Heliyon 10 (2024) e27521

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Research article

Comparative efficacy of interventional therapies and devices for coronary in-stent restenosis: A systematic review and network meta-analysis of randomized controlled trials

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ARTICLE INFO

Keywords:
Percutaneous coronary intervention
Drug-eluting stent
Drug-coated balloon
Coronary in-stent restenosis
Network meta-analysis

ABSTRACT

Background: In-stent restenosis (ISR) has become a significant obstacle to interventional therapy for atherosclerotic cardiovascular disease. The optimal percutaneous coronary intervention (PCI) strategy for patients with coronary ISR remains controversial. This network meta-analysis (NMA) was aimed to compare and estimate the effectiveness of different PCI strategies and commercial devices for the treatment of patients with coronary ISR.

Methods: In present study, we systematically searched PubMed, Embase, Web of Science, and Cochrane Library from database inception to October 20, 2022, to identify randomized controlled trials. We included studies comparing various PCI strategies for the treatment of any type of coronary ISR. The study was registered with PROSPERO, CRD 42022364308.

Results: We included 44 eligible trials including 8479 patients, 39 trials comparing the treatment effects of 10 PCIs, and 5 trials comparing the efficacy between different types of drug-eluting stent (DES) or drug-coated balloon (DCB) devices. Among the PCIs, everolimus-eluting stent was the optimal strategy considering target lesion revascularization (TLR), percent diameter stenosis (% DS), and binary restenosis (BR), and sirolimus-coated balloon was the optimal strategy considering late lumen loss (LLL). In the comparison of commercial devices, the combination strategy excimer laser coronary angioplasty plus SeQuent Please paclitaxel-coated balloon showed promising therapeutic prospects.

Conclusions: DCB and DES remain the preferred treatment strategies for coronary ISR, considering both the primary clinical outcome (TLR) and the angiographic outcomes (LLL, BR, %DS). Personalized combination interventions including DCB or DES hold promise as a novel potential treatment pattern for coronary ISR.

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https://doi.org/10.1016/j.heliyon.2024.e27521
Received 26 May 2023; Received in revised form 29 February 2024; Accepted 1 March 2024
Available online 8 March 2024

Abbreviation

BA	Balloon angioplasty
BMS	Bare-metal stent
BR	Binary restenosis
CBA	Cutting balloon angioplasty
CI	Credibility interval
DCB	Drug-coated balloon
DES	Drug-eluting stents
EES	Everolimus-eluting stent
ELCA	Excimer laser coronary angioplasty
IQR	Interquartile range
ISR	In-stent restenosis
IVL	Intravascular lithotripsy
LLL	Late lumen loss
MACE	Major adverse cardiac events
MD	Mean differences
MI	Myocardial infarction
NA	Not applicable
NMA	Network meta-analysis
OR	Odds ratio
PB	Plain balloon
PCB	Paclitaxel-coated balloon
PCI	Percutaneous coronary intervention
RCT	Randomized controlled trial
ROTA	Rotational atherectomy
SCB	Sirolimus-coated balloon
SD	Standard deviation
SES	Sirolimus-eluting stent
ST	Stent thrombosis
SUCRA	Surface under the cumulative ranking curve
TLR	Target lesion revascularization
VBT	Vascular brachytherapy
ZES	Zotarolimus-eluting stent
%DS	Percent diameter stenosis

1. Introduction

Atherosclerotic cardiovascular disease is a severe health hazard worldwide. The development of interventional therapy is slowing the increase in the number of associated deaths, but in-stent restenosis (ISR) in the culprit coronary artery and its complications have become major obstacles to interventional therapy. Notably, patients with certain underlying diseases, such as diabetes and chronic kidney disease, are at significantly higher risk of developing ISR or stent thrombosis (ST) [1]. Fortunately, advances in coronary drug-eluting stent (DES) technology have greatly improved the efficacy and safety of percutaneous coronary interventions (PCIs), which has significantly reduced the risk of ISR to approximately 5%–10% [2]. However, the absolute incidence of ISR is still surging owing to the increase of patients receiving PCIs, and treating ISR remains intractable given the sub-optimal clinical and angiographic prognosis and high recurrence rate of ISR [3,4]. Therefore, it is an important topic of clinical research to develop PCI treatment strategies suitable for different types of ISR cases to improve the prognosis of ISR patients and raise the survival quality of life after treatment [5].

Over the past two decades, various PCI strategies have been used to treat ISR as the primary effective management, such as balloon angioplasty (BA), including plain balloon (PB) and cutting balloon angioplasty (CBA); vascular brachytherapy (VBT); rotational atherectomy (ROTA), bare-metal stent (BMS); drug-coated balloon (DCB), including paclitaxel-coated balloon (PCB) and sirolimus-coated balloon (SCB); and DES, including paclitaxel-eluting stent (PES), sirolimus-eluting stent (SES), everolimus-eluting stent (EES), and zotarolimus-eluting stent (ZES) [3]. However, the efficacy of PCIs varies, and controversies still exist regarding the optimal strategy [6,7].

Current European clinical guidelines recommend either DES or DCB as Class IA for the treatment of patients with BMS- or DES-ISR [8]. In the most recent American College of Cardiology (ACC)/American Heart Association (AHA) coronary revascularization guidelines, repeated DES is recommended for Class IA when using PCI for the treatment of ISR [9]. In the United States, DCBs are not approved for the commercial use of coronary interventions. Previous studies have suggested that DES or DCB is the optimal treatment for most cases of ISR, but comparisons of their efficacy and safety have not been adequately elucidated [10,11]. Siontis et al.

recommended using EES since they found it produced the best angiographic and clinical results, and they also recommended DCB since it provided promising results without adding an additional stent layer [12]. However, there are still many unresolved issues, such as inadequate comprehensive evaluation of the efficacy of newer PCI strategies, including the new generation of DES and DCB, and particularly EES, due to the limitations of randomized controlled trials (RCTs). Meanwhile, no studies have compared different types of commercial devices.

Therefore, in the present network meta-analysis (NMA) study, we included more RCTs comparing the newer generation of DES (such as EES and ZES) and DCB (such as SCB), which enriched the RCTs on EES and the diversity of PCIs. We combined all available direct and indirect evidence to comprehensively estimate the treatment efficacy and inform clinical practice to prevent recurrence and improve prognosis by comparing the effectiveness of different types of PCIs (including older and novel interventions) and different types of DCB or DES commercial devices.

2. Methods

This systematic review and NMA was performed according to a prospectively registered protocol (PROSPERO CRD 42022364308) and was written based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extension statement and PRISMA 2020 statement (Supplementary Table 1) [13,14].

2.1. Information sources and search

We searched the Cochrane Library, PubMed, Embase, and Web of Science from the date of database inception to Oct 20, 2022. We restricted English as the language of publication without applying any date, year, or publication status restrictions. We tried to contact researchers and relevant study authors to supplement incomplete reports or obtain information about specific studies. Comprehensive details on the search strategy are provided in Supplementary Table 2. In addition, we searched for other eligible trials in the reference lists of retrieved publications and reviews of relevant studies.

2.2. Eligibility criteria

For the NMA, we included all RCTs comparing different PCI strategies for the treatment of any type of coronary ISR. Currently, ISR is defined as a $\geq$50% stenosis of the coronary vessel diameter at the stent segment and/or the 5-mm segment adjacent to the stent as detected by angiography [3]. RCTs comparing two or more types of PCI strategies for coronary ISR were eligible for inclusion [12]. Inclusion criteria were as follows [1]: RCTs in patients with coronary ISR [2]; patients of any age, gender, ethnicity, and clinical presentation [3]; any type of ISR, including previously implanted BMS and DES (BMS- and DES-ISR) [4]; first-time or recurrent ISR [5]; the same type of PCI but different types of devices, such as the comparison of Agent PCB and SeQuent Please PCB; and [6] a study comparing excimer laser coronary angioplasty plus PCB (ELCA + PCB) with PCB was included in the comparison of different types of DCB and DES devices. Exclusion criteria were as follows [1]: patients with non-coronary ISR were excluded, such as de novo coronary stenosis and ISR in non-native coronaries (such as aortocoronary venous bypass grafts) [2]; non-RCTs were excluded [3]; studies comparing non-PCIs for the treatment of coronary ISR were excluded [4]; comparisons of different doses of the same treatment measure were excluded (e.g., different doses of VBT) [5]; studies with combined interventions were excluded when comparing the efficacy of 10 PCIs (e.g., ELA + BA versus BA); and [6] RCTs with ongoing and unavailable data were excluded.

