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Drug-Eluting Balloons Versus Everolimus-Eluting Stents for In-Stent Restenosis: A Meta-Analysis of Randomized Trials☆

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ABSTRACT

Objectives: Individual randomized trials comparing drug-eluting balloons (DEB) versus everolimus-eluting stents (EES) for in-stent restenosis (ISR) were underpowered for clinical end-points. The objective of this study was to compare the clinical outcomes of DEB versus EES for any ISR.
Materials & methods: Electronic databases were searched for randomized trials which compared DEB versus EES for any ISR (i.e., drug eluting or bare metal stents). Summary estimate risk ratios (RRs) were constructed using a DerSimonian and Laird random effects model.
Results: Five trials with 962 patients were included. In-segment minimum lumen diameter (MLD) was lower with DEB (standardized mean difference −0.24, 95% confidence interval [CI] −0.46 – −0.01) on angiographic follow-up at a mean of 8.6 months. There was no statistically significant difference in the risk of target vessel revascularization (TVR) at 1 year (RR 1.15, 95% CI 0.60–2.19), but TVR was increased with DEB at 3 years (RR 1.87, 95% CI 1.15–3.03). The risk of target lesion revascularization (TLR) was statistically increased with DEB (RR 2.17, 95% CI 1.13–4.19) at a mean of 24.4 months. There was no difference in the risk of MI, stent thrombosis, cardiac mortality and all-cause mortality between both groups.
Conclusion: In patients with any type of ISR, DEB was associated a similar risk of TVR at 1-year, but increased risk of TVR and TLR at longer follow-up, as compared with EES. The quality of evidence was moderate, suggesting the need for further randomized trials with longer follow-up to confirm the role of DEB in the management of ISR.

1. Introduction

Percutaneous coronary intervention (PCI) with stent implantation is considered the cornerstone for management of patients with coronary artery disease [1,2]. However, in-stent restenosis (ISR) due to neointimal hyperplasia or neoatherosclerosis is a known limitation. The incidence of ISR has been estimated to be ~20–40% with bare metal stents (BMS) [3]. The introduction of drug-eluting stents (DES), particularly second-generation DES, has largely reduced the risk of ISR, however; ISR remains a concern even with second-generation DES, particularly for complex lesions (i.e., incidence ~5–10%) [3,4]. Although contemporary PCI is performed mainly with second-generation DES [5], BMS are still used in a minority of patients e.g., those with higher risk of bleeding, to minimize the duration of dual anti-platelet therapy (DAPT). ISR might manifest clinically as stable angina or as acute coronary syndrome [1]. Implantation of a second stent results in an additional metal layer which might in turn reduce the vessel flexibility and contribute to lumen deterioration, especially in small vessels, and might reduce options for future intervention [6]. Other interventions have been previously proposed for the management of ISR such as brachytherapy, laser atherectomy and balloon angioplasty, however; the efficacy of these interventions has been suboptimal [7]. Drug eluting balloons (DEB) have been introduced as an attractive modality which allows the delivery of an anti-proliferative drug without the need for an additional metal implant, and would potentially necessitate a shorter duration of DAPT. Randomized trials have demonstrated that DEB are superior to balloon angioplasty, and are associated with comparable angiographic and clinical outcomes as first-generation DES

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[8–11]. Several small randomized trials have compared the angiographic outcomes of DEB versus second-generation DES [12–18], however; these trials have been largely underpowered for clinical outcomes. Previous meta-analyses comparing DEB with second-generation DES (namely everolimus-eluting stents [EES]) were limited by including observational studies, and/or by the inclusion of first-generation DES in the comparator arm, which are associated with worse outcomes as compared with second-generation DES [19–26]. Therefore, we aimed at performing a comprehensive meta-analysis of randomized trials to compare the clinical outcomes of DEB versus EES.

2. Methods

2.1. Data sources

The following electronic databases: Medline, Web of Science, and the Cochrane Register of Controlled Trials (CENTRAL), as well as major scientific sessions were searched without language restriction from inception through February 2018 using the keywords and Medical Subject Heading: "drug eluting stent", and "drug eluting balloon". This meta-analysis was prospectively registered at the PROSPERO international prospective register of systematic reviews (CRD42017078766) [27], and was conducted according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines [28].

