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Drug-Coated Balloons vs. Plain Balloon Angioplasty for Side Branch Management in Coronary Bifurcation Lesions: A Systematic Review and Meta-Analysis

ABSTRACT

Background: Bifurcation lesions pose unique challenges during percutaneous coronary intervention (PCI) and are associated with suboptimal outcomes. The standard approach involves provisional stenting of the main branch (MB) with plain balloon angioplasty (BA) for compromised side branches (SBs). It remains unclear whether drug-coated balloon (DCB) or plain balloon angioplasty pose a better strategy to treat SB in bifurcation lesions. This systematic review and meta-analysis compared the efficacy of DCB versus BA in managing SBs of bifurcation lesions.

Methods: MEDLINE, Cochrane, and EMBASE databases were searched for randomized controlled trials (RCTs) comparing DCB and BA for treating bifurcation lesions. Outcomes included SB late lumen loss (LLL), major adverse cardiovascular events (MACE), all-cause mortality, myocardial infarction (MI), and target lesion revascularization (TLR).

Results: Five RCTs were included, encompassing 1,255 patients, of whom 628 (50.4%) underwent DCB angioplasty; 946 (75.4%) were male, and the mean age was 63.5 years. Drug-coated balloons significantly reduced MI risk (risk ratio [RR] = 0.56, 95% CI: 0.35-0.88, $P = .010$). DCB use resulted in similar LLL in the SB compared with BA (mean difference (MD) = −0.12 mm, 95% CI: −0.24-0.01, $P = .070$). No significant differences were observed in TLR (RR = 1.19, 95% CI: 0.45-3.14, $P = .720$), MACE (RR = 0.70, 95% CI: 0.48-1.02, $P = .070$), and all-cause mortality (RR = 2.35, 95% CI: 0.61-9.00, $P = .210$).

Conclusion: In this meta-analysis of RCTs, DCB significantly reduced MI without affecting LLL, TLR, MACE, and all-cause mortality compared with BA in the SB of bifurcation lesions.

Keywords: Coronary bifurcation lesions, drug-coated balloons, meta-analysis

META-ANALYSIS

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INTRODUCTION

Bifurcation lesions represent 15%-20% of coronary lesions treated with percutaneous coronary intervention (PCI). Stenting bifurcation lesions pose significant technical challenges and are associated with suboptimal clinical outcomes.[1] The current preferred strategy is provisional stenting of the main branch (MB) first, with side branch (SB) rescue stenting performed only when necessary.[2,3]

Side branch pre-dilation prior to MB stenting is not recommended for provisional stenting to reduce the need for SB stenting.[4,5] Balloon angioplasty is typically performed if the SB becomes compressed, resulting in severe stenosis.[2,3] However, BA often leads to complications such as SB dissection or abrupt occlusion, which may require placing a second stent in the SB.[2,3]

Drug-coated balloons have been associated with positive vessel remodeling, enhanced vascular healing leading to late lumen enlargement, and the reduction and stabilization of plaque.[6,7] Additionally, previous studies have highlighted the benefits of drug-coated balloons (DCBs) in managing in-stent restenosis and treating small coronary artery lesions.[8-10] However, there is a lack of adequately powered randomized clinical trials (RCTs) evaluating the effectiveness of DCBs in

treating coronary artery bifurcation lesions. Thus, a systematic review and meta-analysis was conducted to compare the efficacy of DCB and BA in treating the SB of coronary bifurcation lesions.

METHODS

Search Strategy

This study was performed and reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) protocol.[11] Thus, this review was prospectively registered with the National Institute for Health Research International Registry of Systematic Reviews (PROSPERO, CRD42024617764). PubMed, Cochrane Central Register of Controlled Trials, and EMBASE databases were systematically searched from inception to November 2024. The complete search strategy for each database can be found in the Supplemental Material. References of eligible papers and systematic reviews were also searched for additional studies of interest.

Eligibility Criteria and Data Extraction

There was no restriction regarding the date of publication and publication status. The search was limited to the English language. Studies with the following characteristics were included: (1) RCTs that compare outcomes of DCB vs BA; (2) patients with bifurcation lesions eligible for PCI; (3) the presence of a control group with BA; and (4) adult patients older than 18 years. Articles with different study designs and/or those that did not report any outcomes of interest were excluded.

Stenting of SB was permitted in all studies if suboptimal results were observed, which were defined as persistent residual stenosis, vessel recoil, or flow-limiting dissection. Treatment of the MB could involve BA, DCB, bare-metal stent (BMS), or drug-eluting stent (DES) in either treatment group.