We did not subdivide BA into PB and CBA because they show equivalent efficacy in the treatment of ISR and are commonly used as pre-dilatation methods at present. BA alone is rarely used as a single treatment in coronary interventions. The primary role of balloon dilation is to pre-treat the lesion before the intervention strategy to increase efficacy. Lesion preparation with conventional balloons (plain or cutting balloons) or non-conventional balloons (e.g., scoring balloons) prior to treatments (e.g., brachytherapy, stents, and DCBs) is not considered as a combined intervention [11,12].

2.3. Interventions and outcomes

For all included trials, we evaluated 10 types of PCIs: BA, VBT, ROTA, BMS, PCB, SCB, ZES, EES, SES, and PES. To explore the potential influence of different DES or DCB commercial devices, we also evaluated different types of DCB and/or DES devices, including SeQuent Please PCB, XIENCE EES, Cypher SES, Taxus PCB, LONGTY PCB, Shenqi PCB, Restore PCB, Agent PCB, Promus EES, and ELCA + SeQuent Please PCB.

The primary clinical outcome was target lesion revascularization (TLR) as a measurement of clinical efficacy. When TLR was not available, we used target vessel revascularization (TVR) as a replacement. As secondary outcomes, we analyzed major adverse cardiovascular events (MACE), all cause death, myocardial infarction (MI), and ST (definite or probable). Angiographic follow-up outcomes included percent diameter stenosis (%DS), late lumen loss (LLL), and binary restenosis (BR). TLR was defined as any revascularization due to recurrent stenosis of the target lesion segment, which included percutaneous and surgical intervention. TVR was defined as any revascularization of the target vessel (including percutaneous or surgical intervention). MACE was defined as the composite of death, MI, TVR, or TLR, which were slightly adjusted according to the specific situation. LLL was defined as the angiographic difference in minimum lumen diameter of the target lesion between immediately after the intervention and at follow-up. The definitions of TLR, TVR, MI, ST, and all cause death were in accordance with the Academic Research Consortium criteria [15]. If there were multiple follow-up reports for the same study, we chose the one with the longest available angiographic or clinical

follow-up time as the endpoint. If one study included two non-overlapping patient groups, we considered them as two separate studies [12]. We prioritized events associated with in-segment restenosis; if unavailable, we included events associated with in-lesion restenosis.

2.4. Data collection

Pairs of independent reviewers (from GST, BCC, WX, LTT, ZZY and CXY) selected the studies, reviewed the titles, abstracts, full texts, and supplementary materials, extracted the available information from the included trials, and assessed the risk of bias. Using a structured form, we extracted from all eligible studies the study characteristics (year of publication, number of participants); participant characteristics (age, sex, restenosis type, and other baseline characteristics); intervention characteristics (PCI strategy, device type); potential effect modifiers; and follow-up time and outcomes (clinical and angiographic outcomes) [11]. When in doubt, we tried to contact the authors of the study to clarify whether the two trials reported shared the same participants [16]. We also tried to contact study authors for missing or unclear outcome data, and we made the utmost effort to ensure the integrity and reliability of the included data [17]. Any discrepancies in study inclusion or data collection were carefully examined and resolved by discussion with other review team members (LZ and YMF).

2.5. Risk of bias

Pairs of independent reviewers (from GST, YJW, HWX and MDD) independently appraised the risk of bias of each included RCT by using the Cochrane risk of bias tool (RoB 2) consisting of the following seven perspectives: random sequence generation, allocation concealment, the blind method for participants and personnel, the blind method for outcome assessment, selective report, incomplete outcome data, and other bias [18]. Each perspective was classified at three levels: “unclear” (lack of relevant information or uncertain bias), “high” (high bias), and “low” (low bias). Review Manager 5.4 was used to visualize the results of the risk bias assessment for the included literature.

2.6. Statistical analysis

Transitivity is the crucial underlying assumption of an NMA [19]. We assessed network transitivity by estimating characteristics of eligible studies: average patient age, proportion of sex, underlying disease conditions, length of clinical and angiographic follow-up, and risk of bias assessment [20]. Studies were eligible for data synthesis if the distribution of study characteristics was identified as sufficiently comparable. The NMA package in Stata 17 software was used to draw network plots, funnel plots, forest plots, rankograms, and cumulative ranking curves for each intervention. Network relationship plots for outcomes were used to show which PCIs had been compared within the RCTs visually. The nodes represent individual interventions, and lines connecting nodes indicate direct comparisons between different interventions in a study. The size of a node correlates with the number of participants. The width of a line is proportional to the number of trials comparing the corresponding pair of treatments [21]. Funnel plots were used to assess the existence of small-study effects and publication bias for each treatment pair. We analyzed the consistency and inconsistency of each outcome in the treatment network to evaluate the stability of the results [22]. We then performed NMA of all outcomes using a random effects model based on a frequentist framework, assuming equal heterogeneity across all comparisons [16]. We included multi-arm trials, accounting for the inherent correlation between their treatment arms [19]. Analyses were conducted according to the intention-to-treat principle.

We estimated summary odds ratios (ORs) as effect size indicators for dichotomous outcomes (TLR, ST MI, all cause death, MACE, BR) with their 95% confidence intervals (CIs) according to the data availability [23,24]. The mean differences (MDs) acted as effect size indicators for continuous outcomes (%DS, LLL) with their 95% CIs. $P < 0.05$ was considered to indicate statistical significance. We assessed the relative probability of a PCI being the best strategy by calculating mean treatment rankings and the surface under the cumulative ranking curve (SUCRA) [25]. SUCRA was used to estimate the overall ranking of each treatment, as a higher SUCRA value means better efficacy.

2.7. Patient and public involvement

No patients or public members were directly involved in this study since no primary data were collected. Several authors of this study regularly come into contact with coronary ISR or coronary heart disease patients and discuss the benefits and harms of PCIs during their routine clinical practice. The experiences from these interactions were considered during this systematic review’s planning, conduct, and reporting [19].

3. Result

3.1. Search results

From 5976 records initially retrieved from the search results, we included 44 RCTs (encompassing 8479 people with coronary ISR) that were eligible for inclusion in the systematic review after screening and selection. Fig. 1 shows each phase of the screening process. Overall, 39 RCTs compared 10 types of PCIs with each other, and 5 RCTs compared the effectiveness of different DCB or DES devices.

To ensure that the included trials were as informative as possible, we divided this NMA into two arms; one compared different types of PCIs for treating coronary ISR (as shown in Fig. 2), and the other compared different DCB and/or DES devices (as shown in Fig. 3). There was an overlap between the trials of these two arms. Comprehensive network diagrams for each of the two main study arms display the number of strategies investigated and the number of comparisons conducted among them (Supplementary Fig. 82 and Supplementary Fig. 83).

3.2. Characteristics of included trials

The full description of included study characteristics is in Table 1 [26–85]. A total of 1767 (20.8%) patients received BA, 1088 (12.8%) VBT, 282 (3.3%) ROTA, 298 (3.5%) BMS, 1381 (16.3%) PCB, 25 (0.3%) SCB, 146 (1.7%) ZES, 761 (9.0%) EES, 1057 (12.5%) SES, and 842 (9.9%) PES (in 39 studies). The remaining five studies containing 832 (9.8%) patients compared different devices or combinations. The publication year ranged from 2001 to 2021, the clinical follow-up ranged from 6 to 60 months, and the angiographic follow-up ranged from 6 to 9 months. The included participants had a mean age of 64 years, were prevalently male (73.6%), and the prevalence of diabetes was highly variable across trials (14.0%–74.0%). Almost 20 (45.5%) trials included only BMS-ISR patients, 13 (29.5%) trials included only DES-ISR patients, 7 (15.9%) trials included both BMS-ISR and DES-ISR patients, and 4 (9.1%) trials were unclear. Supplementary Tables 3 and 4 provide detailed follow-up results on the clinical outcomes (TLR, all cause death, MI, ST MACE) and angiographic outcomes (LLL, %DS, BR) of all ISR patients included in each study.

3.3. Risk of bias

The included 44 RCTs were assessed for risk of bias (Supplementary Table 5). Studies were at low risk of bias as follows: 25 (57%) studies in random sequence generation, 14 (32%) in allocation concealment, 5 (11%) in blinding of participants and personnel, 25 (57%) in blinding of outcome assessment, 34 (77%) in incomplete outcome data, 28 (64%) in selective reporting, and 34 (77%) in other bias. The visualization results of bias within each study are displayed in Supplementary Fig. 1. In addition, 31 (70%) of 44 trials had high risk of bias in blinding of participants and personnel.

3.4. Publication bias

The funnel plots of all outcomes are presented in Supplementary Sections 1 and 2. The funnel plots indicated that a majority of the scatter points, representing included studies, were evenly distributed on both sides and were essentially symmetric, suggesting no publication bias in the present study [86].

