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ORIGINAL RESEARCH

Head-to-head comparison of limus- versus paclitaxel-coated balloons in the treatment of in-stent restenosis: a meta-analysis

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ABSTRACT

BACKGROUND: There is a lack of robust comparative data between limus drug-coated balloons (DCBs) versus paclitaxel-coated balloons (PCBs) on their efficacy and safety in treating in-stent restenosis (ISR).

AIMS: The objective of this systematic review and meta-analysis was to compare the efficacy and safety of limus DCBs versus PCBs in terms of clinical and angiographic outcomes during a 12-month follow-up.

METHODS: Following PRISMA guidelines, we systematically explored PubMed, Scopus, and Cochrane databases up to 20 February 2025 for studies comparing limus DCBs versus PCBs in terms of safety, efficacy, and angiographic outcomes in treating ISR. The primary outcomes were the incidence of clinically driven target lesion revascularisation (TLR) and failure (TLF). Secondary endpoints were major adverse cardiovascular events (MACE) and angiographic findings during follow-up.

RESULTS: Data from six randomised controlled trials (RCTs), including a total of 639 patients treated with limus DCBs and 569 with PCBs for ISR, were analysed with a mean follow-up of 12 months. In this analysis, all six RCTs reported on TLR (limus DCB 14% vs PCB 11.4%) and TLF (limus DCB 15% vs PCB 14%) incidence, showing no significant difference between the limus DCB and PCB groups. No significant differences were observed in MACE (16.4% vs 13.5%), all-cause mortality (1.8% vs 1.4%), cardiac death (1.4% vs 1.0%) or target vessel myocardial infarction (0.9% vs 1.0%), for limus DCBs versus PCBs, respectively. Angiographic outcomes showed no significant differences in post-intervention minimal lumen diameter (standardised mean difference [SMD] +0.06, 95% confidence interval [CI]: –0.07 to 0.18; I^2=0%) or binary restenosis (limus DCB 19.5% vs PCB 12.9%) at follow-up between the groups. The risk of late lumen loss was also comparable between limus DCBs and PCBs for both in-segment (SMD +0.02, 95% CI: –0.18 to 0.23; I^2=32%) and in-lesion (SMD –0.03, 95% CI: –0.31 to 0.24; I^2=27%) analyses. Low heterogeneity was observed across the studies.

CONCLUSIONS: Our findings suggest that limus DCBs are equally as effective and safe as PCBs for treating ISR, demonstrating non-inferiority in both clinical and angiographic outcomes at 12 months post-intervention.

KEYWORDS: angiographic; biolimus; clinical outcomes; drug-coated balloons; paclitaxel; sirolimus

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The introduction of drug-eluting stents (DES) has significantly altered the treatment of coronary artery disease. The critical differences in the new stent's era were drug-coating advancements and decreased strut thickness[1]. Compared with bare metal stents (BMS), DES have ameliorated the outcomes of percutaneous coronary intervention (PCI), mainly by suppressing smooth muscle cell proliferation and subsequent neointimal hyperplasia, the main contributor of in-stent restenosis (ISR). Despite the advancements and innovations in the field, the incidence of ISR remains relatively high[2]. During the past decade, ISR-related interventions in the United States have consistently remained around 1/10 of all PCI, while the rate for target lesion revascularisation (TLR) hovers at 1-2% per year[3]. The treatment of ISR is a field of extensive research, with DES and drug-coated balloons (DCBs) being its main options. Considering the disadvantages of implanting an additional DES, DCBs have a notable convenience, since they can provide the remedy without the need for an additional stent to be implanted. However, until now, experts have recommended the use of DES as a first choice for treating ISR, leaving the use of DCBs to the discretion of the operator after considering several anatomical and procedural aspects[4,5].

There is a significant interest in developments in DCB technology; specifically, trying to avoid a second stent layer and increased incidence of recurrent ISR. DCBs have proven highly effective in treating ISR, with the most widely available being paclitaxel-coated balloons (PCBs) and limus DCBs. Paclitaxel is a well-established antiproliferative agent known for its rapid cellular uptake due to its lipophilic nature[4,5]. Recent advancements in drug delivery technologies for limus DCBs have increased their use in clinical practice. New-generation sirolimus DCBs have shown promising results in recent trials, positioning them as a potential alternative to the widely used PCBs. Another emerging option is biolimus A9 (Biosensors International Group, Ltd.), a sirolimus derivative with enhanced lipophilicity compared to other limus agents, with retained rapamycin-inhibitory properties[6]. However, there is a lack of robust comparative data between limus DCBs versus PCBs on their efficacy and safety in treating ISR, making it difficult to generalise the results from individual studies.

The objective of this systematic review and meta-analysis was to compare the efficacy and safety of limus DCBs with the most extensively studied PCBs in patients with DES-ISR.

Impact on daily practice

Drug-coated balloons (DCBs) have proven highly effective in treating in-stent restenosis (ISR). Our findings showed that there are no significant differences between paclitaxel-coated balloons (PCBs) and limus DCBs in the risk of major clinical outcomes, including all-cause mortality, cardiac death, and clinically driven target lesion revascularisation. Limus DCBs achieve at least equal angiographic outcomes compared with PCBs without significant differences in late lumen loss during 12-month follow-up. The study indicates that limus DCBs are a reliable alternative to PCBs in daily clinical practice for managing ISR. Future larger prospective studies might aim to validate these results for various indications.

Methods

The present systematic review (SR) was performed according to the guidelines of the Cochrane Handbook for SRs[7] and on the basis of a preregistered PROSPERO protocol (CRD42024583030). Reporting was performed based on the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) 2020 statement. A checklist of the reported PRISMA 2020 items is presented in **Supplementary Table 1**.

INFORMATION SOURCES AND SEARCH STRATEGY

Systematic searches were conducted in MEDLINE (via PubMed), Scopus, and the Cochrane Library from inception up to 20 February 2025 without language restrictions. A search strategy was developed using the following search algorithm: [(Paclitaxel or Pacitaxel or Onxol or Taxane or Taxol or PTX or Abraxane) AND (Sirolimus or Rapamycin or mTOR or Rapamune or Zotarolimus or ABT-578 or Everolimus or Biolimus or Afinitor or Certican or RAD001) AND (balloon)]. Reference lists from selected studies and pertinent reviews and abstracts of international conferences from the last ten years were also scrutinised.

ELIGIBILITY CRITERIA

POPULATION AND INTERVENTIONS

Adults (>18 years old) with clinical evidence of stable or unstable angina or a positive functional study and DES-ISR treated with a DCB were considered for enrolment. Eligible studies were required to compare any limus-based coated balloon – sirolimus- or biolimus-coated – with paclitaxel-coated balloons in terms of effectiveness and/or safety.

OUTCOMES

The primary outcomes were the incidence of clinically driven TLR and target lesion failure (TLF; defined as a composite of cardiac death, target vessel myocardial infarction [TVMI], and repeated – either surgical or percutaneous – TLR or clinically indicated TLR) during a one-year follow-up. Angiographic outcomes included in-segment and in-lesion late lumen loss

Abbreviations

BMS	bare metal stent	**LLL**	late lumen loss	**SMD**	standardised mean difference
DCB	drug-coated balloon	**MACE**	major adverse cardiovascular events	**TLF**	target lesion failure
DES	drug-eluting stent	**MLD**	minimal lumen diameter	**TLR**	target lesion revascularisation
DS	diameter stenosis	**PCI**	percutaneous coronary intervention	**TVMI**	target vessel myocardial infarction
ISR	in-stent restenosis	**RR**	risk ratio		

(LLL; difference between the postprocedural and follow-up minimal lumen diameter [MLD], evaluated by quantitative coronary angiography), MLD, diameter stenosis (DS), and acute gain during the follow-up. Additional endpoints included procedural success (defined as the ability of balloon inflation to reach a <30% final stenosis, Thrombolysis in Myocardial Infarction 3 flow, no flow-limiting dissection, and freedom from in-hospital major adverse cardiovascular events [MACE]), MACE (occurrence of cardiac death, target vessel myocardial infarction, or clinically driven TLR) during follow-up, as well as individual clinical endpoints at 12-month follow-up (stent thrombosis, cardiac death, or target vessel myocardial infarction). Myocardial infarction (MI) was defined according to the established 4th Universal Definition of Myocardial Infarction[8]. Stent thrombosis, cardiac death, TVMI, and clinically driven TLR were defined according to the Academic Research Consortium consensus document[9]. Periprocedural complications were also recorded (dissections, perforations, slow-flow or no-reflow phenomena).