2.2. Selection criteria and data extraction

Trials that randomized patients with ISR (irrespective of the type of the initial stent type, could be BMS or DES) to DEB versus EES were included. Data from the longest available reported follow-up time was preferentially used. Two independent authors (AYE and MKM) extracted data on study design, sample size, intervention strategies, outcomes, and other study characteristics from the included studies. Discrepancies were resolved by consensus among the authors.

2.3. Outcomes and definitions

The main outcomes of interest were ischemia driven target vessel revascularization (TVR), and ischemia driven target lesion revascularization (TLR). The other outcomes which were assessed in this study: major adverse cardiac events (MACE) as defined per the individual trials, stent thrombosis, myocardial infarction (MI), cardiac mortality, and all-cause mortality. We preferentially utilized data from the longest available follow-up, whenever applicable. The angiographic outcomes were acute lumen gain, and in-segment as well as in-lesion minimum lumen diameter (MLD), diameter stenosis, and binary restenosis at 6–12 months.

2.4. Quality assessment

The Cochrane Collaboration's tool for assessing the risk of bias was used to assess the individual study risk of bias. This tool consists of seven points that tests for selection, performance, detection, attrition, reporting and other biases, respectively [29]. The overall quality of evidence for each outcome was evaluated using the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) tool.

2.5. Statistical analysis

Outcomes were evaluated by an intention-to-treat analysis. Random effects summary risk ratios (RR) were primarily estimated with the DerSimonian and Laird model [30]. Summary odds ratios (OR) were also constructed with a Peto model as a secondary analysis [31]. Statistical heterogeneity was measured using the I^2 statistic [32]. Egger's method was used to assess publication bias [33]. Standardized mean differences (SMDs) were used for continuous variables. All P-values were 2-tailed, with statistical significance set at 0.05, and confidence intervals (CI) were calculated at the 95% level for the overall estimates effect. All analyses were performed using STATA software version 14 (STATA Corporation; College Station, Texas). Subgroup analyses were performed for: i) TVR and TLR at 12 months, and beyond 12 months; and ii) comparing the treatment effect for DES-ISR versus BMS-ISR. A sensitivity analysis was conducted excluding the trials with significant degree of loss to follow-up. Random effects meta-regression analyses for the main outcomes were pre-specified in relation to diabetes mellitus, lesion length, and baseline reference vessel diameter [34].

3. Results

3.1. Included studies

The electronic search identified 77 articles that were screened by reviewing the title and/or abstract, eventually we identified 5 trials that met our inclusion criteria (Supplemental Fig. 1) [12–18]. One trial (i.e., BIOLUX RCT) compared paclitaxel-eluting balloon with the bioresorbable polymer sirolimus-eluting stents (Orsiro), which was not the focus of our meta-analysis [35], thus was excluded. Two trials (i.e., RIBS IV and RIBS V) reported the outcomes at both 1-year and at 3-years [13–16], thus we utilized the 3-year outcome data [14,16]. A final number of 5 trials with 962 patients: 483 patients in the DEB arm and 479 patients in the EES arm were included in this meta-analysis. The paclitaxel-eluting balloon was the DEB evaluated in all the included trials. Three trials (i.e., TIS, RIBS V, and SEDUCE) focused on BMS-ISR [12,14,17], the RIBS IV trial focused on DES-ISR [16], while the DARE trial included patients with both DES and BMS-ISR (56% of the patients had DES) [18]. The baseline characteristics of the included studies are summarized in the Table 1. Details regarding the quality of the included studies are reported in the Supplemental Table 1. All trials were deemed to be of low risk of bias, except for the SEDUCE trial where there was a large degree of loss to follow-up [12]. All the studies were multicenter, and followed a prospective randomized open blinded end-point design. The follow-up for clinical outcomes ranged from 12–36 months, the weighted mean follow-up duration was 24.4 months (95% CI 6.0–42.9 months).

