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CLINICAL RESEARCH

CORONARY

Stent Thrombosis With Drug-Eluting Stents and Bioresorbable Scaffolds

Evidence From a Network Meta-Analysis of 147 Trials

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ABSTRACT

OBJECTIVES This study sought to perform a systematic review and network meta-analysis to compare the relative safety and efficacy of contemporary DES and BVS.

BACKGROUND To improve outcomes of patients undergoing percutaneous coronary revascularization, there have been advances in the design of drug-eluting stents (DES), including the development of drug-eluting bioresorbable vascular scaffolds (BVS).

METHODS Prospective, randomized, controlled trials comparing bare-metal stents (BMS), paclitaxel-eluting stents (PES), sirolimus-eluting stents (SES), Endeavor zotarolimus-eluting stents (E-ZES), cobalt-chromium (CoCr) everolimus-eluting stents (EES), platinum-chromium (PtCr)-EES, biodegradable polymer (BP)-EES, Resolute zotarolimus-eluting stents (R-ZES), BP biolimus-eluting stents (BP-BES), hybrid sirolimus-eluting stents (H [Orsiro]-SES), polymer-free sirolimus- and probucol-eluting stents, or BVS were searched in online databases. The primary endpoint was definite or probable stent thrombosis at 1 year.

RESULTS A total of 147 trials including 126,526 patients were analyzed in this study. All contemporary DES were superior to BMS and PES in terms of definite or probable stent thrombosis at 1 year. CoCr-EES, PtCr-EES, and H-SES were associated with significantly lower risk than BVS. CoCr-EES and H-SES were superior to SES and BP-BES. The risk of myocardial infarction was significantly lower with H-SES than with BVS. There were no significant differences regarding all-cause or cardiac mortality. Contemporary devices including BVS showed comparably low risks of repeat revascularization.

CONCLUSIONS Contemporary DES, including biocompatible DP-DES, BP-DES, and polymer-free DES, showed a low risk of definite or probable stent thrombosis at 1 year. BVS had an increased risk of device thrombosis compared with CoCr-EES, PtCr-EES, and H-SES. Data from extended follow-up are warranted to confirm the long-term safety of contemporary coronary devices. (J Am Coll Cardiol Intv 2016;9:1203–12) © 2016 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

BMS = bare-metal stent(s)

BP-BES = biodegradable polymer biolimus A9-eluting stent(s)

BP-EES = biodegradable polymer everolimus-eluting stent(s)

BVS = bioresorbable vascular scaffolds

CoCr-EES = cobalt-chromium everolimus-eluting stent(s)

CrI = credible interval

DES = drug-eluting stent(s)

DP = durable polymer

Dual DES = polymer-free sirolimus- and probucol-eluting stent(s)

E-ZES = endeavor zotarolimus-eluting stent(s)

H-SES = hybrid sirolimus-eluting stent(s)

MI = myocardial infarction

PES = paclitaxel-eluting stent(s)

PtCr-EES = platinum-chromium everolimus-eluting stent(s)

R-ZES = Resolute zotarolimus-eluting stent(s)

SES = sirolimus-eluting stent(s)

ST = stent thrombosis

Drug-eluting stents (DES) have become an essential component in the treatment of coronary artery disease (1,2). The main advantage of DES is the reduction of repeat revascularization compared with bare-metal stents (BMS). However, concerns about the long-term safety of earlier generation DES have provoked recent advances in DES (3). Thin-strutted devices have replaced previous thick-strutted ones. Because studies suggested that polymer may trigger local inflammation and, subsequently, late stent thrombosis, there has been diversification in polymer choice and coating technology, including durable but biocompatible polymers, biodegradable polymers (BP), and even polymer-free devices (4). The latest development was the introduction of bioresorbable vascular scaffolds (BVS), which provide transient mechanical support and antirestenotic drug delivery followed by complete resorption for years (5–7).

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Previous network meta-analyses showed that BP-DES and BMS were not necessarily safer than biocompatible durable polymer (DP)-DES (8–10). After publication of those studies, a growing amount of clinical experience and research have led to a better understanding of the advantages and disadvantages of diverse devices. First, clinical data regarding second-generation DES with biocompatible permanent polymers have accumulated. Second, DES with novel designs have been introduced, such as BP-DES with better profiles, polymer-free DES, and everolimus-eluting BVS. In particular, the use of BVS has steeply increased with the expectations of its safety (11,12). However, data regarding BVS are still limited. Recent studies have shown that BVS is as efficacious as cobalt-chromium everolimus-eluting stents (CoCr-EES) in terms of repeat revascularization, but safety concerns have been raised as well (11–14).

In this study, we compared the safety of various contemporary DES including BVS in terms of the risk of stent thrombosis (ST) or device thrombosis. Due to the low incidence rates of ST, a very large sample size was required to detect differences in a single trial setting. A network meta-analysis has the advantage of providing comprehensive information by combining data from a complex network of multiple trials. For this purpose, we performed a systematic literature review of randomized controlled trials and updated a multiple-treatment network meta-analysis using a Bayesian framework.

