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Outcomes With Drug-Coated Balloons vs. Drug-Eluting Stents in Small-Vessel Coronary Artery Disease

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Outcomes With Drug-Coated Balloons vs. Drug-Eluting Stents in Small-Vessel Coronary Artery Disease

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ABSTRACT

Background: The use of drug-coated balloons (DCBs) in small-vessel coronary artery disease (SVD) remains controversial.
Methods: We performed a meta-analysis of all randomized controlled trials (RCTs) reporting the outcomes of DCB vs. DES in de-novo SVD. We included a total of 5 RCTs (1459 patients), with (DCB $n = 734$ and DES $n = 725$).
Results: Over a median follow-up duration of 6 months, DCB was associated with smaller late lumen loss (LLL) compared with DES (mean difference −0.12 mm) (95% confidence intervals (CI) [−0.21, −0.03 mm], $p = 0.01$). Over a median follow-up of 12 months, both modalities had similar risk of major adverse cardiovascular events (MACE) (8.7% vs. 10.2%; odds ratio (OR): 0.94, 95% CI [0.49–1.79], $p = 084$), all-cause mortality (1.17% vs. 2.38%; OR: 0.53, 95% CI [0.16–1.75], $p = 0.30$), target lesion revascularization (TLR) (7.9% vs. 3.9%; OR: 1.26, 95% CI [0.51–3.14], $p = 0.62$), and target vessel revascularization (TVR) (8.2% vs. 7.8%; OR: 1.06, 95% CI [0.40–2.82], $p = 0.91$). DCBs were associated with lower risk of myocardial infarction (MI) compared with DES (1.55% vs. 3.31%; OR: 0.48, 95% CI [0.23–1.00], $p = 0.05$, I2 = 0%).
Conclusion: PCI of SVD with DCBs is associated with smaller LLL, lower risk of MI, and similar risk of MACE, death, TLR, and TVR compared with DES over one year. DCB appears as an attractive alternative to DES in patients with de-novo SVD, but long-term clinical data are still needed.

1. Introduction

Small vessel coronary artery disease (SVD) is often treated with percutaneous coronary intervention (PCI) [1], but is a complex lesion subset and is associated with high risk of major adverse cardiovascular events (MACE). Current treatment options for SVD include standard balloon angioplasty, drug-eluting stents (DES), and drug-coated balloons (DCBs). Balloon angioplasty is associated with high restenosis rates due to elastic recoil and adverse remodeling [2]. DES have been associated with worse outcomes in smaller compared with larger vessels [3–5] likely due to the small vessel caliber with little room to accommodate neointimal tissue growth.

Drug-coated balloon (DCB)-only PCI has emerged as an alternative treatment option to de-novo coronary artery disease and in-stent restenosis (ISR). [6–8] However, the outcomes with DCB in SVD have been controversial [9–15]. We performed a systematic review and meta-analysis to compare the angiographic and clinical outcomes of DCB vs. DES in SVD.

2. Methods

The current meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (PRISMA) [16]. We performed a systematic computerized search limited to the English language through Medline, Embase, and Cochrane databases from January 2000 to January 2021 using the following search

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terms separately and in combination; "Drug-eluting balloon," "DEB," "drug-coated balloon," "DCB," "paclitaxel-coated balloon," "PCB," "small-vessel coronary artery disease," and "small-vessel disease." We screened the retrieved studies' bibliographies, previous reviews, and ClinicalTrials.gov for any relevant studies not found through the initial search.

2.1. Study selection and data collection

We included randomized controlled trials (RCTs) that compared outcomes with DCB vs. DES in the treatment of de-novo SVD (reference vessel diameter ≤ 3 mm) (Fig. S1). In the DCB arm, stenting was allowed only as a bailout strategy in case of suboptimal results, defined as persistent residual stenosis, vessel recoil, or flow-limiting dissection.

