Long-Term Safety of Drug-Eluting and Bare-Metal Stents

Evidence From a Comprehensive Network Meta-Analysis

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ABSTRACT

BACKGROUND Previous meta-analyses have investigated the relative safety and efficacy profiles of different types of drug-eluting stents (DES) and bare-metal stents (BMS); however, most prior trials in these meta-analyses reported follow-up to only 1 year, and as such, the relative long-term safety and efficacy of these devices are unknown. Many recent studies have now reported extended follow-up data.

OBJECTIVES This study sought to investigate the long-term safety and efficacy of durable polymer-based DES, bioabsorbable polymer-based biolimus-eluting stents (BES), and BMS by means of network meta-analysis.

METHODS Randomized controlled trials comparing DES to each other or to BMS were searched through MEDLINE, EMBASE, and Cochrane databases and proceedings of international meetings. Information on study design, inclusion and exclusion criteria, sample characteristics, and clinical outcomes was extracted.

RESULTS Fifty-one trials that included a total of 52,158 randomized patients with follow-up duration ≥3 years were analyzed. At a median follow-up of 3.8 years, cobalt-chromium everolimus-eluting stents (EES) were associated with lower rates of mortality, definite stent thrombosis (ST), and myocardial infarction than BMS, paclitaxel-eluting stents (PES), and sirolimus-eluting stents (SES) and less ST than BES. Phosphorylcholine-based zotarolimus-eluting stents had lower rates of definite ST than SES and lower rates of myocardial infarction than BMS and PES. The late rates of target-vessel revascularization were reduced with all DES compared with BMS, with cobalt-chromium EES, platinum chromium-EES, SES, and BES also having lower target-vessel revascularization rates than PES.

CONCLUSIONS After a median follow-up of 3.8 years, all DES demonstrated superior efficacy compared with BMS. Among DES, second-generation devices have substantially improved long-term safety and efficacy outcomes compared with first-generation devices. (J Am Coll Cardiol 2015;65:2496–507) © 2015 by the American College of Cardiology Foundation.

Although first-generation sirolimus-eluting stents (SES) (Cypher, Cordis Corp., Miami Lakes, Florida) and paclitaxel-eluting stents (PES) (Taxus, Boston Scientific, Natick, Massachusetts) significantly reduced the risk of restenosis and ischemia-driven target-vessel revascularization (TVR) compared with bare-metal stents (BMS) (1,2), an ongoing propensity for very late stent thrombosis (ST) and adverse events emerged with both types of stent (3). To mitigate these risks, newer devices were developed that used novel stent materials, platforms, and delivery systems, with more biocompatible polymers (both durable and bioresorbable) than their predecessors. Several randomized controlled trials (RCTs) and meta-analyses have suggested that these newer devices may have a better safety profile not only compared with first-generation drug-eluting stents (DES) but also when compared with BMS (4,5); however, most of these studies had a limited follow-up of 1 year, with very few reporting data beyond 2 years. The long-term relative safety and efficacy of second-generation DES have therefore not been investigated in depth.

An example of the importance of extended follow-up may be seen from the PROTECT trial (Patient-Related Outcomes With Endeavor Versus Cypher Stenting Trial), in which reduced rates of ST with phosphorylcholine-based zotarolimus-eluting stents (PC-ZES) (Medtronic, Santa Rosa, California) compared with SES emerged only at 4 years of follow-up (6). Similarly, any advantages of bioabsorbable polymer-based DES compared with permanent polymer-based DES might only be expected to be present at long-term follow-up.

Since the publication of the most recent meta-analysis comparing different types of DES with each other or with BMS (7), several RCTs have significantly extended their period of surveillance, reporting data at 3 to 6 years after stent implantation (8–20). For this reason, to examine the long-term relative safety and efficacy of different DES and BMS, we performed an updated network meta-analysis including only trials with a follow-up duration of at least 3 years.

METHODS

OBJECTIVES, DEFINITIONS, AND STUDY DESIGN. The primary endpoint of this network meta-analysis was the long-term rate of definite ST defined according to the Academic Research Consortium criteria (21). Only RCTs investigating currently U.S. Food and Drug Administration (FDA)-approved DES and BMS with a follow-up duration of ≥3 years were included in the meta-analysis. In addition, we also included studies with biolimus-eluting stents (BES) (BioMatrix, Biosensors, Newport Beach, California; and Nobori, Terumo Clinical Supply, Kakamigahara, Japan), because these devices have been investigated extensively in several large-scale RCTs (22–26) and are the most widely used bioabsorbable polymer-based DES outside the United States. Thus, the DES studied in the present report were SES, PES, cobalt-chromium everolimus-eluting stents (CoCr-EES) (Abbott Vascular, Santa Clara, California), platinum-chromium EES (PtCr-EES) (Boston Scientific), PC-ZES, Resolute ZES (Re-ZES) (Medtronic), and BES.

Secondary pre-specified endpoints included long-term rates of Academic Research Consortium definite/probable ST and very late (>1 year) definite and definite/probable ST, as well as death, cardiac death, myocardial infarction (MI), and TVR. This review was performed according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) statements.

DATA SOURCE AND STUDY SELECTION. Relevant RCTs to include in this meta-analysis were searched through MEDLINE, the Cochrane database, the EMBASE database, the Transcatheter Cardiovascular

ABBREVIATIONS AND ACRONYMS

BES = biolimus-eluting stent(s)

BMS = bare-metal stent(s)

CI = credible interval

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

DES = drug-eluting stent(s)

HR = hazard ratio

MI = myocardial infarction

PC-ZES = phosphorylcholine-based zotarolimus-eluting stent(s)

PES = paclitaxel-eluting stent(s)

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

RCT = randomized controlled trial

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

SES = sirolimus-eluting stent(s)

ST = stent thrombosis

TVR = target-vessel revascularization

FIGURE 1 Evidence Network Between Stents Included in Meta-Analysis
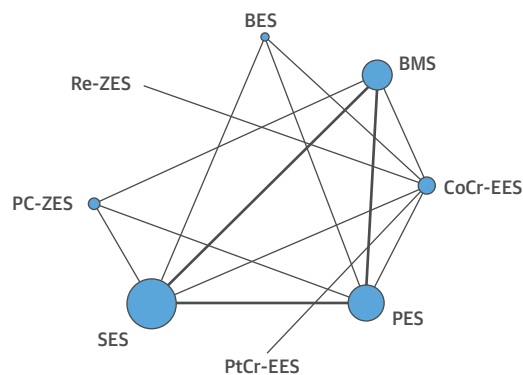
BES = biolimus-eluting stent(s); BMS = bare-metal stent(s); CoCr-EES = cobalt-chromium everolimus-eluting stent(s); PC-ZES = phosphorylcholine polymer–based zotarolimus-eluting stent(s); PES = paclitaxel-eluting stent(s); PtCr-EES = platinum-chromium everolimus-eluting stent(s); Re-ZES = Resolute zotarolimus-eluting stent(s); SES = sirolimus-eluting stent(s).

