Web appendix: Supplementary material

Treatment strategies for coronary in-stent restenosis: a systematic review and hierarchical Bayesian network meta-analysis of 24 randomised trials and 4,880 patients.

Daniele Giacoppo[1], MD; Giuseppe Gargiulo[1], MD; Patrizia Aruta[1], MD; Piera Capranzano[1,2], MD; Corrado Tamburino[1,2], PhD; Davide Capodanno[1,2], PhD.

[1]Catheterization Laboratory, Cardio-Thoracic-Vascular Department, Ferrarotto Hospital, via Citelli, 95124, Catania, Italy

[2] Department of General Surgery and Medical-Surgical Specialties, University of Catania, Italy

LIST OF TRIALS INCLUDED IN THE NETWORK META-ANALYSIS

Alfonso et al.[1]

ARTIST[2]

CRISTAL[3]

Habara et al. (2011)[4]

Habara et al. (2013)[5]

INDEED[6]

ISAR DESIRE[7]

ISAR DESIRE 3[8]

Montorsi et al.[9]

PACCOCATH ISR I/II[10]

PEPCAD II[11]

PEPCAD DES[12]

PEPCAD China ISR[13]

Ragosta et al.[14]

RESCUT[15]

RIBS[16]

RIBS II[17]

RIBS IV[18]

RIBS V[19]

SEDUCE[20]

SISR[21]

Song et al.[22]

TAXUS V ISR[23]

Wiemer et al.[24]

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LIST OF ACRONYMS IDENTIFYING TRIALS INCLUDED IN THE NETWORK META-ANALYSIS

ARTIST = Angioplasty Versus Rotational Atherectomy for Treatment of Diffuse In-Stent Restenosis Trial.

CRISTAL = Cypher Restenosis Intra-Stent Trial. (NCT00323895)

INDEED = Treatment of diffuse IN-stent restenosis with Drug-Eluting stents vs. intracoronary bEta-raDiation therapy.

ISAR DESIRE = Intracoronary Stenting and Angiographic Results: Drug Eluting Stents for In-Stent Restenosis.

ISAR DESIRE 3 = Intracoronary Stenting and Angiographic Results Drug Eluting Stents for In-Stent Restenosis 3: Efficacy Study of Paclitaxel-eluting Balloon, -Stent vs. Plain Angioplasty for Drug-eluting Stent Restenosis. (NCT00987324)

PACCOCATH ISR I/II = Treatment of In-Stent Restenosis by Paclitaxel-Coated PTCA Balloons I/II. (NCT00106587, NCT00409981)

PEPCAD II = Paclitaxel-Eluting PTCA Balloon Catheter in Coronary Artery Disease II. (NCT00393315)

PEPCAD China ISR = A Prospective, Multicenter, Randomized Trial of Paclitaxel-Coated versus Paclitaxel-Eluting Stent for the Treatment of Drug-Eluting Stent In-Stent Restenosis. (NCT01622075)

PEPCAD DES = Treatment of DES-In-Stent Restenosis With SeQuent® Please Paclitaxel Eluting PTCA Catheter. (NCT00998439)

RESCUT = The Restenosis Cutting Balloon Evaluation Trial.

RIBS = A Randomized Comparison of Repeat Stenting With Balloon Angioplasty in Patients With In-Stent Restenosis.

RIBS II = Restenosis Intrastent: Balloon Angioplasty Versus Elective Sirolimus-Eluting Stenting.

RIBS IV = Restenosis Intra-Stent of Bare-Metal Stents IV: Paclitaxel-Eluting Balloon Versus Everolimus-Eluting Stent. (NCT01239940)

RIBS V = Restenosis Intra-Stent of Drug-Eluting Stents V: Paclitaxel-Eluting Balloon Versus Everolimus-Eluting Stent. (NCT01239953)

SEDUCE = Safety and Efficacy of a Drug-Eluting Balloon in Coronary Artery Restenosis. (NCT01065532)

SISR = Sirolimus-Eluting Stent vs. Intravascular Brachytherapy in In-Stent Restenotic Coronary Artery Lesions. (NCT00231257)

TAXUS V ISR = Randomized Trial Evaluating Slow-Release Formulation TAXUS Paclitaxel-Eluting Coronary Stent in the Treatment of In-Stent Restenosis. (NCT00287573)

KEY WORDS USED FOR REPORTS IDENTIFICATION

“restenosis”, “coronary restenosis”, “ISR”, “in-stent restenosis”, “intra-stent restenosis”, “in-segment restenosis”, “percutaneous coronary intervention”, “coronary angioplasty”, “drug eluting stent”, “DES”, “bare metal stent”, “BMS”, “drug eluting balloon”, “DEB”, “drug coated balloon”, “DCB”, “brachytherapy”, “plain balloon angioplasty”, “POBA”, “cutting”, “rotablator”, “rotablation”, “rotational atherectomy”.

SUPPLEMENTARY TABLE 1. Inclusion and exclusion criteria of the trials included in the network meta-analysis

Study	Inclusion Criteria	Exclusion Criteria
ARTIST	Angina and/or objective evidence of target vessel-related ischemia, documented ISR >70% by visual assessment within a stent ±5 mm of the stent edges, stent diameter ≥2.5 mm, ISR as the only lesion for treatment, ISR length of 10-50 mm by visual assessment, and lesion accessible for rotational ablation.	Acute MI within the previous month, LVEF <30%, evidence of intraluminal thrombus or dissection, unprotected ostium lesion, missing visualization of the distal lumen after crossing with a guidewire, stents obviously not fully expanded, stents at or directly distal to a bend >45°, stents implanted within the previous 3 months, stents with a classic coil design that might impair QCA.
RESCUT	Angina or ischemia at functional test, ISR length ≤25 mm.	ISR in a bifurcated stent, MI <72 hours, concomitant angioplasty in another vessel during the same procedure or <30 days, additional BT after the randomised mechanical treatment of ISR by cutting balloon or conventional balloon, lesion located in an internal mammary artery, saphenous vein bypass graft or unprotected left main coronary artery, known allergy to investigational medications.
RIBS	Angina or objective evidence of myocardial ischemia with ISR, lesions amenable to both interventional strategies, first ISR, ISR length ≤32 mm, vessel >2.5 mm.	Lesions located in severely tortuous or calcified vessels and those presenting as total occlusions, prior stent implantation within the previous month, severe concomitant systemic illness, conditions likely to preclude follow-up angiography.
Ragosta et al.	First ISR occurred within 1 year from initial stent placement.	Vessel <2.5 mm, lesions not appropriately treatable by either of the randomised techniques.

