Percutaneous coronary interventional strategies for treatment of in-stent restenosis: a network meta-analysis

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Summary

Background **Percutaneous coronary intervention (PCI) with drug-eluting stents is the standard of care for treatment of native coronary artery stenoses, but optimum treatment strategies for bare metal stent and drug-eluting stent in-stent restenosis (ISR) have not been established. We aimed to compare and rank percutaneous treatment strategies for ISR.**

Methods **We did a network meta-analysis to synthesise both direct and indirect evidence from relevant trials. We searched PubMed, the Cochrane Library Central Register of Controlled Trials, and Embase for randomised controlled trials published up to Oct 31, 2014, of different PCI strategies for treatment of any type of coronary ISR. The primary outcome was percent diameter stenosis at angiographic follow-up. This study is registered with PROSPERO, number CRD42014014191.**

Findings **We deemed 27 trials eligible, including 5923 patients, with follow-up ranging from 6 months to 60 months after the index intervention. Angiographic follow-up was available for 4975 (84%) of 5923 patients 6–12 months after the intervention. PCI with everolimus-eluting stents was the most effective treatment for percent diameter stenosis, with a difference of –9·0% (95% CI –15·8 to –2·2) versus drug-coated balloons (DCB), –9·4% (–17·4 to –1·4) versus sirolimus-eluting stents, –10·2% (–18·4 to –2·0) versus paclitaxel-eluting stents, –19·2% (–28·2 to –10·4) versus vascular brachytherapy, –23·4% (–36·2 to –10·8) versus bare metal stents, –24·2% (–32·2 to –16·4) versus balloon angioplasty, and –31·8% (–44·8 to –18·6) versus rotablation. DCB were ranked as the second most effective treatment, but without significant differences from sirolimus-eluting (–0·2% [95% CI –6·2 to 5·6]) or paclitaxel-eluting (–1·2% [–6·4 to 4·2]) stents.**

Interpretation **These findings suggest that two strategies should be considered for treatment of any type of coronary ISR: PCI with everolimus-eluting stents because of the best angiographic and clinical outcomes, and DCB because of its ability to provide favourable results without adding a new stent layer.**

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See **Comment** pages 627 and 628

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See **Online** for appendix

Introduction

Drug-eluting stents (DES), introduced in 2002, have improved clinical outcomes of patients with coronary artery disease by mitigating the risk of in-stent restenosis (ISR) compared with bare metal stents (BMS).[1,2] Early-generation DES have been largely substituted by new-generation, thin-strut DES, with biocompatible polymers releasing predominantly limus analogues, which has improved on the safety and efficacy profile of early devices.[3,4] Nevertheless, ISR needing repeat revascularisation is still encountered in 5–10% of patients undergoing percutaneous coronary intervention (PCI) with DES, and in 20–30% after PCI with BMS.[5–7]

The optimum percutaneous treatment strategy for patients presenting with ISR is still debated.[8] Different strategies have yielded variable results, including balloon angioplasty (BA), vascular brachytherapy (VBT), rotablation (ROTA), BMS implantation, drug-coated balloons (DCB) angioplasty, and DES implantation. However, evidence derived from randomised trials is limited to few and small-scale studies.[8] In view of the different comparators used in these trials, traditional meta-analysis methods do not allow adequate assessment of the comparative effectiveness of all treatment strategies. Therefore, we did a network meta-analysis of all relevant randomised evidence to comprehensively compare and rank percutaneous strategies for ISR treatment.

Methods

Search strategy and selection criteria

We identified randomised controlled trials (RCTs) published up to Oct 31, 2014, comparing different PCI strategies for treatment of coronary ISR by searching the following databases: PubMed, the Cochrane Library Central Register of Controlled Trials, and Embase. We screened the ClinicalTrials.gov and Current Controlled Trials registries to ensure identification of all trials. We developed and adapted a modified search algorithm for each database with a combination of relevant terms as proposed by Cochrane for systematic reviews of RCTs (appendix). We contacted principal investigators of trials available only as conference abstracts or presentations at the time of our search to substantiate accuracy of the data needed. Finally, we searched for additional eligible trials

For the **protocol** see http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42014014191

in reference lists of retrieved publications and relevant meta-analyses in the discipline. Two independent investigators (GCMS and GGS) completed the search for eligible studies on Oct 31, 2014.

