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# Drug-Coated balloons vs drug-eluting stents for the treatment of small coronary artery disease: A meta-analysis of randomized trials

Jorge Sanz Sánchez MD, PhD[1] | Mauro Chiarito MD[1] | Bernardo Cortese MD[2] | Andrea Moretti MD[3] | Paolo Pagnotta MD[1] | Bernhard Reimers MD[1] | Giulio G. Stefanini MD, PhD[1] | Giuseppe Ferrante MD, PhD[1]

[1]Department of Biomedical Sciences, Humanitas University, Department of Cardiovascular Medicine, Humanitas Clinical and Research Center, IRCCS, Via Alessandro Manzoni, 56, Rozzano (Milan), 20089, Italy

[2]Cardiovascular Research Group, Clinica San Carlo, Milan, Italy

[3]Department of Heart and Great Vessels, Sapienza University of Rome, Rome, Italy

**Correspondence**
Giuseppe Ferrante, MD, PhD, Humanitas University, Department of Cardiovascular Medicine, Humanitas Research Hospital, Via Manzoni, 56, 20089, Rozzano, Milan, Italy.
Email: giu.ferrante@hotmail.it

## Abstract

**Objectives and background:** There is conflicting evidence about the effects of drug-coated balloons (DCB) compared with drug-eluting stents (DES) in patients with native small vessel coronary artery disease (CAD).

**Methods:** The PubMed, Embase, Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov databases and main international conference proceedings were searched for randomized controlled trials (RCT) comparing DCB versus DES in patients with native small vessel CAD. Data were pooled by meta-analysis using a random-effects model. The primary endpoint was target vessel revascularization (TVR). Secondary clinical endpoints were: myocardial infarction (MI), target lesion revascularization (TLR), all-cause death, cardiac death, and stent thrombosis or target vessel thrombosis. Secondary angiographic outcomes were: in-segment restenosis, in-segment percentage-diameter stenosis, in-segment late lumen loss, in-segment net luminal gain, and in-segment minimal lumen diameter.

**Results:** Five trials enrolling 1,459 patients were included. Mean clinical follow-up was 10.2 months. The use of DCB, compared with DES, was associated with similar risk of TVR (odds ratio [OR]: 0.97; 95% confidence interval [CI] 0.56 to 1.68; $p = .92$), TLR (OR: 1.74; 95% CI: 0.57 to 5.28; $p = .33$), all-cause death (OR: 1.03; 95% CI: 0.14 to 7.48; $p = .98$), with a trend toward a lower risk of MI (OR: 0.49; 95% CI: 0.23 to 1.03; $p = .06$), and with significant lower risk of vessel thrombosis (OR: 0.12; 95% CI: 0.01 to 0.94; $p = .04$). DCB use was associated with similar risk of angiographic restenosis (OR: 1.12; 95% CI 0.69 to 1.84; $p = .64$), comparable late luminal loss (standardized mean difference (SMD): −0.18; 95% CI: −0.39 to 0.03; $p = .09$), while leading to significant higher percentage diameter stenosis (SMD: 0.27; 95% CI 0.12 to 0.41; $p < .01$) and smaller minimal luminal diameter (SMD: -0.52; 95% CI: −0.86 to −0.18; $p = .003$).

Drs Jorge Sanz-Sánchez and Mauro Chiarito contributed equally to this work.

  

**Conclusion:** Compared with DES, the use of DCB for the treatment of native small vessel CAD is associated with similar TVR and restenosis and reduces the risk of vessel thrombosis, although DES implantation yields slightly better angiographic surrogate endpoints.

**KEYWORDS**
drug coated balloons, drug eluting stents, percutaneous coronary intervention, small vessel coronary artery disease

## 1 | INTRODUCTION

Small vessel coronary artery disease (CAD) is present in about 40% of patients undergoing percutaneous coronary interventions (PCI).[1] Its interventional treatment remains challenging owing to an increased risk of technical failure, restenosis and need of repeated revascularization.[2-4] In the early 2000s, several randomized controlled trials (RCT), have compared PCI with bare-metal stents (BMS) to balloon angioplasty for the treatment of small vessel CAD.[5-12]

Drug-coated balloons (DCB) have been shown to be a valuable option for the treatment of in-stent restenosis after BMS or drug-eluting stents (DES) and have been tested as an alternative strategy to DES for the treatment of native small vessel CAD.[13,14] DCB provide a fast and high-dose delivery of antiproliferative drugs to the vessel wall, and carry several anticipated benefits over DES such as the lack of permanent scaffold and the need for a shorter duration of dual antiplatelet therapy.

Two early RCTs reported conflicting results about the effects of DCB, as compared to first-generation DES, on angiographic outcomes in patients with native small vessel CAD.[15,16] More recently larger RCT with the use of second-generation DES and novel DCB devices have provided new evidence about the clinical and angiographic effects of these treatments.[17,18] Nevertheless, the individual studies with a non-inferiority design may not provide adequately powered analyses about the comparison between these technologies, thus prompting the need for a systematic appraisal of treatment effects and quality of evidence.

The aim of this study was to provide a comprehensive and quantitative assessment of evidence from early as well as contemporary studies about the safety and efficacy of DCB compared with DES in native small vessel CAD.