Two authors (M.O. and S.D.) independently performed the data search and study selection. Initially, eligible studies were selected for full-text review. If no outcomes of interest were reported in the manuscript and supplemental material, the results (adverse event) section of the study page was searched on ClinicalTrials.gov. Disagreements were resolved through consensus by reviewing the full article and eligibility criteria with the senior author (C.Y.).

Study Outcomes

The primary outcome of interest was SB LLL assessed by quantitative coronary angiography during follow-up. Secondary outcomes included TLR, defined as revascularization of the bifurcation, and the risk of MACE which was defined as a composite of all-cause mortality, MI, and TLR. Two investigators (M.O. and S. D.) independently extracted the data of interest from the studies, and all data points were confirmed by the senior author (C.Y.).

Quality Assessment

Quality assessment was performed using the Cochrane tool for assessing risk of bias in RCTs (RoB-2), according to the recommendations from the *Cochrane Handbook for Systematic Reviews of Interventions*[12] and was documented by 2 independent investigators (M.O. and S.D.) on a standardized table (Supplementary Table 1). Disagreements were resolved with the senior author (C.Y.).

Data Analysis

Binary endpoints were summarized using the Mantel-Haenszel test with a random effects model risk ratio (RR) and 95% CI as a measure of effect size. Continuous endpoints were summarized using mean difference (MD) and 95% CI. Heterogeneity was assessed using Cochrane's Q statistic and Higgins and Thompsons' I^2 statistic. *P* values inferior to .10 and I^2 > 35% were considered significant for heterogeneity. Sensitivity analyses was performed using the "leave-one-out" approach. Publication bias was also assessed using funnel plot analysis. Review Manager 5.4 was used for statistical analysis (The Nordic Cochrane Centre, The Cochrane Collaboration, Denmark).

Artificial Intelligence Disclosure

We confirm that no artificial intelligence (AI)-assisted technologies, including Large Language Models, chatbots, or image generators, were used in the creation of this submitted work.

RESULTS

As detailed in Figure 1, the initial search yielded 731 results. After removal of duplicate records and exclusion based on title/abstract, 18 eligible studies were fully reviewed following the inclusion and exclusion criteria. Ultimately, 5 RCTs encompassing 1255 patients were included in this systematic review and meta-analysis.[13-17] There were 628 (50.04 %) patients, with a mean age of 63.18, in the DCB group. Follow-up ranged from 9 months to 24 months. Further characteristics of the included studies are reported in Table 1.

Drug-coated balloons significantly reduced target vessel MI (TVMI) compared with BA (RR = 0.56, 95% CI: 0.35-0.88, *P* = .010, I^2 = 0%, Figure 2). The use of DCB did not reduce MACE (RR = 0.70, 95% CI: 0.48-1.02, *P* = .070, I^2 = 25, Figure 3)

HIGHLIGHTS

- This meta-analysis of 5 randomized controlled trials compared drug-coated balloons (DCBs) to plain balloon angioplasty (BA) for side branch (SB) management in coronary bifurcation lesions. Drug-coated balloons significantly reduced target vessel myocardial infarction (MI) risk.
- There was no significant difference in late lumen loss in the SB between DCB and BA. Drug-coated balloons did not significantly reduce major adverse cardiovascular events. The risk of target lesion revascularization was similar between DCB and BA. Additionally, there was no significant difference in all-cause mortality between the 2 groups.
- While DCBs offer a promising strategy for SB treatment due to their reduced MI risk, further large-scale studies with standardized methodologies and longer follow-up are needed to confirm these findings.