STUDY DESIGN

Eligible studies were randomised controlled trials (RCTs) of any duration including a minimum sample size of ten patients.

EXCLUSION CRITERIA

Records were excluded based on the following criteria: (1) case reports/case series, narrative reviews; (2) expert opinions, dissertations, protocols; (3) studies including animals and/or *in vitro* studies.

SELECTION PROCESS

All records retrieved from the search strategy were screened by title and abstract by two investigators (M. Sagris and N. Ktenopoulos) independently. Subsequently, the same authors also independently screened the remaining studies' full texts. Discrepancies at any stage were resolved by discussion or consultation with a third reviewer (S. Soulaidopoulos). The EndNote X7 software (Clarivate) was used for reference management.

DATA EXTRACTION

A data extraction form was created, piloted, and standardised after discussion and calibration exercises. The following variables were extracted: first author; publication year; title; journal's title; study type; distribution of randomised participants in each group; inclusion/exclusion criteria; demographic and population characteristics; comorbidities; interventions; comparator; angiographic, efficacy and safety outcomes; number of events; and number of patients in each group (priority to intention-to-treat [ITT] analysis).

QUALITY ASSESSMENTS

The methodological quality of the included studies was evaluated using the revised Cochrane risk of bias 2 (RoB 2) tool[10] for RCTs. Methodological quality was evaluated by two authors independently, and any disagreements were resolved through discussion or involvement of a third author. Regarding the quality and risk of bias assessment, the criteria for the ascertainment of points and the allocation of points for each study are given in **Supplementary Table 2**.

DATA ANALYSIS

All analyses were performed using Stata 16.0 (StataCorp). Frequencies with percentages (%) are presented for categorical variables, means with standard deviation for Gaussian continuous variables, and medians with interquartile range for non-normally distributed continuous variables. Summary estimates for categorical variables are reported as risk ratios (RRs), and for continuous variables, they are reported as the standardised mean difference (SMD). The RRs, SMDs and 95% confidence intervals (CIs) were calculated using the DerSimonian-Laird estimator for random-effects models. In case of zero events in a treatment arm, a continuity correction was applied. Heterogeneity was assessed using the I^2 test and was formally tested with Cochran's Q test. Rough cutoff values were 25%, 50%, and 75%, indicating low, moderate, and high heterogeneity, respectively[11]. Small-study effects (including publication bias) for each outcome were visually assessed with funnel plots and formally tested with the Egger's test. For all statistical tests, a two-tailed p-value less than 0.05 was considered statistically significant.

Results

STUDY SELECTION

A comprehensive literature search resulted in 1,245 potentially relevant records (864 in MEDLINE/PubMed, 198 in Cochrane Library and 183 in Scopus). Once duplicates were removed, 652 studies were identified. After screening titles and abstracts, 68 articles were retrieved for full-text evaluation. A total of six RCTs (five full articles[12-16] and one presented as a late-breaking clinical trial[17]) met the predetermined eligibility criteria and were included in this meta-analysis, as shown in the PRISMA flow diagram **(Supplementary Figure 1)**. All studies were published in the last three years, from 2022 to 2024.

BASELINE CHARACTERISTICS

A total of 639 versus 569 patients with ISR were included in the analysis in the limus DCB and PCB groups, respectively, with a mean follow-up of 12 months. The total number of treated lesions included 674 limus DCBs and 598 PCBs. The mean age of the limus DCB and PCB groups, respectively, was 66±9.8 years versus 65.8±9.9 years, and the majority of patients were male. Of the treated lesions, 3% (N=10/335)/1.5% (N=5/327) were located at the left main artery, 42.9% (N=209/487)/45.6% (N=219/480) at the left anterior descending artery, 20.3% (N=99/487)/17.3% (N=83/480) at the circumflex artery, and 33.2% (N=162/487)/35.2% (N=169/480) at the right coronary artery, in the limus DCB and PCB groups, respectively. Preprocedural examinations revealed a mean lesion length of 17.2±7.9 mm for limus DCBs versus 16±7.3 mm for PCBs. The mean maximum inflation pressure was 11±3.3 bar versus 11±4.4 bar, with a mean inflation duration of 58.4±7.6 seconds versus 58.4±9.4 seconds, for limus DCB and PCB groups, respectively. Full patient characteristics are presented in **Table 1** and **Table 2**.

TLR AND TLF OUTCOMES

All six RCTs reported on TLR incidence, showing no statistical difference between the two groups of limus DCBs

Table 1. Characteristics of the included studies.

Study	Design	Arm A (limus DCB), N	Arm B (PCB), N	Lesions at baseline, N		Lesions at follow-up, N		Clinical/ angiographic follow-up, months		Lesion length, mm	
B. Scheller 2022 (Malaysia)[14]	RCT (SCB vs PCB)	25	25	26	25	26	25	12	6	14.2±7.8	13.2±7.1
B. Scheller 2022 (Europe)[14]	RCT (SCB vs PCB)	25	26	26	26	26	27	12	6	13.2±6.5	14.3±9.2
C. Briguori 2023[13]	RCT (SCB vs PCB)	186	186	186	186	n/a	n/a	12	n/a	19±5	18±6
S. Fitzgerald 2023[17]	RCT (Biolimus DCB vs PCB)	135	67	135	67	121	55	12	6	20.5±10.3	18.5±9.5
H. Liu 2025[16, 33]	RCT (SCB vs PCB)	130	128	149	141	149	141	12	9	13.4±7.5	12.7±6.4
Y. Chen 2024[15]	RCT (Biolimus DCB vs PCB)	138	137	152	153	114	116	12	9	16.2±7.2	15.9±6.8

Values are N or mean±standard deviation. DCB: drug-coated balloon; N: number of patients; n/a: not available; PCB: paclitaxel-coated balloon; RCT: randomised controlled trial; SCB: sirolimus-coated balloon

Table 2. Patient characteristics of the included studies.

Study	Arm A (limus DCB), N	Arm B (PCB), N	Males, N		DM, N		HTN, N		DLP, N		LVEF, %	
B. Scheller 2022 (Malaysia)[14]	25 (SeQuent[a])	25 (SeQuent Please[a])	22	19	18	19	24	23	23	21	57±7	56±14
B. Scheller 2022 (Europe)[14]	25 (SeQuent[a])	26 (SeQuent Please[a])	21	20	9	11	25	25	21	22	49±10	56±11
C. Briguori 2023[13]	186 (Devoir[b])	186 (RESTORE[c])	139	143	104	103	167	171	160	167	51±10	50±7
S. Fitzgerald 2023[17]	135 (Biosensors biolimus)	67 (SeQuent Please[a])	110	51	42	17	117	53	112	55	n/a	n/a
H. Liu 2025[16,33]	130 (SeQuent[a])	128 (SeQuent Please[a])	95	97	44	53	87	90	23	18	59.2±8	60.6±7.5
Y. Chen 2024[15]	138 (Biosensors biolimus)	137 (SeQuent Please Neo[a])	103	101	51	59	86	98	61	53	61±8	60.8±9

Values are N or mean±standard deviation. [a]By B. Braun; [b]by APR Medtech; [c]by Cardionovum GmbH. DCB: drug-coated balloon; DLP: dyslipidaemia; DM: diabetes mellitus; HTN: hypertension; LVEF: left ventricular ejection fraction; N: number of patients; n/a: not applicable; PCB: paclitaxel-coated balloon

versus PCBs (14% vs 11.4%; RR 1.16, 95% CI: 0.82-1.64; I^2=14%) at one-year follow-up. Four studies reported on TLF rates, also without statistical difference between the two groups (15% vs 14%; RR 1.14, 95% CI: 0.86-1.53; I^2=0%). Low heterogeneity was observed among the studies **(Figure 1)**.

PROCEDURAL AND CLINICAL OUTCOMES

Overall procedural success was similar between the two groups, with favourable outcomes in nearly all cases (limus DCB: 188/188 cases vs PCB: 187/188 cases). During the periprocedural/30-day post-intervention period, there was one case of dissection in the limus DCB group. There were no differences in the incidence of MACE (16.4% vs 13.5%; RR 1.11, 95% CI: 0.84-1.46; I^2=0%) at one-year follow-up **(Figure 2)**. More specifically, the pooled all-cause mortality (1.8% vs 1.4%; RR 1.25, 95% CI: 0.50-3.08; I^2=0%) and cardiac death (1.4% vs 1%; RR 1.19, 95% CI: 0.42-3.41; I^2=0%) rates during the one-year follow-up across the six studies showed no statistical differences between the limus DCB and PCB groups, respectively **(Figure 2)**. Additionally, no differences were observed in TVMI (0.9% vs 1%; RR 0.58, 95% CI: 0.20-1.67; I^2=0%) or any MI (1.8% vs 0.9%; RR 0.58, 95% CI: 0.20-1.67; I^2=0%) **(Figure 3)**. Finally, there were no statistical differences in the incidence of stent thrombosis (0% vs 0.3%; RR 0.44, 95% CI: 0.06-3.06; I^2=0%) or the rates of any vessel revascularisation (8.7% vs 7.2%; RR 1.34, 95% CI: 0.91-1.98; I^2=10%) during this period. Low heterogeneity was observed among the studies.