## 2 | METHODS

### 2.1 | Data sources and search strategy

A meta-analysis of RCTs was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2009 guidelines.[19] Two reviewers independently identified the relevant studies by an electronic search of the MEDLINE, Embase, Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov databases (from inception to September 2019). In addition, we searched abstracts from 2017 to 2019 presented at relevant scientific meetings (American Heart Association, American College of Cardiology, European Society of Cardiology, EuroPCR, and Transcatheter Cardiovascular Therapeutics). The principal investigator (BC) of one trial whose results have been presented at the Transcatheter Cardiovascular Therapeutics 2019 was contacted for study and patient data. The following search terms and key words were used: “drug-eluting stents,” “drug-coated balloons,” “drug-eluting balloons,” “small vessel” and “small coronary”. No language, publication date or publication status restrictions were imposed. This study is registered with PROSPERO, number CRD42019137500.

### 2.2 | Study selection

Two reviewers independently assessed trial eligibility on the basis of titles, abstracts, and full-text reports. Discrepancies in study selection were discussed and resolved with another investigator. Eligible studies had to satisfy the following pre-specified criteria: (a) RCTs comparing PCI with DCB to PCI with DES; (b) study population including patients with native small vessel CAD (i.e., defined as vessel diameter < 3 mm); (c) availability of clinical outcome data with follow-up duration of at least 6 months. Exclusion criteria were: (a) lack of a randomized design; (b) studies including patients undergoing treatment for in-stent restenosis; (c) lack of any clinical outcome data; (d) length of follow-up <6 months; (e) duplicated publications.

### 2.3 | Data extraction and quality assessment

Three investigators independently extracted data (baseline characteristics, definition of outcomes and number of events) using a standardized data abstraction form. The same investigators independently and systematically assessed the studies' methodological quality using the Risk of Bias Assessment Tool from the Cochrane handbook for RCT,[20] assessing five domains of bias for each outcome: (a) randomization process, (b) deviations from intended interventions, (c) missing outcome data, (d) measurement of the outcome and (e) selection of the reported results (Supplementary appendix)[21]. Disagreements were resolved with another investigator.

## 2.4 | Data synthesis and data analysis

### 2.4.1 | Outcome measures

The primary endpoint was target vessel revascularization (TVR). Secondary clinical endpoints were: myocardial infarction (MI), target lesion revascularization (TLR), all-cause death, cardiac death, and stent thrombosis or target vessel thrombosis. Secondary angiographic outcomes were: in-segment restenosis, in-segment percentage-diameter stenosis, in-segment late lumen loss, in-segment net luminal gain, and in-segment minimal lumen diameter. Endpoints were attributed according to the definition used in each study.

## 2.5 | Statistical analysis

For dichotomous outcomes the odds ratios (ORs) with 95% confidence intervals (CI) were calculated from the available data and trial-specific OR were combined with the DerSimonian and Laird random-effects model with the estimate of heterogeneity being taken from the Mantel–Haenszel model.[22] For continuous outcomes the standardized mean difference (SMD) with 95% CI was used as the summary statistic and trial-specific data were pooled with the inverse-variance random-effects method. The presence of heterogeneity among studies was evaluated with the Cochran Q chi-square test with $p \leq .1$ considered to be of statistical significance, estimating the between-studies variance tau-square, and using the $I^2$ test to evaluate inconsistency. The $I^2$ statistic is derived from the Q statistic ($100\% \times [Q - df]/Q$), and describes the percentage of total variation across studies that is due to heterogeneity; a value of 0% indicates no observed heterogeneity, and larger values show increasing heterogeneity. $I^2$ values of 25%, 50%, 75% have been assigned adjectives of low, moderate, and high heterogeneity, respectively.[23] The presence of publication bias for each endpoint was investigated by visual estimation with the use of contour-enhanced funnel plots when data was available in least three studies.[24,25] The interpretation and meaning of contour-enhanced funnel plots have been reported elsewhere.[25]

### 2.5.1 | Sensitivity analyses

The effects of DCB and DES on outcomes were also assessed by calculating ORs with 95% CI using a fixed-effects model with the Mantel and Haenszel method for dichotomous outcomes and SMD with 95% CI using the inverse-variance fixed-effects method for continuous outcomes. Risk ratios with 95% CI were also calculated with both fixed-effects and random-effects models for dichotomous outcomes.

In order to account for different lengths of follow-up across studies, another sensitivity analysis was performed using the Poisson regression model with random intervention effects to calculate inverse-variance weighted averages of study-specific log stratified incidence rate ratios (IRRs). Results were displayed as IRRs, which are exponential coefficients of the regression model.

Random-effect metaregression analyses were performed to assess the impact of the following variables on treatment effect with respect to the primary endpoint: that is, the percentage of patients with acute coronary syndrome, and with diabetes mellitus in the DCB group and the prevalence of second-generation DES use. A leave-one-out sensitivity analysis was performed by leaving out exactly one study also. The statistical level of significance was 2-tailed $p < .05$. Stata version 14.2 (StataCorp LP, College Station, Texas), was used for statistical analyses.