	Year	Type of ISR	Interventions	Sample size (control/intervention)	Follow-up (months)	
					Angiographic	Clinical
VBT						
Gamma-1[25]	2001	BMS	BA *vs* VBT	252 (121/131)	6	9
START[26,27]	2002	BMS	BA *vs* VBT	476 (232/244)	8	24
Reynen et al[28]	2006	BMS	BA *vs* VBT	165 (78/78)	6	12
ROTA						
ARTIST[29-31]	2002	BMS	BA *vs* ROTA	298 (146/152)	6	6
ROSTER[32]	2004	BMS	BA *vs* ROTA	200 (100/100)	6–9	12
BMS						
RIBS[33-35]	2003	BMS	BA *vs* BMS	450 (226/224)	6	52
Ragosta et al[36]	2004	BMS	BA *vs* BMS	58 (29/29)	NA	9
Ragosta et al[36]	2004	BMS	ROTA *vs* BMS	55 (30/25)	NA	9
Alfonso et al[37]	2005	BMS	BA *vs* BMS	40 (20/20)	6	24
DES						
ISAR-DESIRE[38]	2005	BMS	BA *vs* PES *vs* SES	300 (100/100/100)	6	12
RIBS-II[39,40]	2006	BMS	BA *vs* SES	150 (74/76)	9	38
SISR[41-43]	2006	BMS	VBT *vs* SES	384 (125/259)	6	60
TAXUS V ISR[44,45]	2006	BMS	VBT *vs* PES	396 (201/195)	9	24
Schukro et al[46]	2007	BMS	VBT *vs* PES	37 (17/20)	6	6
INDEED[47]	2008	BMS	VBT *vs* SES	129 (64/65)	6	12
ISAR-DESIRE 2[48]	2010	DES	PES *vs* SES	450 (225/225)	6–8	12
CRISTAL[49]	2012	DES	BA *vs* SES	197 (61/136)	12	12
Song et al[50]	2012	DES	BA *vs* SES	96 (48/48)	9	12
Song et al[50]	2012	DES	SES *vs* EES	66 (32/34)	9	12
RIBS V[51]	2014	BMS	DCB *vs* EES	189 (95/94)	9	12
RIBS IV[52]	2015	DES	DCB *vs* EES	309 (154/155)	9	12
DCB						
PACCOCATH-ISR I[53-55] and II[54,55]	2006 (I)–2008 (II)	BMS and DES	BA *vs* DCB	108 (54/54)	6	60
PEPCAD II[56]	2009	BMS	PES *vs* DCB	131 (65/66)	6	12
Habara et al[57]	2011	DES	BA *vs* DCB	50 (25/25)	6	6
PEPCAD-DES[58]	2012	DES	BA *vs* DCB	110 (38/72)	6	6
Habara et al[59]	2013	BMS and DES	BA *vs* DCB	210 (72/138)	6	6
ISAR-DESIRE 3[60]	2013	DES	BA *vs* PES *vs* DCB	402 (134/131/137)	6–8	12
PEPCAD China ISR[61]	2014	DES	PES *vs* DCB	215 (106/109)	9	12

ISR=in-stent restenosis. VBT=vascular brachytherapy. START=Stents And Radiation Therapy. BMS=bare metal stents. BA=balloon angioplasty. ROTA=rotablation. ARTIST=Angioplasty Versus Rotational Atherectomy for Treatment of Diffuse In-Stent Restenosis Trial. ROSTER=Rotational Atherectomy Versus Balloon Angioplasty for Diffuse In-Stent Restenosis. RIBS=Restenosis Intra-stent: Balloon Angioplasty Versus Elective Stenting. NA=not available. DES=drug-eluting stents. ISAR-DESIRE=Intracoronary Stenting and Angiographic Results: Drug Eluting Stents for In-Stewnt Restenosis. PES=paclitaxel-eluting stents. SES=sirolimus-eluting stents. SISR=Sirolimus-Eluting Stents Versus Vascular Brachytherapy for In-Stent Restenosis. TAXUS V ISR=Paclitaxel-eluting Stents vs Brachytherapy for In-stent Restenosis. INDEED=In-stent Restenosis with Drug-Eluting Stents *vs* Intracoronary Beta-radiation. CRISTAL=Cypher Restenosis Intrastent Trial. EES=everolimus-eluting stents. DCB=drug-coated balloons. PACCOCATH-ISR=Treatment of In-Stent Restenosis by Paclitaxel Coated Percutaneous Transluminal Coronary Angioplasty Balloons. PEPCAD=Paclitaxel Coated Percutaneous Transluminal Coronary Angioplasty Balloon in Coronary Artery Disease.

Table 1: **Randomised controlled trials included in the network meta-analysis**

Study selection and data extraction

We included RCTs that investigated any type of PCI strategy for treatment of coronary ISR. Trials were eligible irrespective of the type of ISR (BMS-related or DES-related restenosis). We excluded studies that allowed a combination of interventions in one study arm (ie, BA, ROTA, or stenting), those with laser atherectomy as the only intervention in a study arm because we did not deem this intervention effective as single therapy, and those comparing cutting balloon with traditional BA because we deemed cutting balloons equivalent to BA for ISR treatment. Two investigators (GCMS and GGS) selected studies independently. Any discrepancies were resolved by consensus and arbitration by a third investigator (SW).

Two investigators (GCMS and KCS) independently reviewed the main reports and supplementary materials and extracted study and patient characteristics, lesion characteristics, and details about PCI strategies and antiplatelet regimens and in-segment and in-stent quantitative angiographic measurements before PCI, immediately after the procedure, and at the time of angiographic follow-up.

Outcomes

We considered the longest available angiographic and clinical follow-up periods for our analysis. To assess device-specific angiographic effectiveness, we chose percent diameter stenosis at the time of angiographic follow-up as the primary endpoint and binary restenosis as a secondary endpoint. Another key secondary endpoint was target–lesion revascularisation (TLR) as a measure of clinical effectiveness; when TLR was not reported, we documented target–vessel revascularisation. Additional secondary endpoints were myocardial infarction and all-cause mortality. If two different groups of randomisation of non-overlapping patient groups (ie, A *vs* B and C *vs* D) were included in the same report, we considered each group separately.

Quality assessment—risk of bias

To assess the risk of bias, we used the Cochrane risk of bias assessment tool,[9] which includes the following items: allocation sequence generation, allocation concealment, participant masking, personnel and outcome assessors, completeness of outcome data, and selective outcome reporting. We deemed masking complete when outcome assessors were masked. We did not deem patient or performing physician masking pertinent because of the procedural nature of the interventions. Two investigators (GCMS and KCS) reviewed the studies and judged the risk of bias.

