Journal of the American Heart Association

SYSTEMATIC REVIEW AND META-ANALYSIS

Clinical and Angiographic Outcomes With Drug-Coated Balloons for De Novo Coronary Lesions: A Meta-Analysis of Randomized Clinical Trials

Islam Y. Elgendy, MD; Mohamed M. Gad, MD; Akram Y. Elgendy, MD; Ahmad Mahmoud, MD; Ahmed N. Mahmoud, MD; Javier Cuesta, MD; Fernando Rivero, MD; Fernando Alfonso, MD, PhD

BACKGROUND: The role of drug-coated balloons (DCBs) in the treatment of de novo coronary lesions is not well established.

METHODS AND RESULTS: Electronic databases and major conference proceedings were searched for randomized controlled trials that compared DCBs with stents or angioplasty for de novo coronary lesions. The primary outcome was target lesion revascularization. Summary estimates were conducted using random-effects analysis complemented by several subgroup and sensitivity analyses. A total of 14 randomized controlled trials with 2483 patients were included. At a mean follow up of 12 months, DCBs were associated with no difference in the incidence of target lesion revascularization as compared with alternative strategies (risk ratio [RR], 0.79; 95% CI, 0.35–1.76). There was no difference in treatment effect based on the indication (ie, small-vessel disease, myocardial infarction, bifurcation, or high bleeding risk) ($P_{interaction}$=0.22). DCBs were associated with lower target lesion revascularization compared with bare metal stents and similar target lesion revascularization compared with drug-eluting stents ($P_{interaction}$=0.03). There was no difference between DCBs and control in terms of major adverse cardiac events, vessel thrombosis, or cardiovascular mortality. However, DCBs were associated with a lower incidence of myocardial infarction (RR, 0.48; 95% CI, 0.25–0.90) and all-cause mortality (RR, 0.45; 95% CI, 0.22–0.94).

CONCLUSIONS: In patients with de novo coronary lesions, use of DCBs was associated with comparable clinical outcomes irrespective of the indication or comparator device. DCBs had a similar rate of target lesion revascularization compared with drug-eluting stents. A randomized trial powered for clinical outcomes and evaluating the role of DCBs for all-comers is warranted.

Key Words: coronary artery disease ■ de novo lesions ■ drug-eluting stent ■ drug-coated balloon ■ meta-analysis ■ mortality ■ small vessels

Drug-eluting stents (DESs), particularly second-generation, remain the cornerstone management during percutaneous coronary intervention.[1] Coronary restenosis as a result of the persistence of the metallic struts within the vessel as well as the need for dual antiplatelet therapy remain major limitations even with the current generation of DESs.[2,3] In this context, drug-coated balloons (DCBs) offer an attractive therapeutic modality because these devices allow for local delivery of the antiproliferative agent directly into the artery wall with a single balloon inflation without the need for the metallic implant.[4] Several randomized trials have established the role of DCBs in treatment of in-stent restenosis of both DESs and bare metal stents (BMSs),[5–8] and the use of DCBs is currently endorsed by the 2018 European Society of Cardiology guidelines for myocardial revascularization as a class I recommendation for this indication.[9]

Correspondence to: Fernando Alfonso, MD, PhD, Cardiology Department, Hospital Universitario de La Princesa, IIS-IP, CIBER-CV, Universidad Autónoma de Madrid, c/Diego de León 62, Madrid 28006, Spain. E-mail: falf@hotmail.com

Supplementary Materials for this article are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.120.016224

For Sources of Funding and Disclosures, see page 10.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- In patients with de novo coronary lesions, drug-coated balloons were associated with comparable clinical outcomes irrespective of the indication or comparator device.
- Drug-coated balloons had a similar rate of target lesion revascularization compared with drug-eluting stents.

What Are the Clinical Implications?

- These findings suggest the value of drug-coated balloons as an attractive "leave-nothing-behind strategy" for selected patients with de novo coronary lesions provided a satisfactory result is obtained after lesion predilation.
- A randomized trial powered for clinical outcomes and evaluating the role of drug-coated balloons for all-comers is warranted.

Nonstandard Abbreviations and Acronyms

BMS	bare metal stent
DCB	drug-coated balloon
DES	drug-eluting stents
MLD	minimum lumen diameter
MI	myocardial infarction
TLR	target lesion revascularization

However, the role of DCBs is not as established for de novo coronary lesions.[4] Recently, several small-to-moderate–sized, randomized trials have evaluated the merits of DCBs for patients with small-vessel disease,[10,11] high risk of bleeding,[12] and myocardial infarction (MI).[13,14] However, most of these individual trials were not powered to assess the differences in clinical outcomes.[10,13,14] Moreover, the trials that were powered for clinical outcomes were noninferiority trials and did not routinely evaluate angiographic outcomes.[11–13] To address this knowledge gap, we performed a comprehensive systematic review and meta-analysis of randomized trials to evaluate the impact of DCBs for de novo coronary lesions on angiographic and clinical outcomes.

METHODS

The authors declare that all supporting data are available within the article (and in the accompanying supplementary material online).

Data Sources and Search Strategy

Electronic databases, including MEDLINE, Embase, and the Cochrane Register of Controlled Trials, as well as major scientific sessions, were searched without language restriction from inception through November 2019 using the search algorithm in Table S1. The bibliography of the retrieved articles was reviewed. The search was independently performed by 2 authors (I.Y.E., F.A.). The protocol for this meta-analysis was prospectively registered at the PROSPERO international prospective register of systematic reviews (CRD42019143329),[15] and was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[16]

Selection Criteria and Data Extraction

Trials that randomized patients with obstructive de novo coronary lesions to DCBs versus any comparator were included (ie, DES, BMS, angioplasty only). We excluded trials that electively performed routine BMS placement after DCBs, but included trials that permitted bailout stent placement after DCBs. Clinical and angiographic data from the longest available reported follow-up time were preferentially used. Observational studies were excluded for inherent risk of bias. Two independent authors (I.Y.E., A.Y.E.) extracted data on study design, sample size, intervention strategies, outcomes, and other study characteristics from the included studies. Discrepancies were resolved by consensus.

Assessment of Quality of Included Studies

The Cochrane Collaboration's tool was used for the assessment of the risk of bias. This consists of 7 points that test for selection, performance, detection, attrition, reporting, and other biases.[17] Performance bias (ie, blinding of participants and physicians) was found to be irrelevant due to the interventional nature in both arms. The overall risk of bias for each trial was classified as low, unclear, or high risk, based on whether level of bias in each domain could have resulted in biases in risk estimation.

Outcomes

The primary clinical outcome was target lesion revascularization (TLR). The secondary clinical outcomes included: major adverse cardiac events, as defined by the individual trials (Table S2); target vessel revascularization; MI; vessel thrombosis; cardiovascular mortality; and all-cause mortality. The following angiographic outcomes were assessed: minimum lumen diameter (MLD); diameter stenosis; late lumen loss; and binary restenosis.