# 3 | RESULTS

## 3.1 | Search results

Figure 1 displays the preferred reporting items for Systematic Reviews and Meta-Analyses flow diagram for study search and selection.

Of the 823 citations screened, 753 were excluded as they were considered non-relevant, 45 were excluded because the studies did not have a randomized design, 11 citations were excluded because in these studies DCB was employed for the treatment of peripheral vascular disease, 6 citations were excluded because DCB was used for the treatment of in-stent restenosis, and 2 citations were related to studies including large vessel (i.e., > 3 mm diameter) CAD. The BELLO (Balloon Elution and Late Loss Optimization) trial[15] with 1-year clinical follow-up was included in the main analysis, while publications regarding the same trial with clinical data at 2 and 3 years were considered in a sensitivity analysis using IRRs. The PICCOLETO II trial was also included (Personal Communication, Bernardo Cortese, MD. Drug-coated balloon vs drug eluting stent for small coronary vessel disease: 6-mo primary outcome of the PICCOLETO II randomized clinical trial. Presented at: TCT 2019. September 27, 2019. San Francisco, CA). Therefore, a total of 5 RCT including 1,459 patients were selected and included in the meta-analysis.[15-18]

## 3.2 | Study characteristics and bias assessment

The main trial and patient characteristics of the included studies are reported in Table 1. All studies had a non-inferiority design. A clinical primary endpoint was selected in one study,[17] while angiographic primary endpoints were prespecified in the remaining studies. Two trials[15,16] enrolled patients treated with first-generation DES (Taxus paclitaxel eluting stent, Boston Scientific Company, Marlborough), one study[17] included patients treated with both first-generation DES (Taxus) and second-generation DES (Xience everolimus eluting stent, Abbott Vascular, Santa Clara), two trials enrolled patients treated with second-generation DES: Resolute Onyx zotarolimus eluting stent[18] (Medtronic, Minneapolis) or Xience everolimus eluting stent (Abbott Vascular, Santa Clara) (PICCOLETO II). All patients allocated to DCB-PCI in the five trials were treated with Paclitaxel drug-eluting balloons. MI was defined according to the first[15] or third [17,18] (PICCOLETO II) universal definition.

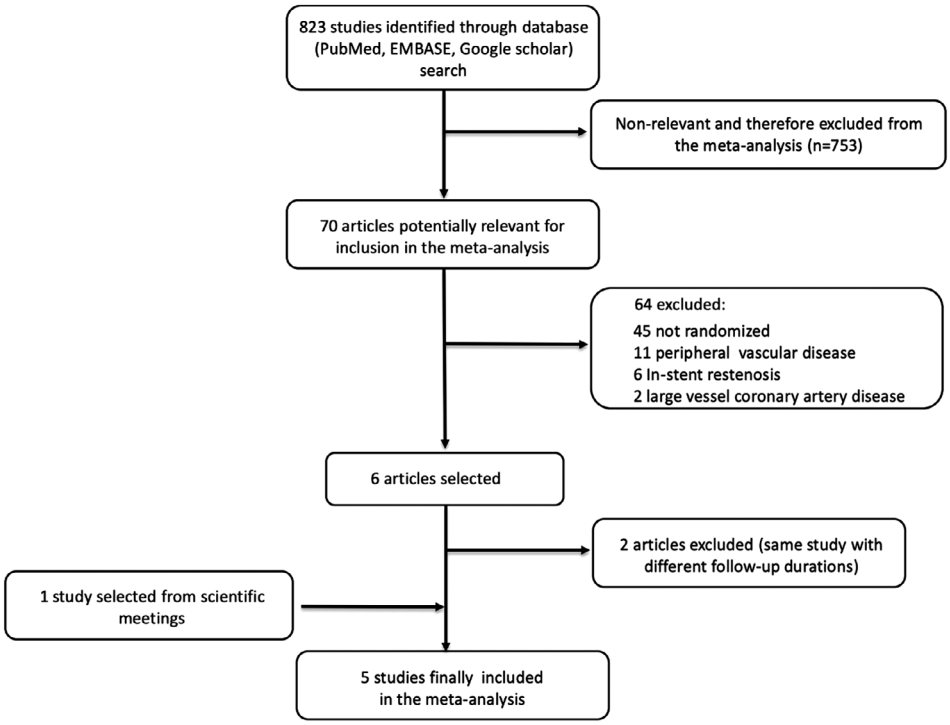


**FIGURE 1** Flow Diagram of the Search for Studies Included in the Meta-Analysis According to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement

Online Figure 1 summarizes the systematic bias assessment of the included studies. There was low risk of bias for most domains across four studies,[15-18] except for the domain of deviations from intended interventions that showed high risk of bias in two studies[15,16] and some concern in one study[17] and for the domain of measurement of the outcome that was associated with some concern in one study.[17] The risk of bias was high for the PICCOLETO II trial (Personal communication, Bernardo Cortese MD, TCT 2019).