The data were extracted by two independent investigators (KB, MM) and confirmed by a third investigator (MS). The data included baseline study characteristics, baseline clinical and angiographic characteristics of the included patients and lesions, and the outcomes of interest. Discrepancies among investigators were settled by consensus. The included studies' bias risk was assessed using the Cochrane risk assessment tool for RCTs (Table S2) [17]. Potential publication bias was assessed using the Egger test by visually examining the funnel plots (Fig. S2).

2.2. Study outcomes

The clinical outcomes of the current study included periprocedural myocardial infarction (MI) and long-term outcomes, including MACE, target lesion revascularisation (TLR), target vessel revascularisation (TVR), MI, all-cause mortality, and angiographic late lumen loss (LLL) measured by quantitative coronary angiography. Definitions of outcomes by each study included are shown in Table S1. Results were reported at the longest follow-up time available and according to the intention-to-treat analysis.

2.3. Statistical analysis

Statistical analysis was conducted using Review Manager software (Version 5.3.5. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). Descriptive analyses were conducted using frequencies for categorical variables and means with standard deviations (SD) for continuous variables. Categorical variables were compared using Fisher's exact or chi-square tests, while continuous variables were analysed using the two-sample *t*-test. Tests were two-tailed, and a *p*-value of ≤0.05 was considered statistically significant.

Odds ratios (ORs) or mean differences (MD) with 95% confidence intervals (CIs) were presented as summary statistics. Statistical heterogeneity across trials was assessed by I^2 statistics, with I^2 statistic values <25%, 25% to 50%, and >50% considered as low, moderate, and a high degree of heterogeneity, respectively. The DerSimonian and Laird random-effects model and inverse variance model were used to calculate OR and MD, respectively. We performed a sensitivity analysis excluding the study by Cortese et al. given use of a first-generation DCB and lack of adequate lesion preparation (25%) [11]. We performed another sensitivity analysis comparing DCBs vs. second-generation DES [10,12,14].

3. Results

We included a total of 5 RCTs (1459 patients), with (DCB $n = 734$ and DES $n = 725$). The characteristics of the included studies are described in Table 1. Only three studies compared the outcomes with DCB vs. second-generation DES [10,12,14]. We used both the 6 months (for angiographic outcomes) and 3 years (for clinical outcomes) publications for the BELLO study [13,18]. Bailout stenting in the DCB-only group occurred in 10% of patients ranging between 5.1% to 35.7%, with recent studies reporting fewer bailout stenting events. The baseline clinical and angiographic characteristics of the included patients and lesions are summarized in Table 2.

3.1. Outcomes

Both technical (98.8 vs. 99.2%, $p = 0.96$) and procedural (97.1% vs. 98.1%, $p = 0.26$) success was similar between both groups. There was no difference in the risk of periprocedural MI with DCB compared with DES (2.2% vs. 3.9%; OR: 0.56, 95% CI [0.21, 1.48], $p = 0.25$, $I^2 = 0\%$) (Figs. 1 and 2).

During a median follow-up duration of 6 months (range 6–9 months), DCBs were associated with smaller LLL compared with DES (MD: −0.12 mm (95% CI [−0.21, −0.03 mm], $p = 0.01$, $I^2 = 56\%$)). Over a median follow-up of 12 months (range 9–36 months), both arms had similar risk of MACE (8.7% vs. 10.2%; OR: 0.94, 95% CI [0.49, 1.79], $p = 0.84$, $I^2 = 59\%$), all-cause mortality (1.17% vs. 2.38%; OR: 0.53, 95% CI [0.16, 1.75], $p = 0.30$, $I^2 = 0\%$), TLR (7.9% vs. 3.9%; OR:

Table 1
Characteristics of the included studies.