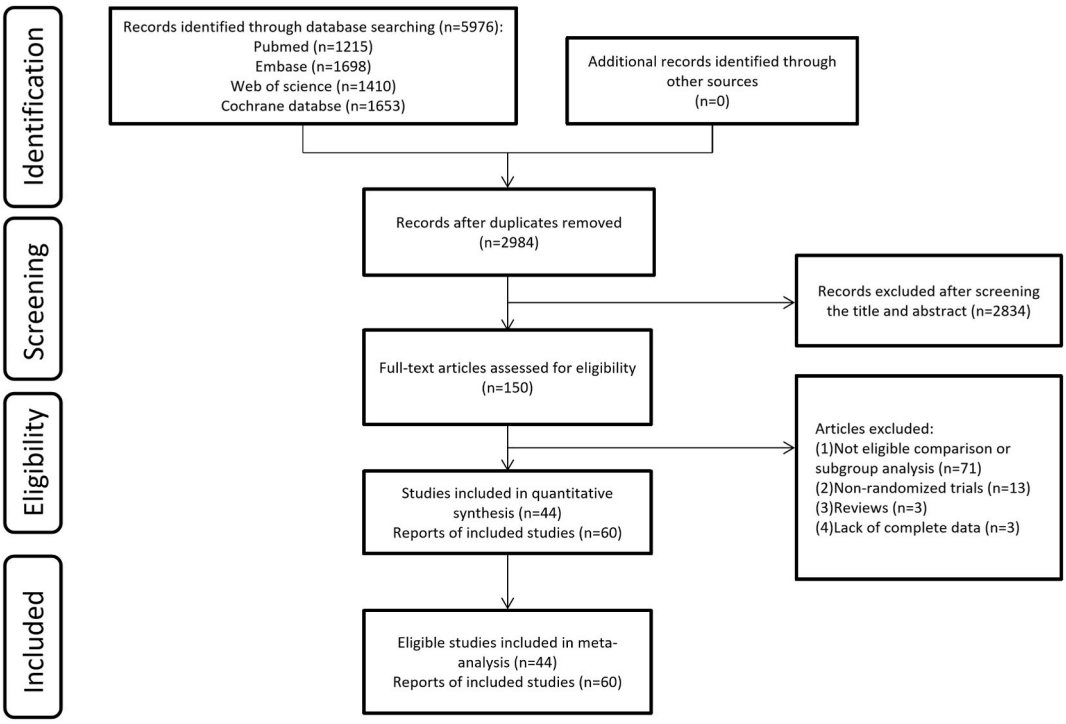

Fig. 1. Flow diagram of trials search and screening.
The studies by Ragosta et al. and Song et al. each had two cohorts that were considered as two separate studies.

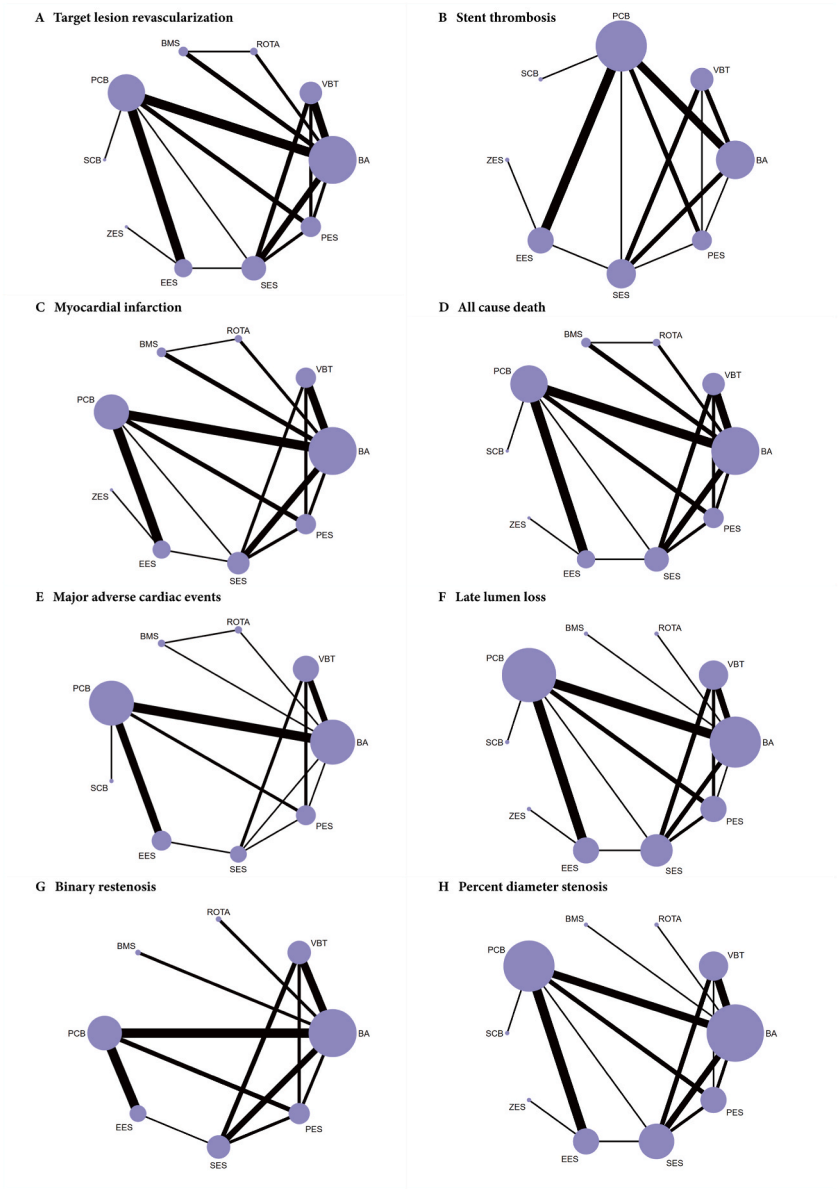

Fig. 2. Network evidence plots of eligible direct comparisons for each outcome in comparison of 10 types of PCIs.
Each circle (node) represents an interventional therapy, and lines between nodes represent direct comparisons. The size of a node correlates with the number of participants. The width of a line is proportional to the number of trials comparing each pair of treatments. BA = balloon angioplasty; BMS = bare-metal stent; EES = everolimus-eluting stent; ELCA = excimer laser coronary angioplasty; PCB = paclitaxel-coated balloon; ROTA = rotational atherectomy; SCB = sirolimus-coated balloon; SES = sirolimus-eluting stent; VBT = vascular brachytherapy; ZES = zotarolimus-eluting stent.

3.5. Comparison of 10 types of PCIs

3.5.1. Clinical outcomes

Clinical outcomes included TLR, ST, MI, death, and MACE, among which TLR was the primary clinical outcome. Fig. 4A shows the ORs and 95% CIs for TLR comparing various PCIs. The cumulative ranking curves and rankograms show all five outcomes (Fig. 3 and Supplementary Section 1).

3.5.1.1. TLR. Thirty-nine RCTs including 7578 participants reported 1514 (20.0%) TLR events in the comparison of 10 types of PCIs. We mainly judged the treatment effect based on the SUCRA, where a larger SUCRA indicates a higher ranking of treatment effect, and we used the ranking probability as a secondary judgment criterion. Considering TLR, according to the cumulative ranking curves

