Review Article

Drug-Eluting Balloons versus Second-Generation Drug-Eluting Stents for Treating In-Stent Restenosis in Coronary Heart Disease after PCI: A Meta-Analysis

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Background. In-stent restenosis (ISR) remains a common problem following percutaneous coronary intervention (PCI). However, the best treatment strategy remains uncertain. There is some controversy over the efficacy of drug-eluting balloons (DEBs) and second-generation drug-eluting stents (DESs) for treating ISR. Methods. A meta-analysis was used to compare the efficacy of the DEB and second-generation DES in the treatment of ISR. The primary endpoint is the incidence of target lesion revascularization (TLR). The secondary endpoint is the occurrence of target vessel revascularization (TVR), myocardial infarction (MI), all-cause death (ACM), cardiac death (CD), major adverse cardiac events (MACEs), minimum luminal diameter (MLD), late luminal loss (LLL), binary restenosis (BR), and percent diameter stenosis (DS%). Results. A total of 12 studies (4 randomized controlled trials and 8 observational studies) including 2020 patients with a follow-up of 6–25 months were included in the present study. There was a significant difference in the MLD between the two groups during follow-up ($P=0.007$, RR $=0.23$, and 95% CI: 0.06–0.4 mm). There was no significant difference in LLL, BR, or DS% and the overall incidence of MACEs between the two groups. Subgroup analysis showed no significant difference in the incidence of primary and secondary endpoints when considering RCTs or observational studies only. Conclusions. The efficacy of the DEB and second-generation DES in the treatment of ISR is comparable. However, our results need further verification through multicenter randomized controlled trials.

1. Introduction

Over the past few decades, an exponential increase in percutaneous coronary intervention (PCI) has led to a significant improvement in the clinical outcomes of coronary artery disease (CAD) patients. PCI has also been widely adopted as part of the standard treatment for CAD. However, in-stent restenosis (ISR) has become one of the main problems affecting the prognosis of patients after PCI, especially for complex diseases such as chronic occlusive disease or calcification or in patients with diabetes mellitus and chronic renal insufficiency [1–3]. Studies have shown that the incidence of ISR (BMS-ISR) is as high as 16–44% after implantation of bare-metal stents (BMSs) [4]. The first generation of the DES (sirolimus DES and paclitaxel DES) used permanent materials for coating, which increased the risk of advanced and late-stage thrombosis [5]. The incidence of ISR (DES-ISR) is as high as 5–15% [4]. A new generation of the DES uses a different stent framework material, new antiproliferative drugs (including biolimus, everolimus, and zotarolimus), and biodegradable materials for coating compared to the first generation (including cobalt chromium alloy and platinum chromium alloy) of the DES. Due to its improved biocompatibility and thinner stent beam, the new generation of the DES will result in earlier endothelialization, reducing the incidence of neointimal hyperplasia, restenosis, and late and very late stent thrombosis [5]. China’s I-LOVE-IT 2 study [6] showed that the target lesion failure rate in the new generation of the biodegradable coating DES was not inferior to that of the permanent coating DES within 1 year of follow-up. Furthermore, the efficacy and safety of the DES with a biodegradable coating after 6 months of dual antiplatelet therapy (DAPT) were not inferior to those after 12 months.
of DAPT [7]. The DEB releases antirestenosis drugs in local lesions through the balloon surface during dilation for treatment. DEBs are recommended for the treatment of restenosis with BMSs or DESs [8, 9]. Currently, DEBs may be considered to be the preferred treatment regimen for patients with restenosis associated with BMSs and DESs, particularly in patients with multiple stents, large branching lesions, and DAPT intolerance [5]. Additionally, the efficacy of the DEB has been demonstrated in both randomized controlled trials and real-world scenarios [10]. Previous studies have suggested that, for the treatment of ISR, the DEB is superior to plain old balloon angioplasty (POBA) but is not inferior to the DES [11, 12]. However, many studies have compared the effectiveness and safety between the DEB and first-generation DES [10]. The second-generation DES, such as the everolimus-eluting stent (EES), has been widely used due to the lower incidence of target vessel revascularization and stent thrombosis [13]. Many studies have reported the comparative effectiveness and safety between the DEB and second-generation DES [14–24], but the results remain controversial. To further explore the efficacy of the DEB and second-generation DES, we searched the recent literature to perform a meta-analysis.

2. Materials and Methods

The inclusion and exclusion criteria were in accordance with the Cochrane Handbook for Systematic Reviews manual [26].

2.1. Inclusion Criteria. The inclusion criteria for this study are as follows:

1. **Subjects**: the original study clearly articulated that the subjects met the diagnostic criteria of coronary artery ISR, including BMS-ISR and DES-ISR.
2. **Number of patients included in the study**: at least 20 adult patients.
3. **Outcome measures**: the follow-up interval was 6 to 25 months. The primary endpoint is the incidence of target lesion revascularization (TLR). The secondary endpoint is the occurrence of a major adverse cardiovascular event (MACE). A MACE is mainly defined as target vessel revascularization (TVR), myocardial infarction (MI), all-cause death (ACM), and cardiac death (CD). Angiographic findings included minimum luminal diameter (MLD), late luminal loss (LLL), intrastent restenosis (BR), and percent diameter stenosis (DS%). When multiple follow-up events were reported, the outcome of the longest follow-up period was analyzed.
4. **Type of the study**: RCT or observational study.

2.2. Exclusion Criteria. The exclusion criteria for this study are as follows:

1. Non-Chinese and non-English literature
2. Duplicate published articles or earlier reports of the same outcome in the same study
3. Conference abstracts, letters, case reports, editorials, or expert opinions
4. Data, incomplete data, or documents that cannot be extracted

2.3. Search Strategy. The two authors (Wen-Juan Xiu and Hai-Tao Yang) conducted systematic literature searches using PUBMED, MEDLINE, EMBASE, Cochrane Database, ClinicalTrials.gov, and Wanfang to collect data on RCTs and observational studies, as well as the retrieval time of the DEB and second-generation DES in coronary ISR until June 2017. The keywords used were (“Drug-eluting balloon,” OR “DEB,” OR “Drug-coated balloon,” OR “DCB”) AND (“Drug eluting stent,” OR “DES,” OR “everolimus eluting stent,” OR “EES,” OR “Xience,” OR “Promus,” OR “Zotarolimus eluting stent,” OR “ZES,” OR “Resolute”) AND (“in stent restenosis,” OR “ISR”).