Study	Trial/registry	Study type	Number of patients with DCB/DES	Balloon/stent type	Country (# of centers)	Follow-up time (months)	Enrolment dates	Vessel size	Bailout stenting %	Primary endpoint
Cortese et al. 2020	PICCOLETO II	RCT	118/114	Elutax DCB (AR Baltic Medical, Vilnius, Lithuania)/Xience DES (Boston Scientific, USA)	Europe (5)	12	May 2015 – May 2018	2.00–2.75 mm	6.8%	In-lesion LLL at 6 months
Tian et al. 2020	RESTORE-SVD	RCT	116/114	RESTORE DCB (Cardionovum, Germany)/RESOLUTE DES (Medtronic, USA)	China (12)	24	August 2016 – June 2017	2.25–2.75 mm	5.2%	Percentage diameter stenosis at 9 months
Jeger et al. 2018	BASKET-SMALL 2	RCT	382/376	SeQuent Please DCB (B. Braun, Germany)/Xience (Abbott Vascular, USA) or Taxus or Promus DES (Boston Scientific, USA)	Europe (14)	12	April 2012 – February 2017	<3 mm in diameter	5.1%	MACE at 12 months
Latib et al. 2012	BELLO	RCT	90/92	IN.PACT Falcon DCB (Medtronic, USA)/Taxus Liberte DES (Boston Scientific, USA)	Italy (15)	6–36 months	Not discussed	<2.8 mm	20.2%	In-segment LLL ta 6 months
Cortese et al. 2010	PICCOLETO	RCT	28/29	Dior DCB (Eurocor, Germany)/Taxus DES (Boston Scientific, USA)	Italy (1)	9	August 2007 and August 2008	≤2.75 mm	35.7%	Percentage diameter stenosis at 6 months

DCB: drug-coated balloon; DES: drug-eluting stent; LLL: late lumen loss; MACE: major adverse cardiovascular events; RCT: arandomized controlled trial.

Table 2
Baseline characteristics of the included patients and lesions.

	DCB (n = 734)	DES (n = 725)	p-value
Age mean ± SD	65.30 ± 10.23	66.47 ± 10.40	0.030
Men %	74.68	73.37	0.609
Multivessel Disease %	70.96 [588]	66.46 [582]	0.110
Hypertension %	78.01	81.75	0.086
Dyslipidemia %	66.02	64.76	0.652
Diabetes %	35.79	37.02	0.664
Current smoking %	22.11	20.16	0.396
Previous MI %	38.46	32.12	0.013
Family history of CAD %	36.78	30.73	0.017
Prior CABG	7.37	7.56	0.969
Prior PCI	53.93	52.69	0.673
Vessel involved			
LAD	28.83	27.12	0.503
LCx	40.47	39.28	0.681
RCA	17.44	19.20	0.423
Diagonal	14.24 [206]	10.97 [206]	0.395
OM/Ramus Intermedius	13.54 [206]	17.22 [206]	0.369
PDA/PL	21.31 [206]	22.26 [206]	0.909
LVEF Baseline mean ± SD	58.18 ± 4.77	59.60 ± 4.219	$p < 0.001$
Lesion/procedural characteristics			
Bifurcation lesion	8.31 [528]	9.84 [519]	0.451
AHA B2/C Lesion	44.47 [234]	46.67 [235]	0.700
Minimal luminal diameter (mm)	0.61 ± 0.25	0.61 ± 0.26	1.000
Reference vessel diameter (mm)	2.42 ± 0.25	2.41 ± 0.29	0.480
Lesion length (mm)	12.91 ± 6.46	12.81 ± 6.27	0.764
Predilation	80.21 [738]	78.93 [731]	0.587
Bailout stenting	10.04 [328]	0.9 [228]	p < 0.001
Procedural success	97.11 [738]	98.13 [731]	0.267
Lesion success	98.85 [262]	99.20 [257]	0.967

CABG: Coronary artery bypass graft; CAD: coronary artery disease; DCB: drug-coated balloon; DES: drug-eluting stent; LAD: left anterior descending; LCx: left circumflex; LVEF: Left ventricular ejection fraction; MI: Myocardial infarction; OM: obtuse marginal; PCI: Percutaneous coronary intervention; PDA: posterior descending artery; PL: posterolateral; RCA: right coronary artery.
Numbers between square brackets represent the number of subjects with a reported variable when different from the baseline.