METHODS

ELIGIBILITY CRITERIA. Randomized controlled trials comparing 2 or more coronary stents or scaffolds in patients undergoing percutaneous coronary intervention were analyzed. In this study, we focused on stents of interest as follows: (1) BMS; (2) paclitaxel-eluting stents (PES) (Boston Scientific, Natick, Massachusetts); (3) sirolimus-eluting stents (SES) (Cordis, Warren, New Jersey); (4) Endeavor zotarolimus-eluting stents (E-ZES) (Medtronic, Santa Rosa, California); (5) CoCr-EES (Abbott Vascular, Santa Clara, California and Boston Scientific); (6) platinum-chromium everolimus-eluting stents (PtCr-EES) (Boston Scientific); (7) BP-EES (Boston Scientific); (8) Resolute zotarolimus-eluting stents (R-ZES) (Medtronic); (9) BP biolimus A9-eluting stents (BP-BES) (Biosensors, Newport Beach, California and Terumo, Tokyo, Japan); (10) hybrid SES (H-SES) (Orsiro model; Biotronik, Newport Beach, California); (11) polymer-free sirolimus- and probucol-eluting stents (dual DES; B. Braun, Newport Beach, California); and (12) BVS (Abbott Vascular). Some of the currently available devices such as the polymer-free biolimus A9-coated stent (BioFreedom, Biosensors) and DESolve bioresorbable coronary scaffold (Elixir Medical, Sunnyvale, California), which have been approved by major regulatory authorities, were not included in this study, because they had limited comparisons with other devices (15,16). Exclusion criteria included studies comparing 2 stents with different stent designs within the same category described here, studies in which the specific type of DES was not predefined and the choice among available DES was left to the investigators' discretion (e.g., BMS vs. any DES), and studies published in a language other than English. No restrictions were imposed on study period, sample size, publication status, or patient or lesion criteria.

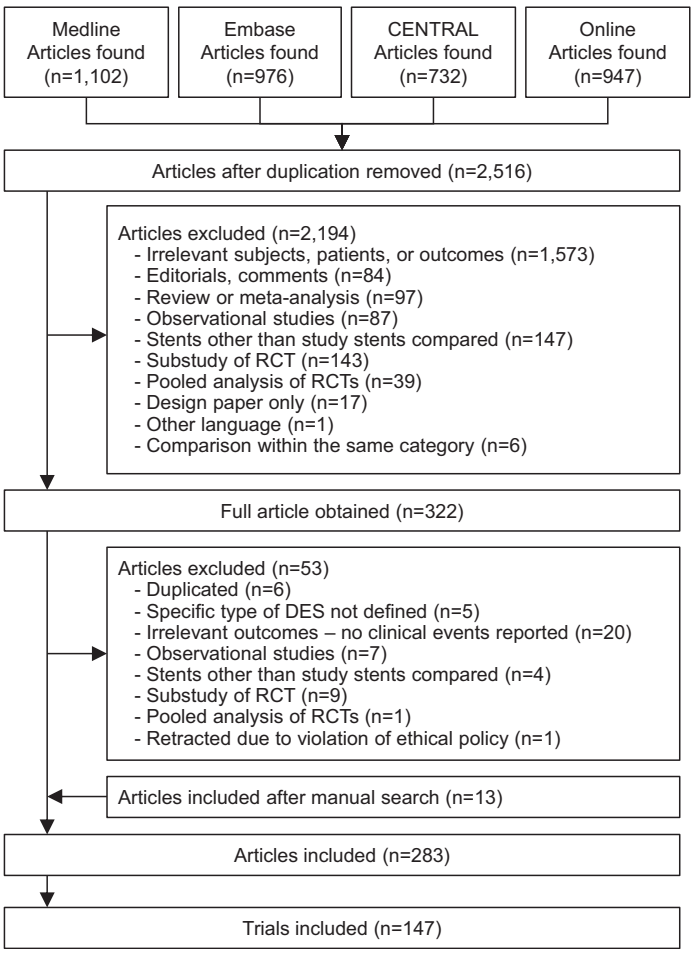
DATA SOURCES AND SEARCHES. An electronic search was performed in PubMed, Embase, Cochrane Central Register of Controlled Trials, and relevant Websites (www.crtonline.org; www.clinicaltrialresults.com; www.tctmd.com; www.cardiosource.com; and www.pcronline.com) from the inception of each database to December 2015 (search terms are described in Online Table 1). A manual review of reference lists of included articles complemented the search. References of recent reviews, editorials, and meta-analyses were also examined. Two investigators (S.H.K. and D.Y.K.) screened titles and abstracts, identified

duplicates, reviewed full articles, and determined their eligibility. Disagreement between reviewers was resolved by discussion. The most updated data for each study were searched manually and chosen for abstraction. Data extraction was performed by 1 reviewer (S.H.K.) and subsequently crosschecked by a second reviewer (H.L.). The quality of eligible randomized controlled trials was assessed using the Cochrane Collaboration tool for assessing the risk of bias (17). Risk of bias was assessed by 1 reviewer (H.L.) and crosschecked by a second reviewer (S.H.K.).

STUDY OUTCOMES AND DEFINITIONS. The principal safety endpoint was definite or probable ST or device thrombosis defined according to the Academic Research Consortium at 1 year (18). Studies reporting the incidence of ST in a way other than that of the Academic Research Consortium consensus were excluded from the analysis. Other safety endpoints included early ST, late ST, definite ST, all-cause death, cardiac death, and myocardial infarction (MI). Efficacy endpoints included target vessel revascularization and target lesion revascularization. Outcomes up to 1 year were analyzed in this study because recently developed devices still have limited long-term data.

DATA SYNTHESIS AND ANALYSIS. A Bayesian random effects model for multiple treatment comparisons was constructed to compare clinical outcomes of different stent types. We used Bayesian extension of the hierarchical random effects model proposed by Lumley for networks of multiarm trials (19,20). We used Markov chain Monte Carlo samplers in WinBUGS version 1.4.3 (MRC Biostatistics Unit, Cambridge, United Kingdom) running 3 chains with different starting values. Vague, non-informative prior distributions with very small precision were given. A burn-in phase of 20,000 iterations was used to ensure convergence. The convergence was checked by running 3 chains at different starting values using the Gelman-Rubin methods, which were stable in all instances. For inference, 50,000 iterations were used. Pairwise odds ratios were estimated from the median of the posterior distribution, and credible intervals (CrI) were taken from the 2.5% and 97.5% percentiles. To rank the risk of ST of each stent, the surfaces under the cumulative ranking line were calculated. An estimated relative effect was considered significant, when the upper or lower CrI did not include one. Sensitivity analyses were performed excluding studies with any potential risk of bias as evaluated with the Cochrane Collaboration's tool, studies with a sample size of <100, and studies that compared BMS, PES, SES, or E-ZES, which are no longer used in clinical practice. Entries for patient blinding and operator blinding were not considered for the former. Node-splitting models were constructed to assess the level of inconsistency between the estimates from direct and indirect evidence. Statistical analyses were performed with the use of WinBUGS and R software.

