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Article

Drug-eluting stent and drug-coated balloon for in-stent restenosis: A meta-analysis

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Abstract: The optimal strategy for patients with in-stent restenosis (ISR) is controversial. We aimed to compare the effects of a drug-coating balloon (DCB) and drug-eluting stent (DES) in ISR treatment. Clinical trials were extensively collected, and retrieved items were screened for inclusion. Both clinical (major adverse cardiac event (MACE); myocardial infarction (MI); and target lesion revascularization (TLR) and angiographic (minimal lumen diameter (MLD), and stenosis relative to reference lumen diameter (SRLD) endpoints were extracted and compared. MACE and MI were not significantly different between the groups. Pooled results of TLR showed a marginal effect that DES was superior to DCB (13.50% for DCB vs. 11.17% for DES, RR = 1.256, 95% CI: 0.997 to 1.583, P = 0.053), with heterogeneity across studies (I^2 = 42.0%, Cochrane Q-test = 0.069). Meta-regression identified bare metal stent (BMS) or drug eluting stents (DES) implanted in the previous intervention and proportions of diabetes in the DCB group as sources of heterogeneity. DES implantation also significantly improved angiographic outcomes (WMD for MLD: −0.318, 95% CI: −0.424 to −0.213, P < 0.001; WMD for SRLD: 6.164%, 95% CI: 4.915% to 7.412%, P < 0.001). All DES, including everolimus-eluting ones, did not benefit BMS-ISR patients compared with DCB treatment. DES implantation, which is superior to DCB angioplasty only in DES-ISR patients, should be preferred in the DES-ISR population to reduce TLR. DCB may be preferred in BMS-ISR to avoid increasing stent layers.

Keywords: coronary artery disease; coronary angiography; clinical trials; meta-analysis; percutaneous coronary intervention

1. Introduction

Percutaneous coronary intervention (PCI) with coronary stent implantation is the main revascularization technique for coronary heart disease. In-stent restenosis (ISR), which oftentimes is a silent process and usually leads to angina and even acute coronary syndrome or ischemic heart disease, occurs in more than 10% and up to 30% of patients, respectively after drug-eluting stent (DES) and bare metal stent (BMS) implantations, respectively [1]. Therefore, with the increasing number of PCIs, the number of ISR will be increased and the strategy of ISR treatment is increasingly becoming a matter of concern.

Some randomized trials have been performed, and meta-analyses sought to determine the efficacy of different techniques for ISR treatment. Among all these strategies, DES implantation and drug-coating balloon (DCB) angioplasty are reported to be superior to other methods. Despite both of the two techniques being extensively

adopted and current guidelines providing the same recommendation level for each [2–4], priority for one of the two remains controversial. Previous network meta-analyses have been conducted, but the results are conflicting. On the one hand, a network meta-analysis concluded that an everolimus-eluting stent (EES) was the best [3] for ISR, while others reported similar effects for a DES and DCB [2,5,6]. DCB angioplasty was shown to be associated with better angiographic outcomes and results observed by optical coherence tomography. Based on similar results with a DES and DCB, later studies even concluded that DCB angioplasty should be recommended first in ISR because of the advantage of avoiding adding stent layers [5].

Recently, high quality clinical trials (RCTs) comparing DES and DCB in ISR patients have emerged and some previous studies reported longer follow-up results [7–10]. Hence, it is necessary to re-analyze all the data comparing the effects of DCB and DES in ISR treatment and draw more plausible conclusions.

2. Methods

2.1. Selection criteria and data extraction

The systematic review was performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocol (PRISMA) guidelines [11]. Published trials, including RCTs and non-RCTs that compared DCB angioplasty and DES implantation in patients with ISR were included. All relevant studies published before April 2022 were searched in a comprehensive search of electronic databases (Medline, EMBase, Cochrane Library, Web of Science, China Biology Medicine disc, WanFang database). Searched terms included ‘coronary’, ‘drug-coated balloon’, ‘paclitaxel-coated balloon’, ‘drug-eluting stent’, and ‘restenosis’. Review articles, editorials, and internet-based sources of information on trials of interest were also considered.

Three reviewers (W-H L, R-L S and Q C) independently reviewed and extracted data. Disagreements were solved by discussion or consultation with other reviewers (H-W L, H-F Z and Z-X C) if necessary. The quality of the included studies was assessed according to the Cochrane Handbook. Both clinical (major adverse cardiac events, MACEs; myocardial infarction, MI; and target lesion revascularization, TLR) and angiographic (minimal lumen diameter, MLD, and stenosis relative to reference lumen diameter, SRLD) outcomes were extracted for further analysis.

2.2. Statistical analysis

Statistical analysis was performed using STATA software version 12 (STATA Corp, College Station, USA) [12]. Risk ratios (RRs) with 95% confidence intervals (CIs) were calculated to assess MACE, MI, and TLR, while weighted mean differences (WMDs) were used for the evaluation of MLD and SRLD. The I^2 statistic and Cochrane Q-test were used for heterogeneity tests. The Mantel-Haenszel fixed effects model was used if no significant heterogeneity existed (Cochrane Q-test $P \geq 0.05$). Otherwise, the DerSimonian-Laird random effects model was used [13,14]. Publication bias assessment with Begg’s test was performed, and a funnel plot was produced [15].

To further explore the potential heterogeneity and yield more precise results, we performed a meta-regression and subgroup analysis if significant heterogeneity was found. Meta-regression was conducted using the restricted maximum likelihood estimation method [16]. In addition, subgroup analyses of RCTs or non-RCTs, EES or non-EES, and first- or second-generation stents were performed regardless of the meta-regression results because this difference may indicate the clinical heterogeneity.

In addition, to clarify the precision of the estimated results, we calculate the power of this meta-analysis using the 'metapower' package with R statistics, as described in the previous report [17].

3. Results

3.1. Eligible studies

Of the 262 potentially relevant articles initially screened, a total of 11 randomized studies [7–10,18–24] involving 2063 patients (1141 in the DEB group and 922 in the DES group) were finally included. A flow diagram depicting the overall search strategy and inclusion criteria is shown in **Figure 1**. Included studies are listed in the **Table 1** and demographic characteristics of included trials are listed in the **Table 2**. All studies listed a series of coronary heart disease risk factors, details of target lesions, and diameters and lengths of previously implanted stents. The included individuals were all approximately 60–70 years old, predominantly male, with multiple coronary artery disease factors, and target vessels ranging from 2.5 mm to 3.0 mm. Second-generation DESs were used in 8 studies [7,10,18–21], and the remaining three studies adopted first-generation stents [8,9,22]. DCBs used in the included studies were all paclitaxel-coated balloons produced by the same manufacturer (SeQuent Please, B. Braun Surgical, Melsungen, Germany). Most of the included studies were high in quality except for a blinded method. A summarized quality of the included studies is shown in **Figure 2**.

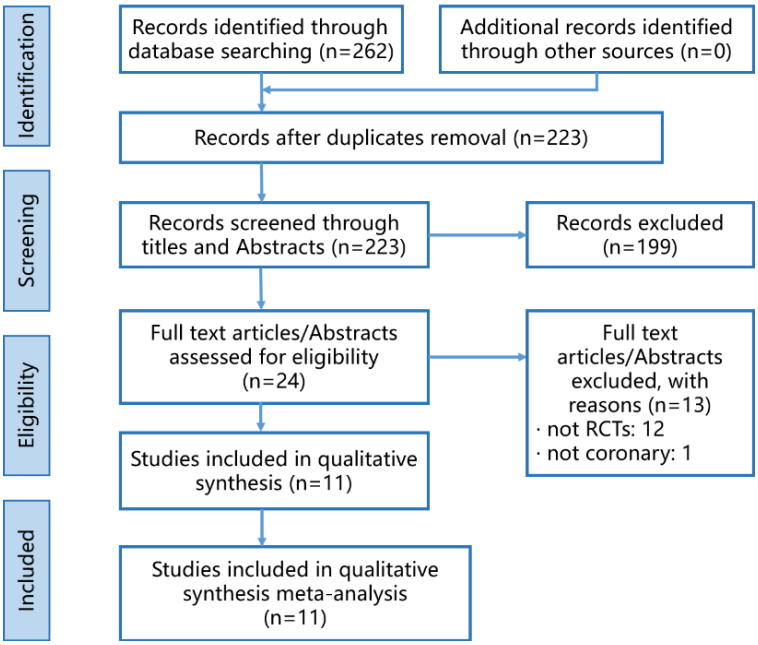

Figure 1. Study flow chart.