2.4. Document Quality Evaluation and Data Extraction. Quality assessment of the retrieved literature was evaluated by the two authors (Wen-Juan Xiu and Hai-Tao Yang) based on preestablished assessment criteria. The data of the published articles were then summarized. Randomized controlled trials were extracted in a standardized format, and the details of the observational studies were taken and transformed into a standardized scale. In the event of a dispute, the authors assisted one another in coming to an agreement through mutual discussion or referral by a third party (Xiang Xie).

The two authors (Wen-Juan Xiu and Hai-Tao Yang) extracted the tables based on predesigned data. The authors then independently extracted and cross-checked the data, and in cases of a dispute, they assisted one another in coming to an agreement through mutual discussion or third parties (Xiang Xie). Data extraction included (1) the basic information included in the study, including the research topics, year of publication, first author, specific model of the DEB and DES, dual antiplatelet therapy (DAPT), MACEs, and end event; (2) the baseline characteristics of the study population, including the age, gender, and risk factors; and (3) the results of the outcome measures and indicators.

2.5. Definition of Endpoints. The primary endpoint was target lesion revascularization (TLR) at long-term follow-up. The secondary endpoints included major cardiovascular adverse events (MACES), target vessel revascularization (TVR), myocardial infarction (MI), all-cause mortality (ACM), and cardiac death. The results of the angiography were minimum luminal diameter (MLD), late luminal loss (LLL), percent diameter stenosis (DS%), and stent restenosis (IR). When there were multiple follow-up time points when the outcome of the case was reported, the longest follow-up of the outcome of the incident situation analysis was used.

2.6. Statistical Analysis. Meta-analysis was performed using RevMan 5.3 software. On comparing the outcomes of patients with coronary artery ISR treated with the DEB...
versus second-generation DES, the risk ratio (RR) and its 95% confidence interval (CI) were used to assess the incidence of TLR, TVR, MI, all-cause mortality, and MACEs. The mean (M), standard deviation (SD), and 95% confidence interval (CI) were used to assess the incidence of MLD and DS% rate and LLL. Heterogeneity testing between studies was conducted using the Cochran Q and I² tests. I² values of 25, 50, and 75% correspond to low, medium, and high levels of heterogeneity, respectively. For the expected heterogeneous nature of the studies, we first used random effects models to analyze the data. To further reconcile the heterogeneity among studies, sensitivity analyses were performed by observing the change of the effect index after removing individual study results one by one. Publication bias was assessed using a funnel plot.

3. Results

3.1. Literature Search Results. A total of 230 articles were screened in the first screening. The articles were then screened out in layers, excluding review articles, duplicated literature, and those in which the authors failed to obtain the full text. A total of 12 articles were included in the final meta-analysis [14–24]. The literature search strategy and results are shown in Figure 1.

3.2. Characteristics of the Included Studies. Four RCTs comparing the DEB versus second-generation DES [15, 16, 20, 24] including 684 patients and eight observational studies [14, 17–19, 21–23] including 1336 patients were included in the present study. One thousand patients with ISR were enrolled in the DEB group, and 1020 cases of ISR were included in the DES group. Three studies focused on BMS-ISR [15, 16, 24], five studies focused on DES-ISR [17, 20–22, 22], and two included BMS-ISR and DES-ISR [14, 23]. One study focused on the bifurcation of the ISR [18] via an ISR recursive treatment of the DEB [19]. Six studies [14, 17, 18, 21, 22] provided only clinical follow-up information and did not provide angiographic information. The clinical follow-up of each study ranged from 1 month to 5 years, and the follow-up results from 6 to 12 months were analyzed. The clinical characteristics of each study are shown in Tables 1–3. The quality of the included studies was acceptable. A flow chart of the quality assessment of the studies is shown in Figure 2.

3.3. Target Lesion Revascularization. As shown in Figure 3(a), ten [14–20, 22, 23] studies reported the incidence of TLR (P = 0.17) between the DEB group (14%) and DES group (10.6%). When only RCTs were considered, the heterogeneity of the results was lower (I² = 22%; P = 0.28). In the RCTs, the incidence of TLR in the DEB group had a tendency to increase, but the P value did not reach statistical significance (P = 0.07). We did not find a significant difference in the incidence of TLR between the two groups in the observational studies (P = 0.48).

3.4. Target Vessel Revascularization. As shown in Figure 3(b), nine studies [15–18, 20–22, 22, 24] reported the incidence of TVR at follow-up. There was no significant difference in the incidence of TVR (P = 0.30) between the DEB group (14.6%) and DES group (10.5%) in either the RCTs or observational studies.
Table 1: Characteristics of the included studies.

| Trial (year)                  | Treatment and no. of patients (n) | BMS- or DES-ISR | Type of the device | Study type | DAPT protocol | CAG F/U | Clinical F/U | MACE definition | Endpoint |
|------------------------------|-----------------------------------|-----------------|-------------------|------------|---------------|---------|--------------|------------------|----------|
| Marquis-Gravel et al. [14]   | 100 102                           | Canadian all comers | Paclitaxel 2nd generation | Observational | NR            | NR      | 15 months    | Death (all), nonfatal MI, TLR | Restenosis, MACE, stroke/TIA |
| Adriaenssens et al. [15]     | 25 25                             | Belgium BMS     | Paclitaxel        | Everolimus  | RCT           | 3 months for DEB, 12 months for DES | 9 months    | Death (all), MI, TVR | CD, MI, TVR |
| Alfonso et al. [16]          | 95 94                             | Spain BMS       | Paclitaxel        | Everolimus  | RCT           | 3 months for DEB, 12 months for DES | 9 months    | MACE, TLR, ST, MACE rate | MACE, TLR, ST, MACE |
| Almalla et al. [17]          | 46 40                             | Germany DES     | Paclitaxel        | Everolimus  | Observational | NR      | NR           | Death (all), TLR | CD, MI, TVR |
| Naganuma et al. [18]         | 73 85                             | Italy bifurcation ISR | Paclitaxel        | Everolimus/ zotarolimus | Observational | NR      | 23 months    | CD, MI, TVR | TLR, MACE |
| Kubo et al. [19]             | 37 52                             | Japan recurrent ISR after DEB | Paclitaxel        | Everolimus  | Observational | 3 months for PCB, 12 months for DES | 6-8 months | NR           | ACM, CD, nonfatal MI, ST, TLR, MLD | MLD, MACE |
| Alfonso et al. [20]          | 154 155                           | Spain DES-ISR   | Paclitaxel        | Everolimus  | RCT           | 3 months for DEB, 12 months for DES | 6-9 months | 12 months | CD, MI, TVR | MACE |
| Alfonso et al. [21]          | 182 56                            | DES             | SeQuent Please    | Everolimus  | Observational | 1 month for DCB, 12 months for DES | 12 months | CD, MI, TVR | MACE |
| Basavarajaiah et al. [22]    | 81 166                            | DES             | Paclitaxel        | Everolimus  | Observational | 1 month for DCB, 12 months for DES | 12 months | Death (all), TLR, ST, MACE | MACE |
| Kawamoto et al. [23]         | 65 68                             | BMS- or DES-ISR | In.Pact Falcon Pantera Lux | 2nd generation | Observational | 1 month for DEB, 12 months for DES | NR         | ACM, MI, TLR | ST, MACE |
| Pleva et al. [24]            | 68 68                             | BMS             | Paclitaxel        | Everolimus  | RCT           | 3 months for DEB, 6-12 months for DES | 12 months | 6 months | ACM, any MI, AR | LLL, BR, ST, MACE |
| Cui et al. [25]              | 74 109                            | DES             | SeQuent Please    | Everolimus  | Observational | 3 months for DEB, 12 months for DES | NR         | 12 months | CD, nonfatal MI, TVR | MACE, no-event survival rate, ACM, TLR |