Montorsi et al.	ISR >50% diameter stenosis.	N/A
ISAR DESIRE	SA or myocardial ischemia.	Acute MI, left main, DES ISR, allergy to investigational drugs.
Alfonso et al.	>50% ISR, first ISR, ISR length ≤30 mm, lesions amenable to both interventional strategies, vessel ≥2.5 mm.	Severely tortuous or calcified vessels, total occlusions, prior stent implantation <1 month, severe concomitant systemic illness, conditions likely to preclude follow-up angiography.
RIBS II	First ISR, indication for PCI.	Vessel <2.5 mm, ISR length >32 mm, occlusive ISR, ISR <30 days, acute MI, prior brachytherapy, severe disease interfering with follow up, contraindications to investigational medications.
SISR	History of SA or UA or documented silent ischemia, ISR length 15-40 mm, vessel 2.5-3.5 mm, vessel 1 cm distal to the target lesion ≥2.5 mm.	MI <24 hours, LVEF <40%, prior thoracic radiation or intravascular brachytherapy, total occlusions, unprotected left main coronary artery disease with >50% stenosis, treatment of a non-target lesion <30 days or planned after the index study procedure, serum creatinine >2 mg/dL, initial stent placement in the target lesion <4 weeks.
TAXUS V ISR	≥18 years, SA or UA or inducible ischemia, single BMS ISR, native coronary artery, length ≤46 mm, vessel 2.5-3.75 mm.	Left main stenosis, ostium lesion, excessive vessel or lesion calcification, tortuosity, or angulation, bifurcation disease, target lesion occlusion or thrombus, planned atherectomy, prior treatment of the ISR lesion with

		BMS, previous or planned use of brachytheraphy, external beam radiotherapy, any anti-restenotic DES in the target vessel, ataxia-telangiectasia or other known genetic radiation sensitivity disorders, MI ≤72 hours or creatine kinase-MB level >2 times the upper normal limit, LVEF <25%, stroke <6 months, planned CABG <9 months, hemorrhagic diatheses or contraindications or allergy to investigational medications, contrast media or devices, current or future warfarin use anticipated <6 months, chemotherapy <12 months, planned use of colchicine <9 months, serum creatinine level >2.0 mg/dL, leukocyte count <3500/µL or platelet count $<100x10^3$/µL or $>750x10^3$/µL, woman of child-bearing potential without a recent negative pregnancy test or lactating, man or woman with planned procreation <3 months, comorbid conditions limiting life expectancy <24 months or that could affect protocol adherence, planned procedure requiring antiplatelet therapy withdrawal <6 months, current participation in other investigational trials.
INDEED	Diffuse ISR, native coronary artery, angina and documented myocardial ischemia.	MI ≤72 h, serum creatinine >3.0 mg/dL, pregnancy, contraindication to antiplatelet therapy, concomitant serious disease with expected survival of <2 years.
PEPCAD II	≥18 years, SA or UA or silent ischemia	MI <48 hours, eGFR <30 ml/min, hypersensitivity or contraindications to investigational drugs, malignancy with life expectancy <2 years, ISR length >22 mm, ISR <70%, unprotected left main, lesions covering >2 mm side branch.
Habara et al. (2011)	≥18 years, SA.	Recurrent ISR, ACS, PCI with stenting <6 months before, eGFR <30 ml/min, vessel <2.5 mm or >3.5 mm, ISR length ≥26 mm, ostium lesion, left main,

		bifurcations, occlusive ISR, severe systemic disease, conditions precluding angiographic follow up, contraindications.
Wiemer et al.	Diffuse ISR ≥50% limited to the stent body, objective signs of exercise-induced myocardial ischemia.	MI <4 weeks, intolerance to antiplatelet therapy, history of gastrointestinal bleeding, pregnancy, left main coronary artery disease, significant lesion calcification, ISR in arterial or venous bypass-grafts, oral anticoagulation.
PACCOCATH ISR I/II	≥18 years, SA or UA or silent ischemia, single DES or BMS ISR.	MI ≤72 hours, serum creatinine >2.0 mg/dL, ISR length >30 mm, vessel <2.5 mm, heavy calcification, thrombotic burden, malignancy with life expectation <2 years, hypersensitivity or contraindications to investigational medications.
PEPCAD DES	DES ISR (SES,PES,EES), vessel 2.5-3.5 mm, ISR length <22 mm.	Recent MI, cardiogenic shock, recent stroke, bifurcations, ostium lesion, left main, occlusive ISR, thrombotic burden, multiple lesions in the target vessel, platelets <100.000, severe hepatic dysfunction, planned surgery <6 months after, malignancy, contraindications to investigational medications.
Song et al. (Cohort 1)	SA or ACS or inducible ischemia, ISR ≥50% (QCA).	ST-segment elevation MI necessitating primary PCI, LVEF <30% or cardiogenic shock, allergy to drugs, contrast media and devices, left main coronary artery disease >50%, serum creatinine level ≥2.0 mg/dl or dependence on dialysis, terminal illness, elective surgery planned <6 months, participation in another coronary device study or inability to

		follow the protocol.
CRISTAL	≥18 years, SA or UA or silent ischemia, vessel ≥2.25 - ≤4.00 mm, native vessel ISR, ISR length ≤60 mm, <5 mm from proximal or distal stent edge.	MI ≤72 hours, serum creatinine >2.95 mg/dL, previous PCI in the target vessel < 30 days before or planned PCI <30 days after, graft, left main, ostium lesion, thrombotic burden, heavy calcification, bifurcation with side branch ≥2.25 mm requiring stenting, prior brachytherapy in the target vessel, heart transplantation recipient, life expectancy <1 year, contraindications to drugs or devices.
ISAR DESIRE 3	>18 years, ischemic symptoms or ischemia.	eGFR <30 ml/min, STEMI <48 hours, cardiogenic shock, malignancy or severe disease with life expectancy <1 year, high non-compliance risk, left main, graft, allergy or contraindications to drugs or devices, stated or suspected or planned pregnancy.
Habara et al. (2013)	>20 years, SA or UA or inducible ischemia, 1 or 2 ISR lesions (BMS or SES or ZES or EES), vessel ≥2.0 - ≤4.0 mm, ISR length ≤22 mm.	MI ≤72 Hours, coronary intervention <28 days, DES implantation <6 months, CVA <6 months, serum creatinine >1.5 mg/dl, LVEF <30%, proximal/distal tortuosity with angulation >90°, multiple lesions in the target vessel, graft, heavy calcification, left main >50%, bifurcation with side branch >2.0 mm, occlusive ISR, severe systemic disease, hemorrhagic gastric ulcer <6 months, potential pregnancy, childbearing, intolerance to drugs or contrast media.
PEPCAD China ISR	18/80 years, ISR of 70% or ≥50%, ischemia, vessel 2.5-4.0 mm, ISR	MI <7 days, eGFR <30 ml/min, severe CHF or NYHA IV, severe valve disease, stroke < 6 months, extensive thrombotic burden, unprotected left

	length ≤ 30 mm.	main, bifurcations with side branch ≥2.5 mm.
RIBS V	ISR >50%, angina or ischemia.	ISR <30 days, vessel ≤2.0 mm, ISR length >30 mm, acute MI, thrombotic burden, severe renal and hepatic dysfunction, severe peripheral artery disease, life expectancy <1 year, contraindications to investigational medications, major systemic disease interfering with follow up.
SEDUCE	≥18 years, ischemic symptoms, single or multiple Lesion, ISR >70% - <100%, ISR length <24 mm, vessel ≥2.0 - ≤4.0 mm, patients eligible for PCI, patients willing to undergo clinical/angiographic follow up.	LVEF <30%, serum creatinine >2.0 mg/dl, bifurcations, left main, previous brachytherapy, planned major surgery <6 months, life expectancy <1 year, pregnancy or breastfeeding, allergy to investigational medications.
RIBS IV	20-85 years, >50% DES ISR, angina or silent ischemia, ISR amenable for balloon angioplasty and stenting.	Undefined stent location, ISR <1 month, thrombotic burden, vessel <2.0 mm, ISR length >30 mm, ISR not involving a stent, occlusive ISR, <1 month ISR, acute MI, thrombotic burden, life expectancy <1 year, female in childbearing age, probable non-compliance to follow up angiography, intolerance to investigational medications, LVEF <25%.