FIGURE 1 Flow Diagram of Systematic Review

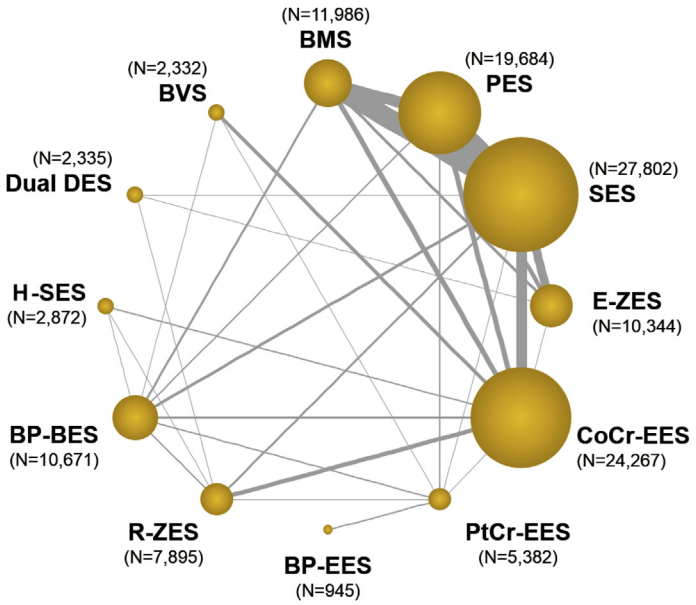


The study flow is shown following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. DES = drug-eluting stent(s); RCT = randomized controlled trial.

RESULTS

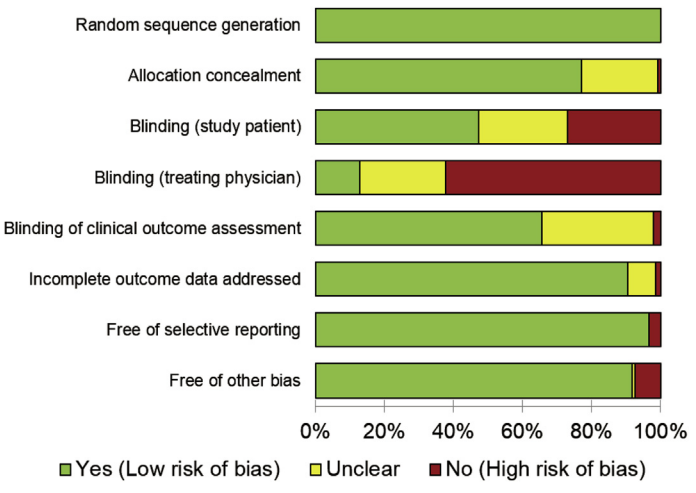
STUDY SELECTION AND SYSTEMATIC REVIEW. Figure 1 shows the flow diagram of this study. Among 2,516 potentially relevant items, 147 trials including 126,526 patients were finally selected for this meta-analysis. The network plot had a polygonal network configuration with mixed connections (Figure 2). There were almost fully closed loops among BMS, PES, SES, E-ZES, CoCr-EES, R-ZES, and BP-BES. However, newer devices such as BP-EES, H-SES,

FIGURE 2 Network Plot of Included Trials



Each stent is represented by a node. The size of the node is proportional to the sample size randomized to each stent, whereas the thickness of the line connecting the nodes is proportional to the total randomized sample size in each pairwise treatment comparison. BMS = bare-metal stent(s); BP-BES = biodegradable polymer biolimus-eluting stent(s); BP-EES = biodegradable polymer everolimus-eluting stent(s); BVS = bioresorbable vascular scaffolds; CoCr-EES = cobalt-chromium everolimus-eluting stent(s); dual DES = sirolimus- and probucol-eluting stent(s); E-ZES = Endeavor zotarolimus-eluting stent(s); H-SES = hybrid sirolimus-eluting stent(s); PES = paclitaxel-eluting stent(s); PtCr-EES = platinum-chromium everolimus-eluting stent(s); R-ZES = Resolute zotarolimus-eluting stent(s); SES = sirolimus-eluting stent(s).

FIGURE 3 Risk of Bias Assessment



Risk of bias of each included trial was assessed with the Cochrane Collaboration's tool. This risk-of-bias graph illustrates the proportion of studies with each of the judgments for each entry in the tool. **Green** represents "yes" (low risk of bias); **yellow** is "unclear"; **red** is "no" (high risk of bias).

dual DES, and BVS had small sample sizes and limited comparisons with other devices.

Characteristics of the included trials are summarized in Online Table 2. There were 9 trials with a 3-arm design and 1 trial with a 4-arm design. Thirteen trials dedicatedly enrolled patients with diabetes mellitus, 25 enrolled those with ST-segment elevation MI, and 6 enrolled those with chronic total occlusion. An "all-comer design" was adopted in many of the recent large-scale clinical trials. Most trials comparing BVS had stringent inclusion and exclusion criteria. **Figure 3** shows the distribution of the risk of bias of the included trials according to the Cochrane Collaboration's tool. All trials were described as randomized controlled trials. Although several earlier studies used a double-blind design, open-label or single-blind designs were more common. Blinding for clinical outcome assessment was performed in 66% of the trials.