3.2. Clinical outcomes

The clinical outcomes were reported by all the trials, except for MACE which was not reported in the SEDUCE trial [12], and for TLR which was not reported in the DARE and TIS trials [17,18]. MACE was defined as the composite of death, MI, and TVR in 2 studies [13,14,18], and as the composite of cardiac death, MI, and TVR in 2 other studies [15–17]. Compared with EES, DEB were associated with a similar risk of TVR (12.5% versus 9.7%; RR 1.14, 95% CI 0.65–2.02, $I^2 = 49\%$, $P = 0.65$) (Fig. 1). The evidence was moderate by GRADE assessment. This effect was observed at 1 year (RR 1.15, 95% CI 0.60–2.19, $I^2 = 51\%$, $P = 0.68$), but TVR was increased with DEB at 3 years (RR 1.87, 95% CI1.15–3.03, $I^2 = 0\%$, $P = 0.01$) (Fig. 2). Subgroup analysis showed a possible increased risk of TVR with DEB for DES-ISR (RR 1.89, 95% CI 1.10–3.26, $P = 0.02$), but not for BMS-ISR (RR 0.78, 95% CI 0.30–1.98, $P = 0.60$), however this interaction was not statistically significant ($P_{interaction} = 0.38$). The sensitivity analysis excluding the SEDUCE trial (i.e., trial with remarkable degree of loss to follow-up) yielded a similar effect (RR 1.25, 95% CI 0.69–2.27, $I^2 = 53\%$, $P = 0.46$). Meta-regression analysis did not identify a difference in treatment effect based on diabetes mellitus, lesion length, and reference vessel diameter ($P = 0.10$, and 0.25, 0.42 respectively).

The risk of TLR, which was reported by only 3 trials, was higher with DEB (12.0% versus 5.4%; RR 2.17, 95% CI 1.13–4.19, $I^2 = 6\%$, $P = 0.02$) (Fig. 3). The quality of evidence was moderate by GRADE assessment. There was a non-statistical significant increase in the risk of TLR at 1 year with DEB (RR 2.38, 95% CI 0.75–7.50, $I^2 = 25\%$, $P = 0.14$),

Table 1
Baseline patient and lesions characteristics.

Characteristic	DARE[18]	TIS[17]	RIBS IV[15,16]	RIBS V[13,14]	SEDUCE[12]
Study characteristics					
Publication Year	2017	2016	2015	2014	2014
Study	Multicenter	Multicenter	Multicenter	Multicenter	Multicenter
Country	Netherlands	Czech Republic	Spain	Spain	Belgium
Follow up, months	12	12	12	36	12
Primary outcome	Minimal lumen diameter	In-segment late lumen loss	Minimal lumen diameter	Minimal lumen diameter	Percentage of uncovered stent struts
DAPT duration, months	12/12	3/6–12	3/12	3/12	NR
Follow up completion	100	92	88	90	80
Trial registration number	NTR2189	NCT01735825	NCT01239940	NCT01239953	NCT01065532
Patient characteristics					
Patients, n	137/141	68/68	154/155	95/94	25/25
Age, years, mean	66/65	66/66	66/66	67/64	68/64
Male, %	72/84	63/68	82/84	86/87	72/100
Diabetes mellitus, %	31/33	25/26	49/43	32/20	24/4
Hypertension, %	64/67	NR	71/78	72/72	64/60
Hyperlipidemia, %	59/60	NR	71/78	73/66	96/96
Smoker, %	17/13	46/43	58/56	59/75	21/12
Prior myocardial infarction, %	53/52	63/60	47/50	60/60	48/40
Prior coronary artery bypass grafting, %	14/16	4/9	10/11	4/7	NR
Time to restenosis, months[a]	46/40	12/17	17/18	13/12	20/8
Length of previous stent, mm	22/22	23/19	21/21	19/18	20/18
Reference vessel diameter, mm	2.6/2.6	2.6/2.7	2.6/2.7	2.6/2.6	3.0/2.8
Presentation					
Stable angina/silent ischemia, %	NR	65/63	48/49	60/56	52/68
Unstable angina, %	44/42	NR	52/51	40/45	20/20
Non-ST-elevation myocardial infarction, %	NR	NR	0/0	0/0	4/4
Target vessel					
Left anterior descending artery, %	41/39	47/54	50/46	37/39	24/44
Left circumflex artery, %	20/24	22/14	18/22	22/23	20/28
Right coronary artery, %	37/35	30/30	28/29	39/34	52/24
Left main coronary artery, %	0/1	0/0	0/0	0/0	0/4
Saphenous vein graft, %	1/1	1/3	4/3	2/3	4/0
Mehran class					
Class I, %	51/53	41/28	63/64	40/36	32/36
Class II, %	32/34	46/47	34/28	47/45	52/40
Class III/IV, %	16/13	14/24	3/8	13/19	16/24