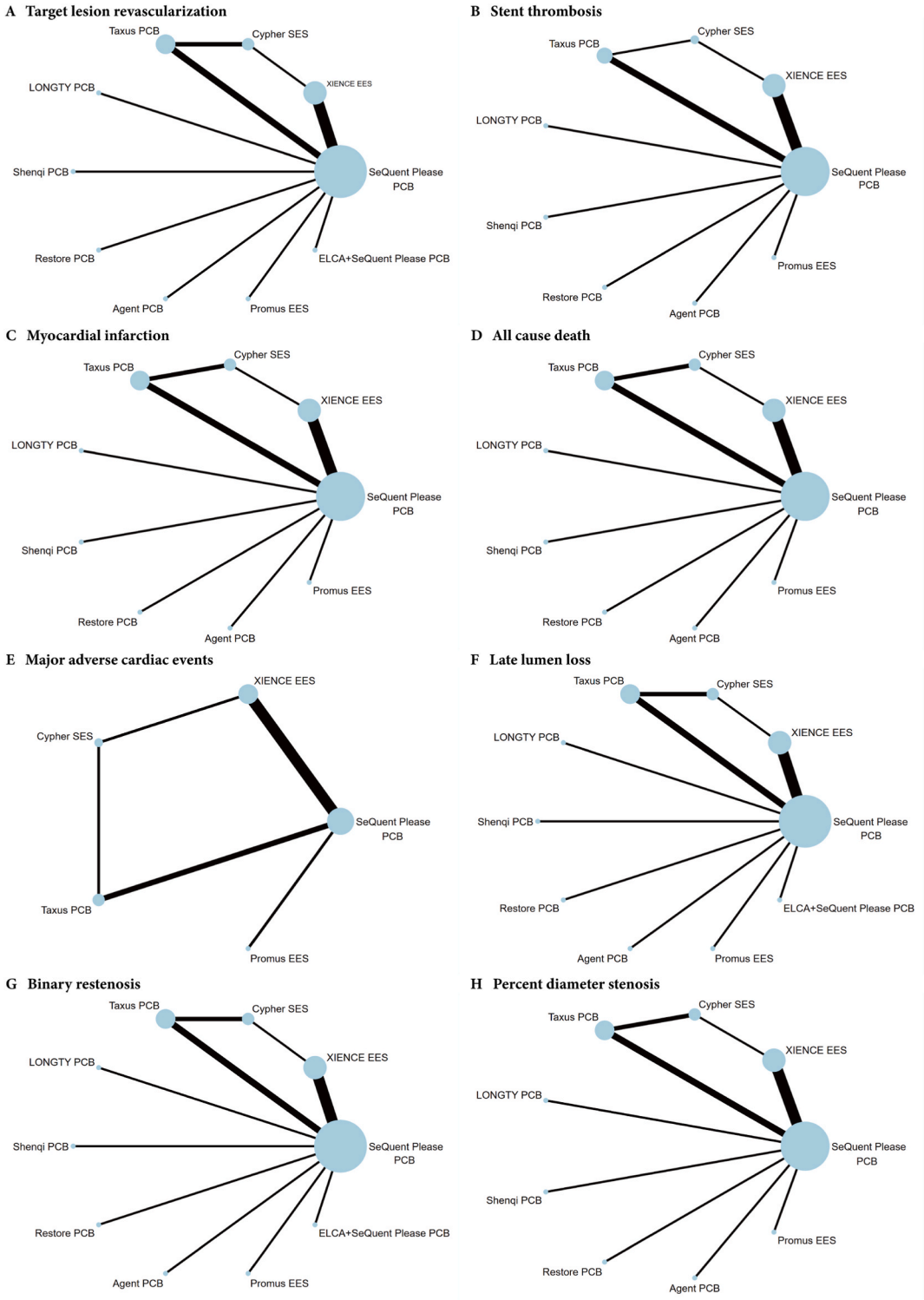

Fig. 3. Network evidence plots of eligible direct comparisons for each outcome in comparison of different drug-coated balloon (DCB) and drug-eluting stent (DES) devices.
BA = balloon angioplasty; BMS = bare-metal stent; EES = everolimus-eluting stent; ELCA = excimer laser coronary angioplasty; PCB = paclitaxel-coated balloon; ROTA = rotational atherectomy; SCB = sirolimus-coated balloon; SES = sirolimus-eluting stent; VBT = vascular brachytherapy; ZES = zotarolimus-eluting stent.

Table 1
Characteristics of the included studies.

Interventions	Year	Study or author (year)	Type of ISR	Sample size (control/ intervention)	Average age (years)	Males, n (%)	Diabetes, n (%)	Angiographic follow-up (months)	Clinical follow-up (months)
Comparison of different types of percutaneous coronary interventions									
BA vs. VBT	2001	Gamma-1 [26]	BMS	252 (121/131)	59.4	188 (74.6)	79 (31.3)	6	9
	2001	Schühlen et al. [27]	NA	21 (10/11)	65.5	14 (66.7)	6 (28.6)	6	12
	2002	INHIBIT [28]	NA	332 (166/166)	61.5	237 (71.4)	99 (29.8)	9	9
	2002	START [29,30]	BMS	476 (232/244)	61.3	314 (66.0)	150 (31.5)	8	24
	2006	Reynen et al. [31]	BMS	165 (83/82)	64	127 (77.0)	56 (33.9)	6	12
BA vs. ROTA	2002	ARTIST [32,33]	BMS	298 (146/152)	61.3	239 (80.2)	75 (25.2)	6	6
	2004	ROSTER [34]	BMS	200 (100/100)	64	143 (71.5)	61 (30.5)	6–9	12
BA vs. BMS	2003	RIBS [35,36]	BMS	450 (226/224)	61	349 (77.6)	118 (26.2)	6	36–60
	2004	Ragosta et al. [1, 37]	BMS	58 (29/29)	62	39 (67.2)	9 (15.5)	NA	9
	2005	Alfonso et al. [38]	BMS	40 (20/20)	66	32 [80]	14 [35]	6	24
BA vs. SES	2006	RIBS-II [39,40]	BMS	150 (74/76)	64	113 (75.3)	52 (34.7)	9	36–48
	2012	CRISTAL [41]	DES	197 (61/136)	67.7	141 (71.6)	77 (39.1)	9–12	12
	2012	Song et al. [1,42]	DES	96 (48/48)	63.3	71 (74.0)	33 (34.4)	9	12
BA vs. PCB	2006	PACCOCATH-ISR I and II [43–45]	BMS and DES	108 (54/54)	65.9	73 (67.6)	29 (26.9)	6–9	60
	2011	Habara et al. [46]	DES	50 (25/25)	69.4	43 (86.0)	31 [62]	6	6
	2012	PEPCAD-DES [47,48]	DES	110 (38/72)	67.8	78 (70.9)	39 (35.5)	6	36
	2013	Habara et al. [49]	BMS and DES	210 (72/138)	69.0	172 (82.9)	93 (44.3)	6	6
	2014	PATENT-C [50–52]	BMS	61 (28/33)	64.5	44 (72.1)	24 (39.3)	6	24
BA vs. PES vs. SES	2005	ISAR-DESIRE [53]	BMS	300 (100/100/ 100)	64.3	235 (78.3)	83 (27.7)	6–8	12
BA vs. PES vs. PCB	2013	ISAR-DESIRE 3 [54,55]	DES	402 (134/131/ 137)	67.9	288 (71.6)	167 (41.5)	6–8	36
VBT vs. SES	2006	SISR [56–58]	BMS	384 (125/259)	63.0	258 (67.2)	123 (32.0)	6	60
	2008	INDEED [59]	BMS	129 (64/65)	59.8	102 (79.1)	40 (31.0)	6	12
	2011	Wiemer et al. [60]	NA	91 (47/44)	64.2	65 (71.4)	44 (48.4)	6	36
VBT vs. PES	2006	TAXUS V ISR [61, 62]	BMS	396 (201/195)	63	262 (66.2)	139 (35.1)	9	24
	2007	Schukro et al. [63]	BMS	37 (17/20)	60.8	20 (54.1)	12 (32.4)	6	6
ROTA vs. BMS	2004	Ragosta et al. [2, 37]	BMS	55 (30/25)	59	34 (61.8)	22 [40]	NA	9
PCB vs. PES	2009	PEPCAD II [64, 65]	BMS	131 (66/65)	64.8	98 (74.8)	39 (29.8)	6	36
	2014	PEPCAD China ISR [66,67]	DES	215 (109/106)	61.9	174 (80.9)	79 (36.7)	9	24
PCB vs. EES	2014	RIBS V [68,69]	BMS	189 (95/94)	65.5	164 (86.8)	49 (25.9)	6–9	36
	2014	SEDUCE [70]	BMS	50 (25/25)	65.9	43 [86]	7 (14.0)	9	12
	2015	RIBS IV [71,72]	DES	309 (154/155)	66	257 (83.2)	141 (45.6)	6–9	36
	2016	TIS [73,74]	BMS	136 (68/68)	65.6	89 (65.4)	35 (25.7)	12	36

(*continued on next page*)

Table 1 (*continued*)

Interventions	Year	Study or author (year)	Type of ISR	Sample size (control/ intervention)	Average age (years)	Males, n (%)	Diabetes, n (%)	Angiographic follow-up (months)	Clinical follow-up (months)
	2018	DARE [75]	DES and BMS	278 (137/141)	65.5	216 (77.7)	88 (31.7)	6	12
	2018	RESTORE [76]	DES	172 (86/86)	66.5	123 (71.5)	81 (47.1)	9	12
PCB vs. SES	2018	BIOLUX [77]	DES and BMS	229 (157/72)	67.9	171 (74.7)	72 (31.4)	6	18
SES vs. PES	2010	ISAR-DESIRE 2 [78]	DES	450 (225/225)	66.8	345 (76.7)	162 (36.0)	6–8	12
SES vs. EES	2012	Song et al. [2,42]	DES	66 (32/34)	62.8	34 (51.5)	20 (30.3)	9	12
ZES vs. EES	2016	RESTENT-ISR [79]	DES	304 (146/158)	63.2	158 (52.0)	111 (36.5)	9	36
PCB vs. SCB	2019	Ali et al. [80]	DES	50 (25/25)	60.1	41 [82]	37 (74.0)	6	12
Comparison of different drug-coated balloon and drug-eluting stent devices									
Restore PCB vs. SeQuent Please PCB	2018	RESTORE ISR China [81]	DES and BMS	240 (120/120)	63.8	183 (76.3)	92 (38.3)	9	12
ELCA + PCB vs. PCB	2020	Sato et al. [82]	DES and BMS	40 (20/20)	69.1	35 (87.5)	25 (62.5)	12	12
Agent PCB vs. SeQuent Please PCB	2020	AGENT ISR [83]	DES and BMS	125 (65/60)	68.5	102 (81.6)	46 (36.8)	6	12
LONGTY PCB vs. SeQuent Please PCB	2021	LONGTY ISR China [84]	NA	211 (105/106)	64.0	159 (75.4)	85 (40.3)	9	24
SeQuent Please PCB vs. Shenqi PCB	2021	Zhu et al. [85]	DES	216 (106/110)	63.2	164 (75.9)	85 (39.4)	9	12

ISR = in-stent restenosis; NA = not applicable.