STENT THROMBOSIS. The primary endpoint, definite or probable ST at 1 year, was available in 110 studies including 111,088 patients. **Table 1** shows the relative risk for each pair of comparisons derived from the Bayesian random effects model. All DES except for PES and BVS were superior to BMS in terms of the primary endpoint, whereas all others except BVS and E-ZES were superior to PES. CoCr-EES, H-SES, and PtCr-EES were associated with a significantly lower risk of ST than BVS and E-ZES. In addition, CoCr-EES and H-SES were significantly better than SES and BP-BES. Forest plots of the estimated odds ratios for PtCr-EES, R-ZES, H-SES, and BVS are shown in **Figure 4**. The ranks of study stents are illustrated in **Figure 5**: (BP-EES was asymptotically equal to [≒] PtCr-EES ≒ H-SES ≒ Dual DES ≒ CoCr-EES) > (ZES-R ≥ BP-BES ≥ SES) > (E-ZES) > (BVS ≥ PES ≥ BMS). Risk estimates for early and late ST are shown in Online Tables 3 and 4, respectively.

Regarding definite ST, 107 studies involving 106,543 patients contributed to the analysis. As shown in **Table 2**, BP-BES, SES, R-ZES, H-SES, CoCr-EES, and PtCr-EES were superior to BMS, and SES, CoCr-EES, and PtCr-EES were superior to PES. In addition, CoCr-EES was associated with a lower risk of ST than E-ZES, BP-BES, and SES. The rank of each stent was as follows: (BP-EES ≒ PtCr-EES ≒ CoCr-EES ≒ H-SES) > (dual DES ≥ R-ZES ≥ SES ≥ BP-BES ≥ BVS) > (E-ZES ≥ PES ≥ BMS).

OTHER SAFETY AND EFFICACY ENDPOINTS. There were no statistical differences in any comparisons between study stents in terms of all-cause death or cardiac death (Online Tables 5 and 6). The results of MI within 1 year were similar to those of the primary endpoint (Online Table 7). SES, R-ZES, BP-

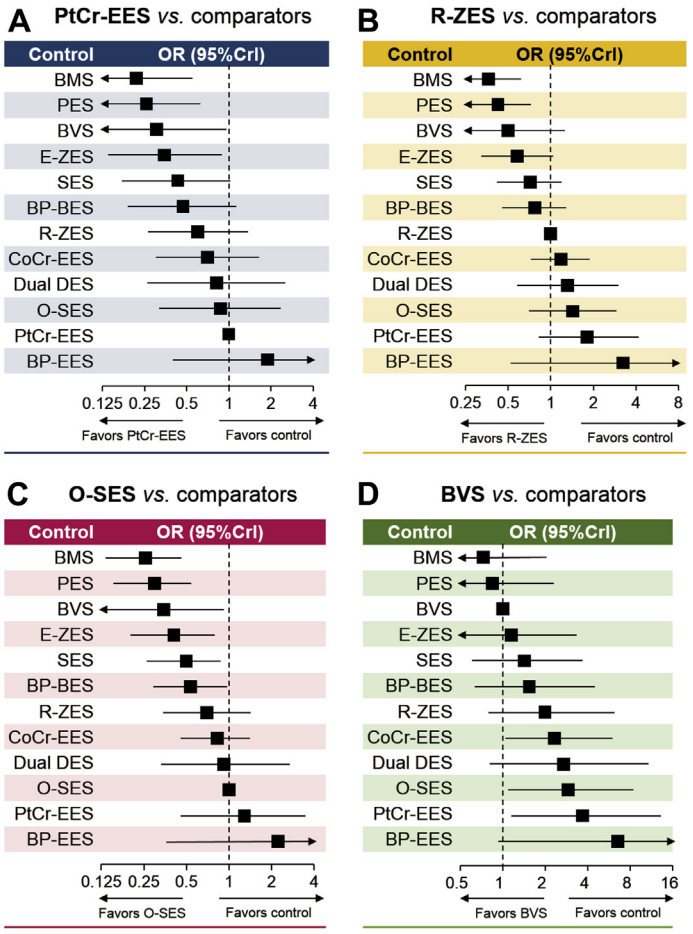
TABLE 1 Pairwise Comparisons of Definite or Probable Stent Thrombosis Between Study Stents

