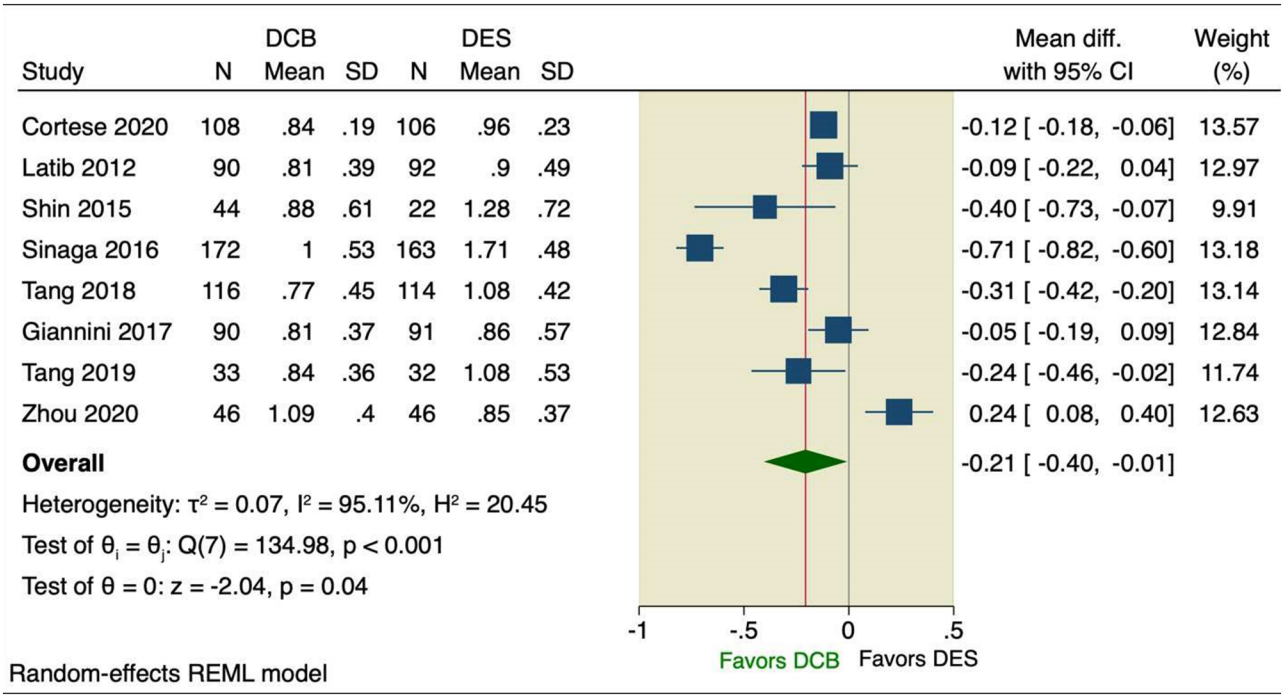

Fig. 8 Forest plot of NLG

which could lead to some biases in the pooled estimates, however, sensitivity analyses were performed to test the robustness of the results. Secondly, the study was unable to compare the effectiveness of different types of DCB or DES as there was limited data available, so this study could be a hypothesis-generating study on some insights on the difference between DCB and DES. Third, bailout stenting with BMS in the DCB may make it difficult to directly compare the effectiveness of DCB versus DES. Fourth, the sequence of devices (DEB first or BMS first) could have contributed to heterogeneity. Lastly, the criteria for defining small vessels and the length of follow-up varied between the included studies.

Impact on daily practice

Interventional approaches for the management of small CAD, yet, not well established in the clinical practice, here we conducted a systematic review and meta-analysis assessing the efficacy and safety of DCB compared to DES in the setting of small CAD. Our study showed that DCB intervention, when compared to DES setting, showed non-inferiority according to clinical outcomes assessed as MACE, all-cause death, cardiac death, MI, TLR, TVR, and stent thrombosis; however, it showed superiority in angiographic outcomes as MLD and NLG. While there was no significant difference in terms of LLL, after sensitivity analysis, DCB was superior to DES. On the other hand, DCB was associated with higher odds regarding in-segment binary restenosis, and by performing a sensitivity analysis, DCB was not-inferior to DES. So, DCB intervention is a safe and feasible intervention to treat small coronary artery disease in patients undergoing PCI. This study can be a guide of using DCB as a primary intervention in patients with de novo small CAD undergoing PCI regards to its safety profile and feasibility approach.

Conclusion

In conclusion, the present meta-analysis suggested that, in terms of clinical outcomes, DCB is comparable to DES in the therapeutic efficacy and safety of de novo small CAD. However, regarding angiographic outcomes, DCB showed favorable results in terms of MLD, NLG outcomes, and LLL but after a sensitivity analysis model. Hence, DCB should be validated as an alternative treatment of choice for patients presented with small CAD with respect to the characteristics of the patients, and the complexity of the lesions. Large-volume RCTs with long-term follow-up durations are necessary to gain a more comprehensive clue understanding of the safety and efficacy of DCB in the treatment of small vessel CAD.

Abbreviations

DCB	Drug-coated balloons
DES	Drug-eluting stents
CAD	Coronary artery disease
PCI	Percutaneous coronary intervention
PRISMA	Systematic Reviews and Meta-analysis
TSA	Trial sequential analysis
OR	Odds ratio
NA	Not Assigned

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12872-024-04426-5.

Supplementary Material 1

Supplementary Material 2

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Nothing to declare.

Author contributions
Ahmed Abdelaziz: Conceptualization, Supervision, data collection revision, statistical analysis, writing – original draft and editing. Hanaa Elsayed: screening, data collection, original draft writing Karim Atta: Full-text screening, data collection, data validation, TSA analysis. Muhammad Desouky: data validation, data revision, Final version, Mahmoud Gomaa: data collection, writing – revision, Manuscript revision. Hallas Kadhim: data collection, quality assessment. Ahmed Mechi: data collection, data validation, Final version, TSA analysis. Mohamed Abdelaziz: screening, data collection, revision of data collection, quality assessment. Mahmoud Ezzat: screening, data collection, data revision for analysis. Manar Alaa Mabrouk: quality assessment, data collection, writing – revision, TSA analysis. Mohamed Hatem Elabban: summary and characteristics, quality assessment, writing – revision. Emad Addin Zawaneh: summary and characteristics, quality assessment, writing – revision. Abdelrahman Hafez: summary and characteristics, quality assessment, writing – revision. Mohamed Yasser Elnaggar: quality assessment, manuscript drafting and writing.Ahmed O. Sena: writing – original draft, data revision, Manuscript revision. Ahmed Bahnasy: summary and characteristics, writing – revision, TSA analysis. Emad Singer: writing – revision, data revision, Manuscript revision, supervision.

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

Declarations

Ethical approval
Not applicable.

Research involving human participants and/or animals
Not applicable.

Informed consent
Not applicable.

Consent for publication
Not applicable.

Financial interests
The authors declare they have no financial interests.

Competing interests
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