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Comparison Among Drug-Eluting Balloon, Drug-Eluting Stent, and Plain Balloon Angioplasty for the Treatment of In-Stent Restenosis

A Network Meta-Analysis of 11 Randomized, Controlled Trials

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ABSTRACT

OBJECTIVES A Bayesian network meta-analysis was performed comparing the efficacy and safety of drug-eluting balloons (DEB), drug-eluting stents (DES), or plain old balloon angioplasty (POBA) for treatment of in-stent restenosis (ISR).

BACKGROUND Optimal treatment options for ISR have not been well established.

METHODS Randomized, controlled trials comparing DEB, DES, and POBA for the treatment of ISR after percutaneous coronary intervention with bare metal stent or DES were included. The primary outcome was target lesion revascularization (TLR). The pairwise posterior median odds ratio (OR) with 95% credible interval (CrI) was the effect measure.

RESULTS This analysis included 2,059 patients from 11 RCTs. The risk of TLR was markedly lower in patients treated with DEB (OR: 0.22, 95% CrI: 0.10 to 0.42) or DES (OR: 0.24, 95% CrI: 0.11 to 0.47) than in those treated with POBA in a random-effects model. In a comparison of DEB and DES, the risk of TLR (OR: 0.92, 95% CrI: 0.43 to 1.90) was similar. The risk of MI or all-cause mortality was lowest in the DEB group compared with the DES and POBA groups, which did not meet statistical significance. The risk of major adverse cardiac events, which was mainly driven by TLR, was also significantly lower in the DEB or and DES group (OR: 0.28, 95% CrI: 0.14 to 0.53) than in the POBA group, but it was similar between the DEB and DES groups (OR: 0.84, 95% CrI: 0.45 to 1.50). The probability of being ranked as the best treatment was 59.9% (DEB), 40.1% (DES), and 0.1% (POBA) in terms of TLR, whereas it was 63.0% (DEB), 35.3% (POBA), and 1.7% (DES) in terms of MI.

CONCLUSIONS Local drug delivery by DEB or DES for ISR lesions was markedly better than POBA in preventing TLR, but not for MI or mortality. Among the 2 different strategies of drug delivery for ISR lesions, treatment with DEB showed a trend of less development of MI than did treatment with DES. (J Am Coll Cardiol Intv 2015;8:382-94) © 2015 by the American College of Cardiology Foundation.

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In-stent restenosis (ISR) has been a major drawback with percutaneous coronary intervention (PCI). Intervention of ISR lesions constituted 20% to 40% of all PCIs in the era of bare metal stents (BMS) (1). Although drug-eluting stents (DES) substantially reduced the rates of ISR compared with BMS, the expansion of indications for PCI to complex coronary lesions in high-risk patients still makes ISR an important issue with a incidence of 3% to 20% of patients (1,2). Given its progressive onset, ISR has been believed to be a benign phenomenon. However, a substantial proportion of ISR after BMS or DES implantation can present as unstable angina (26% to 53% for BMS, 16% to 66% for DES) or even as myocardial

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infarction (MI) (3.5% to 20% for BMS, 1% to 20% for DES), leading to a worse clinical outcome than in those without ISR (1,2). Despite the clinical and prognostic importance of ISR, current evidence regarding treatment options for ISR have been limited (1). American College of Cardiology/American Heart Association/Society for Cardiovascular Intervention (ACCF/AHA/SCAI) guidelines for PCI recommend BMS ISR to be treated by DES (Class I, Level of Evidence: A) and DES ISR by plain old balloon angioplasty (POBA), BMS, or DES (3). The European Society of Cardiology/European Association for Cardio-Thoracic Surgery guidelines for myocardial revascularization recommend a drug-eluting balloon (DEB) to treat BMS ISR (Class IIa, Level of Evidence: B) (4). However, the ACCF/AHA/SCAI guidelines are on the basis of limited trials and 1 meta-analysis, especially with regard to the treatment strategy for DES ISR. In addition, the European Society of Cardiology/European Association for Cardio-Thoracic Surgery guidelines for treating BMS ISR were also on the basis of 1 first-in-human trial and 2 randomized, controlled trials (RCTs) with a relatively small sample size (5–7). Currently, there is no clear optimal treatment option for ISR for either BMS ISR or DES ISR. Although DEB coated with paclitaxel is an emerging treatment option for ISR without implantation of additional metal alloy, RCTs on the use of DEB have been sporadically conducted and have focused on angiographic outcomes with limited statistical power for clinical outcomes. Therefore, we performed comprehensive Bayesian network meta-analysis of RCTs to compare the efficacy and safety of the current treatment options (DEB, DES, and POBA) for ISR.

METHODS

An expanded description of the study methods are presented in the Online Appendix.

DATA SOURCES AND SEARCHES. PubMed, Embase, Cochrane Central Register of Controlled Trials, and the U.S. National Institutes of Health registry of clinical trials, and relevant websites were all searched for pertinent published or unpublished studies. The detailed search strategy is presented in the Online Appendix.

STUDY SELECTION. We included RCTs assessing treatment strategies for BMS and DES ISR that met the following criteria. First, we included only RCTs. Second, each trial compared various types of intervention for BMS or DES ISR (e.g., DEB vs. DES, DEB vs. POBA, DES vs. POBA, or DEB vs. DES vs. POBA). Finally, clinical outcomes of efficacy (target lesion revascularization [TLR] or target vessel revascularization [TVR]) and safety (MI or all-cause mortality) during the minimal follow-up period of 6 months were clearly reported. We did not include trials that used cutting balloon angioplasty, vascular brachytherapy, or rotablation for ISR treatment.

DATA EXTRACTION AND QUALITY ASSESSMENT. Summary data as reported in the published articles were used in the analysis. A standardized form was used to extract detailed information from the RCTs. We primarily focused our analysis on the effect of the treatment strategies on TLR, not on the angiographic surrogate markers of restenosis (e.g., late lumen loss). The quality of eligible RCTs was assessed using the Cochrane Collaboration's tool for assessing the risk of bias for RCTs (Online Table 1). The last search was performed in March 2014.

OUTCOMES AND DEFINITIONS. The primary outcome was the incidence of TLR after treatment of ISR at the longest available follow-up. If the included trials reported only TVR instead of TLR, it was used for the primary outcome analysis. Secondary clinical outcomes included the incidence of any MI, all-cause mortality, and major adverse cardiovascular events (MACE) at the longest available follow-up. The definitions of repeat revascularization and MI in the each included trials are presented in Online Table 2. Secondary angiographic outcome included the rate of binary restenosis (>50% of diameter stenosis) at 6- to 9-month follow-up angiography.

