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Percutaneous Coronary Interventions for the Treatment of Stenoses in Small Coronary Arteries

A Network Meta-Analysis

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ABSTRACT

OBJECTIVES This study evaluated the most appropriate percutaneous coronary intervention (PCI) for the treatment of stenoses in small coronary arteries.

BACKGROUND PCI in small coronary arteries is associated with an increased risk of lesion failure and restenosis.

METHODS Randomized trials comparing different PCI strategies were identified through a broad search of published reports. Primary angiographic outcome was %DS (%DS). A pairwise meta-analysis was performed by using random effects model, followed by a network meta-analysis synthesizing direct and indirect evidence.

RESULTS Overall, 19 trials were eligible, which included 5,072 patients comprising a network without closed loops among 5 identified interventions (early generation sirolimus-eluting stents [SES], paclitaxel-eluting stents [PES], drug-coated balloons [DCB], bare-metal stents [BMS], and balloon angioplasty [BA]). No dedicated trial was identified evaluating new generation drug-eluting stents. Early generation SES yielded the best angiographic results according to %DS. For %DS, SES was ranked as the most effective treatment, followed by PES (standardized mean differences [SMD]: -0.44; 95% confidence interval [CI]: -0.92 to 0.05 vs. SES) and DCB (SMD: -0.89; 95% CI: -1.53 to -0.25 vs. SES). In terms of absolute differences, SES yielded a reduction of 18% in diameter stenosis compared to DCB. SES significantly reduced the risk of target-lesion revascularization compared to PES (odds ratio [OR]: 0.39; 95% CI: 0.16 to 0.93), DCB (OR: 0.34; 95% CI: 0.10 to 0.97), BMS (OR: 0.21; 95% CI: 0.13 to 0.36), and BA (OR: 0.16; 95% CI: 0.09 to 0.29).

CONCLUSIONS Early generation SES yielded the most favorable angiographic and clinical outcomes for the treatment of stenoses in small coronary arteries. New generation DES need to be evaluated against this standard in future randomized trials. (J Am Coll Cardiol Intv 2016;9:1324–34) © 2016 by the American College of Cardiology Foundation.

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Small-vessel coronary artery disease (CAD) is common among patients undergoing percutaneous coronary intervention (PCI) and has been documented in 30% to 40% of cases (1,2). Myocardial revascularization of small vessels remains challenging owing to an increased rate of technical failure in the domain of coronary artery bypass grafting (3) and an increased risk of restenosis resulting in repeat intervention in the field of PCI (4). Although drug-eluting stents (DES) and, more recently, drug-coated balloons (DCB) have shown promising results, the optimal treatment strategy of patients undergoing PCI for small coronary arteries remains poorly defined. Current evidence derived from randomized trials is limited to relatively few and small-scale studies, and evidence from head-to-head comparisons of the available interventions is lacking. Therefore, we performed a network meta-analysis of all randomized trials to comprehensively evaluate available interventions for the treatment of small-vessel disease, to obtain more precise results, to estimate the relative effectiveness between pairs of interventions that have never been compared head-to-head, and to provide a hierarchy of treatments according to the outcomes of interest.

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METHODS

SEARCH STRATEGY. Randomized trials comparing any PCI strategy for the treatment of coronary stenoses located exclusively in vessels of small diameter were identified through a broad systematic search of PubMed, EMBASE, and Cochrane Library Central Register of Controlled Trials (CENTRAL). Clinical trial registries (ClinicalTrials.gov and Current Controlled Trials [controlled-trials.com] registries) also were scrutinized. A search algorithm that included a combination of relevant text terms and key words was used for each database (Online Appendix). We did not consider reports of trials that had been presented only at conferences when the full manuscript was not available at the time of our search (last search, August 2015). Finally, we scrutinized the reference lists of retrieved publications for other eligible studies and any relevant meta-analyses in the field. Two investigators (G.C.M.S., F.P.) scrutinized all entries for eligibility in titles and abstracts.

ELIGIBLE TRIALS AND INTERVENTIONS CONSIDERED FOR THIS REVIEW. We included randomized trials that investigated any type of PCI technique under different clinical settings for the treatment of stenoses in small coronaries. Trials with 2 or more arms of interventions were eligible. No language, year of publication, or sample size restrictions were applied. We excluded studies that allowed a mixture of interventions of interest in 1 study arm (i.e., balloon angioplasty followed by stenting based on operator discretion) and studies that were not completed at the time of our search.

We considered trials that compared 2 or more of the following PCI techniques for the treatment of coronary stenoses in small vessels: balloon angioplasty (BA), bare-metal stent (BMS), DCB, or DES with different antiproliferative drugs. For the primary and any additional analyses, we considered DES separately according to the type of antiproliferative agent. We also included in our analysis cases of PCI strategies other than those that were pre-specified that were identified through our search and were deemed eligible. We were interested mainly in PCI that used DES or DCB, because DES is considered the preferred strategy for the treatment of native coronary stenosis, and DCB has emerged as an alternative treatment for lesions in small coronary vessels and in-stent restenosis (5).