ANGIOGRAPHIC OUTCOMES

The mean angiographic follow-up for both arms was 7.2±1.6 months. There was no significant difference in binary restenosis (19.5% vs 12.9%; RR 1.45, 95% CI: 0.77-2.71; I^2=63%) between the two groups during the follow-up

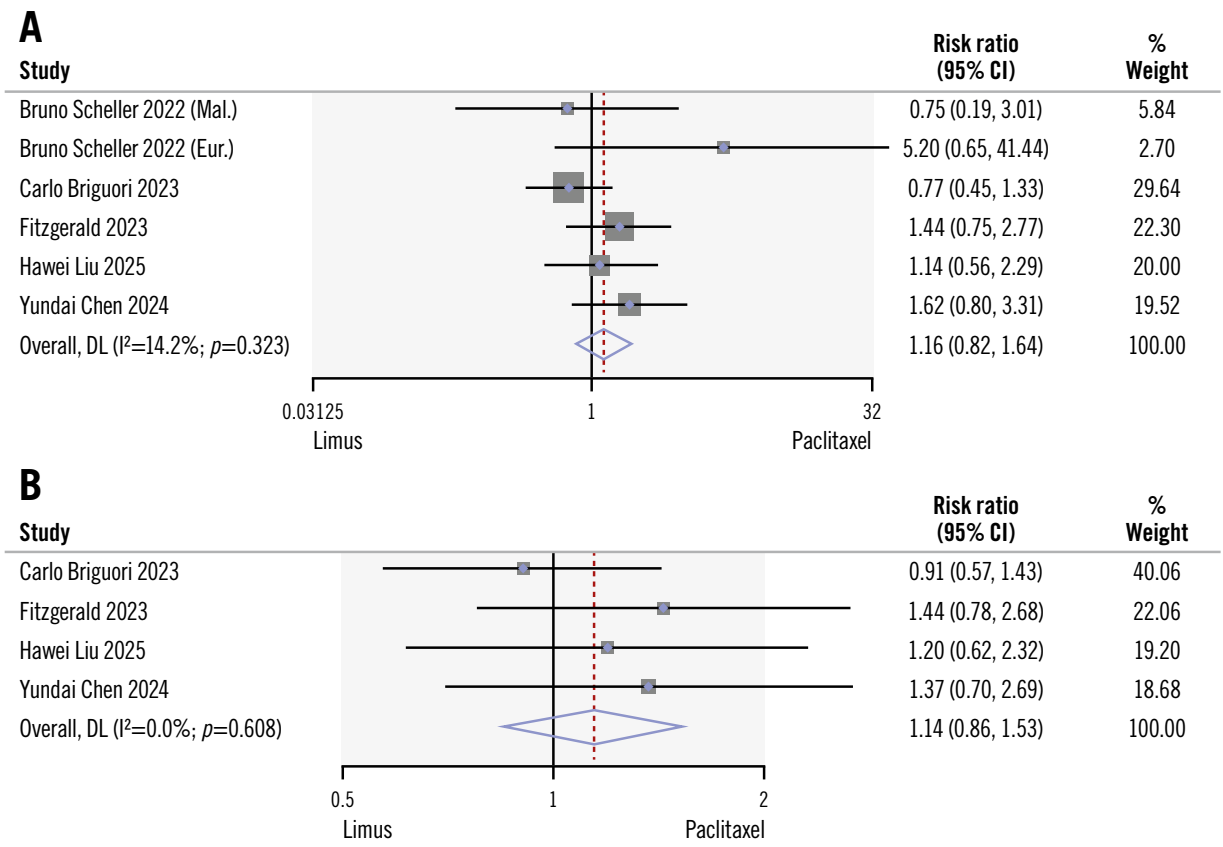


Figure 1. *Comparison of limus DCBs versus PCBs in terms of TLR and TLF. A) TLR; (B) TLF. Study references are provided in* ***Table 1*** *and* ***Table 2****. CI: confidence interval; DL: DerSimonian-Laird; DCB: drug-coated balloon; PCB: paclitaxel-coated balloon; TLF: target lesion failure; TLR: target lesion revascularisation*

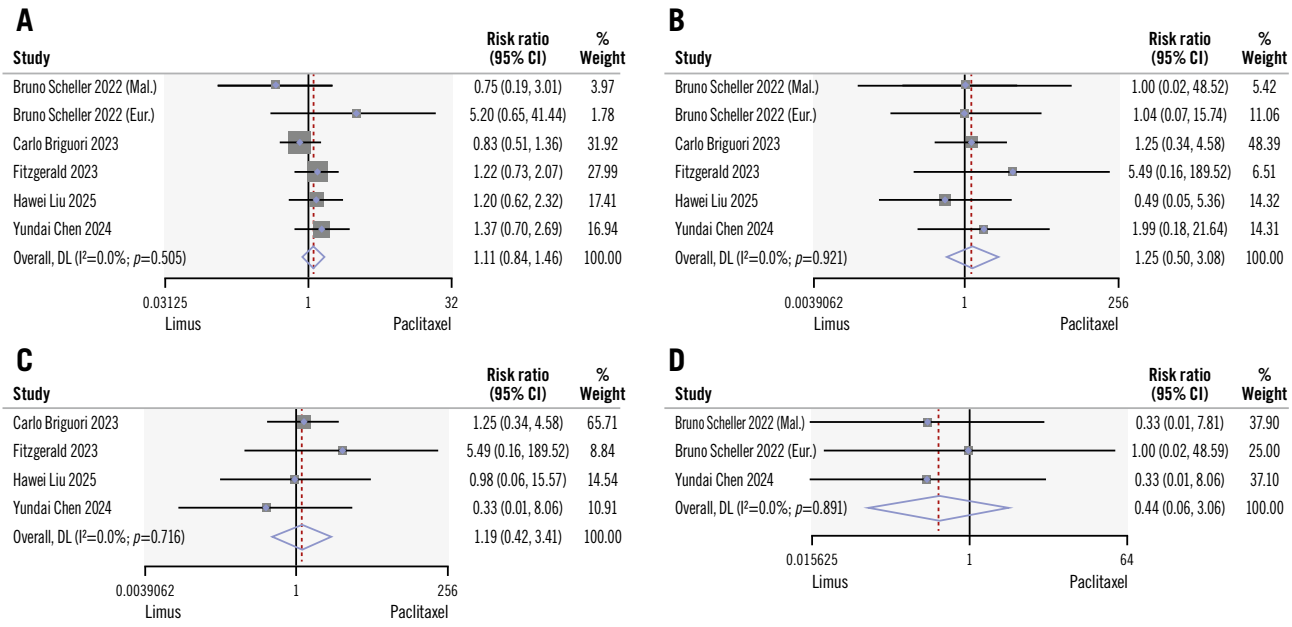


Figure 2. *Comparison of limus DCBs versus PCBs in terms of MACE, all-cause mortality, cardiac death, and stent thrombosis. A) MACE; (B) all-cause mortality; (C) cardiac death; (D) stent thrombosis. Study references are provided in* ***Table 1*** *and* ***Table 2****. CI: confidence interval; DL: DerSimonian-Laird; DCB: drug-coated balloon; MACE: major adverse cardiovascular events; PCB: paclitaxel-coated balloon*