DATA SYNTHESIS AND ANALYSIS. A Bayesian random effects model for multiple treatment comparisons was constructed to compare primary and secondary outcomes among the 3 treatment groups

ABBREVIATIONS AND ACRONYMS

ACCF/AHA/SCAI = American College of Cardiology/American Heart Association/Society for Cardiovascular Intervention

BMS = bare metal stent(s)

DAPT = dual-antiplatelet therapy

DEB = drug-eluting balloon(s)

DES = drug-eluting stent(s)

%DS = percentage of diameter stenosis

ISR = in-stent restenosis

MACE = major adverse cardiac event(s)

MI = myocardial infarction

PCI = percutaneous coronary interventions

POBA = plain old balloon angioplasty

RCT = randomized, controlled trial

TLR = target lesion revascularization

TVR = target vessel revascularization

(DEB, DES, and POBA). Odds ratios (ORs) with 95% credible intervals (CrIs) are presented as summary statistics. Sensitivity analyses were performed by: 1) repeating the main computations using a fixed-effects model; 2) analysis was restricted to trials with BMS ISR and, DES ISR; 3) first-generation DES as a treatment option for the ISR; 4) dual-antiplatelet agent treatment (DAPT) duration longer than 6 months, 5) DAPT duration <6 months, or 6) blinded outcome assessment by an independent clinical event adjudication committee. The present study was performed in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines; the review protocol has not been registered (Online Table 3).

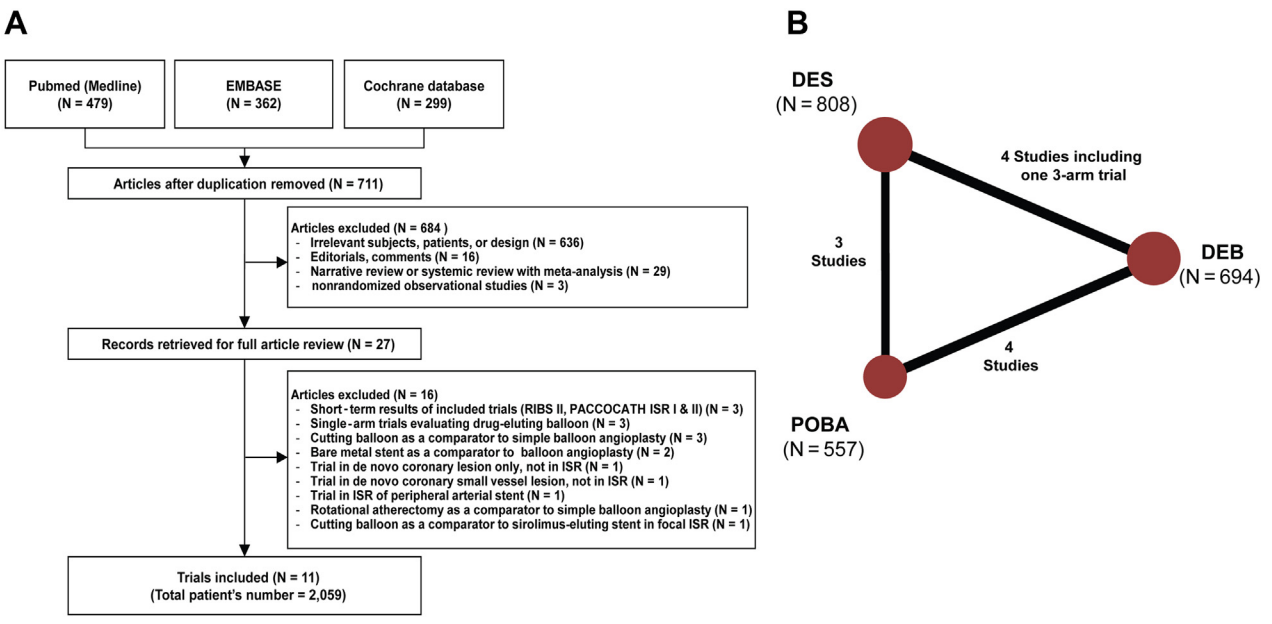
RESULTS

An expanded description of the study methods (trial characteristics, risk of bias within trials) are presented in the Online Appendix.

SEARCH RESULTS. We identified 1,140 citations, retrieved 27 studies for detailed evaluation, and found 11 RCTs that met the inclusion criteria (**Figure 1A**) (7-17) after excluding 16 studies whose characteristics are summarized in the Online Appendix. The interobserver agreement for study selection was high (κ = 0.91). The 11 RCTs included a total of 2,059 patients with BMS or DES ISR. They were treated with DES (n = 808, 39.2%), DEB (n = 694, 33.7%), or POBA (n = 557, 27.1%). Among 11 RCTs, 3 trials compared DES with DEB, 4 trials compared DEB with POBA, 3 trials compared DES with POBA, and one 3-arm trial compared DES, DEB, and POBA. The primary outcome (TLR) was collected from the longest available follow-up data, whereas 1-year secondary clinical outcomes (TLR, MI, all-cause mortality, and MACE) were extracted from the earlier reports. Among the 11 RCTs, 2 trials reported short- and long-term data separately: 1) the RIBS II (Restenosis In-Stent: Balloon Angioplasty vs. Elective Sirolimus-Eluting Stenting) trial separately reported 1-year (2006) and more than 3-year follow-up data (2008) (9,18); and 2) the PACCOCATH ISR (Treatment of In-Stent Restenosis by Paclitaxel-Coated Balloon) trial separately published the results of PACCOCATH ISR I first-in-human trial (2006) (5), PACCOCATH ISR I and II pooled 2-year outcomes (2008) (6), and PACCOCATH ISR I and II pooled long-term analysis (more than 5-year follow-up data [2012]) (12).

TRIAL CHARACTERISTICS. The main characteristics of the individual studies are summarized in **Table 1**. Regarding the type of ISR, 4 trials (7-9,19) exclusively enrolled BMS ISR, and 5 trials (10,11,14,16,17)

FIGURE 1 Flow Diagram of Trial Selection and Network Plot of Meta-Analysis Model



(A) The study flow diagram depicted following the PRISMA guidelines. **(B)** Network plot of meta-analysis model. DEB = drug-eluting balloon; DES = drug-eluting stent; ISR = in-stent restenosis; POBA = plain old balloon angioplasty.