ACS=Acute Coronary Syndrome; BMS=Bare-Metal Stent; BT=Brachytherapy; CHF=Chronic Heart Failure; CVA=Cerebrovascular Accident; DES=Drug-Eluting Stent; EES=Everolimus-Eluting Stent; eGFR=Estimated Glomerular Filtration Rate; ISR=In-Stent Restenosis; LVEF=Left Ventricular Ejection Fraction; MI=Myocardial Infarction; NYHA=New York Heart Association; PCI=Percutaneous Coronary Intervention; PES=Paclitaxel-Eluting Stent; QCA=Quantitative Coronary Angiography; SA=Stable Angina; SES=Sirolimus-Eluting Stent; STEMI=ST-Elevation Myocardial Infarction; UA=Unstable Angina; ZES=Zotarolimus-Eluting Stent.

SUPPLEMENTARY TABLE 2: Investigational devices characteristics in the network subanalysis plain balloon-drug-coated balloon-drug-eluting stent.

Study	Treatments Specifications		
	PB	**DCB**	**DES**
ISAR DESIRE	Not Specified	-	• Stainless Steel Sirolimus-Eluting (CYPHER) • Stainless Steel Paclitaxel-Eluting (TAXUS)
RIBS II	Not Specified	-	Stainless Steel Sirolimus-Eluting (CYPHER)
PEPCAD II	-	Paclitaxel-Eluting (SeQuent Please)	Stainless Steel Paclitaxel-Eluting (TAXUS Libertè)
Habara et al. (2011)	Not Specified	Paclitaxel-Eluting (SeQuent Please)	-
PACCOCATH ISR I/II	Orbus X	Paclitaxel-Eluting (Orbus X DCB)	-
PEPCAD DES	Not Specified	Paclitaxel-Eluting (SeQuent Please)	-
CRISTAL	Not Specified	-	Stainless Steel Sirolimus-Eluting (CYPHER)
ISAR DESIRE 3	Not Specified	Paclitaxel-Eluting (SeQuent Please)	Cobalt-Chromium Paclitaxel-Eluting (TAXUS Libertè)

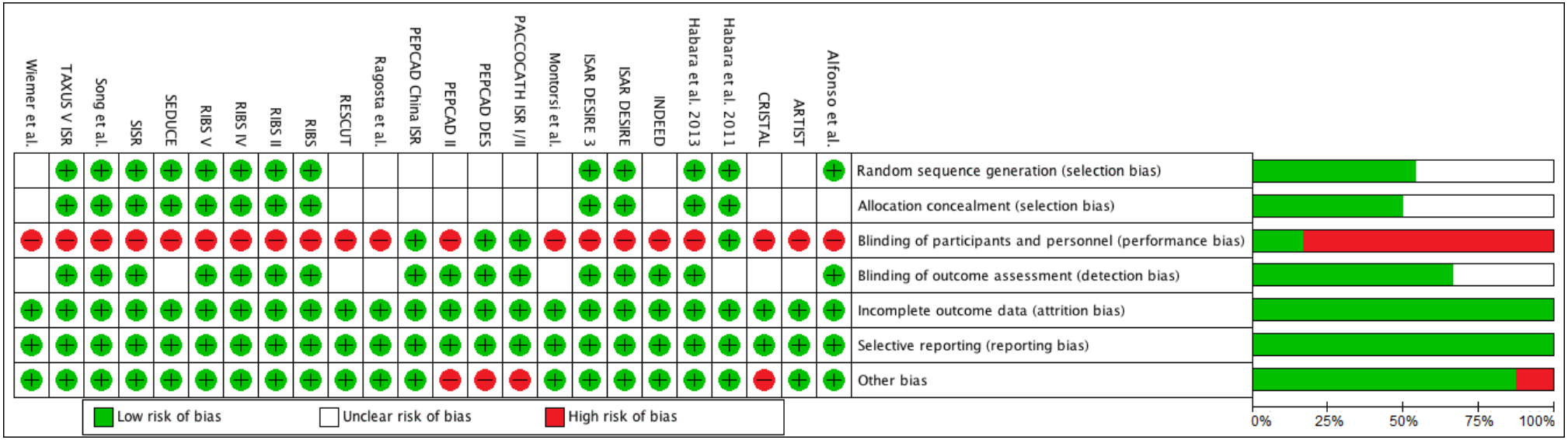
Habara et al. (2013)	Not Specified	Paclitaxel-Eluting (SeQuent Please)	-
PEPCAD China ISR	-	Paclitaxel-Eluting (SeQuent Please)	Stainless Steel Paclitaxel-Eluting (TAXUS Libertè)
RIBS V	-	Paclitaxel-Eluting (SeQuent Please)	Cobalt-Chromium Everolimus-Eluting (XIENCE Prime)
SEDUCE	-	Paclitaxel-Eluting (SeQuent Please)	Cobalt-Chromium Everolimus-Eluting (XIENCE V/ XIENCE Prime)
RIBS IV	-	Paclitaxel-Eluting (SeQuent Please)	Cobalt-Chromium Everolimus-Eluting (XIENCE V/ XIENCE Prime)

SUPPLEMENTARY TABLE 3: Dual antiplatelet therapy duration following in-stent restenosis treatment in the network subanalysis plain balloon-drug-coated balloon-drug-eluting stent.