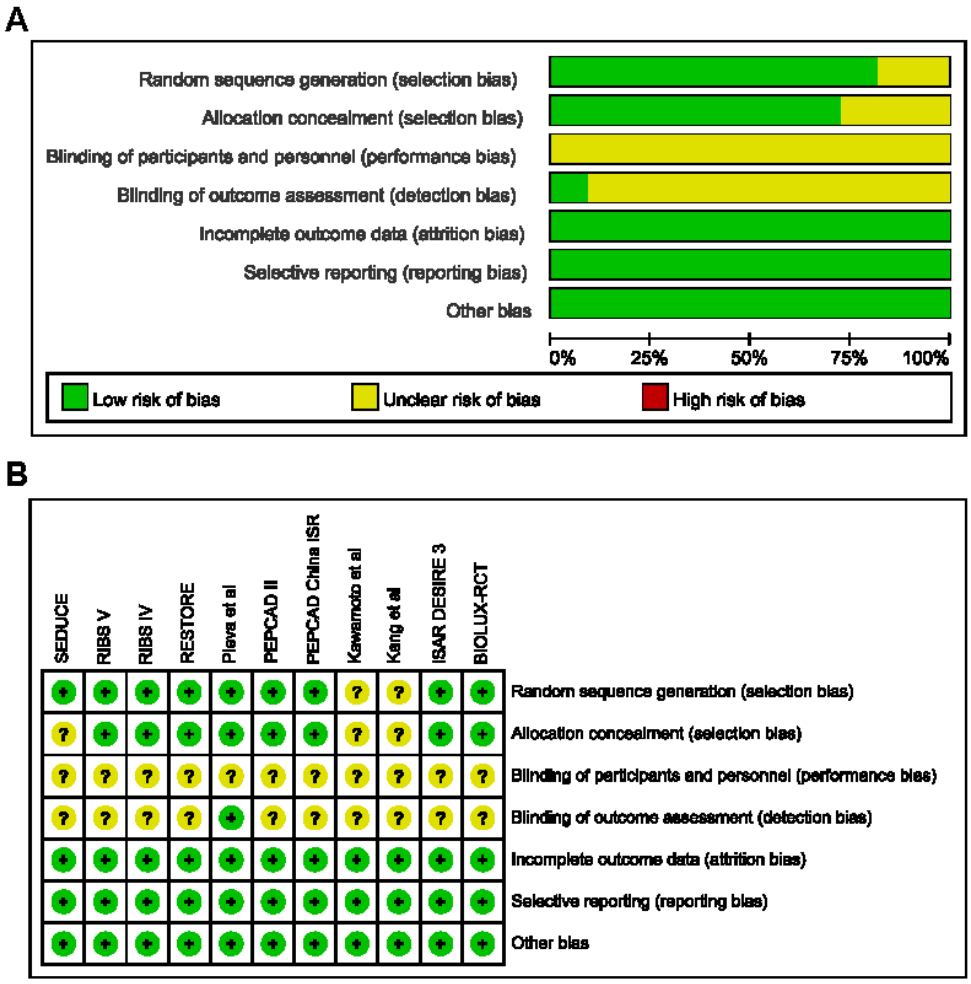

Figure 2. Summary of risk bias using the Cochrane bias risk assessment tool.

Table 1. Clinical trials included in the meta-analysis.

Trials	Year of Publication	Previous stent	Sample size (DCB/DES)	Eluting Drugs	Follow-up (months)
IBS V	2014	BMS	189 (95/94)	Everolimus	12
RIBS IV	2015	DES	309 (154/155)	Everolimus	12
Kang et al.	2015	DES	238 (182/56)	2nd-Generation	24
Kawamoto et al.	2015	DES	133 (65/68)	2nd-Generation	24
ISAR DESIRE 3	2015	DES	268 (137/131)	Paclitaxel	36
PEPCAD-II	2015	BMS	131 (66/65)	Paclitaxel	36
Pleva et al.	2016	BMS	136 (68/68)	Everolimus	12
PEPCAD China ISR	2016	DES	209 (107/102)	Paclitaxel	24
RESTORE	2018	DES	172 (86/86)	Everolimus	12
SEDUCE	2014	BMS	50 (25/25)	Everolimus	12
BIOLUX RCT	2016	Both	232 (157/72)	Sirolimus	18

Table 2. Demographic characteristics of included trials.

Trials	Age (year)	Male (*n*, %)	Sample size (DCB/DES)	BMS/DES-ISR	Eluting Durg	Follow-up (months)
RIBS V	66	164 (86.8)	189 (95/94)	BMS	Everolimus	12
RIBS IV	66	257 (83.2)	309 (154/155)	DES	Everolimus	12
Kang et al.	62	161 (67.6)	238 (182/56)	DES	2nd Generation	24
Kawamoto et al.	66	120 (90.2)	133 (65/68)	DES	2nd Generation	24
ISAR DESIRE 3	68	193 (72.0)	268 (137/131)	DES	Paclitaxel	36
PEPCAD II	65	98 (74.8)	131 (66/65)	BMS	Paclitaxel	36
Pleva et al.	66	89 (65.4)	136 (68/68)	BMS	Everolimus	12
PEPCAD China ISR	62	174 (83.3)	209 (107/102)	DES	Paclitaxel	24
RESTORE	67	123 (71.5)	172 (86/86)	DES	Everolimus	12
SEDUCE	65.9	18 (72)	50 (25/25)	BMS	Everolimus	12
BIOLUX RCT	67.9	NA	232 (157/72)	Both	Sirolimus	18

3.2. Subsection DES implantation may benefit TLR

The incidences of MACE, MI, and TLR were obtained in all included studies. Pooled MACE rates were 18.40% and 18.98% for DCB and DES treatments, respectively. As shown in **Figure 3**, there was no significant difference in MACE rates between the two groups, and little heterogeneity was found (RR = 1.034, 95% CI: 0.867 to 1.236, $P = 0.709$; $I^2 = 11.80\%$, Cochrane Q-test $P = 0.332$, statistical power 0.0914, **Figure 3A**). Similar results were yielded in the analysis of MI with no inter-variance across studies (2.705% for DCB vs. 2.814% for DES, RR = 1.033, 95% CI: 0.621 to 1.719, $P = 0.901$; $I^2 = 0\%$, Cochrane Q-test $P = 0.858$, statistical power 0.0852, **Figure 3B**). A TLR analysis showed a marginal significant result with moderate heterogeneity among studies (13.50% for DCB vs. 11.17% for DES, RR = 1.256, 95% CI: 0.997 to 1.583, $P = 0.053$, **Figure 3C**; $I^2 = 42.0\%$, Cochrane Q-test = 0.069, statistical power 0.9905). Subgroup analyses by RCTs/non-RCT did not alter results or reduce the heterogeneity in TLR (**Figure 4A,B,C**).