DATA COLLECTION AND OUTCOMES. Citations were independently screened and subjected to full-text review by 2 investigators (G.C.M.S., F.P.) using the predetermined selection criteria. Disagreements were resolved by consensus with a third investigator (S.W.). We extracted data that included clinical design characteristics, selection criteria, relevant population demographics and lesion characteristics, quantitative angiographic measurements, length of clinical and angiographic follow-up, and clinical outcomes of interest. We extracted outcomes of interest at the longest available follow-up time according to the intention-to-treat principle.

Because most of the clinical trials applied primary angiographic endpoints for the assessment of the efficacy of different PCI strategies, %DS (%DS) was chosen as the primary endpoint in the present study to provide sufficient precision and to arrive at a conclusive answer. It is known that PCI techniques for the treatment of small-vessel CAD have limited effect on measurable clinical outcomes and that most trials have been underpowered to detect any differences for such outcomes. Therefore, %DS is an appropriate endpoint, sensitive enough for the evaluation of angiographic effectiveness compared to binary restenosis, which is included as a secondary endpoint in our analysis. We extracted any given summary metric (mean ± SD) or median (interquartile

ABBREVIATIONS AND ACRONYMS

%DS = percent diameter stenosis
BA = balloon angioplasty
BMS = bare-metal stent(s)
CAD = coronary artery disease
DCB = drug-coated balloon(s)
DES = drug-eluting stent(s)
PCI = percutaneous coronary interventions
PES = paclitaxel-eluting stent(s)
SES = sirolimus-eluting stent(s)
TLR = target-lesion revascularization

range [IQR]) and sample size) that was reported for each arm of intervention for the primary continuous angiographic outcome of interest at follow-up (%DS). For the secondary outcomes of interest (binary restenosis, target lesion revascularization [TLR], myocardial infarction, and overall mortality), the respective number of participants in each arm of the interventions and the number of participants with one of the events of interest were recorded.

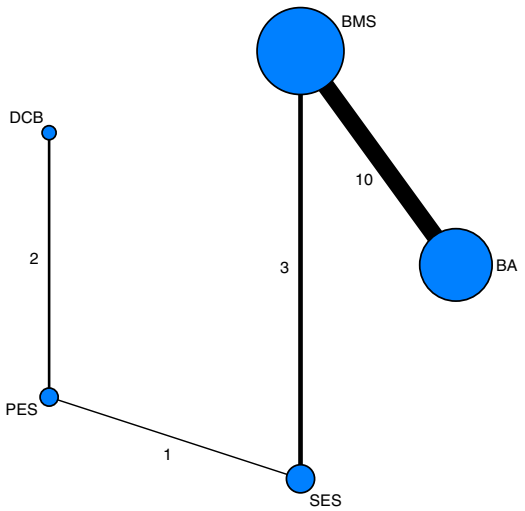
DATA SYNTHESIS. We used network meta-analysis to compare different PCI techniques for the treatment of stenoses located in small coronary arteries. Network meta-analysis synthesizes both direct and indirect evidence; estimates the relative effectiveness between pairs of interventions, even if these interventions have never been compared directly in randomized trials; and provides a ranking of interventions (6-9). For comparison of, for example, DES versus DCB, direct evidence was provided by trials directly comparing these 2 interventions, whereas indirect evidence was provided if there was an indirect path linking these 2 treatments (e.g., if both DES and DCB were compared to BMS) (10). By combining direct and indirect evidence, we obtained estimates with increased precision. We performed network meta-analysis using the "mvmeta" command (11-13) and self-programmed software routines (Stata software, College Station, Texas) (14). We used the restricted maximum likelihood method to estimate heterogeneity, assuming a common heterogeneity variance across the different comparisons. We computed the I^2 variable that showed the percentage of variation that was not attributed to random error. Assessment of statistical heterogeneity in the entire network was based on the magnitude of the heterogeneity variance parameter estimated from network meta-analysis models. For dichotomous outcomes, magnitude of heterogeneity variance was compared with the empirical distribution as derived by Turner. Ranking probabilities for all treatments of being at each possible rank for each intervention were calculated by using the "mvmeta" command in Stata software (12), whereas subsequently, we obtained a hierarchy of the competing interventions using "rankograms" (15). Finally, we obtained a treatment hierarchy using the surface under the cumulative ranking curve (SUCRA) and mean ranks, and produced the relevant plots, using the Stata commands described by Chaimani et al (14).

A pair-wise meta-analysis was also performed using a random effects model. A random effects model assumes that different studies assessed different yet related treatment effects. We estimated the pairwise relative treatment effects of competing interventions by using standardized mean differences (SMDs) for the primary outcome (%DS), whereas odds ratios (OR) were estimated for dichotomous outcomes. In addition, we back-transformed SMDs to differences in %DS on the basis of a typical pooled SD of 20% found in previously published trials of the topic with adequate design. On the basis of the random effects model, the 95% prediction intervals also were calculated for the primary outcome of %DS (16). These intervals show the expected effect distribution in a future individual study setting. In the case of %DS, improvement was associated with lower values; therefore, negative differences indicate that the intervention which is considered experimental is more efficacious than the control treatment. We produced summary results for all outcomes and provide 95% confidence intervals (CIs). All analyses were performed using Stata version 13.0 software.