Study	DAPT Duration		
	PB	**DCB**	**DES**
ISAR DESIRE	≥6 Months	-	≥6 Months
RIBS II	9 Months	-	9 Months)
PEPCAD II	-	3 Months	6 Months
Habara et al. (2011)	≥3 Months	≥3 Months	-
PACCOCATH ISR I/II	1 Month	1 Month	-
PEPCAD DES	6 Months	6 Months	-
CRISTAL	1 Month	-	≥6 Months
ISAR DESIRE 3	≥6 Months	≥6 Months	≥6 Months

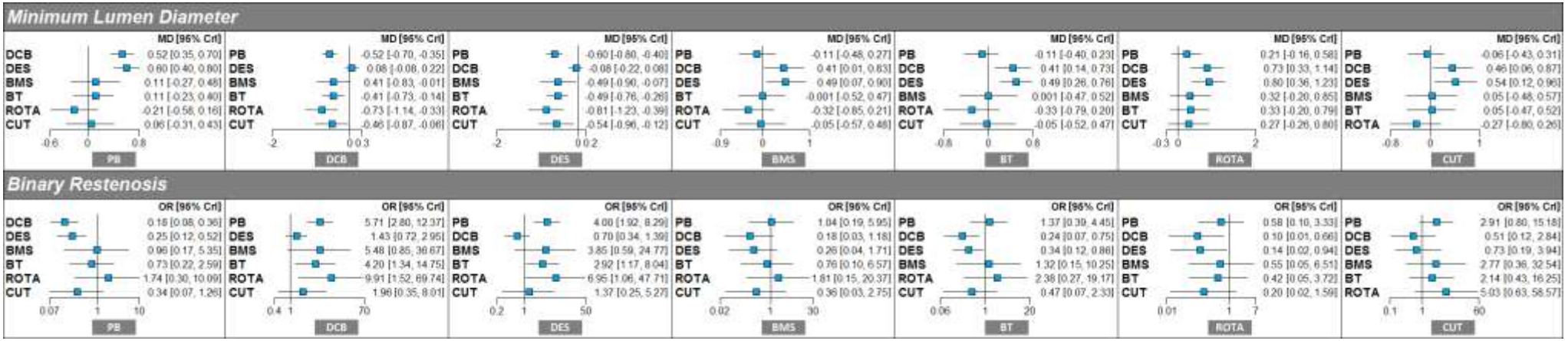
Habara et al. (2013)	≥3 Months	≥3 Months	-
PEPCAD China ISR	-	12 Months	12 Months
RIBS V	-	3 Months	12 Months
SEDUCE	-	N/A	N/A
RIBS IV	-	3 Months	12 Months

SUPPLEMENTARY FIGURE 1: Bias assessment.



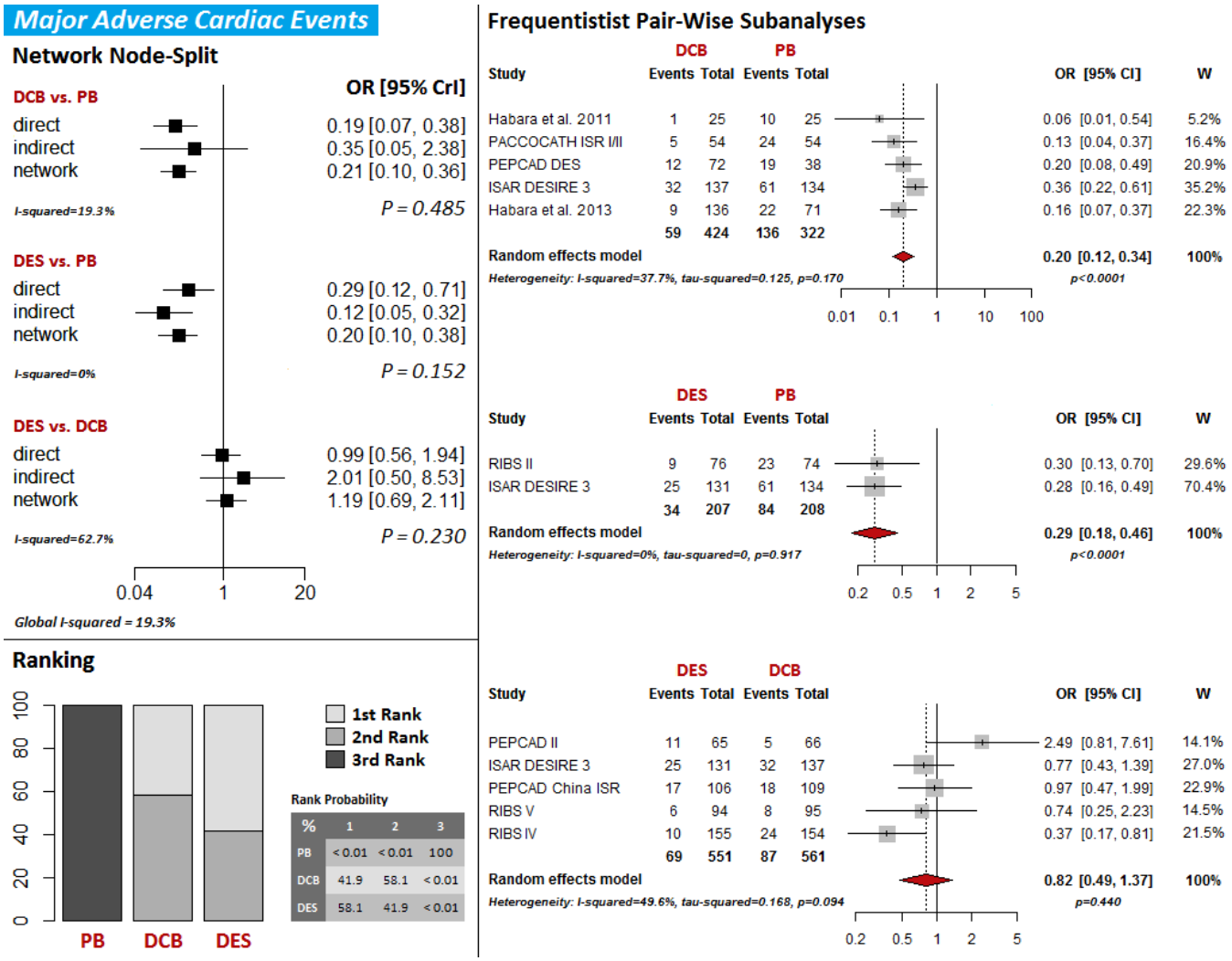
The figure shows the bias assessment according to the Cochrane Collaboration recommendations. Available judgments for each of the seven specific domains (sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, completeness of outcome data, selective reporting of outcome, other potential sources of bias such as remarkable conflict of interests or selective financial support from industries) are shown. Almost all trials were open-label but this is an unavoidable consequence of the very different constitutive properties of the devices under investigation that - with few exceptions - do not allow concealment.