TABLE 1   Randomized Controlled Trials Included in Network Meta-Analysis

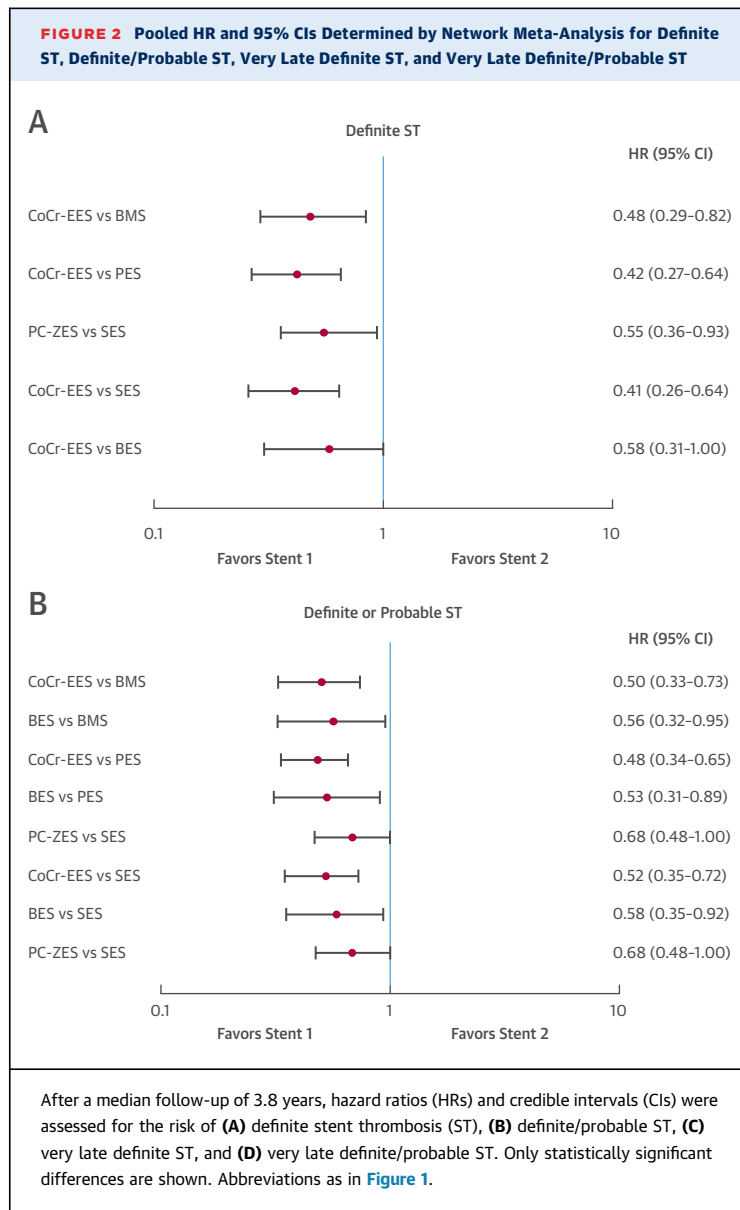| Study/First Author*	Primary Endpoint	Design	Randomization Ratio	Latest Follow-Up Available	Stent Comparators	Results of the Primary Endpoint
COMPARE	Death, MI, TVR at 1 yr	Single center, superiority	1:1	5 yrs	CoCr-EES/PES 1,800 (897/903)	CoCr-EES superior to PES
COMPARE II	Cardiac death, nonfatal MI, TVR at 1 yr	Multicenter, noninferiority	1:2	3 yrs	CoCr-EES/BP-BES 2,707 (912/1,795)	BES noninferior to CoCr-EES
DES DIABETES	In-segment restenosis at 6 months	Multicenter, superiority	1:1	4 yrs	SES/PES 400(200/200)	SES superior to PES
ENDEAVOR II	TVF at 9 months	Multicenter, superiority of PC-ZES vs. BMS	1:1	5 yrs	PC-ZES/BMS 1,193 (597/596)	PC-ZES superior to BMS
ENDEAVOR III	Late lumen loss at 8 months	Multicenter, noninferiority	1:3	5 yrs	SES/PC-ZES 436 (113/323)	PC-ZES inferior to SES
ENDEAVOR IV	TVF at 9 months	Multicenter, noninferiority	1:1	3 yrs	PES/PC-ZES 1,548 (775/773)	PES noninferior to PC-ZES
HORIZONS-AMI	1) TLR at 1 yr; 2) death, MI, stroke, or ST at 1 yr	Multicenter, superiority for TLR; noninferiority for death, MI, stroke, ST	3:1	3 yrs	BMS/PES 3,006 (2,257/749)	PES superior for TLR and noninferior for clinical endpoints
ISAR DESIRE	Late lumen loss at 8 months	Two-center, noninferiority	1:1	5 yrs	PES/SES 450 (225/225)	PES noninferior to SES
ISAR DIABETES	Late lumen loss at 6 months	Two-center, noninferiority	1:1	5 yrs	PES/SES 250 (125/125)	PES inferior to SES
ISAR SMART III	In-stent late luminal loss at 8 months	Two-center, noninferiority	1:1	5 yrs	PES/SES 360 (180/180)	PES inferior to SES
ISAR TEST IV	Cardiac death, MI, and TLR at 1 yr	Two-center, noninferiority	1:1	3 yrs	CoCr-EES/SES 1,304 (652/652)	CoCr-EES noninferior to SES
Kim et al.	Cardiac death, MI, TLR	Multicenter, superiority	1:1	3 yrs	PES/SES 169 (84/85)	PES nonsuperior to SES
LEADERS	Cardiac death, MI, TVR at 9 months	Multicenter, noninferiority	1:1	4 yrs	BP-BES/SES 1,707 (857/850)	BES noninferior to BP-SES
MISSION !	In-segment late luminal loss at 9 months	Single center, noninferiority	1:1	5 yrs	BMS/SES 310 (152/158)	SES superior to BMS
MULTISTRATEGY	Death, MI, clinically driven TVR at 8 months	Multicenter, superiority	1:1	3 yrs	BMS/SES 744 (372/372)	SES superior to BMS
NAPLES	Death, nonfatal MI, clinically driven TVR at 3 yrs	Single center, superiority	1:1:1	3 yrs	PES/SES/PC-ZES 226 (75/76/75)	PES and SES superior to PC-ZES
NOBORI I phase I	In-stent late loss at 9 months	Multicenter, noninferiority	1:2	5 yrs	BP-BES/PES 120 (35/85)	BP-BES noninferior to PES
NOBORI JAPAN	TVF at 9 months	Multicenter, noninferiority	3:2	3 yrs	BP-BES/SES 326 (194/132)	BP-BES noninferior to SES
Pasceri et al.	Death, MI, recurrent ischemia at 1 yr	Single center, safety outcome	1:1	6 yrs	BMS/SES 65 (33/32)	No significant differences between stents
PASEO	TLR at 12 months	Single center, superiority	1:1:1	4 yrs	BMS/PES/SES 270 (90/90/90)	PES and SES superior to BMS
PASSION	Cardiac death, MI, TLR at 2 yrs	Two center, superiority	1:1	5 yrs	BMS/PES 619 (310/309)	Superiority not demonstrated
PLATINUM	TLF at 1 yr	Multicenter, noninferiority	1:1	3 yrs	PtCr-EES/CoCr-EES 1,530 (768/762)	PtCr-EES noninferior to CoCr-EES
PRISON II	Angiographic in-segment restenosis at 6 months	Two center, superiority	1:1	3 yrs	BMS/SES 200 (100/100)	SES superior to BMS
PROSIT	Death, MI, TVR, ST at 1 yr	Multicenter, superiority	1:1	3 yrs	PES/SES 308 (154/154)	Superiority not demonstrated
PROTECT	Definite or probable ST at 3 yrs	Multicenter, superiority	1:1	4 yrs	C-SES vs. E-ZES 8,791 (4,352/4,357)	E-ZES nonsuperior to C-SES
RACES MI	Cardiac death, reinfarction, definite or probable ST, and TVR at 3 yrs	Single center, superiority	1:1	3 yrs	EES/SES 500 (250/250)	EES has similar efficacy as SES but is associated with a significant reduction in ST
RAVEL	In-stent late lumen loss at 6 months	Multicenter, superiority	1:1	4 yrs	BMS/SES 238 (120/118)	SES superior to BMS
RESOLUTE	TLF at 12 months	Multicenter, noninferiority	1:1	4 yrs	CoCr-EES/Re-ZES 2,292 (1,152/1,140)	Re-ZES noninferior to CoCr-EES
SCANDSTENT	Minimal lumen diameter at 6 months	Multicenter, superiority	1:1	3 yrs	SES/BMS 322 (163/159)	SES superior to BMS
SCORPIUS	Late luminal loss at 12 months	Multicenter, superiority	1:1	5 yrs	SES/BMS 200 (98/102)	SES superior to BMS