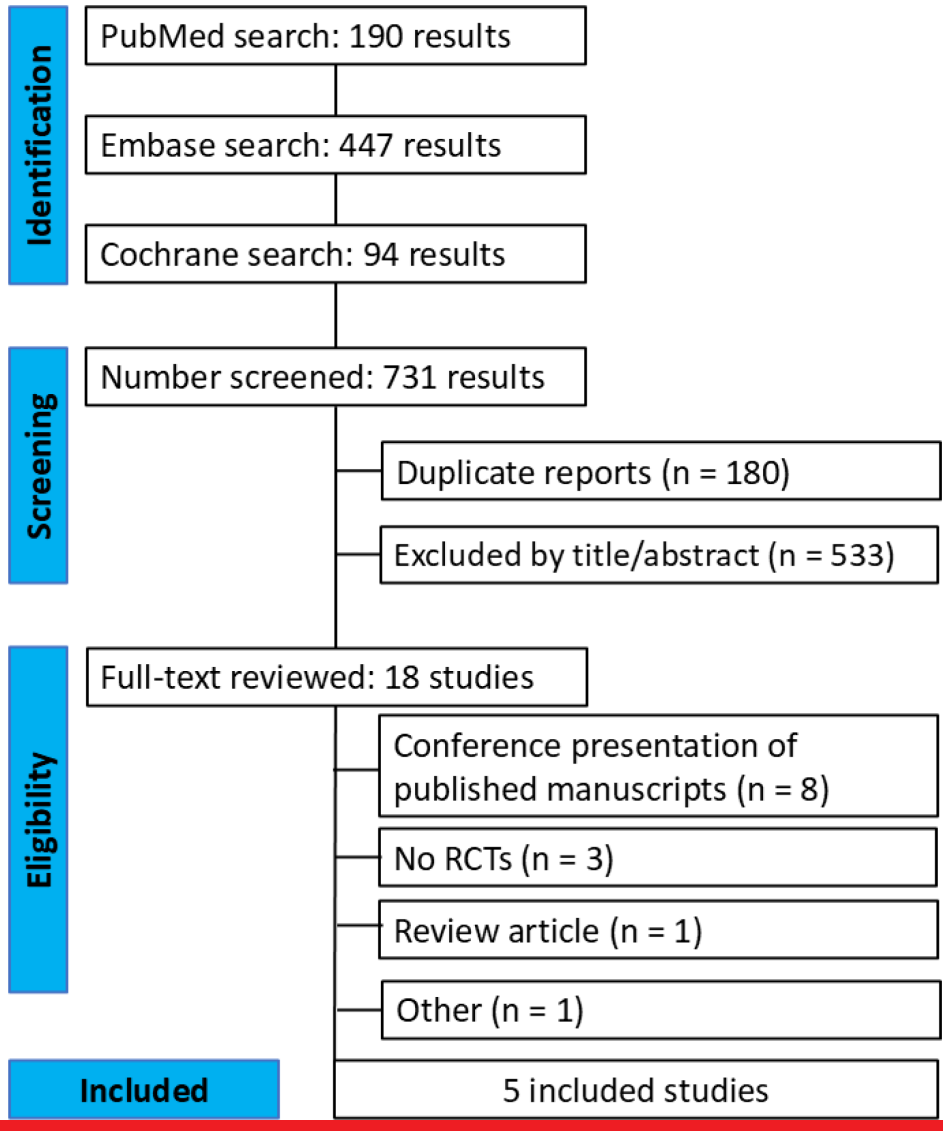

Figure 1. PRISMA flow diagram of study screening and selection.

compared with BA. Drug-coated balloon was also associated with similar LLL in the SB compared with BA (MD= −0.12 mm, 95% CI: −0.24-0.01, $P = .070$, $I^2 = 34\%$, Figure 4). There was no difference in the risk of TLR (RR = 1.19, 95% CI: 0.45-3.14, $P = .720$, $I^2 = 54\%$, Figure 5) between DCB and BA. Drug-coated balloon group had a similar all-cause mortality rate to the BA group (RR = 2.35, 95% CI: 0.61-9.00, $P = .210$, Figure 6).

No study had a high risk of bias (Supplementary Table 1), and no funnel plot asymmetry or outliers were observed for LLL, MACE, or MI (Supplementary Figure 1). In the sensitivity analysis, the I^2 values remained very low (0.0%-0.3%). Leave-one-out analysis for MI are presented in Supplementary Figure 2. MI effect size showed a notable shift towards the null effect when omitting Gao 2024.

DISCUSSION

In this systematic review and meta-analysis of 5 RCTs and 1255 patients, DCB was compared with BA in patients undergoing PCI for bifurcation lesions. The main findings were (1) DCB was associated with a 44% relative risk reduction in MI and (2) no statistically significant differences between groups for LLL in the SB, TLR, MACE, or all-cause mortality.

Percutaneous coronary intervention for bifurcation lesions is more complex and has higher complication rates compared with PCI for non-bifurcation lesions.[18] Bifurcation lesions involve the origin of a significant SB, which introduces variability in anatomy, such as the angle at which the SB originates from MB or differences in vessel diameters.[19,20] This complexity results in decreased procedural success rates,[21,22] an increased risk of MACEs,[20,23] which necessitates careful planning and execution to ensure optimal outcomes. The study aims to help clinicians guide their decisions during this process.