TABLE 1 Characteristics of the Study

Trial (Year)	Treatment and No. of Patients (N = 1,862)			BMS or DES ISR	Inclusion Criteria	Exclusion Criteria	Type of Device		Repeat Revascularization Indication	MACE Definition	DAPT Protocol	CAG F/U	Clinical F/U
	DEB (N = 672)	DES (N = 694)	POBA (N = 496)				DEB	DES					
ISAR-DESIRE (2005)	N/A	200	100	BMS ISR	Angina pectoris and/or a positive stress test + BMS ISR >50%	AMI, LM, DES-ISR	N/A	Cypher, Taxus	Symptoms or documented ischemia with stenosis >50% in target vessel	N/R	6 months	6 months	1 yr
RIBS II (2008)	N/A	76	74	BMS ISR	Angina or documented ischemia with BMS ISR >50%	AMI, early (<4 wk) ISR, before brachytherapy	N/A	Cypher	Symptoms or documented ischemia with stenosis >50% in target vessel	Death (all) + MI + TVR	9 months	9 months	4 yrs
PEPCAD II (2009)	66	65	N/A	BMS ISR	Angina or documented ischemia with BMS ISR >70%	AMI, LM, ESRD, vessel diameter <2.5 mm, length >22 mm	Sequent Please	Taxus, Liberte	Symptoms or documented ischemia with stenosis >70% in target lesion	Death (all) + MI + TLR	3 months in DEB, 6 months in DES	6 months	1 yr
Habara et al. (2011)	25	N/A	25	DES ISR	Angina or documented ischemia with sirolimus- eluting stent ISR >50%	ACS, ESRD, ISR within 6 months, vessel diameter <2.5 mm or >3.5 mm, length >26 mm	Sequent Please	N/A	Symptoms or documented ischemia with stenosis >50% in target lesion	Death (all) + MI + TLR	6 months	6 months	6 months
ISAR-DESIRE 3 (2012)	137	131	134	DES ISR	Angina or documented ischemia with DES ISR >50% (everolimus-, biolimus-, zotarolimus-eluting stent)	Acute STEMI, LM, cardiogenic shock, ESRD	Sequent Please	Taxus Liberte	Symptoms or documented ischemia with stenosis >50% in target lesion	Death (all) + MI + TLR	6 months	6-8 months	1 yr
PEPCAD-DES (2012)	72	38	N/A	DES ISR	Angina or documented ischemia with DES ISR >50% (rapamycin-, everolimus-, sirolimus-, paclitaxel-eluting stent)	AMI, bifurcation, total occlusion of coronary artery, LM, vessel diameter <2.5 mm or >3.5 mm, length >22 mm	Sequent Please	N/A	Symptoms or documented ischemia with stenosis >50% in target lesion	Death (cardiac) + MI + TLR	6 months	6 months	6 months
PACCOCATH-ISR I&II Pooled Analysis (2012)	54	N/A	54	96% BMS ISR, 4% DES ISR	Angina or documented ischemia with BMS or DES ISR >70%	AMI, CRF (serum Cr >2.0 mg/dl), vessel diameter <2.5 mm, length ≥30 mm	PACCOCATH	N/A	Symptoms or documented ischemia with stenosis >70% in target lesion	Death (all) + MI + TLR + stroke	1 month	6 months	5 yrs
CRISTAL (2012)	N/A	136	61	DES ISR	Angina or documented ischemia with BMS or DES ISR >50% (sirolimus-, paclitaxel-eluting stent)	AMI, LM, thrombotic occlusion, bifurcation lesion, CRF (serum Cr >2.95 mg/dl), vessel diameter <2.25 mm or >4 mm, length >60 mm	N/A	Cypher Select	Symptoms or documented ischemia with stenosis >50% in target lesion	N/R	1 month for POBA, 6 months for DES	9 months	1 yr

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TABLE 1 Continued

Trial (Year)	Treatment and No. of Patients (N = 1,862) DEB (N = 672)	DES (N = 694)	POBA (N = 496)	BMS or DES ISR	Inclusion Criteria	Exclusion Criteria	Type of Device DEB	DES	Repeat Revascularization Indication	MACE Definition	DAPT Protocol	CAG F/U	Clinical F/U
Habara et al. (2013)	136	N/A	71	58% BMS ISR, 42% DES ISR	Angina or documented ischemia with BMS or DES ISR >50%	AMI, LVEF <30%, CRF (serum Cr >1.5 mg/dl), vessel diameter <2.0 mm or >4.0 mm, length >22 mm	Sequent Please	N/A	Symptoms or documented ischemia with stenosis >50% in target lesion	Death (all) + MI + TVR + ST	3 months	6 months	6 months
PEPCAD China ISR (2014)	109	106	N/A	DES ISR	Angina or documented ischemia with DES ISR >50%	AMI, bifurcation, thrombus in target vessel, CHF with NYHA functional class IV, ESRD, vessel diameter <2.5 mm or >4.0 mm, length >30 mm	Sequent Please	Taxus Liberte	Symptoms or documented ischemia with stenosis >50% in target lesion	TLF (CD + TVMI + TLR)	12 months	9 months	1 yr
RIBS V (2014)	95	94	N/A	BMS ISR	Angina or documented ischemia with BMS ISR >50%	AMI, Early (<4 wk) ISR, thrombus in target vessel, vessel diameter ≤2.0 mm, length >30 mm	Sequent Please	Xience Prime	Symptoms or documented ischemia with stenosis >50% in target vessel	Death (all) + MI + TVR	3 months for DEB, 1 yr for DES	6-9 months	1 yr

Trial (Year)	Age, yrs	Male	Proportion of Comorbidities HTN	DM	Dyslipidemia	Pre-MLD, mm Group 1		Group 2	Pre-DS Group 1		Group 2	Lesion Length, mm Group 1		Group 2	Post-MLD, mm Group 1		Group 2	Post-DS Group 1		Group2
ISAR-DESIRE (2005)	64.3	78.3	54.3	27.7	56.7	DES 0.94		POBA 0.95	DES 62.4		POBA 61.8	DES 11.95		POBA 12.3	DES 2.54*		POBA 2.07	DES 9.35*		POBA 19.9
RIBS II (2008)	64.0	75.3	54.7	34.7	61.3	DES 0.74		POBA 0.70	DES 72.0		POBA 74.0	DES 16.9		POBA 15.7	DES 2.69*		POBA 2.29	DES 8*		POBA 40
PEPCAD II (2009)	64.8	74.8	81.7	29.8	74.8	DEB 0.74		DES 0.77	DEB 73.9		DES 72.8	DEB 15.7		DES 15.4	DEB 2.30		DES 2.56*	DEB 19.5		DES 11.2*
Habara et al. (2011)	69.4	86.0	64.0	62.0	62.0	DEB 0.99		POBA 0.92	DEB 64.1		POBA 68.4	DEB 12.7		POBA 13.2	DEB 1.99		POBA 2.00	DEB 25.7*		POBA 31.0
ISAR-DESIRE 3 (2012)	67.9	71.6	73.6	41.5	77.9	DEB 0.97	DES 0.93	POBA 0.88	DEB 64.4	DES 66.7	POBA 67.7	DEB N/R	DES N/R	POBA N/R	DEB 2.29*	DES 2.53*	POBA 2.10	DEB 18.5*	DES 12.8*	POBA 23.3
PEPCAD-DES (2012)	67.8	70.9	94.5	35.4	78.2	DEB 0.66		POBA 0.62	DEB 72.1		POBA 74.0	DEB 11.2		POBA 12.2	DEB 2.15		POBA 2.14	DEB 12.6		POBA 13.7
PACCOCATH-ISR I&II Pooled Analysis (2012)	65.9	67.6	81.5	26.9	75.0	DEB 0.70		POBA 0.63	DEB N/R		POBA N/R	DEB 18.6		POBA 18.3	DEB 2.34		POBA 2.43	DEB N/R		POBA N/R
CRISTAL (2012)	67.7	71.6	75.1	39.1	79.2	DES 1.09		POBA 1.18	DES 58.8		POBA 53.7	DES 14.6		POBA 13.4	DES 2.51*		POBA 2.12	DES 9.5*		POBA 18
Habara et al. (2013)	69.0	82.7	84.6	44.7	82.7	DEB 0.86		POBA 0.84	DEB 65.6		POBA 66.1	DEB 12.8		POBA 13.7	DEB 1.97		POBA 1.90	DEB 21.9		POBA 23.1