Statistical analysis

Details of the applied statistical approaches are provided in the appendix and in the protocol. We initially did a pair-wise meta-analysis by using a random-effects

model.[10] We estimated relative treatment effects of the competing interventions by using standardised mean differences[11] for continuous outcomes and odds ratios (OR) for dichotomous outcomes. To allow intuitive interpretation, we back transformed standardised mean differences to differences in percent diameter stenosis on the basis of a typical pooled standard deviation of 20% noted in large-scale trials. In the case of percent diameter stenosis, improvement is associated with low values, therefore negative differences show that the experimental treatment is more efficacious than the control.

For indirect and mixed comparisons, we used network meta-analysis to compare different strategies.[12–14] We did network meta-analysis in Stata version 13.0 using the mvmeta command and self-programmed Stata routines.[15–17] We estimated the relative ranking probability of each treatment and obtained the treatment hierarchy of competing interventions using rankograms, surface under the cumulative ranking curve, and mean ranks.[15,18] We used the restricted maximum likelihood method to estimate heterogeneity, assuming a common estimate for heterogeneity variance across different comparisons. We computed I^2 and its 95% CI, which shows the percentage of variation that is not attributed to random error. For dichotomous outcomes, we compared magnitude of heterogeneity variance with empirical distribution, as derived by Turner and colleagues.[19]

To check for the presence of inconsistency, we used the loop-specific approach that assesses the difference between direct and indirect estimates for a specific comparison in the loop (inconsistency factor).[20] We assumed a common heterogeneity estimate within each loop.[21] We used the previously described node-splitting method,[22] which separates evidence for a particular comparison into direct and indirect, excluding one direct comparison at a time and estimating the indirect treatment effect for the excluded comparison. To check the assumption of consistency in the entire network, we used the design-by-treatment model of Higgins and colleagues.[23] Finally, we did subgroup analyses according to the type of coronary ISR (BMS as opposed to DES) for all assessed outcomes and meta-regression for percent diameter stenosis by using the following effect modifiers as possible sources of inconsistency or heterogeneity: year of study publication, sample size, clinical manifestation of ISR (stable angina or acute coronary syndrome), and type of underlying ISR (BMS *vs* DES ISR)

This study is registered with PROSPERO, number CRD42014014191.[24]

Role of the funding source

There was no funding source for this study. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

We identified 152 potentially eligible reports by reviewing study titles and abstracts. We excluded 115 reports for the following reasons: non-eligible interventions or reports limited to subgroups of eligible trials (n=83), duplicate reports (n=26), or pairwise meta-analyses of ISR trials (n=6; appendix). Finally, we deemed 37 reports of 27 trials eligible and included them in this network meta-analysis (table 1).[25–61] Two trials[36,50] provided two independent datasets for two different comparisons (BA *vs* BMS and ROTA *vs* BMS,[36] and BA *vs* sirolimus-eluting stents [SES] and SES *vs* everolimus-eluting stents [EES][50]), which we considered separately. For each intervention of interest, two or more eligible trials contributed in the respective networks (table 1, figure 1, and appendix).

5923 patients included in 27 trials (published between 2001 and 2014) were randomly assigned to a PCI treatment strategy (table 1). Individual trial sample size ranged between 37[46] and 476[26,27] participants (mean of 219 [SD 134]). Investigators of 16 trials (3710 patients) recruited patients with BMS-ISR only,[25–47,51,56] investigators of eight (1895 patients) recruited those with DES-ISR,[48–50,52,57,58,60,61] and investigators of three (318 patients) recruited those with both types of coronary ISR.[53–55,59] Characteristics of patients, lesions, and angiographic measurements are summarised in the appendix. Different regimens and durations of antiplatelet therapy were recommended across the trials (appendix). DES and DCB devices used in the included trials are summarised in the appendix. Three different DES platforms (paclitaxel-eluting stents [PES], SES, and EES) and one type of DCB were used. Angiographic follow-up was available in 4975 (84%) of

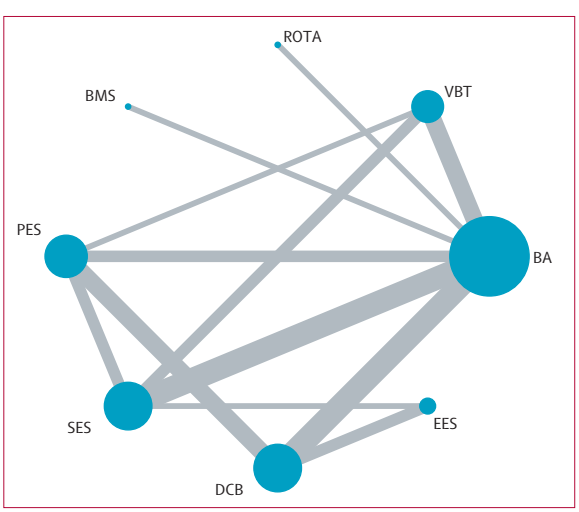

Figure 1: **Network of available treatment comparisons for any type of coronary in-stent restenosis for percent diameter stenosis**
The size of nodes is proportional to the number of individuals randomised to each intervention and the thickness of lines to the number of direct comparisons in trials. BA=balloon angioplasty. BMS=bare metal stents. DCB=drug-coated balloons. EES=everolimus-eluting stents. PES=paclitaxel-eluting stents. ROTA=rotablation. SES=sirolimus-eluting stents. VBT=vascular brachytherapy.