This study has certain differences from the previous meta-analysis in several respects.[24] First, the previous meta-analysis included both RCTs and observational studies, which raises concerns about the risk of bias. Second, the overall population of the previous meta-analysis was less than

Table 1. Baseline Characteristics of Included Studies

Study	Follow-Up, months	No. of Patients, DCB/BA	Male, % DCB/BA	Age†, y DCB/BA	DM, % DCB/BA	Lesion Type LAD, % DCB/BA	Lesion Type LCX, % DCB/BA	SB Bail-Out stenting, % DCB/BA	SBRD†, mm DCB/BA	SBMLD† mm DCB/BA	SBLL† mm DCB/BA	SBDS, % DCB/BA
Kleber 2016[16]	9	32/32	75/71.9	66/69	11/12	43.8/53.1	50/40.6	0/15.6	2.38/2.41	0.57/0.60	6.5/5.6	76.3/75.4
Stella 2012[14]	12	40/37	62.5/78.4	63.3/61.8	2/5	77.5/83.8	20/10.8	10/5.4	2.53/2.35	1.65/1.67	3.8/4.7	52.9/50.4
Jing 2020[13]	9	113/109	79.7/65.1	59.9/61.8	34/38	75.2/78	13.3/15.6	0/0	2.15/2.10	0.84/0.89	3.8/4.2	57.9/56
Gao 2024[17]	12	391/393	78/75.6	63.8/63.6	147/140	66.5/69.5	11.0/11.7	3.8/3.4	2.24/2.25	1.03/1.04	5.9/6.5	54/53.78
Mínguez 2014[15]	24	52/56	63.5/66.1	63.9/65.6	14/20	61.5/66.1	28.8/23.2	7.8/8.9	2.29/2.35	1.08/1.10	8.7/8.1	52.4/52.7

BA: uncoated balloon angioplasty; DCB: drug-coated balloon; DM: diabetes mellitus LAD: left anterior descending artery; LCX: left circumflex artery; PCB: paclitaxel-eluting balloon; RCA: right coronary artery; SB: side-branch; SBDS: side branch diameter stenosis; SBLL: side branch lesion length; SBMLD; side branch minimal lumen diameter; SBRD; side branch reference diameter.
†Mean.

one-fourth of the patient population was analyzed in this study. Third, the results suggest that DCB may be associated with a reduced risk of MI.

The BEYOND (A drug-eluting Balloon for the trEatment of coronarY bifurcatiON lesions in the side branch: a prospective multicenter ranDomized) trial, a multicenter randomized study involving 222 patients with coronary bifurcation lesions, reported that patients treated with DCBs had less TVR and LLL compared with the BA group. However, these findings did not correlate with clinical outcomes such as non-fatal MIs or MACEs.[13] In contrast, the DCB-BIF trial, with a larger population enrolled, showed that DCB for a compromised SB was associated with a lower 1-year risk of MACE, along with a reduced incidence of TVMI although there were no significant differences between the groups for revascularization compared with BA for the SB. This difference was driven by fewer TVMIs, especially spontaneous infarctions occurring more than 48 hours after the procedures, in the DCB group compared with the BA group. No significant difference was observed between the 2 groups regarding TVMI attributable to periprocedural MI.[17]

The apparent benefit of DCB use on TVMI seems primarily driven by the findings of the DCB-BIF study, as demonstrated in the leave-one-out analysis (Supplementary Figure 2).[17] When the DCB-BIF study was excluded in the leave-one-out analysis, DCB did not significantly reduce TVMI compared with BA. In the DCB-BIF study,[17] high-sensitivity troponin was measured prior to the procedure, every 6 to 9 hours during the first 24 hours, and then every 24 hours up to 48 hours after PCI, which is an approach inconsistent with current guidelines.[25] More frequent troponin assessments may have contributed to higher reported myocardial infarction rates, which were not reflected in clinical presentations such as chest pain or stent thrombosis within the study population compared to other studies.[26] However, spontaneous MI occurring more than 48 hours after PCI was still significantly lower in DCB patients. One possible explanation for the reduced TVMI observed with DCB in this study may be the longer duration of inflation at lower pressure, which could enhance drug delivery and penetration into the vascular wall, possibly leading to a more effective anti-restenosis effect. Another reason may be the routine use of non-compliant balloon inflation after DCB in the SB, at low pressure, to facilitate drug penetration into the vascular wall.

A more detailed analysis of this study[17] also reveals that the average SB vessel diameters were ≤2.5 mm, and SB lesion lengths were typically <10 mm.[17] Similar characteristics were observed across the other 4 randomized studies included in this analysis.[13-16] These findings indicate that the populations studied predominantly had simple bifurcation lesions, rather than complex ones.