RESULTS

STUDY SELECTION AND PATIENT POPULATION. Electronic searches yielded 632 relevant studies, of which 27 potentially eligible articles were analyzed; 8 reports were excluded because they did not meet our eligibility criteria (Online Figure 1). Overall, 19 randomized trials were deemed eligible and were included in our network meta-analysis, 16 of which provided adequate data for the primary angiographic outcome of interest (**Figure 1**, Online Figure 1) (17-36). The following 5 interventions were examined across the included trials: early generation sirolimus-eluting stents (SES), paclitaxel-eluting stents (PES), DCB, BMS, and BA. All trials were 2-armed studies; no trial examined a combination of interventions. Overall, 5,072 patients were assigned to 1 of the aforementioned interventions; and 4,349 patients (16 trials) with angiographic follow-up contributed to the main analysis of the primary angiographic outcome. The sample size in individual studies ranged from 60 to 502 patients, with a median sample size of 257 (IQR: 182 to 360) patients. Most patients (62% [3,178 of 5,072]) presented with stable CAD (**Table 1**). The time of angiographic follow-up ranged from 6 to 9 months. All trials reported clinical endpoints. Detailed information for lesion characteristics are summarized in Online Tables 1 and 2. Information related to the devices used is provided in Online Table 3.

FIGURE 1 Network of Treatment Comparisons for the Primary Outcome of %DS



16 trials provided appropriate data and contributed to the network meta-analysis. The **size of the nodes** corresponds to the number of trials that evaluated the same intervention. Directly comparable interventions are linked with a **line**, the thickness of which corresponds to the number of trials that assess the respective comparison. DCB = drug-coated balloon; PES = paclitaxel-eluting stent(s); SES = sirolimus-eluting stent(s); BMS = bare-metal stent(s); BA = balloon angioplasty.

NETWORK META-ANALYSIS RESULTS. Percent diameter stenosis and binary restenosis. The geometry of the network of interventions for the primary angiographic outcome of %DS yielded an opened network without closed loops among the 5 interventions, which led to limited diversity (**Figure 1**). The network consisted of 16 trials (median of 257 patients) (18,19,21,24-37). Each comparison is represented only by direct or indirect comparisons; and no trial provided direct evidence between SES and DCB.

For the primary angiographic outcome, early generation SES was ranked the best PCI technique followed by PES with SMD of -0.44 (95% CI: -0.92 to 0.05) for SES versus PES; by DCB with SMD of -0.89 (95% CI: -1.53 to -0.25) for SES versus DCB; by BMS with SMD of -1.43 (95% CI: -1.74 to -1.12) for SES versus BMS; and by BA with SMD of -1.58 (95% CI: -1.93 to -1.23) for SES versus BA (**Table 2**, **Figure 2A**, Online Figure 2). DCB was found to be as effective as BMS (SMD = -0.53; 95% CI: -1.24 to 0.18) and BA (SMD = -0.69; 95% CI: -1.42 to 0.04) without statistically significant differences among these techniques for the endpoint %DS (**Table 2**). In terms of absolute differences at the time of angiographic follow-up, SES yielded a significant reduction of 18% in diameter stenosis compared to DCB (**Table 2**). There were no differences between the available direct pairwise and indirect comparisons. The hierarchy of effect size on the basis of SUCRA rankings is illustrated in the respective ranking plots (**Figure 2A**, Online Figure 2). SES was ranked the best treatment strategy but with considerable uncertainty. For the 2 available interventions of major interest (SES and DCB) according to the primary angiographic outcome of %DS, the respective 95% prediction interval was wider but entirely below zero (95% prediction interval of -1.76 to -0.02), indicating that SES would remain more effective than DCB in a future individual study setting. These findings are not expected to change following the addition of the results of new trials (**Figure 3**). Considering binary restenosis, the secondary angiographic outcome, SES remained the intervention ranked best (**Figure 2B**), with OR ranging between 0.03 and 0.69 (**Figure 4**). SES, PES, and DCB were significantly better than BMS and BA, without any significant differences among them in terms of binary restenosis (**Figure 4**).

Clinical outcomes. All trials (19 trials, including 5,072 patients) contributed to the analysis of TLR (Online Table 4). The median target lesion revascularization rate was 7% for SES compared to 15% and 13% for PES and DCB, respectively. SES significantly reduced the odds of TLR compared to PES (OR: 0.39; 95% CI: 0.16 to 0.93), DCB (OR: 0.34; 95% CI: 0.10 to 0.97), BMS (OR: 0.21; 95% CI: 0.13 to 0.36), and BA (OR: 0.16; 95% CI: 0.09 to 0.29) (**Figures 2C** and **3**, Online Figure 2, Online Table 5). Findings between direct and indirect estimates were in agreement; there was no evidence of considerable heterogeneity among trials.