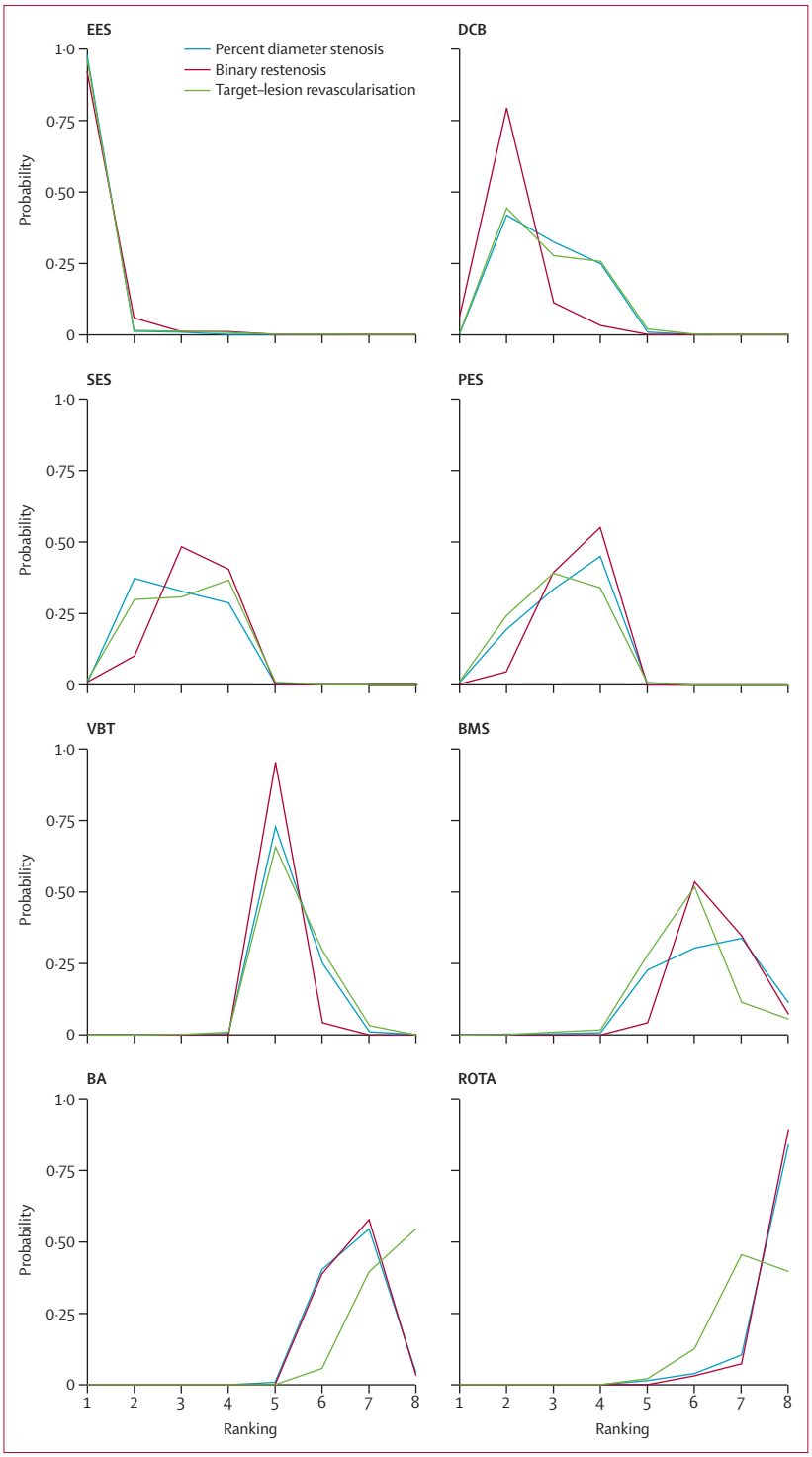

***Figure 2*: Rankogram of available percutaneous coronary intervention strategies for any type of coronary in-stent restenosis for percent diameter stenosis, binary restenosis, and target-lesion revascularisation**
EES=everolimus-eluting stents. DCB=drug-coated balloons. SES=sirolimus-eluting stents. PES=paclitaxel-eluting stents. VBT=vascular brachytherapy. BMS=bare metal stents. BA=balloon angioplasty. ROTA=rotablation.

5923 patients, ranging from 6 months to 12 months; clinical follow-up was available for a maximum of 60 months (table 1).

Risk of bias was difficult to assess mainly due to absence of detailed reporting (appendix). Hence, most studies are at unclear risk of bias. We did not identify any studies with definite high risk of bias in sequence generation and selective outcome reporting areas. Masking conditions were high risk in two studies. Two studies were high risk for allocation concealment bias and one study had evidence of incomplete outcome data.