All variables are reported in percentage.
All variables are reported as drug eluting balloon/drug eluting stents.
[a] Median.

which was statistically significant at 3 years (RR 2.42, 95% CI 1.30–4.50, $I^2 = 0\%$, $P = 0.005$). Subgroup analysis showed possible increased risk of TLR with DEB for DES-ISR (RR 2.20, 95% CI 1.11–4.33, P = 0.02), but not for BMS-ISR (RR 1.71, 95% CI 0.23–12.56, P = 0.60), however this interaction was not statistically significant ($P_{interaction} = 0.90$).

There was no statistically significant difference in the risk of MACE (15.8% versus 13.1%; RR 1.18, 95% CI 0.79–1.76, $I^2 = 32\%$, P = 0.43), MI (3.1% versus 3.1%; RR 1.01, 95% CI 0.50–2.05, $I^2 = 0\%$, P = 0.98), stent thrombosis (0.6% versus 0.4%; RR 1.28, 95% CI 0.28–5.90, $I^2 = 0\%$, P = 0.75), cardiac mortality (1.9% versus 1.9%; RR 1.00, 95% CI 0.41–2.45, $I^2 = 0\%$, P = 0.99), and all-cause mortality (4.6% versus 3.5%; RR 1.25, 95% CI 0.66–2.36, $I^2 = 0\%$, P = 0.49) between DEB and EES. Supplemental Table 2 summarizes the summary estimates for the outcomes with both models. There was no evidence of publication bias with Egger's test for all the outcomes assessed in this meta-analysis.

3.3. Angiographic outcomes

Acute lumen gain was lower with DEB compared with DES (1.17 mm [95% CI 0.96–1.38 mm] versus 1.42 mm [95% CI 1.09–1.74 mm]; SMD −0.51, 95% CI −0.74 - [−0.28], $I^2 = 65\%$, P < 0.0001). The angiographic follow-up was performed at a mean of 8.6 months (range 6–12 months). DEB was associated with a significantly lower in-segment MLD (1.86 mm [95% CI 1.66–2.07 mm] versus 2.02 mm [95% CI 1.69–2.34 mm]; SMD −0.24, 95% CI −0.46 – [−0.01], $I^2 = 64\%$, P = 0.04), and a trend towards higher in-segment diameter stenosis with DEB (30.3% [95% CI 23.9–36.8%] versus 25.4% [95% CI 14.3–36.8%]; SMD 0.24, 95% CI −0.02–0.51, $I^2 = 75\%$, P = 0.07). There was no difference in in-segment late lumen loss (0.19 mm [95% CI 0.07–0.31 mm] versus 0.26 mm [95% CI 0.02–0.51 mm]; SMD −0.14, 95% CI −0.55–0.28, $I^2 = 89\%$, P = 0.51) (Supplemental Fig. 2). There was no difference in in-segment binary restenosis (15.0% [95% CI 8.7–21.3%%] versus 13.5% [95% CI 4.3–22.7%], P = 0.77).

In addition, DEB were associated with lower in-lesion MLD (1.90 mm [95% CI 1.72–2.09 mm] versus 2.20 mm [95% CI 1.86–2.55 mm]; SMD −0.51, 95% CI −0.71 – [−0.30], I2 = 48%, P < 0.0001), higher in-lesion diameter stenosis (29.0% [95% CI 21.4–36.6%] versus 19.8% [95% CI 9.22–30.3%]; SMD 0.49, 95% CI −0.30–0.68, $I^2 = 40\%$, P < 0.0001). There was no difference in in-lesion late lumen loss (0.12 mm [95% CI −0.50–0.74 mm] versus 0.19 mm [95% CI −0 28–0.65 mm]; SMD 0.09, 95% CI −0.66–0.84, I2 = 83%, P = 0.82) (Supplemental Fig. 3).