TABLE 1 Continued

Study/First Author*	Primary Endpoint	Design	Randomization Ratio	Latest Follow-Up Available	Stent Comparators	Results of the Primary Endpoint
SESAMI	Binary restenosis at 1 yr	Single center, superiority	1:1	5 yrs	BMS/SES 320 (160/160)	SES superior to BMS
SIRIUS	TVF at 9 months	Multicenter, superiority	1:1	4 yrs	BMS/SES 1,058 (533/525)	SES superior to BMS
E-SIRIUS	In-stent minimum lumen diameter at 8 months	Multicenter, superiority	1:1	4 yrs	BMS/SES 352 (175/177)	SES superior to BMS
C-SIRIUS	In-stent minimum lumen diameter at 8 months	Multicenter, superiority	1:1	4 yrs	BMS/SES 100 (50/50)	SES superior to BMS
SIRTAX LATE	Cardiac death, MI, TLR at 9 months	Single center, superiority	1:1	5 yrs	PES/SES 1,012 (509/503)	Superiority not demonstrated
SORT OUT III	Cardiac death, MI, TVR at 9 months	Multicenter, superiority	1:1	5 yrs	SES/PC-ZES 2,332 (1,170/1,162)	SES superior to PC-ZES
SORT OUT IV	Cardiac death, MI, definite ST, and TVR at 9 months	Multicenter, noninferiority	1:1	5 yrs	CoCr-EES/SES 2,774 (1,390/1,384)	CoCr-EES noninferior to SES
SORT OUT V	Cardiac death, MI, definite ST and clinically driven TVR at 9 months	Multicenter, noninferiority	1:1	3 yrs	BP-BES/SES 2,468 (1,229/1,239)	Noninferiority not demonstrated
SOS	Angiographic restenosis at 12 months	Multicenter, superiority	1:1	3 yrs	BMS/PES 80 (41/39)	PES superior to BMS
SPIRIT I	In-stent late loss at 180 days	Multicenter, superiority	1:1	5 yrs	CoCr-EES/BMS 60 (28/32)	CoCr-EES superior to BMS
SPIRIT II	In-stent late loss at 6 months	Multicenter, noninferiority	3:1	5 yrs	CoCr-EES/PES 300 (223/77)	CoCr-EES noninferior to PES
SPIRIT III	In-segment late loss at 9 months	Multicenter, noninferiority or superiority	2:1	5 yrs	CoCr-EES/PES 1,002 (669/333)	CoCr-EES superior to PES
SPIRIT IV	TLF at 1 yr	Multicenter, noninferiority or superiority	2:1	3 yrs	CoCr-EES/PES 3,687 (2,458/1,229)	CoCr-EES superior to PES
STRATEGY	Death, MI, stroke, binary restenosis at 8 months	Two center, superiority	1:1	5 yrs	BMS/SES 175 (87/88)	SES superior to BMS
TAXI	Cardiac death, MI, TLR at 6 months	Single center, superiority	1:1	3 yrs	PES/SES 202 (100/102)	Superiority not demonstrated
TAXUS I	Death, MI, TVR, ST at 12 months	Multicenter, safety study	1:1	4 yrs	BMS/PES 61 (31/30)	PES as safe as BMS
TAXUS II	Neointimal proliferation by IVUS at 6 months	Multicenter, superiority	1:1	4 yrs	BMS/PES 536 (266/270)	PES superior to BMS
TAXUS IV	Ischemia-driven TVR at 9 months	Multicenter, superiority	1:1	4 yrs	BMS/PES 1,314 (662/652)	PES superior to BMS
TAXUS V	Ischemia-driven TVR at 9 months	Multicenter, superiority	1:1	4 yrs	BMS/PES 1,156 (577/579)	PES superior to BMS
TAXUS VI	TVR 9 months	Multicenter, superiority	1:1	5 yrs	BMS/PES 446 (219/227)	PES superior to BMS
TYPHOON	TVF at 1 yr	Multicenter, superiority	1:1	4 yrs	BMS/SES 712 (355/357)	SES superior to BMS

*References for each individual trial are reported in Online Table 1.

BES = biolimus-eluting stent(s); BMS = bare-metal stent(s); BP-BES = biodegradable polymer biolimus-eluting stent(s); CoCr-EES = cobalt-chromium everolimus-eluting stent(s); COMPARE = A Randomized Controlled Trial of Everolimus-Eluting Stents and Paclitaxel-Eluting Stents for Coronary Revascularization in Daily Practice; C-SES = Cypher sirolimus-eluting stent(s); C-SIRIUS = Study of the Bx VELOCITY Stent in the Treatment of De Novo Coronary Artery Lesions; DES = drug-eluting stent(s); E-SIRIUS = Study of the Bx VELOCITY Stent in Patients With De Novo Coronary Artery Lesions; E-ZES = Endeavor zotarolimus-eluting stent(s); HORIZONS-AMI = Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction; ISAR DESIRE = Intracoronary Stenting and Angiographic Results: Optimizing Treatment of Drug Eluting Stent In-Stent Restenosis; ISAR DIABETES = The Intracoronary Stenting and Angiographic Results: Do Diabetic Patients Derive Similar Benefit from Paclitaxel-Eluting and Sirolimus-Eluting Stents; ISAR SMART III = Intracoronary Drug-Eluting Stenting to Abrogate Restenosis in Small Arteries; ISAR TEST IV = Intracoronary Stenting and Angiographic Results: Test Efficacy of 3 Limus-Eluting Stents; IVUS = intravascular ultrasound; LEADERS = Limus Eluted From a Durable Versus Erodable Stent Coating; MI = myocardial infarction; MULTISTRATEGY = Multicentre Evaluation of Single High-Dose Bolus Tirofiban vs Abciximab With Sirolimus-Eluting Stent or Bare Metal Stent in Acute Myocardial Infarction Study; PASEO = Paclitaxel or Sirolimus-Eluting Stent Versus Bare Metal Stent in Primary Angioplasty; PASSION = Paclitaxel-Eluting Stent Versus Conventional Stent in Myocardial Infarction With ST-Segment Elevation; PC-ZES = phosphorylcholine-based zotarolimus-eluting stent(s); PES = paclitaxel-eluting stent(s); PLATINUM = Prospective, Randomized, Multicenter Trial to Assess an Everolimus-Eluting Coronary Stent System [PROMUS Element] for the Treatment of up to Two De Novo Coronary Artery Lesions; PRISON II = Primary Stenting of Totally Occluded Native Coronary Arteries II; PROSIT = Prospective Randomized cOmparison of SIrolimus- versus pacliTaxel-eluting stents for the treatment of acute STEMI; PROTECT = Patient-Related Outcomes With Endeavor Versus Cypher Stenting Trial; PtCr-EES = platinum chromium everolimus-eluting stent(s); RACES MI = Randomized Comparison of Everolimus Eluting Stents and Sirolimus Eluting Stent in Patients With ST Elevation Myocardial Infarction; RAVEL = Randomized Study With the Sirolimus-Coated Bx VELOCITY Balloon-Expandable Stent in the Treatment of Patients With de Novo Native Coronary Artery Lesions; RESOLUTE = Resolute All-Comers Trial; Re-ZES = Resolute zotarolimus-eluting stent(s); SCANDSTENT = Randomized Multicenter Comparison of Sirolimus Versus Bare Metal Stent Implantation in Complex Coronary Lesions; SCORPIUS = German Multicenter, Randomized, Controlled, Open-Label Study of the Cypher Sirolimus-Eluting Stent in the Treatment of Diabetic Patients With De Novo Native Coronary Artery Lesions; SES = sirolimus-eluting stent(s); SESAMI = Sirolimus-Eluting Stent in Acute Myocardial Infarction; SIRIUS = Multicenter, Randomized, Double-Blind Study of the Sirolimus-Eluting Balloon-Expandable Stent in the Treatment of Patients With De Novo Native Coronary-Artery Lesions; SIRTAX LATE = Sirolimus-Eluting Versus Paclitaxel-Eluting Stents for Coronary Revascularization extended follow-up; SORT OUT = Scandinavian Organization for Randomized Trials With Clinical Outcome; SOS = Stenting of Saphenous Vein Grafts; SPC-ZES = phosphorylcholine polymer based zotarolimus-eluting stent(s); SPIRIT = Clinical Evaluation of the XIENCE V Everolimus Eluting Coronary Stent System in the Treatment of Patients With de Novo Native Coronary Artery Lesions; ST = stent thrombosis; STRATEGY = Single High-Dose Bolus Tirofiban and Sirolimus Eluting Stent Versus Abciximab and Bare Metal Stent in Acute Myocardial Infarction; TAXI = Prospective Randomized Comparison Between Paclitaxel and Sirolimus Stents in the Real World of Interventional Cardiology; TAXUS = Randomized, Double-Blind, Controlled Study of the Safety and Performance of the NIRx Paclitaxel-Coated Conformer Coronary Stent; TLF = target-lesion failure, defined as cardiac death, target-vessel MI, or TLR; TLR = target-lesion revascularization; TVF = target-vessel failure, defined as cardiac death, target-vessel MI, or TVR; TVR = target-vessel revascularization; TYPHOON = Trial to Assess the Use of the Cypher Stent in Acute Myocardial Infarction Treated With Balloon Angioplasty.