21 trials involving 4442 patients provided adequate data for the primary angiographic outcome (appendix). Detailed results of pairwise meta-analyses are given in the appendix. PCI with EES was the most effective treatment for the primary endpoint of percent diameter stenosis compared with the other strategies in all prespecified analyses of ISR of any type and BMS and DES ISR (figure 2, table 2, and appendix). EES was ranked first according to the estimated surface under the cumulative ranking curve values, with differences of diameter stenosis of –9·0% (95% CI –15·8 to –2·2) versus DCB, –9·4% (–17·4 to –1·4) versus SES, –10·2% (–18·4 to –2·0) versus PES, –19·2% (–28·2 to –10·4) versus VBT, –23·4% (–36·2 to –10·8) versus BMS, –24·2% (–32·2 to –16·4) versus BA, and –31·8% (–44·8 to –18·6) versus ROTA. For the same outcome, DCB were more effective than were VBT, BMS, BA, and ROTA, but not significantly different to SES or PES. Besides EES, SES and PES were always significantly more effective than were BMS, VBT, BA, and ROTA as single treatments. If only patients with BMS ISR were considered, EES was ranked as best treatment and SES second best, followed by DCB (appendix). In the DES ISR subgroup, EES was the best treatment, with a diameter stenosis difference of –6·0% (–14·0 to 2·0) versus DCB, –6·4% (–15·6 to 3·0) versus PES, –8·8% (–17·8 to 0·00) versus SES, and –17·2 (–26·2 to –8·0) versus BA (standardised mean difference estimates are provided in the appendix).

We also noted that EES was hierarchically the best for binary restenosis across all types of ISR (table 3, figure 2, and appendix). EES was ranked as the most effective treatment, with a non-significant OR of 0·60 (0·30–1·19) compared with DCB, and significant differences for the remaining interventions, with ORs ranging from 0·06 to 0·44 favouring EES for any type of ISR. Additionally, BMS, VBT, BA and ROTA were shown to be ineffective alternatives as single strategies.

We did not note any inconsistencies between evidence derived from direct and indirect comparisons in any of the main or subgroup analyses for percent diameter stenosis, irrespective of the method of inconsistency assessment (appendix). Finally, by applying the design-by-treatment inconsistency model, we did not find significant differences in relative effects. In the binary restenosis analyses, we detected inconsistency in only one loop of comparisons: DCB-PES-BA (p=0·045) in the any type of ISR group.

	EES	DCB	SES	PES	VBT	BMS	BA	ROTA
EES	99·6 (0·98)	–9·0% (–15·8 to –2·2)	–9·4% (–17·4 to –1·4)	–10·2% (–18·4 to –2·0)	–19·2% (–28·2 to –10·4)	–23·4% (–36·2 to –10·8)	–24·2% (–32·2 to –16·4)	–31·8% (–44·8 to –18·6)
DCB	..	73·7 (0·00)	–0·2% (–6·2 to 5·6)	–1·2% (–6·4 to 4·2)	–10·2% (–17·0 to –3·4)	–14·4% (–25·6 to –3·2)	–15·2% (–20·4 to –10·2)	–22·8% (–34·4 to –11·0)
SES	..	..	72·8 (0·01)	–0·8% (–6·4 to 4·6)	–10·0% (–15·4 to –4·4)	–14·2% (–25·2 to –3·2)	–15·0% (–19·4 to –10·4)	–22·4% (–33·8 to –11·0)
PES	..	..	..	67·7 (0·01)	–9·0% (–15·6 to –2·4)	–13·2% (–24·6 to –2·0)	–14·2% (–19·4 to –8·8)	–21·6% (–33·2 to –9·8)
VBT	..	..	..	..	38·9 (0·00)	–4·2% (–15·4 to 7·0)	–5·0% (–10·2 to 0·00)	–12·6% (–24·2 to –0·8)
BMS	..	..	..	..	..	24·3 (0·00)	–0·8% (–10·8 to 9·2)	–8·2% (–22·8 to 6·2)
BA	..	..	..	..	..	..	19·7 (0·00)	–7·4% (–18·0 to 3·0)
ROTA	..	..	..	..	..	..	..	3·2 (0·00)

Estimates are expressed as differences in percent diameter stenosis, with 95% CIs in parentheses; estimates expressed as standardised mean differences are given in the appendix. Negative differences show that the intervention listed in the left column is more beneficial than the one in the top row. Interventions are ordered according to efficacy ranking. Surface under the cumulative ranking curve values are given in the diagonal, with the probability of being the best treatment in parentheses. The larger the surface under the cumulative ranking curve value, the better the treatment. EES=everolimus-eluting stents. DCB=drug-coated balloons. SES=sirolimus-eluting stents. PES=paclitaxel-eluting stents. VBT=vascular brachytherapy. BMS=bare metal stents. BA=balloon angioplasty. ROTA=rotablation.

Table 2: **Estimated differences of the effect of interventions on percent diameter stenosis**

	EES	DCB	SES	PES	VBT	BMS	BA	ROTA
EES	98·5 (0·92)	0·60 (0·30–1·19)	0·44 (0·19–0·99)	0·42 (0·19–0·92)	0·20 (0·09–0·45)	0·11 (0·04–0·28)	0·10 (0·05–0·22)	0·06 (0·02–0·16)
DCB	..	84·2 (0·06)	0·72 (0·43–1·22)	0·69 (0·44–1·09)	0·33 (0·19–0·56)	0·18 (0·09–0·36)	0·17 (0·11–0·26)	0·09 (0·04–0·21)
SES	..	..	67·4 (0·01)	0·96 (0·64–1·45)	0·45 (0·30–0·69)	0·25 (0·12–0·49)	0·23 (0·16–0·34)	0·13 (0·06–0·29)
PES	..	..	..	64·3 (0·00)	0·47 (0·31–0·72)	0·26 (0·13–0·51)	0·24 (0·17–0·35)	0·14 (0·06–0·30)
VBT	..	..	..	..	42·3 (0·00)	0·14 (0·06–0·30)	0·14 (0·06–0·30)	0·29 (0·13–0·62)
BMS	..	..	..	..	..	22·2 (0·00)	0·93 (0·53–1·65)	0·53 (0·22–1·29)
BA	..	..	..	..	..	..	19·5 (0·00)	0·57 (0·29–1·13)
ROTA	..	..	..	..	..	..	..	1·9 (0·00)