(Fig. 5A), the overall treatment ranking of 10 PCIs from high to low according to SUCRA was as follows: EES (87.0) > SCB (75.6) > SES (72.1) > PCB (68.5) > PES (61.1) > ZES (59.7) > VBT (34.1) > BMS (26.1) > ROTA (10.0) > BA (6.0). As the best PCI treatment strategy with regard to TLR, EES can significantly reduce the risk of TLR compared with BA (OR 5.95, 95% CI [2.79, 12.67]), VBT (2.84, [1.25, 6.44]), ROTA (5.50, [2.05, 14.75]), and BMS (3.63, [1.31, 10.04]). DES (ZES, EES, SES, PES) and DCB (PCB, SCB) were all ranked higher than BA, VBT, ROTA, and BMS, but there was no statistically significant difference between DCB and DES. BA had the relatively worst treatment effect, PES (0.27, [0.16, 0.44]), SES (0.23, [0.14, 0.37]), EES (0.17, [0.08, 0.36]), ZES (0.27, [0.08, 0.97]), PCB (0.24, [0.15, 0.39]), VBT (0.48, [0.32, 0.72]) were associated with lower target vessel revascularization compared with BA. SCB had the highest probability of ranking first (46.0%) with no statistically significant difference compared to other treatment measures.

3.5.1.2. ST. Twenty-eight RCTs including 5906 participants reported 90 (1.5%) ST events in the comparison of 8 types of PCIs. Considering ST, according to the cumulative ranking curves (Fig. 5B), the overall treatment ranking of 8 PCIs from high to low according to SUCRA was as follows: ZES (83.1) > SCB (77.2) > EES (72.2) > PCB (60.2) > BA (50.6) > PES (32.1) > VBT (17.5) > SES (7.0). ZES was the best treatment strategy with regard to ST. The incidence of ST in SES was significantly higher than that in EES (0.16, [0.03, 0.77]), ZES (0.09, [0.01, 0.89]), PCB (0.24, [0.07 0.80]), or BA (0.33, [0.12, 0.89]). Although it had the second highest SUCRA, SCB had the highest probability of ranking first (49.2%).

3.5.1.3. MI. Thirty-seven RCTs including 7440 participants reported 300 (4.0%) MI events in the comparison of 9 types of PCIs. Considering MI, according to the cumulative ranking curves (Fig. 5C), the overall treatment ranking of 9 PCIs from high to low according to SUCRA was as follows: BMS (91.9) > PCB (65.7) > BA (59.4) > EES (54.6) > PES (50.9) > VBT (44.8) > ZES (35.0) > ROTA (31.7) > SES (16.0). BMS showed the best treatment effect and had the highest probability of ranking first (70.6%). SES significantly increases the risk of MI compared with BMS (0.29, [0.10, 0.82]).

3.5.1.4. All cause death. Thirty-nine RCTs including 7580 participants reported 294 (3.9%) all cause death events in the comparison of 10 types of PCIs. Considering all cause death, according to the cumulative ranking curves (Fig. 5D), the overall treatment ranking of 10 PCIs from high to low according to SUCRA was as follows: EES (82.2) > PCB (72.1) > BMS (60.1) > SCB (57.2) > VBT (49.2) > SES (47.8) > ROTA (42.6) > BA (38.5) > ZES (28.6) > PES (21.7). EES was the best treatment strategy with regard to all cause death. Although it ranked fourth in treatment effectiveness, SCB had the highest probability of ranking first (41.6%). PES was inferior to EES (0.40, [0.18, 0.91]) and PCB (0.50, [0.28, 0.89]) for all cause death.

PES	1.11 (0.70,1.75)	1.78 (0.91,3.47)	——	——	1.51 (0.95,2.42)	**0.24 (0.11,0.52)**	**0.18 (0.08,0.40)**	**0.48 (0.31,0.75)**	**0.22 (0.15,0.33)**
1.18 (0.69,2.01)	**SES**	1.61 (0.78,3.29)	——	——	1.37 (0.79,2.37)	**0.22 (0.10,0.47)**	**0.17 (0.08,0.36)**	**0.43 (0.28,0.68)**	**0.20 (0.13,0.30)**
1.60 (0.73,3.51)	1.36 (0.61,3.00)	**EES**	——	——	0.85 (0.52,1.39)	**0.13 (0.05,0.34)**	**0.10 (0.04,0.26)**	**0.27 (0.13,0.55)**	**0.12 (0.06,0.24)**
0.99 (0.27,3.62)	0.84 (0.23,3.08)	0.62 (0.22,1.73)	**ZES**	——	——	——	——	——	——
1.58 (0.24,10.52)	1.34 (0.20,9.00)	0.99 (0.15,6.68)	1.60 (0.18,13.99)	**SCB**	——	——	——	——	——
1.13 (0.66,1.93)	0.96 (0.55,1.69)	0.71 (0.39,1.28)	1.14 (0.35,3.74)	0.72 (0.12,4.41)	**PCB**	**0.16 (0.07,0.35)**	**0.12 (0.06,0.26)**	**0.32 (0.19,0.54)**	**0.15 (0.09,0.23)**
0.44 (0.19,1.03)	**0.37 (0.16,0.86)**	**0.28 (0.10,0.76)**	0.44 (0.10,1.89)	0.28 (0.04,2.06)	**0.39 (0.17,0.90)**	**BMS**	0.77 (0.30,1.96)	2.02 (0.95,4.28)	0.93 (0.48,1.80)
0.29 (0.13,0.65)	**0.25 (0.11,0.55)**	**0.18 (0.07,0.49)**	0.29 (0.07,1.22)	0.18 (0.03,1.34)	**0.26 (0.12,0.57)**	0.66 (0.29,1.53)	**ROTA**	**2.63 (1.24,5.58)**	1.21 (0.62,2.34)
0.56 (0.33,0.97)	**0.48 (0.29,0.79)**	**0.35 (0.16,0.80)**	0.57 (0.15,2.12)	0.36 (0.05,2.40)	**0.50 (0.28,0.89)**	1.28 (0.57,2.88)	1.94 (0.90,4.16)	**VBT**	**0.46 (0.32,0.65)**
0.27 (0.16,0.44)	**0.23 (0.14,0.37)**	**0.17 (0.08,0.36)**	**0.27 (0.08,0.97)**	0.17 (0.03,1.12)	**0.24 (0.15,0.39)**	0.61 (0.30,1.23)	0.92 (0.49,1.76)	**0.48 (0.32,0.72)**	**BA**

(A)