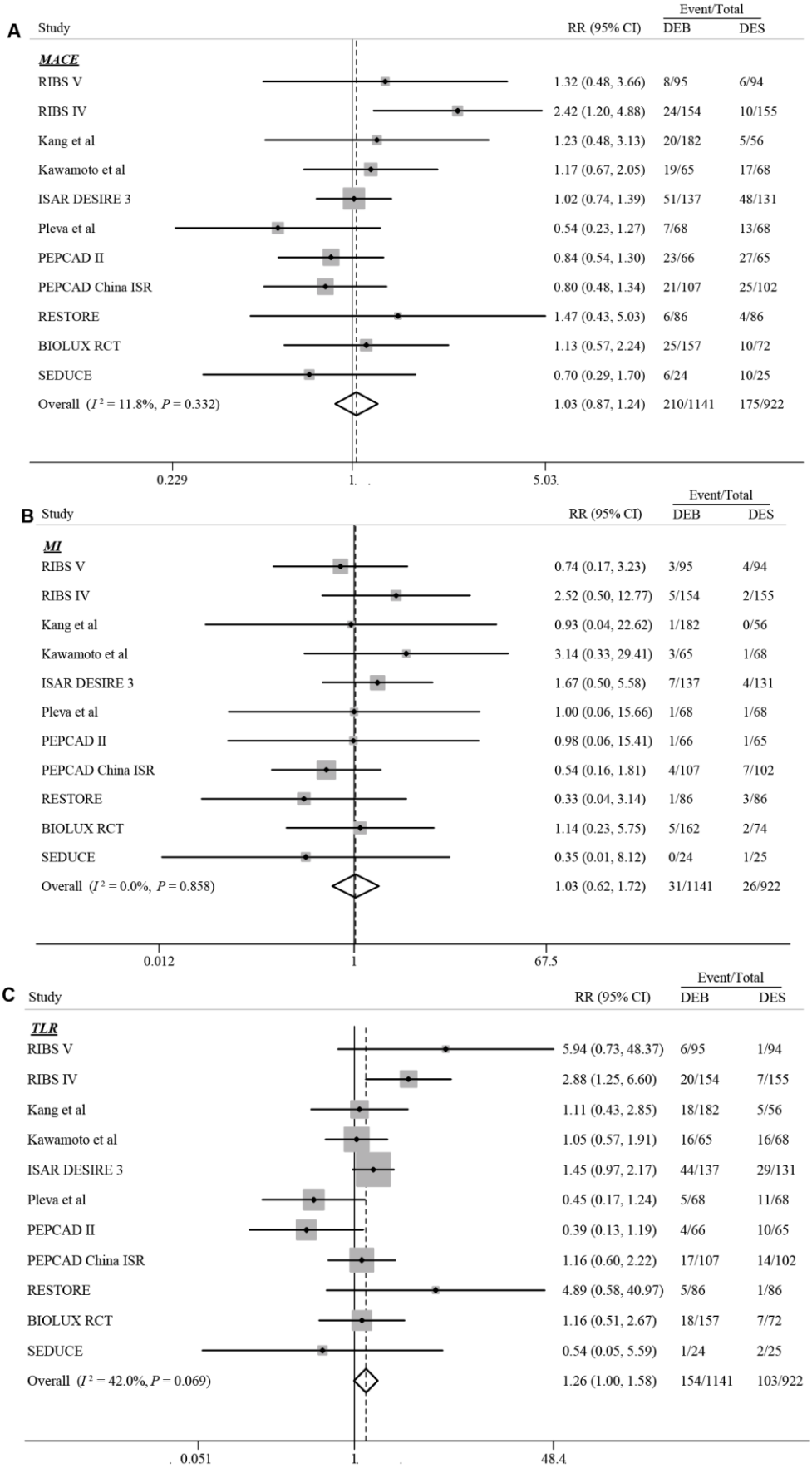

Figure 3. Forest plots for clinical endpoints of relative risk for **(A)** MACE; **(B)** MI; and **(C)** TLR.

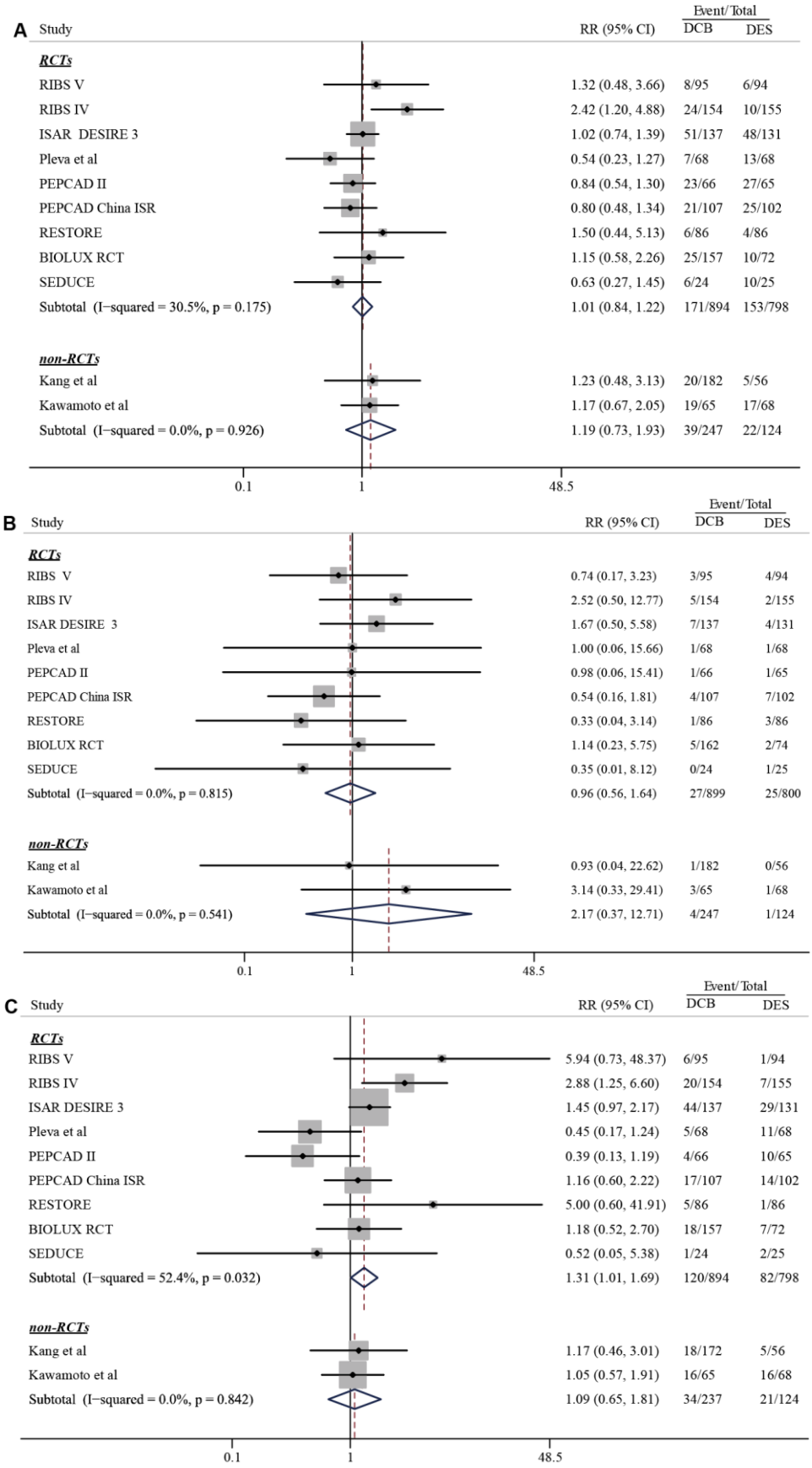

Figure 4. Forest plot for relative risk of **(A)** MACE; **(B)** MI; and **(C)** TLR.
Randomized clinical trials and non-randomized clinical trials were compared respectively. Statistical powers were 0.0642 in RCT and 0.3638 in non-RCT of MACE, 0.1304 in RCT and 0.9999 in non-RCT of MI, and 0.9999 in RCT and 0.1367 in non-RCT of TLR.

3.3. DES reduced TLR only in DES-ISR patients

Heterogeneity among studies may imply distinct effect sizes, and a meta-regression was used to identify sources of heterogeneity in the analysis of TLR. Acute coronary syndrome, diabetes mellitus, hypertension, smoking and hyperlipidemia contributed to outcomes of interventional treatments. Everolimus-eluting stents (EESs) have been reported to be the best stents for ISR. Therefore, we performed meta-regression to assess the influence of these potential confounding factors on intra-study variance. In addition, BMS-ISR and DES-ISR may have different underlying pathologies and may also affect the results. Thus, BMS-ISR or DES-ISR was also included as an independent variable in the meta-regression.

The proportions of hypertensive patients among the studies were similar, and we excluded this factor from the meta-regression. Results from the meta-regression showed an insignificant contribution of smoking and hyperlipidemia on TLR between treatments, with *P*-values of 0.281 and 0.788, respectively. The proportion of ACS patients in the DCB group was not associated with the heterogeneity (P = 0.332). Besides, study design and EES application did not make up for the heterogeneity, either (RCT or non-RCT: P = 0.793; EES or non-EES: P = 0.426). Notably, the proportion of diabetic patients (T2DM) in the DCB group accounted for all the variance among studies (P = 0.016, adjusted R^2 = 100%, **Figure 5A**). Using BMS-ISR or DES-ISR in the meta-regression indicated a marginal effect (P = 0.071, adjusted R^2 = 100%, **Figure 5B**). These results indicated that different T2DM proportions in the DCB group and BMS/DES in the previous PCI may both be the sources of heterogeneity.

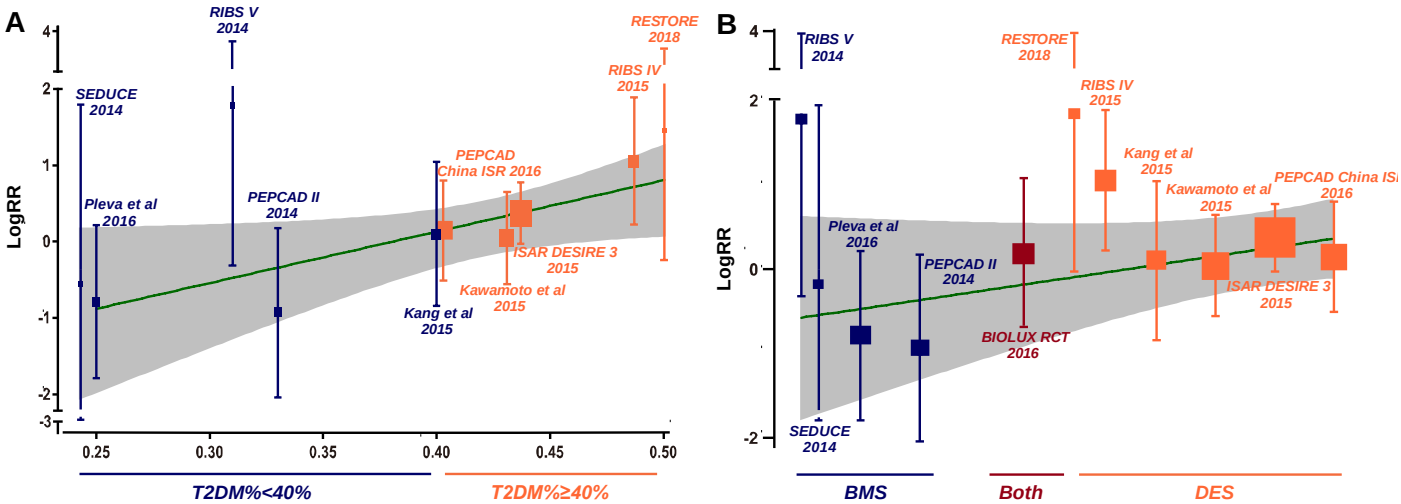

Figure 5. Meta-regression of **(A)** TLR using diabetes proportions in drug-coated balloon arm; and **(B)** BMS-ISR/DES-ISR.