In the BABILON (The Paclitaxel-Coated Balloon in Bifurcated Lesions Trial) trial,[15] patients assigned to the DCB group underwent BMS implantation in the MB. This likely contributed to the higher restenosis rate in the DCB group compared

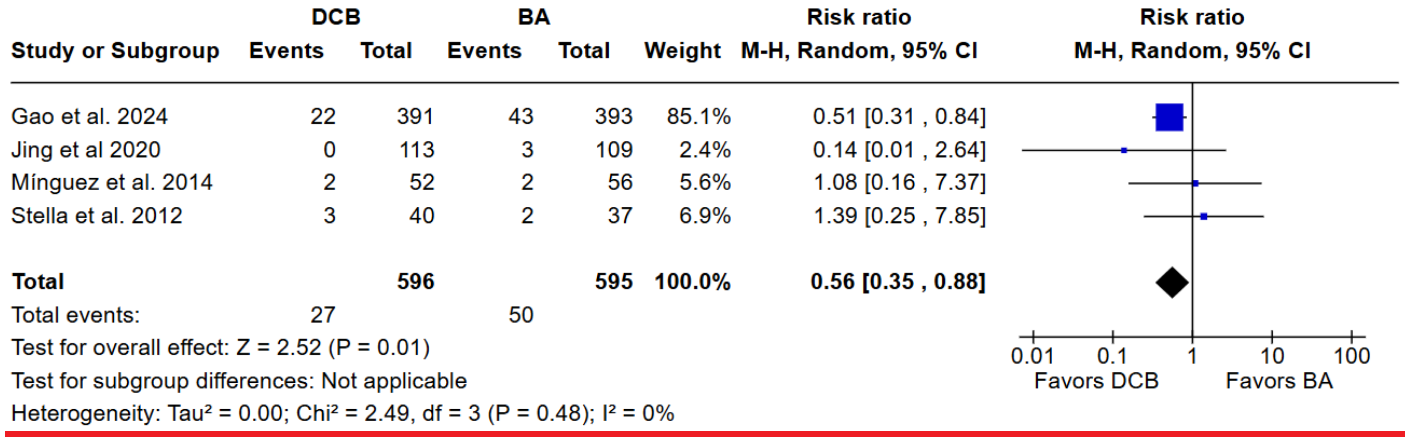

Figure 2. Drug-coated balloon (DCB) significantly reduced myocardial infarction (MI) after percutaneous coronary intervention (PCI) of bifurcation lesions.

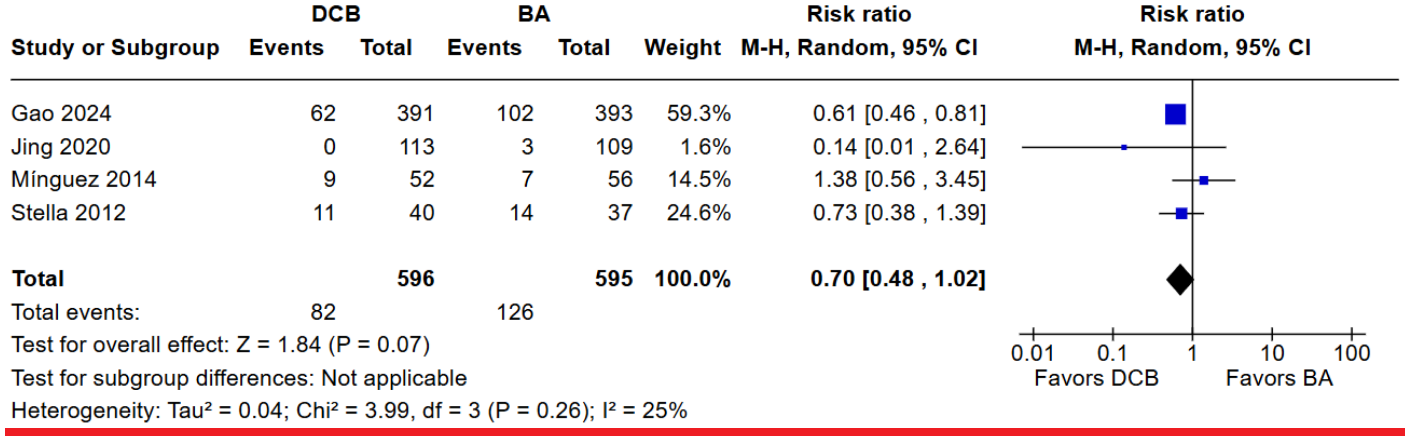

Figure 3. There was no significant difference in major cardiovascular events (MACE) between drug-coated balloon (DCB) and plain balloon angioplasty (BA) after percutaneous coronary intervention (PCI) for bifurcation lesions.