4. Discussion

In this comprehensive meta-analysis of five randomized controlled trials with 962 patients, we demonstrated that there was no statistically significant difference in the risk of TVR between DEB and EES for DES or BMS-ISR at 1 year, but there was an increased risk of TVR with DEB at 3 years. The risk of TLR was significantly increased with DEB. There was a potential increased risk of TVR and TLR with DEB for DES-ISR. The quality of evidence was moderate with GRADE assessment. DEB were associated with lower in-segment and in-lesion MLD at angiographic follow up (mean 8.6 months). There was no difference in the

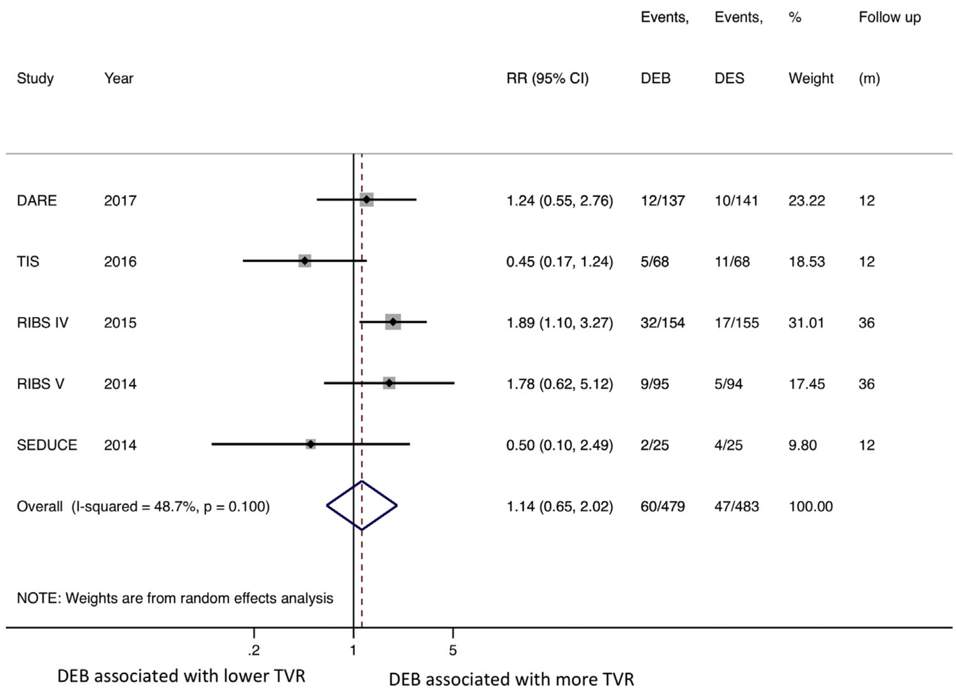

Fig. 1. Summary plot for target vessel revascularization. The relative size of the data markers indicates the weight of the sample size from each study. DEB = drug-eluting balloon; CI = confidence interval; RR = risk ratio; TVR = target vessel revascularization.

risk of MI, stent thrombosis, cardiac mortality and all-cause mortality between both groups (Fig. 4). There was evidence of moderate statistical heterogeneity for TVR but not for TLR. Thus, we performed several subgroup and meta-regression analyses to explore the statistical heterogeneity, we found no evidence of statistical heterogeneity for TVR at 3 years, however; this analysis was driven by only 2 trials.

DEB have been introduced as a strategy to deliver the drug locally without the need for an additional stent [36]. The procedural technique for angioplasty with DEB is quite different from DES implantation as there are key methodological steps for DEB use such as accurate pre-dilatation, fast delivery of the balloon to the target lesion to avoid drug loss, prolonged inflation, and avoidance of geographic mismatch. As a result of the encouraging findings from early randomized trials comparing DEB with first-generation DES [8–11], the European Society of Cardiology guidelines provide a level 1A recommendation for either DEB or DES for treatment of ISR [37], however; this has not been