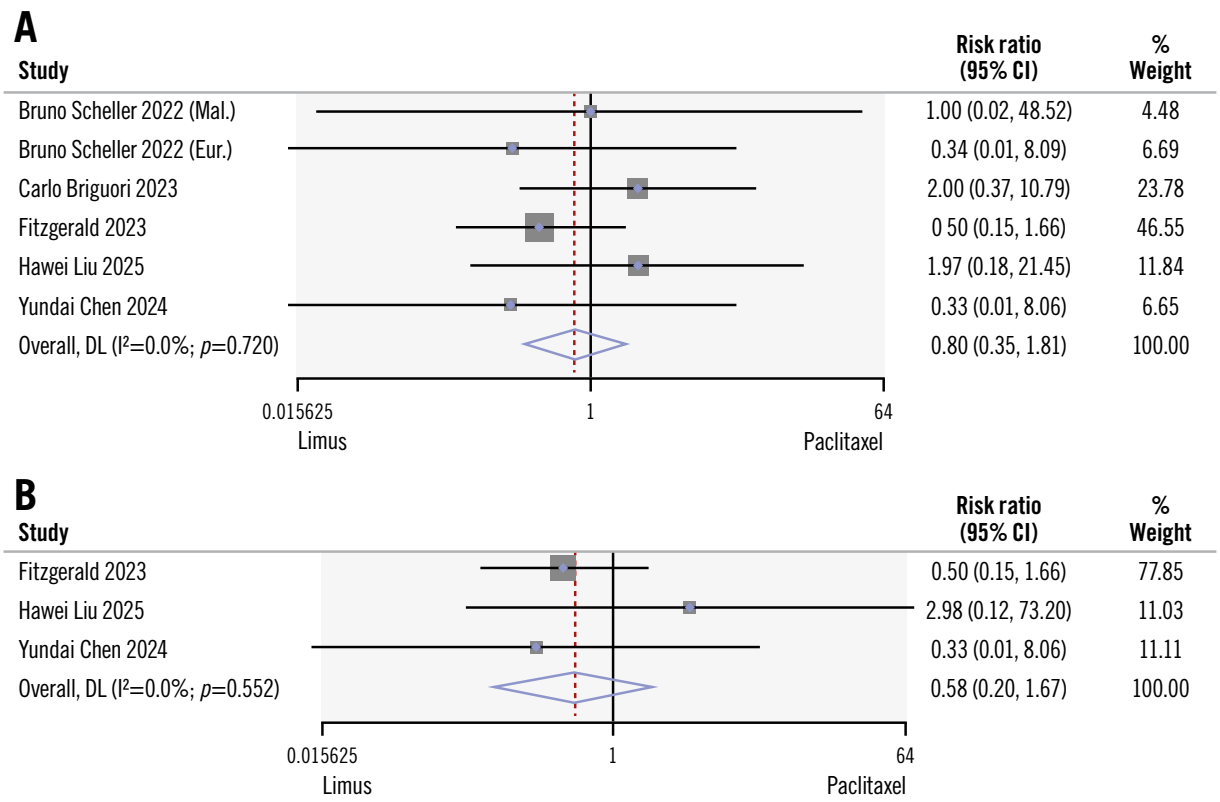


Figure 3. *Comparison of limus DCBs versus PCBs in terms of myocardial infarction and target vessel myocardial infarction. A) Myocardial infarction; (B) target vessel myocardial infarction. Study references are provided in* ***Table 1*** *and* ***Table 2****. CI: confidence interval; DL: DerSimonian-Laird; DCB: drug-coated balloon; PCB: paclitaxel-coated balloon*

(Figure 4). Based on the quantitative coronary angiography measurements, the mean minimal lumen diameter at baseline and follow-up were analysed, presenting an SMD of +3.30 (95% CI: 2.64-3.95; I^2=90%) for the limus DCB group and +3.27 (95% CI: 2.69-3.85; I^2=87%) for the PCB group. When comparing the mean MLD of the two groups at follow-up, data from five studies showed no significant difference between the limus DCB and PCB groups, with an SMD of +0.06 (95% CI: –0.07 to 0.18; I^2=0%) **(Figure 4)**. The mean DS was also analysed at baseline and follow-up, presenting an SMD of –3.77 (95% CI: –4.75 to –2.79; I^2=96%) for the limus DCB group and –4.61 (95% CI: –5.15 to –4.08; I^2=79%) for the PCB group. The acute lumen gain from four studies presented an SMD of +0.09 (95% CI: –0.06 to 0.23; I^2=0%) **(Supplementary Figure 2)**. The overall estimated mean DS from six studies **(Supplementary Figure 3)** at follow-up showed a favourable trend towards the PCB group, but this did not reach statistical significance, with an SMD of +0.21 (95% CI: –0.02 to 0.45; I^2=71%).

Finally, the risk of LLL at follow-up (in-segment LLL: 0.4±0.54 mm vs 0.28±0.43 mm; in-lesion LLL: 0.27±0.48 mm vs 0.29±0.43 mm) was similar between the limus DCB and PCB groups, with an SMD of +0.02 (95% CI: –0.18 to 0.23; I^2=70.6%) for in-segment LLL analysis and –0.03 (95% CI: –0.31 to 0.24; I^2=0.0%) for in-lesion LLL analysis **(Figure 5)**. An intragroup analysis was performed for the reference vessel diameter (RVD) at baseline and follow-up, with the limus DCB group presenting an SMD of +0.55 (95% CI: 0.28-0.82; I^2=27%) and the PCB group an SMD of +0.31 (95% CI: –0.09 to 0.70; I^2=62%). Comparing the two groups in terms of the follow-up RVD measurements, there was no significant statistical difference, with an SMD of +0.39 (95% CI: –0.22 to 1.01; I^2=83%) **(Supplementary Figure 4)**. Low heterogeneity was observed among the analysed studies.

Discussion

This is a meta-analysis of 12-month follow-up data from six RCTs including a total of 1,208 patients comparing the main use of paclitaxel- to limus-coated balloons for the treatment of coronary ISR. Our findings indicate that there were no significant differences between PCBs and limus DCBs in the risk of major clinical outcomes, including all-cause mortality, cardiac death, and clinically driven TLR. Limus DCBs achieve at least equal angiographic outcomes compared to PCB without significant differences in LLL during follow-up **(Central illustration)**.

In fact, the management of ISR in the DES era constitutes a considerable clinical and technical challenge, often necessitating revascularisation interventions[5]. Despite ongoing improvement in DES technologies, a substantial rate of ISR with current stent platforms ranging from 1-8% per year has been recorded[18]. To that end, several materials and techniques have been proposed for the optimal management of these

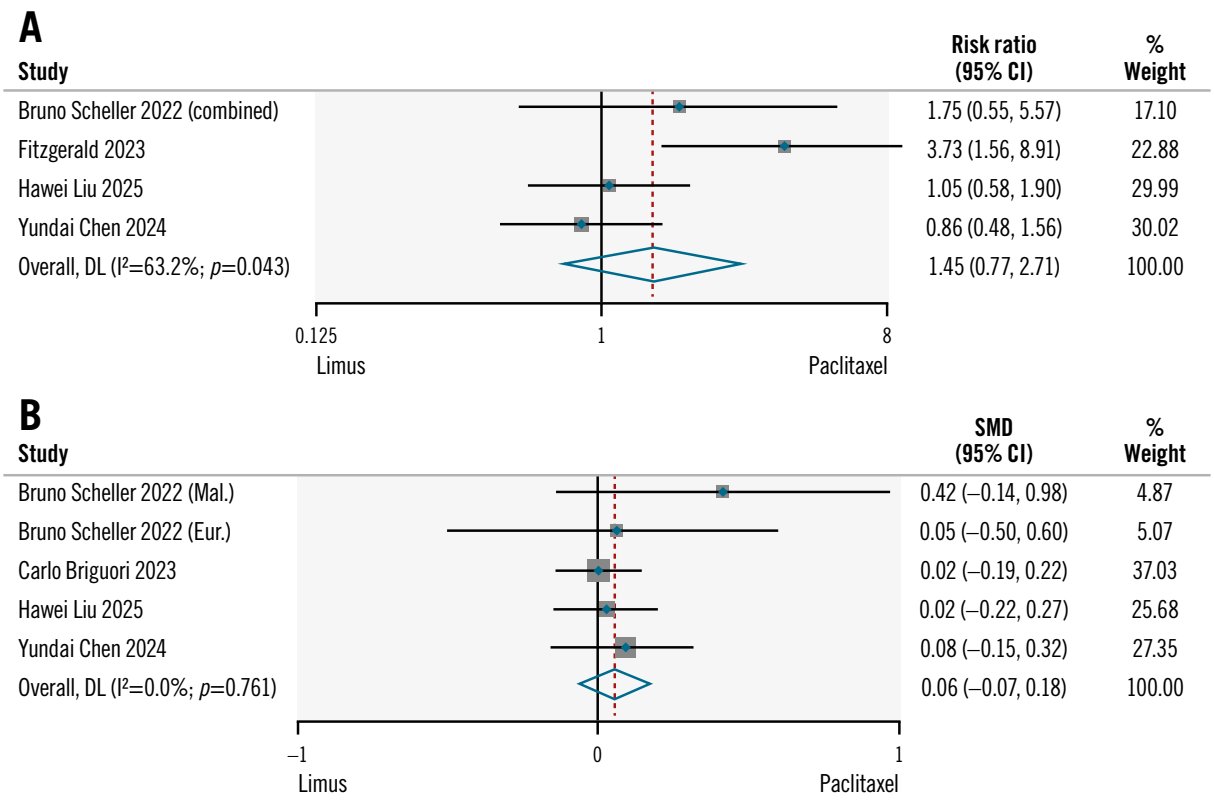


Figure 4. *Comparison of limus DCBs versus PCBs in terms of binary restenosis during the follow-up and minimal lumen diameter post-intervention. A) Binary restenosis; (B) post-intervention minimal lumen diameter. Study references are provided in* ***Table 1*** *and* ***Table 2****. CI: confidence interval; DL: DerSimonian-Laird; DCB: drug-coated balloon; PCB: paclitaxel-coated balloon; SMD: standardised mean difference*