PES	2.41 (-2.86,7.67)	5.84 (-0.79,12.48)	5.11 (-6.59,16.82)	3.02 (-12.25,18.28)	0.94 (-4.23,6.10)	**-16.35 (-27.96,-4.74)**	**-25.25 (-37.10,-13.41)**	**-10.12 (-16.22,-4.03)**	**-17.35 (-22.59,-12.12)**
0.03 (-0.10,0.17)	**SES**	3.44 (-2.99,9.87)	2.71 (-8.88,14.30)	0.61 (-14.65,15.87)	-1.47 (-6.61,3.68)	**-18.76 (-29.99,-7.53)**	**-27.66 (-39.14,-16.18)**	**-12.53 (-17.49,-7.57)**	**-19.76 (-24.10,-15.42)**
0.07 (-0.10,0.25)	0.04 (-0.12,0.20)	**EES**	-0.73 (-10.38,8.92)	-2.83 (-17.86,12.21)	**-4.91 (-9.34,-0.47)**	**-22.20 (-34.26,-10.13)**	**-31.10 (-43.39,-18.80)**	**-15.97 (-23.11,-8.83)**	**-23.20 (-29.38,-17.01)**
0.02 (-0.32,0.37)	-0.01 (-0.35,0.33)	-0.05 (-0.35,0.25)	**ZES**	-2.10 (-19.96,15.77)	-4.18 (-14.79,6.44)	**-21.47 (-36.91,-6.02)**	**-30.37 (-45.99,-14.74)**	**-15.24 (-27.24,-3.24)**	**-22.47 (-33.92,-11.01)**
0.26 (-0.17,0.70)	0.23 (-0.20,0.66)	0.19 (-0.24,0.62)	0.24 (-0.28,0.76)	**SCB**	-2.08 (-16.45,12.29)	**-19.37 (-37.68,-1.06)**	**-28.27 (-46.73,-9.81)**	-13.14 (-28.67,2.39)	**-20.37 (-35.46,-5.28)**
0.13 (-0.00,0.27)	0.10 (-0.03,0.23)	0.06 (-0.06,0.18)	0.11 (-0.21,0.43)	-0.13 (-0.54,0.28)	**PCB**	**-17.29 (-28.64,-5.94)**	**-26.19 (-37.78,-14.60)**	**-11.06 (-16.96,-5.16)**	**-18.29 (-22.92,-13.66)**
-0.73 (-1.06,-0.40)	**-0.77 (-1.09,-0.44)**	**-0.81 (-1.14,-0.47)**	**-0.76 (-1.21,-0.31)**	**-1.00 (-1.52,-0.48)**	**-0.87 (-1.19,-0.55)**	**BMS**	-8.90 (-23.74,5.94)	6.23 (-5.02,17.48)	-1.00 (-11.36,9.36)
-0.58 (-0.91,-0.26)	**-0.62 (-0.94,-0.30)**	**-0.66 (-0.99,-0.32)**	**-0.61 (-1.05,-0.16)**	**-0.85 (-1.37,-0.33)**	**-0.72 (-1.03,-0.40)**	0.15 (-0.27,0.57)	**ROTA**	**15.13 (3.64,26.62)**	7.90 (-2.73,18.53)
-0.12 (-0.27,0.03)	**-0.15 (-0.28,-0.02)**	**-0.19 (-0.37,-0.01)**	-0.14 (-0.49,0.21)	-0.38 (-0.82,0.06)	**-0.25 (-0.40,-0.10)**	**0.62 (0.29,0.94)**	**0.47 (0.15,0.79)**	**VBT**	**-7.23 (-11.61,-2.85)**
-0.34 (-0.49,-0.20)	**-0.38 (-0.50,-0.25)**	**-0.42 (-0.58,-0.26)**	**-0.37 (-0.70,-0.03)**	**-0.61 (-1.04,-0.18)**	**-0.48 (-0.59,-0.36)**	**0.39 (0.09,0.69)**	0.24 (-0.05,0.53)	**-0.23 (-0.36,-0.10)**	**BA**

(B)

Fig. 4. Network meta-analysis of the effects of interventions for primary clinical and angiographic outcomes.
Figures should be read from left to right. Efficacy estimates are located at the intersection between the column-defining treatment and the row-defining treatment. (A): For TLR (upper white fields) and BR (lower shaded fields), data are expressed as mean differences (95% CI). (B): For LLL (upper white fields) and %DS (lower shaded fields), data are expressed as odds ratios (95% CI). Odds ratios less than one show that the column-defining treatment is more beneficial. Mean differences less than zero show that the column-defining treatment is more beneficial. Bold font indicates statistically significant differences. BA = balloon angioplasty; BMS = bare-metal stent; EES = everolimus-eluting stent; ELCA = excimer laser coronary angioplasty; PCB = paclitaxel-coated balloon; ROTA = rotational atherectomy; SCB = sirolimus-coated balloon; SES = sirolimus-eluting stent; VBT = vascular brachytherapy; ZES = zotarolimus-eluting stent.

3.5.1.5. MACE. Twenty-seven RCTs including 5138 participants reported 1330 (25.9%) MACE in the comparison of 9 types of PCIs. Considering MACE, according to the cumulative ranking curves (Fig. 5E), the overall treatment ranking of 9 PCIs from high to low according to SUCRA was as follows: EES (84.7) > SCB (77.3) > PCB (74.2) > BMS (64.2) > PES (54.8) > SES (43.3) > ROTA (28.9) > VBT (21.7) > BA (0.9). EES was the best treatment strategy with regard to MACE, and it was significantly superior to BA (3.94, [2.39, 6.47]), VBT (2.34, [1.39, 3.93]), and ROTA (2.20, [1.03, 4.07]). Although it had the second highest SUCRA, SCB had the highest probability of ranking first (52.8%). There was no significant difference between DES (EES, SES, PES) and DCB (PCB, SCB).

3.5.2. Angiographic outcomes

Angiographic outcomes included LLL, %DS, and BR. Fig. 4 (A, B) shows the OR MD, and 95% CI comparing various PCIs. The cumulative ranking curves and rankograms show all three outcomes (Supplementary Section 1).

3.5.2.1. LLL. Thirty-four RCTs including 6041 participants reported LLL in the comparison of 10 types of PCIs. Considering LLL, according to the cumulative ranking curves (Fig. 5F), the overall treatment ranking of 10 PCIs from high to low according to SUCRA was as follows: SCB (89.5) > PCB (86.2) > EES (71.4) > SES (63.9) > ZES (61.9) > PES (56.0) > VBT (37.4) > BA (21.8) > ROTA (9.1) > BMS (2.7). SCB showed the best treatment effect with regard to LLL and had the highest probability of ranking first (68.5%). SCB can significantly reduce the risk of LLL compared with BMS (MD 1.00, 95% CI [0.48, 1.52]), ROTA (0.85, [0.33, 1.37]), and BA (0.61, [0.18, 1.04]).

3.5.2.2. BR. Thirty-four RCTs including 5911 participants reported 1607 (27.2%) BR events in the comparison of 8 types of PCIs. Considering BR, according to the cumulative ranking curves (Fig. 5G), the overall treatment ranking of 8 PCIs from high to low according to SUCRA was as follows: EES (94.1) > PCB (87.0) > SES (70.0) > PES (63.2) > VBT (42.3) > BMS (19.0) > BA (16.1) > ROTA (8.3). EES showed the best treatment effect with regard to BR and had the highest probability of ranking first (70.9%). There were no statistically significant differences between DES (EES, SES, PES) and DCB (PCB). DES and DCB were significantly superior to BA, VBT, ROTA, and BMS.