FIGURE 2 Pooled HR and 95% CIs Determined by Network Meta-Analysis for Definite ST, Definite/Probable ST, Very Late Definite ST, and Very Late Definite/Probable ST

After a median follow-up of 3.8 years, hazard ratios (HRs) and credible intervals (CIs) were assessed for the risk of **(A)** definite stent thrombosis (ST), **(B)** definite/probable ST, **(C)** very late definite ST, and **(D)** very late definite/probable ST. Only statistically significant differences are shown. Abbreviations as in **Figure 1**.

Continued on the next page

Therapeutics (TCT) website, the Clinical Trials website, the Clinical Trial Results website, the American College of Cardiology website, and abstracts and presentations from major cardiovascular meetings, such as TCT, EuroPCR, American College of Cardiology, American Heart Association, and TCTAP, using the keywords *randomized clinical trial, drug-eluting stent, biolimus-eluting stent, everolimus-eluting stent, paclitaxel-eluting stent, sirolimus-eluting stent, zotarolimus-eluting stent,* and *bare-metal stent.* Two investigators (T.P. and D.D.R.) independently reviewed the titles, abstracts, and studies to determine whether they met the inclusion criteria. Conflicts between reviewers were

resolved by consensus. No language, publication date, or publication status restrictions were imposed. The most updated data for a given study were selected. Internal validity of RCTs was assessed by evaluating concealment of allocation, blind adjudication of ST, and inclusion of all randomized patients in the analysis according to the intention-to-treat principle.

STATISTICAL ANALYSIS. Network meta-analysis was performed within a bayesian framework computing hazard ratio (HR) and 95% credible intervals (CIs) with a random-effect hierarchical model by means of Markov chain Monte Carlo methods with Gibbs sampling from 1,000 iterations obtained after a 5,000-iteration training phase. Convergence was appraised graphically according to Gelman and Rubin. Model fit was assessed by use of the deviance information criterion. Inconsistency was assessed by contrasting direct evidence with indirect evidence from the entire network on each node (node splitting). The measure of conflict p was implemented using Markov chain Monte Carlo by counting the proportion of times the direct treatment effect exceeded the indirect treatment effect. Analysis of heterogeneity for the given network was performed with per-comparison I^2 statistics. Small study effects were explored by inspecting comparison-adjusted funnel plots. Bayesian Markov chain Monte Carlo simulations were performed by means of JAGS software in R using GeMTC (R package version 0.6) and rjags (R package version 3-13). Funnel plots were obtained in RevMan 5 (The Cochrane Nordic Center, Copenhagen, Denmark).

RESULTS

The flow diagram of the study analysis is shown in Online Figure 1. Of 2,815 potentially relevant articles initially screened, 51 trials met the inclusion criteria and were included in the final meta-analysis, with a total of 52,158 randomized patients. The evidence network is shown in **Figure 1**. The major characteristics of the included trials appear in **Table 1**. Median follow-up (determined as described previously) was 3.8 years (range 3 to 6 years) (27). The major inclusion and exclusion criteria and internal validity assessment for each trial are reported in Online Table 1. The clinical characteristics of patients enrolled in the RCTs included in the meta-analysis are reported in Online Table 2. Updated RCTs with extended follow-up compared with prior reports are shown in Online Table 3.
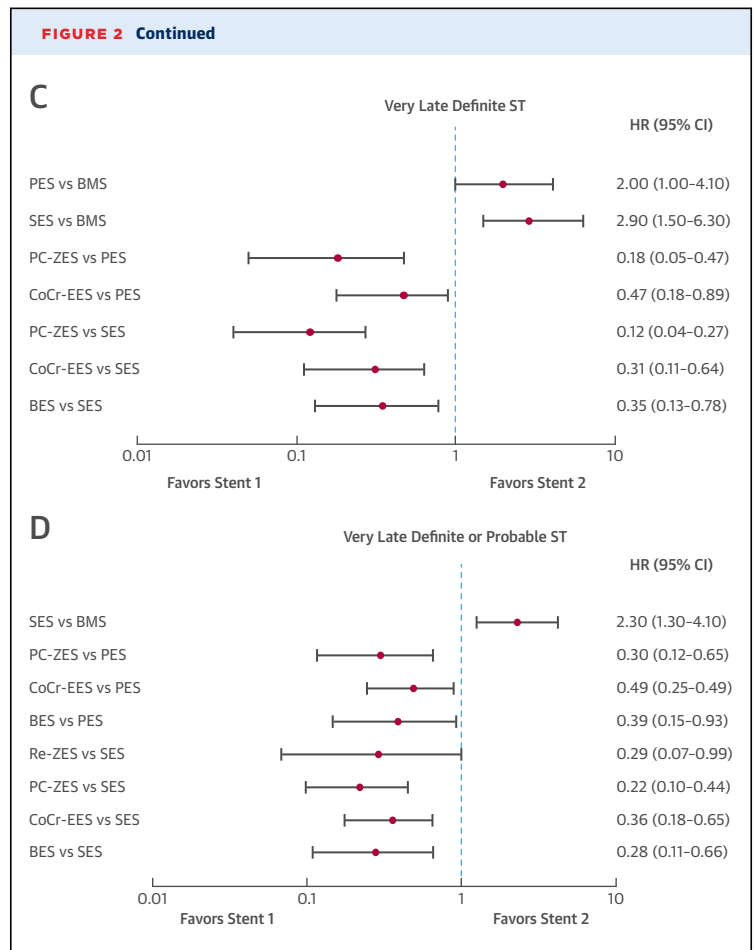
LONG-TERM ST. As shown in **Figure 2** and **Table 2**, at a median follow-up duration of 3.8 years, CoCr-EES