According to the median T2DM proportion (40%) in the DCB group, we next performed subgroup analyses. The pooled results favored DES application in the population with a higher prevalence of diabetes (diabetic proportions ≥ 40%, RR = 1.493, 95% CI: 1.134–1.970, P = 0.004, Statistical power 0.9999, **Figure 6**), while this advantage was absent in the population with a lower proportion of diabetes (diabetic proportions < 40%; RR = 0.771, 95% CI: 0.464 to 1.281, P = 0.315,

Statistical power 0.6547, **Figure 6**). Notably, the subgroup analysis dismissed heterogeneity both in higher and lower diabetes prevalence cohort (**Figure 6**), which confirmed that diabetes patients in DCB arm was the source of heterogeneity.

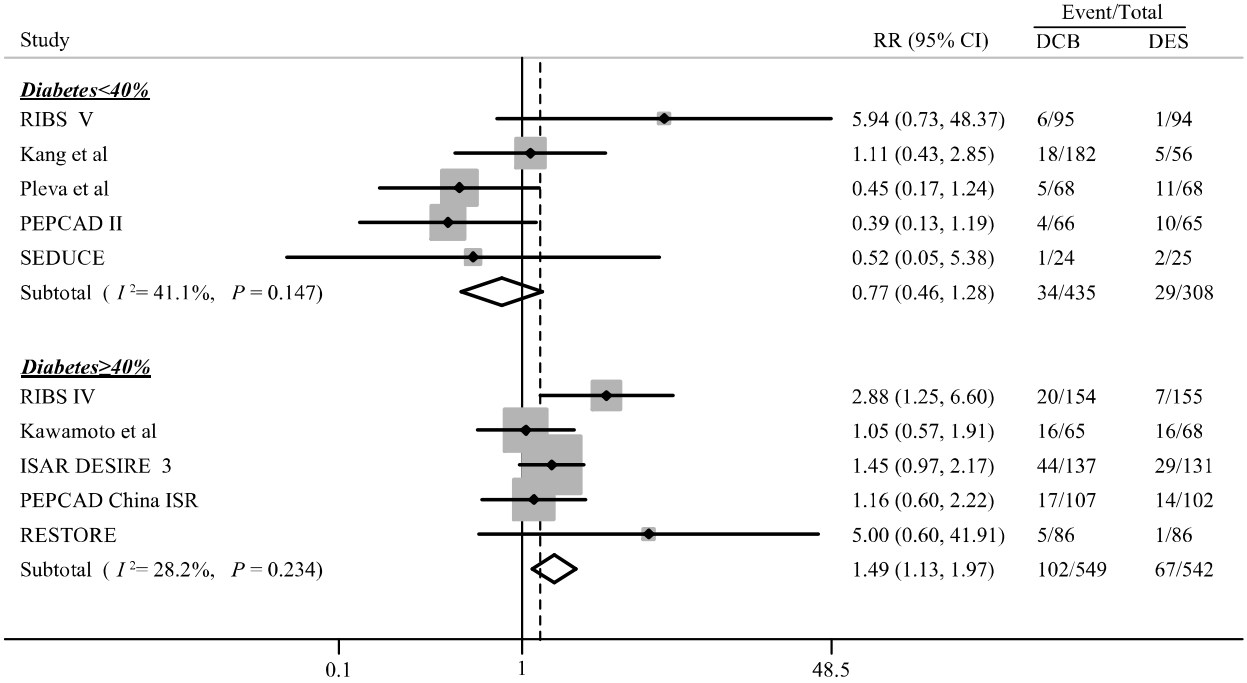

Figure 6. Forest plots for TLR in subgroup analysis according to low (<40%) or high (≥40%) prevalence of diabetic in drug-coated balloon group.

We continued to perform subgroup analyses according to the BMS/DES implantation in the previous PCI. The aggregated TLR rates of DES and DCB treatments for patients with a previous DES implantation were 13.66% and 19.48, respectively. The meta-analysis confirmed that DES was superior to DCB angioplasty in treating DES-ISR (RR = 1.455, 95% CI: 1.116–1.897, P = 0.006; I^2 = 14.0%, Cochrane Q-test, P = 0.325; **Figure 6**). A total of four studies [7,18,21,24] included in the BMS-ISR subgroup and a pooled analysis of them did not yield any significant difference in TLR with moderate but non-significant heterogeneity (RR = 0.664, 95% CI: 0.362 to 1.219, P = 0.186; I^2 = 46.7%, Cochrane Q-test, P = 0.131; **Figure 7**). One of the studies did not explicitly show which kind of stent was used in patients with previous PCI and result from this study was also insignificant (RR = 1.161, 95% CI: 0.505 to 2.666; P = 0.725). In addition, a subgroup analysis (either based on diabetes or BMS/DES implantation in the previous PCI) on MACE and MI did not reveal any significance between DES and DCB (data not shown). These results consistently supported DES conferring more advantages than DCB only in the DES-ISR population.

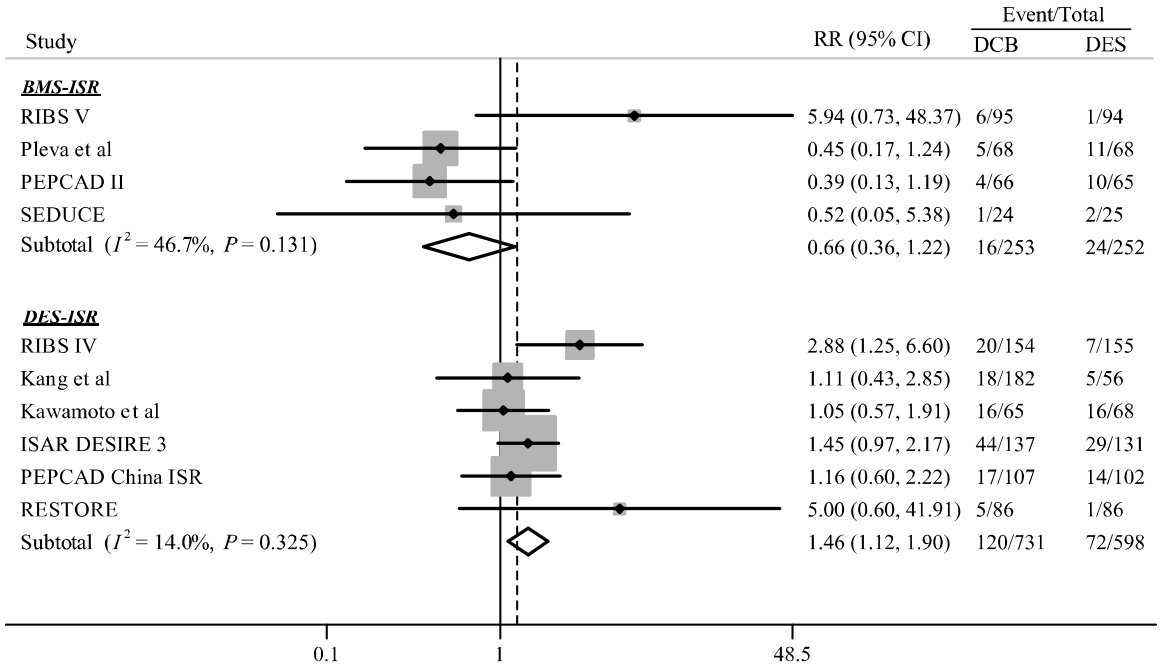

Figure 7. Forest plots for TLR in subgroup analysis according to BMS-ISR or DES-ISR. Statistical powers were 0.7645 in BMS-ISR subgroup and 0.9999 in DES-ISR subgroup.