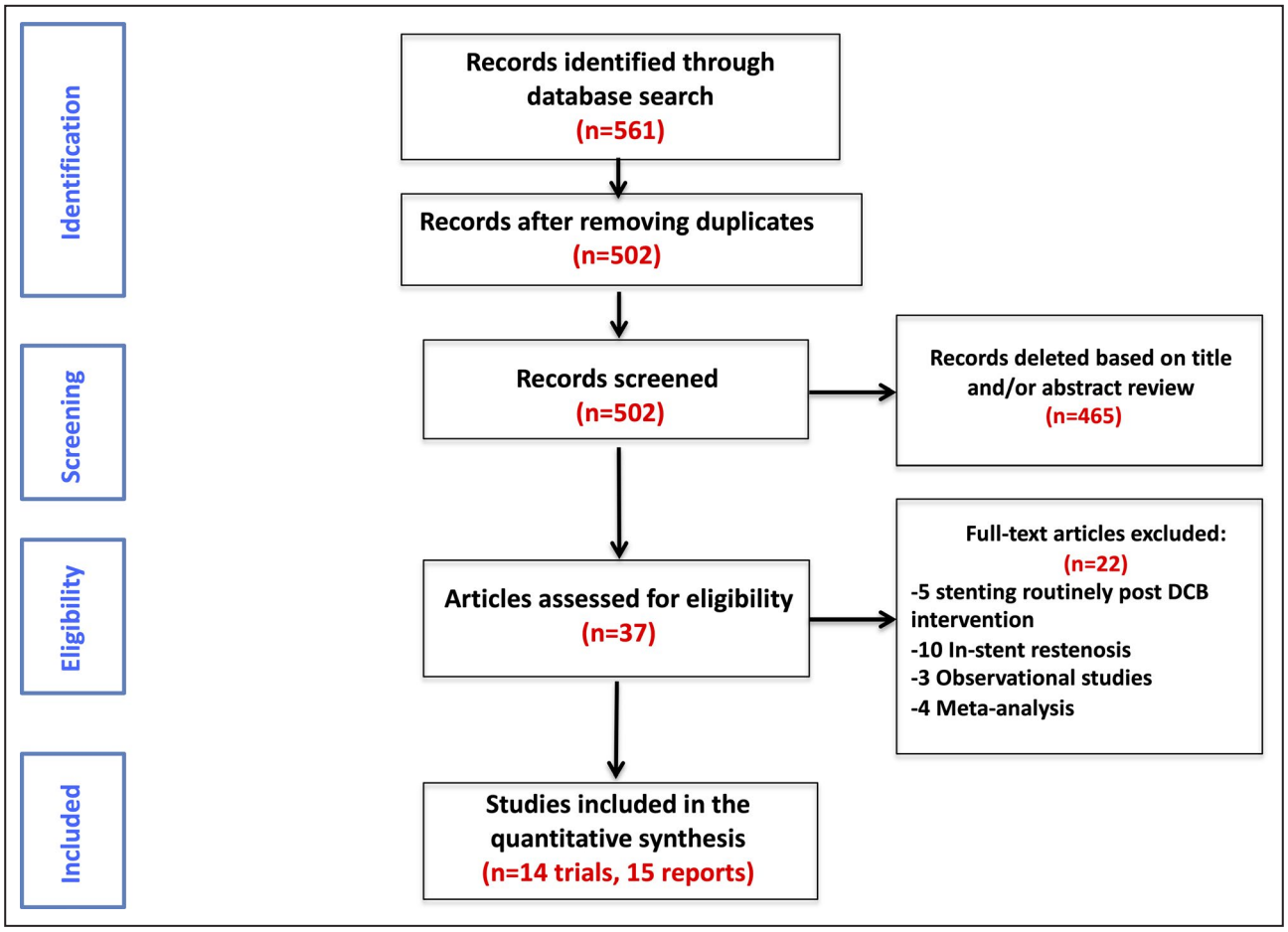

Figure 1. Study search diagram.
Summary of how the systematic search was conducted and eligible studies were identified. DCB indicates drug-coated balloon.

Statistical Analysis

Outcomes were evaluated by an intention-to-treat analysis. Random-effects summary risk ratios were primarily estimated with the DerSimonian and Laird model, because we anticipated a high degree of statistical heterogeneity.[18] Summary odds ratios were also estimated with a Peto model as a secondary analysis due to the low incidence of events.[19] Statistical heterogeneity was assessed using the Cochrane Q and I^2 statistics.[20] Egger's method was used to calculate publication bias.[21] Standardized mean differences were used for continuous variables. All P-values were 2-tailed, with statistical significance set at 0.05, and CIs were calculated at the 95% level for the overall estimates effect. All analyses were performed using the RStudio software meta package (RStudio, Inc, Boston, MA).

The following prespecified subgroup analyses were performed for the primary outcome (TLR): (1) according to indication; and (2) by comparing DESs versus BMSs. In addition, the following prespecified sensitivity analyses for TLR were also conducted by: (1) excluding trials using the first-generation DCB, which is no longer available[22]; (2) excluding trials using angioplasty alone in the control arm; (3) limiting to trials utilizing second-generation DESs as the control; and (4) excluding trials with high risk of bias. Random-effects meta-regression analyses for the primary outcome were prespecified in relation to baseline reference vessel diameter, diabetes mellitus, and proportion of bailout stent placement in the DCBs arm.[23] Finally, a sensitivity analysis limited to trials using second-generation DESs as the control was performed for the angiographic outcomes, and a sensitivity analysis limited to trials that defined MI as spontaneous (ie, not procedure-related) was also conducted.

RESULTS

Included Studies

The systematic search identified 502 studies after removal of the duplicates, among which 37 were reviewed for eligibility. The final number of records included in this meta-analysis was 14 trials from 15

Table. Characteristics, Interventional Strategies, and Follow-Up of the Included Trials

Trial (Reference No.)	Year	Indication	Drug-Coated Balloon Type	Control Group	Patients (n)	Clinical Follow-Up (months)	Angiographic Follow-Up (months)	Primary Outcome	Reference Vessel Diameter (mm)	Bailout Stenting in DCB Arm (%)
PICCOLETO II[24]	2019	Small-vessel disease	Elutax SV/Emperor	Second-generation DES	118/114	6	6	Late lumen loss	2.2/2.2	6.8
RESTORE CVD[10]	2019	Small-vessel disease	Restore	Second-generation DES	116/114	12	9	Diameter stenosis	2.4/2.4	5.2
BASKET-SMALL 2[11]	2019	Small-vessel disease	SeQuent Please	Second-generation DES	382/376	12	NR	MACE	NR	NR
Funatsu et al[25]	2017	Small-vessel disease	SeQuent Please	POBA	92/41	6	6	TVF	2.0/2.0	2.9
BELLO[26,27]	2012/2015	Small-vessel disease	IN.PACT Falcon	First-generation DES	90/92	36	6	Late lumen loss	2.4/2.4	20.2
PICCOLETO[22]	2010	Small-vessel disease	Dior	First-generation DES	29/31	9	6	Diameter stenosis	2.4/2.4	NR
PEPCAD NSTEMI[13]	2019	Myocardial infarction	SeQuent Please SeQuent Please Neo	BMS/second-generation DES	104/106	9	NR	Target lesion failure	NR	7.3
REVELATION[14]	2019	Myocardial infarction	Pantera Lux	Second-generation DES	60/60	9	9	FFR value	3.3/3.2	18.0
Gobic et al[28]	2017	Myocardial infarction	SeQuent Please	Second-generation DES	41/37	6	6	Late lumen loss	2.6/3.0	7.3
Shin et al[29]	2019	High bleeding risk	SeQuent Please	BMS	20/20	12	9	Late lumen loss	3.0/3.2	NR
DEBUT[12]	2019	High bleeding risk	SeQuent Please	BMS	102/106	9	NR	MACE	NR	2.0
PEPCAD-BIF[30]	2016	Bifurcational lesion	SeQuent Please	POBA	32/32	9	9	Late lumen loss	2.4/2.4	0
BABILON[31]	2014	Bifurcational lesion	SeQuent Please	POBA	52/56	24	9	Late lumen loss	2.3/2.3	7.8
Nishiyama et al[32]	2016	Unspecified	SeQuent Please	Second-generation DES	30/30	8	8	Not specified	2.9/2.7	10.0

Results are presented as drug-coated balloon/control. ACS indicates acute coronary syndrome; BABILON, The Paclitaxel-Coated Balloon in Bifurcated Lesions Trial; BASKET-SMALL 2, The Basel Kosten Effektivitäts Trial–Drug-Coated Balloons versus Drug-eluting Stents in Small Vessel Interventions; BELLO, Balloon Elution and Late Loss Optimization; BMS, bare metal stent; DCB, drug-coated balloon; DEBUT, Drug-Eluting Balloon in Stable and Unstable Angina: A Randomized Controlled Non-Inferiority Trial; DES, drug-eluting stent; FFR, fractional flow reserve; MACE, major adverse cardiac events; NR, not reported; PEPCAD-BIF, Drug eluting balloons as stand alone procedure for coronary bifurcational lesions; PEPCAD NSTEMI, Bare Metal Stent Versus Drug Coated Balloon With Provisional Stenting in Non-ST–Elevation Myocardial Infarction; PICCOLETO, Paclitaxel-coated balloon versus drug-eluting stent during PCI of small coronary vessels; PICCOLETO II, Drug Eluting Balloon Efficacy for Small Coronary Vessel Disease Treatment; POBA, "plain old" balloon angioplasty; RESTORE SVD, Assess the Efficacy and Safety of RESTORE Paclitaxel Eluting Balloon Versus RESOLUTE Zotarolimus Eluting Stent for the Treatment of Small Coronary Vessel Disease; REVELATION, Revascularization With Paclitaxel-Coated Balloon Angioplasty Versus Drug-Eluting Stenting in Acute Myocardial Infarction; and TVF, target vessel failure.

reports (Figure 1).[10–14,22,24–32] One trial reported angiographic and clinical outcomes at 6 months[26] and reported an extended follow-up for the clinical outcomes at 36 months.[27] A total of 2483 patients were included: 1268 in the DCBs group and 1215 in the control group. The indication for DCBs was small-vessel disease in 5 trials,[10,11,22,24–27] MI in 3 studies,[13,14,28] high bleeding risk in 2 trials,[12,29] bifurcational lesions in 2 studies,[30,31] and unspecified de novo lesions in 1 study.[32] In the bifurcational lesion trials, 1 trial compared "plain old" balloon angioplasty followed by DCB versus plain old balloon angioplasty alone to the main or side branch,[30] whereas the other trial randomized patients with bifurcational lesions to a strategy of side-branch dilation with DCB versus plain old balloon angioplasty.[31] The SeQuent Please paclitaxel-coated balloon was used by most of the included studies (9 of 14). Only 1 trial tested the Dior paclitaxel-coated balloon, which is no longer available.[22] The control group was exclusively second-generation DES in 6 trials,[10,11,14,24,28,32] first-generation DESs in 2 trials,[22,26] BMSs in 2 trials,[12,29] and plain old balloon angioplasty alone in 3 trials.[25,30,31] In 1 trial, the control was second-generation DESs or BMSs, and a subgroup analysis was reported for the outcomes based on the stent type.[13] The weighted mean reference vessel diameter was 2.5 mm. Table shows the baseline trial characteristics, follow-up duration, and interventional strategies. Table S3 summarizes the pertinent patient demographics and trial information. Performance bias was unclear in all the trials. One trial was at high risk for detection bias and unclear for allocation bias,[32] otherwise the remainder of the trials were considered to be of high quality (Table S4).