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TABLE 1 Continued

Trial (Year)	Age, yrs	Male	Proportion of Comorbidities			Pre-MLD, mm		Pre-DS		Lesion Length, mm		Post-MLD, mm		Post-DS	
			HTN	DM	Dyslipidemia	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2	Group 1	Group2
PEPCAD China ISR (2014)	61.9	80.9	68.4	36.7	34.0	DEB	DES	DEB	DES	DEB	DES	DEB	DES	DEB	DES
						0.85	0.86	68.3	68.4	12.5	13.1	2.39	2.56*	10.5	7.1*
RIBS V (2014)	65.5	86.8	72.0	25.9	69.3	DEB	DES	DEB	DES	DEB	DES	DEB	DES	DEB	DES
						1.02	0.93	61.0	65.0	13.7	13.8	2.16	2.38*	19.0	11.0*

Values are % unless otherwise indicated. Asterisks denote statistically significant difference in the parameters compared with other treatment groups.

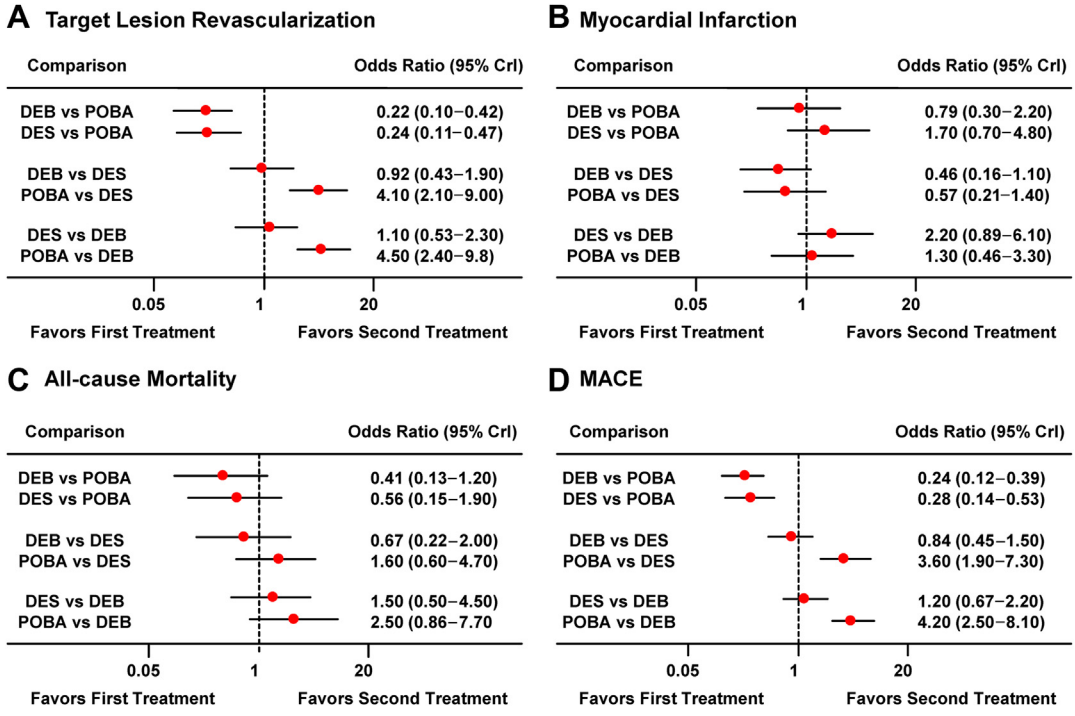
ACS = acute coronary syndrome; AMI = acute myocardial infarction; BMS = bare-metal stent; CAG = coronary angiography; CHF = congestive heart failure; Cr = creatinine; CRF = chronic renal failure; CRISTAL = Cypher Restenosis IntraSTent triAL; DAPT = dual antiplatelet therapy; DEB = drug-eluting balloon; DES = drug-eluting stent; DM = diabetes mellitus; DS = diameter stenosis; ESRD = end-stage renal disease (estimated glomerular filtration rate <30 ml/min); F/U = follow-up; HTN = hypertension; ISAR-DESIRE = The Intracoronary Stenting or Angioplasty for Restenosis Reduction - Drug-Eluting Stents for In-Stent Restenosis; ISR = in-stent restenosis; LM = left main; LVEF = left ventricular ejection fraction; MACE = major adverse cardiovascular event(s); MI = myocardial infarction; MLD = minimal lumen diameter; N/A = not applicable; N/R = not reported; NYHA = New York Heart Association; PACCOCATH-ISR = Treatment of In-Stent Restenosis by Paclitaxel-Coated Balloon; PEPCAD II = Paclitaxel-Eluting PTCA Balloon Catheter in Coronary Artery Disease; PEPCAD DES = Treatment of DES-In-Stent Restenosis With SeQuent® Please Paclitaxel Eluting PTCA Catheter in Coronary Artery Disease; POBA = plain old balloon angioplasty; RIBS = Restenosis Intra-stent: Drug-eluting Balloon vs. Everolimus-eluting Stent; ST = stent thrombosis; STEMI = ST-segment elevation myocardial infarction; TLF = target lesion failure; TLR = target lesion revascularization; TVR = target vessel revascularization; TVMI = target vessel myocardial infarction.

exclusively enrolled DES ISR. The remaining 2 trials enrolled BMS or DES ISR; however, the majority were BMS ISR (96% in the PACCOCATH ISR I and II pooled analysis published in 2012; 58% in Habara et al. [15] published in 2013) (12,15). Regarding the complexity of lesion or clinical profiles, all trials excluded the patients who had high-risk features of PCI. Thus, all trials enrolled patients with stable or unstable angina without high-risk features of PCI. The DAPT protocols were different across the trials, as presented in **Table 1**. Regarding treatment strategies, trials with DEB as one of the treatment arms used a paclitaxel-eluting balloon (Sequent Please, B. Braun Melsungen AG, Berlin, Germany or PACCOCATH, Bayer AG, Leverkusen, Germany), which were coated with 3 μg/mm^2 of paclitaxel on the balloon surface. All trials (except the RIBS V trial) with DES as one of the treatment arms used first-generation DES including sirolimus-eluting stents (Cypher or Cypher Select, Cordis Corporation, Miami Lakes, Florida) or paclitaxel-eluting stent (Taxus or Taxus Liberte, Boston Scientific Corporation, Natick, Massachusetts). Only the RIBS V trial used second-generation DES (everolimus-eluting stent, Xience Prime, Abbott Vascular, Illinois) to treat ISR of the previous stent (**Table 1**) (13). As expected, the DES group mostly showed a significantly greater post-treatment minimal lumen diameter or lower percentage of diameter stenosis (%DS) than the DEB or POBA group. However, there were no significant differences in post-treatment minimal lumen diameter or %DS between the DEB and POBA groups (**Table 1**).