## 3.3 | Heterogeneity

With respect to clinical outcomes, there was low heterogeneity for TVR ($p$ = .23, $I^2$ = 28.9%), moderate heterogeneity for TLR ($p$ = .07, $I^2$ = 56.9%), and no heterogeneity for all-cause death ($p$ = .99, $I^2$ = 0%) or myocardial infarction ($p$ = .46, $I^2$ = 0%). With respect to angiographic outcomes, high heterogeneity was detected for net luminal gain ($p$ < .01, $I^2$ = 93.5%) and minimal luminal diameter ($p$ < .01, $I^2$ = 81.2%), moderate heterogeneity was found for late luminal loss ($p$ = .1, $I^2$ = 52.8%), and low heterogeneity for angiographic restenosis ($p$ = .29, $I^2$ = 18.4%) and percentage diameter stenosis ($p$ = .35, $I^2$ = 9.1%).

## 3.4 | Publication bias and asymmetry

Contour-enhanced funnel plots are reported in the Supplementary appendix. Plots suggest the presence of publication bias for target vessel revascularization, MI, target lesion revascularization, percentage diameter stenosis, and net luminal gain (online Figures 2,3,5,6,9). Asymmetry due to publication bias and other factors based on statistical significance was observed for minimal luminal diameter and late luminal loss (online Figures 7,8). No asymmetry was detected for angiographic restenosis (online Figure 4).

## 3.5 | Outcomes

### 3.5.1 | Clinical outcomes

DCB use, compared with DES, was associated with similar risk of TVR (OR: 0.97; 95% CI: 0.56 to 1.68; $p$ = .92), TLR (OR: 1.74; 95% CI: 0.57 to 5.28; $p$ = .33) and all-cause death (OR: 1.03; 95% CI: 0.14 to 7.48; $p$ = .98) (Table 2, Figure 2-4).

DCB was associated with a trend toward a lower risk of myocardial infarction (OR: 0.49; 95% CI: 0.23 to 1.03; $p$ = .06, Table 2, Figure 5), and significant lower risk of vessel thrombosis (OR: 0.12; 95% CI: 0.014 to 0.94; $p$ = .04, Table 2, Figure 6).

With respect to cardiac death, events were available or occurred in one trial only,[23] therefore a pooled analysis could not be performed.

### 3.5.2 | Angiographic outcomes

Compared with DES, DCB use was associated with similar risk of angiographic restenosis (OR: 1.12; 95% CI 0.69 to 1.84; $p$ = .64) (Table 2, online Figure 10), late luminal loss (SMD: −0.18; 95% CI: −0.39 to 0.03; $p$ = .09) and net luminal gain (SMD: -0.14; 95% CI: −0.72 to 0.44; $p$ = .62) (online Figure 11,12). However, DCB use

**TABLE 1** Baseline trial and patient characteristics included in the meta-analysis

| Study name | BASKET-SMALL 2 [17] | | BELLO[15] | | PICCOLETO[16] | | RESTORE SVD[18] | | PICCOLETO II | |
|---|---|---|---|---|---|---|---|---|---|---|
| Treatment vs control | DCB (*n* = 382) | DES (*n* = 376) | DCB (*n* = 90) | DES (*n* = 92) | DCB (*n* = 28) | DES (*n* = 29) | DCB (*n* = 116) | DES (*n* = 114) | DCB (*n* = 118) | DES (*n* = 114) |
| Device type | SeQuent please | Taxus element/Xience | IN.PACT falcon | Taxus Libertè | Dior | Taxus Libertè | Restore | Resolute integrity | Elutax SV | Xience |
| Vessel size (mm) | 2–3 | | < 2.8 | | 2.25–2.75 | | 2.25–2.75 | | ≤2.75 mm | |
| Primary endpoint | MACE | | In-device LLL | | In-segment %DS | | In-segment %DS | | In-lesion LLL | |
| Study design | Non-inferiority | | Non-inferiority | | Non-inferiority | | Non-inferiority | | Non-inferiority | |
| FU duration (months) | 12 (clinical) | | 12 (clinical) 6 (angiographic) | | 9 (clinical) 6 (angiographic) | | 12 (clinical) 9 (angiographic) | | 6 (clinical and angiographic) | |
| Loss to FU, n (%) | 9 (2.3) | 13 (3.5) | 1 (1.1) | 1 (1.1) | 1 (3.6) | 2 (6.9) | 16 (13.8) | 21 (18.4) | 5 (4.2%) | 3 (2.6%) |
| Age (sd) (yrs) | 67.2 (10.3) | 68.4 (10.3) | 68.4 (8.5) | 66.4 (9.0) | 68 (9) | 67 (10) | 60.1 (10.5) | 60.5 (10.8) | 66 (15.7) | 64 (16) |
| Men, n (%) | 295 (77.2) | 262 (69.7) | 72 (80) | 71 (77.2) | 22 (78.6) | 22 (75.9) | 77 (66.4) | 88 (77.2) | 83 (70.3) | 87 (76.9) |
| Hypertension, n (%) | 324 (84.8) | 332 (88.3) | 72 (80) | 75 (81.5) | 21 (75.0) | 20 (70.8) | 78 (67.2) | 86 (75.4) | 77 (65.2) | 76 (67.2) |
| Dyslipidemia, n (%) | 262 (68.6) | 259 (68.9) | 71 (78.9) | 73 (79.3) | 17 (60.7) | 13 (54.2) | 61(52.6) | 55 (48.2) | 72 (61) | 63 (55) |
| Diabetes mellitus, n (%) | 122 (31.9) | 130 (34.6) | 39 (43.3) | 35 (38) | 13 (37.9) | 11 (46.4) | 46 (39.7) | 48 (42.1) | 45 (38) | 40 (35.4) |
| Current smoker, n (%) | 82 (21.5) | 72 (19.2) | 15 (16.7) | 10 (10.9) | na | na | 34 (29.3) | 36 (31.6) | 23 (19.5) | 19 (16.7) |
| Unstable angina, n (%) | 48 (13) | 42 (11) | 22 (24.4) | 20 (21.7) | 15 (53.6) | 16 (55.2) | 69 (80) | 71.1 (81) | 17 (14.4) | 18 (16) |
| NSTEMI, n (%) | 53 (14) | 56 (15) | Excluded | | Excluded | | Excluded | | 25 (21.1) | 23 (20.3) |
| STEMI, n (%) | 11 (3) | 4 (1) | Excluded | | Excluded | | Excluded | | 9 (8) | 12 (10.3) |
| DAPT duration | | | | | | | | | | |
| Stable CAD | 1 month | 6 months | 1 month | 12 months | 1 month | 12 months | At least 6 months in all pts<br>12 months in 93% all pts | | 1 month | 6 months |
| ACS | 12 months | 12 months | 1 months | 12 months | 12 months | 12 months | | | 12 months | 12 months |