Angiographic Outcomes

Routine angiographic follow-up was performed at a weighted mean of 7 (range, 6–9) months. There was no difference between DCBs and control in terms of MLD (1.9 mm versus 2.0 mm; standardized mean difference, −0.13; 95% CI, −0.32 to 0.06; *P*=0.17), diameter stenosis (28.0% versus 28.1%; standardized mean difference, 0.22, 95% CI, −6.92 to 7.36; *P*=0.95), and binary restenosis (13.9% versus 16.3%; RR, 0.83; 95% CI, 0.40–1.71; *P*=0.61). However, DCBs were associated with lower late lumen loss (0.08 mm versus 0.24 mm; standardized mean difference, −0.17; 95% CI, −0.24 to −0.10; *P*<0.0001) (Figure 2). There was a significant degree of statistical heterogeneity observed for the angiographic outcomes (I^2 ranged from 60% to 94%), which was explained on the sensitivity analysis limited to trials comparing DCBs with second-generation DESs (I^2=0% for all the outcomes, except for diameter stenosis where I^2=56%). The findings of the sensitivity analysis were consistent with the main analysis for all angiographic outcomes except for a lower MLD with DCBs (Figure S1).

Target Lesion Revascularization

The weighted mean follow up for the clinical outcomes was 12 (range, 6–36) months. There was

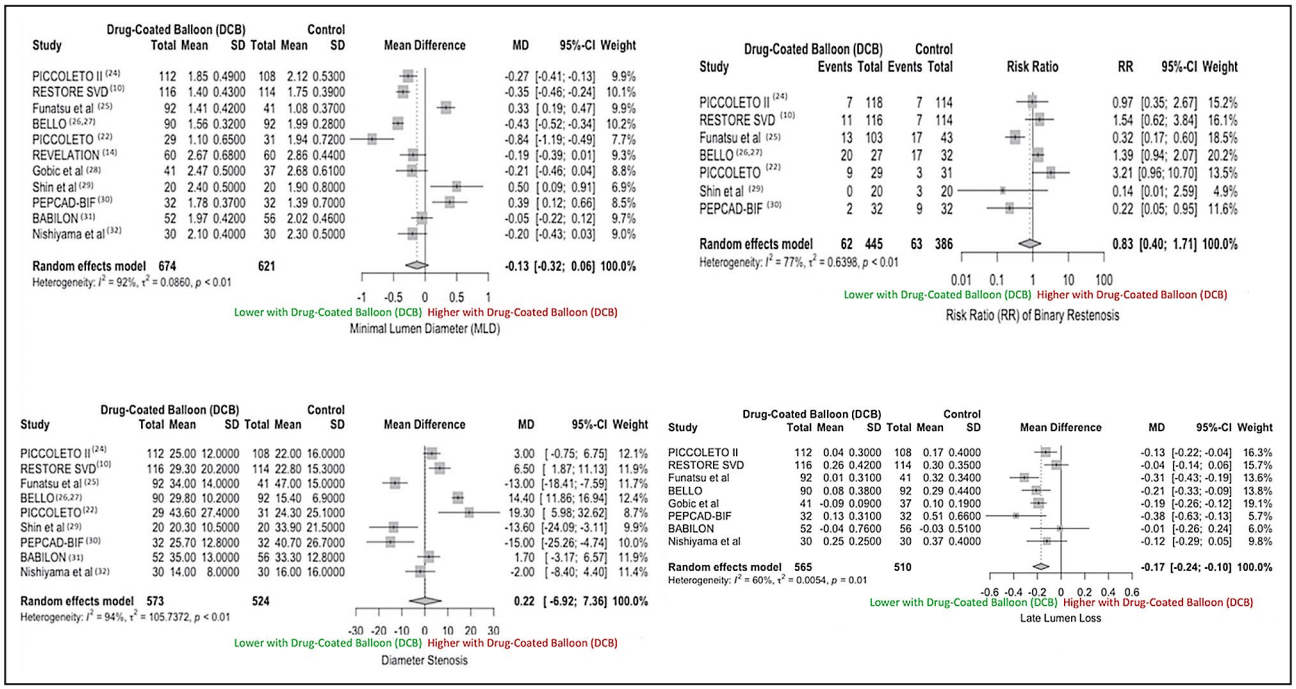

Figure 2. Summary plots for the angiographic outcomes.
The relative size of the data markers indicates weight of sample size from each study. DCB indicates drug-coated balloon; MD, mean difference; MLD, minimal lumen diameter; and RR, risk ratio.

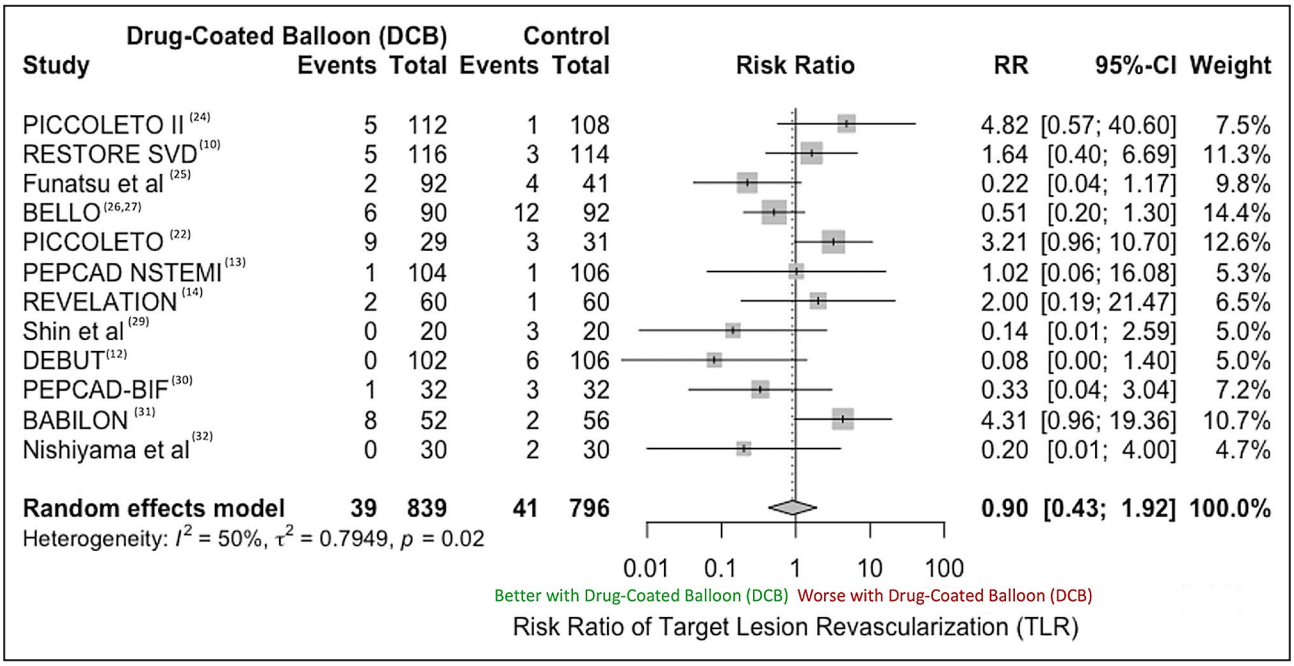

Figure 3. Summary plot for target lesion revascularization.
The relative size of the data markers indicates weight of sample size from each study. DCB indicates drug-coated balloon; and TLR, target lesion revascularization.