SUPPLEMENTARY FIGURE 2: Effect of interventional treatments on minimum lumen diameter and binary restenosis



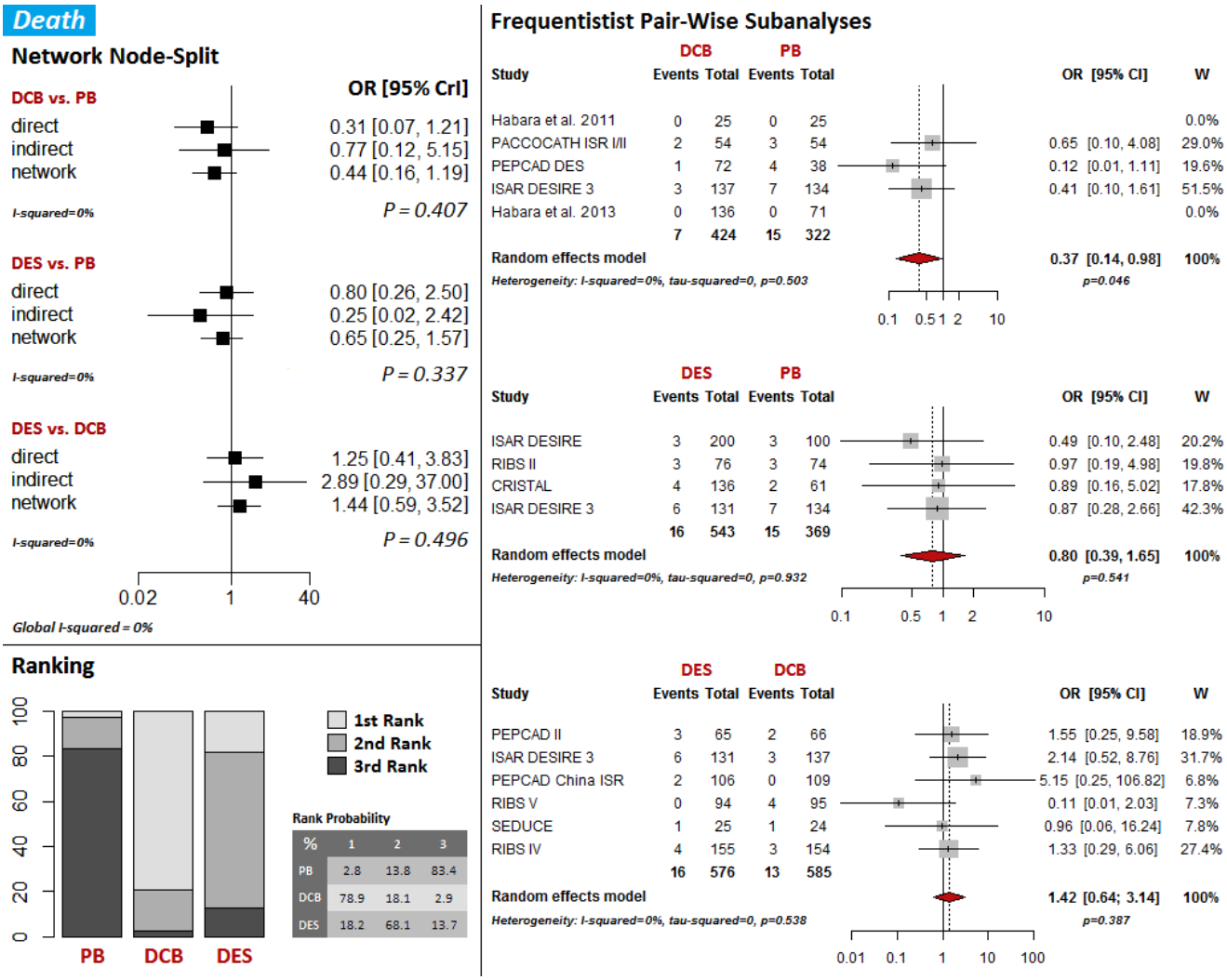
The relative effect of each treatment as compared with a common reference is displayed using forest plots. Minimum lumen diameter (MLD) and binary restenosis (BR) at follow up were in agreement with the distribution of treatment effects observed for target lesion revascularisation (TLR) and late lumen loss (LLL). I^2 values: MLD=45.4%; BR=59.4%. PB=Plain Balloon; DCB=Drug-Coated Balloon; DES=Drug-Eluting Stent; BMS=Bare-Metal Stent; BT=Brachyteraphy; ROTA=Rotational Atherectomy; CUT=Cutting Balloon; OR=Odds Ratio; CrI=Credible Interval.

SUPPLEMENTARY FIGURE 3: Major Adverse Cardiac Events (network subanalysis plain balloon-drug-coated balloon-drug-eluting stent).



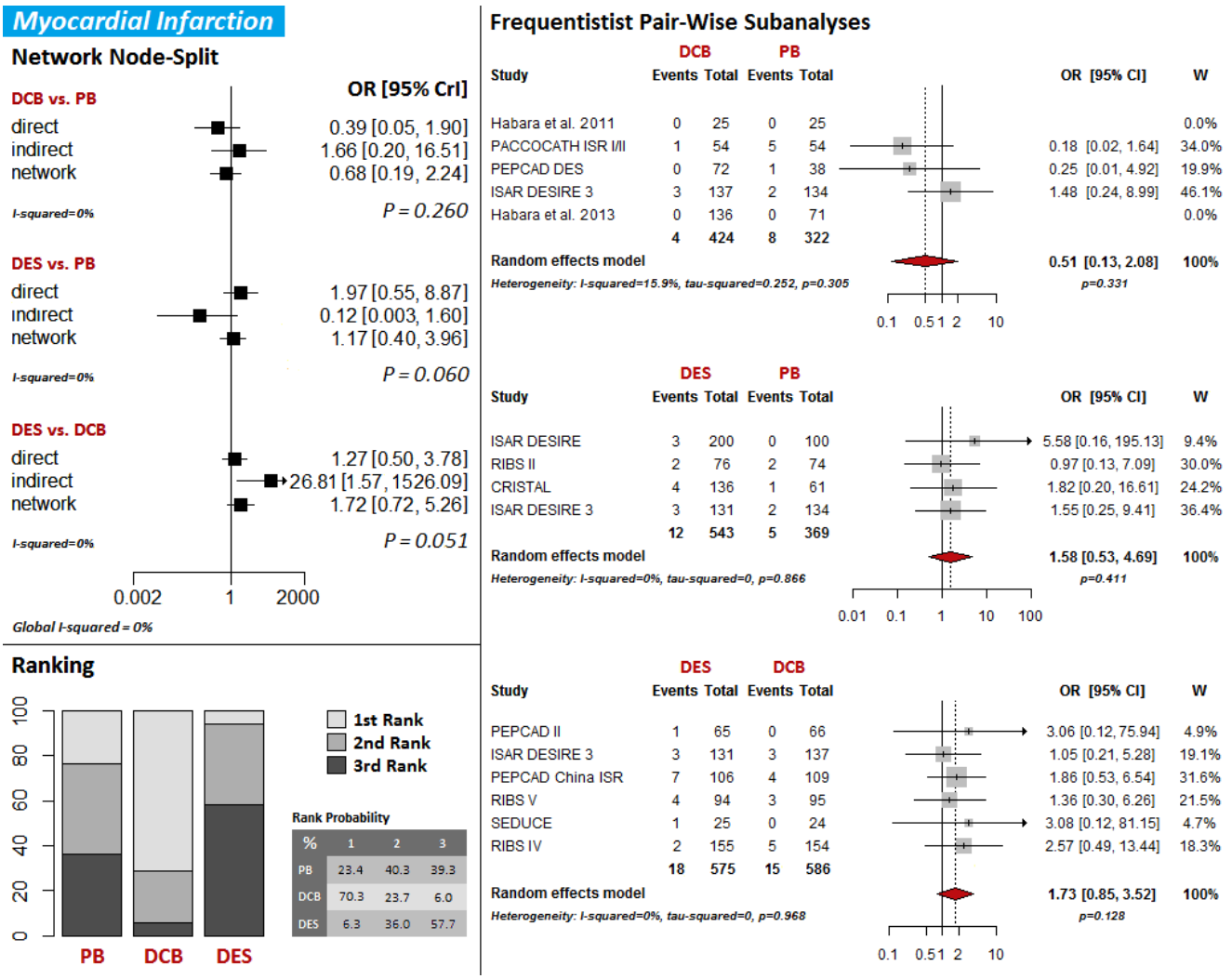
At network meta-analysis the risk reduction was consistent comparing DCB with PB and DES with PB. Pair-wise Bayesian results were in agreement with standard frequentist comparisons. PB=Plain Balloon; DCB=Drug-Coated Balloon; DES=Drug-Eluting Stent; OR=Odds Ratio; CrI=Credible Interval; CI=Confidence Interval.