Abbreviations: %DS, percentage-diameter stenosis; ACS, acute coronary syndrome; CAD, coronary artery disease; DCB, Drug-coated balloon; DES, Drug-eluting stent; LLL, late luminal loss; MACE, major adverse cardiovascular events; na, not available; NSTEMI, Non-ST-segment elevation myocardial infarction; STEMI, ST-elevation myocardial infarction.

**TABLE 2** Pooled analysis of studies comparing DCB versus DES

| | Number of events/number of patients, absolute event rate (%) | | | | |
|---|---|---|---|---|---|
| **Endpoint** | **DCB** | **DES** | **OR** | **95% CI** | ***p*** |
| TVR | 43/734 (5.86) | 46/725 (6.34) | 0.97 | 0.56 to 1.68 | .92 |
| TLR | 25/352 (7.1) | 18/349 (5.16) | 1.74 | 0.57 to 5.28 | .33 |
| MI | 11/734 (1.5) | 23/725 (3.17) | 0.49 | 0.23 to 1.03 | .06 |
| Vessel thrombosis | 0/644 (0) | 8/633 (1.26) | 0.12 | 0.01 to 0.94 | .04 |
| All-cause death | 2/352 (0.57) | 2/349 (0.57) | 1.03 | 0.14 to 7.48 | .98 |
| Angiographic restenosis | 49/394 (12.43) | 47/405 (11.6) | 1.12 | 0.69 to 1.84 | .64 |

Abbreviations: DCB, drug-coated balloons; DES, drug-eluting stents; MI, myocardial infarction; TVR, target vessel revascularization; TLR, target lesion revascularization.

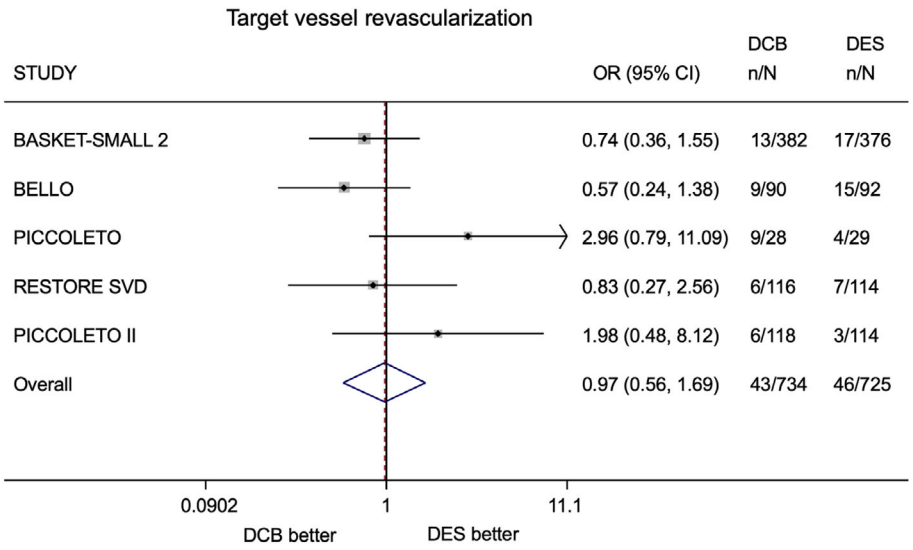


**FIGURE 2** Forest plot reporting trial-specific and summary odds ratios (ORs) with 95% confidence intervals (CIs) for the endpoint of target vessel revascularization. DCB: drug-coated balloons; DES: drug-eluting stents [Color figure can be viewed at wileyonlinelibrary.com]