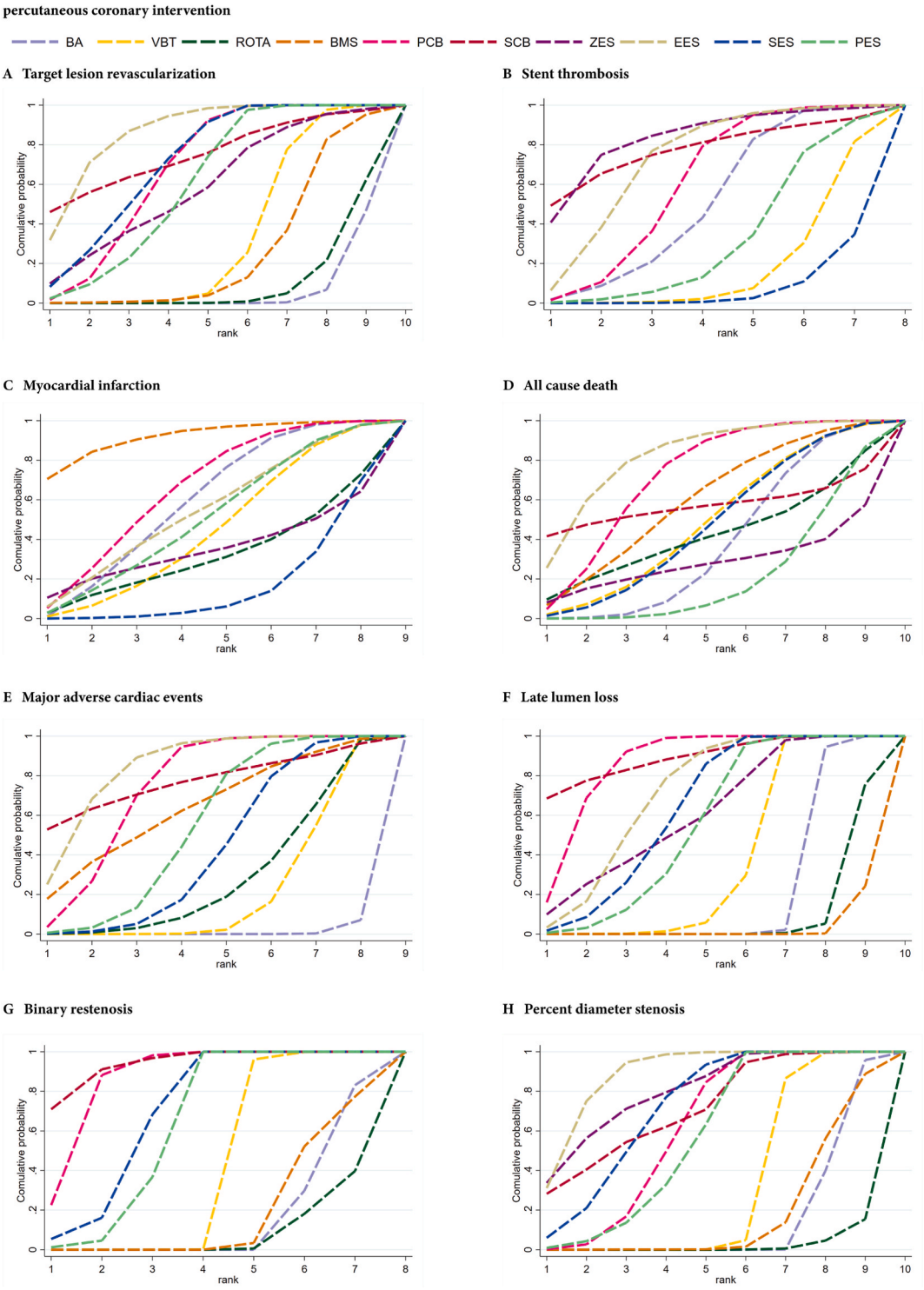

Fig. 5. Cumulative ranking curves for all eight outcomes in comparison of 10 types of PCIs.
Graphs A-H show the cumulative probability of each intervention ranking for each outcome according to the surface under cumulative ranking curve. For example, graph A shows the cumulative ranking curve for target lesion revascularization in comparison of 10 types of PCIs. The larger the surface under the cumulative ranking curve value, the better the treatment. BA = balloon angioplasty; BMS = bare-metal stent; EES = everolimus-eluting stent; ELCA = excimer laser coronary angioplasty; PCB = paclitaxel-coated balloon; ROTA = rotational atherectomy; SCB = sirolimus-coated balloon; SES = sirolimus-eluting stent; VBT = vascular brachytherapy; ZES = zotarolimus-eluting stent.

3.5.2.3. %DS. Thirty-three RCTs including 5868 participants reported %DS in the comparison of 10 types of PCIs. Considering %DS, according to the cumulative ranking curves (Fig. 5H), the overall treatment ranking of 10 PCIs from high to low according to SUCRA was as follows: EES (88.8) > ZES (80.9) > SCB (72.2) > SES (71.9) > PCB (61.5) > PES (57.1) > VBT (32.4) > BMS (17.9) > BA (15.1) > ROTA (2.3). EES was the best treatment strategy with regard to %DS and can significantly reduce the risk of %DS compared with PCB (MD 4.91, 95% CI [0.47, 9.34]), BMS (22.20, [10.13, 34.26]), ROTA (31.10, [18.80, 43.39]), VBT (15.97, [8.83, 23.11]), and BA (23.20, [17.01, 29.38]). Although it had the second highest SUCRA, ZES had the highest probability of ranking first (33.7%). DES (ZES, EES, SES, PES) and DCB (PCB, SCB) were all superior to BA, VBT, ROTA, and BMS, except there was no significant difference between SCB and VBT (13.14, [−2.39, 28.67]). There was no significant difference between DES and DCB, except EES was significantly better than PCB (4.91, [0.47, 9.34]).

SCB was ranked the best strategy for LLL according to SUCRA, and it had the highest probability of ranking first for TLR, ST, all cause death, LLL, and MACE according to rankograms. EES was ranked the best strategy for TLR, all cause death, MACE, %DS, and BR, and it had the highest probability of ranking first for BR. ZES was ranked the best strategy for ST, and it had the highest probability of ranking first for %DS. BMS was ranked the best strategy and had the highest probability of ranking first for MI, but it ranked worst for LLL (2.7). In addition, BA was ranked the worst strategy for TLR (6.0) and MACE (0.9). SES was ranked the worst strategy for both ST (7.0) and MI (16.0). PES was ranked the worst strategy for all cause death (21.7). ROTA was ranked the worst strategy for both BR (8.3) and %DS (2.3).

3.6. Comparison of different DCB and DES devices

As previously mentioned, DCB and DES had the best treatment efficacy in both the primary clinical outcome (TLR) and angiographic follow-up outcomes (LLL, BR, %,%DS). Therefore, we analyzed 17 trials that compared DCB and/or DES and specified the device type. The cumulative ranking curves and rankograms show all clinical and angiographic outcomes (Supplementary section 2).

3.6.1. Clinical outcomes

Considering TLR, XIENCE EES was the best treatment strategy (SUCRA = 78.6). The combination intervention of ELCA + SeQuent Please PCB had the highest probability of ranking first (42.8%), but it was ranked second by SUCRA (73.1). However, there were no significant differences between the 10 types of devices. In addition, no statistically significant differences were shown between any of the 9 devices in terms of MI or ST. Considering ST, Agent PCB was the best strategy (72.8) and had the highest probability of ranking first (30.2%). Considering MI, Shenqi PCB was the best strategy (83.4) and LONGTY PCB had the highest probability of ranking first (42.2%). Considering MACE, XIENCE EES was the best treatment strategy (95.3) and also had the highest probability of ranking first (86.9%). It was associated with lower MACE compared to Promus EES (2.54, [1.04, 6.21]). Considering all cause death, Shenqi PCB was the best treatment strategy (87.8) and ranked first with the greatest probability (57.2%) without any significant difference compared to other strategies. XIENCE EES (0.34, [0.13, 0.86]) and SeQuent Please PCB (0.44, [0.22, 0.87]) were associated with lower all cause death compared to Taxus PES.

3.6.2. Angiographic outcomes

Considering LLL, there was no significant difference between the treatment strategies, except that Promus EES was significantly inferior to SeQuent Please PCB (−0.35, [−0.68, −0.02]). ELCA + SeQuent Please PCB was the best treatment strategy (SUCRA = 70.8) and had the highest probability of ranking first (35.5%). Considering BR, there were no significant differences between the 10 devices. XIENCE EES was the best treatment strategy (78.7) and Agent PCB had the highest probability of ranking first (35.5%). Considering % DS, XIENCE EES was the best treatment strategy (93.3) and had the highest probability of ranking first (58.6%), plus it was significantly superior to Promus EES (11.23, [1.55, 20.91]), Restore PCB (10.93, [2.40, 19.46]), Taxus PES (7.74, [2.22, 13.26]), and SeQuent Please PCB (6.53, [2.98, 10.08]).

ELCA + SeQuent Please PCB was the best strategy for LLL and had the highest probability of ranking first for both TLR and LLL. XIENCE EES was the best strategy and had the highest probability of ranking first for MACE and %DS, and it also was the best strategy for TLR and BR. Agent PCB was the best strategy and had the highest probability of ranking first for ST, and it also had the highest probability of ranking first for BR. Shenqi PCB was the best strategy and had the highest probability of ranking first for all cause death, and it was also the best strategy for MI. Considering TLR and LLL, ELCA + SeQuent Please PCB had greater treatment effects than SeQuent Please PCB, although there were no significant differences between them.

4. Discussion

4.1. Principal findings

ISR is a critical public health problem for which the development of optimal strategies is essential. Advances in intracoronary imaging and updates in interventional techniques provide the potential for personalized treatment of ISR. For instance, intravascular lithotripsy associated with a lower incidence of short-term adverse outcomes is feasible and safe for the treatment of ISR, including multilayer ISR; additionally, bioresorbable vascular scaffolds allow for the delivery of anti-proliferative drugs combined with transient vessel scaffolding and will not add another permanent stent layer [87–89].

In the present NMA study, we synthesized data from 44 studies and showed the relative efficacy rankings of different types and devices of PCI strategies. Our systematic review and NMA showed that DES and DCB are still the best choices for coronary ISR, which is

consistent with previous reports. All included DES and DCB strategies were considered as the best strategies for TLR, LLL, BR, and %DS according to SUCRA, and were significantly preferred to BA, VBT, ROTA, and BMS. EES exhibited more favorable treatment efficacy compared to other treatments considering TLR, all cause death, MACE, %DS, and BR. In addition, SCB showed promising results and was ranked as the best strategy considering LLL. While previous data on DCB included only PCB, our trial included SCB for the first time, and SCB exhibited promising treatment outcomes. This emphasizes that DCB has an excellent therapeutic prospect due to its non-inferior therapeutic effect, the absence of additional stenting, and the possible reduction of complications such as neointimal proliferation [90]. Considering the secondary outcomes MI, ST, and all cause death, there were fewer occurrences of these outcomes, which may limit the reliability of the results. Therefore, DES and DCB remain the best treatment strategies for coronary ISR in terms of the primary clinical outcome and angiographic follow-up outcomes.