RISK OF BIAS WITHIN TRIALS. Expanded descriptions of the risk of bias assessment are presented in the Online Appendix. A full description of the summary of risk of bias judgments of each study is available in Online Figures 1 and 2 and Online Table 1.

COMPARISON OF OVERALL CLINICAL OUTCOMES OF THE 3 TREATMENT STRATEGIES FOR ISR. As shown in **Figure 1**, this meta-analysis included 11 RCTs (7–17), all of which provided the incidence of TLR, MI, and all-cause mortality. **Figure 2** illustrates the Bayesian ORs and 95% CrIs in a pooled comparison of DEB, DES, and POBA to treat ISR. Both DEB (OR: 0.22, 95% CrI: 0.10 to 0.42) and DES (OR: 0.24, 95% CrI: 0.11 to 0.47) significantly reduced the risk of TLR at the longest available follow-up in a random-effects model compared with POBA as the reference group. In a comparison of DEB and DES, the risk of TLR was similar in the 2 groups (OR: 0.92, 95% CrI: 0.43 to 1.90). The odds of POBA were ~4.1 to 4.5 times higher than the odds of DEB or DES (**Figure 2A**). The significant benefit of DEB or DES compared with POBA was

FIGURE 2 Results of Bayesian Network Meta-Analysis for Overall Rates of Clinical Outcomes in a Random Effects Model



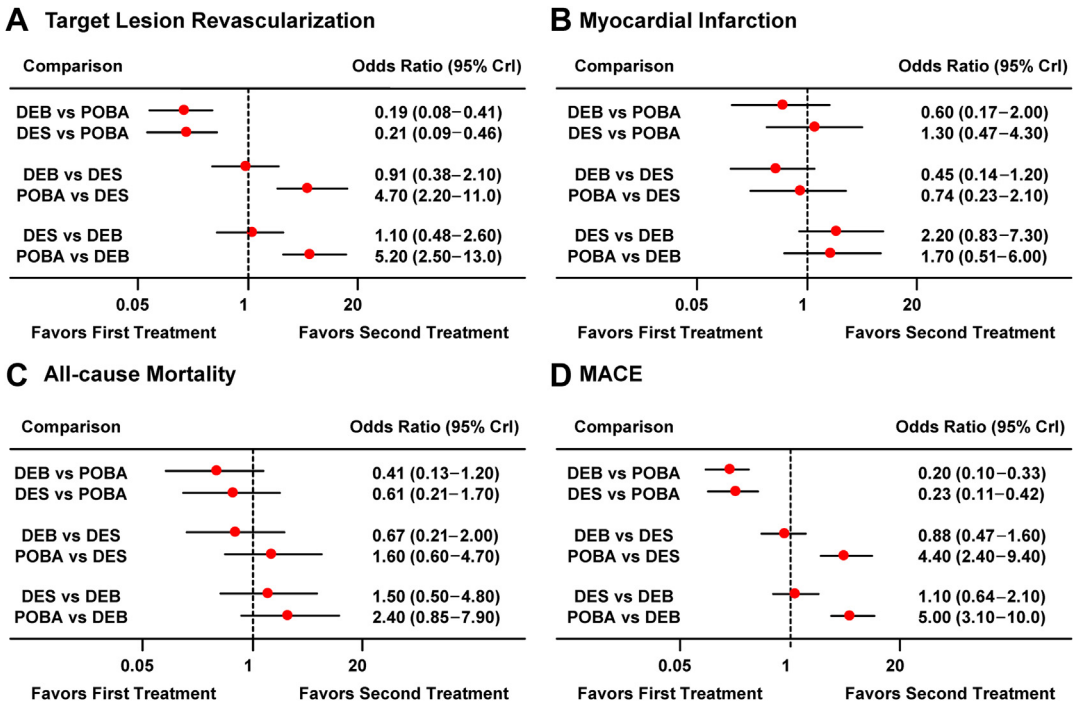
Results of a Bayesian network meta-analysis with a random-effects model for the risk of target lesion revascularization **(A)**, myocardial infarction **(B)**, all-cause mortality **(C)**, major adverse cardiovascular events in longest available follow-up periods **(D)**. CrI = 95% credible interval; MACE = major adverse cardiac events; other abbreviations as in Figure 1.

consistently observed in both direct and indirect estimates of the comparison with an acceptable range of statistical heterogeneity (Online Figure 3A). Regarding the risk of MI or all-cause mortality, there was no difference in the 3 strategies. However, the risk of MI was slightly higher after DES compared with DEB and POBA, and all-cause mortality was slightly higher after POBA compared with DEB or DES, although these results were insignificant (**Figures 2B and 2C**). The risk of MACE, mainly driven by TLR, was significantly lower in the DEB and DES groups than in the POBA group, whereas it was similar in the DEB and DES groups (**Figure 2D**). The pooled estimates on direct and indirect comparison were also consistent without significant heterogeneity in each comparison for the risk of MI, all-cause mortality, and MACE (Online Figures 3B to 3D). A fixed-effects model of a Bayesian network meta-analysis showed results similar to those of a random-effects model (Online Figure 4).

COMPARISON OF CLINICAL OUTCOMES IN 1-YEAR OF THE 3 TREATMENT STRATEGIES FOR ISR. Because each trial had a different clinical follow-up period, all clinical events at 1-year follow-up were also compared. As with the results of overall clinical events, the risk of TLR or MACE at 1 year was significantly lower after DEB and DES than after POBA, whereas it was similar between the DEB and DES (**Figures 3A and 3D**). The risk of MI or all-cause mortality showed a similar trend with overall clinical events: insignificantly higher MI after DES than after DEB and insignificantly higher mortality after POBA than after DEB (**Figures 3B and 3C**).