3.4. EES is not superior to non-EES in reducing TLR

Despite the lack of support from meta-regression for utilizing EES as the primary source of heterogeneity, previous studies have reported a correlation between EES and improved clinical outcomes. Consequently, we pose the question of whether EES should be taken into consideration in the management of patients with ISR. Five EES studies [7,10,18,21,24] were included and the pooled TLR rates were 8.644% (DCB treated) and 5.140% (EES treated) from studies comparing EES and DCB. Unexpectedly, the summarized results from the random-effects model showed that EES was not superior to DCB, with great heterogeneity among the included studies (RR = 1.682, 95% CI: 0.546 to 5.186, P = 0.365, Statistical power 0.9999, **Figure 8A**). Similarly, no significant difference between DCB and non-EES treatments could be found (RR = 1.147, 95% CI: 0.885 to 1.487, P = 0.300, Statistical power 0.6662, **Figure 8B**). The pooled results from the three BMS-ISR studies [7,18,24] comparing EES and DCB showed that EES was not superior to DCB in this population (RR = 0.859, 95% CI: 0.408 to 1.806, P = 0.688, Statistical power 0.2141, **Figure 8C**). However, the results [10,21] from DES-ISR patients comparing EES and DCB showed an advantage in reducing TLR conferred by EES (RR = 3.142, 95% CI: 1.451 to 6.804, P = 0.004, Statistical power 1, **Figure 8D**). These results further confirmed that DES, even EES, exhibited a benefit only in DES-ISR patients.

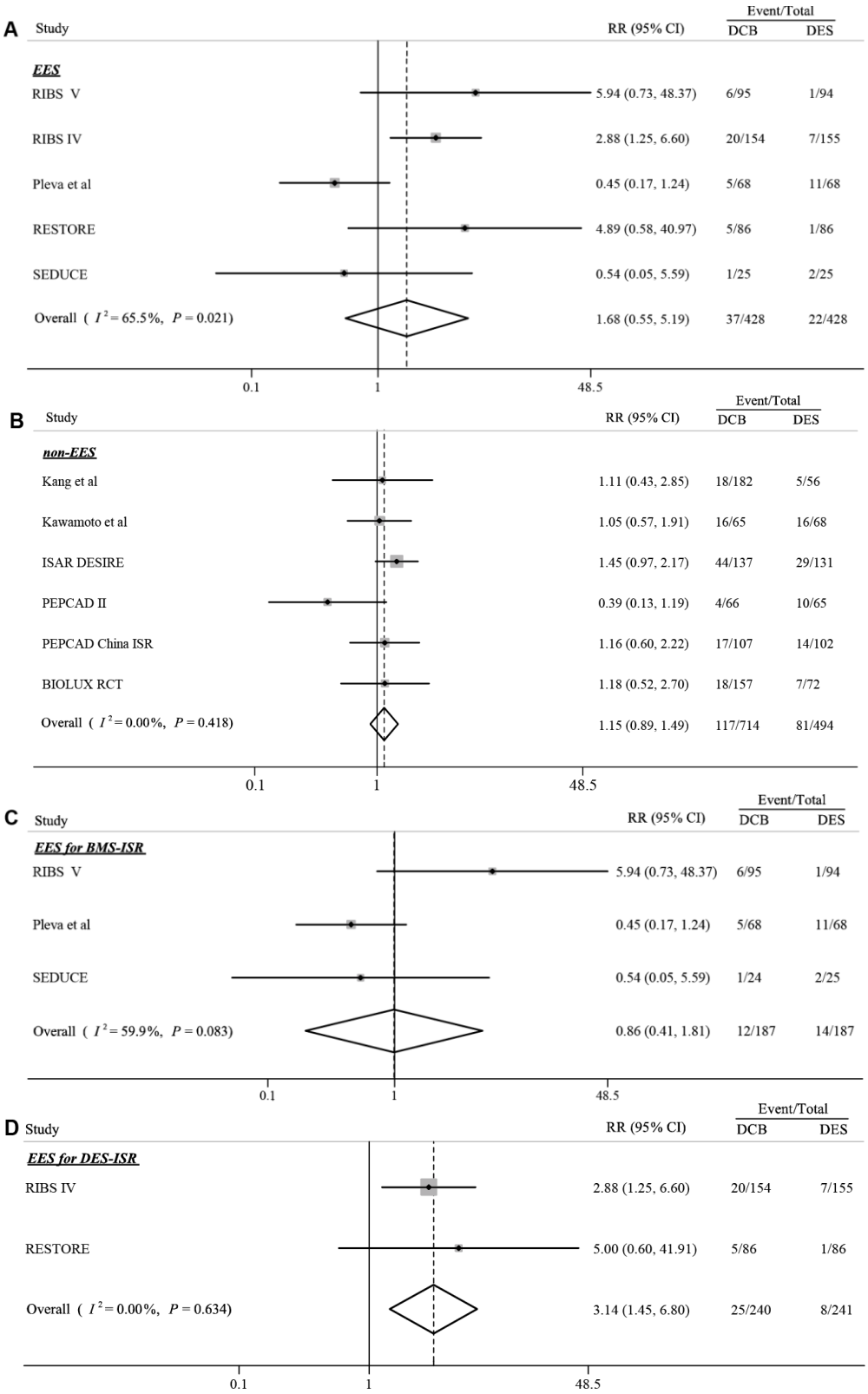

Figure 8. Forest plots for TLR in the **(A)** EES; **(B)** non-EES; **(C)** BMS-ISR treated with EES; and **(D)** DES-ISR treated with EES subgroups.

In addition to EES, three studies adopted the second-generation stent [19,23,25] instead of paclitaxel-eluting ones. Eluting drugs of this newer generation of stent may have similar properties, and we sought to explore whether they could be better than

the first-generation stent in reducing TLR. Unexpectedly, a subgroup analysis according to the first/second-generation DESs did not yield any significant difference between DCB and DES in the overall or DES subgroup analyses (**Figure 9A,B**).

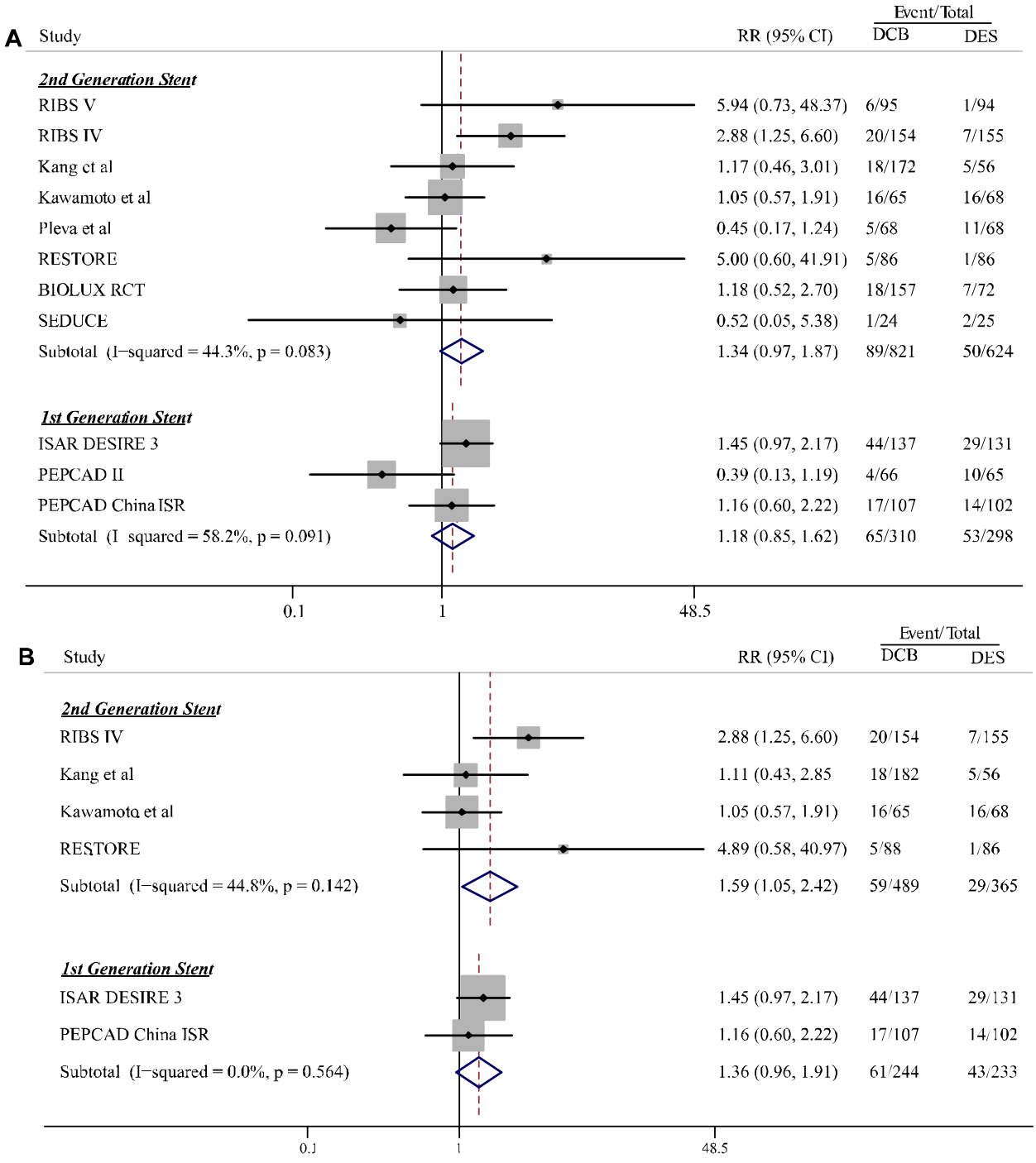

Figure 9. Forest plot for relative risk of TLR. Analysis were performed according to different generation stents in **(A)** overall studies; and **(B)** DES studies. As for overall studies, statistical powers were 0.9945 in 2nd Generation Stent subgroup and 0.3699 in 1st Generation Stent subgroup. As for DES studies, statistical powers were 0.9996 in 2nd Generation Stent subgroup and 0.9082 in 1st Generation Stent subgroup.