Eighteen trials (4,576 patients) contributed to the analysis of myocardial infarction (18-25,27-37). Online Table 4 presents the numbers of events separately for each included trial. In summary, 218 patients experienced myocardial infarction during the entire follow-up. DCBs were ranked first followed by PES and SES (**Figure 2D**), but there were no statistically significant differences in rate of myocardial infarction among patients treated with SES, PES, DCB, or BMS (**Figure 4**, Online Table 5). SESs were significantly associated with a lower rate of myocardial infarction than BA (OR: 0.38; 95% CI: 0.17 to 0.89), whereas such differences were not documented across the other interventions (**Figure 4**). All 19 trials contributed to the analysis of overall mortality (Online Table 4), with overall 66 deaths in 5,072 patients. No differences were detected between the evaluated interventions (**Figure 4**, Online Table 5).

TABLE 1 Trials and Patient Characteristics

Trial/First Author (Ref. #)	Year	Interventions	Sample Size	Reference Vessel, mm	Age, Yrs	Males	DM	HTN	HLP	Smoking	Previous MI	Stable Angina
BELLO (17,18)	2012	DCB vs. PES	182	<2.8	65 ± 9; 66 ± 9	72 (80); 71 (77)	39 (43); 35 (38)	72 (80); 75 (82)	71 (79); 73 (79)	15 (17); 10 (11)	46 (51); 33 (36)	68 (76); 72 (78)
PICCOLETO (19)	2010	DCB vs. PES	60	≤2.75	68 ± 9; 67 ± 10	22 (79); 22 (76)	13 (38); 11 (46)	21 (75); 20 (71)	17 (61); 13 (54)	ND	5 (18); 6 (21)	13 (46); 13 (45)
SES-SMART (20)	2009	SES vs. BMS	257	2.25–2.75	63 ± 12; 64 ± 11	99 (77); 85 (66)	25 (19); 39 (30)	84 (65); 81 (64)	79 (61); 83 (65)	24 (19); 18 (14)	74 (29); 38 (30)	56 (43); 63 (50)
ISAR-SMART 3 (21)	2006	SES vs. PES	360	<2.8	67 ± 11; 66 ± 10	55 (31); 45 (25)	0; 0	116 (64); 120 (67)	100 (56); 99 (55)	27 (15); 22 (12)	53 (29); 56 (31)	131 (73); 117 (75)
LASMAL I (22)	2005	BMS vs. BA	246	<2.9	ND	100 (82); 91 (73)	31 (25); 34 (28)	77 (63); 81 (65)	82 (67); 66 (53)	32 (27); 43 (35)	ND	43 (35); 51 (41)
LASMAL II (23)	2005	BMS vs. BA	220	2.0–2.9	ND	81 (73); 84 (77)	111 (100); 109 (100)	71 (64); 68 (62)	65 (59); 59 (54)	29 (26); 21 (19)	ND	28 (26); 34 (31)
C-SIRIUS (24)	2004	SES vs. BMS	100	2.5–3.0	60 ± 11; 61 ± 9	35 (70); 34 (68)	12 (24); 12 (24)	28 (56); 24 (48)	42 (84); 43 (86)	18 (36); 19 (38)	24 (48); 21 (42)	5 (10); 7 (14)
Ardissino et al. (25)	2004	SES vs. BMS	257	≤2.75	63 ± 12; 64 ± 11	99 (77); 85 (66)	25 (19); 39 (30)	84 (65); 81 (64)	79 (61); 83 (65)	24 (19); 18 (14)	38 (30); 36 (28)	56 (43); 63 (50)
Hanekamp et al. (26)	2004	BMS vs. BA	496	<3.0	61 ± 9; 61 ± 10	160 (64); 175 (71)	43 (17); 39 (16)	105 (42); 108 (44)	148 (59); 150 (61)	78 (31); 64 (26)	80 (32); 79 (32)	195 (78); 185 (75)
Hausleiter et al. (27)	2004	BMS vs. BA	502	≤2.5	66 ± 10; 66 ± 10	70 (28); 66 (27)	64 (25); 75 (30)	145 (57); 135 (54)	123 (49); 127 (51)	39 (15); 36 (15)	98 (39); 86 (35)	ND
COMPASS (28)	2004	BMS vs. BA	106	<3.0	64 ± 8; 66 ± 7	39 (78); 44 (79)	21 (42); 23 (41)	25 (50); 30 (54)	25 (50); 34 (61)	31 (62); 34 (61)	25 (50); 26 (46)	ND
Kinsara et al. (29)	2003	BMS* vs. BA	202	≤2.5	54 ± 11; 56 ± 11	83 (86); 74 (70)	48 (50); 65 (61)	55 (57); 56 (53)	81 (84); 82 (77)	81 (84); 81 (76)	57 (59); 68 (64)	82 (85); 89 (84)
E-SIRIUS (30)	2003	SES vs. BMS	352	2.5–3.0	62 ± 11; 63 ± 10	123 (70); 126 (71)	33 (19); 48 (27)	109 (63); 114 (64)	132 (77); 124 (71)	63 (36); 53 (30)	71 (41); 76 (43)	73 (44); 70 (42)
SISA (31)	2001	BMS vs. BA	351	<3.0	61 ± 10; 60 ± 11	112 (66); 122 (67)	30 (18); 38 (21)	79 (47); 93 (51)	88 (52); 98 (54)	108 (64); 106 (58)	54 (32); 64 (35)	112 (66); 129 (71)
BESMART (32)	2001	BMS vs. BA	381	<3.0	62 ± 10; 61 ± 10	140 (74); 149 (79)	42 (22); 23 (12)	98 (51); 76 (40)	108 (56); 110 (58)	110 (57); 115 (61)	61 (32); 79 (42)	74 (39); 77 (41)
SISCA (33)	2001	BMS* vs. BA	145	2.1–3.0	63 ± 12; 62 ± 10	49 (67); 52 (73)	9 (12); 10 (14)	31 (42); 33 (47)	55 (74); 48 (68)	15 (20); 10 (14)	31 (42); 32 (45)	58 (74); 56 (79)
ISAR-SMART (34)	2000	BMS vs. BA	404	2.0–2.8	65 ± 11; 67 ± 11	158 (78); 152 (76)	51 (25); 49 (25)	ND	ND	46 (23); 33 (17)	71 (35); 78 (39)	117 (57); 127 (63)
Park et al. (35)	2000	BMS vs. BA	120	<3.0	60 ± 8; 62 ± 8	39 (65)	37 (62)	24 (40); 21 (35)	5 (8); 7 (12)	24 (40); 27 (45)	9 (15); 6 (10)	49 (82); 48 (80)
STRESS (36)	1998	BMS vs. BA	331	<3.0	59 ± 10; 61 ± 11	121 (74); 114 (68)	28 (17); 27 (16)	86 (53); 87 (52)	85 (52); 96 (57)	41 (25); 34 (20)	31 (19); 41 (25)	72 (44); 87 (52)