were associated with lower rates of definite ST than BMS (HR: 0.48; 95% CI: 0.29 to 0.82), PES (HR: 0.42; 95% CI: 0.27 to 0.64), and SES (HR: 0.41; 95% CI: 0.26 to 0.64). A borderline significant reduction in definite ST was apparent with CoCr-EES compared with BES (HR: 0.58; 95% CI: 0.31 to 1.00). PC-ZES were associated with significantly lower rates of definite ST than SES (HR: 0.55; 95% CI: 0.36 to 0.93). Similar results were apparent when the broader definition of definite/probable ST was considered. In addition, BES were associated with lower rates of definite/probable ST than BMS (HR: 0.56; 95% CI: 0.32 to 0.95), PES (HR: 0.53; 95% CI: 0.31 to 0.89), and SES (HR: 0.58; 95% CI: 0.35 to 0.92). BMS, PC-ZES, and CoCr-EES were associated with lower rates of very late definite ST than PES and SES. Similar results were apparent for very late definite/probable ST. The number of definite and definite/probable STs associated with each stent type in pooled pairwise comparisons is reported in Online Table 4. Visual inspection of funnel plots did not suggest any small study effects or publication bias (Online Figure 2).

OTHER CLINICAL OUTCOMES. At a median follow-up of 3.8 years, CoCr-EES were associated with borderline lower rates of death than SES, PES, or BMS and lower rates of cardiac death than BMS. CoCr-EES also were associated with lower rates of MI than BMS, SES, or PES (Figure 3, Table 3). Re-ZES, PC-ZES, and SES were associated with lower rates of MI than PES. PC-ZES also were associated with borderline significant reductions in cardiac death and MI compared with BMS. All DES were associated with lower rates of TVR than BMS. In addition, CoCr-EES, PtCr-EES, SES, and BES were associated with lower rates of MI than PES, and CoCr-EES were associated with a borderline reduction in TVR compared with PC-ZES. The number of adverse events associated with each stent type in pooled pairwise comparisons is reported in Online Table 5.

DISCUSSION

With a median follow-up of nearly 4 years, the present study is the largest, most comprehensive report to date comparing the long-term safety and efficacy between different types of DES and between DES and BMS. The principal finding is that second-generation DES have eliminated the late safety issues that became apparent with first-generation DES, and even demonstrate a substantially improved late safety and efficacy profile compared with BMS. Specifically, 1) CoCr-EES were associated with lower

FIGURE 2 Continued

C Very Late Definite ST

	HR (95% CI)
PES vs BMS	2.00 (1.00–4.10)
SES vs BMS	2.90 (1.50–6.30)
PC-ZES vs PES	0.18 (0.05–0.47)
CoCr-EES vs PES	0.47 (0.18–0.89)
PC-ZES vs SES	0.12 (0.04–0.27)
CoCr-EES vs SES	0.31 (0.11–0.64)
BES vs SES	0.35 (0.13–0.78)

Favors Stent 1   Favors Stent 2

D Very Late Definite or Probable ST

	HR (95% CI)
SES vs BMS	2.30 (1.30–4.10)
PC-ZES vs PES	0.30 (0.12–0.65)
CoCr-EES vs PES	0.49 (0.25–0.49)
BES vs PES	0.39 (0.15–0.93)
Re-ZES vs SES	0.29 (0.07–0.99)
PC-ZES vs SES	0.22 (0.10–0.44)
CoCr-EES vs SES	0.36 (0.18–0.65)
BES vs SES	0.28 (0.11–0.66)

Favors Stent 1   Favors Stent 2

rates of long-term definite ST than BMS, PES, SES, and BES, whereas PC-ZES were associated with lower rates of definite ST than SES; 2) CoCr-EES were associated with lower rates of long-term death than BMS, PES, and SES and with lower rates of MI than BMS, SES, and PES, whereas PC-ZES, SES, and Re-ZES were associated with significantly lower rates of MI than PES; and 3) all DES were associated with significantly lower rates of TVR than BMS; in addition, CoCr-EES, SES, PtCr-EES, and BES were associated with lower rates of TVR than PES, and CoCr-EES had lower rates of TVR than PC-ZES (Central Illustration).

RCTs, observational studies, and meta-analyses have suggested that second-generation DES have a better safety and efficacy profile than first-generation DES (12,28,29). In addition, recent network meta-analyses have suggested that the second-generation permanent polymer-based CoCr-EES may be associated with lower rates of ST not only compared with first-generation DES but also compared with bio-absorbable polymer-based BES and BMS (4,7,30); however, follow-up was limited to 1 year in most of

TABLE 2 Estimates of Risk of ST According to Various Definitions Between Different DES and BMS