DEB: drug-eluting balloon; DES: drug-eluting stent; BMS: bare-metal stent; ISR: in-stent restenosis; RCT: randomized controlled trial; DAPT: dual antiplatelet therapy; CAG: coronary angiography; F/U: follow-up; N/A: not applicable; MACE: major adverse cardiac event; CD: cardiac death; ACM: all-cause mortality; MI: myocardial infarction; ST: stent thrombosis; TVR: target vessel revascularization; TLR: target lesion revascularization; MLD: minimum luminal diameter; LLL: late lumen loss; PCB: paclitaxel-coated balloon.
| Study                      | Cohort | Demographics | Risk factors (n) | Indications (n) |
|---------------------------|--------|--------------|-----------------|-----------------|
| Marquis-Gravel et al. [14]| Overall | 65 | 145 | 65 | 145 | NR | 91 | NR | NR | NR | NR | 145 | NR |
| Adriaenssens et al. [15]  | DEB    | 67.6±7.7 | 18 | 16 | 6 | 5 | 24 | 12 | NR | 5 | 17 | 13 | 1 | 6 |
|                           | DES    | 64.2±11  | 25 | 15 | 1 | 3 | 24 | 10 | NR | 5 | 17 | 1 | 2 |
| Alfonso et al. [16]       | DEB    | 67 ±11   | 82 | 68 | 30 | 56 | 69 | 57 | 4 | 38 | 43 | NR | 14 |
|                           | DES    | 64 ±12   | 82 | 68 | 19 | 70 | 62 | 56 | 7 | 42 | 41 | NR | 11 |
| Almalla et al. [17]       | DEB    | 69.6±9.6 | 38 | 37 | 18 | 14 | NR | 17 | 10 | NR | NR | NR |
|                           | DES    | 67.7±10.8| 28 | 34 | 14 | 21 | NR | 21 | 4 | NR | NR | NR |
| Naganuma et al. [18]      | DEB    | 67.2±10.4| 67 | 52 | 29 | 5 | 54 | 34 | 14 | 17 | 56 (including silent ischaemia and SAP) | NR | NR |
|                           | DES    | 65.2±10.1| 74 | 61 | 32 | 6 | 69 | 45 | 17 | 14 | 71 (including silent ischaemia and SAP) | NR | NR |
| Kubo et al. [19]          | DEB    | 69.7±9.7 | 32 | 30 | 18 | 28 | 24 | 19 | 6 | NR | NR | NR |
|                           | DES    | 71.3±8.8 | 41 | 41 | 26 | 36 | 37 | 28 | 6 | NR | NR | NR |
| Alfonso et al. [20]       | DEB    | 66±10    | 127 | 110 | 75 | 89 | 110 | 73 | 16 | 80 | 74 (including silent ischaemia) | NR | NR |
|                           | DES    | 66±10    | 130 | 121 | 66 | 87 | 121 | 77 | 17 | 79 | 79 (including silent ischaemia) | NR | NR |
| Kang et al. [21]          | DEB    | 63.1±9.8 | 125 | 132 | 80 | 85 | 165 | NR | NR | NR | 60 | NR | NR |
|                           | DES    | 59.5±11.0| 36 | 39 | 16 | 26 | 46 | NR | NR | 24 | NR | NR |
| Basavarajaiah et al. [22] | DEB    | 66.8±9.0 | 73 | 58 | 38 | 7 | 59 | 30 | 25 | NR | NR | NR |
|                           | DES    | 65.7±9.6 | 143 | 119 | 55 | 12 | 127 | 85 | 56 | NR | NR | NR |
| Kawamoto et al. [23]      | DEB    | 64.9±9.1 | 57 | 51 | 28 | 6 | 51 | 36 | 17 | NR | NR | NR |
|                           | DES    | 67.2±8.9 | 63 | 54 | 28 | 9 | 54 | 42 | 27 | NR | NR | NR |
| Pleva et al. [24]         | DEB    | 65.6±10.9| 43 | NR | 17 | NR | NR | 43 | 3 | NR | 23 (including STEMI) | 24 | 3 |
|                           | DES    | 65.5±10.6| 46 | NR | 18 | NR | NR | 41 | 6 | NR | 18 (including STEMI) | 25 | 10 |
| Cui et al. [25]           | DEB    | 61.9±9.0 | 56 | 56 | 39 | 35 | 38 | 25 | 6 | 7 | NR | NR | NR |
|                           | DES    | 61.5±9.5 | 82 | 68 | 43 | 50 | 47 | 32 | 2 | 11 | NR | NR | NR |