	BMS	PES	BVS	E-ZES	SES	BP-BES	R-ZES	CoCr-EES	Dual DES	O-SES	PtCr-EES	BP-EES
vs. BMS	-	0.87 (0.64-1.18)	0.73 (0.31-2.06)	**0.64 (0.43-0.90)**	**0.51 (0.38-0.69)**	**0.48 (0.31-0.72)**	**0.37 (0.21-0.63)**	**0.31 (0.22-0.44)**	**0.28 (0.10-0.69)**	**0.25 (0.13-0.48)**	**0.22 (0.09-0.55)**	**0.12 (0.02-0.72)**
vs. PES	1.15 (0.85-1.56)	-	0.85 (0.36-2.34)	0.73 (0.50-1.05)	**0.59 (0.45-0.80)**	**0.55 (0.33-0.85)**	**0.43 (0.24-0.71)**	**0.36 (0.26-0.49)**	**0.32 (0.12-0.78)**	**0.29 (0.15-0.55)**	**0.26 (0.10-0.62)**	**0.13 (0.02-0.84)**
vs. BVS	1.38 (0.49-3.21)	1.18 (0.43-2.77)	-	0.88 (0.29-2.09)	0.71 (0.25-1.65)	0.65 (0.22-1.59)	0.51 (0.17-1.22)	**0.44 (0.16-0.93)**	0.39 (0.10-1.22)	**0.35 (0.11-0.91)**	**0.31 (0.08-0.96)**	0.16 (0.02-1.15)
vs. E-ZES	**1.57 (1.11-2.31)**	1.36 (0.95-2.00)	1.13 (0.48-3.39)	-	0.81 (0.57-1.17)	0.75 (0.44-1.25)	0.58 (0.32-1.03)	**0.49 (0.33-0.75)**	0.44 (0.16-1.08)	**0.40 (0.21-0.80)**	**0.35 (0.14-0.89)**	0.18 (0.03-1.15)
vs. SES	**1.95 (1.45-2.61)**	**1.70 (1.25-2.23)**	1.41 (0.61-3.93)	1.24 (0.85-1.77)	-	0.93 (0.61-1.37)	0.72 (0.42-1.17)	**0.61 (0.44-0.81)**	0.54 (0.21-1.30)	**0.50 (0.27-0.92)**	0.43 (0.17-1.03)	0.24 (0.04-1.42)
vs. BP-BES	**2.10 (1.39-3.25)**	**1.81 (1.18-3.06)**	1.54 (0.63-4.52)	1.33 (0.80-2.28)	1.07 (0.73-1.63)	-	0.77 (0.45-1.29)	**0.66 (0.43-0.99)**	0.58 (0.22-1.44)	**0.53 (0.30-0.96)**	0.47 (0.19-1.12)	0.25 (0.04-1.55)
vs. R-ZES	**2.69 (1.59-4.79)**	**2.33 (1.41-4.12)**	1.96 (0.82-5.87)	1.71 (0.97-3.12)	1.39 (0.85-2.41)	1.30 (0.78-2.23)	-	0.84 (0.55-1.38)	0.74 (0.34-1.62)	0.69 (0.35-1.42)	0.60 (0.27-1.38)	0.32 (0.06-1.93)
vs. CoCr-EES	**3.20 (2.27-4.54)**	**2.79 (2.03-3.88)**	**2.28 (1.07-6.29)**	**2.02 (1.33-3.07)**	**1.63 (1.23-2.26)**	**1.53 (1.01-2.31)**	1.18 (0.73-1.83)	-	0.89 (0.35-2.10)	0.80 (0.47-1.44)	0.71 (0.30-1.65)	0.38 (0.06-2.33)
vs. Dual DES	**3.63 (1.44-9.57)**	**3.13 (1.27-8.27)**	2.59 (0.82-10.3)	2.29 (0.92-6.10)	1.86 (0.77-4.82)	1.71 (0.70-4.48)	1.35 (0.62-2.94)	1.12 (0.48-2.82)	-	0.94 (0.33-2.64)	0.82 (0.26-2.53)	0.42 (0.06-3.21)
vs. O-SES	**3.94 (2.10-7.52)**	**3.40 (1.80-6.48)**	**2.83 (1.10-8.90)**	**2.50 (1.26-4.85)**	**2.02 (1.09-3.74)**	**1.88 (1.04-3.37)**	1.45 (0.71-2.89)	1.24 (0.69-2.14)	1.06 (0.38-2.99)	-	0.87 (0.32-2.36)	0.45 (0.07-3.06)
vs. PtCr-EES	**4.56 (1.82-11.3)**	**3.87 (1.60-9.81)**	**3.28 (1.04-12.1)**	**2.88 (1.12-7.28)**	2.31 (0.97-5.76)	2.12 (0.89-5.27)	1.67 (0.73-3.76)	1.42 (0.60-3.34)	1.22 (0.39-3.80)	1.15 (0.42-3.14)	-	0.53 (0.11-2.50)
vs. BP-EES	**8.51 (1.39-54.7)**	**7.44 (1.19-46.9)**	6.13 (0.87-49.5)	5.50 (0.87-33.8)	4.24 (0.70-27.6)	4.05 (0.65-26.1)	3.09 (0.52-18.2)	2.64 (0.43-16.5)	2.36 (0.31-16.2)	2.20 (0.33-14.8)	1.90 (0.40-8.84)	-

Odds ratios and 95% credible intervals are presented. Comparisons that are statistically significant are highlighted in **bold**. Comparisons with significantly lower risk were highlighted with **red**, and those with higher risk were with **blue**.

BMS = bare-metal stent(s); BP-BES = biodegradable polymer biolimus-eluting stent(s); BP-EES = biodegradable polymer everolimus-eluting stent(s); BVS = bioresorbable vascular scaffold(s); CoCr-EES = cobalt-chromium everolimus-eluting stent(s); dual DES = sirolimus- and probucol-eluting stent(s); E-ZES = Endeavor zotarolimus-eluting stent(s); O-SES = Orsiro sirolimus-eluting stent(s); PES = paclitaxel-eluting stent(s); PtCr-EES = platinum-chromium everolimus-eluting stent(s); R-ZES = Resolute zotarolimus-eluting stent(s); SES = sirolimus-eluting stent(s).

FIGURE 4 Definite or Probable Stent Thrombosis at 1 Year



Forest plots compare definite or probable stent thrombosis within 1 year of **(A)** platinum-chromium everolimus-eluting stent(s) (Pt-EES), **(B)** Resolute zotarolimus-eluting stent(s) (R-ZES), **(C)** hybrid sirolimus-eluting stent(s) (O-SES), and **(D)** bioresorbable vascular scaffolds (BVS) versus comparators. The **squares** and **horizontal lines** indicate pairwise odds ratios (OR) and their 95% credible intervals (CrI) estimated with a multiple-treatment meta-analysis. Other abbreviations as in Figure 2.