1.26, 95% CI [0.51, 3.14], $p = 0.62$, $I^2 = 54\%$), and TVR (8.2% vs. 7.8%; OR: 1.06, 95% CI [0.40, 2.82], $p = 0.91$, $I^2 = 46\%$) (Figs. 2 and 3). DCB was associated with lower risk of MI compared with DES (1.55% vs. 3.31%; OR: 0.48, 95% CI [0.23, 1.00], $p = 0.05$, $I^2 = 0\%$).

On sensitivity analysis and exclusion of the study by Cortese et al. 2010, both modalities had similar risk of MACE (OR: 0.74, 95% CI [0.43, 1.27], $p = 0.28$, $I^2 = 39\%$), all-cause mortality (OR: 0.46, 95% CI [0.13, 1.71], $p = 0.25$, $I^2 = 0\%$), TLR (OR: 0.87, 95% CI [0.40, 1.89], $p = 0.72$, $I^2 = 23\%$), and TVR (OR: 0.68, 95% CI [0.29, 1.59], $p = 0.38$, $I^2 = 0\%$). DCBs remained associated with lower risk of MI compared with DES (OR: 0.43, 95% CI [0.20, 0.92], $p = 0.03$, $I^2 = 0\%$). This sensitivity analysis yielded similar results with much reduction in heterogeneity (Fig. S3).

DCB had similar risk of MACE (OR: 0.97, 95% CI [0.61, 1.53], $p = 0.89$, $I^2 = 0\%$), all-cause mortality (OR: 0.60, 95% CI [0.07, 4.90], $p = 0.63$, $I^2 = 0\%$), TLR (OR: 1.29, 95% CI [0.53, 3.18], $p = 0.57$, $I^2 = 0\%$), TVR (OR: 0.76, 95% CI [0.42,1.39], $p = 0.37$, $I^2 = 0\%$), and MI (OR: 0.48, 95% CI [0.21, 1.08], $p = 0.08$, $I^2 = 0\%$) compared with second-generation DES (Fig. S4). A summary of the study results is shown in Fig. 4.

4. Discussion

The main findings of our study can be summarized as follows: 1) the use of DCB in SVD PCI is associated with smaller late lumen loss over 6 months and a lower incidence of MI during a median follow-up of 12 months, 2) both DCBs and DES are associated with a similar risk of MACE, death, TLR, and TVR when used in PCI of SVD, 3) When comparing DCBs and second-generation DES, both modalities were comparable with a similar risk of clinical events at a median follow-up of 12 months.

In our analysis, DCBs were associated with lower risk of MI compared with DES during a median follow-up of 1 year. DES are currently commonly used in SVD PCI. Other options include regular balloon angioplasty or medical therapy, which might not be adequate in severely symptomatic patients or when the goal is to achieve complete revascularization. However, DES may have limitations in SVD, as suggested by the higher MI risk with DES in our study. DES are associated with neointimal hyperplasia and late occurrence of neoatherosclerosis and stent thrombosis, which can be exaggerated in small vessels with little room to accommodate the neointima [19]. DES had more LLL in our study. The risk of ISR is higher in smaller caliber vessels, longer lesions, and patients with diabetes mellitus, that are commonly associated with SVD [20]. Previous studies have demonstrated that the risk of MACE, including MI, was almost double in small vessels as compared with large vessels treated with DES [4,5]. It is possible that with further follow-up, the gap favoring DCB will widen given that the current-generation DES have a perpetual 2% yearly risk of stent-related adverse events [21], but longer-term studies are required.