lesions, including angioplasty with cutting or scoring balloons, DCBs, or placement of a new DES. The main advantage of DCBs is their ability to release an antiproliferative drug without leaving an additional metallic layer on the treated lesion. Although this concept seems quite attractive when treating ISR, where additional stent layers could increase the risk of new restenosis, the DAEDALUS analysis of 10 randomised trials demonstrated that DCB angioplasty and repeat stenting with DES are similarly effective and safe in the treatment of BMS-ISR, whereas DCB angioplasty was found to be less effective compared with DES implantation in the treatment of DES-ISR[19]. Nevertheless, DCBs could be the preferred option for less complex restenotic lesions, multilayer ISR cases (to avoid an additional metallic layer), BMS restenosis, and in patients at high bleeding risk to minimise the required duration of dual antiplatelet therapy[5].

Until recently, paclitaxel was the drug of choice for most available DCBs. Owing to its lipophilic properties, paclitaxel rapidly penetrates the cell membrane, binds to the microtubules and inhibits their depolymerisation, thus irreversibly blocking cell division[20]. This mechanism explains the drug's anti-inflammatory and antiproliferative effects. Limus-based drugs, on the other hand, although demonstrating higher safety and efficacy, are characterised by inferior lipophilicity compared with paclitaxel, a characteristic that poses a significant limitation to adequate drug distribution and retention when used in DCBs. However, technological advances have successfully overcome these challenges, with the encapsulation of the drug in a lipophilic nanocarrier leading to the development of limus DCBs with remarkable efficacy in the treatment of both *de novo* coronary lesions and ISR[20,21]. As a result, initial doubts have gradually yielded to restrained enthusiasm regarding the use of limus-coated balloons for ISR, with a history similar to that of limus and paclitaxel DES[22]. In this meta-analysis, sirolimus- and biolimus-coated balloons were pooled into a single limus-coated balloon group. This approach is justified by their shared mechanism of action as mammalian target of rapamycin inhibitors, cytostatic effects on smooth muscle cell proliferation, and favourable endothelial healing profile compared with paclitaxel. The differences between sirolimus and biolimus are mainly in their pharmacokinetic properties (lipophilicity and tissue uptake) rather than their mechanisms.

Particularly for *de novo* coronary lesions, a recent meta-analysis demonstrated similar rates of clinically driven TLR and MACE with limus and paclitaxel DCBs among patients undergoing DCB-only PCI[23]. On the other hand, the risk of TLR seems to be higher in DCB-only PCI for ISR. The analysis of the one-year clinical follow-up of 642 patients enrolled in the EASTBOURNE registry, which evaluated the performance of a sirolimus DCB, showed a considerably higher incidence of TLR in patients treated for ISR compared with those

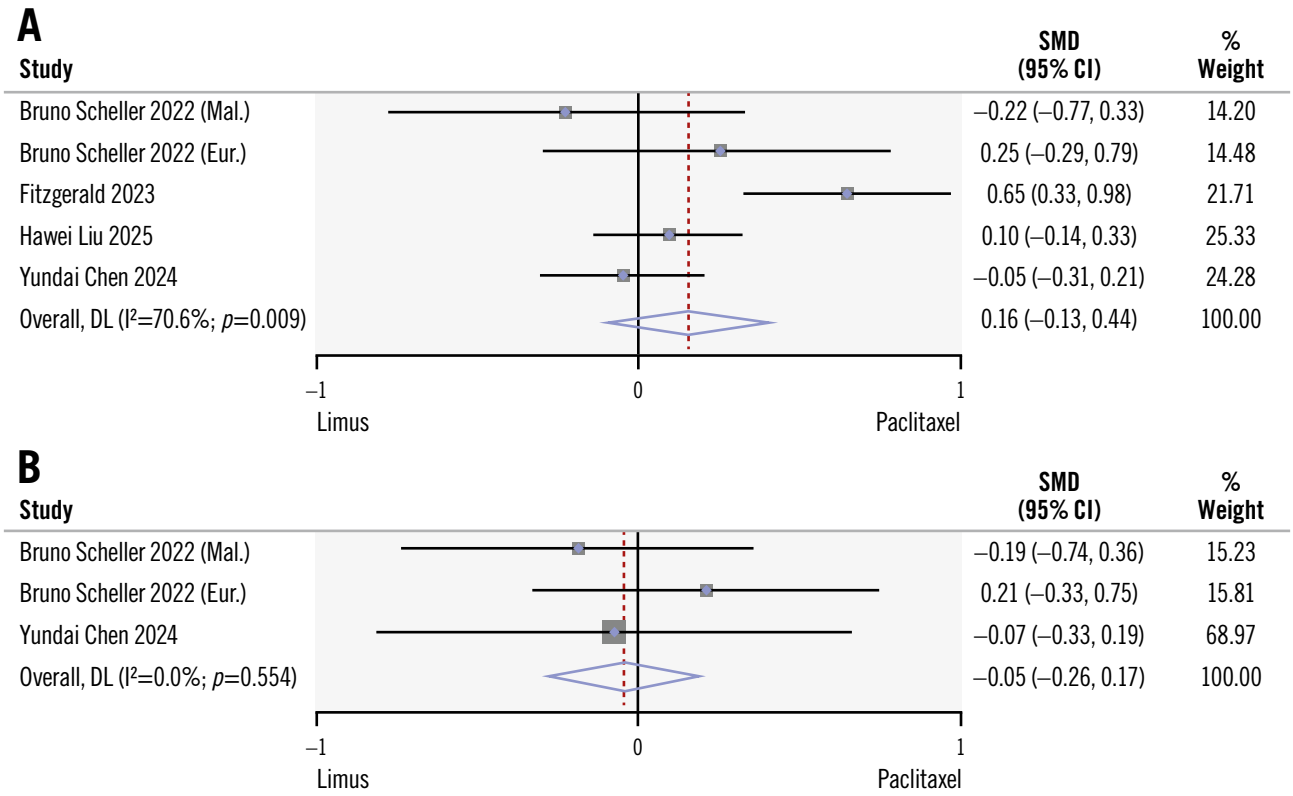


Figure 5. *Comparison of limus DCBs versus PCBs in terms of in-segment and in-lesion late lumen loss during the follow-up. A) In-segment LLL; (B) in-lesion LLL. Study references are provided in* ***Table 1*** *and* ***Table 2****. CI: confidence interval; DL: DerSimonian-Laird; DCB: drug-coated balloon; LLL: late lumen loss; PCB: paclitaxel-coated balloon; SMD: standardised mean difference*