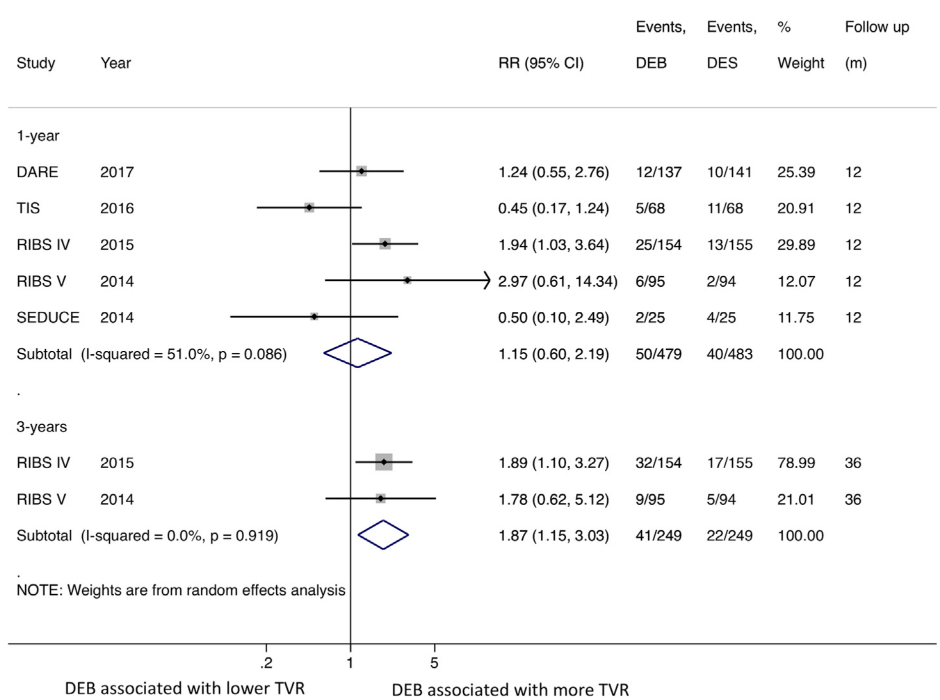

Fig. 2. Summary plot for target vessel revascularization at 1 year and at 3 years. The relative size of the data markers indicates the weight of the sample size from each study. DEB = drug-eluting balloon; CI = confidence interval; RR = risk ratio; TVR = target vessel revascularization.

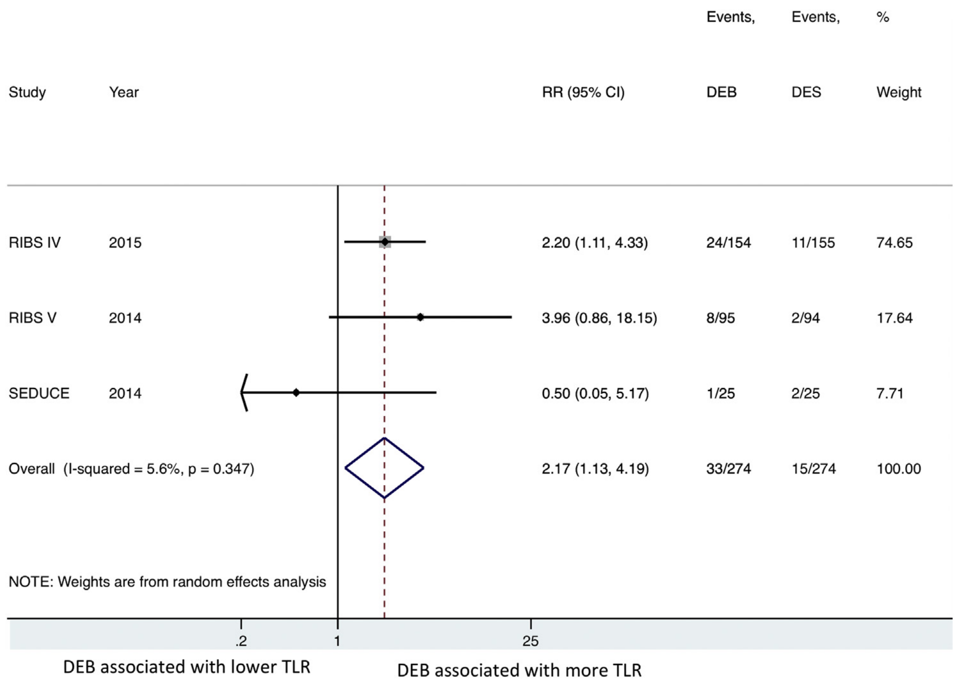

Fig. 3. Summary plot for target lesion revascularization. The relative size of the data markers indicates the weight of the sample size from each study. DEB = drug-eluting balloon; CI = confidence interval; RR = risk ratio; TLR = target lesion revascularization.