HTN: hypertension; DM: diabetes mellitus; MI: myocardial infarction; CABG: coronary artery bypass graft; UAP: unstable angina pectoris; SAP: stable angina pectoris; NSTEMI: non-ST elevation myocardial infarction.
| Study | Pre-MLD  | Pre-DS%  | Lesion length (mm) | Post-MLD  | Post-DS%  |
|-------|----------|----------|-------------------|-----------|-----------|
|       | DEB      | DES      | DEB               | DES       | DEB       | DES       | DEB       | DES       | DEB       | DES       |
| Adriaenssens [15] | 0.98 ± 0.60 | 0.57 ± 0.37 | 67.7 ± 18.4 | 79.4 ± 13.5 | NR | NR | 2.13 ± 0.45 | 2.12 ± 0.51 | 26.6 ± 13 | 25.9 ± 16.8 |
| Alfonso et al. [16] | 1.02 ± 0.40 | 0.93 ± 0.4 | 61 ± 14 | 65 ± 13 | 13.7 ± 7 | 13.8 ± 6 | 2.16 ± 0.5 | 2.38 ± 0.5 | 19 ± 11 | 11 ± 11 |
| Almalla et al. [17] | 0.57 ± 0.30 | 0.51 ± 0.41 | NR | NR | 9 ± 5.2 | 12.3 ± 11 | 2.42 ± 0.36 | 2.5 ± 0.5 | NR | NR |
| Kubo et al. [19] | 0.96 ± 0.45 | 0.80 ± 0.47 | 67 ± 14.9 | 72.2 ± 15.1 | 16.7 ± 12.9 | 15.7 ± 8.2 | 2.02 ± 0.4 | 4.56 ± 0.54 | 31.8 ± 10.3 | 16.2 ± 7.4 |
| Alfonso et al. [20] | 0.79 ± 0.40 | 0.75 ± 0.40 | 69 ± 17 | 72 ± 15 | 10.4 ± 5.6 | 10.7 ± 5.4 | 2.1 ± 0.4 | 2.22 ± 0.5 | 18 ± 10 | 13 ± 11 |
| Kang et al. [21] | 0.80 ± 0.40 | 0.80 ± 0.60 | 71.7 ± 5.2 | 74.6 ± 9.2 | 19.5 ± 8.9 | 21.3 ± 11.8 | 2.2 ± 0.4 | 2.7 ± 0.4 | 20.6 ± 11.9 | 13.6 ± 10.5 |
| Kawamoto et al. [23] | 0.74 ± 0.49 | 0.66 ± 0.43 | 74.8 ± 15.8 | 81.2 ± 14.4 | 18.7 ± 14.6 | 16.1 ± 9.6 | 2.34 ± 0.54 | 2.65 ± 0.48 | 18.2 ± 8.6 | 13.8 ± 7.6 |
| Pleva et al. [24] | 0.92 ± 0.45 | 0.79 ± 0.48 | 71.8 ± 13.9 | 78 ± 13.4 | NR | NR | 2.18 ± 0.39 | 2.51 ± 0.38 | 19.5 ± 7.4 | 16.3 ± 8.9 |

MLD: minimum luminal diameter; DS%: percent diameter stenosis; LLL: late lumen loss.
3.5. Myocardial Infarction. As shown in Figure 3(c), eleven [14–17, 19–24] studies reported the incidence of myocardial infarction at follow-up. We did not find a difference in the incidence of myocardial infarction between the DEB group (2.7%) and the DES group (2.3%; \( P = 0.79 \)).

3.6. All-Cause Mortality. As shown in Figure 3(d), eight [14–17, 19, 20, 22, 23] studies provided data on all-cause mortality at follow-up. There was no significant difference in the incidence of ACM between the DEB group (5.2%) and DES group (3.1%; \( P = 0.13 \)).

3.7. Cardiac Death. As shown in Figure 4(a), eight [16, 18–22, 22, 24] studies provided the incidence of cardiac death at follow-up. The incidence of cardiac death in the DEB group demonstrated an increasing trend compared to the DES group; however, this result did not reach statistical significance (1.8% versus 0.9%; RR = 1.77; \( P = 0.18 \)).

3.8. Major Adverse Cardiovascular Events (MACEs). As shown in Figure 4(b), 10 studies [14, 16–18, 20–24] provided the MACE incidence at follow-up. The overall incidence of MACEs between the DEB group (16.6%) and DES group (13.7%) was not significantly different \( (P = 0.23) \). When only RCTs were considered, we also did not find significant difference in the incidence of MACEs when comparing the DEB group to the DES group (14.5% versus 11%; RR = 1.23; \( P = 0.60 \)).

3.9. Angiography Results. As shown in Figure 5, five studies [15, 16, 19, 20, 23, 24] provided angiography results. There was a statistically significant difference in the MLD between the DEB group and DES group \( (RR = 0.23; P = 0.007) \). However, the incidence of late loss, binary restenosis, and DS % was not significantly different between the two groups.

3.10. Subgroup Analysis according to BMS-ISR and DES-ISR. The meta-analysis results suggested that, in DES-IRS but not in BMS-IRS, the difference in the MLD was significant. However, the incidence of TLR, TVR, MI, ACM, CD, MACEs, late loss, binary restenosis, and DS% was not significantly different between the DES group and DEB group (data not shown).
2.1.1. RCT

| Study or subgroup | DEB | DES | Weight | Odd ratio | Odd ratio |
|-------------------|-----|-----|--------|-----------|-----------|
|                   | Events | Total | Events | Total | M-H, random, 95% CI | M-H, random, 95% CI |
| Adriaenssens et al. [15] | 1 | 25 | 2 | 25 | 4.0% | 0.48 [0.04, 5.65] |
| Alfonso et al. [16] | 6 | 95 | 1 | 94 | 5.0% | 6.27 [0.74, 53.12] |
| Alfonso et al. [20] | 20 | 154 | 7 | 155 | 12.4% | 3.16 [1.29, 7.70] |
| Subtotal (95% CI) | 274 | 274 | 21.3% | 2.69 [0.94, 7.69] |
| Total events | 27 | 10 |