Ranges in parentheses are 95% CIs. Odds ratios less than 1 show that the intervention listed in the left column is more beneficial than the one in the top row. Interventions are ordered according to efficacy ranking. Surface under the cumulative ranking curve values are given in the diagonal, with the probability of being the best treatment in parentheses. The larger the surface under the cumulative ranking curve value, the better the treatment. EES=everolimus-eluting stents. DCB=drug-coated balloons. SES=sirolimus-eluting stents. PES=paclitaxel-eluting stents. VBT=vascular brachytherapy. BMS=bare metal stents. BA=balloon angioplasty. ROTA=rotablation.

Table 3: **Odds ratios of the effect of interventions for binary restenosis**

For the network meta-regression, we ranked the examined treatment strategies according to the hierarchy derived from the primary analysis: EES, DCB, SES, PES, VBT, BMS, BA, and ROTA. None of the examined variables were significant, although the type of ISR was marginally non-significant, but without effect on the results and ranking (regression coefficients 0·01 [95% CI –0·01 to 0·03] for year of publication; 0·03 [–1·72 to 1·77] for sample size; 0·16 [–0·003 to 0·33] for type of ISR; and 0·11 [–0·18 to 0·39] for clinical presentation of ISR; appendix). Figure 3 is an extension of the common funnel plot in cases of multiple treatment comparisons[15] and shows the absence of small-study effects for the primary outcome of interest.

Adequate data for meta-analysis of TLR was available in all included trials (appendix). PCI with EES for any type of ISR was consistently associated with a significantly lower risk of TLR than with all other strategies, with ORs ranging between 0·09 and 0·36 (table 4). Overall, DCB were associated with a higher risk of repeat revascularisation than with EES and a similar risk to other DES. EES was the top-ranked treatment in all assessed subgroups (figure 2 and appendix). In the DES ISR subgroup, EES was the top-ranked treatment, PES the second, and SES the third, whereas EES and PES were associated with significantly lower risk of repeat revascularisation than with DCB (EES OR 0·38 [95% CI 0·16–0·88]; PES 0·61 [0·38–0·98]). These findings were consistent in direct and indirect comparisons (appendix).

Results for myocardial infarction and all-cause mortality are summarised in the appendix. We identified significant discrepancies in event rates between the

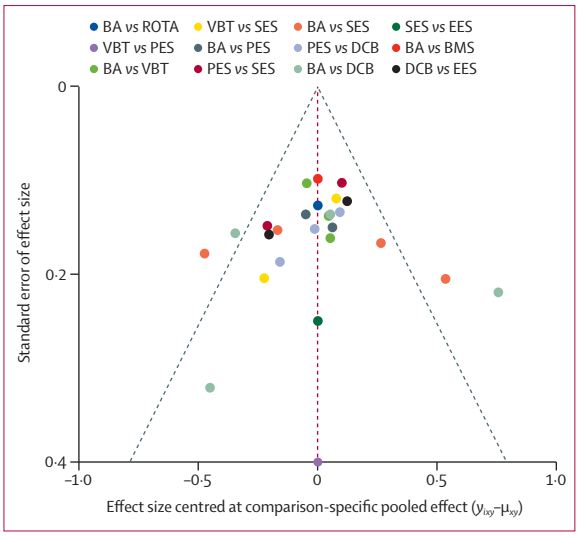

Figure 3: **Comparison-adjusted funnel plot**
The red dotted line represents the null hypothesis that the study-specific effect sizes do not differ from the respective comparison-specific pooled effect estimates. The two black dashed lines represent a 95% CI for the difference between study-specific effect sizes and comparison-specific summary estimates. y_{ixy} is the noted effect size in study *i* that compares *x* with *y*. μ_{xy} is the comparison-specific summary estimate for *x* versus *y*. BA=balloon angioplasty. BMS=bare metal stents. DCB=drug-coated balloons. EES=everolimus-eluting stents. PES=paclitaxel-eluting stents. ROTA=rotablation. SES=sirolimus-eluting stents. VBT=vascular brachytherapy.

included trials. Ranking of interventions derived for myocardial infarction and all-cause mortality was very imprecise.[62] EES seemed to be the most effective intervention with respect to overall mortality, followed by DCB, but, generally, the rankograms show similar distributions for the rest of the interventions (appendix).

Discussion

This network meta-analysis represents the most comprehensive synthesis of data for currently available treatment strategies for coronary ISR. Our findings can be summarised as follows: EES are the most effective strategy for treatment of ISR, with the lowest risks of restenosis and repeat revascularisation compared with other treatments; DCB ranked second in terms of angiographic and clinical effectiveness; conversely, BA, VBT, ROTA, and BMS cannot be deemed effective alternatives to ISR treatment; and these results were consistent, irrespective of the type of stent underlying ISR.