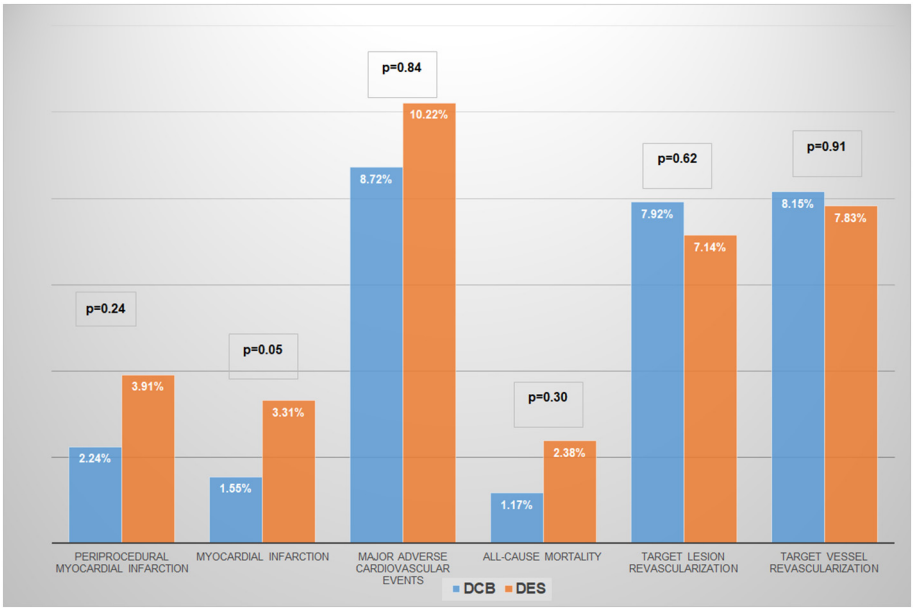

Fig. 1. Outcomes with drug-coated balloons vs. drug-eluting stents in small vessel coronary artery disease. DCB: drug-coated balloon; DES: drug-eluting stent.