3.5. DES is associated with improved in-stent MLD

The lumen area is an important predictor of cardiac events and is of great value

in assessing the effects of ISR treatment. Therefore, we evaluated the lumen area using the pooled MLD and SRLD. According to the above findings, we analyzed BMS-ISR and DES-ISR separately. Of the six DES-ISR studies [8,10,19–22] data on MLD and SRLD were available for five [10,19–22] of them, involving 669 and 533 patients in the DCB and DES arms, respectively. The averaged MLDs were 2.106 mm^2 in the DCB group and 2.422 mm^2 in the DES group. A meta-analysis showed a statistical significance between the groups (WMD = −0.318, 95% CI: −0.428 to −0.213, $P < 0.001$, **Figure 10**). Significant heterogeneity was found using this analysis (I^2 = 68.90%, Cochrane *Q*-test $P = 0.012$). An exclusion of the non-RCTs [20], which was also identified as a source of heterogeneity by a meta-regression ($P = 0.042$; adjusted R^2 = 100%) dismissed all the heterogeneity (I^2 = 0%, Cochrane *Q*-test $P = 0.844$), and the results supported the beneficial effects of DES (WMD = −0.257, 95% CI: −0.325 to −0.189; $P < 0.001$). A subgroup analysis by either EES/non-EES or first/second-generation stents consistently showed that a DES was associated with a larger MLD (**Figure 11A,B**). MLD data were available in three of the four BMS-ISR studies. Pooled analysis showed a potential benefit of DES in improving MLD in this population, with a marginal statistical significance (WMD = −0.273, 95% CI: −0.543 to −0.004, $P = 0.047$; **Figure 12**).

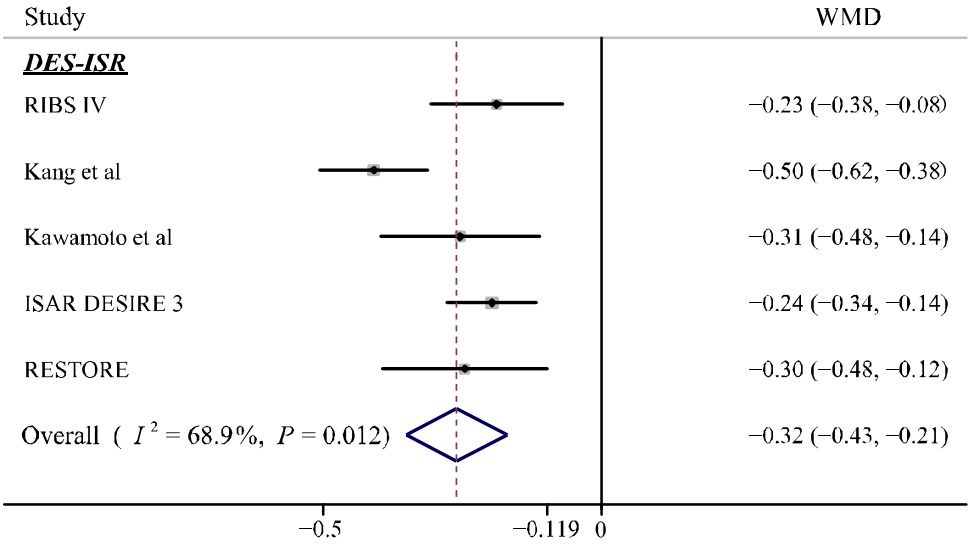

Figure 10. Forest plots for angiographic outcomes of weighted mean difference for minimal lumen diameter in DES-ISR population.

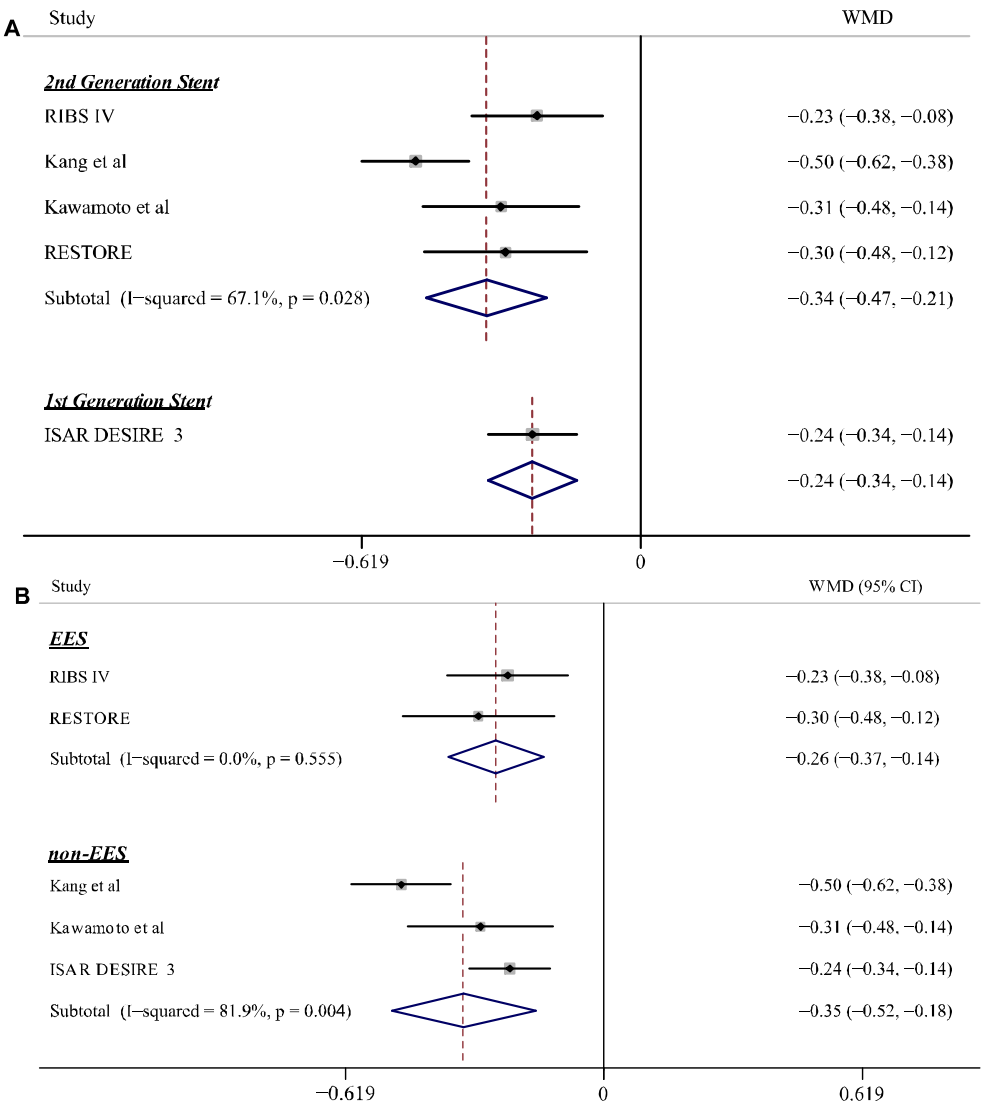

Figure 11. Forest plot of minimal lumen diameter in DES-ISR studies. Subgroup analyses were done according to **(A)** first/second generation stents; and **(B)** everolimus-eluting/non-everolimus eluting stents.