The optimum treatment strategy for patients presenting with ISR is a matter of debate.[8] The most recent guidelines on myocardial revascularisation from the European Society of Cardiology[63] provide a similar recommendation (ie, class I, Level A) for both new-generation DES and DCB in management of ISR. In this meta-analysis, we identified EES as the best strategy for treatment of any type of ISR with respect to both angiographic and clinical effectiveness. Specifically, EES has a more than 90% probability of being the best treatment in terms of percent diameter stenosis, binary restenosis, and TLR. The advantage of EES in this setting might be attributable to the thin-strut profile of its cobalt–chromium platform; the antiproliferative potency of the released limus analogue, with a homogeneous effect over the treated segment; and the biocompatibility and thromboresistant properties of its polymer coating, made of poly(n-butyl methacrylate) and poly(vinylidene fluoride-co-hexafluoropropylene).[64] The role of EES as a benchmark for safety and effectiveness in contemporary PCI has been supported by several observational studies, randomised trials, and meta-analyses, in a wide range of patients and coronary lesions.[4,65,66] Our findings extend this role of EES to treatment of patients with ISR.

All three RCTs[50–52] that examined effectiveness of EES for BMS and DES ISR used the same EES technology. Therefore, we were not able to assess any differences between the different commercially available EES platforms. Other non-EES new-generation DES have not been investigated in the specific setting of ISR. However, several new-generation DES, such as the Resolute zotarolimus-eluting, Biomatrix and Nobori biolimus-eluting, Yukon Choice sirolimus-eluting, and Orsiro sirolimus-eluting stents, have been non-inferior to EES in trials of all-comer patient populations that included patients with ISR.[67–70] Therefore, other new-generation DES might have similar effectiveness profiles to EES for treatment of ISR. However, in the absence of dedicated randomised comparisons, definitive conclusions on use of other new-generation DES for ISR are not possible.

Use of DCB for treatment of ISR has potential advantages related to avoidance of deployment of an additional stent layer and rapid absorption of the antiproliferative drug after its release from the DCB into the neointimal matrix.[71] Findings from preclinical studies[72] have suggested adequate antiproliferative potency of DCB, and findings from preliminary clinical studies[53] have shown favourable results in the setting of ISR. Investigators of RCTs[56,60] have shown that the angiographic effectiveness of DCB is better than BA and similar to early-generation PES in patients with ISR. These findings have been substantiated by our meta-analysis. A network meta-analysis[73] of seven trials of PCI strategies for DES ISR proposed iopromide-based paclitaxel-eluting DCB as the most effective treatment, followed by EES. After publication of that meta-analysis, however, results of the RIBS-IV trial[52] were released, showing that EESs were better than DCB. Inclusion of the RIBS-IV data in our analyses resulted in top ranking of EES. Specifically, precision in the estimate of relative effectiveness of EES and DCB increased by 25% by inclusion of these data. Another network meta-analysis[74] of DES, DCB, and BA comparisons from 11 RCTs was published after submission of our study for publication. The authors concluded that the risk of TLR was similar with both DES and DCB, and both were better than BA. However, the RIBS-IV trial was not included in that analysis and no distinction was made between different DES types.

	EES	DCB	PES	SES	VBT	BMS	ROTA	BA
EES	99·1 (0·97)	0·36 (0·14–0·94)	0·34 (0·12–1·00)	0·34 (0·12–0·97)	0·17 (0·06–0·51)	0·14 (0·04–0·47)	0·09 (0·03–0·31)	0·09 (0·03–0·25)
DCB	..	73·7 (0·01)	0·93 (0·51–1·71)	0·93 (0·55–1·58)	0·47 (0·26–0·86)	0·38 (0·17–0·84)	0·26 (0·12–0·55)	0·24 (0·15–0·40)
PES	..	..	70·7 (0·02)	1·00 (0·59–1·68)	0·50 (0·30–0·84)	0·41 (0·19–0·90)	0·28 (0·13–0·59)	0·26 (0·16–0·42)
SES	..	..	..	70·0 (0·01)	0·50 (0·30–0·85)	0·41 (0·19–0·90)	0·28 (0·13–0·58)	0·26 (0·16–0·41)
VBT	..	..	..	..	38·0 (0·00)	0·82 (0·38–1·76)	0·55 (0·27–1·14)	0·52 (0·34–0·80)
BMS	..	..	..	..	..	30·3 (0·00)	0·68 (0·32–1·46)	0·64 (0·34–1·21)
ROTA	..	..	..	..	..	..	11·0 (0·00)	0·94 (0·53–1·67)
BA	..	..	..	..	..	..	..	7·3 (0·00)

Ranges in parentheses are 95% CIs. Odds ratios less than 1 show that the intervention listed in the left column is more beneficial than the one in the top row. Interventions are ordered according to efficacy ranking. Surface under the cumulative ranking curve values are given in the diagonal, with the probability of being the best treatment in parentheses. The larger the surface under the cumulative ranking curve value, the better the treatment. EES=everolimus-eluting stents. DCB=drug-coated balloons. PES=paclitaxel-eluting stents. SES=sirolimus-eluting stents. VBT=vascular brachytherapy. BMS=bare metal stents. ROTA=rotablation. BA=balloon angioplasty.