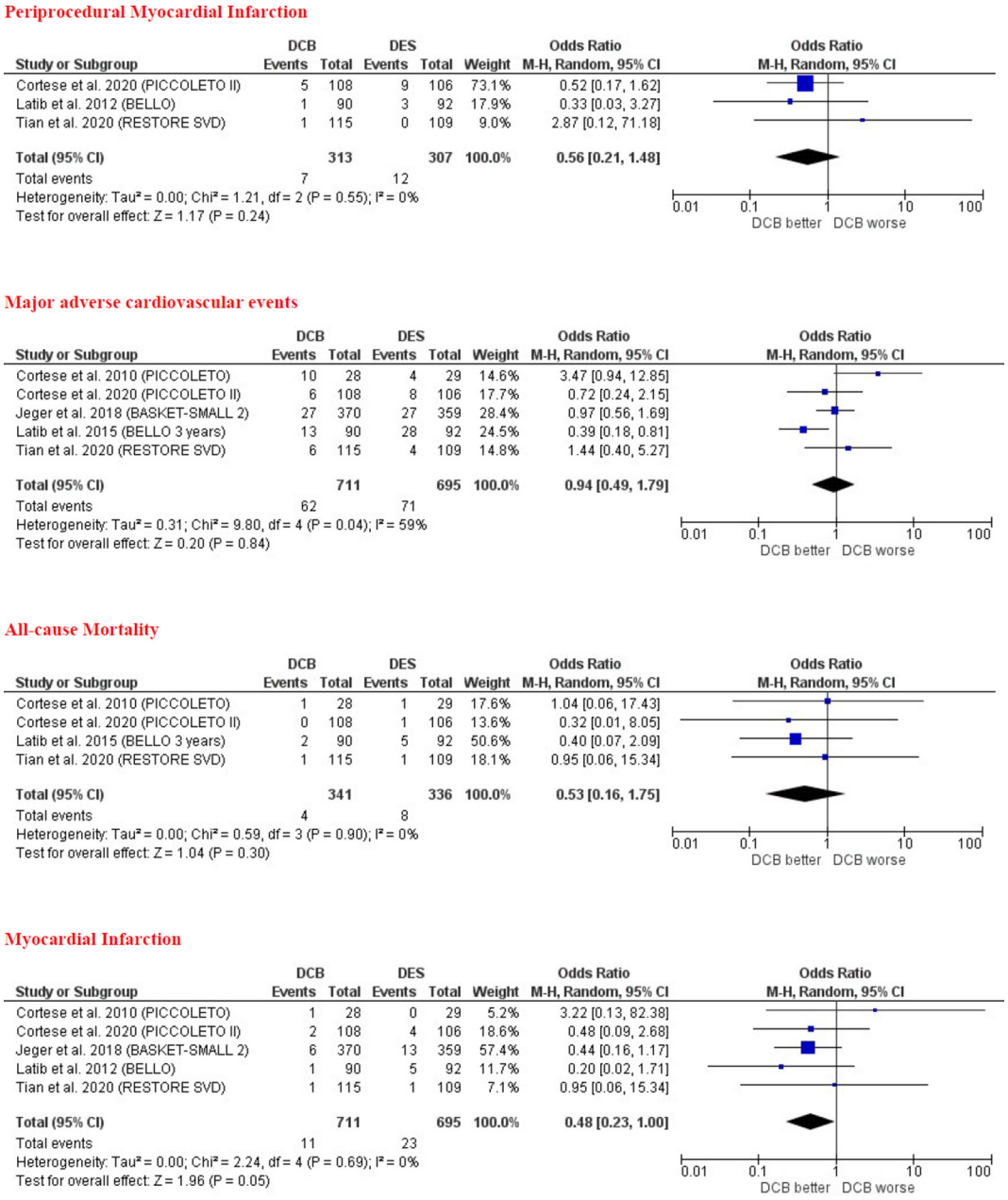

Fig. 2. Pooled analysis of the odds of periprocedural myocardial infarction, major adverse cardiovascular events, all-cause mortality, and myocardial infarction with drug-coated balloons vs. drug-eluting stents in small vessel coronary artery disease; the summary statistic is the odds ratios and mean differences calculated according to the Mantel-Haenszel method with random effects, respectively; marker size is proportional to the study weight. DCB: drug-coated balloon; DES: drug-eluting stent.

The use of DCBs in SVD offers many advantages, mainly due to avoiding permanent prosthesis implantation. Having a smaller profile, they are more deliverable in smaller vessels compared with DES. They are more attractive to use in patients at higher bleeding risk, as the recommended duration of dual antiplatelet therapy is only four weeks [12,22]. Most importantly, DCBs are associated with vascular healing and positive remodeling, particularly in small coronary lumens [23,24]. In our analysis, late lumen loss was lower with DCBs compared with DES at six months, an effect that is expected to be more pronounced with more extended angiographic follow-up.

The use of DCBs in SVD has limitations. DCBs require adequate lesion preparation, which sometimes can be difficult and carries the risk of suboptimal results (e.g., persistent residual stenosis and dissections), necessitating bailout stenting. Iatrogenic dissections have a higher chance of healing with DCBs [25]. The risk of restenosis is higher type for C or greater dissections, hence such lesions should be treated with bailout stenting. In contrast, types A and B dissections can be treated with a DCB-only strategy. Our study found that the rate of bailout stenting in more recent studies did not exceed 7%, which appears acceptable. The acceptance of this strategy, especially by less experienced operators, might be a challenge as the default response to most dissections is stenting. Another limitation of DCBs is that, unlike DES, the class effect of DCBs cannot be established. The notion that "not all DCBs are created equal" is crucial in understanding clinical outcomes and choosing the right tool. There is heterogeneity in the excipient, drug mounting technology, and drug transfer rate, leading to mixed clinical trial results. The lack of a "class effect" was also shown in the SCAAR "Swedish Coronary Angiography and Angioplasty Registry" [26] and emphasized in the European revascularization guidelines [27]. There are emerging promising data on the use of sirolimus-coated balloons but direct comparison with the currently available paclitaxel-coated balloons is still required [28].