incorporated in the US guidelines as DEB are not approved for this indication in the US [38]. Second-generation DES are superior to first-generation DES in reducing adverse events, including restenosis [5]. Emerging randomized trials have aimed at comparing DEB with second-generation DES [12–18], however these trials were small-sized, and thus underpowered for clinical outcomes. This meta-analysis suggests that DEB was associated with an increased risk of TVR and TLR with DEB at longer follow up. Some real world observational studies comparing DEB with EES have shown similar findings [39,40]. Moreover, one observational study had suggested that EES is superior to paclitaxel-eluting balloon for restenosis after DEB failure [41].

Although several network meta-analyses of randomized trials comparing the different strategies for ISR have suggested that DEB and second-generation DES are the best strategies for the management of DES or BMS ISR [7,42,43], these network meta-analyses have ranked PCI with EES, as more efficacious in direct and indirect comparisons as compared with DEB regarding clinical outcomes. Importantly, these network meta-analyses predated the publication of two recent trials (i.e., TIS and DARE) [17,18], as well as the 3 year data of the RIBS IV

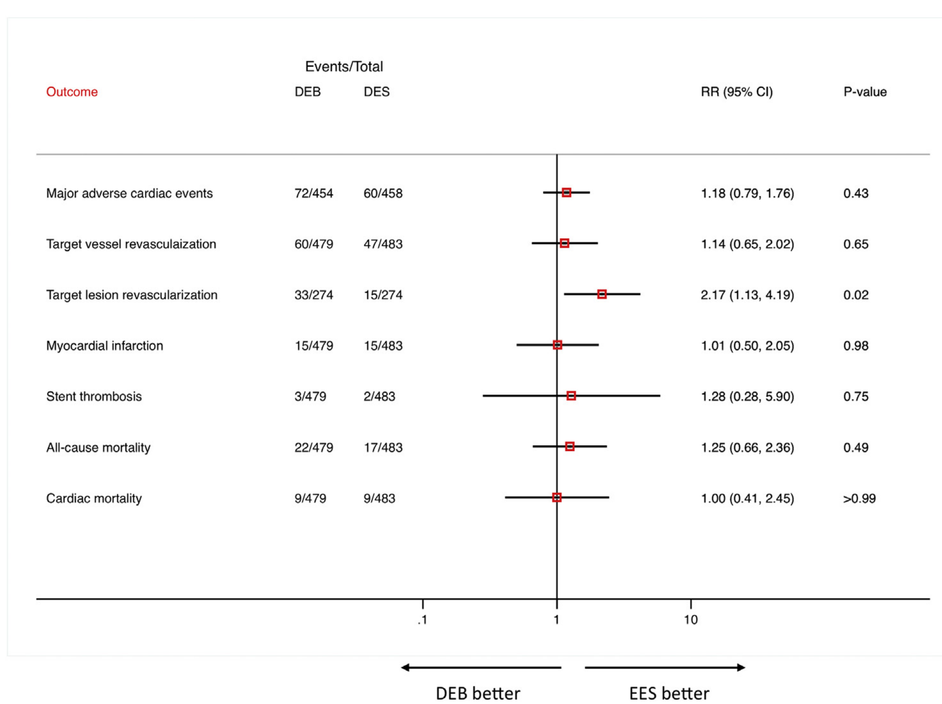

Fig. 4. Forest plot summary for the outcomes assessed in this meta-analysis.

and RIBS V trials [14,16]. It is important to note that the results of this meta-analysis are applicable to EES, which was the comparator in all of the included trials. However, one randomized trial of 304 lesions has shown that EES and zotarolimus-eluting stents had comparable clinical outcomes for DES ISR at 3 years [44].