Values are n, n (%) or mean ± SD. Data are presented for each arm of reported intervention separated by semicolon. *Heparin-coated stent.

BA = balloon angioplasty; BMS = bare-metal stent(s); DCB = drug-coated balloon; DM = diabetes mellitus; HLP = hyperlipidemia; HTN = hypertension; MI = myocardial infarction; ND = no data; PES = paclitaxel-eluting stent(s); SES = sirolimus-eluting stent(s).

DISCUSSION

This network meta-analysis including 5,072 patients across 19 randomized trials represents the most comprehensive synthesis of data for available PCI strategies for the treatment of stenoses located in small-diameter coronary arteries. Principal findings were, first, early generation SESs were the most

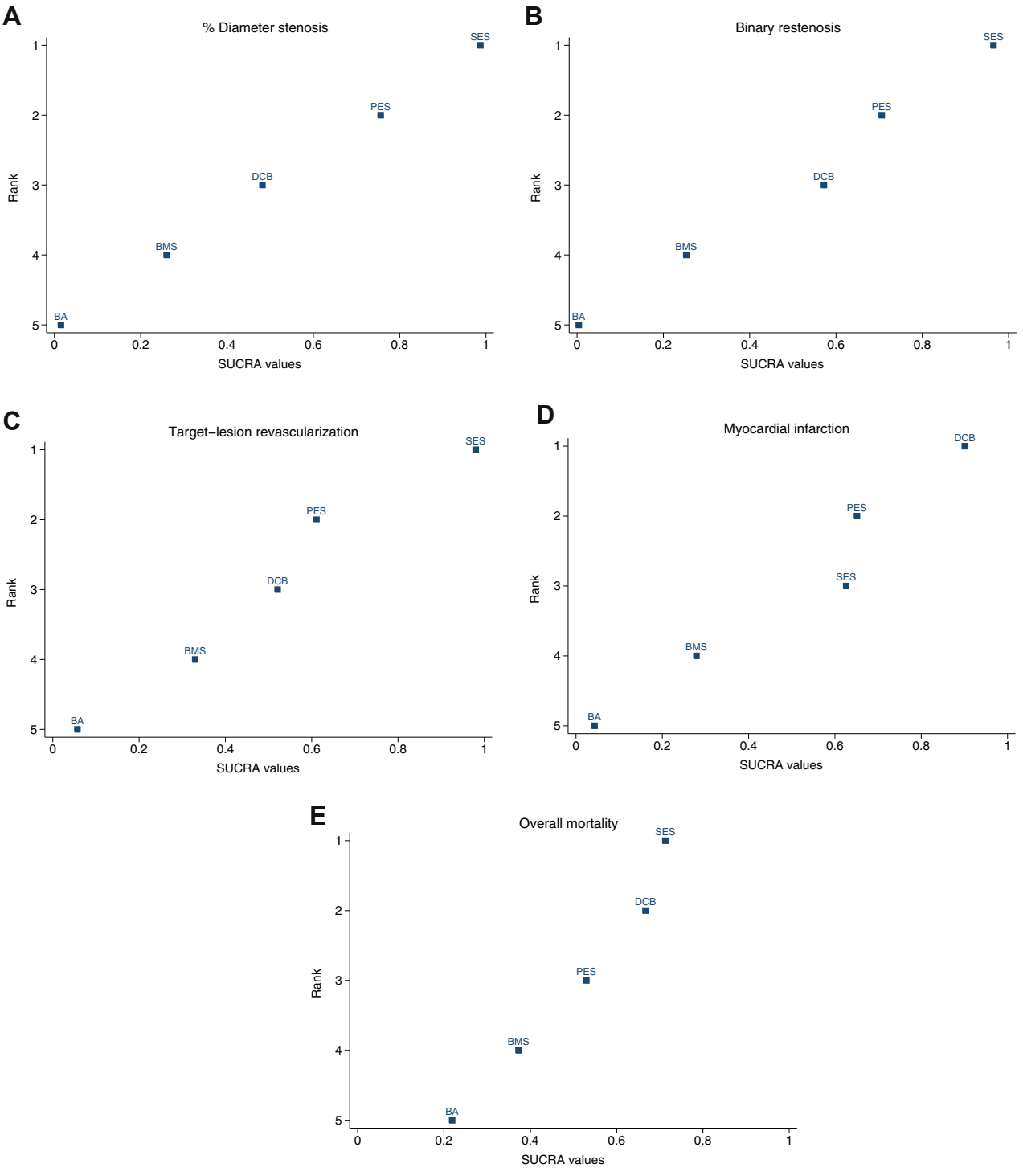
TABLE 2 League Table for the Primary Angiographic Outcome of Interest of Percent Diameter Stenosis