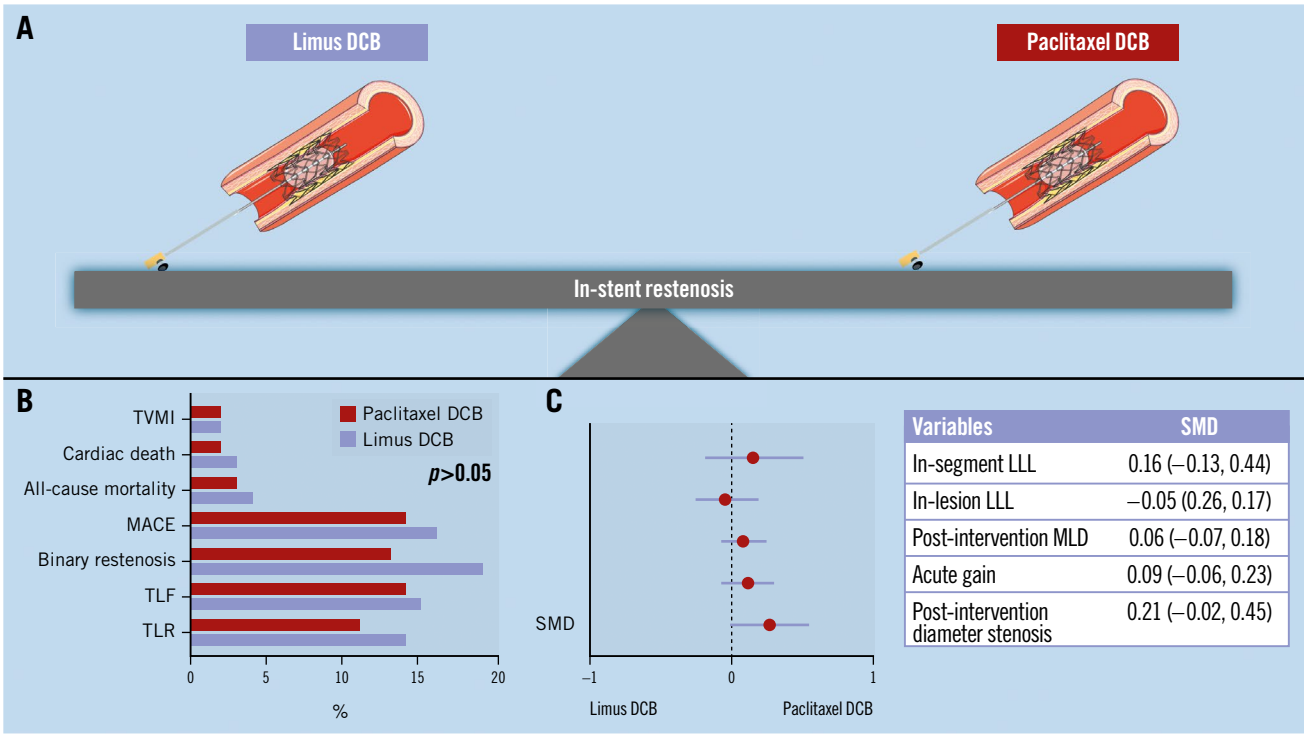
with *de novo* coronary lesions (5.4 vs 0.2%; p=0.0008)[24]. Similar findings were reached in the retrospective analysis of 288 patients treated with the MagicTouch sirolimus-coated balloon (Concept Medical), with higher rates of TLR being observed among patients with ISR (17%) compared to those with *de novo* lesions (9%)[25].

Multiple factors contribute to the higher rates of stenosis recurrence when treating ISR compared to *de novo* lesions. These are mainly procedural issues associated with the placement and condition of the existing stent. Studies using optical coherence tomography have identified several dominant predictors of adverse long-term outcomes when restenting ISR lesions. These include underexpansion of the older stent, the total amount of neoatherosclerotic or peristent calcium as well as the presence of multiple layers of stent struts[26]. Understanding the underlying mechanism of ISR by utilising intracoronary imaging techniques is of crucial importance for planning the optimal treatment strategy and choosing the proper devices for PCI. For instance, it is important to optimise the old stent's expansion and apposition using balloon dilatation when detecting stent underexpansion and underdeployment as the possible cause of restenosis before proceeding to further treatment with a new stent or a DCB. Detection of severe neointimal hyperplasia or neoatherosclerosis as the primary cause of ISR may necessitate the use of debulking strategies prior to DCB or DES implantation, such as cutting and scoring balloons, which create small fissures in the atherosclerotic plaque, allowing for deeper drug penetration[27,28]. Furthermore, advanced technologies such as intravascular lithotripsy and rotational atherectomy provide the potential for more aggressive plaque modification and have demonstrated promising results in the management of failed, underexpanded stents implanted in heavily calcified lesions or severely calcified in-stent neoatherosclerosis[29-31]. All these interventions are essential for optimal lesion preparation before applying DCBs and stent implantation, ultimately contributing to improved long-term outcomes. Indeed, performance of optimised predilatation of the restenotic lesion appears to be a more significant predictor of TLR rates than the specific type of DCB used when treating ISR[13].

To that end, factors related to optimised lesion preparation must be carefully considered when evaluating long-term angiographic outcomes in the comparison between PCBs and limus DCBs for the treatment of restenotic lesions. It is true that the methods utilised for successful lesion preparation are not thoroughly described in the included studies. Of note, though, neither of the two types of DCBs compared in this analysis was associated with worse angiographic outcomes. This comes in contrast with a recent pooled analysis of trials comparing paclitaxel and limus DCBs by Sedhom et al, including both *de novo* and ISR lesions, which associated the use of PCBs with

AsiaIntervention Central **Illustration**

Comparison of limus- versus paclitaxel-coated balloons for treating ISR.



Variables	SMD
In-segment LLL	0.16 (−0.13, 0.44)
In-lesion LLL	−0.05 (0.26, 0.17)
Post-intervention MLD	0.06 (−0.07, 0.18)
Acute gain	0.09 (−0.06, 0.23)
Post-intervention diameter stenosis	0.21 (−0.02, 0.45)

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A) Limus DCBs were equally effective as paclitaxel DCBs; (B) comparison of endpoints; (C) comparison of SMD between variables. Limus-coated balloons are as effective as paclitaxel-coated balloons for treating in-stent restenosis, demonstrating non-inferiority in both clinical and angiographic outcomes at 12 months following the intervention. DCB: drug-coated balloon; LLL: late lumen loss; MACE: major adverse cardiovascular events; MLD: minimal lumen diameter; SMD: standardised mean difference; TLF: target lesion failure; TLR: target lesion revascularisation; TVMI: target vessel myocardial infarction

better late angiographic outcomes, demonstrating lower rates of LLL along with higher rates of late lumen enlargement[23]. A significant limitation of that study is the combination of two distinct lesion types, *de novo* and ISR, within the same analysis. This approach obscures clear results, making it difficult to draw definitive conclusions, as these lesions have significantly different clinical and angiographic outcomes when treated with DCBs[23]. In our meta-analysis, in-segment LLL was slightly higher with PCBs compared with limus DCBs, despite similar in-lesion outcomes. This suggests that edge restenosis – potentially driven by paclitaxel's short diffusion profile, which might cause less drug coverage at balloon edges and the drug "flake-off" phenomenon during catheter transit – may be more prominent with paclitaxel. In terms of ISR, on the other hand, among the studies included in our analysis, it was only the REFORM trial that failed to show non-inferiority for angiographic outcomes for biolimus DCBs compared with PCBs[6]. Possible factors explaining these discrepancies include the inclusion of both BMS and DES-ISR in the REFORM study, as well as variations in the quality and manufacturing process of the biolimus A9-coated balloon.

Aiming to provide more insight into this matter, the ongoing Sirolimus-Coated Balloon Versus Paclitaxel-Coated Balloon for the Treatment of Coronary In-Stent Restenosis trial (SIBLINT ISR; ClinicalTrials.gov: NCT04240444) will randomise 260 participants with ISR to receive either a sirolimus or a paclitaxel DCB. The primary endpoint of this study will be in-segment LLL at 9 months after the intervention.

Limitations

We acknowledge that our analysis is not free from certain limitations. First of all, a substantial number of high-risk patients with complex restenotic lesions were excluded from these trials. In addition to this, the methods utilised for lesion preparation are not thoroughly described in the included studies, though we assumed that all ISR lesions were optimally dilated before applying the DCBs. It was not possible to provide a robust comparative sensitivity analysis between sirolimus- and biolimus-coated balloons or drug-coating dosages due to the small sample size. Within the same context, the use of intravascular imaging modalities that enable detection of the mechanism of ISR

and optimised lesion preparation before DCB application was inconsistent across the included studies. The total number of patients included in this meta-analysis was relatively low, a fact that, in combination with the low rate of clinical events, may also somewhat limit the statistical power of our results.

Conclusions

This meta-analysis of RCTs shows that limus-coated balloons are as effective as paclitaxel-coated balloons for treating ISR, demonstrating non-inferiority in both clinical and angiographic outcomes at 12 months following the intervention. We can observe that there is a trend for slightly better outcomes in the paclitaxel group in terms of luminology, however, without reaching statistical significance, considering the clinical outcomes at 12-month follow-up. These findings support the notion that both types of DCBs constitute an acceptable choice for the treatment of challenging ISR. There is still a need for future trials, though, to evaluate the effectiveness of new-generation DCBs and DES before establishing the best approach for the management of ISR.

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Conflict of interest statement

The authors have no conflicts of interest to declare.

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Supplementary data

Supplementary Table 1. Checklist of reported items of the PRISMA 2020 statement.

Supplementary Table 2. Risk of bias assessment of randomised controlled trials with the Cochrane assessment tool.

Supplementary Figure 1. PRISMA flow diagram.