Among the various types of DCB and DES devices, ELCA + SeQuent Please PCB was the best strategy considering LLL, and XIENCE EES was the best strategy considering TLR, BR, MACE, and %DS. The combination strategy ELCA + SeQuent Please PCB showed excellent treatment efficacy, with higher treatment rankings than SeQuent Please PCB in TLR and LLL, but there was no significant difference between them. Combination strategies, especially those involving DES or DCB, may add a new potential treatment pattern for coronary ISR. Therefore, PCI strategies and relevant commercial devices should be selected based on a patient's specific conditions.

4.2. Strengths and limitations of this study

There were several significant strengths of our study. First, we included more comprehensive DES and DCB types and devices such as ZES, SCB, Orsiro SES, and Promus EES. Second, our NMA offers the first estimation of the intervention effects of different types of DES and DCB commercial devices in patients with ISR, because, in previous studies, no distinction was applied to the different commercial devices when comparing different PCI strategies. Third, we conducted a comprehensive search of the database and clinical registry trials and critically reviewed trial eligibility, data extraction, and risk of bias. We searched the literature as comprehensively as possible and obtained additional material through feasible methods. To the best of our knowledge, this study provides the most comprehensive data synthesis on PCIs for patients with coronary ISR. Certainly, the possibility of the absence of unpublished studies and the overestimation of efficacy in published reports still exists. We appreciate any information that may help rectify any errors or omissions in our dataset. Finally, we ranked the various strategies by cumulative ranking curves and rankograms as well as estimated summary ORs and MDs with 95% CIs.

Certainly, we acknowledge that there were several limitations of our study. First, our study only included RCTs, resulting in a relatively smaller sample size and volume of data, which caused the greatest limitations. Although we included all existing DES or DCB reported by RCTs and also assessed differences between the different commercially available DCE or DES devices, high-quality and large-scale RCTs that include novel treatment technologies, new generation DES and DCB, and various commercial devices are still required. Some new technologies for the treatment of ISR may not be inferior to the current best strategies, so it is difficult to draw more comprehensive and reliable conclusions. Notably, although some strategies appeared to be more effective and safer on the ranking curve, their relative benefits versus other strategies should be interpreted cautiously. The efficacy may be overestimated because these estimates were based on a single or few RCTs especially for the analysis of different DES or DCB devices.

Second, we only analyzed the average treatment efficacy because relevant data at the individual patient level were unavailable. Moreover, long-term clinical and angiographic outcome data were inadequate. Limited by the small number of included trials and incomplete data, the low incidence of certain events did not allow us to draw reliable conclusions about this endpoint, such as MI, ST, and all cause death. Available data did not allow a comparison of PCI strategies based on first or recurrent ISR. In addition, patients with ISR may benefit from extended duration of dual antiplatelet therapy, but the evidence is limited due to the lack of detailed data related to antiplatelet therapy [91].

Third, there was heterogeneity across trials regarding the period of investigation, baseline characteristics (such as proportions of diabetes mellitus and focal or diffuse angiographic patterns of ISR), and duration of follow-up, which can lead to undesirable transitivity. Included studies covered approximately 20 years. Changes such as device modernization, enhancements in treatment techniques (e.g., maturation of interventional techniques and development of lesion preparation techniques), more advanced diagnostic approaches, and more rational drug management can lead to unmeasured differences between PCIs.

Fourth, it is unclear whether the optimal choice of treatment for ISR depends on the type of restenosis stent (BMS or DES) [5]. Because of the popularity of DES in the treatment of coronary artery disease and the poor prognosis of DES-ISR, DES-ISR is becoming a challenging problem. Yang et al. showed that DES and DCB might be more effective for BMS-ISR than DES-ISR [92]. Giacoppo et al. demonstrated that in DES-ISR patients, repeat DES implantation was significantly more effective and apparently equally safe at long-term follow-up compared to DCB [5]. An NMA also showed that DES was superior to DCB in terms of TLR for DES-ISR patients [11]. Studies have shown that VBT can be a safe and effective treatment option and may be an attractive treatment strategy for refractory and complex DES-ISR [93,94]. However, no large RCT has compared the effects of BMS, CBA, VBT, ELA, and ROTA in DES-ISR.

Fifth, the types of DES-ISR (initial DES type) were variable across patients. Almost all RCTs combined EES-, SES- and PES-ISR into DES-ISR. Notably, most of the available evidence on DES-ISR comes from RCTs recruiting patients with early DES-ISR, and evidence for ISR with new generation DES is unavailable, but their mechanisms appear to be similar [92]. Thus, further exploration is needed for treatment of more definitive DES-ISR types.

Finally, we did not consider the potential cost-effectiveness and side effects associated with implementing PCIs as a treatment for ISR patients.

4.3. Future prospects

The global burden of ISR remains a critical clinical issue. Identifying treatments that lead to sustained angiographic and clinical improvement is quite challenging, especially for DES-ISR. Optimizing PCI strategies in combination with excellent assistant measures is the key to managing ISR. Lesion preparation methods such as scoring balloon and non-slip element balloon have demonstrated desirable benefits in increasing the efficacy of DCB [95,96]. In addition, identifying the underlying etiology and mechanisms of ISR is crucial for guiding management decisions and preventing recurrence [7]. Individualized therapeutic measures based on formation mechanisms and risk factors of ISR are necessary. The advancement of intracoronary imaging technology has enabled better characterization and evaluation of ISR, such as intravascular ultrasound or optical coherence tomography [7]. It is desirable to guide clinical interventions by using intracoronary imaging to characterize and identify the potential mechanisms and substrates of ISR [3]. It is also essential to actively prevent ISR based on various predictors. Developing novel stents targeting the pathogenesis of restenosis is critical for further reducing the risk of ISR [4]. Personalized comparative efficacy estimates and predictions based on patient-specific characteristics are key directions of future research in this field.

In summary, the results of this NMA represent the best and most comprehensive evidence base presently available to guide the choice of PCI strategies for coronary ISR. All conclusions drawn from this study should take into account potential limitations of existing studies and evidence, differences in baseline patient characteristics, and constraints of statistical analysis [16]. We hope that these results may contribute to evidence-based clinical practice for patients, medical personnel, and guideline developers.

5. Conclusions

DCB and DES remain the preferred treatment strategies for coronary ISR, considering the primary clinical outcome (TLR) and the angiographic outcomes (LLL, BR, %DS). Among the DCB and DES strategies, EES was the optimal strategy considering TLR, %DS, and BR, and SCB was the optimal strategy considering LLL. Among the commercial devices, XIENCE EES was the optimal strategy considering TLR, BR, and %DS, and ELCA + SeQuent Please PCB was the optimal strategy considering LLL. The combination strategy ELCA + SeQuent Please PCB showed promising therapeutic prospects. Thus, personalized combination interventions including DCB or DES hold promise as a novel potential treatment pattern for coronary ISR.

Funding

This work was supported by grants from the National Natural Science Foundation of China (No. 81873120 and 82000252), the Zhejiang Medical Health Science and Technology Project (No. 2020KY332), Research and Innovation Fund of Shaoxing University Students (No. 2021124).

Availability of data and materials

Not applicable.

Ethics approval and consent to participate

Not applicable.

Consent for publication

All authors agreed to publish this article.

Data availability statement

Data included in article/supp. material/referenced in article.

Additional information

No additional information is available for this paper.

CRediT authorship contribution statement

Shitian Guo: Writing – review & editing, Writing – original draft, Formal analysis, Data curation. **Chenchen Bi:** Writing – original draft, Investigation, Funding acquisition, Formal analysis. **Xiang Wang:** Software, Resources, Project administration. **Tingting Lv:** Visualization, Validation, Supervision. **Ziyi Zhang:** Supervision, Resources, Investigation. **Xinyi Chen:** Methodology, Formal analysis. **Junwei Yan:** Software, Investigation. **Dandan Mao:** Visualization, Investigation. **Wenxi Huang:** Project administration, Investigation. **Mengfei Ye:** Investigation. **Zheng Liu:** Writing – review & editing, Funding acquisition, Conceptualization. **Xiaojie Xie:** Writing – review & editing, Validation, Supervision, Methodology, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

We thank LetPub (www.letpub.com) for its linguistic assistance during the preparation of this manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e27521.

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