no difference in the incidence of TLR with DCBs compared with control (random effects: 4.6% versus 5.1%; RR, 0.79; 95% CI, 0.35–1.76; P=0.56; fixed effects: OR, 0.91; 95% CI, 0.58–1.44; P=0.69) (Figure 3). There was no evidence of publication bias using Egger's test (P=0.45). The outcome was characterized by moderate heterogeneity (I^2=50%; χ^2=22.1; $P_{heterogeneity}$=0.02). DCBs showed similar TLR compared with control, irrespective of the indication ($P_{interaction}$=0.22) (Figure 4). The incidence of TLR was similar when DCBs compared with DESs (RR, 1.37; 95% CI, 0.62–3.05; I^2=34%), but DCBs were associated with a lower incidence of TLR compared with BMSs (RR, 0.19; 95% CI, 0.04–1.00; I^2=0%) ($P_{interaction}$=0.03) (Figure 5). The findings of the prespecified sensitivity analyses for TLR were consistent with the overall analysis: (1) excluding trials that utilized the older generation DCBs (RR, 0.76; 95% CI, 0.35–1.65; I^2=43%; χ^2=17.6; $P_{heterogeneity}$=0.06) (Figure S2); (2) excluding trials using angioplasty alone in the control arm (RR, 0.97; 95% CI, 0.42–2.27; I^2=45%; χ^2=14.5; $P_{heterogeneity}$=0.07) (Figure S3); (3) limited to trials utilizing second-generation DESs as control (RR, 1.65; 95% CI, 0.65–4.34; I^2=0%; χ^2=2.9; $P_{heterogeneity}$=0.57) (Figure S4); and (4) excluding the trial with high risk of bias (RR, 0.97; 95% CI, 0.45–2.12; I^2=52%; χ^2=21.0; $P_{heterogeneity}$=0.02) (Figure S5). Meta-regression analysis did not identify a difference in the treatment effect based on baseline reference vessel diameter (P=0.81), diabetes mellitus (P=0.37), and proportion of bailout stent placement (P=0.63).

Secondary Clinical Outcomes

Compared with control, DCBs were associated with no difference in the incidence of target vessel revascularization (6.0% versus 5.3%; RR, 1.21; 95% CI, 0.60–2.44; P=0.59; I^2=52%; χ^2=8.3; $P_{heterogeneity}$=0.08), major adverse cardiac events (6.9% versus 9.1%; RR, 0.83; 95% CI, 0.50–1.36; P=0.46; I^2=53%; χ^2=23.3; $P_{heterogeneity}$=0.02), vessel thrombosis (0.3% versus 1.1%; RR, 0.38; 95% CI, 0.13–1.13; P=0.08; I^2=0%; χ^2=0.5; $P_{heterogeneity}$=0.91), and cardiovascular mortality (1.5% versus 1.5%; RR, 0.90; 95% CI, 0.27–3.00; P=0.86; I^2=56%; χ^2=6.8; $P_{heterogeneity}$=0.08). Importantly, DCBs were associated with a lower incidence of all-cause mortality (1.2% versus 2.9%; RR, 0.45; 95% CI, 0.22–0.94; P=0.03; I^2=0%; χ^2=0.78; $P_{heterogeneity}$=0.85), and MI (1.1% versus 2.9%; RR, 0.48; 95% CI, 0.25–0.90; P=0.02; I^2=0%; χ^2=6.2; $P_{heterogeneity}$=0.62) (Figures 6 and S6 through S11). In the sensitivity analysis limited to trials that defined MI as spontaneous MI, DCBs were associated with lower incidence of spontaneous MI (RR, 0.49; 95% CI, 0.25–0.96; P=0.04; I^2=0%) (Figure S12). There was no evidence of publication bias for any of the secondary clinical outcomes using Egger's test (all P>0.05).

DISCUSSION

In this meta-analysis of 14 randomized trials including 2483 patients with de novo coronary lesions undergoing percutaneous coronary intervention irrespective of

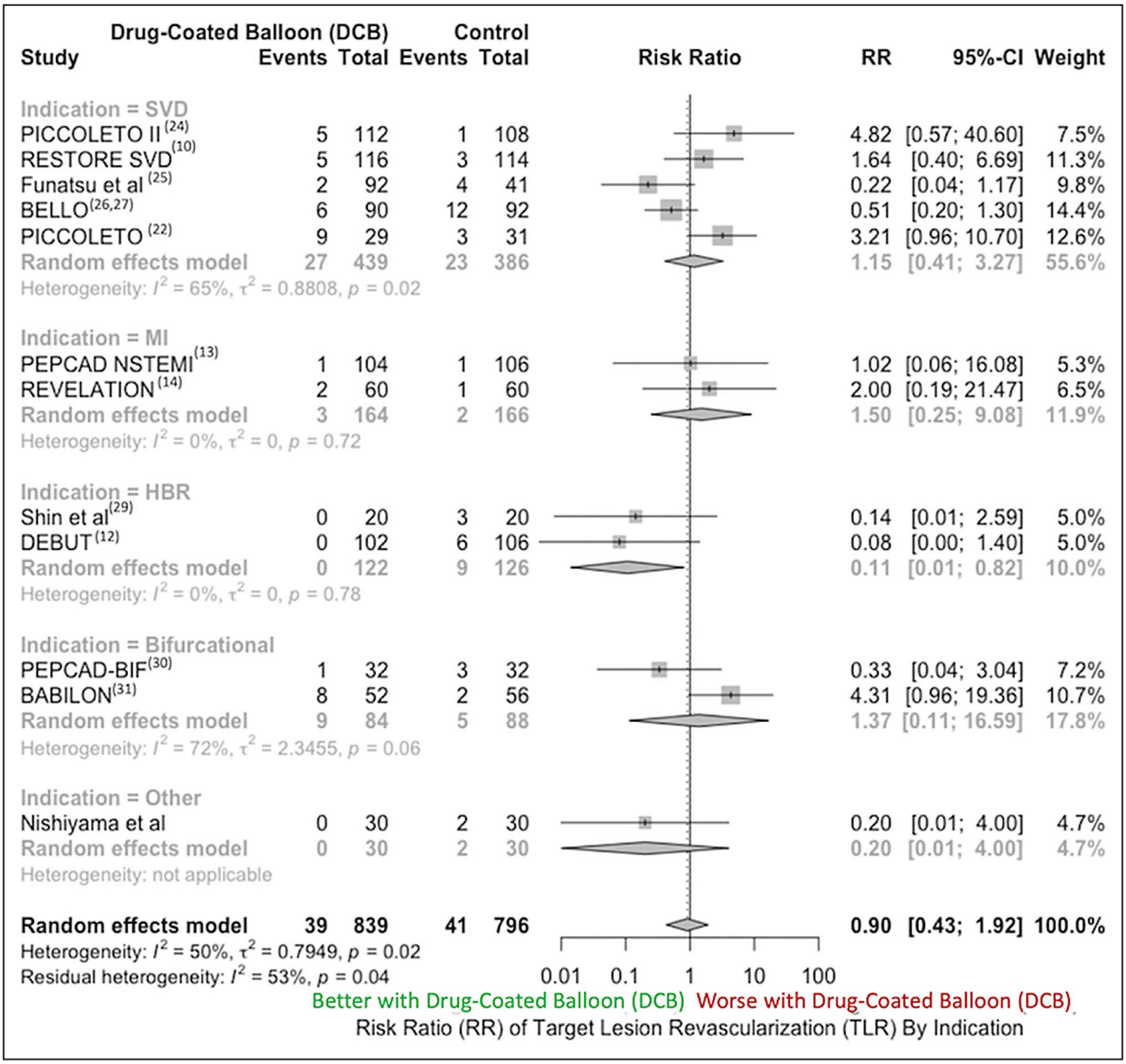

Figure 4. Subgroup analysis for target lesion revascularization according to indication.
The relative size of the data markers indicates weight of sample size from each study. There was no difference in treatment effect according to the different indications ($P_{interaction}$=0.22). DCB indicates drug-coated balloon; and TLR, target lesion revascularization.

indication, we documented that DCBs were associated with similar MLD, diameter stenosis, binary restenosis, and lower late lumen loss compared with control on routine angiographic follow up at a mean of 7 months. These findings were similar when DCBs were only compared with second-generation DESs (except that DCBs were associated with lower MLD). At a mean of 12 months, DCBs were associated with no difference in the incidence of TLR compared with control. This effect was consistent, regardless of indication (ie, small-vessel disease, high bleeding risk, MI, or bifurcational lesions), and on multiple sensitivity analyses, including comparing DCBs with second-generation DESs. DCBs were associated with lower risk of TLR compared with BMS. There was a moderate degree of statistical heterogeneity for TLR, which was partly explained by our subgroup analysis comparing DCBs with DESs versus BMSs, and on the sensitivity analysis limited to second-generation DESs. DCBs were also associated with no difference in the incidence of target vessel revascularization, major adverse cardiac events, vessel thrombosis, and cardiovascular mortality. Importantly, the incidence of all-cause mortality and MI (even when spontaneous MI was analyzed separately)