There are potential explanations that might explain why DEB might be associated with an increased risk of revascularization at longer follow-up. The acute lumen gain was inferior with DEB as compared with EES. Further, DEB was associated with lower in-segment and in-lesion MLD, and higher diameter stenosis at late angiographic follow-up. In addition, all the included trials utilized paclitaxel-eluting balloon as the DEB. Paclitaxel is generally considered less effective than the other antiproliferative agents from the limus family, such as sirolimus [45]. The loss of the coating en route may also impact the delivered dose. A sirolimus-eluting balloon has shown promising angiographic outcomes and low event rates at 12-months in a single arm study [46]. Moreover, the delivery of the medication at the lesion might be suboptimal. One randomized trial suggested that neointimal modification with a scoring balloon improved the anti-restenotic efficacy of paclitaxel-eluting balloon [47]. A pooled analysis of 6 randomized trials showed that recurrent restenosis occurred in 1 out of 5 patients with ISR treated with DEB. In that study, longer lesions and small vessel diameter were independent predictors of restenosis [48]. Our meta-regression analysis did not identify lesion length or the reference vessel diameter as an effect modifier; the small number of studies included in this meta-analysis could explain this finding. It is important to highlight that the mean reference vessel among the included studies in this meta-analysis was 2.5–3.0 mm, and the findings might not be extended to a reference vessel <2.5 mm (i.e., small vessels). In this case, DEB might be considered a reasonable option [36].

Prior meta-analyses have demonstrated conflicting evidence regarding the efficacy and safety of DEB as compared with DES for the treatment of ISR. Some meta-analyses have suggested that clinical outcomes with DEB are comparable to DES [19–25]. These meta-analyses included first-generation DES which are associated with worse outcomes and not routinely used in contemporary practice as compared with second-generation DES. In addition, some of these meta-analyses included observational studies which are prone to selection and ascertainment biases [20–25]. Consistent with our findings, one meta-analysis of randomized and observational studies which compared DEB with second-generation DES showed that DEB might be associated with worse angiographic and clinical outcomes [26]. Even though that meta-analysis performed a subgroup analysis for randomized trials only, it was conducted prior to the publication of the 2 recent trials (i.e., TIS and DARE), and did not include the 3 year data for RIBS IV and RIBS V [26].

4.1. Study limitations

This study should be interpreted in the context of some limitations. First, TLR was reported by only 3 trials. Thus, we performed our analyses with a focus on both TVR and TLR. It is important to note that TLR would mechanistically better correlate with the angiographic parameters, as revascularization of other lesions in the same vessel could dilute the potential differences in the efficacy between the two strategies. Second, there was evidence of moderate statistical heterogeneity for TVR. Thus, we performed multiple subgroup and meta-regression analyses to explore the heterogeneity and found no evidence of statistical heterogeneity for TVR at 3 years. Third, while we applied the recommended statistical analyses to explore for statistical heterogeneity, some considerations of clinical heterogeneity are worth mentioning. For example, we included trials which compared both strategies for any ISR. While this could be a source of heterogeneity, this was performed since BMS ISR is still seen in clinical practice. Fourth, lack of patient-level data precluded a careful evaluation for the patient and lesion characteristics that could benefit from DEB. Fifth the definition of MACE was not consistent across the trials. Sixth, we evaluated MI, rather than target vessel MI, since target vessel MI was only reported by one trial [18]. Seventh, the included trials were conducted in Europe which may represent a more homogenous population and may not be widely generalizable. Finally, one of the included trials had a significant degree of loss to follow-up [12], thus we performed a sensitivity analysis excluding this trial which yielded a similar treatment effect.

5. Conclusion

In this meta-analysis including only randomized trials of patients with DES or BMS ISR, paclitaxel-eluting balloon (i.e., current generation of DEB) was associated with an increased risk of TVR and TLR at longer follow-up, as compared with the use of EES. In addition, EES provided better late angiographic outcomes. However, the quality of evidence was moderate, suggesting the need for further randomized trials with longer follow-up to confirm the role of paclitaxel-eluting balloon in the management of ISR.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.carrev.2018.08.010.

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