BES, E-ZES, PtCr-EES, CoCr-EES, and H-SES had a significantly lower risk of MI than BMS, whereas SES, BP-BES, E-ZES, PtCr-EES, CoCr-EES, and H-SES had a significantly lower risk of MI than PES. PtCr-EES was superior to SES, and H-SES was superior to BVS.

All contemporary DES and BVS showed low risks of target vessel revascularization and target lesion revascularization (Online Tables 8 and 9). All DES were associated with reduced risk of repeat revascularization compared with BMS. PES and E-ZES were shown to be inferior to other contemporary devices. In particular, BVS had a similar risk for repeat revascularization as the other DES such as SES, R-ZES, CoCr-EES, PtCr-EES, BP-BES, and H-SES.

SENSITIVITY ANALYSIS. A sensitivity analysis was performed for studies with low risk of bias. After excluding studies with any potential risk of bias (unclear or no) assessed according to the Cochrane Collaboration's tool, 70 trials involving 88,011 patients contributed to the analysis (Online Table 10). The inferiority of BVS to CoCr-EES, H-SES, and PtC-EES and the inferiority of BP-BES to CoCr-EES and H-SES lost statistical significance. Results were otherwise similar to that of the primary analysis.

A second sensitivity model was constructed excluding trials with a sample size <100. A total of 110 trials including 111,088 patients contributed to the analysis (Online Table 11). The sensitivity analysis showed the same results as the main analysis except for the loss of statistical significance for the superiority of PtCr-EES to BVS.

The third sensitivity analysis was done comparing currently utilized stents only, namely CoCr-EES, PtCr-EES, BP-EES, R-ZES, BP-BES, H-SES, dual DES, and BVS (Online Table 12). There was a remarkable reduction in statistical power: 28 studies including 37,137 patients contributed to the analysis. Although the trends were similar to the main analysis, no comparisons were statistically significant, mainly due to the decrease in statistical power. Estimates from direct and indirect evidence were mostly consistent (Online Table 13); inconsistency was represented by a p value of 0.979 for the comparison between H-SES and BP-BES, and p value of 0.900 for BVS versus CoCr-EES (Online Figure 1).

DISCUSSION

To our knowledge, this study is the most comprehensive and updated network meta-analysis comparing contemporary coronary stents and scaffolds. The major findings of this study are as follows: 1) all currently available DES including biocompatible DP-DES, BP-DES, and polymer-free dual DES were associated with low risk of ST compared with BMS or first-generation devices; 2) in particular, PtCr-EES, H-SES, and CoCr-EES exhibited excellent safety; 3) all contemporary devices including BVS showed low risks of repeat revascularization; and 4) the risk of device thrombosis after treatment with BVS was significantly higher than that of CoCr-EES, PtCr-EES, or H-SES. However, caution should be taken in interpreting the study results, as BP-EES, H-SES, dual DES, and BVS had limited numbers of comparisons, and some of the studies had a potential risk of bias.

DIFFERENT POLYMER TYPES: BIOCOMPATIBLE PERMANENT AND BIOABSORBABLE POLYMERS. Preclinical and autopsy data showed that delayed

vascular healing after DES implantation is an important determinant of ST (4,21). Recent advances in DES designs were largely driven by the efforts to reduce the risk of thrombotic events. Biocompatible DP was one of the initial innovations. Experimental studies showed that biocompatible polymer coatings serve as corrosive barriers and reduce acute thrombogenicity compared with bare metallic surfaces (22,23). Such observations were confirmed by clinical studies that demonstrated CoCr-EES, a second-generation DP-DES, reduced the risk of ST compared with first-generation DES and BMS (24–27). A more recent approach was BP that dissolves within the body after a certain period, allowing for stable release of antirestenotic drugs. However, a previous network meta-analysis showed that BP-BES was associated with a higher risk of ST than CoCr-EES (8). An ex vivo preclinical study also showed that CoCr-EES offers thromboresistance compared with contemporary DES with biodegradable coatings (28).

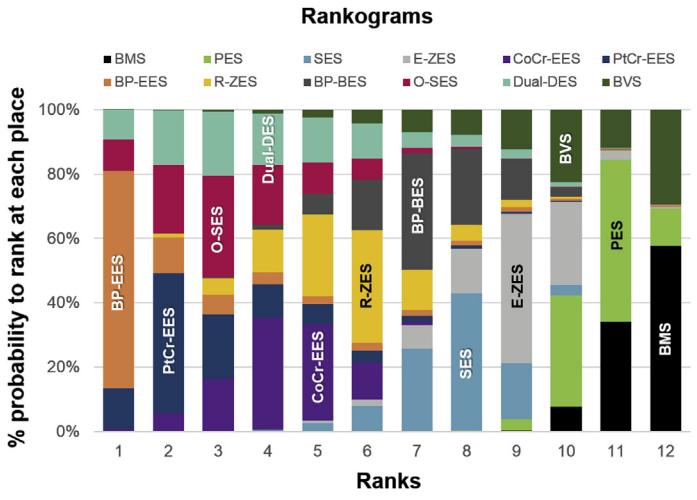
This study confirms the safety of contemporary DP-DES and BP-DES in terms of ST at 1 year. R-ZES, CoCr-EES, dual DES, H-SES, PtCr-EES, and BP-EES exhibited comparably low risks of ST. CoCr-EES, PtCr-EES, and H-SES, among others, showed impressive performance in terms of both definite or probable ST and definite ST. Dual DES and BP-EES were also shown to reduce the risk of ST compared with BMS, despite the limited number of comparisons.