	Definite ST	Definite/Probable ST	Very Late Definite ST	Very Late Definite/ Probable ST	No. of Trials
PES vs. BMS	1.20 (0.80-1.70)	1.10 (0.79-1.40)	**2.00 (1.00-4.10)**	1.70 (0.95-3.00)	6
SES vs. BMS	1.20 (0.81-1.70)	0.97 (0.71-1.30)	**2.90 (1.50-6.30)**	**2.30 (1.30-4.10)**	11
Re-ZES vs. BMS	1.10 (0.37-3.70)	0.81 (0.34-1.70)	0.68 (0.09-4.60)	0.68 (0.16-2.40)	0
PC-ZES vs. BMS	0.65 (0.39-1.20)	0.66 (0.44-1.10)	**0.34 (0.10-1.00)**	0.49 (0.20-1.20)	1
PtCr-EES vs. BMS	0.64 (0.14-2.90)	0.58 (0.11-2.70)	2.60 (0.12-91.00)	1.90 (0.13-39.00)	0
CoCr-EES vs. BMS	**0.48 (0.29-0.82)**	**0.50 (0.33-0.73)**	0.92 (0.30-2.10)	0.82 (0.37-1.60)	1
BES vs. BMS	0.83 (0.45-1.60)	**0.56 (0.32-0.95)**	1.00 (0.31-2.80)	0.65 (0.23-1.60)	0
SES vs. PES	1.00 (0.68-1.50)	0.92 (0.70-1.20)	1.50 (0.78-3.00)	1.40 (0.76-2.30)	10
Re-ZES vs. PES	0.99 (0.32-3.20)	0.75 (0.33-1.50)	0.35 (0.05-2.10)	0.41 (0.10-1.30)	0
PC-ZES vs. PES	0.56 (0.34-1.01)	0.62 (0.42-1.02)	**0.18 (0.05-0.47)**	**0.30 (0.12-0.65)**	2
PtCr-EES vs. PES	0.55 (0.12-2.40)	0.55 (0.10-2.50)	1.40 (0.07-47.00)	1.20 (0.08-22.00)	0
CoCr-EES vs. PES	**0.42 (0.27-0.64)**	**0.48 (0.34-0.65)**	**0.47 (0.18-0.89)**	**0.49 (0.25-0.89)**	4
BES vs. PES	0.72 (0.39-1.40)	**0.53 (0.31-0.89)**	0.54 (0.18-1.30)	**0.39 (0.15-0.93)**	1
Re-ZES vs. SES	0.97 (0.32-3.20)	0.82 (0.36-1.60)	0.23 (0.03-1.40)	**0.29 (0.07-0.99)**	0
PC-ZES vs. SES	**0.55 (0.36-0.93)**	**0.68 (0.48-1.00)**	**0.12 (0.04-0.27)**	**0.22 (0.10-0.44)**	4
PtCr-EES vs. SES	0.55 (0.12-2.40)	0.59 (0.11-2.60)	0.88 (0.04-32.00)	0.85 (0.06-16.00)	0
CoCr-EES vs. SES	**0.41 (0.26-0.64)**	**0.52 (0.35-0.72)**	**0.31 (0.11-0.64)**	**0.36 (0.18-0.65)**	3
BES vs. SES	0.72 (0.42-1.20)	**0.58 (0.35-0.92)**	**0.35 (0.13-0.78)**	**0.28 (0.11-0.66)**	3
Re-ZES vs. PC-ZES	1.80 (0.52-6.00)	1.20 (0.48-2.80)	2.00 (0.25-16.00)	1.30 (0.29-5.20)	0
PtCr-EES vs. PC-ZES	0.97 (0.19-4.20)	0.84 (0.17-4.00)	7.70 (0.34-3.3e)	3.90 (0.25-79.00)	0
CoCr-EES vs. PC-ZES	0.75 (0.39-1.30)	0.75 (0.44-1.20)	2.60 (0.77-8.40)	1.70 (0.64-3.90)	0
BES vs. PC-ZES	1.30 (0.61-2.50)	0.85 (0.44-1.50)	3.00 (0.82-11.00)	1.30 (0.43-3.80)	0
PtCr-EES vs. Re-ZES	0.55 (0.10-3.10)	0.69 (0.17-3.60)	3.90 (0.13-2.1e)	3.00 (0.19-67.00)	0
CoCr-EES vs. Re-ZES	0.42 (0.15-1.20)	0.65 (0.33-1.30)	1.30 (0.22-10.00)	1.30 (0.40-4.00)	1
BES vs. RE-ZES	0.73 (0.22-2.50)	0.71 (0.31-1.70)	1.50 (0.21-14.00)	0.98 (0.24-4.40)	0
CoCr-EES vs. PtCr-EES	0.76 (0.19-3.30)	0.88 (0.20-4.30)	0.33 (0.01-5.70)	0.42 (0.02-5.10)	1
BES vs. PtCr-EES	1.30 (0.30-6.20)	0.99 (0.19-4.80)	0.38 (0.01-8.20)	0.31 (0.02-5.30)	0
CoCr-EES vs. BES	**0.58 (0.31-1.00)**	0.89 (0.55-1.50)	0.86 (0.31-2.30)	1.30 (0.51-3.30)	1

Values are hazard ratio (95% credible interval). Statistically significant comparisons are highlighted in **bold**.
Abbreviations as in **Table 1**.

these reports, with very few studies reporting data beyond 2 years. Late events accruing after the first year have been reported with second-generation DES, which calls into question the durability of the benefits of even these new devices (8,11). With the exception of the PROTECT study, which compared the 4-year outcomes of SES and PC-ZES (6,7), the long-term safety and efficacy of second-generation DES have not been investigated in adequately powered studies, and therefore, whether they maintain their absolute benefit compared with first-generation DES and BMS remains unclear.

To address these issues, we undertook the present large-scale, comprehensive network meta-analysis, which included 51 RCTs with more than 50,000 randomized patients with ≥3 year follow-up. The present analysis has substantially increased the period of surveillance after stent implantation from a median of 1.7 years in previous reports (7,31) to 3.8 years in the current study. The main finding of the present study is that the previously noted safety and efficacy

benefits of second-generation DES compared with both first-generation DES and BMS are maintained with longer-term follow-up. In particular, after a median follow-up of almost 4 years, CoCr-EES were associated with lower rates of definite ST and MI than BMS, SES, and PES. CoCr-EES were also associated with lower rates of mortality than BMS, PES, and SES and lower rates of TVR than BMS, PES, and PC-ZES.

Among the other second-generation DES, PC-ZES were associated with lower rates of definite ST than SES, lower rates of MI than BMS and PES, and clear efficacy (TVR) compared with BMS. Although previous studies demonstrated higher rates of late lumen loss with PC-ZES than with other DES within the first year after implantation (32,33), PC-ZES were safe and effective over long-term follow-up in the present analysis, although with higher TVR rates than CoCr-EES. Of note, the long-term safety and efficacy profile of the more potent Re-ZES was not significantly different from that of PC-ZES in the

TABLE 3 Estimates of Risk of Death, Cardiac Death, Myocardial Infarction, and Target-Vessel Revascularization With Different Types of Drug-Eluting Stents and BMS

	Death	Cardiac Death	Myocardial Infarction	Target-Vessel Revascularization
PES vs. BMS	1.00 (0.82–1.20)	0.86 (0.71–1.04)	1.00 (0.87–1.20)	**0.58 (0.50–0.67)**
SES vs. BMS	0.95 (0.79–1.10)	0.86 (0.70–1.05)	0.84 (0.70–1.01)	**0.44 (0.38–0.51)**
Re-ZES vs. BMS	0.79 (0.52–1.20)	0.83 (0.51–1.60)	0.65 (0.42–1.02)	**0.45 (0.29–0.68)**
PC-ZES vs. BMS	0.88 (0.70–1.10)	**0.73 (0.55–1.00)**	**0.77 (0.60–0.96)**	**0.50 (0.41–0.62)**
PtCr-EES vs. BMS	0.73 (0.40–1.40)	0.45 (0.19–1.10)	0.62 (0.29–1.20)	**0.34 (0.19–0.57)**
CoCr-EES vs. BMS	**0.81 (0.64–1.00)**	**0.71 (0.54–0.91)**	**0.66 (0.52–0.85)**	**0.40 (0.32–0.49)**
BES vs. BMS	0.95 (0.71–1.30)	0.76 (0.55–1.04)	0.81 (0.61–1.04)	**0.40 (0.30–0.52)**
SES vs. PES	0.95 (0.81–1.10)	1.00 (0.83–1.20)	**0.82 (0.68–0.99)**	**0.76 (0.66–0.88)**
Re-ZES vs. PES	0.79 (0.54–1.20)	0.97 (0.60–1.80)	**0.63 (0.41–0.98)**	0.78 (0.51–1.20)
PC-ZES vs. PES	0.88 (0.71–1.10)	0.85 (0.64–1.10)	**0.74 (0.58–0.93)**	0.86 (0.71–1.10)
PtCr-EES vs. PES	0.74 (0.41–1.40)	0.53 (0.22–1.30)	0.59 (0.28–1.20)	**0.58 (0.34–0.98)**
CoCr-EES vs. PES	**0.81 (0.68–1.00)**	0.83 (0.66–1.10)	**0.64 (0.52–0.78)**	**0.69 (0.57–0.82)**
BES vs. PES	0.95 (0.74–1.30)	0.89 (0.64–1.20)	0.78 (0.59–1.02)	**0.69 (0.53–0.90)**
Re-ZES vs. SES	0.84 (0.56–1.20)	0.96 (0.62–1.70)	0.77 (0.51–1.20)	1.00 (0.67–1.50)
PC-ZES vs. SES	0.93 (0.76–1.10)	0.85 (0.68–1.04)	0.91 (0.75–1.10)	1.10 (0.95–1.40)
PtCr-EES vs. SES	0.77 (0.42–1.40)	0.53 (0.21–1.10)	0.71 (0.34–1.40)	0.76 (0.44–1.30)
CoCr-EES vs. SES	**0.86 (0.70–1.00)**	0.84 (0.68–1.01)	**0.78 (0.64–0.95)**	0.90 (0.75–1.10)
BES vs. SES	1.00 (0.80–1.30)	0.89 (0.66–1.10)	0.95 (0.75–1.20)	0.90 (0.72–1.10)
Re-ZES vs. PC-ZES	0.90 (0.58–1.40)	1.10 (0.71–1.90)	0.86 (0.56–1.30)	0.90 (0.57–1.40)
PtCr-EES vs. PC-ZES	0.83 (0.45–1.60)	0.62 (0.24–1.40)	0.78 (0.37–1.60)	0.67 (0.38–1.20)
CoCr-EES vs. PC-ZES	0.92 (0.71–1.20)	0.99 (0.74–1.30)	0.86 (0.67–1.10)	**0.80 (0.62–1.00)**
BES vs. PC-ZES	1.10 (0.82–1.50)	1.10 (0.73–1.50)	1.00 (0.79–1.40)	0.80 (0.59–1.10)
PtCr-EES vs. Re-ZES	0.92 (0.47–1.90)	0.54 (0.19–1.20)	0.93 (0.41–2.10)	0.75 (0.40–1.40)
CoCr-EES vs. Re-ZES	1.00 (0.70–1.40)	0.86 (0.56–1.30)	1.00 (0.68–1.50)	0.89 (0.61–1.30)
BES vs. RE-ZES	1.20 (0.77–1.90)	0.92 (0.50–1.50)	1.20 (0.78–2.00)	0.89 (0.57–1.40)
CoCr-EES vs. PtCr-EES	1.10 (0.62–1.90)	1.60 (0.77–3.90)	1.10 (0.56–2.20)	1.20 (0.73–1.90)
BES vs. PtCr-EES	1.30 (0.68–2.40)	1.70 (0.73–4.40)	1.30 (0.66–2.70)	1.20 (0.68–1.10)
CoCr-EES vs. BES	0.85 (0.65–1.10)	0.94 (0.70–1.30)	0.82 (0.62–1.10)	1.00 (0.77–1.30)