Supplementary Figure 2. Comparison of limus DCBs versus PCBs in terms of mean acute lumen gain immediately after the intervention.

Supplementary Figure 3. Comparison of limus DCBs versus PCBs in terms of mean diameter stenosis after the intervention.

Supplementary Figure 4. Comparison of limus DCBs versus PCBs in terms of mean reference vessel diameter after the intervention.

Data availability statement.

The supplementary data are published online at: https://AsiaIntervention.pcronline.com/doi/10.4244/AIJ-D-25-00029

Supplementary data

Supplementary Table 1. Checklist of reported items of the PRISMA 2020 statement. Reproduced with permission from[32].

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Done
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	4-5
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	3-4
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	5-6
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	5
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	5
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	6-7
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	7-8
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	5-6
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	6-7
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	7-8
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the	8

		synthesis or presentation of results.	
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	8
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	8
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	8
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	8
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	8
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	8
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	8
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Not applicable
Section and Topic	**Item #**	**Checklist item**	**Location where item is reported**
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Suppl. Figure S1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Suppl. Figure S1
Study characteristics	17	Cite each included study and present its characteristics.	9 and Table 1,2
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Suppl. Table 2
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Figures 1-5 and Suppl. Figures 2-4
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	8-11
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	8-11
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Figures 1-5 and Suppl. Figures 2-4
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	9-10
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	9-11

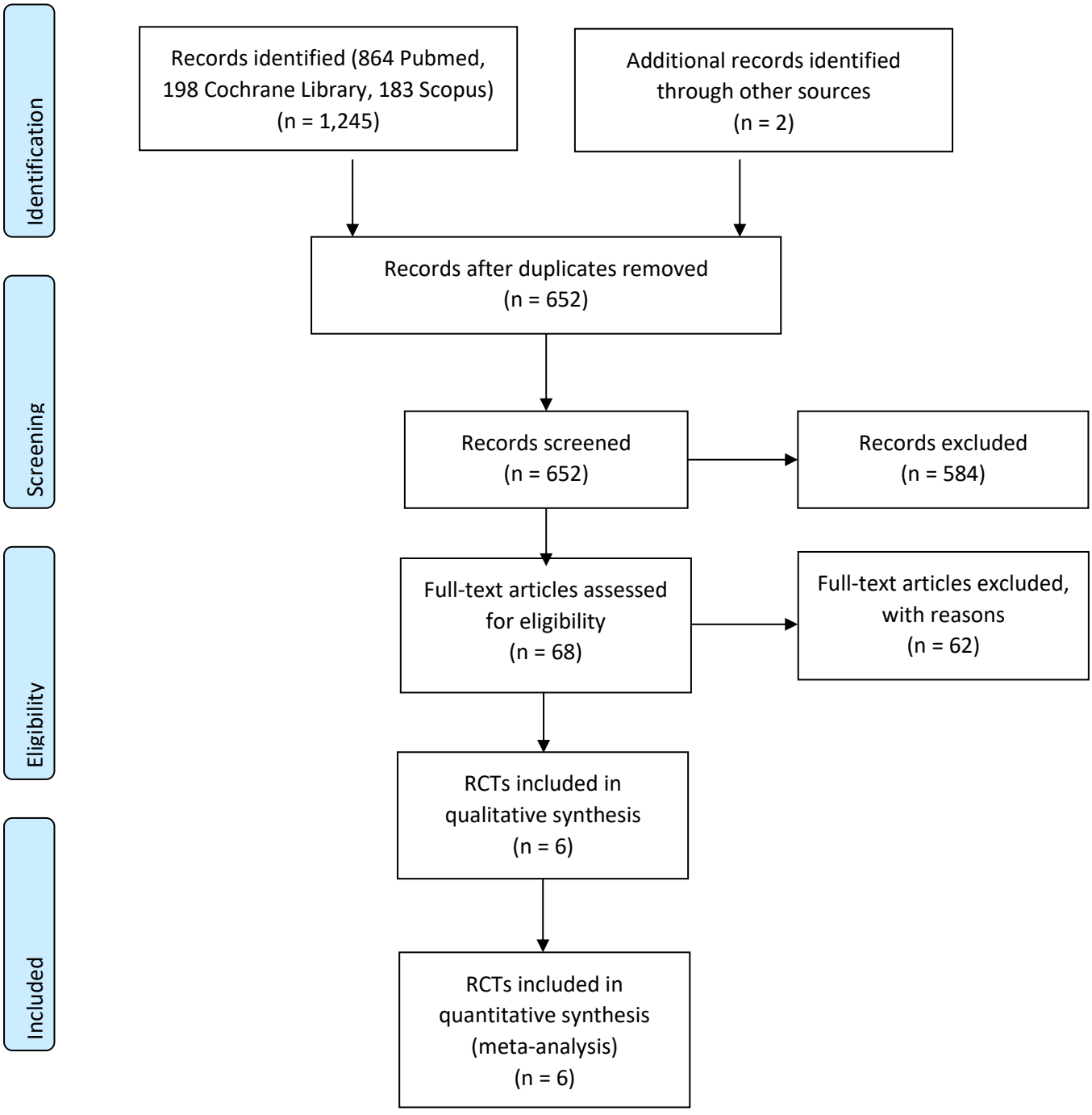
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Not applicable
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	12-14
	23b	Discuss any limitations of the evidence included in the review.	15-16
	23c	Discuss any limitations of the review processes used.	14-16
	23d	Discuss implications of the results for practice, policy, and future research.	12-16
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	5-6
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	5-6
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	No amendments were made
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	17
Competing interests	26	Declare any competing interests of review authors.	17
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	17

For more information, visit: http://www.prisma-statement.org/

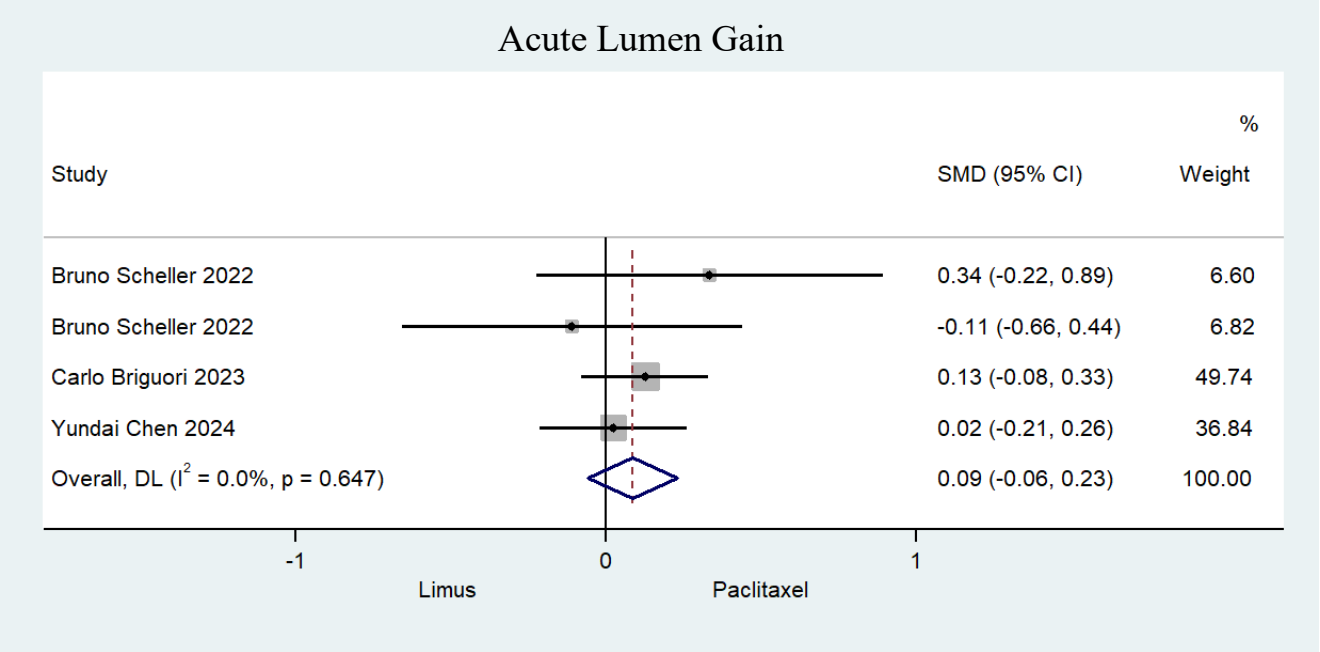
Supplementary Table 2. Risk of bias assessment of randomised controlled trials with the Cochrane assessment tool.