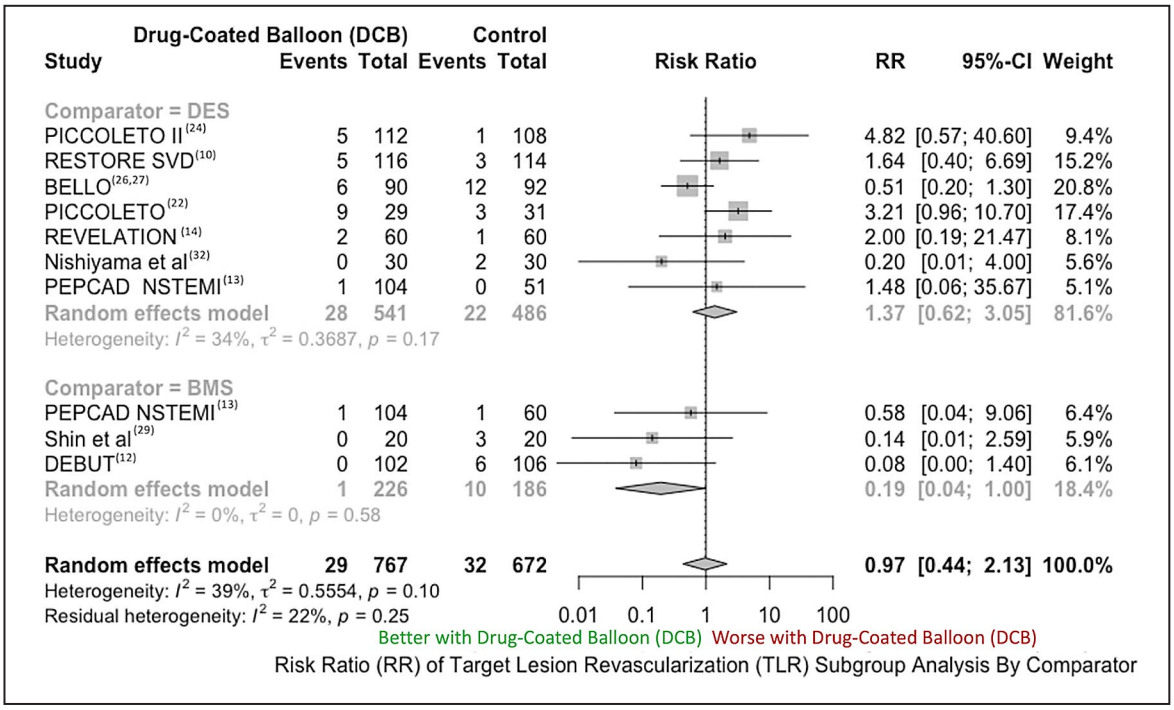

Figure 5. Subgroup analysis for target lesion revascularization comparing bare metal and drug-eluting stents.
The relative size of the data markers indicates the weight of the sample size from each study. Drug-coated balloon use was associated with lower target lesion revascularization compared with bare metal stents and similar target lesion revascularization compared with drug-eluting stents ($P_{interaction}$=0.03). DCB indicates drug-coated balloon; and TLR, target lesion revascularization.

was lower with DCBs. However, these findings were based on a small number of trials and the number of events was low, and therefore should be only considered as hypothesis-generating. Altogether, our findings strongly suggest the value of DCBs as an attractive "leave–nothing-behind strategy" for selected patients with de novo coronary lesions provided a satisfactory result is obtained after lesion predilation.

DCBs offer the advantage of locally delivering the antiproliferative drug without the need for

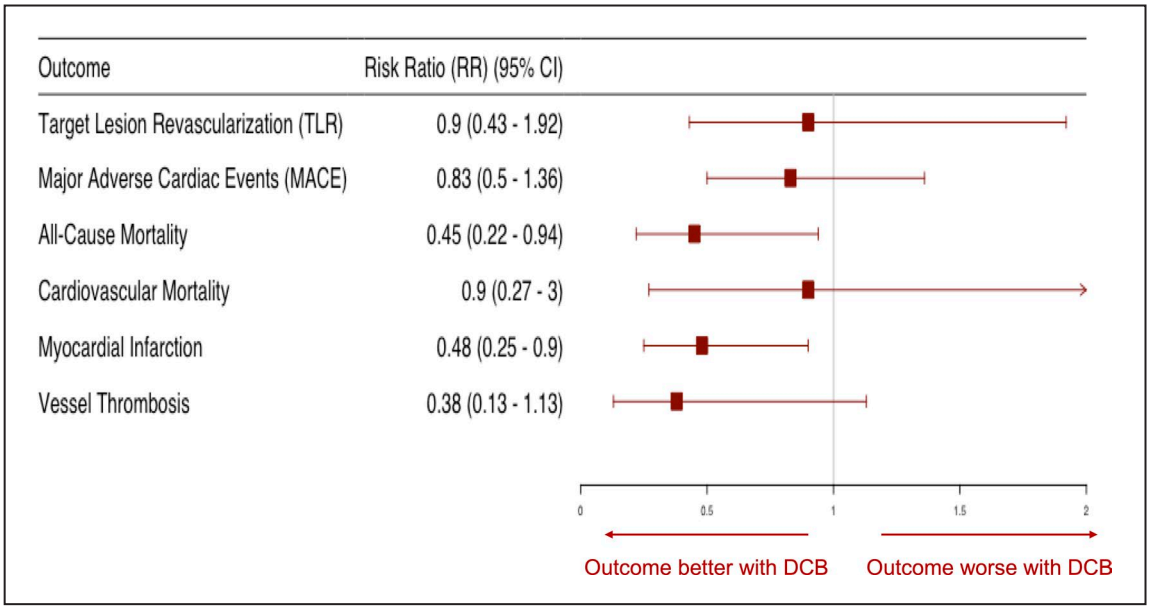

Figure 6. Forest plots for the clinical outcomes evaluated in this meta-analysis.
For each comparison, boxes and horizontal lines correspond to the respective point estimate and accompanying 95% CI. DCB indicates drug-coated balloon; MACE, major adverse cardiac events; and TLR, target lesion revascularization.

metal struts, thus directly inhibiting the process of neointimal hyperplasia and negative remodeling.[4] Although use of DCBs in patients with in-stent restenosis has been extensively investigated,[9] trials evaluating DCBs for de novo lesions have been small and evaluated specific indications. Our meta-analysis, including the most recent trials, has demonstrated that DCBs were associated with favorable clinical outcomes irrespective of the indication, even when compared with second-generation DESs. Although most patients undergoing percutaneous coronary intervention are treated with a second-generation DES,[1] BMSs are still used in a minority of patients, such as those with a high risk of bleeding to minimize the duration of antiplatelet therapy. Our meta-analysis showed that DCBs represent a reasonable therapeutic strategy for this subset of patients.

Second-generation DESs may not offer an effective therapeutic strategy in small vessels due to the late lumen loss resulting in late in-stent restenosis.[34] In this challenging setting, several randomized trials have shown that DCBs are noninferior to DESs for major adverse cardiac events.[10,11] By significantly increasing the sample size, the current meta-analysis has extended our knowledge by showing that DCBs are associated with similar TLR compared with any control, including second-generation DESs. Moreover, our meta-regression analysis has shown that there was no difference in treatment effect based on the reference vessel diameter.

One meta-analysis of randomized trials has raised some concerns about late mortality with DCBs for patients with peripheral artery disease.[35] That meta-analysis was subject to several limitations,[36] and the late mortality finding was not replicated in several large observational studies and patient-level meta-analysis.[37,38] Our meta-analysis provides some support for the use of DCBs for coronary lesions. However, the lower mortality seen with DCBs in our meta-analysis should be interpreted with caution given the limited number of studies that evaluated all-cause mortality and the low number of events.

Previous meta-analyses addressed use of DCBs for a specific indication, such as small-vessel disease or bifurcational lesions.[39–41] In addition, those meta-analyses included observational studies, which are prone to ascertainment and selection biases.[39–41] Furthermore, those works did not include the results of several recently published and presented trials.[10,13,14,24] The present meta-analysis only included randomized trials and has provided a comprehensive overview of the angiographic and clinical outcomes of DCBs irrespective of indication. In addition, we performed several subgroup and sensitivity analyses to explore the statistical heterogeneity.

Our meta-analysis has several limitations. First, although all the included studies used a paclitaxel-coated balloon, there are several pharmacokinetic differences between the devices. For example, one trial used the first-generation Drior paclitaxel-coated balloon, which was shown to be inferior in terms of deliverability and is no longer available. Thus, we performed a sensitivity analysis excluding this trial for the primary clinical outcome. Second, there were differences in the core laboratory assessment of the angiographic outcomes across the trials, which could be a source of the significant heterogeneity noted with these outcomes. However, we observed no heterogeneity for most of the angiographic outcomes on the sensitivity analysis comparing DCBs with second-generation DESs. Third, we noted a moderate degree of statistical heterogeneity for the primary clinical outcome (ie, TLR). We attempted to mitigate this by using a random-effects model. In addition, we performed multiple subgroup, sensitivity, and meta-regression analyses to explore the heterogeneity; however, the number of studies included in some of these subgroup and sensitivity analyses was small, so the findings can only be considered as hypothesis-generating. Fourth, one of the included trials was at high risk for bias,[32] so we performed a sensitivity analysis excluding that trial for TLR. Fifth, despite the extensive subgroup, sensitivity, and meta-regression analyses conducted, there may be some considerations about clinical and methodologic heterogeneity, because the meta-analysis included different comparators and the indication for DCBs were variable. Finally, the lack of patient-level data precluded a careful evaluation for the patient and lesion characteristics that would benefit most from DCBs.