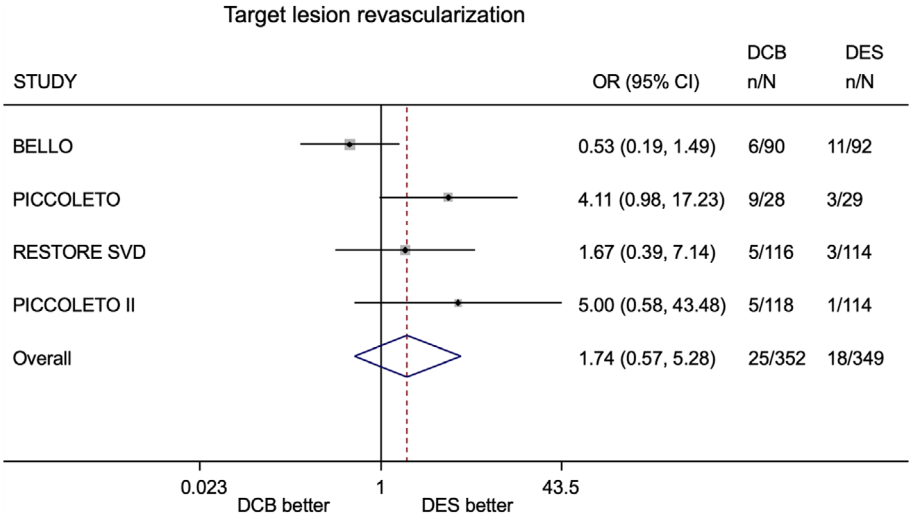


**FIGURE 3** Forest plot reporting trial-specific and summary odds ratios (ORs) with 95% confidence intervals (CIs) for the endpoint of target lesion revascularization. DCB: drug-coated balloons; DES: drug-eluting stents [Color figure can be viewed at wileyonlinelibrary.com]

yielded significant higher percentage diameter stenosis (SMD: 0.27; 95% CI 0.12 to 0.41; $p < .01$, online Figure 13), and significant smaller minimal luminal diameter (SMD: −0.52; 95% CI: −0.86 to −0.18; $p = .003$, online Figure 14).

### 3.6 | Sensitivity analysis

Findings remained consistent with the main analysis after calculation of ORs using a fixed-effects model as well as risk ratios with both

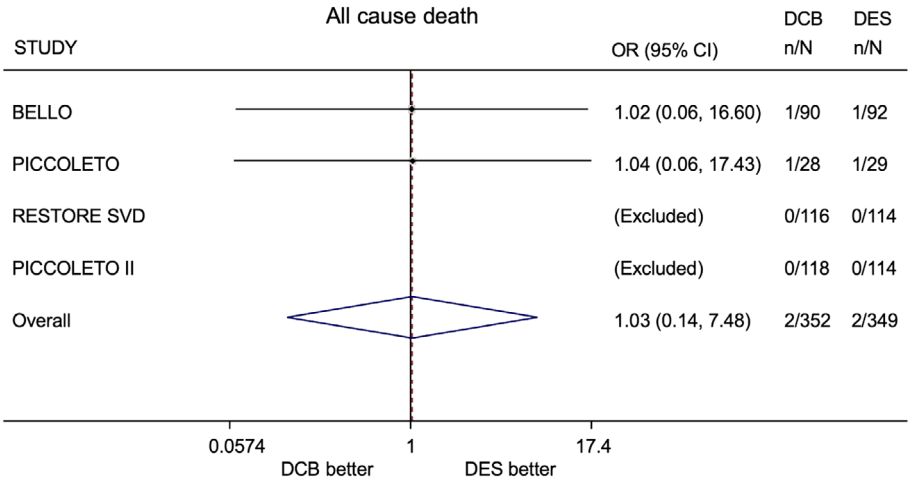


**FIGURE 4** Forest plot reporting trial-specific and summary odds ratios (ORs) with 95% confidence intervals (CIs) for the endpoint of all-cause death. DCB: drug-coated balloons; DES: drug-eluting stents [Color figure can be viewed at wileyonlinelibrary.com]

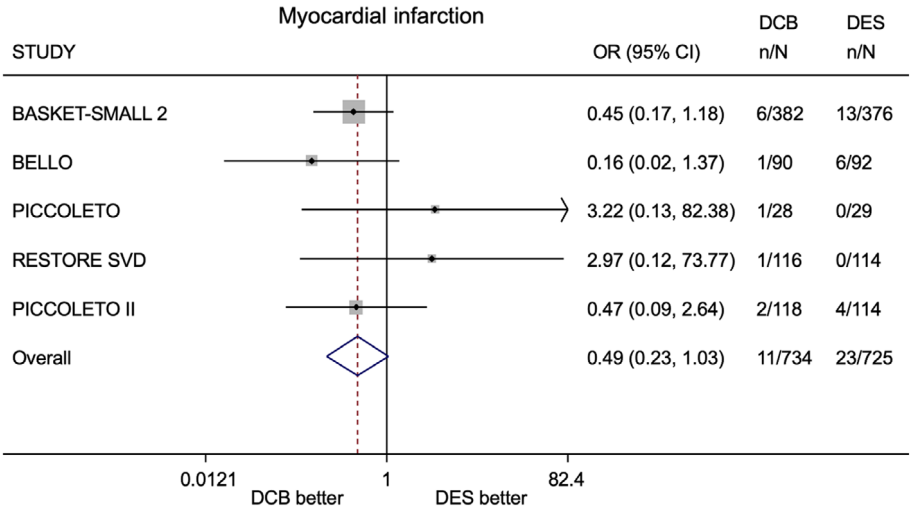


**FIGURE 5** Forest plot reporting trial-specific and summary odds ratios (ORs) with 95% confidence intervals (CIs) for the endpoint of myocardial infarction. DCB: drug-coated balloons; DES: drug-eluting stents [Color figure can be viewed at wileyonlinelibrary.com]