Values are hazard ratio (95% credible interval). Statistically significant comparisons are highlighted in **bold**.

Abbreviations as in Table 1.

CENTRAL ILLUSTRATION Pooled HR and 95% CI Determined by Network Meta-Analysis After Median Follow-Up of 3.8 Years for Risk of Definite ST and All-Cause Death
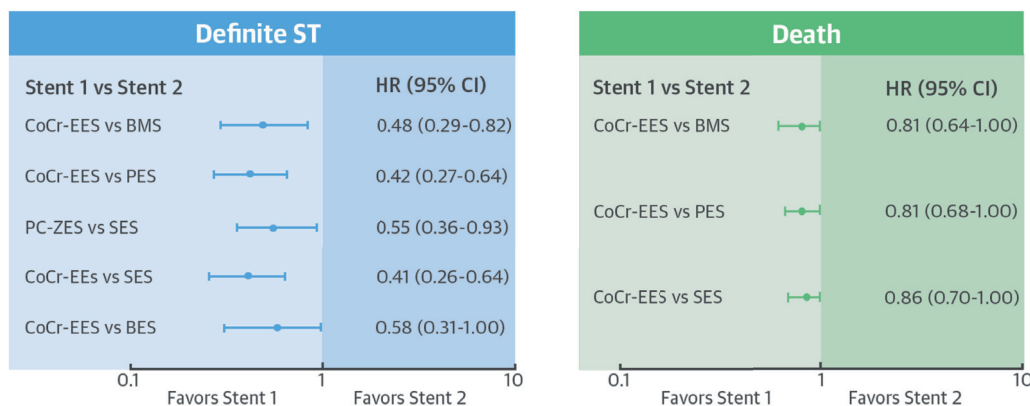

Palmerini, T. et al. J Am Coll Cardiol. 2015; 65(23):2496–507.

Only statistically significant differences are shown. BES = biolimus-eluting stent(s); BMS = bare-metal stent(s); CI = credible interval; CoCr-EES = cobalt-chromium everolimus-eluting stent(s); HR = hazard ratio; PC-ZES = phosphorylcholine polymer-based zotarolimus-eluting stent(s); PES = paclitaxel-eluting stent(s); SES = sirolimus-eluting stent(s).

FIGURE 3 Pooled HR and 95% CIs Determined by Network Meta-Analysis for Death, Cardiac Death, and Target-Vessel Revascularization
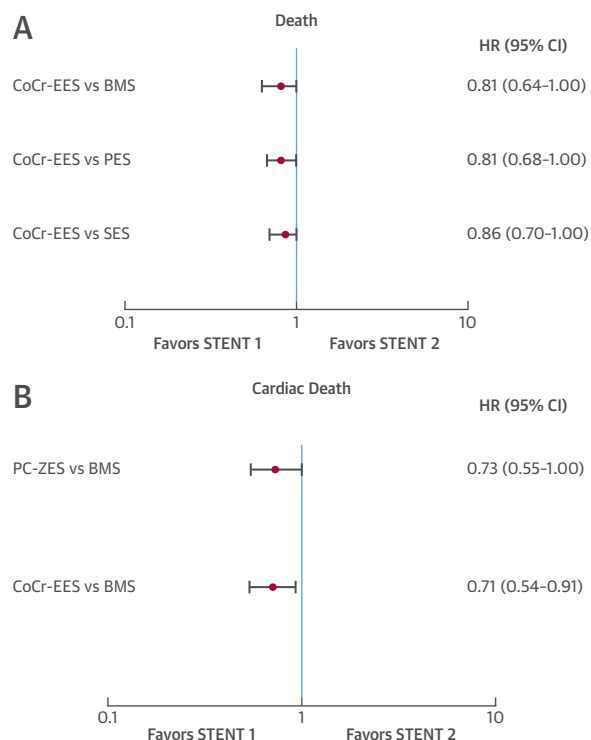
After a median follow-up of 3.8 years, hazard ratios (HRs) and 95% credible intervals (CIs) were determined for the risk of **(A)** death, **(B)** cardiac death, **(C)** myocardial infarction, and **(D)** target-vessel revascularization. Only statistically significant differences are shown. Abbreviations as in **Figure 1**.

present study. Thus, early angiographic measures might be less predictive of late-term outcomes. A large-scale RCT of Re-ZES versus PC-ZES with extended follow-up is required to determine the magnitude of clinical differences between these 2 stent platforms.

Bioabsorbable polymer-based DES have been developed to mitigate the risk of very late (>1 year) adverse events attributable to the presence of permanent polymers. Among these new devices, BES have undergone the most extensive investigation and are in widespread use (although are not yet approved in the United States) (22–26). Although BES were associated with significantly lower rates of definite/probable ST than first-generation DES, no safety or efficacy advantages were apparent with BES compared with other second-generation DES. Conversely, the signal suggesting lower rates of definite ST with CoCr-EES than with BES that was reported at 1 year in prior studies was still apparent

at 4 years (7,34). These findings challenge the notion that polymer bioabsorption is necessary to minimize the risk of very late ST with metallic DES and are consistent with in vitro studies demonstrating that fluorinated polymers are thromboresistant in blood-contact applications (35) and cause less platelet adhesion and activation in experimental stent perfusion studies (36). Whether other bioabsorbable polymers that are biodegraded faster (e.g., PLGA that is absorbed in 3 to 4 months from the everolimus-eluting Synergy stent compared with PLGA that is absorbed in 6 to 9 months with BES) will permit the potential benefits of these new devices to emerge at an earlier time period deserves further investigation; however, in the large-scale EVOLVE (A Prospective Randomized Multicenter Single-Blind Non-inferiority Trial to Assess the Safety and Performance of the Evolution Everolimus-Eluting Monorail Coronary Stent System for the Treatment of a De Novo Atherosclerotic Lesion) II trial, similar rates of target-lesion failure and ST at 1 year were noted in 1,684 patients randomized to the Synergy stent versus PtCr-EES (37).