CONCLUSIONS

In this meta-analysis of 14 randomized trials comprising 2483 patients with de novo coronary lesions, DCBs were associated with similar MLD, diameter stenosis, acute lumen gain, binary restenosis, and lower late lumen loss compared with control on routine angiographic follow up. There was no difference in the incidence of TLR between DCBs compared with control. This effect was observed regardless of indication (ie, small-vessel disease, high bleeding risk, MI, or bifurcational lesions), and was maintained when compared with second-generation DES alone. Finally, DCBs were associated with lower risk of MI and all-cause mortality, albeit with a low number of events, so our work should be only considered hypothesis-generating. Our findings support the need for a randomized trial powered for clinical outcomes evaluating the role of the DCBs in all-comers.

ARTICLE INFORMATION

Received February 12, 2020; accepted April 8, 2020.

Affiliations

From the Division of Cardiology, Massachusetts General Hospital and Harvard Medical School, Boston, MA (I.Y.E.); Department of Medicine, Cleveland Clinic Foundation, Cleveland, OH (M.M.G.); Division of Cardiovascular Medicine, University of Florida, Gainesville, FL (A.Y.E., A.M.); Division of Cardiology, University of Washington, Seattle, WA (A.N.M.); Cardiology Department, Hospital Universitario de La Princesa, IIS-IP, CIBER-CV, Universidad Autónoma de Madrid, Spain (J.C., F.R., F.A.).

Sources of Funding

None.

Disclosures

None.

Supplementary Materials

Tables S1–S4
Figures S1–12
References 10–14, 22, 24–27, 29, and 31

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Supplemental Material

Table S1. Search strategy.

Database	Search Strategy	Filters	Number
Pubmed	((Eluting balloon AND coronary) OR (coated balloon AND coronary)	Human Species	326
CENTRAL	((Eluting balloon) OR (coated balloon) AND (coronary))	Clinical trials	131
Embase	((Eluting balloon) OR (coated balloon) AND (coronary))	Controlled clinical trial/ Randomized controlled trial	102

Table S2. Definition of major adverse cardiac events per the individual trials.

Trial (ref#)	Definition of major adverse cardiac events
PICCOLETO II[24]	Cardiac death, non-fatal myocardial infarction, target lesion revascularization
RESTORE SVD[10]	Cardiac death, target vessel myocardial infarction, target lesion revascularization
BASKET-SMALL 2[11]	Cardiac death, non-fatal myocardial infarction, target vessel revascularization
Funatsu et al[25]	Cardiac death, non-fatal myocardial infarction, target vessel revascularization
BELLO[26,27]	All-cause death, non-fatal myocardial infarction, target vessel revascularization
PICCOLETO[22]	Death, ST elevation myocardial infarction, target lesion revascularization
PEPCAD NSTEMI[13]	Cardiac death, non-fatal myocardial infarction, target lesion revascularization
REVELATION[14]	Cardiac death, non-fatal myocardial infarction, target lesion revascularization
Gobic et al[28]	Cardiac death, non-fatal myocardial infarction, target lesion revascularization, stent thrombosis
Shin et al[29]	Cardiac death, non-fatal myocardial infarction, target lesion revascularization, stent thrombosis
DEBUT[12]	Cardiac death, non-fatal myocardial infarction, target lesion revascularization
BABILON[31]	Cardiac death, non-fatal myocardial infarction, target lesion revascularization

Table S3. Baseline patient and trial characteristics.

Trial (ref#)	Single/multicenter	Country	Trial registration number	Age, years	Men, %	Diabetes mellitus, %	Hypertension, %	Acute coronary syndrome, %
PICCOLETO II[24]	Multicenter	Italy	NCT03899818	64/66	70/77	38/35	65/67	45/44
RESTORE SVD[10]	Multicenter	China	NCT02946307	60/61	66/77	40/42	67/75	69/71
BASKET-SMALL 2[11]	Multicenter	Switzerland, Germany, Austria	NCT01574534	67/68	77/70	32/35	85/89	30/27
Funatsu et al[25]	Multicenter	Japan	UMIN000026760	68/69	78/68	48/32	84/73	NR
BELLO[26,27]	Multicenter	Italy	NCT01086579	65/66	80/77	43/38	80/82	24/22
PICCOLETO[22]	Single center	Italy	EudraCT: 2009-012268-15	68/67	79/76	38/46	75/71	54/55
PEPCAD NSTEMI[13]	Multicenter	Germany	NCT01489449	66/67	66/68	27/36	79/88	100/100
REVELATION[14]	Single center	Netherlands	NCT02219802	57/57	87/87	13/7	30/32	100/100
Gobic et al[28]	Single center	Croatia	NR	57/54	71/73	5/11	32/35	100/100
Shin et al[29]	Single center	Korea	NCT02456402	58/62	70/75	35/25	40/45	30/40
DEBUT[12]	Multicenter	Finland	NCT01781546	78/76	62/64	26/49	MACE	46/46
PEPCAD-BIF[30]	Multicenter	Germany	NR	66/69	75/72	34/38	87/91	28/19
BABILON[31]	Multicenter	Spain	NCT01278186	64/66	64/66	27/38	NR	68
Nishiyama et al[32]	Single center	Japan	NR	67/70	67/80	40/43	77/90	100/100

Data are reported as drug-coated balloon/control

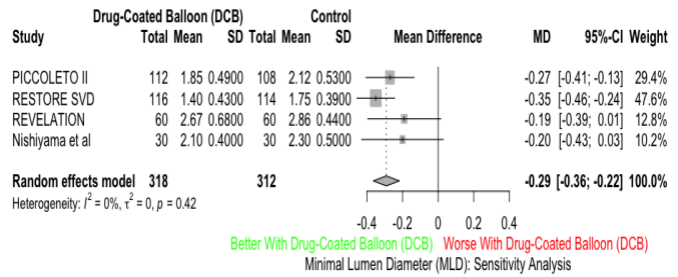
NR= not reported

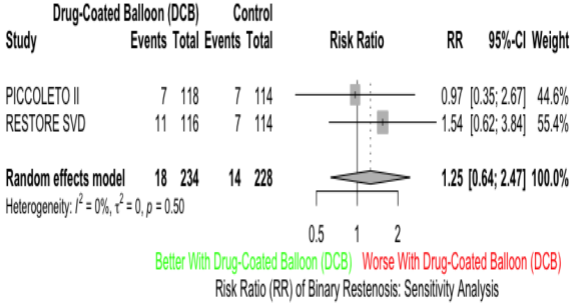
Table S4. Risk of bias of the individual studies by Cochrane risk assessment tool.

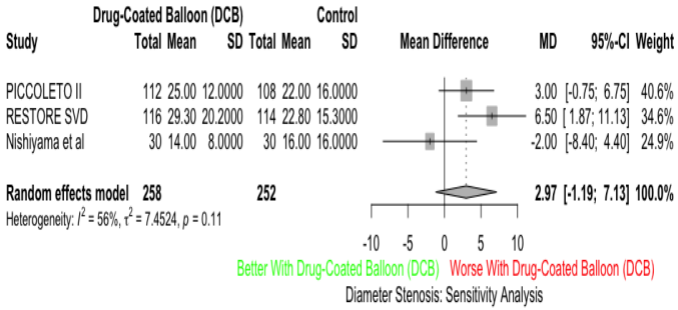
	PICCOLETO II[24]	RESTORE SVD[10]	BASKET-SMALL 2[11]	Funatsu et al[25]	BELLO[26,27]	PICCOLETO[22]	PEPCAD NSTEMI[13]	REVELATION[14]	Gobic et al[28]	Shin et al[29]	DEBUT[12]	PEPCAD-BIF[30]	BABILON[31]	Nishiyama et al[32]
Random sequence generation *(Selection bias)*	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Allocation concealment *(Selection bias)*	+	+	+	+	+	+	+	+	+	+	+	+	+	?
Blinding of participants and personnel *(Performance bias)*	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Blinding of outcome assessment *(Detection bias)*	+	+	+	+	+	+	+	+	+	+	+	+	+	-
Incomplete outcome data *(Attrition bias)*	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Selective reporting *(Reporting bias)*	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Other sources of bias	+	+	+	+	+	+	+	+	+	+	+	+	+	+

+ = Low risk of bias - = Risk of bias ? = Unclear

Figure S1. Sensitivity analysis for the angiographic outcomes limited to trials with second-generation drug eluting stents as control.