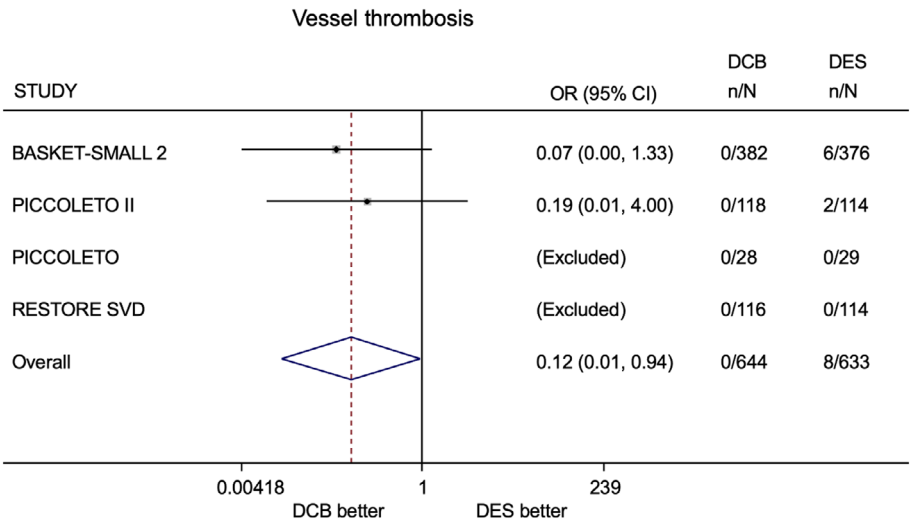


**FIGURE 6** Forest plot reporting trial-specific and summary odds ratios (ORs) with 95% confidence intervals (CIs) for the endpoint of stent thrombosis/ vessel thrombosis. DCB: drug coated balloons; DES: drug-eluting stents [Color figure can be viewed at wileyonlinelibrary.com]

fixed- and random-effects models (online Table 1). Similarly, in a sensitivity analysis with the use of estimated IRRs to account for different lengths of follow-up findings were unchanged (online Table 2).

Treatment effect on continuous angiographic outcomes calculated using a fixed-effects model were consistent with the main analysis (online Table 3).

Random effect meta-regression analysis found no significant impact of the proportion of patients presenting with acute coronary syndrome (OR: 1.05; 95% CI: 0.98 to 1.12; $p$ = .12) or diabetes mellitus (OR: 0.98; 95% CI: 0.79 to 1.20; $p$ = .78) on treatment effect with respect to the primary endpoint. Similarly, the prevalence of second-generation DES use did not affect the treatment effect on the primary endpoint (OR: 0.99; 95% CI: 0.96 to 1.04; $p$ = .73). A leave-one-out pooled analysis was performed for all endpoints except for all-cause death and vessel or stent thrombosis, as these events occurred in two studies only. Treatment effects were consistent with the main analysis for all endpoints. Nevertheless, the trend toward a lower risk of MI associated with DCB use became significant after removal of the PICCOLETO[16] or RESTORE-SVD[18] studies, while largely attenuated leaving out the BASKET-SMALL 2,[17] PICCOLETO II or BELLO[15] studies.

## 4 | DISCUSSION

The main findings of this study, which provides a comprehensive and updated quantitative analysis of available evidence about the direct comparison of DCB vs DES in native small vessel CAD, including 1,459 patients from 5 RCTs, are as follows:

(a) DCB use was associated with similar risk of TVR and TLR at follow-up; (b) DCB was associated with similar angiographic restenosis and late luminal loss, although it yielded a small increase of percentage diameter stenosis and small reduction of minimal lumen diameter at follow-up; (c) DCB use reduced the risk of vessel thrombosis and was associated with a trend toward lower risk of MI at follow-up.

The effect of DCB on the risk of TVR was not affected by the proportion of patients presenting with acute coronary syndrome or diabetes, as well as the prevalence of second-generation DES use as assessed by metaregression analysis.