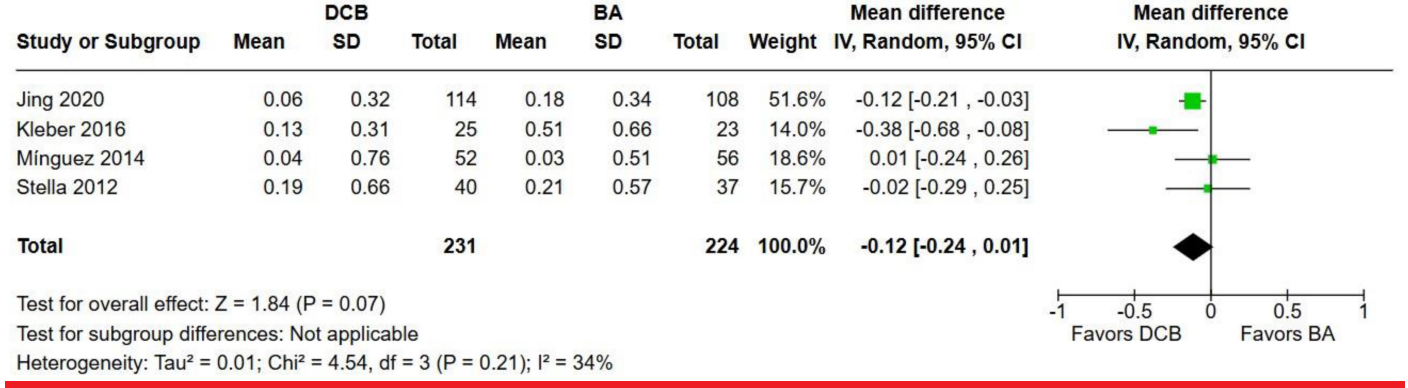

Figure 4. There was no significant difference in late lumen loss (LLL) between drug-coated balloon (DCB) and plain balloon angioplasty (BA) after percutaneous coronary intervention (PCI) of bifurcation lesions.

to the DES group, although there was no difference in MI rates between the 2 groups at the 24-month follow-up. On the other hand, the AGENT IDE trial reported a reduced incidence of TVMI with the use of a DCB for treating in-stent restenosis.[27] The meta-analysis findings were similar to those of the AGENT IDE trial,[27] in that there were no significant differences in any of the outcomes studied, except for the reduced MI risk. Although a previous meta-analysis showed less LLL with DCB to the SB compared with BA only, there was no significant reduction in lumen loss in the DCB to the SB group compared with BA only.[24]

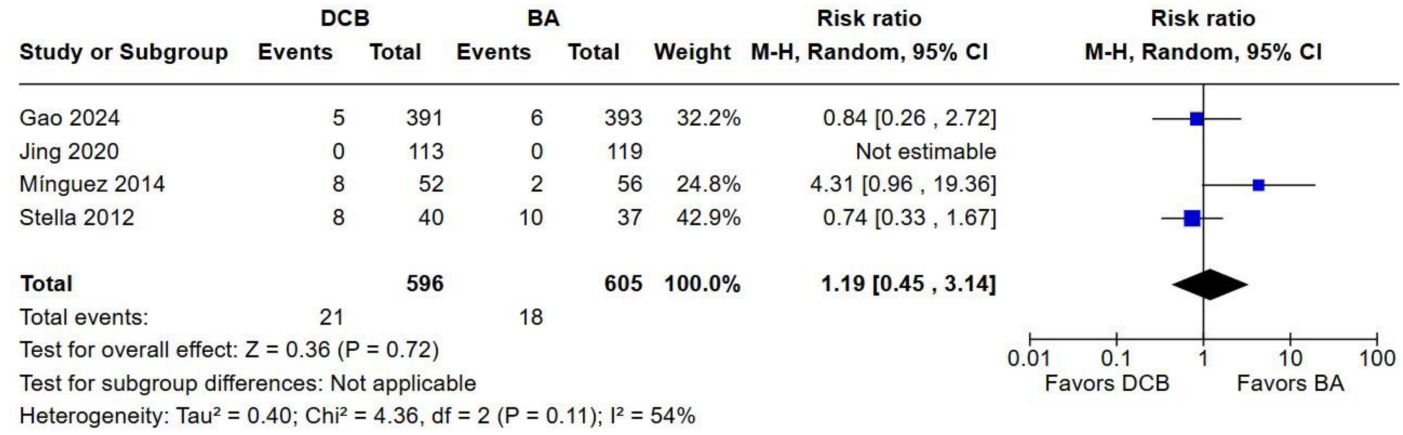

Figure 5. There was no significant difference in target-lesion revascularization (TLR) between drug-coated balloon (DCB) versus plain balloon angioplasty (BA) after percutaneous coronary intervention (PCI) of bifurcation lesions.