COMPARISON OF ANGIOGRAPHIC OUTCOMES AT 6- TO 9-MONTH FOLLOW-UP ANGIOGRAPHY AND THE INCIDENCE OF STENT THROMBOSIS. All trials reported the incidence of binary restenosis, which was evaluated at 6- to 9-month follow-up angiography and quantitative coronary angiographic analysis. The risk of binary restenosis was significantly lower in the DEB (OR: 0.13, 95% CrI: 0.06 to 0.25) and DES (OR: 0.20, 95% CrI: 0.09 to 0.40) groups than in the POBA group, whereas it was not different between the DEB and DES groups (OR: 0.66, 95% CrI: 0.31 to 1.30) (**Figure 4A**). There was neither inconsistency nor significant heterogeneity across

FIGURE 3 Results of Bayesian Network Meta-Analysis for 1-Year Rates of Clinical Outcomes in Random-Effects Model



Results of a Bayesian network meta-analysis with a random-effects model for the risk of target lesion revascularization **(A)**, myocardial infarction **(B)**, all-cause mortality **(C)**, major adverse cardiovascular events within 1-year follow-up period **(D)**. Abbreviations as Figures 1 and 2.

the direct or indirect comparison of risk of binary restenosis (Figure 4C). Of the 11 RCTs, all trials except ISAR-DESIRE (The Intracoronary Stenting or Angioplasty for Restenosis Reduction - Drug-Eluting Stents for In-Stent Restenosis) reported the incidence of Academic Research Consortium-defined stent thrombosis. The risk of stent thrombosis (definite, probable, or possible) was not different in the 3 treatment groups; however, a statistically significant inconsistency was observed (Figures 4B and 4D).

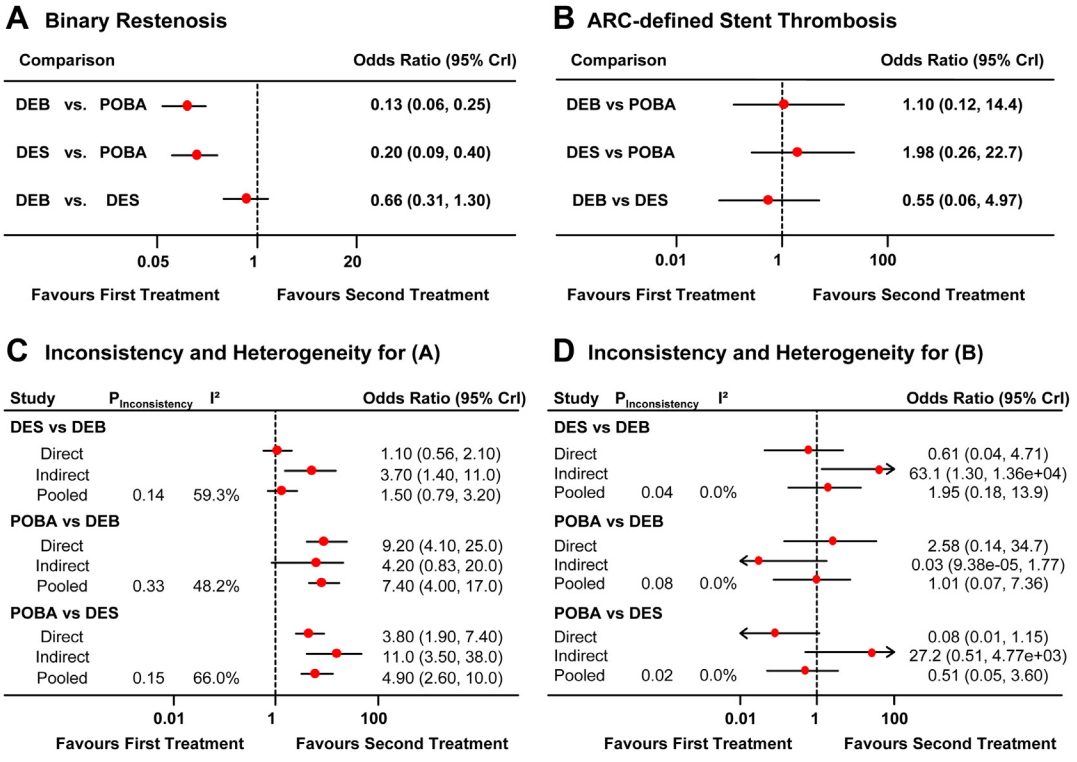
RANKING THE PROBABILITY OF EFFICACY AND SAFETY OUTCOMES. Figure 5 shows the ranking probability for each treatment option associated with the lowest rate of each clinical outcome. For repeat revascularization (efficacy), there was a 59.9% probability that DEB were associated with the lowest rates of TLR compared with DES (40.1%) and POBA (<0.1%) (Figure 5A). As with the results of TLR, DEB consistently showed the highest probability to be ranked as the better treatment option for ISR in terms of MI (63.0%), all-cause mortality (78.9%), and MACE (74.1%) (Figures 5B to 5D). DES showed the highest probability of being ranked as the second treatment option for ISR in terms of TLR, all-cause mortality, or MACE, whereas in terms of MI, DES showed lowest rank probability to reduce the risk of MI after treatment for ISR (Figure 5B).

SENSITIVITY ANALYSES. For the risk of overall TLR, sensitivity analyses were performed, as presented in Figure 6. The results of the sensitivity analysis were mostly similar to the results of the main analysis, which showed significantly reduced TLR with DEB or DES than with POBA with no difference in the DEB and DES groups. However, analysis of trials that exclusively enrolled patients with BMS ISR or trials with a DAPT duration <6 months showed a statistically nonsignificant trend favoring DEB or DES rather than POBA. In addition, analysis after excluding trials with unclear or non-blinded outcome assessment showed similar results to the main analysis (Figure 6).

DISCUSSION

This is the first Bayesian network meta-analysis that compared the clinical efficacy and safety of 3 different current strategies (DEB, DES, and POBA) to treat ISR of previously implanted BMS or DES. Our results clearly show the superiority of DEB or DES to POBA in

FIGURE 4 Results of Bayesian Network Meta-Analysis for Binary Restenosis at 6- to 9- Month Follow-up Angiography and ARC-Defined Stent Thrombosis