		Standardized Mean Difference			
Absolute difference	**SES**	−0.44 (−0.94 to 0.07)	−0.89 (−1.56 to −0.23)	−1.43 (−1.80 to −1.06)	−1.59 (−1.99 to −1.18)
	−0.09 (−0.19 to 0.01)	**PES**	−0.46 (−0.89 to −0.03)	−0.99 (−1.61 to −0.37)	−1.15 (−1.79 to −0.50)
	−0.18 (−0.31 to −0.05)	−0.09 (−0.18 to −0.01)	**DCB**	−0.53 (−1.29 to 0.22)	−0.69 (−1.47 to 0.09)
	−0.29 (−0.36 to −0.21)	−0.20 (−0.32 to −0.07)	−0.11 (−0.26 to 0.04)	**BMS**	−0.16 (−0.32 to 0.01)
	−0.32 (−0.40 to −0.24)	−0.23 (−0.36 to −0.10)	−0.14 (−0.29 to 0.02)	−0.03 (−0.06 to 0.00)	**BA**

Standardized mean differences with 95% confidence intervals (column vs. row) of the effect of interventions are shown on the **upper right part of the table**, whereas absolute differences are shown on the **lower left of the table**. Values lower than zero favor the column-defining treatment. Interventions are ordered according to efficacy ranking.

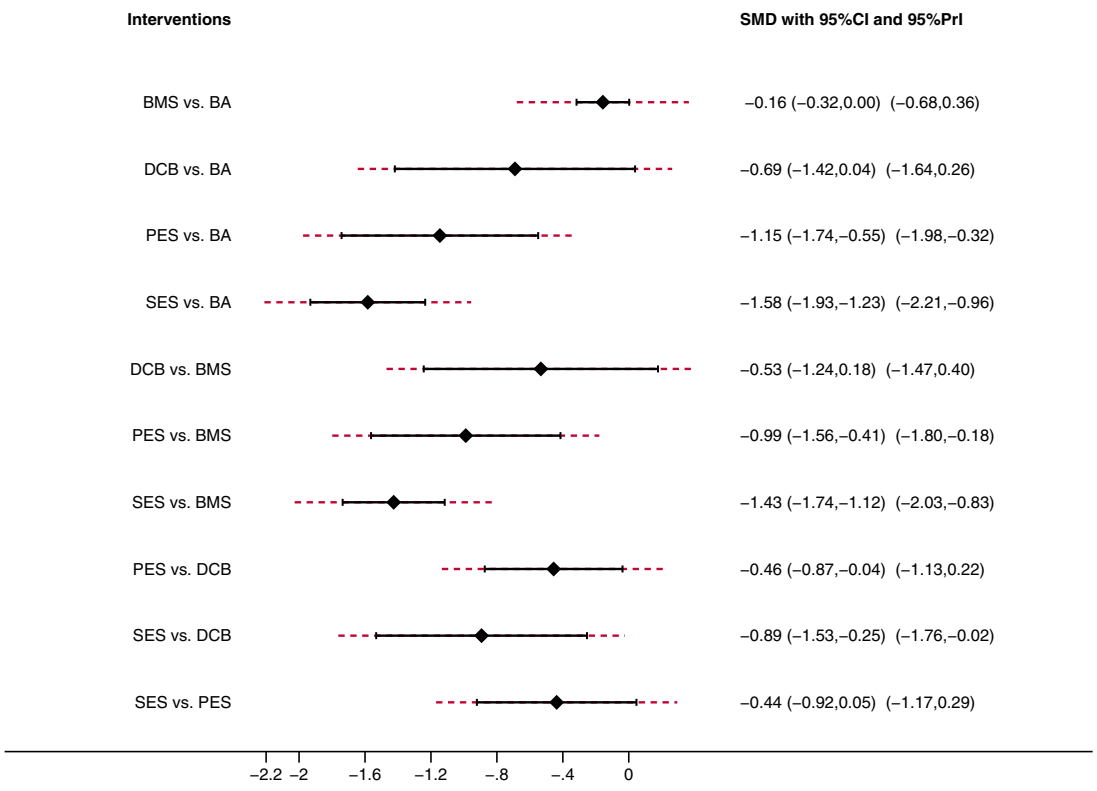
Abbreviations as in Table 1.