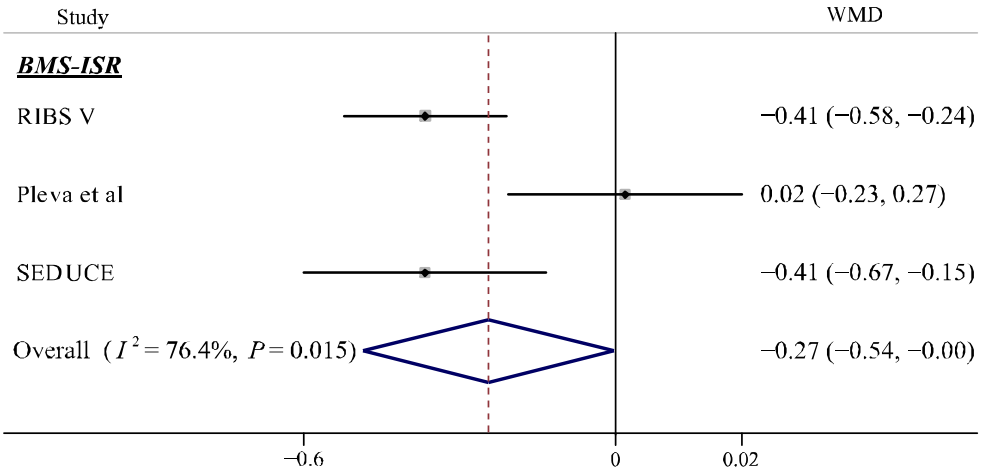

Figure 12. Forest plots for angiographic outcomes of weighted mean difference for minimal lumen diameter in BMS-ISR population.

Data on SRLD were available in the same population as above. The averaged SRLDs were 23.66% in the DCB group and 16.04% in the DES group. The meta-analysis resulted in a significant difference (WMD = 6.164%, 95% CI: 4.915% to 7.412%, $P < 0.001$; **Figure 13**), with moderate heterogeneity ($I^2 = 48.30\%$, Cochrane Q-test $P = 0.102$). Subgroup analysis by either EES/non-EES or first/second-generation stents supported the advantages of DES (**Figure 14**). All these results consistently confirmed that, compared with DCB treatment, DES implantation significantly improved MLD and SRLD in DES-ISR patients. Similar to the above MLD data in BMS-ISR patients, data on SRLD were available in three studies. Summarized results from these studies did not support that the beneficial role of DES in BMS-ISR patients comparing to DCB (WMD = 2.169, 95% CI: −5.836 to 10.173, $P = 0.595$; **Figure 15**).

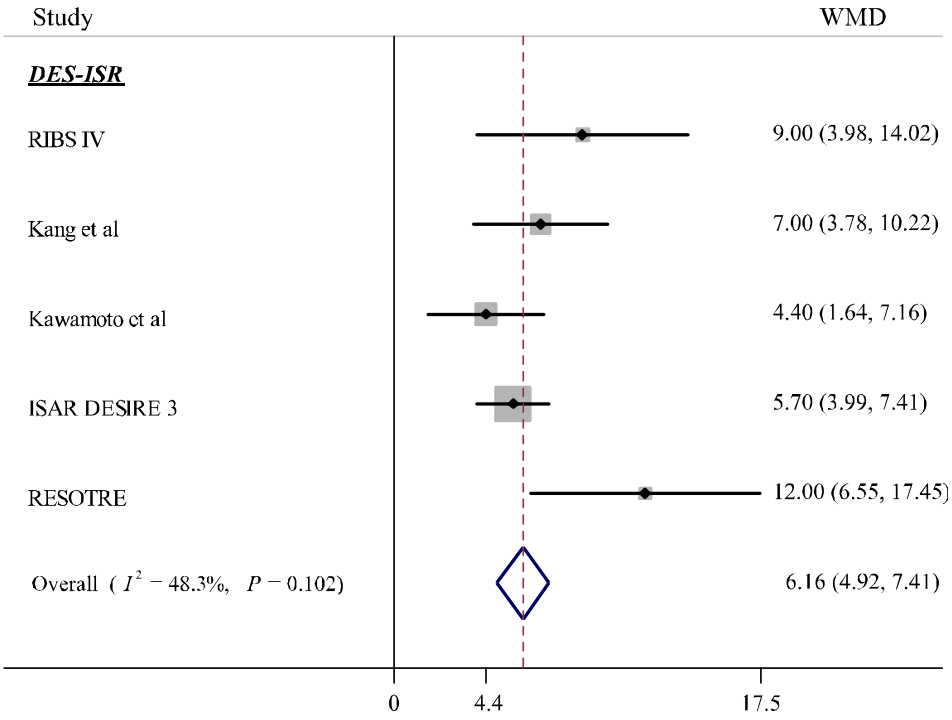

Figure 13. Forest plots for angiographic outcomes of weighted mean difference for stenosis relative to the reference lumen diameter in DES-ISR population.

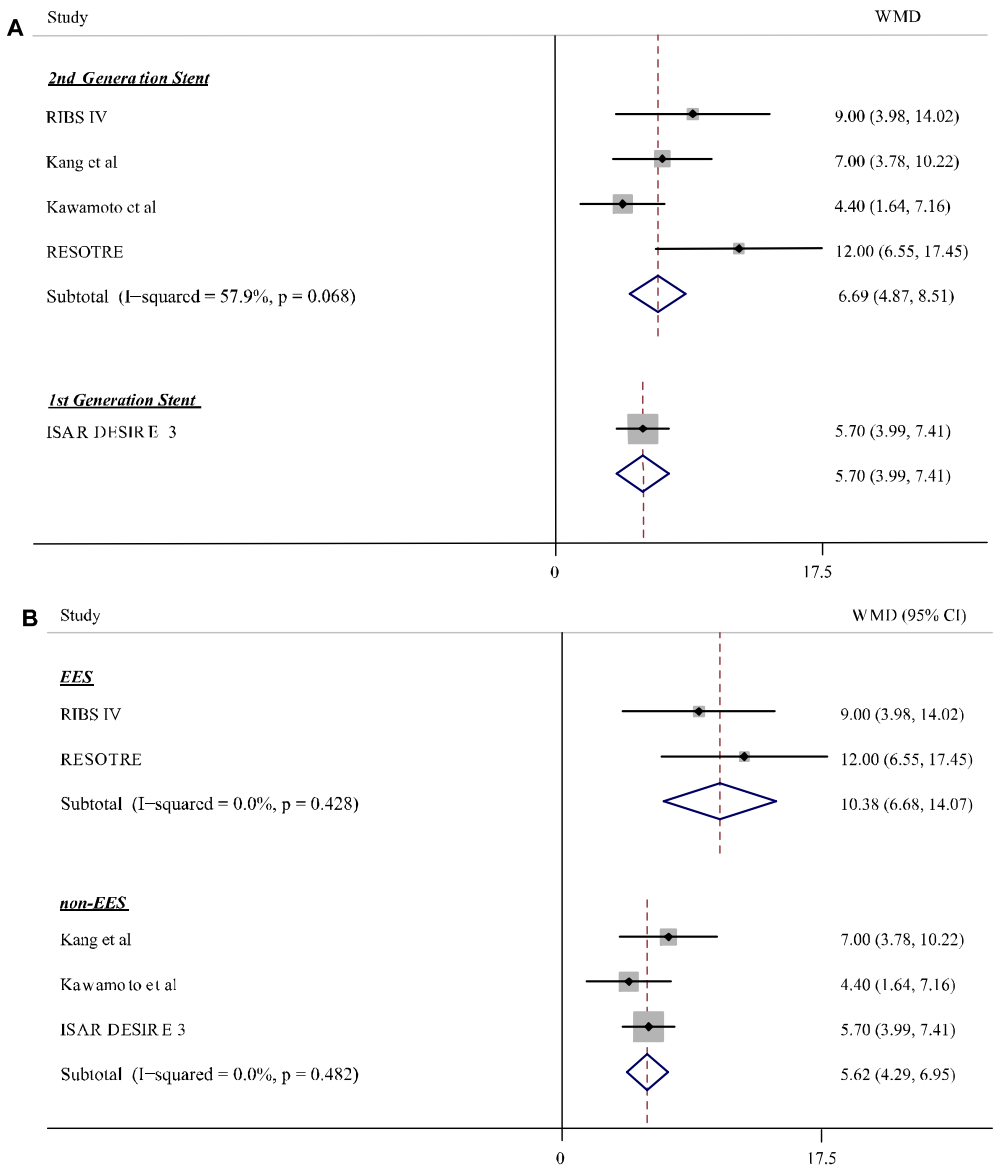

Figure 14. Subgroup analysis on stenosis relative to reference lumen diameter in DES-ISR population by **(A)** first/second-generation stents; and **(B)** non-everolimus eluting stents.