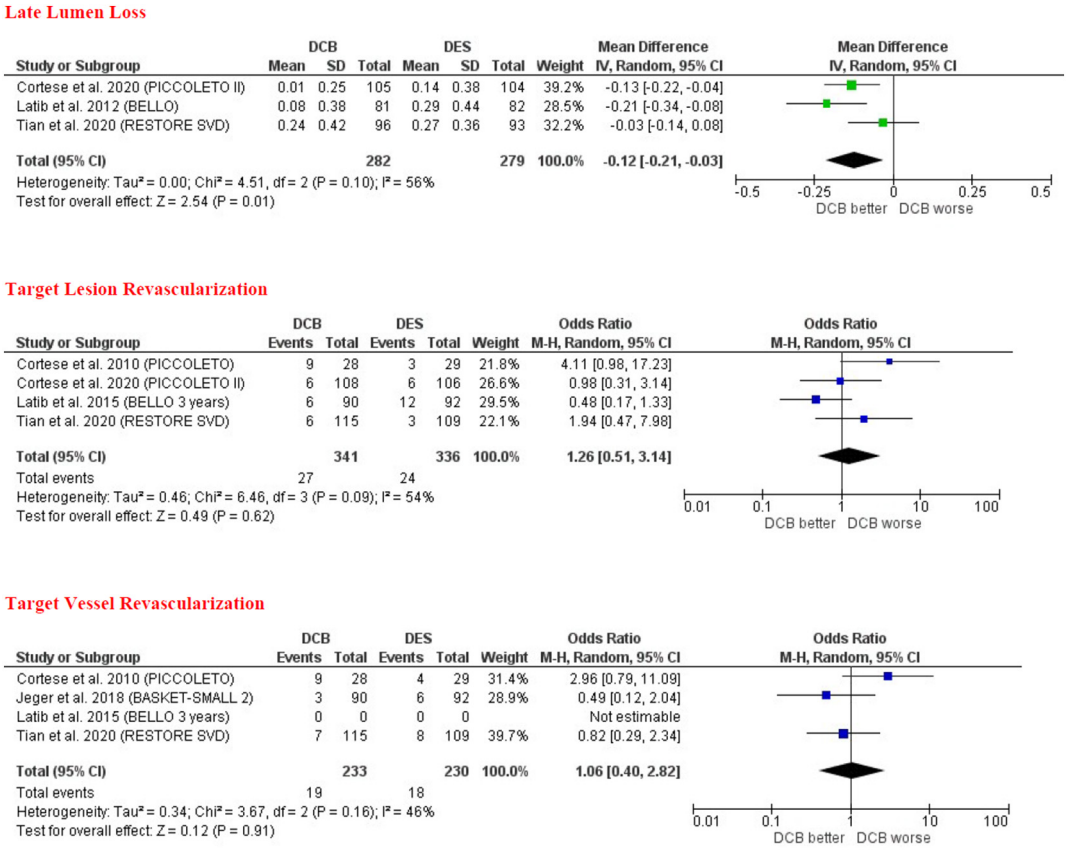

Fig. 3. Pooled analysis of the odds of target lesion revascularization and target vessel revascularization and mean difference in late lumen loss with drug-coated balloons vs. drug-eluting stents in small vessel coronary artery disease; the summary statistic is the odds ratios and mean differences calculated according to the Mantel-Haenszel method and inverse variance method with random effects, respectively; marker size is proportional to the study weight. DCB: drug-coated balloon; DES: drug-eluting stent.