FIGURE 2 **Ranking Plots for All the Outcomes of Interest**



Interventions have been ranked according to the surface under the cumulative ranking curves (SUCRA) values. Abbreviations as in Figure 1.

FIGURE 3 Predictive Interval Plot for the Primary Outcome of %Ds on a Logarithmic Scale

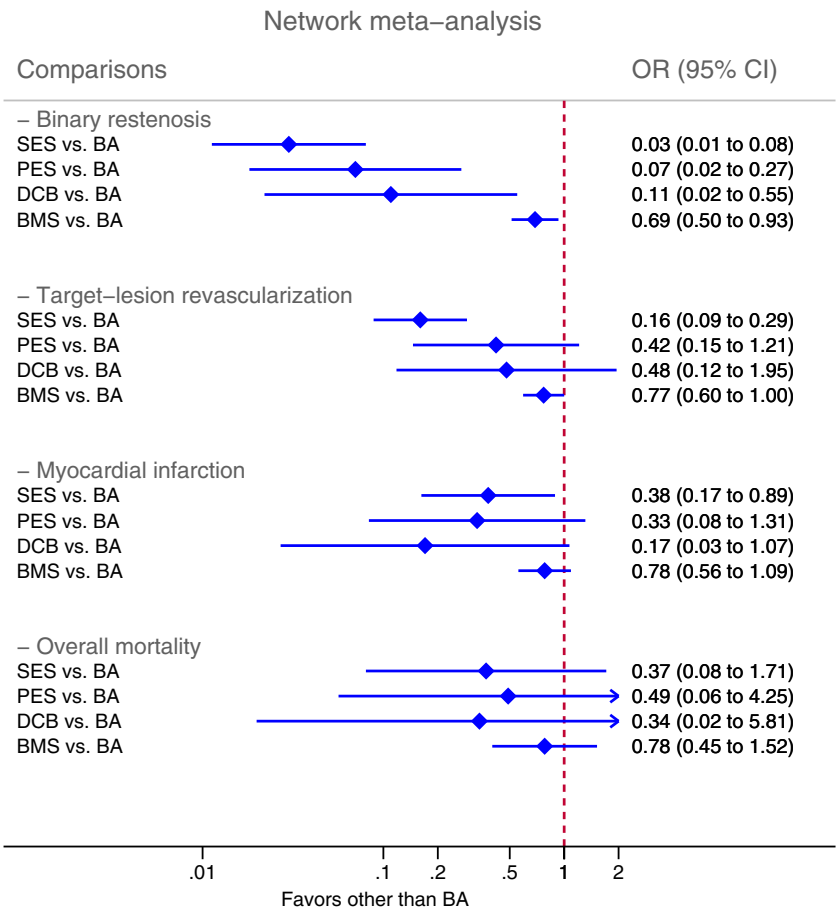


The **black solid lines** represent the confidence intervals for SMD for each comparison and the **red lines** the respective predictive intervals. DCB = drug-coated balloon; SMD = standardized mean difference; CI = confidence interval; PrI = prediction interval; other abbreviations as in Figure 1.

effective treatment in terms of angiographic performance assessed by %DS, which also translated into a significant decrease in risk of TLR compared with other treatments. Second, both SES and PES were associated with a significant reduction in %DS compared with DCB, albeit only SES significantly reduced the risk of TLR by 31%. Third, BMS and BA had the worst ranking position for all study outcomes and therefore could not be considered effective alternatives for patients undergoing PCI of small-vessel disease.

Small vessel coronary artery intervention carries a higher risk of restenosis and repeat revascularization regardless of the type of treatment (37). In a large cohort of patients, 10,004, treated with stent implantation that included newer generation DES, small-vessel diameter was the most powerful predictor of angiographic restenosis, with a 60% higher risk of restenosis for each decrease in reference vessel diameter by 0.50 mm (4). Moreover, small-vessel CAD is frequently associated with additional high-risk features, including multivessel disease and diabetes mellitus (1,2). Because the amount of neointimal hyperplasia is independent on vessel size, restenosis is more common in smaller vessels due to their limited ability to accommodate neointimal hyperplasia. As a result, the relative reduction in lumen diameter is greater in small than in large vessels for a fixed amount of neointimal tissue (37). A pairwise meta-analysis by Agostoni et al. (38) showed a heterogeneous reduction in the risk of TLR with BMS compared to BA for the treatment of small-vessel CAD, because stent implantation was not superior to BA in patients with a residual diameter stenosis <20%. Therefore, DCB became an attractive treatment option among patients with small-vessel disease by sharing features similar to those in BA but delivering at the same time the antiproliferative drug via non-stent-based platforms (39). The shorter duration of drug release limited to the time of the highest activity of the neointimal overgrowth after barotrauma, coupled with the uniform, strut-independent drug delivery may represent additional features favoring DCB over DES use in this