Table 4: **Odds ratios of the effect of interventions for target-lesion revascularisation**

Little evidence is available for direct comparisons of DCB with the more effective and safer new-generation DES. Findings from two RCTs (RIBS V[51] and RIBS IV[52]) reported better angiographic outcomes with EES than with DCB for treatment of both BMS[51] and DES[52] ISR. In our network meta-analysis, EES were better than DCB in terms of angiographic and clinical effectiveness. EES were associated with a better treatment effect for percent diameter stenosis than with DCB and a 40% risk reduction for binary restenosis and 64% risk reduction for TLR as compared with DCB. Worse outcomes with DCB than with EES might be attributable to use of the antiproliferative drug paclitaxel, which has been shown to less effectively suppress neointimal hyperplasia than do limus analogues.[2] Additionally, the drug release pharmacokinetics of contemporary DCB and the limited exposure time during balloon inflation could be insufficient to offer a potent antiproliferative effect. Although DCB had inferior angiographic and clinical effectiveness, they could remain a valuable therapeutic alternative because of their ability to provide favourable results in the absence of an additional metallic stent layer. This layer could be particularly important for patients with recurrent coronary ISR.

We noted no significant differences between treatments in terms of the clinical safety outcomes of myocardial infarction and all-cause mortality. None of the RCTs included in this analysis identified any significant differences for such outcomes. These findings are reassuring with respect to the safety profile of available technologies for ISR treatment. Nevertheless, our analysis might be underpowered to provide definitive conclusions for ranking of strategies for hard clinical endpoints in view of the low event rates of myocardial infarction and all-cause mortality.

Potential limitations of our study merit discussion. First, our findings need to be considered as average effects because we did not have access to individual patient data that would allow us to identify potential differential effects of available strategies in subgroups of patients. Second, detailed data for duration of dual antiplatelet treatment were not available, but patients with ISR have been suggested to benefit from extended dual antiplatelet treatment duration because of an increased risk of ischaemic adverse events.[75] Third, our findings are the result of direct and indirect comparisons in a network meta-analysis. Although this method is widely accepted,[4,14,76] it does not substitute results from large-scale RCTs. The applied model is based on relative treatment effects, and the analysis accounts for differences in patient characteristics and medical co-interventions between trials by preserving randomisation. In clinical terms, patient characteristics in the component trials were sufficiently similar to justify combination in our network. Moreover, the low statistical heterogeneity for all analysed outcomes, absence of inconsistency between direct and indirect comparison, and the excellent model fit support the validity of our findings. However, with few closed loops and studies per comparison, the I^2 values could be uncertain. We explored the distribution of potential effect modifiers in all comparisons without finding any differences, but nevertheless, the number of studies per comparison is small and we might have lacked power to spot any differences. Finally, the available evidence on DES ISR is mostly derived from RCTs that recruited patients with ISR of early-generation DES. Even though this might somewhat limit the generalisability of our findings to ISR of new-generation DES, the mechanisms underlying new-generation and early-generation DES ISR seem to be similar.[77]

The findings of this comprehensive network meta-analysis provide robust evidence supporting the same treatment strategy for any type of coronary ISR encountered in daily clinical practice. Two strategies should be considered for treatment of coronary ISR: PCI with EES because of the better angiographic and clinical results than with the other treatment strategies, and DCB because of their ability to provide favourable results without adding a new stent layer. BA, VBT, ROTA, and BMS cannot be deemed therapeutic alternatives for treatment of ISR.

Contributors

GCMS, GGS, DM, GS, PJ, and SW designed the study. GCMS and GGS identified and acquired reports of relevant trials. GCMS and KCS extracted data. FA, MJP-V, RAB, and AK provided data from trials. DM and GS analysed data. GCMS, GGS, DM, KCS, FA, MJP-V, RAB, AK, BM, GS, PJ, and SW interpreted the data. GCMS, GGS, DM, KCS, and SW drafted the manuscript. FA, MJP-V, RAB, AK, BM, GS, and PJ critically reviewed the document. All authors approved the final submitted version.

Declaration of interests

GGS has received speaker's fees from Abbott Vascular, AstraZeneca, Biosensors, and Biotronik, outside the submitted work. RAB has received speaker's fees from Biotronik and B Braun Melsungen, outside the submitted work. AK has submitted patents in relation to several drug-eluting stent technologies and received consulting or lecture fees from Abbott, Biosensors, and Biotronik, outside the submitted work. BM has received research grants to his institution (Bern University Hospital) and personal fees from Abbott, Biotronik, Boston Scientific, Biosensors, and Medtronic, outside the submitted work. PJ is an unpaid member of a steering group of trials funded by Biosensors and St Jude Medical. PJ's institution (Clinical Trials Unit Bern, part of the University of Bern), has a staff policy to not accept individual honoraria or consultancy fees. However, the Clinical Trials Unit Bern is involved in design, conduct, or analysis of clinical studies funded by Abbott Vascular, Ablynx, Amgen, AstraZeneca, Biosensors, Biotronik, Boehrhinger Ingelheim, Eisai, Eli Lilly, Exelixis, Geron, Gilead Sciences, Nestlé, Novartis, Novo Nordisc, Padma, Roche, Schering-Plough, St Jude Medical, Swiss Cardio Technologies, Terumo, and The Medicines Company. PJ has received institutional grants and a grant from the Swiss National Science Foundation (33CM30_140336 I 1), neither of which were specifically used for this study. SW has received research grants to his institution (Bern University Hospital) from Abbott, Biotronik, Boston Scientific, Edwards Lifesciences, Medtronic, Medicines Company, and St Jude Medical, and speaker's fees from AstraZeneca, Eli Lilly, Abbott, Biotronik, Boston Scientific, Bayer, and Biosensors, outside the submitted work. SW has received a grant from the Swiss National Science Foundation (33CM30_140336 I 1), which was not specifically used for this study. DM and GS have received research funding from the European Research Council (IMMA 260559), which were not used specifically for this study. All other authors declare no competing interests.

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