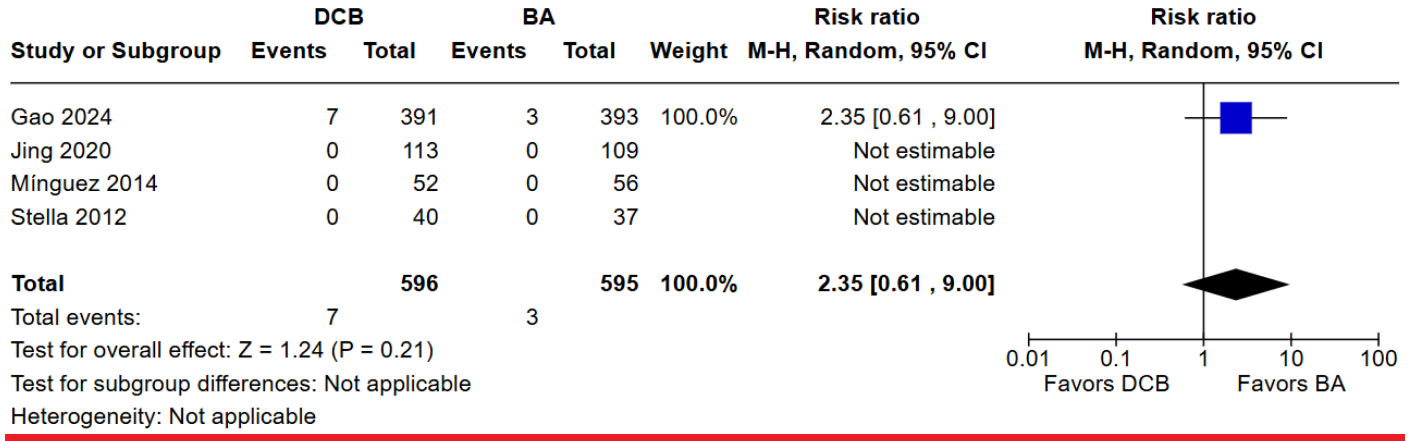

Figure 6. All-cause mortality did not differ between drug-coated balloon (DCB) and plain balloon angioplasty (BA) after percutaneous coronary intervention (PCI) of bifurcation lesions.

The observed reduction in MI risk may be explained by mechanisms mediated by the drug used in DCBs. The local delivery of drug directly to the lesion can potentially help in (1) reducing restenosis risk similar to Drug Eluting Stents;[28] (2) providing immediate vessel patency and sustained inhibition of neointimal proliferation;[28] (3) reducing local inflammation by reducing levels of vascular inflammatory cytokines;[28] and (4) modifying plaque structure, and stabilizing plaques.[30] Although these mechanisms could all play a role in that observation, further investigation for the exact pathophysiological basis is still warranted.

This study has limitations. First, subgroup analysis based on SB size, as well as the severity and hemodynamic significance of SB lesions, could not be performed due to lack of data for interest of outcomes based on SB size. Second, only 5 RCTs were included, which may limit the statistical power and generalizability of the findings, particularly for outcomes with high heterogeneity. The heterogeneity may stem from differences in study design, patient populations, treatment protocols, treatment strategies for the MB, and follow-up durations. Third, all studies in this meta-analysis focused on simple bifurcation lesions, limiting generalizability to more complex cases. Fourth, there was a low overall representation of female patients, and fifth, a low incidence of both non-ST-segment elevation and ST-segment elevation myocardial infarction cases in the study population, indicating the need for further research to better understand the effects on MI patients, particularly among women.

These limitations highlight the need for further high-quality, larger-scale RCTs with standardized methodologies and extended follow-up periods to confirm and refine the findings.

In this meta-analysis of RCTs comparing DCB and BA for SB treatment, a significant reduction was found in MI risk for patients who underwent DCB angioplasty, without differences in LLL, TLR, MACEs or all-cause mortality. While the use of DCB may be a viable option for SB treatment, there is a need for further high-quality, large-scale studies with standardized protocols and longer follow-up durations.