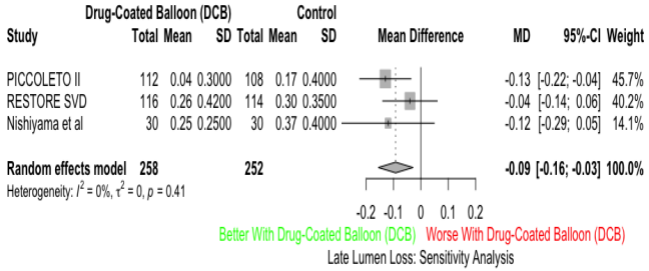
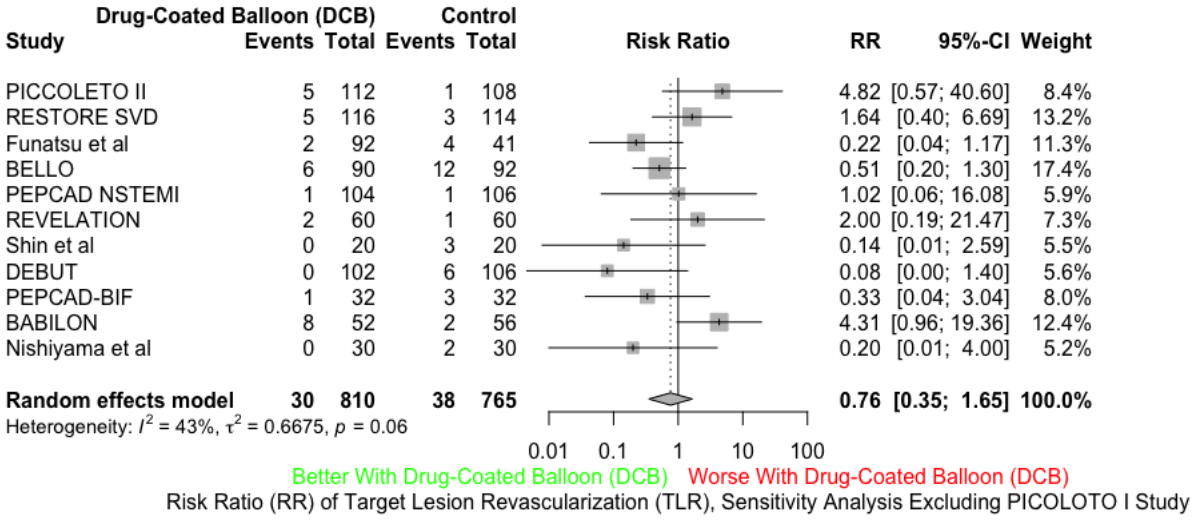


Figure S2. Sensitivity analysis for target lesion revascularization excluding trial using older generation drug coated balloon.



Risk Ratio (RR) of Target Lesion Revascularization (TLR), Sensitivity Analysis Excluding PICOLOTO I Study

Figure S3. Sensitivity analysis for target lesion revascularization excluding trials using angioplasty alone in the control arm.

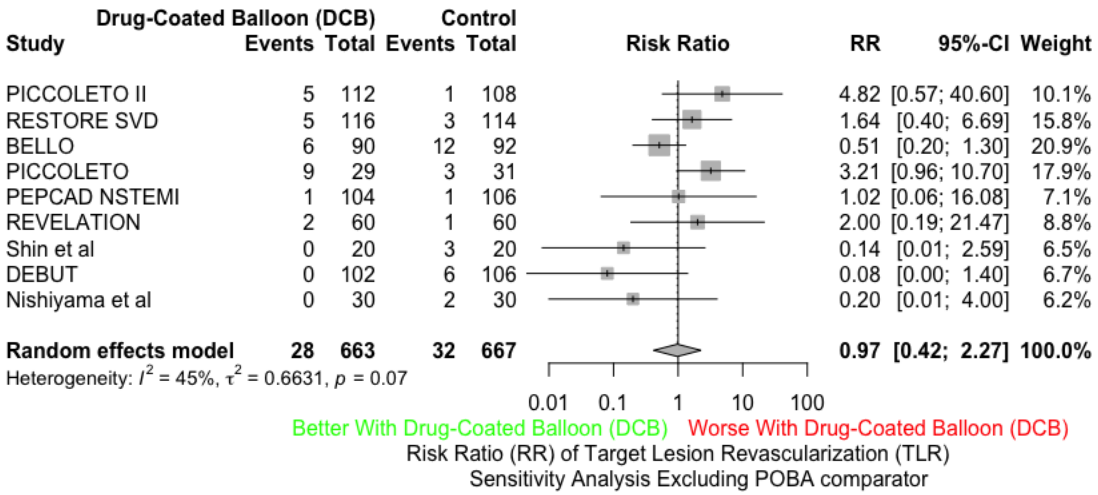


Figure S4. Sensitivity analysis for target lesion revascularization limited to trials utilizing second-generation drug-eluting stent as control.

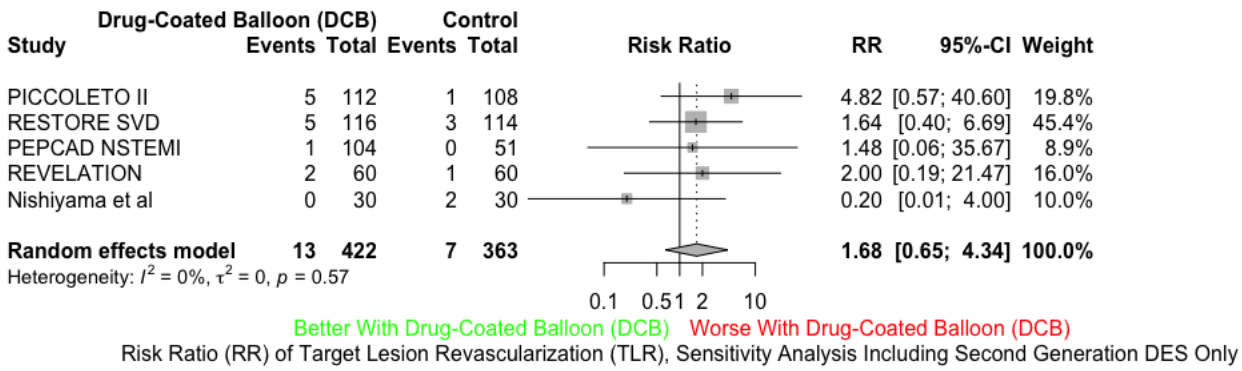


Figure S5. Sensitivity analysis for target lesion revascularization excluding the trial at high risk of bias.

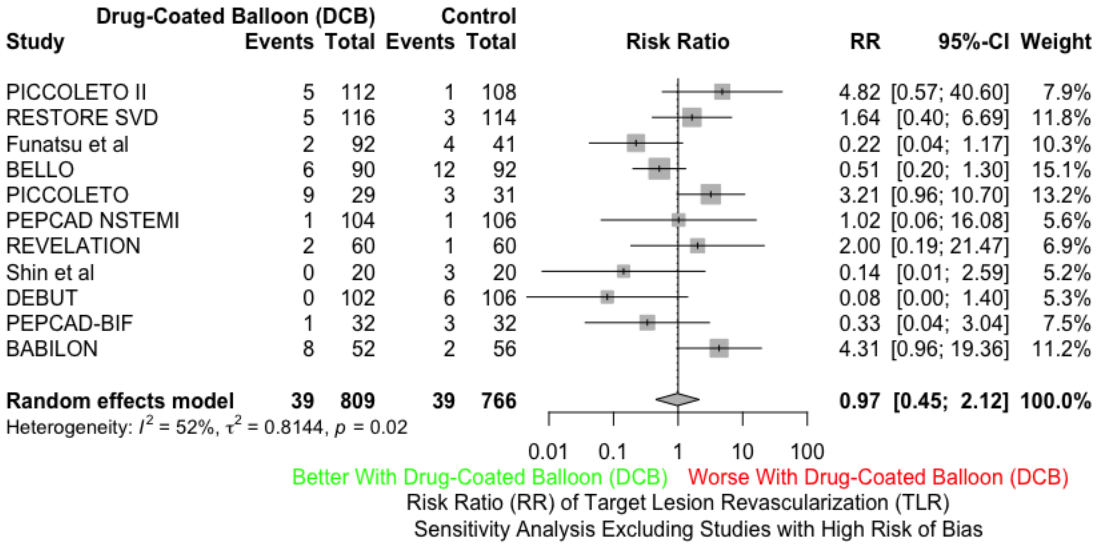


Figure S6. Forest plot for target vessel revascularization.