Heterogeneity: $\chi^2 = 0.24, \chi^2 = 2.58, df = 2 (P = 0.28); I^2 = 22$

Test for overall effect: $Z = 1.85 (P = 0.06)$

1.1.2. Observational

| Study or subgroup | DEB | DES | Weight | Odd ratio | Odd ratio |
|-------------------|-----|-----|--------|-----------|-----------|
|                   | Events | Total | Events | Total | M-H, random, 95% CI | M-H, random, 95% CI |
| Almala et al. [17] | 2 | 46 | 9 | 40 | 7.3% | 0.16 [0.03, 0.78] |
| Basavarajaiah et al. [22] | 16 | 81 | 26 | 166 | 14.2% | 1.33 [0.67, 2.64] |
| Cui 2016 | 6 | 74 | 3 | 109 | 8.4% | 3.12 [0.75, 12.88] |
| Kawamoto et al. [23] | 16 | 65 | 16 | 68 | 13.2% | 1.06 [0.48, 2.35] |
| Kubo et al. [19] | 17 | 37 | 7 | 52 | 11.2% | 5.46 [1.96, 15.24] |
| Marquis-Gravel et al. [14] | 7 | 100 | 10 | 102 | 11.4% | 0.69 [0.25, 1.90] |
| Naganuma et al. [18] | 14 | 73 | 14 | 85 | 13.0% | 1.20 [0.53, 2.72] |
| Subtotal (95% CI) | 476 | 622 | 78.7% | 1.26 [0.67, 2.37] |
| Total events | 78 | 85 |

Heterogeneity: $\chi^2 = 0.46, \chi^2 = 17.52, df = 6 (P = 0.008); I^2 = 66$

Test for overall effect: $Z = 0.71 (P = 0.48)$

Total (95% CI) | 750 | 896 | 100.0% | 1.47 [0.84, 2.57] |

Total events | 105 | 95 |

Heterogeneity: $\chi^2 = 0.45, \chi^2 = 23.39, df = 9 (P = 0.005); I^2 = 62$

Test for overall effect: $Z = 1.35 (P = 0.18)$

Test for subgroup differences: $\chi^2 = 1.48, df = 1 (P = 0.22); I^2 = 32.6$

(a)

2.1.1. RCT

| Study or subgroup | DEB | DES | Weight | Risk ratio | Risk ratio |
|-------------------|-----|-----|--------|------------|------------|
|                   | Events | Total | Events | Total | M-H, random, 95% CI | M-H, random, 95% CI |
| Adriaenssens et al. [15] | 2 | 25 | 4 | 25 | 7.2% | 0.50 [0.10, 2.49] |
| Alfonso et al. [16] | 6 | 95 | 2 | 94 | 7.4% | 2.97 [0.61, 14.34] |
| Alfonso et al. [20] | 25 | 154 | 13 | 155 | 14.3% | 1.94 [1.03, 3.64] |
| Pleva et al. [24] | 5 | 68 | 11 | 68 | 11.2% | 0.45 [0.17, 1.24] |
| Subtotal (95% CI) | 342 | 342 | 40.1% | 1.09 [0.43, 2.74] |
| Total events | 38 | 30 |

Heterogeneity: $\chi^2 = 0.53, \chi^2 = 8.16, df = 3 (P = 0.04); I^2 = 63$

Test for overall effect: $Z = 0.18 (P = 0.85)$

1.1.2. Observational

| Study or subgroup | DEB | DES | Weight | Risk ratio | Risk ratio |
|-------------------|-----|-----|--------|------------|------------|
|                   | Events | Total | Events | Total | M-H, random, 95% CI | M-H, random, 95% CI |
| Almala et al. [17] | 3 | 46 | 9 | 40 | 9.5% | 0.29 [0.08, 1.00] |
| Basavarajaiah et al. [22] | 19 | 81 | 30 | 166 | 15.3% | 1.30 [0.78, 2.16] |
| Cui 2016 | 6 | 74 | 3 | 109 | 8.7% | 2.95 [0.76, 11.41] |
| Kang et al. [21] | 18 | 81 | 5 | 166 | 11.6% | 7.38 [2.84, 19.16] |
| Naganuma et al. [18] | 18 | 73 | 19 | 85 | 14.8% | 1.10 [0.63, 1.94] |
| Subtotal (95% CI) | 355 | 566 | 59.9% | 1.55 [0.69, 3.52] |
| Total events | 64 | 66 |

Heterogeneity: $\chi^2 = 0.64, \chi^2 = 19.91, df = 4 (P = 0.0005); I^2 = 80$

Test for overall effect: $Z = 1.06 (P = 0.29)$

Total (95% CI) | 697 | 908 | 100.0% | 1.35 [0.77, 2.37] |

Total events | 102 | 96 |

Heterogeneity: $\chi^2 = 0.47, \chi^2 = 28.15, df = 8 (P = 0.0004); I^2 = 72$

Test for overall effect: $Z = 1.04 (P = 0.30)$

Test for subgroup differences: $\chi^2 = 0.32, df = 1 (P = 0.57); I^2 = 0$

(b)

Figure 3: Continued.
3.1.2 Observational

Heterogeneity: $\tau^2 = 0.00, \chi^2 = 1.83, df = 3 (P = 0.61); I^2 = 0\%$
Test for overall effect: $Z = 0.19 (P = 0.85)$

| Study or subgroup | DEB Events Total | DES Events Total | Weight | Risk ratio M-H, random, 95% CI |
|-------------------|------------------|------------------|--------|-----------------------------|
| Adriaenssens et al. [15] | 0 25 1 | 25 1 | 3.2% | [0.01, 7.81] |
| Alfonso et al. [16] | 3 95 4 | 94 4 | 14.8% | [0.17, 3.23] |
| Alfonso et al. [20] | 5 154 2 | 155 2 | 12.1% | [0.50, 12.77] |
| Pleva et al. [24] | 1 68 1 | 68 1 | 4.2% | [0.06, 15.66] |
| Subtotal (95% CI) | 342 | 342 | 34.4% | [0.42, 2.88] |
| Total events | 9 | 8 |

Heterogeneity: $\tau^2 = 0.00, \chi^2 = 2.03, df = 2 (P = 0.30); I^2 = 16\%$
Test for overall effect: $Z = 0.39 (P = 0.70)$

3.1.1 RCT

Heterogeneity: $\tau^2 = 0.00, \chi^2 = 0.10, df = 4 (P = 0.73); I^2 = 0\%$
Test for overall effect: $Z = 1.56 (P = 0.12)$

| Study or subgroup | DEB Events Total | DES Events Total | Weight | Risk ratio M-H, random, 95% CI |
|-------------------|------------------|------------------|--------|-----------------------------|
| Adriaenssens et al. [15] | 1 25 1 | 25 1 | 4.5% | [0.07, 15.12] |
| Alfonso et al. [16] | 4 95 0 | 94 0 | 3.9% | [0.49, 163.15] |
| Alfonso et al. [20] | 3 154 4 | 155 4 | 15.0% | [0.09, 3.32] |
| Subtotal (95% CI) | 274 | 274 | 23.3% | [0.33, 5.16] |
| Total events | 8 | 5 |