A possible factor confounding the results of our network meta-analysis is the different duration of dual-antiplatelet therapy between DES and BMS; however, previous reports have suggested a significant difference in ST between CoCr-EES and either BMS or first-generation DES as early as 30 days (4), a period in which all patients undergoing stent implantation are treated with dual-antiplatelet therapy irrespective of stent type. In addition, no study has ever suggested a benefit in mortality with extended dual-antiplatelet therapy (38), and therefore, it is unlikely that the reduced mortality with CoCr-EES compared with BMS was influenced by different durations of dual-antiplatelet therapy.

Of note, CoCr-EES, BES, and PC-ZES were associated with significantly lower rates of very late ST compared with first-generation DES. The mechanisms underlying these findings may be related to enhanced endothelialization of second-generation DES compared with first-generation DES, with greater strut coverage, less inflammation and chronic hypersensitivity reactions, and less fibrin deposition (39). In addition, some studies have suggested lower rates of late stent fractures and late malapposition (40), as well as less endothelial dysfunction with second-generation DES compared with first-generation DES (41).

STUDY LIMITATIONS. As with any meta-analysis, our report shares the limitations of the original studies. Moreover, by exploiting potentially complex evidence network and indirect comparisons as well as direct comparisons, network meta-analysis

assumes that patients enrolled in the component studies could have been sampled from the same theoretical population and that similar comparators between different trials have a consistent risk-benefit ratio. However, no inconsistencies were apparent between the direct and indirect estimates for the endpoints considered across all comparisons, which provides strong scientific support for the reliability of the network.

Results were analyzed on aggregate data, and therefore, we could not assess whether all baseline characteristics were balanced between the groups. Estimates of risk of adverse clinical outcomes between CoCr-EES and BMS were largely on the basis of indirect comparison and therefore should be considered hypothesis generating; however, these results are consistent with a recently reported individual patient-level meta-analysis from the 5 RCTs in which 4,896 patients were randomized to CoCr-EES versus BMS, which showed reduced rates of ST and cardiac mortality with CoCr-EES compared with BMS (42).

Finally, several of the observed reductions in event rates were of borderline statistical significance, and even greater numbers of patients with longer-term follow-up would add greater precision to the present results.
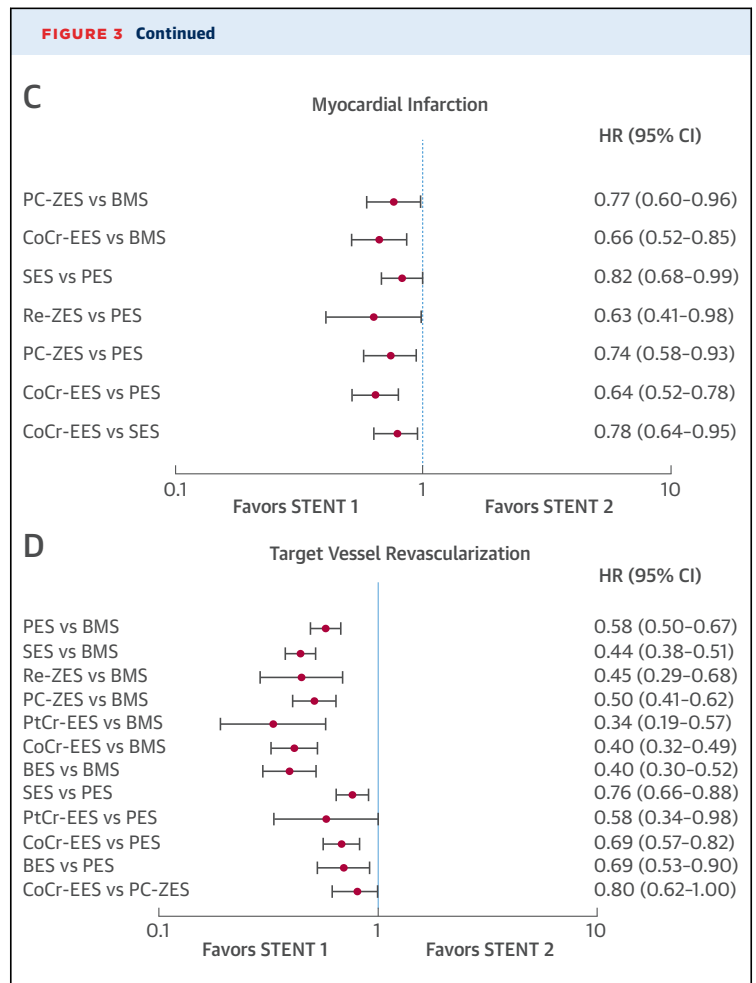
CONCLUSIONS

In the present network meta-analysis of 51 trials that included 52,158 randomized patients, at median follow-up of nearly 4 years, all DES demonstrated superior efficacy in reducing TVR compared with BMS. Second-generation DES have substantially improved long-term safety and efficacy outcomes compared with first-generation devices. Among the second-generation DES, durable fluoropolymer-based CoCr-EES were associated with the lowest rates of long-term adverse events and maximum efficacy.

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FIGURE 3 Continued

C Myocardial Infarction

	HR (95% CI)
PC-ZES vs BMS	0.77 (0.60–0.96)
CoCr-EES vs BMS	0.66 (0.52–0.85)
SES vs PES	0.82 (0.68–0.99)
Re-ZES vs PES	0.63 (0.41–0.98)
PC-ZES vs PES	0.74 (0.58–0.93)
CoCr-EES vs PES	0.64 (0.52–0.78)
CoCr-EES vs SES	0.78 (0.64–0.95)

Favors STENT 1   Favors STENT 2

D Target Vessel Revascularization

	HR (95% CI)
PES vs BMS	0.58 (0.50–0.67)
SES vs BMS	0.44 (0.38–0.51)
Re-ZES vs BMS	0.45 (0.29–0.68)
PC-ZES vs BMS	0.50 (0.41–0.62)
PtCr-EES vs BMS	0.34 (0.19–0.57)
CoCr-EES vs BMS	0.40 (0.32–0.49)
BES vs BMS	0.40 (0.30–0.52)
SES vs PES	0.76 (0.66–0.88)
PtCr-EES vs PES	0.58 (0.34–0.98)
CoCr-EES vs PES	0.69 (0.57–0.82)
BES vs PES	0.69 (0.53–0.90)
CoCr-EES vs PC-ZES	0.80 (0.62–1.00)

Favors STENT 1   Favors STENT 2

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: First-generation DES are associated with a lower risk of restenosis than BMS but a higher risk of late stent thrombosis. Second-generation DES have been developed with novel materials and delivery systems. By a meta-analysis of 51 comparative trials, second-generation DES exhibited better safety and efficacy than either first-generation DES or BMS after a median follow-up of nearly 4 years.

TRANSLATIONAL OUTLOOK: More studies are needed to determine whether bioresorbable vascular scaffolds can lower the risk of late events further in patients undergoing percutaneous coronary revascularization.

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KEY WORDS bare-metal stent(s), drug-eluting stent(s), meta-analysis, stent thrombosis

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