A previous network meta-analysis including 19 RCTs compared different treatment strategies in patients with native small vessel CAD, including plain old balloon angioplasty, BMS, DCB and first-generation DES.[13] DES was ranked the most effective treatment in terms of percentage diameter stenosis, risks of binary restenosis and TLR at follow-up, while DCB was the second most effective one. However, the recently published BASKET-SMALL 2 trial[17] and the RESTORE study[18] were not included in that analysis. At variance with the PICCOLETO study which reported the inferiority of DCB as compared with DES in terms of percent diameter stenosis and angiographic restenosis at 6-month follow-up,[16] DCB use was associated with reduced late loss and similar angiographic restenosis in the BELLO study at 6 months,[15] and was found to be non-inferior in terms of percentage diameter stenosis at 9 months in the RESTORE study.[18] Further, DCB use was associated with comparable risks of TLR and major adverse cardiovascular events at 6 months in the BELLO study,[15] of target lesion failure in the RESTORE study,[18] and of major adverse cardiovascular events at 12 months in the BASKET-SMALL 2 study,[17] while the PICCOLETO study reported a trend toward higher major adverse cardiovascular events rate at 9 months in the DCB group.[16] The divergent results of the PICCOLETO trial mostly depend on the use of first-generation DCB, the absence of routine lesion predilatation in the DCB arm and on a large percentage of bailout BMS implantation (up to 36%) after DCB due to suboptimal acute angiographic result. Pocock et al. found a "S"-shaped curve relationship between the risk of TLR and in-segment percentage diameter stenosis after DES, reporting very low rates of TLR below 30% percent diameter stenosis and lack of further risk reduction below this threshold.[26] This data may provide some explanations for the disconnection, observed in our study, between angiographic surrogate endpoints (i.e., percent diameter stenosis and minimal luminal diameter) at follow-up that were in favor of DES and rates of angiographic restenosis or repeat revascularization that were similar in both the DCB and DES groups.

Further, no thrombotic event was observed with the use of DCB, underscoring the clinical safety of DCB and a numerically lower rate of MI in the DCB group observed in our study is in line with previous reports.[27] Previous studies have shown that in-stent restenosis after DES is not a benign phenomenon, presenting as an acute coronary syndrome in about 70% of the cases, with 5–10% of these resulting in MI.[28] It could be speculated that the lack of permanent scaffold with DCB, as compared to DES, may predispose to a less aggressive pattern of restenosis and may not increase the risk of thrombotic vessel closure beyond 1 month when vessel healing after balloon dilation is expected to occur.

Nevertheless, our results should be interpreted in light of the observed heterogeneity of the included studies as well as the presence of some bias. The variability of vessel size as inclusion criteria, that is, < 3 mm in one study,[17] < 2.8 mm in another study,[15] and ≤ 2.75 mm in three studies[16,18] (PICCOLETO II) is an important issue as vessel size has been shown to be inversely correlated with the risk of restenosis after PCI.[28,29] We could not assess the impact of vessel size on treatment effect owing to lack of individual patient data. Given the excellent performance of second-generation DES in vessels with diameters >2.5 mm, our study findings might more prudently support DCB use as an appealing first-line therapeutic option for native vessels with diameters of 2.0 to 2.5 mm. Further, despite all studies included in this meta-analysis compared Paclitaxel-DCB with DES, several technical and pharmacokinetics characteristics differed among these devices. There was heterogeneity in the type of DES across studies. Paclitaxel first-generation DES which was used in the BELLO, PICCOLETO and in 28% of patients in the BASKET-SMALL 2 trial, has shown higher rates of TVF and MACE (cardiac death, myocardial infarction or TLR) compared to second-generation Everolimus-DES that was used in the PICCOLETO II and in 72% of patients in the BASKET SMALL 2.[31,32] Therefore, our findings might not be directly generalized to patients receiving newer generation DES.

In general, for patients with stable CAD and small vessel disease, in particular those with distal vessel disease, medical treatment alone could be considered an alternative treatment option that is associated with good clinical outcomes at follow-up.[33]

We acknowledge additional limitations. The lack of individual patient-data did not allow to assess the impact of baseline clinical and

angiographic variables on treatment effects. Angiographic follow-up was not available in one study,[17] and there was lack of confirmation with an angiographic core lab assessment, leading to an increased risk of bias. The length of clinical follow-up varied from 6 months to 36 months across studies, however our sensitivity analysis with the use of IRRs showed consistent findings.[15,17,18] Nevertheless, a longer clinical follow-up in all studies would be critical for establishing the safety and efficacy of DCB, as compared to DES, over time. The limited number of studies and the small event rate for some endpoints, such as cardiac death or stent thrombosis, may reduce the power for detecting smaller significant differences between groups. The presence of bias as well as of heterogeneity (in particular with respect to some angiographic endpoints) requires a larger randomized trial of head-to-head comparison of DCB to second-generation DES in patients with "truly" small-vessel CAD, defined as vessels with diameters <2.5 mm, to increase the strength of our hypothesis-generating findings.

## 5 | CONCLUSIONS

This meta-analysis of five RCTs provides evidence that DCB use, compared with DES, for the treatment of native small vessel CAD is associated with similar TVR and restenosis and reduces the risk of vessel thrombosis, although DES implantation yields slightly better angiographic surrogate endpoints at mid-term follow-up.

DCB might represent an appealing treatment option for small vessel CAD.

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### ORCID

*Jorge Sanz Sánchez* https://orcid.org/0000-0003-4991-6549
*Mauro Chiarito* https://orcid.org/0000-0002-9333-2658
*Bernardo Cortese* https://orcid.org/0000-0002-5808-7810

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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