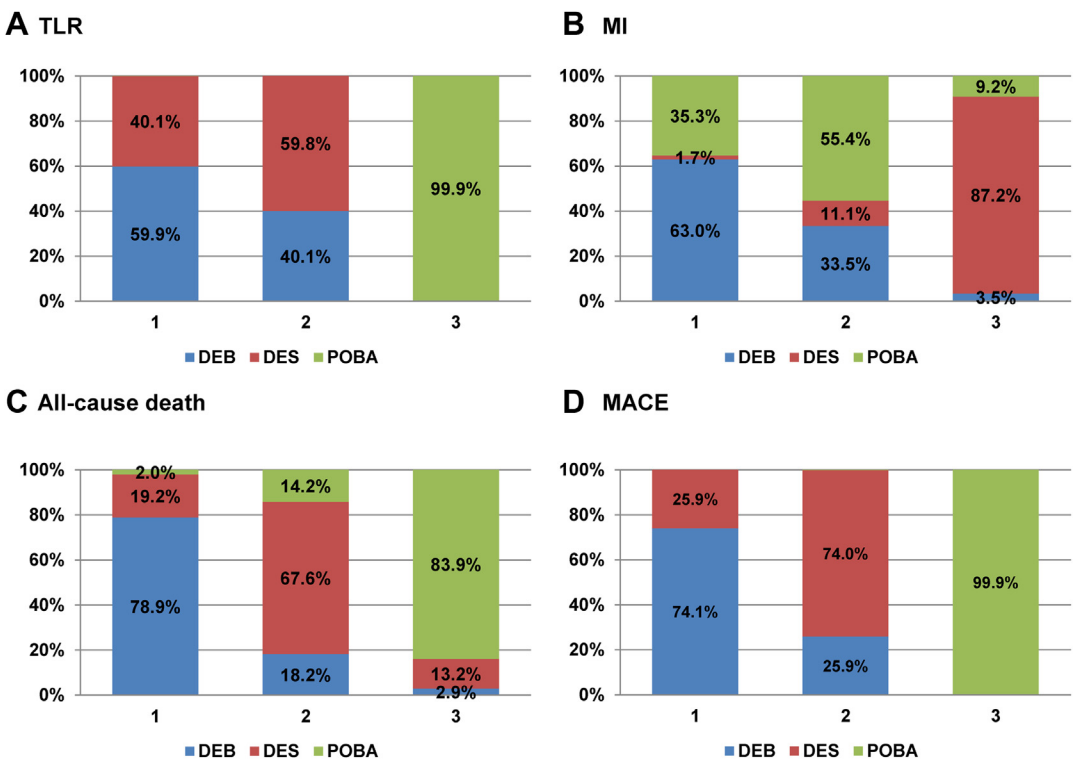


Results of a Bayesian network meta-analysis with a random-effects model for the risk of binary restenosis **(A)**, which was a measure by quantitative coronary angiography, at 6- to 9-month follow-up angiography, and ARC-defined stent thrombosis (definite, probable, or possible stent thrombosis) **(B)**. Analysis of consistency and heterogeneity in the network meta-analysis model for binary restenosis **(C)** and stent thrombosis **(D)**. ARC = Academic Research Consortium; other abbreviations as in Figures 1 and 2.

the prevention of repeat revascularization of target lesions or major adverse cardiovascular outcome. On angiographic outcome analysis, DEB or DES also showed a significantly lower risk of binary restenosis at 6- to 9-month follow-up angiography than POBA. When we compared DEB and DES, the efficacy was comparable, whereas in terms of safety, DEB showed a trend of lower risk of MI or all-cause mortality than DES without statistical significance. DEB had the highest probability of being ranked as the first treatment option for ISR with the lowest risk of TLR, MI, all-cause mortality, and MACE. The beneficial effects of DEB in reducing the risk of TLR were consistently observed in various sensitivity analyses, regardless of whether previous treatment was with BMS or DES. DES had the highest probability of being ranked as the second treatment option for ISR in terms of TLR, all-cause mortality, and MACE. However, in terms of MI, it showed lowest rank probability in reducing the risk of MI after treatment for ISR.

CURRENT STATUS OF STENT FAILURE: CLINICAL IMPACT AND GUIDELINES. With the introduction of contemporary second- or third-generation DES, the rate of repeat revascularization due to ISR decreased, but its prevalence is not negligible: ~3% rate at 1-year follow-up in Asian cohorts such as the EXCELLENT (Efficacy of Xience/promus versus Cypher in rEducing Late Loss after stenting) randomized trial (20) or RESOLUTE Korea registry (21). This failure rate would be higher when PCI is performed in high-risk patients with complex coronary lesions. Patients with complex coronary lesions in Western cohorts showed an ~5% rate of binary restenosis at 13-month follow-up angiography and an 8.6% rate of cumulative TLR at 4-year follow-up in the RESOLUTE All Comers trial (22). The LEADERS (Limus Eluted From A Durable Versus ERodable Stent Coating) trial also showed a 5.5% rate of binary restenosis and a 6.3% rate of TVR at 5-year follow-up (23). Despite the progressive nature of ISR, a substantial proportion of the patients

FIGURE 5 Probability Ranking of Each Treatment Arm Regarding Overall Clinical Outcomes

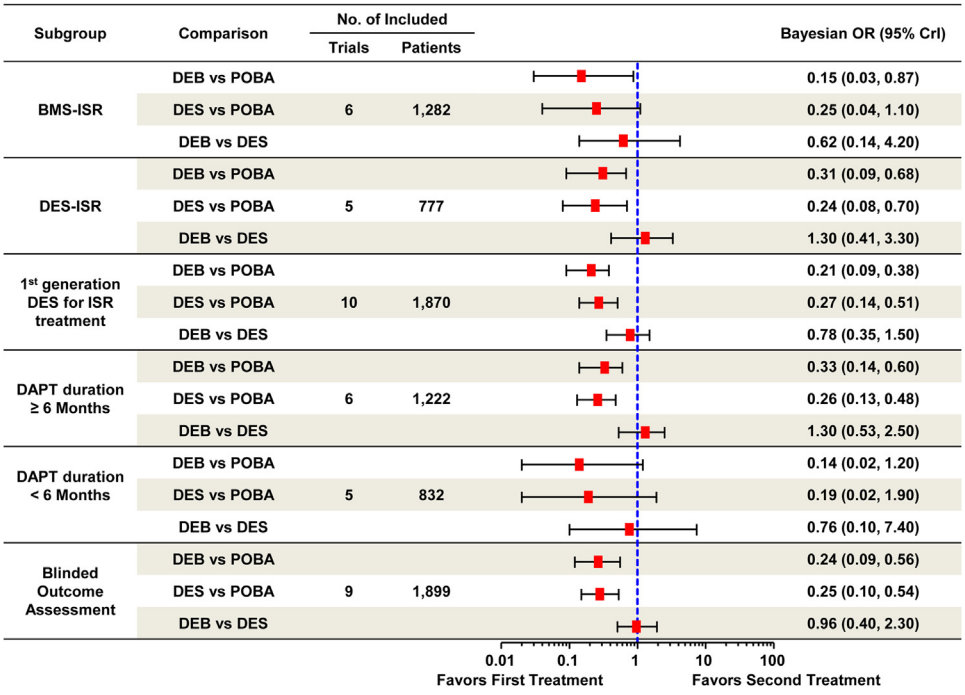


Graphs of the probability ranking of each treatment arm for the risk of target lesion revascularization **(A)**, myocardial infarction **(B)**, all-cause mortality **(C)**, major adverse cardiovascular events **(D)** in longest available follow-up periods. On the horizontal axis is the possible ranking of each treatment (from best to worst according to the outcome). MI = myocardial infarction; TLR = target lesion revascularization; other abbreviations as in Figures 1 and 2.

with ISR could present as acute coronary syndrome, and the patients with ISR showed a significantly worse clinical outcome than the patients without ISR, even after the successful treatment of ISR (1,24). These results of previous studies imply that the optimal treatment of patients with ISR is still an important issue, even in the era of new-generation DES. However, the current guidelines are limited to DES (ACCF/AHA/SCAI 2011 guidelines for PCI; Class I, Level of Evidence: A) or DEB (European Society of Cardiology 2010 guidelines for myocardial revascularization; Class IIa, Level of Evidence: B) for the treatment of BMS ISR (3,4), with no consensus for the treatment of DES ISR, which might be a more important issue in real-world practice (3).