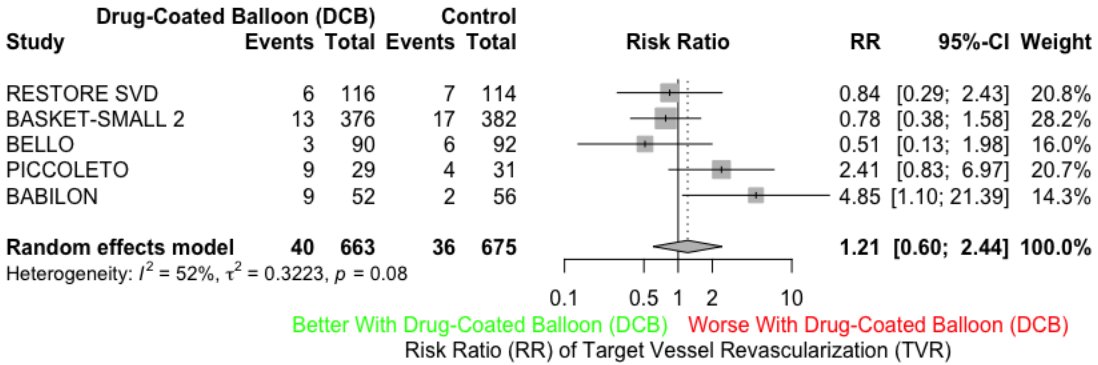


Figure S7. Forest plot for major adverse cardiac events.

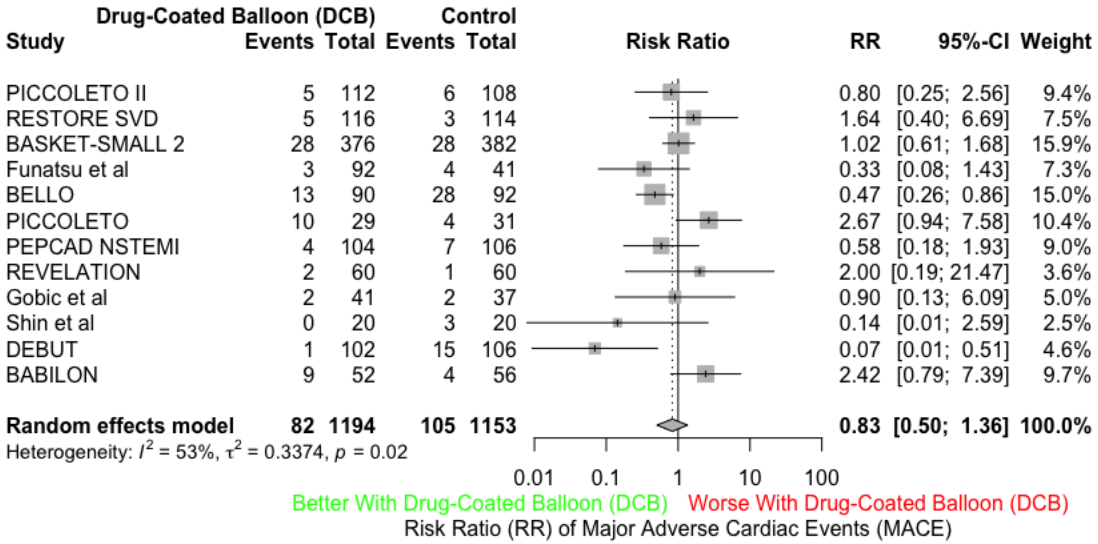


Figure S8. Forest plot for vessel thrombosis.

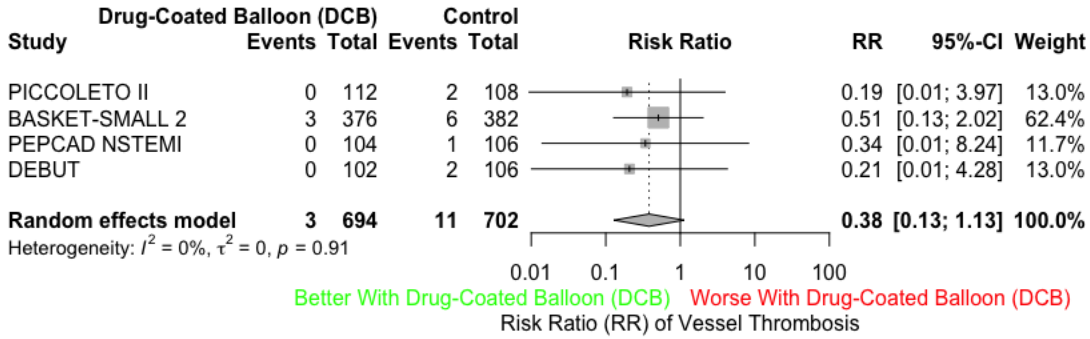


Figure S9. Forest plot for cardiovascular mortality.

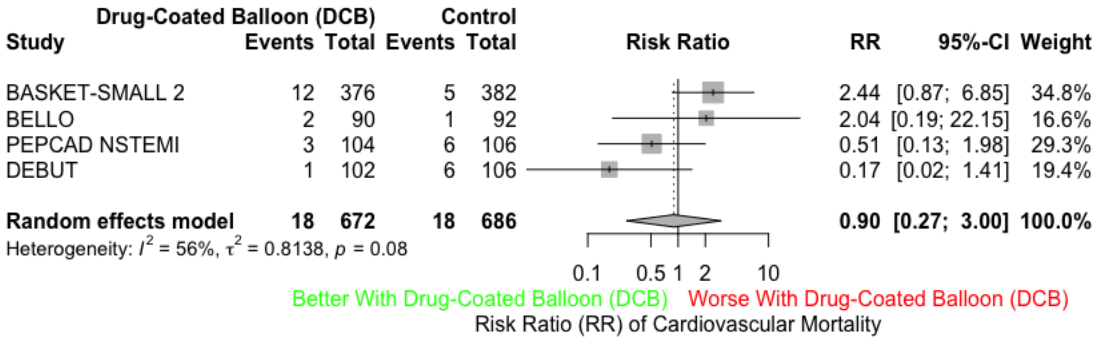


Figure S10. Forest plot for all-cause mortality.

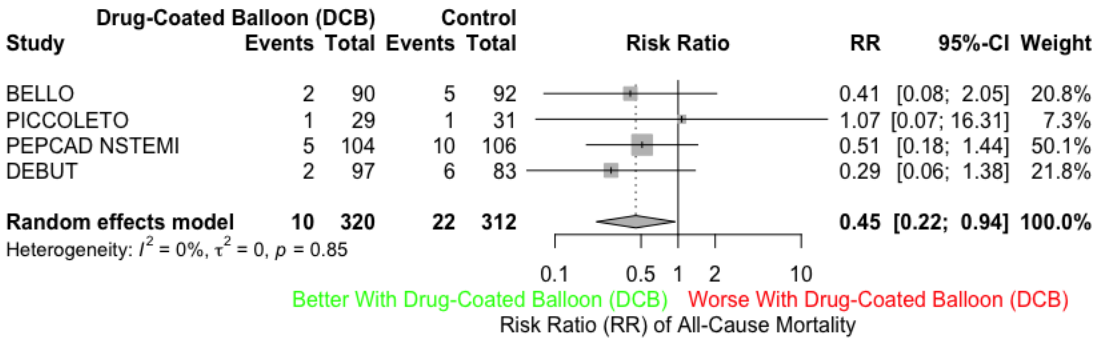


Figure S11. Forest plot for myocardial infarction.

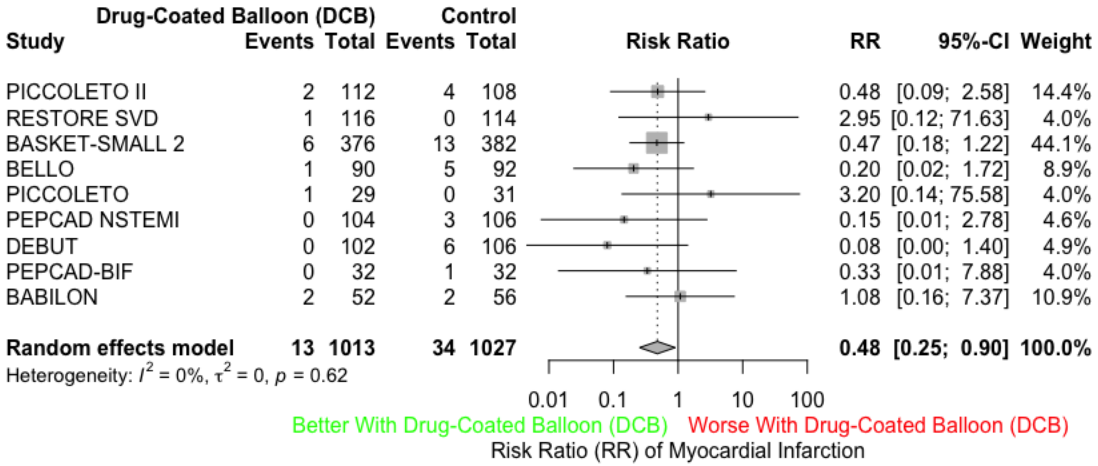


Figure S12. Sensitivity analysis limited to spontaneous myocardial infarction.