CoCr-EES, PtCr-EES, and R-ZES represent the second-generation DES with biocompatible permanent polymers. The safety and efficacy of CoCr-EES have been shown consistently in laboratory and clinical studies (26–28). On the basis of the study results, CoCr-EES is being considered the most competitive comparator in recent studies. In this study, PtCr-EES showed safety comparable to that of CoCr-EES. Besides alloy component and stent geometry, PtCr-EES uses the same drug and polymer formation as CoCr-EES. The results of this study support the concept of low thrombogenicity with a combination of a thin strut and stable fluorinated copolymer coating (23,29).

STENTS WITH BIODEGRADABLE POLYMERS: H-SES VERSUS BP-BES. The disparity between the 2 BP-DES, namely H-SES and BP-BES, provides interesting perspectives regarding the DES designs. Although they share the biodegradable property of the polymers, H-SES was shown to be superior to BP-BES in this study. The 2 devices have several distinctions in drugs, polymer choice, polymer application method, metallic features, and stent geometry. One major difference is the strut thickness. H-SES has an ultrathin strut thickness of 61 μm, whereas BP-BES (Biomatrix or Nobori) has a strut thickness of 120 μm, which is relatively thick. Using a modified Chandler loop model, Kolandaivelu et al. (23) showed that stents with struts 2× thicker were 1.5-fold more thrombogenic than otherwise identical devices with thinner struts. Second, BP-BES have abluminal polymer coatings, whereas the surface of H-SES is fully covered by hybrid coatings. Considering that durable polymer coatings have been shown to reduce thrombogenicity compared with BMS, exposure of bare metal on the luminal surface of the stents may be disadvantageous in terms of platelet aggregation (23). In addition, the hybrid coating design of H-SES blocks exposure of the metallic surfaces to the surrounding tissue by the passive coating after the active coating of poly-L-lactic acid breaks down. Ongoing randomized clinical trials comparing the 2 BP-DES are expected to shed more light on their relative safety and efficacy (NCT02084901, NCT02299011).

ST RISK OF BVS. This study showed the risk of ST at 1 year was significantly higher with BVS than other contemporary DES such as CoCr-EES, PtCr-EES, and H-SES. A recent meta-analysis also showed that the risk of definite or probable ST at 1 year was higher in patients who were treated with BVS than those

FIGURE 5 Ranks for Study Stents Regarding Definite or Probable Stent Thrombosis



Bar plots for ranking probabilities of competing stents. The possible rank of each treatment (from best to worst according to the outcome) is on the **horizontal axis**. The **size of each bar** corresponds to the probability of each treatment to be at a specific rank. Abbreviations as in **Figure 2**.

TABLE 2 Pairwise Comparisons of Definite Stent Thrombosis Between Study Stents

	BMS	E-ZES	PES	BVS	BP-BES	SES	R-ZES	Dual DES	O-SES	CoCr-EES	PtCr-EES	BP-EES
vs. BMS	-	0.79 (0.45-1.48)	0.79 (0.51-1.23)	0.59 (0.19-2.25)	**0.53 (0.29-0.95)**	**0.53 (0.35-0.78)**	**0.42 (0.19-0.91)**	0.35 (0.08-1.27)	**0.28 (0.10-0.79)**	**0.24 (0.14-0.39)**	**0.21 (0.06-0.68)**	0.20 (0.01-2.78)
vs. E-ZES	1.26 (0.68-2.20)	-	1.00 (0.53-1.73)	0.73 (0.22-3.06)	0.66 (0.30-1.34)	0.66 (0.37-1.09)	0.53 (0.21-1.22)	0.43 (0.09-1.63)	0.35 (0.11-1.05)	**0.29 (0.15-0.55)**	**0.26 (0.07-0.88)**	0.25 (0.02-3.60)
vs. PES	1.27 (0.81-1.95)	1.00 (0.58-1.88)	-	0.75 (0.24-2.72)	0.67 (0.35-1.22)	**0.66 (0.44-1.00)**	0.53 (0.23-1.14)	0.44 (0.10-1.62)	0.36 (0.13-1.00)	**0.30 (0.18-0.48)**	**0.27 (0.07-0.87)**	0.25 (0.02-3.56)
vs. BVS	1.70 (0.45-5.24)	1.36 (0.33-4.50)	1.34 (0.37-4.12)	-	0.89 (0.23-2.81)	0.89 (0.24-2.70)	0.71 (0.17-2.43)	0.58 (0.09-2.94)	0.48 (0.10-1.94)	0.40 (0.12-1.11)	0.34 (0.06-1.57)	0.33 (0.02-5.69)
vs. BP-BES	**1.90 (1.05-3.49)**	1.51 (0.75-3.32)	1.50 (0.82-2.84)	1.12 (0.37-4.14)	-	1.00 (0.58-1.74)	0.81 (0.38-1.66)	0.66 (0.15-2.39)	0.53 (0.21-1.41)	**0.45 (0.26-0.80)**	0.40 (0.11-1.25)	0.38 (0.02-5.31)
vs. SES	**1.90 (1.28-2.85)**	1.52 (0.92-2.71)	**1.51 (1.00-2.27)**	1.12 (0.36-4.29)	1.00 (0.57-1.73)	-	0.81 (0.37-1.66)	0.66 (0.15-2.38)	0.54 (0.20-1.48)	**0.45 (0.29-0.70)**	0.40 (0.11-1.23)	0.38 (0.02-5.30)
vs. R-ZES	**2.36 (1.10-5.30)**	1.89 (0.82-4.83)	1.88 (0.88-4.26)	1.40 (0.41-5.79)	1.24 (0.60-2.67)	1.24 (0.60-2.65)	-	0.81 (0.23-2.62)	0.66 (0.22-2.15)	0.56 (0.29-1.12)	0.49 (0.15-1.49)	0.47 (0.03-6.69)
vs. Dual DES	2.87 (0.79-12.7)	2.31 (0.62-10.8)	2.30 (0.62-9.99)	1.72 (0.34-11.2)	1.52 (0.42-6.49)	1.52 (0.42-6.47)	1.23 (0.38-4.41)	-	0.82 (0.18-4.50)	0.68 (0.20-2.80)	0.61 (0.12-3.17)	0.57 (0.03-10.8)
vs. O-SES	**3.55 (1.26-10.1)**	2.82 (0.95-8.84)	2.79 (1.00-7.98)	2.07 (0.52-10.1)	1.87 (0.71-4.82)	1.87 (0.68-5.08)	1.51 (0.47-4.58)	1.22 (0.22-5.67)	-	0.84 (0.32-2.22)	0.73 (0.16-3.09)	0.69 (0.04-11.4)
vs. CoCr-EES	**4.24 (2.60-7.09)**	**3.40 (1.81-6.66)**	**3.34 (2.08-5.49)**	2.49 (0.90-8.20)	**2.24 (1.25-3.91)**	**2.22 (1.43-3.47)**	1.79 (0.89-3.44)	1.46 (0.36-5.07)	1.19 (0.45-3.14)	-	0.88 (0.26-2.63)	0.83 (0.06-11.5)
vs. PtCr-EES	**4.76 (1.46-17.6)**	**3.81 (1.13-15.1)**	**3.76 (1.15-13.7)**	2.91 (0.64-16.4)	2.52 (0.80-8.96)	2.51 (0.82-8.85)	2.04 (0.67-6.62)	1.64 (0.32-8.40)	1.36 (0.32-6.38)	1.13 (0.38-3.84)	-	0.97 (0.09-9.89)
vs. BP-EES	5.07 (0.36-78.5)	4.04 (0.28-65.7)	4.00 (0.28-63.0)	3.06 (0.18-56.6)	2.65 (0.19-40.3)	2.65 (0.19-40.7)	2.13 (0.15-31.9)	1.75 (0.09-32.2)	1.44 (0.09-24.7)	1.20 (0.09-18.0)	1.03 (0.10-11.7)	-