	Random sequence generation *(Selection bias)*	**Allocation concealment** *(Selection bias)*	**Blinding of participants and personnel** *(Performance bias)*	**Blinding of outcome assessment** *(Detection bias)*	**Incomplete outcome data** *(Attrition bias)*	**Selective reporting** *(Reporting bias)*	**Other sources of bias**
B. Scheller et al. 2022 (Malaysia)	+	+	-	+	+	+	+
B. Scheller et al. 2022 (Europe)	+	+	-	+	+	+	+
C. Briguori et al. 2023	+	+	-	+	+	+	+
S. Fitzgerald et al. 2023	+	+	-	+	+	?	+
Y. Han et al. 2024	+	+	-	?	+	?	+
Chen et al. 2024	?	?	-	?	+	?	+

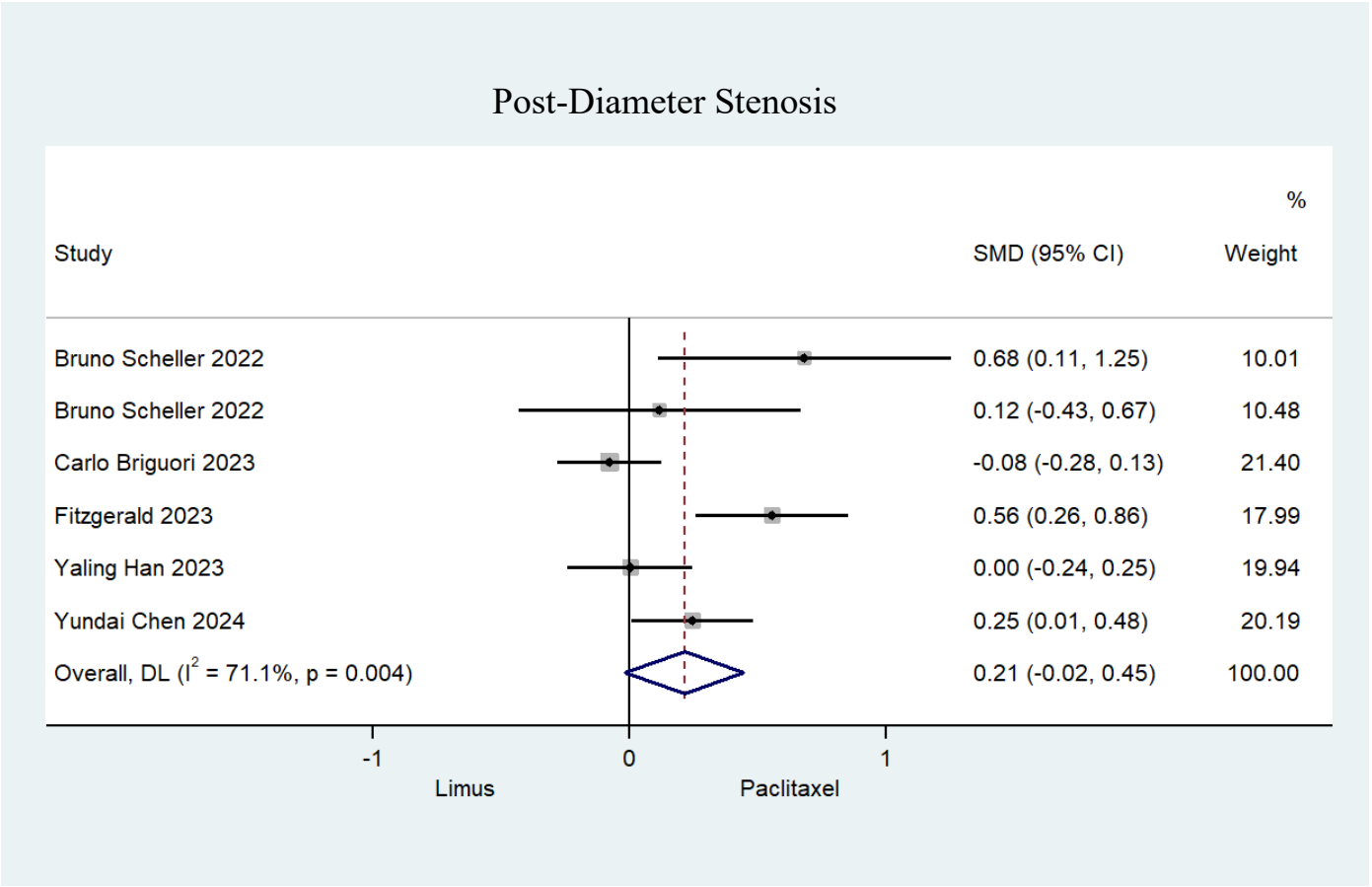
+ = Low risk of bias - = Risk of bias ? = Unclear



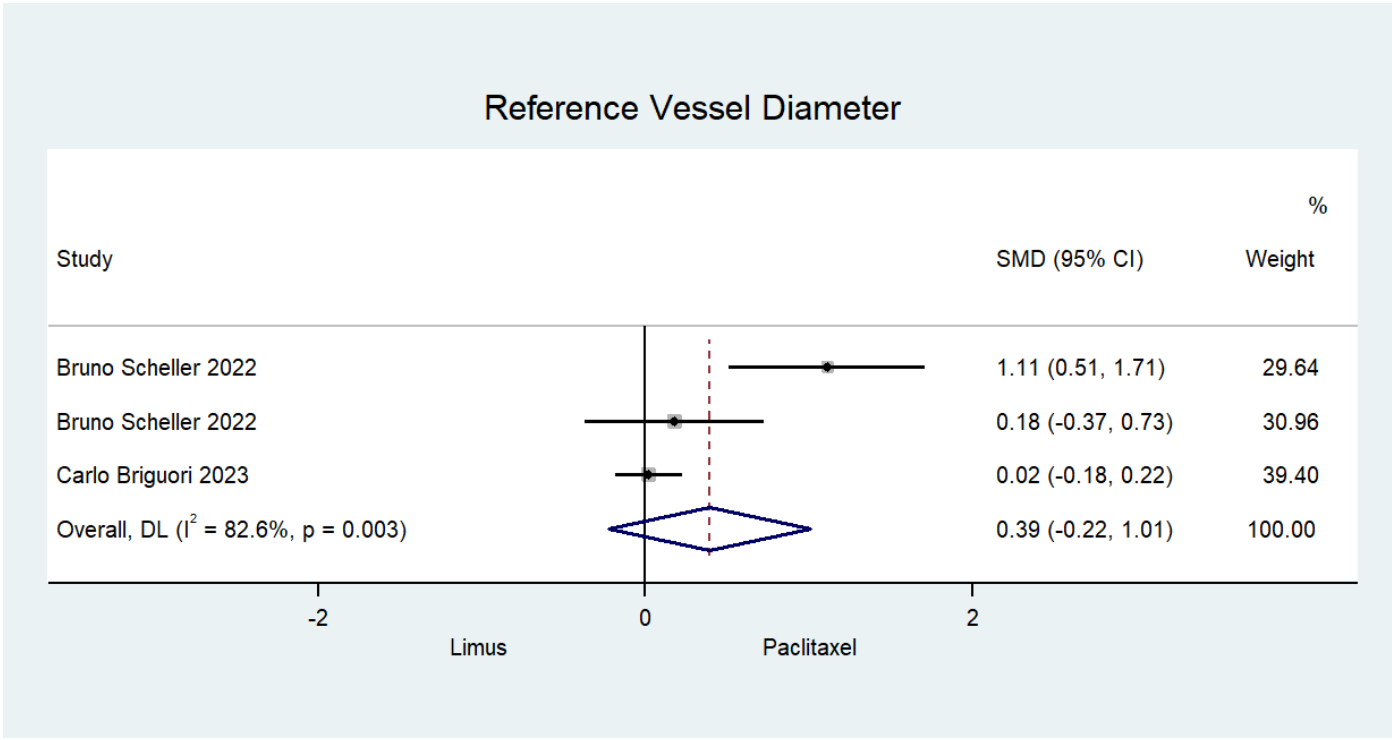
Supplementary Figure 1. PRISMA flow diagram.



Supplementary Figure 2. Comparison of limus DCBs versus PCBs in terms of mean acute lumen gain immediately after the intervention.



Supplementary Figure 3. Comparison of limus DCBs versus PCBs in terms of mean diameter stenosis after the intervention.



Supplementary Figure 4. Comparison of limus DCBs versus PCBs in terms of mean reference vessel diameter after the intervention.

Data availability. Data can be made available by the corresponding author (M. Sagris) upon reasonable request.