Heterogeneity: $\tau^2 = 0.28, \chi^2 = 2.39, df = 2 (P = 0.30); I^2 = 16\%$
Test for overall effect: $Z = 0.39 (P = 0.70)$

4.1.2 Observational

Heterogeneity: $\tau^2 = 0.00, \chi^2 = 2.39, df = 4 (P = 0.73); I^2 = 0\%$
Test for overall effect: $Z = 1.56 (P = 0.12)$

| Study or subgroup | DEB Events Total | DES Events Total | Weight | Risk ratio M-H, random, 95% CI |
|-------------------|------------------|------------------|--------|-----------------------------|
| Almalla et al. [17] | 2 46 1 | 40 1 | 5.9% | [0.16, 1.84] |
| Cui 2016 | 1 74 1 | 109 1 | 4.3% | [0.09, 23.18] |
| Kawamoto et al. [23] | 3 65 2 | 68 2 | 8.8% | [0.15, 7.21] |
| Kubo et al. [19] | 3 37 5 | 52 5 | 17.6% | [0.21, 3.31] |
| Marquis-Gravel et al. [14] | 15 100 6 | 102 6 | 40.1% | [0.03, 6.31] |
| Subtotal (95% CI) | 322 | 371 | 76.7% | [0.87, 3.24] |
| Total events | 23 | 15 |

Heterogeneity: $\tau^2 = 0.00, \chi^2 = 4.54, df = 7 (P = 0.72); I^2 = 0\%$
Test for overall effect: $Z = 1.51 (P = 0.13)$

Figure 3: Clinical outcomes between the DEB group and DES group: (a) TLR; (b) TVR; (c) MI; (d) ACM.
### 3.1.1. RCT

| Study or subgroup | DEB Events Total | DES Events Total | Weight | Risk ratio M-H, random, 95% CI |
|------------------|-----------------|-----------------|--------|-------------------------------|
| Alfonso et al. [16] | 1 95 0 94 7.0% | 2.97 [0.12, 7.19] | |
| Alfonso et al. [20] | 2 154 2 155 18.7% | 1.01 [0.14, 7.05] | |
| Pleva et al. [24] | 1 68 1 68 9.4% | 1.00 [0.06, 15.66] | |
| Subtotal (95% CI) | 317 | 317 35.0% | 1.25 [0.30, 5.17] | |

Total events 4 3

Heterogeneity: $\chi^2 = 0.00, \tau^2 = 0.36, df = 2 (P = 0.84); I^2 = 0$

Test for overall effect: $Z = 0.30 (P = 0.76)$

#### 5.1.2. Observational

| Study or subgroup | DEB Events Total | DES Events Total | Weight | Risk ratio M-H, random, 95% CI |
|------------------|-----------------|-----------------|--------|-------------------------------|
| Naganuma et al. [18] | 4 73 3 85 33.1% | 1.55 [0.36, 6.71] | |
| Almalla et al. [17] | 10 81 14 166 9.6% | 1.46 [0.68, 3.15] | |
| Basavarajiah et al. [22] | 2 182 0 56 7.8% | 1.56 [0.08, 31.97] | |
| Kubo et al. [19] | 5 27 1 52 9.4% | 1.41 [0.09, 21.76] | |
| Marquis-Gravel et al. [14] | 468 | 468 65.0% | 2.14 [0.75, 6.09] | |

Total events 10 4

Heterogeneity: $\chi^2 = 0.00, \tau^2 = 1.56, df = 4 (P = 0.82); I^2 = 0$

Test for overall effect: $Z = 1.43 (P = 0.15)$

Total (95% CI) 764 785 100.0% 1.77 [0.76, 4.11]

Test for overall effect: $Z = 1.33 (P = 0.18)$

Test for subgroup differences: $\chi^2 = 0.36, df = 1 (P = 0.55); I^2 = 0$

### 3.1.1. RCT

| Study or subgroup | DEB Events Total | DES Events Total | Weight | Risk ratio M-H, random, 95% CI |
|------------------|-----------------|-----------------|--------|-------------------------------|
| Alfonso et al. [16] | 11 94 6 95 7.1% | 1.85 [0.71, 4.81] | |
| Alfonso et al. [20] | 28 155 16 154 13.3% | 1.74 [0.98, 3.08] | |
| Pleva et al. [24] | 7 68 13 68 8.3% | 0.94 [0.23, 1.27] | |
| Subtotal (95% CI) | 317 | 317 28.6% | 1.23 [0.58, 2.62] | |

Total events 46 35

Heterogeneity: $\chi^2 = 0.29, \tau^2 = 5.60, df = 2 (P = 0.06); I^2 = 64$

Test for overall effect: $Z = 0.53 (P = 0.60)$

### 3.1.2. Observational

| Study or subgroup | DEB Events Total | DES Events Total | Weight | Risk ratio M-H, random, 95% CI |
|------------------|-----------------|-----------------|--------|-------------------------------|
| Almalla et al. [17] | 5 46 11 40 6.0% | 0.32 [0.11, 0.92] | |
| Basavarajiah et al. [22] | 10 81 14 166 9.6% | 1.46 [0.68, 3.15] | |
| Cui 2016 | 8 74 3 109 4.4% | 3.93 [1.08, 14.32] | |
| Kang et al. [21] | 20 182 5 56 7.3% | 1.23 [0.48, 3.13] | |
| Kawamoto et al. [23] | 19 65 17 68 13.6% | 1.17 [0.67, 2.05] | |
| Marquis-Gravel et al. [14] | 25 100 21 102 14.7% | 1.21 [0.73, 2.02] | |
| Naganuma et al. [18] | 24 73 24 85 15.7% | 1.16 [0.73, 1.87] | |
| Subtotal (95% CI) | 621 | 626 71.4% | 1.18 [0.84, 1.65] | |

Total events 110 95

Heterogeneity: $\chi^2 = 0.07, \tau^2 = 9.54, df = 6 (P = 0.15); I^2 = 37$

Test for overall effect: $Z = 0.95 (P = 0.34)$

Total (95% CI) 938 943 100.0% 1.20 [0.89, 1.62]