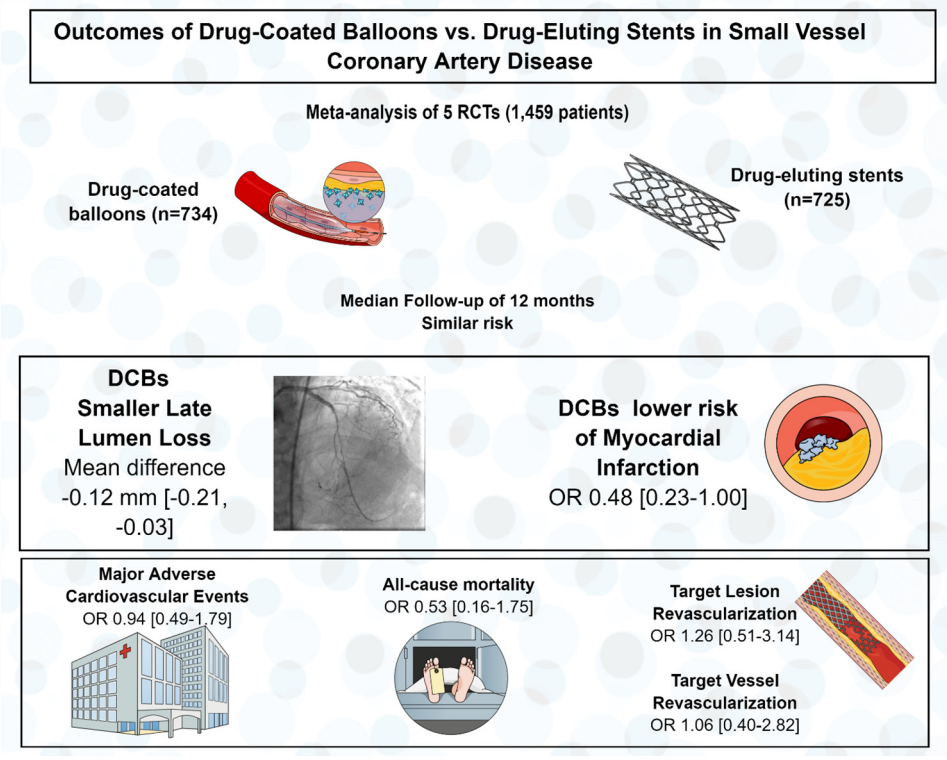

Fig. 4. Summary of the study results.

In our analysis, both DES and DCBs were comparable in MACE, TLR, TVR, and all-cause mortality risk. This equivalency was also demonstrated in our sensitivity analysis comparing DCBs vs. second-generation DES. Our findings, especially with the lower incidence of MI with DCBs, support using DCBs in SVD. Using DCBs fulfils the concept of adequate treatment of atherosclerotic lesions and delivery of anti-restenotic drugs without leaving anything behind. Larger randomized trials with longer follow-up are needed to confirm our findings, and ensure the durability of DCBs in SVD. Our results are generally similar to the study by Sanchez et al. in the overall outcomes [29]. We did not, however, perform metaregression given the low number of included studies. Moreover, we performed a pre-specified sensitivity analysis that showed equivalency of DCBs and second-generation DES.

4.1. Limitations

Our study has several limitations. First, there is significant heterogeneity, given the differences in the type of DCB and the frequency of adequate lesion preparation. We attempted to overcome this limitation using random-effect models and by performing further sensitivity analyses. Second, the study was performed using published data not patient-level data. Third, bleeding outcomes were not consistently reported and could not be analysed. Fourth, our results are reported at a median follow-up time of 12 months, and more extended follow-up data are needed. Finally, the number of trials is still limited and a beta-error still possible for many outcomes assessed.

5. Conclusions

PCI of SVD with DCBs is associated with smaller LLL, a lower risk of MI, and, with the limited data available so far, and similar risk of MACE, death, TLR, and TVR compared with DES over one year. DCB appears as an attractive alternative to DES in patients with de-novo SVD, but long-term clinical data are still needed.

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None.

CRediT authorship contribution statement

Michael Megaly: conceptualization, Development or design of methodology, statistical analysis, writing the initial draft.

Kevin Buda: data curation, development or design of methodology.

Marwan Saad: data curation.

Mariam Tawadros: data curation.

Ayman Elbadawi: data curation.

Mir Basir: critical review, commentary, and revision.

J Dawn Abbott: critical review, commentary, and revision.

Stephane Rinfret: critical review, commentary, and revision.

Khaldoon Alaswad: critical review, commentary, and revision.

Emmanouil Brilakis: Conceptualization oversight and leadership responsibility for the research activity planning and execution. Critical review, commentary, and revision.

Declaration of competing interest

Emmanouil Brilakis: consulting/speaker honoraria from Abbott Vascular, American Heart Association (associate editor Circulation), Amgen, Biotronik, Boston Scientific, Cardiovascular Innovations Foundation (Board of Directors), ControlRad, CSI, Ebix, Elsevier, GE Healthcare, InfraRedx, Medtronic, Siemens, and Teleflex; research support from Regeneron and Siemens. Shareholder: MHI Ventures.

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All other authors have nothing to disclose.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.carrev.2021.03.008.

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