Odds ratios and 95% credible intervals are presented. Comparisons that are statistically significant are highlighted in **bold**. Comparisons with significantly lower risk are highlighted in **red**, and those with higher risk are highlighted in **blue**.

Abbreviations as in Table 1.

treated with CoCr-EES (13). The bioresorbable scaffold analyzed in this study (Absorb, Abbott Vascular) is made of poly-L-lactic acid, which is also used as a polymer in BP-DES. Its strut thickness is 150 μm, and it elutes a 1:1 mixture of poly-D,L-lactic acid and everolimus (6,7). BVS has merits in the preservation of vascular geometry (30), positive remodeling of lumen (31), restoration of vasomotor function and vascular physiology (32), and stable plaque healing (33). Therefore, the hope exists that this device would minimize the risk of late thrombotic events and mitigate the need for long-term dual antiplatelet therapy. Of note, complete degradation of BVS is achieved in 1 to 4 years (34). Thus, the benefit of BVS may emerge after 1 year post-implantation. Considering that ST occurs in 1% of patients during the first year and then in 0.5% per year thereafter, the benefit, if present, would be paramount (35). Consequently, extended follow-up of ongoing clinical trials would provide more insight on this device (11,12). Knowledge regarding BVS is evolving, such as technical issues during BVS implantation, intravascular imaging guidance, and optimal patient selection. In addition, statistical significance in terms of the inferiority of BVS was lost after exclusion of studies with potential risks of bias. Results of other bioresorbable scaffolds under investigation are also expected (6,16).

STUDY LIMITATIONS. First, the primary endpoint was restricted to up to 1 year. As discussed, the benefit of certain devices may be apparent only after a longer follow-up period (36,37). Second, as a meta-analysis of multiple trials, this study inherently shares the limitations of each trial. The potential biases in each study can affect the analyses. Results of a network meta-analysis can be biased when heterogeneity is present in terms of populations or interventions among studies (38). However, consistency in the direct and indirect evidence of this study supports the reliability of our study findings. Third, we pooled trials with different designs, including enrollment criteria and follow-up and medication protocols. Fourth, some study devices had limited sample sizes and comparisons.

CONCLUSIONS

Contemporary DES, including second-generation biocompatible DP-DES, BP-DES, and polymer-free DES, showed excellent safety profiles in terms of definite or probable ST at 1 year. In contrast, BVS was associated with significantly increased risk of device thrombosis compared with CoCr-EES, PtCr-EES, and H-SES. Results from studies with extended follow-up are anticipated to fully appreciate the long-term safety of contemporary coronary devices.

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PERSPECTIVES

WHAT IS KNOWN? BVS have been introduced as an alternative to permanent metallic intracoronary implants. BVS provide transient mechanical support and drug delivery capability, after which complete resorption within the body occurs over years. Recent studies have shown comparable efficacy compared with metallic DES.

WHAT IS NEW? In this network meta-analysis, a total of 147 trials including 126,526 patients were pooled to compare the safety and efficacy of BVS, DES, and BMS. Contemporary DES showed excellent safety profiles in terms of definite or probable ST at 1 year. However, BVS was associated with a significantly increased risk of device thrombosis compared with CoCr-EES, PtCr-EES, and Orsiro hybrid polymer SES.

WHAT IS NEXT? The benefit of BVS may emerge after 1 year, as complete degradation of the BVS is achieved in 1 to 4 years post-implantation. Extended follow-up of ongoing clinical trials would shed more light on the safety of this device. In addition, bioresorbable scaffolds under investigation from other manufacturers are also expected.

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KEY WORDS bare-metal stent(s), bioresorbable vascular scaffolds, drug-eluting stent(s), percutaneous coronary intervention, stent thrombosis

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