FIGURE 4 Forest Plots for Effect Sizes of Different Interventions Compared With Balloon Angioplasty for Secondary Outcomes



Estimated odds ratios (95% CIs) for the secondary outcomes of the network meta-analysis (binary restenosis, target-lesion revascularization, myocardial infarction, overall mortality) of different percutaneous interventions compared with BA. Abbreviations as in Figures 1 and 3.

setting (39). However, results of the present study indicate that DES, particularly SES, are superior to those of DCB for the treatment of small-vessel CAD by providing superior angiographic and clinical outcomes. %DS at the time of angiographic follow-up was chosen as the primary outcome as heterogeneous treatment options (stent and nonstent-based) were anticipated, and this parameter has been suggested as the most appropriate in case of intermodal comparisons (40). Furthermore, the use of SES was safe and associated with a significant reduction in the risk of myocardial infarction compared with BA.

Although our findings pertain to early generation SES, the relative reduction of approximately 30% in risk of TLR may have relevant implications for decision making in clinical practice, as the potential benefit may be even greater with new generation DES. Indeed, the refinements associated with new generation DES resulted not only in a reduction in risk of stent thrombosis but also in improved efficacy with a 10% to 20% lower risk of repeat revascularization compared with early generation DES (41).

In the pooled analysis of SPIRIT III and IV (Clinical Evaluation of the Xience V Everolimus Eluting Coronary Stent System in the Treatment of Patients with de novo Native Coronary Artery Lesions trial), the new generation everolimus-eluting stent decreased the risk of target lesion failure and TLR in the subgroup of patients with small-vessel CAD compared to PES (42). Nevertheless, the superiority of new generation DES compared to early generation SES has not been established for small-vessel disease to date (43,44). By featuring thinner stent struts, biocompatible polymers, and different limus-eluting drug analogs, new generation DES may further improve upon early generation DES, as the

relationship between stent strut thickness and restenosis is particularly evident in small vessels (45). In the TAXUS ATLAS (TAXUS Liberté-SR Stent for the Treatment of De Novo Coronary Artery Lesions) small vessel study, a thin-strut PES (97 μm) reduced the rate of 9-month angiographic restenosis and 12-month TLR compared with a thicker strut PES (132 μm) (46). Moreover, the availability of new generation DES with 2.25- and 2.00-mm diameters may further improve the feasibility and performance of coronary stenting in small vessels (47). Finally, new generation DESs have been associated with an improved safety and efficacy profile compared to early generation DES and DCB in different settings (41,48).

Another finding of this network meta-analysis is that the use of BA for the treatment of small vessels should be avoided as this treatment resulted in the lowest ranking for all study outcomes. It is noteworthy that direct evidence from randomized trials was limited exclusively to the comparison of BMS versus BA, and therefore, the comparative evaluation of BA with newer techniques was possible only indirectly through the network meta-analysis.

STUDY LIMITATIONS. This study should be interpreted in view of the following limitations. First, our network is an open network without closed loops between the compared interventions; therefore, we were not able to assess inconsistency between direct and indirect evidence. Second, our findings need to be considered average effects as we did not have access to individual patient data that would have allowed us to identify potential differential effects of the available strategies in specific subgroups of patients (i.e., according to the size of the treated vessels). Third, available evidence from randomized trials is sparse and derived mainly from studies that investigated the role of BMS with BA as comparator. Dedicated, head-to-head randomized trials are needed to provide more robust data comparing new generation DES with DCB. Fourth, the 2 trials evaluating DCB used devices with 2 different paclitaxel coating technologies (urea and shellac), along with different predilation rates, and this might have affected the results.

CONCLUSIONS

This comprehensive network meta-analysis demonstrated that DES, and particularly SES, represent the most effective treatment modality for the percutaneous treatment of small-vessel CAD. The angiographic effectiveness of early generation SES resulted in a significant reduction in the risk of TLR compared with all other treatments. DCB represented a more effective treatment modality compared only to BMS and BA. Additional randomized trials are warranted evaluating the role of new generation DES to corroborate the results of this meta-analysis.

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PERSPECTIVES

WHAT IS KNOWN? PCI in small coronary arteries is associated with an increased risk of repeat revascularization. Although different treatment modalities are available, the optimal strategy in terms of efficacy is unknown owing to the limited number of dedicated randomized trials.

WHAT IS NEW? This network meta-analysis evaluated different PCI-strategies for the treatment of stenoses in small coronary vessels and demonstrated that early generation SES is the best treatment mode in terms of angiographic and clinical efficacy compared with PES, DCB, BMS, and BA.

WHAT IS NEXT? No dedicated trials have so far been conducted to evaluate new generation drug-eluting stents in this clinical setting. Appropriately designed randomized controlled trials need to be performed to evaluate the role of different platforms of new generation drug-eluting stents.

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