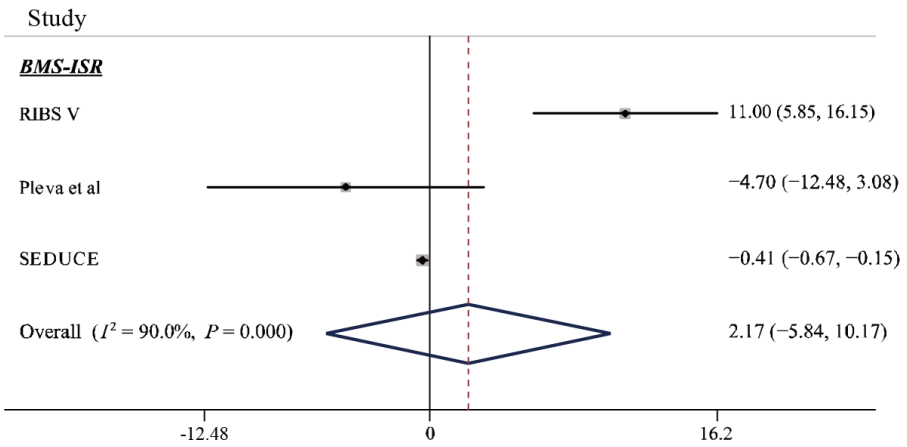

Figure 15. Forest plots for angiographic outcomes of weighted mean difference for stenosis relative to the reference lumen diameter in BMS-ISR population.

3.6. Publication bias

Overall, a visual estimation of publication bias did not find a study falling outside the significance boundaries in any endpoint, suggesting no significant asymmetry for the analyses. A Begg's test did not identify significant publication bias ($t = -0.110$, $P = 0.913$, **Figure 16**).

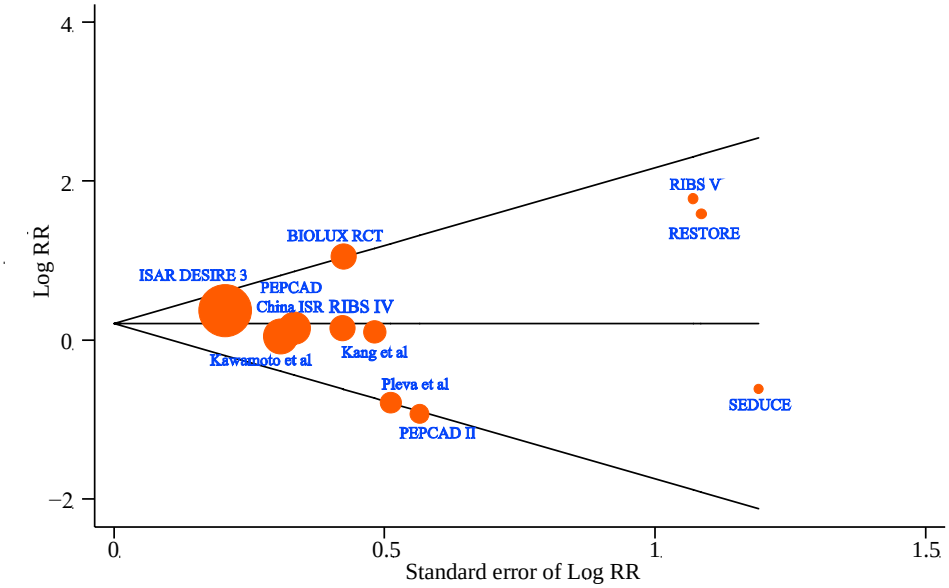

Figure 16. Publication bias test and Begg's plot for TLR in the overall analysis.

4. Discussion

The decision to use a DES or DCB for ISR patients has been highlighted. Some publications and recent meta-analyses provided the impression that DCB angioplasty was comparable to a DES in all ISR patients [6,26]. As a result, the recommendation levels for a DCB and DES in treating ISR from current myocardial revascularization guidelines were the same [4]. However, this issue continues to be of a scientific interest, and new studies have emerged. Very recently, a meta-analysis included 5 randomized trials and concluded that EES was superior to DCB [27]. Our study, which included 11 studies (9 randomized trials) and the sample size is double that of the previous study, demonstrated that DES is superior to DCB in DES-ISR patients but not in BMS-ISR patients, thus providing evidence clearly guiding the strategic decisions in clinical practice: DES should be considered first in DES-ISR patients to reduce TLR, while DCB angioplasty, which is comparable to a DES in BMS-ISR patients, should be encouraged in this population to avoid adding stent layers.

The distinct effects of a DCB on patients with BMS-ISR and DES-ISR have been noted previously. In one prospective study, recurrent stenosis inside the stent occurred in 1.1% and 9.1% of patients with BMS-ISR and DES-ISR patients treated with DCB angioplasty, respectively [28]. Late lumen loss was also much higher in DES-ISR than in BMS-ISR patients, with a 72% reduction in the lumen area [28]. Similarly, in another prospective study, DCB resulted in 8.7% and 24.2% TLR rates, respectively for BMS-ISR and DES-ISR patients [29]. In addition, a large observational study further confirmed that DCB angioplasty was more effective in BMS restenosis than in DES restenosis [30]. All these studies indicated that DCB angioplasty was less

effective in DES-ISR patients than those with BMS-ISR.

From a pathological aspect, neointimal hyperplasia is the main cause of ISR in both BMS and DES, but the tissue characteristics between them are not totally the same. The neointimal hyperplasia of BMS-ISR typically consists of a proteoglycan matrix and a high proportion of vascular smooth muscle cells [25,31]. Conversely, proteoglycan-rich neointimal hyperplasia with relatively few smooth muscle cell is typically found in DES-ISR [25,31]. Furthermore, compared with BMS-ISR, neoatherosclerosis is found to be much greater and earlier in DES-ISR [32]. These findings might partly explain the insufficiency of DCB compared with DES since DCB, despite avoiding stent implantation and complex stent layers, is less effective in enlarging the vessel lumen, which results in the resilience of proteoglycans and neoatherosclerosis inside the stenotic DES because anti-proliferative drugs have little effect on such components [28].

Intriguingly, diabetes alters the effects of DCB and DES and was identified as a source of heterogeneity. For example, in the ISAR-DESIR 3 studies, as many as 43.7% of patients suffered from T2DM in the DCB group, and the long-term effects of DCB and DES were similar with any endpoint [22]. Moreover, further analysis revealed a non-significant interaction between DCB/DES treatments and diabetes, implying that diabetes was not an important factor in the determinate effects of DCB and DES [22]. This finding agreed with the results from the PEPCAD-DES study, showing that late lumen loss was similar in both diabetic and non-diabetic DES-ISR patients receiving DCB angioplasty [8]. Moreover, in the RIBS IV study, including 48.7% and 42.6% diabetic patients in the DCB and DES arms, respectively, the composite outcomes of cardiac death, MI, and TLR were reduced in patients receiving a DES, which could not be found in the diabetes cohort [21]. All these results did not support the distinct effects of DCB and DES in diabetic patients, which seems to conflict with our results. However, of the 6 studies included, more than 40% of diabetic patients were included in the DCB arm, and 5 studies included DES-ISR patients only. Therefore, the meta-regression results identifying diabetes as a source of heterogeneity may actually be masked by DES-ISR patients in these studies.

EES was found to confer benefits in many kinds of coronary lesions during PCI [33,34]. However, we could not find any advantage of EES in BMS-ISR patients. Moreover, EESs were not superior to other kinds of DESs. On the one hand, this result may be due to limited sample size and statistical power leading to a false-negative result. Take the effects of EES in BMS-ISR subgroup for example, the statistical power was 0.2141, much lower than in DES-ISR subgroup (statistical power = 1). Indeed, no benefit conferred by a DES could be found when patients were divided into EES/non-EES subgroups, which further imply that sample size is an important factor for the effect size. On the other hand, ISR pathology may be different from the de novo lesion, which may restrict the beneficial effects of EES. Therefore, more studies on BMS-ISR treated by EES are required.

5. Limitations

Notwithstanding clearly showing that DES is superior to DCB only in DES-ISR patients, some limitations of our studies should be noted. Most importantly, as

mentioned above, we could not ascertain the effects of EES in BMS-ISR due to potentially insufficient sample sizes. In addition, the lack of individual patient data restricted us in a further stratified analysis related to diabetes prevalence, resulting in an unsolved problem that diabetes influenced the effects of DES and DCB on ISR. Moreover, statistical powers in some subgroup analyses were not high enough, it might be one of the reasons for why lack of difference in some subgroup analyses. Finally, given that the subject cohorts were predominantly male, this may limit the external validity of the results.

6. Conclusion

Despite these limitations, the current study updated evidence, with a much larger sample size than the previous studies, reporting the beneficial effects of DES in DES-ISR patients, which resulted in a high recommendation for DES, especially EES, rather than DCB, in DES-ISR patients. More studies, especially those focusing on newer generations of drug-eluting stents (e.g., everolimus-eluting stent), are required.

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