EFFICACY AND SAFETY OF DEB VERSUS DES FOR ISR LESIONS. The current network meta-analysis showed clear efficacy of DEB or DES over POBA in reducing the risk of TLR, regardless of the type of previously placed stent (BMS or DES) (Figure 6). Although DEB was comparable to DES in reducing TLR, it should be noted that DEB group showed a significantly smaller post-procedural minimal lumen diameter (therefore less acute gain) and more severe residual %DS than the DES group in the individual trials (Table 1). Comparable efficacy even with smaller acute gain suggests that late loss after DEB would be less than that of DES. Inserting an additional metal structure in the ISR lesion would induce a substantial degree of new tissue or thrombus deposition, which would be less after using DEB. The most interesting finding regarding the safety of the 3 different strategies for ISR lesions was the disappointing results of DES in MI risk. The probability to be ranked as the first treatment option in terms of MI was 63.0% with DEB and only 1.7% with DES. This result implies the potential hazard of implanting an additional polymer-coated metal structure into the lumen of ISR, such as delayed re-endothelialization and inflammation, which are predisposing factors for stent thrombosis

FIGURE 6 Sensitivity Analysis for Overall Risk of Target Lesion Revascularization



Sensitivity analyses were performed by restricting the Bayesian network meta-analysis in a random-effects model to trials with bare metal stent ISR, DES ISR, first-generation DES as a treatment option for the ISR, DAPT duration of 6 months or longer, DAPT duration <6 months, or blinded outcome assessment. DAPT = dual-antiplatelet therapy; other abbreviations as in Figures 1 and 2.

and the late catch-up phenomenon (2,24). In addition, much less risk of side-branch occlusion with DEB than DES in the treatment of ISR might be one of the potential explanations for less development of MI in the DEB group after treatment of ISR. However, because none of included trials separately provided the detailed incidence of periprocedural MI with the incidence of MI originating from stent thrombosis, this should be interpreted as hypothesis generating.

Previously, 2 meta-analyses evaluated the efficacy and safety of DEB, compared with POBA or DES (25,26). On the basis of 4 or 5 RCTs, the 2 analyses reported superior efficacy of DEB compared with a control group. However, they combined the 2 completely different interventions (i.e., POBA and first-generation DES) into 1 control group. Moreover, only 1 trial in each meta-analysis compared the efficacy of DEB with that of DES. Therefore, the overall superior efficacy of DEB was mainly driven by the comparison with the POBA group. Because DESs have constantly shown superior efficacy in the treatment of ISR compared with POBA, one of the key questions in practice would be the head-to-head comparison of DEB and DES. In this context, mixing the results of DES with POBA compromises the key comparison of importance and cannot be justified. Our results are on the basis of the highest number of RCTs and included the most recent trials, which have not been used in previous meta-analyses. In addition, using the Bayesian approach also enables a true comparison of the 3 different modalities for ISR treatment.

Considering the results of the current network meta-analysis, DEB might be the suitable first-line treatment for ISR of previously implanted BMS or DES, especially in patients who cannot tolerate long-term DAPT. Nonetheless, it should be noted that 6 of 7 RCTs that had a DES arm to treat ISR actually used old-fashioned first-generation DES such as sirolimus-eluting or paclitaxel-eluting stents. Only the RIBS V trial used second-generation everolimus-eluting stent (Xience Prime), which has been proved to be superior to first-generation DES (27). In the RIBSV trial, DES were comparable to DEB both in the rates of MI and TLR (13). However, due to the limited sample size of the RIBS V trial, the comparison of efficacy and safety endpoints between DEB and newer generation DES needs more evidence. Currently, DARE (Drug Eluting bAlloon for In-stent Restenosis)

(NCT01127958) and RIBS IV (NCT01239940) trials are ongoing comparing DEB with everolimus-eluting stents to treat ISR. We hope future trials will clarify the performance of DEB versus DES in the treatment of ISR.

INFLUENCE OF DAPT DURATION ON THE PERFORMANCE OF DEB OR DES FOR ISR LESIONS. On sensitivity analysis according to the DAPT protocol, the superiority of DEB or DES to POBA was inconclusive in a pooled analysis of trials with a DAPT duration <6 months, whereas it was more definite in the trials with DAPT duration of longer than 6 months. This result suggests that strategies of local drug delivery to ISR lesions may delay the healing process and may require a longer duration of DAPT. However, we can point out that some trials with a DAPT duration of <6 months had a different DAPT duration in each treatment arm (7,12,13,15,17). In the CRISTAL (Cypher Restenosis IntraSTent triAL) trial, in the POBA group, a 1-month duration of DAPT was used compared with 6 months in the DES group, and in the RIBS V trial, a 3-month duration of DAPT was used in the DEB group compared with 1 year in the DES group. Therefore, the pooled analysis of trials with a DAPT duration <6 months could be biased among the treatment groups. The optimal duration of DAPT to maximize the clinical outcome after DEB angioplasty remains uncertain. Further RCTs might be warranted regarding this subject.

STUDY LIMITATIONS. Some important limitations of the study should not be ignored. First, this meta-analysis included clinically and methodologically diverse studies, as mentioned earlier. Second, this network meta-analysis has limited information regarding the comparison between DEB and current newer generation DES. Third, as this is a study-level meta-analysis, we could not adjust for patient-level confounders, especially the differences in post-treatment minimal lumen diameter or %DS among the treatment arms. Fourth, 2 of 11 RCTs only reported the incidence of TVR (Online Figure 5A) (8,9), although we used TLR as a primary endpoint. However, excluding those trials that presented only the incidence of TVR, the overall results showed exactly the same results as the original results (Online Figure 5B). In addition, in the pooled analysis regarding the incidence of TVR only, the overall results were also similar to the original results (Online Figure 5B). Fifth, some cautions are warranted in interpreting the results of a pooled analysis of stent thrombosis. There was a total of 16 events of Academic Research Consortium-defined definite or probable stent thrombosis; 7 in the DES group, 4 in the DEB group, and 5 in the POBA group. Among them, 1 in the DEB and 4 in the POBA group were probable or possible stent thrombosis, which was not confirmed by coronary angiography. The incidence of events was extremely low with a wide CrI, and a statistically significant inconsistency was observed in the pooled analysis of stent thrombosis. The duration of DAPT differed among the 3 treatment groups in each trial. Finally, all trials excluded the high-risk PCI population, such as ISR presenting with acute MI or ISR of an unprotected left main stent. Therefore, the results of this network meta-analysis cannot be applied to this high-risk PCI population.

CONCLUSIONS

Given the prognostic importance of ISR, the optimal treatment strategy should be carefully selected. Our results showed the efficacy of DEB and DES to be superior to that of POBA and similar efficacy and safety with DEB and DES.

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KEY WORDS controlled trial, drug-eluting balloons, drug-eluting stents, in-stent restenosis, meta-analysis, randomized

APPENDIX For supplemental material as well as tables and figures, please see the online version of this article.