SUPPLEMENTARY FIGURE 4: Death (network subanalysis plain balloon-drug-coated balloon-drug-eluting stent).



At network meta-analysis there was a trend favoring DCB and DES as compared with PB. However, the low number of events did not allow for definite conclusions. Pair-wise Bayesian results were in agreement with standard frequentist comparisons. PB=Plain Balloon; DCB=Drug-Coated Balloon; DES=Drug-Eluting Stent; OR=Odds Ratio; CrI=Credible Interval; CI=Confidence Interval.

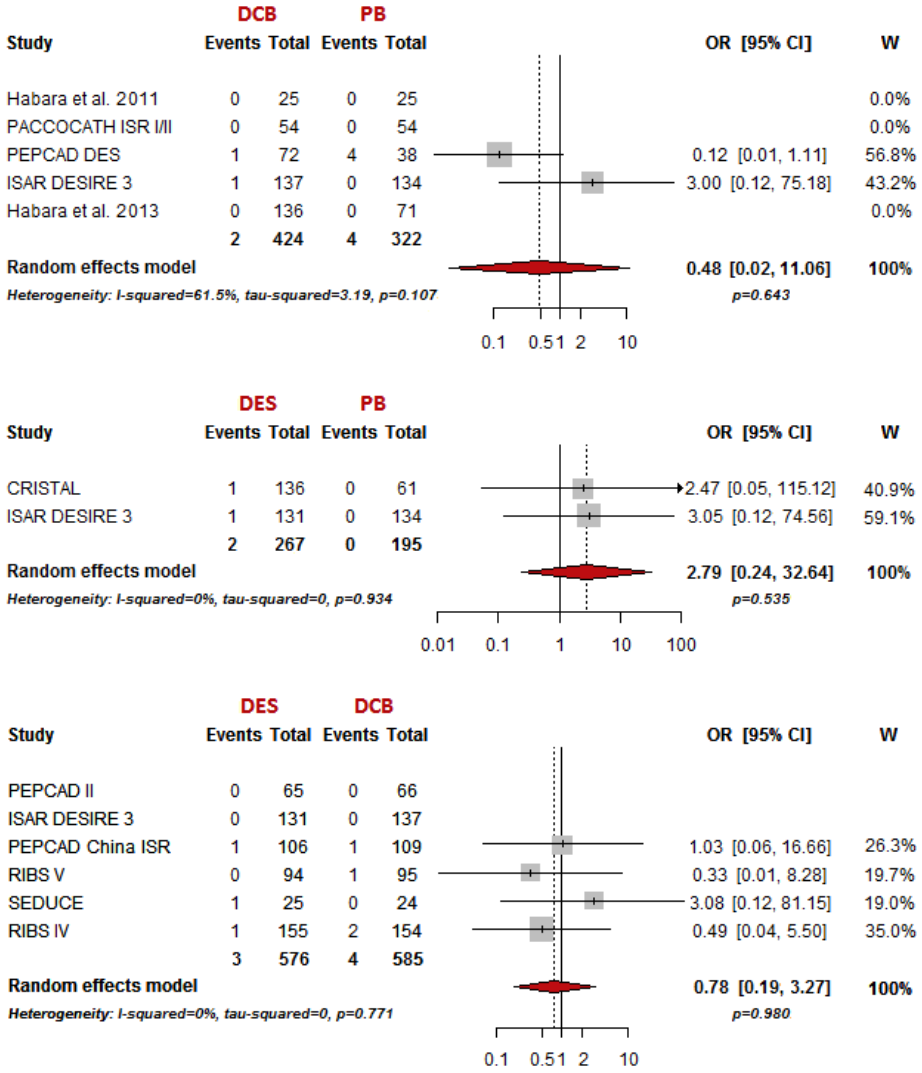
SUPPLEMENTARY FIGURE 5: Myocardial infarction (network subanalysis plain balloon-drug-coated balloon-drug-eluting stent).



At network meta-analysis drug-eluting stent (DES) implantation produced a mild excess in myocardial infarction (MI) as compared with plain balloon (PB) and drug-coated balloon (DCB). At pair-wise frequentist meta-analysis the risk increase associated with DES did not reach the statistical significance and the low number of events did not allow drawing definite conclusions.

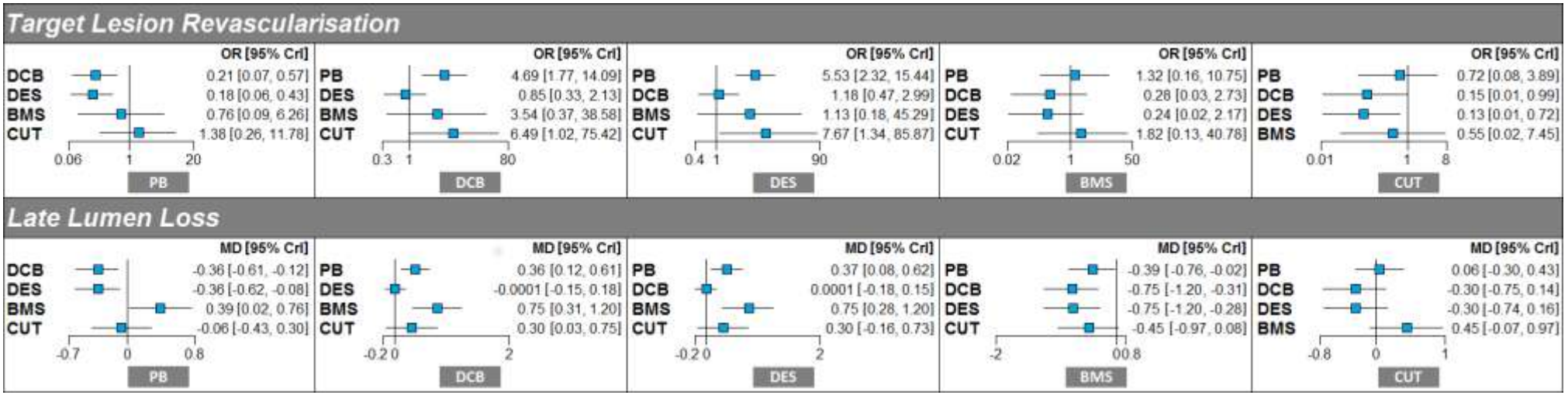
OR=Odds Ratio; CrI=Credible Interval; CI=Confidence Interval.