Test for overall effect: $Z = 1.20 (P = 0.23)$

Test for subgroup differences: $\chi^2 = 0.01, df = 1 (P = 0.92); I^2 = 0$

#### 5.1.2. Observational

| Study or subgroup | DEB Events Total | DES Events Total | Weight | Risk ratio M-H, random, 95% CI |
|------------------|-----------------|-----------------|--------|-------------------------------|
| Alfonso et al. [16] | 1 95 0 94 7.0% | 2.97 [0.12, 7.19] | |
| Alfonso et al. [20] | 2 154 2 155 18.7% | 1.01 [0.14, 7.05] | |
| Pleva et al. [24] | 1 68 1 68 9.4% | 1.00 [0.06, 15.66] | |
| Subtotal (95% CI) | 317 | 317 35.0% | 1.25 [0.30, 5.17] | |

Total events 4 3

Heterogeneity: $\chi^2 = 0.00, \tau^2 = 0.36, df = 2 (P = 0.84); I^2 = 0$

Test for overall effect: $Z = 0.30 (P = 0.76)$

### 3.1.2. Observational

| Study or subgroup | DEB Events Total | DES Events Total | Weight | Risk ratio M-H, random, 95% CI |
|------------------|-----------------|-----------------|--------|-------------------------------|
| Cui 2016 | 1 74 0 109 7.0% | 4.40 [0.18, 106.56] | |
| Kang et al. [21] | 2 182 0 56 7.8% | 1.56 [0.08, 31.97] | |
| Kubo et al. [19] | 1 37 1 52 9.4% | 1.41 [0.09, 21.76] | |
| Subtotal (95% CI) | 447 | 468 65.0% | 2.14 [0.75, 6.09] | |

Total events 10 4

Heterogeneity: $\chi^2 = 0.00, \tau^2 = 2.28, df = 7 (P = 0.94); I^2 = 0$

Test for overall effect: $Z = 1.33 (P = 0.18)$

Test for subgroup differences: $\chi^2 = 0.36, df = 1 (P = 0.55); I^2 = 0$

#### Figure 4: Cardiac death (a) and MACEs (b) between the DEB group and DES group.

3.1. Sensitivity Analysis. We performed a sensitivity analysis to examine the influence of each study on the pooled RRs by removing each study one at a time. The pooled RRs showed no significant change, suggesting the results are stable.

To avoid some of the confounders present in the observational studies, we also excluded the observational studies and only analyzed the results of the RCTs. These results also showed no significant change, suggesting the results are stable.
### 7.1.1. RCT

| Study or subgroup | DEB Mean | DEB SD | DEB Total | DES Mean | DES SD | DES Total | Weight | Mean difference | Mean difference |
|------------------|----------|--------|-----------|----------|--------|-----------|--------|----------------|----------------|
|                   |          |        |           |          |        |           |        | IV, random, 95% CI | IV, random, 95% CI |
| Adriaenssens et al. [15] | 1.97 | 0.53 | 25 | 2.05 | 0.37 | 25 | 18.0% | -0.08 | [-0.33, 0.17] |
| Alfonso et al. [16] | 2.01 | 0.6 | 95 | 2.31 | 0.6 | 94 | 23.0% | -0.3 | [-0.47, -0.13] |
| Alfonso et al. [20] | 1.8 | 0.6 | 154 | 2.03 | 0.7 | 155 | 24.6% | -0.23 | [-0.38, -0.08] |
| Pleva et al. [24] | 2.09 | 0.57 | 68 | 2.07 | 0.8 | 68 | 19.2% | 0.02 | [-0.21, 0.25] |
| Subtotal (95% CI) | 342 | 342 | 84.8% | -0.17 | [-0.31, -0.04] |

Heterogeneity: $\tau^2 = 0.01$, $\chi^2 = 5.71$, $df = 3$ ($P = 0.13$); $I^2 = 47$
Test for overall effect: $Z = 2.51$ ($P = 0.01$)

### 8.1.2. Observational

| Study or subgroup | DEB Mean | DEB SD | DEB Total | DES Mean | DES SD | DES Total | Weight | Mean difference | Mean difference |
|------------------|----------|--------|-----------|----------|--------|-----------|--------|----------------|----------------|
|                   |          |        |           |          |        |           |        | IV, random, 95% CI | IV, random, 95% CI |
| Kubo et al. [19] | 1.45 | 0.68 | 37 | 2.08 | 0.79 | 52 | 15.2% | -0.63 | [-0.94, -0.32] |
| Subtotal (95% CI) | 37 | 52 | 15.2% | -0.63 | [-0.94, -0.32] |

Heterogeneity: not applicable
Test for overall effect: $Z = 4.02$ ($P < 0.0001$)
Total (95% CI) 379 394 100.0% -0.23 [-0.40, -0.06]

Heterogeneity: $r^2 = 0.02$, $\chi^2 = 12.92$, $df = 4$ ($P = 0.001$); $I^2 = 69$
Test for overall effect: $Z = 2.68$ ($P = 0.007$)
Test for subgroup differences: $\chi^2 = 7.21$, $df = 1$ ($P = 0.007$); $I^2 = 86.1$

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**Figure 5: Continued.**
3.12. Publication Bias Analysis. In the present study, we utilized funnel plots to evaluate the publication bias of all of the included studies. We did not find publication biases in this meta-analysis (data not shown).

4. Discussion

In this study, we performed a meta-analysis to compare the efficacy of the DEB to DES in the treatment of ISR. The present study suggests that, during 6–25 months of follow-up, the clinical outcomes are similar between the DEB group and DES group. This result suggests that the DEB is not inferior to the DES in the treatment of ISR.

In clinical practice, many treatment strategies have been developed for ISR patients after PCI, including POBA, cutting balloons, rotational atherectomy, and intravascular brachytherapy. However, most of these techniques have been replaced by the DES due to its side effect of inhibiting neointimal formation. Therefore, the DES has become the standard treatment for ISR. In addition, although there appears to be no evidence that the second-generation DES is superior to the first-generation DES [26], the second-generation DES is more biocompatible and its stent beam is thinner, thereby accelerating DES endothelialization and reducing neointimal formation [27]. However, CAD patients who were implanted with the DES required long-term dual antiplatelet therapy. In addition, reimplantation of the stent after ISR may result in reduced compliance of the coronary vessel wall and may damage branch opening. Furthermore, implantation of the stent may also cause an inflammatory response and stimulate the growth of endothelial tissue. The DEB allows for rapid and uniform release of the drug without the need for polymers and avoids reimplantation of the stent [28].