Ethics Committee Approval: Ethics committee approval is not required for this meta-analysis, as it is based on previously

published data and does not involve direct human or animal subjects.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – M.O., S.D.; Design – M.O., A.G.; Supervision – C.Y., M.O.; Resources – A.G., M.O., B.N.; Materials – B.N., M.O.; Data Collection and/or Processing – M.O., S.D.; Analysis and/or Interpretation – M.O., S.D., A.G.; Literature Search – B.N., M.O.; Writing – C.Y., M.O., S.D., Y.O.; Critical Review – C.Y., Y.O.

Declaration of Interests: All authors report no relationships that could be construed as a conflict of interest. All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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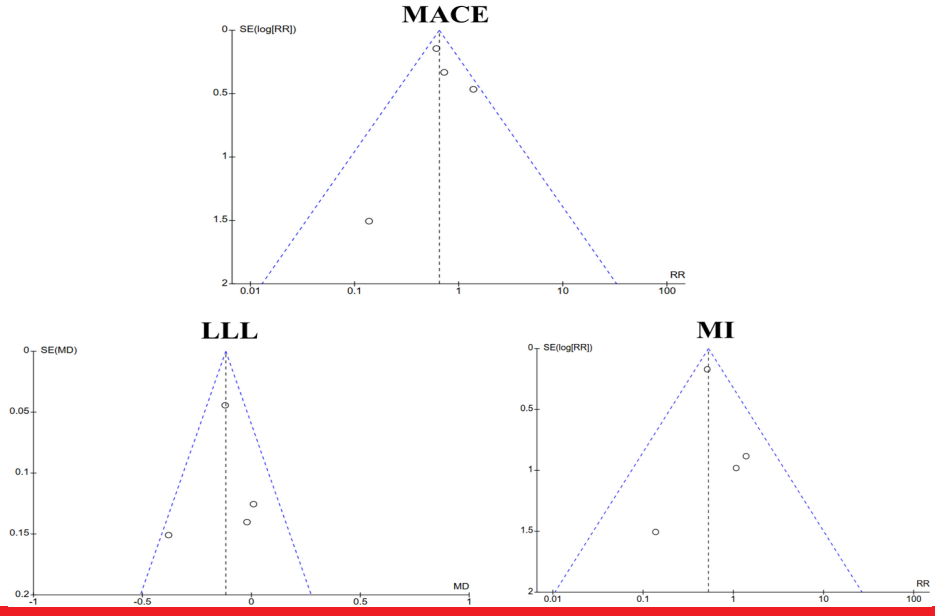
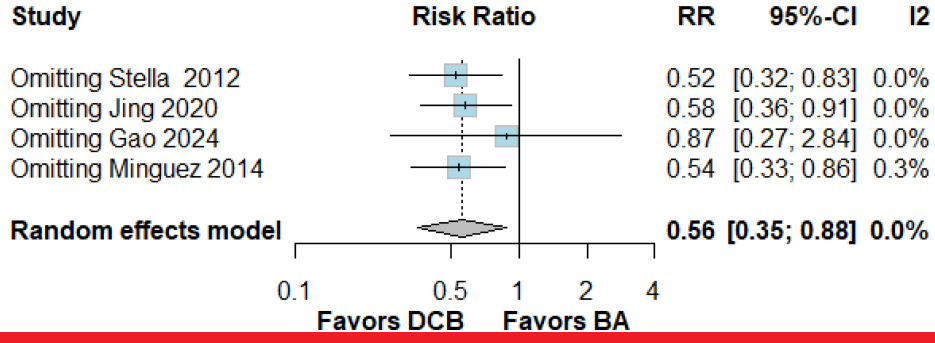
Supplementary Table 1. Risk of bias assessment using the Cochrane tool for Randomized Controlled Trials (RoB-2).

Study	Bias from randomization process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcomes	Bias in selection of the reported result	Overall risk of bias
Stella et al[14] 2012	Low	Some concerns	Low	Low	Low	Some concerns
Mínguez et al[15] 2014	Low	Some concerns	Low	Low	Low	Some concerns
Kleber et al[16] 2016	Low	Low	Low	Low	Low	Low
Jing et al[13] 2020	Some concerns	Some concerns	Low	Some concerns	Low	Some concerns
Gao et al[17] 2024	Low	Some concerns	Low	Low	Low	Some concerns



Supplementary Figure 1. No funnel plot asymmetry or outliers were observed for MACE, LLL, and MI, indicating a low risk of publication bias.



Supplementary Figure 2. Leave one-out analysis for myocardial infarction.