SUPPLEMENTARY FIGURE 6: Stent thrombosis.



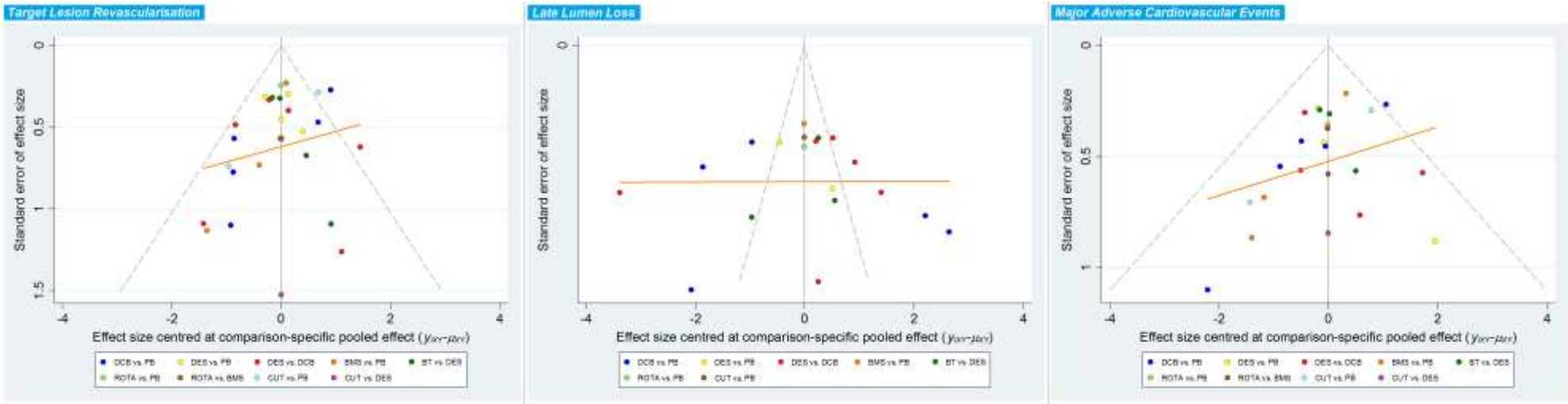
Stent thrombosis was not significantly different among treatments.

SUPPLEMENTARY FIGURE 7: Network subanalysis excluding brachytherapy and rotational atherectomy nodes and applying a study size filter of ≥50 patient per arm.



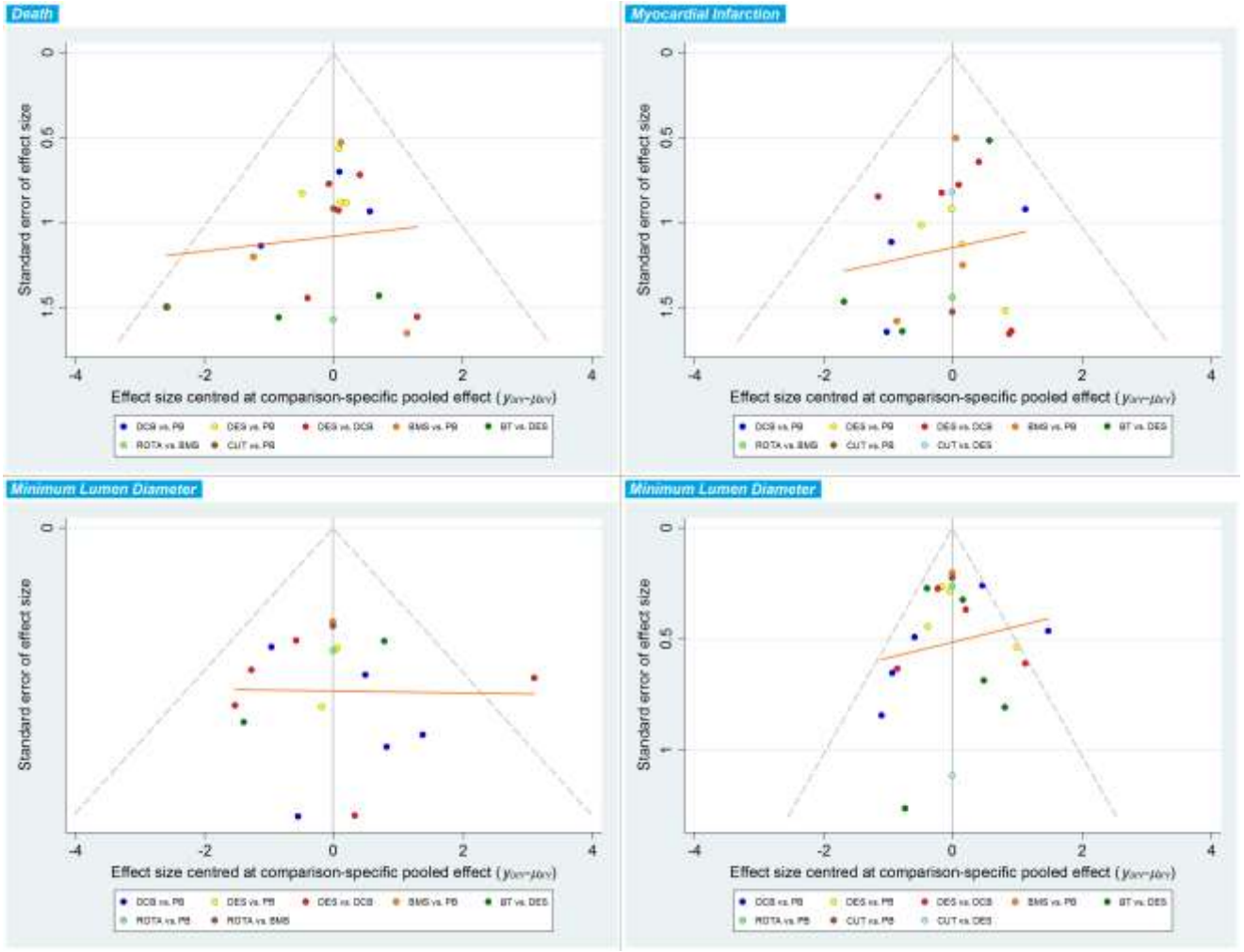
Main results were not different following removal of obsolete treatments and small trials. PB=Plain Balloon; DCB=Drug-Coated Balloon; DES=Drug-Eluting Stent; BMS=Bare-Metal Stent; CUT=Cutting Balloon; OR=Odds Ratio; MD=Mean Difference; CrI=Credible Interval.

SUPPLEMENTARY FIGURE 8: Comparison-adjusted funnel plots for the primary endpoints and major adverse cardiac events.