The literature published to date demonstrates that DEB treatment for BMS-ISR is very effective but is not as effective for the treatment of DES-ISR; in fact, the pathophysiology may be different. The metal in the stent stimulates the proliferation of blood vessels, and the polymer carrier on the surface of the drug stent also inhibits the repair of the vascular endothelium, resulting in the formation of a late thrombus. The drug-eluting balloon releases antiproliferative drugs locally to the vessel wall of coronary arteries, thereby achieving the effect of inhibiting intimal hyperplasia of the blood vessels and avoiding the need for additional stents and stent overlap, which also eliminates the increase of the intracoronary metal load. However, there are potential complications associated with the DEB. Compared with the DES, the DEB has no polymer matrix and no residual metal skeleton, which can reduce intimal inflammation and greatly reduce the risk of thrombosis, shortening the time for dual antiplatelet therapy (only 1 to 3 months after DCB). However, DCB treatment avoids the introduction of foreign bodies, which can result in follow-up treatment. The drug-eluting balloon is also less likely to compromise the ISR’s involvement of the bifurcation’s collaterals and may be more suitable for complex anatomies where stent implantation may not be ideal for drug delivery, such as curved or calcified blood vessels.

Persistent metal skeletons may remain the basis for stent thrombosis and restenosis. In recent years, endovascular neovascularization found in endoluminal imaging has confirmed this concept. In addition, the perpetuating metal skeleton has a risk of fracture, leading to adverse events, and the permanent influence of the metal skeleton on the normal vasomotion function of the stent at stent implantation is also an important factor that can lead to long-term adverse events.

| Study or subgroup | DEB | DES | Risk ratio | Mean difference |
|------------------|-----|-----|-----------|----------------|
|                  | Events | Total | Events | Total | M-H, random, 95% CI | M-H, random, 95% CI |
| **10.1.1. RCT**  |       |     |          |        |                      |                      |
| Adriaenssens et al. [15] | 2 | 25 | 1 | 25 | 6.6% | 2.00 [0.19, 20.67] |
| Alfonso et al. [16] | 8 | 94 | 4 | 95 | 17.0% | 2.02 [0.63, 6.49] |
| Alfonso et al. [20] | 27 | 155 | 15 | 154 | 27.9% | 1.79 [0.99, 3.23] |
| Pleva et al. [24] | 6 | 68 | 13 | 68 | 21.5% | 0.46 [0.19, 1.14] |
| **Total (95% CI)** | 342 | 342 | 73.0% | 1.25 [0.57, 2.75] |
| Total events | 43 | 33 |
| Heterogeneity: $\tau^2 = 0.34$, $\chi^2 = 6.81$, $df = 3$ ($P = 0.08$); $I^2 = 56\%$ |
| Test for overall effect: $Z = 3.21$ ($P = 0.001$) |
| **10.1.2. Observational** |
| Kubo et al. [19] | 20 | 37 | 10 | 52 | 27.0% | 2.81 [1.50, 5.28] |
| Subtotal (95% CI) | 37 | 52 | 27.0% | 2.81 [1.50, 5.28] |
| Total events | 20 | 10 |
| Heterogeneity: not applicable |
| Test for overall effect: $Z = 1.30$ ($P = 0.19$) |
| Test for subgroup differences: $\chi^2 = 2.48$, $df = 1$ ($P = 0.12$); $I^2 = 59.7\%$ |

**Figure 5:** Coronary angiography outcomes between the DEB group and DES group: (a) MLD; (b) late loss; (c) binary restenosis; (d) DS%.
Although the DEB can effectively inhibit the intimal hyperplasia of blood vessels, it cannot overcome the elastic retraction of blood vessels, which plays an important role in restenosis. Therefore, the DEB cannot completely replace the DES, and additional clinical data are still needed. The BRS supports diseased blood vessels early after implantation and is completely degraded after the negative remodeling of blood vessels is completed. After degradation, the BRS can restore the normal physiological and vasomotor function of the blood vessels, reduce inflammation of the blood vessel wall, and remove its influence on side branch vessels. Following repeated interventional treatment of the same lesion, the BRS can also be compatible with magnetic resonance imaging. In addition, at long-term follow-up, the BRS can result in late lumen enlargement.

At present, the materials used to make the BRS are primarily polymers (PLA) and metals (magnesium and iron). The BRS constructed from polymers has a relatively mature manufacturing process, while the BRS made from metals is difficult to use in clinical applications due to problems such as its degradation rate and inflammatory reaction. The only degradable PLA scaffold that has undergone large-scale clinical research and has been CE-approved is Abbott’s Absorb BVS. Since the clinical study was conducted in 2007, the ABSORB series of studies and various small-scale real-world registration studies have demonstrated good clinical efficacy and safety in regard to both clinical and angiographic results during an early follow-up period of 1 to 2 years.

However, the three-year results of the ABSORB II [29] study and ABSORB III [30] study published by the American Society of Cardiology Annual Conference (ACC) in 2017 at the 2016 Annual Meeting of the Transcatheter Cardiovascular Therapeutics (TCT) did not meet the researchers’ expectations. The three-year results of the ABSORB II study showed that the Abbott BVS was not a superior predictor of vasodilatation and failed to show noninferiority expectations in terms of late lumen loss. Furthermore, the results of device-specific composite endpoints, target vessel myocardial infarctions, and advanced/late-stage stent thrombosis were clearly at a disadvantage compared with the Abbott BVS. The 2-year results of the ABSORB III study showed that the target vessel-target lesion failure of the Abbott BVS was significantly higher than that of the XIENCE stent, which was primarily reflected in small vessel lesions.

In our meta-analysis, we did not find a significant difference in clinical outcomes between the DEB group and DES group. The clinical endpoints observed in our analysis may only indicate short-term follow-up results. Clinical outcomes, such as MI, TLR, all-cause mortality, cardiac death, and TVR, may change significantly over time. Therefore, the present results require a large register or more elaborate RCTs with an appropriate long-term follow-up for validation.

5. Limitations of This Study

First, in the present study, only the Chinese literature and English literature were included. Due to differences in the ISR types and specific interventions (DES type and DAPT time) among the study populations, there was a certain level of heterogeneity between the included studies. Second, the shorter follow-up period included in the study and smaller sample size can only increase the reliability of the evaluation results to a certain extent. Finally, the inclusion of studies that failed to consistently report results (TLR, TVR, MI, ACM, CD, and angiographic findings) limited our scope of analysis.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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