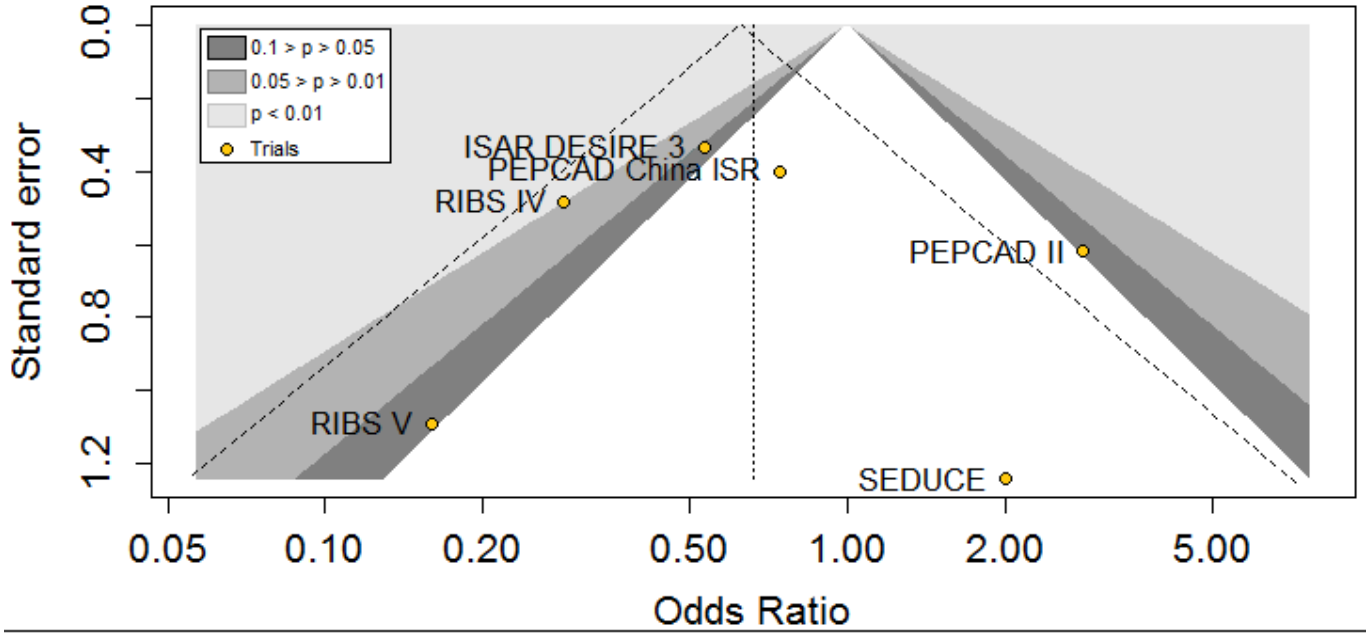
PB=Plain Balloon; DCB=Drug-Coated Balloon; DES=Drug-Eluting Stent; BMS=Bare-Metal Stent; BT=Brachyteraphy; ROTA=Rotational Atherectomy; CUT=Cutting Balloon.

SUPPLEMENTARY FIGURE 9: Comparison-adjusted funnel plots for the secondary endpoints.



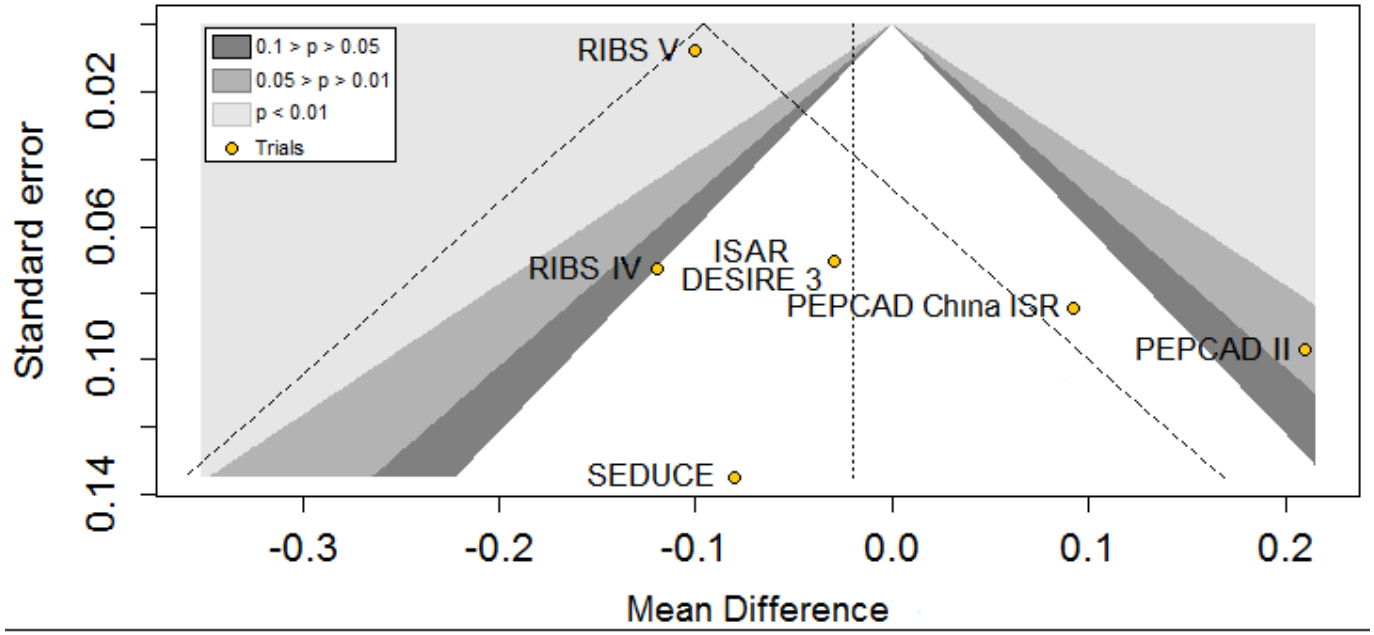
PB=Plain Balloon; DCB=Drug-Coated Balloon; DES=Drug-Eluting Stent; BMS=Bare-Metal Stent; BT=Brachyteraphy; ROTA=Rotational Atherectomy; CUT=Cutting Balloon; OR=Odds Ratio; CrI=Credible Interval.

SUPPLEMENTARY FIGURE 10: Contour-enhanced funnel plot (drug-eluting stent versus drug-coated balloon) implemented with tests for publication bias and small-study effect for target lesion revascularisation.



Peters' Test: slope -1.254, t = 1.420, p = 0.229

SUPPLEMENTARY FIGURE 11: Contour-enhanced funnel plot (drug-eluting stent versus drug-coated balloon) implemented with tests for publication bias and small-study effect for late lumen loss.



PRISMA Checklist for accepted manuscripts

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3-4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6-7
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	NA
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	7-8
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7-8
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	8-9
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	8

Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8-9
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	9
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	9-10
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	10
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	9-10
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	11
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	11
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Appendix
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	12-15
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	12-15
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	11-15
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	12-15
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	16-21
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	21-3
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	23-24
FUNDING			

Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	25