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Clinical Outcomes With Drug-Eluting and Bare-Metal Stents in Patients With ST-Segment Elevation Myocardial Infarction

Evidence From a Comprehensive Network Meta-Analysis

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Objectives The authors investigated the relative safety and efficacy of different drug-eluting stents (DES) and bare metal stents (BMS) in patients with ST-segment elevation myocardial infarction (STEMI) using a network meta-analysis.

Background The relative safety of DES and BMS in patients with STEMI continues to be debated, and whether advances have been made in this regard with second-generation DES is unknown.

Methods Randomized controlled trials comparing currently U.S. approved DES or DES with BMS in patients with STEMI were searched using MEDLINE, EMBASE, and Cochrane databases. Information on study design, inclusion and exclusion criteria, sample characteristics, and clinical outcomes was extracted.

Results Twenty-two trials including 12,453 randomized patients were analyzed. At 1-year follow-up, cobalt-chromium everolimus eluting stents (CoCr-EES) were associated with significantly lower rates of cardiac death or myocardial infarction (MI) and stent thrombosis (ST) than BMS. Differences in ST were apparent as early as 30 days and were maintained for 2 years. CoCr-EES were also associated with significantly lower rates of 1-year ST than paclitaxel-eluting stents (PES). Sirolimus-eluting stents (SES) were also associated with significantly lower rates of 1-year cardiac death/myocardial infarction than BMS. CoCr-EES, PES, and SES, but not zotarolimus-eluting stents, had significantly lower rates of 1-year target vessel revascularization (TVR) than BMS, with SES also showing lower rates of TVR than PES.

Conclusions In patients with STEMI, steady improvements in outcomes have been realized with the evolution from BMS to first-generation and now second-generation DES, with the most favorable safety and efficacy profile thus far demonstrated with CoCr-EES. (J Am Coll Cardiol 2013;62:496–504) © 2013 by the American College of Cardiology Foundation

Primary percutaneous coronary intervention (PCI) performed by an experienced team and in a timely fashion is the treatment of choice for patients with ST-segment elevation acute myocardial infarction (STEMI) (1). The introduction of bare-metal stents (BMS) has provided additional benefit compared to balloon angioplasty by reducing the risk of recurrent ischemia and

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restenosis (2), and drug-eluting stents (DES) have further improved clinical outcomes by further reducing restenosis and target vessel revascularizations (TVR) (3). However, concern has been raised over the ongoing propensity for very late stent thrombosis (StThr) of first-generation sirolimus-eluting stents (SES; Cypher, Cordis Corp., Miami Lakes, Florida) and paclitaxel-eluting stents (PES) (Taxus, Boston Scientific, Natick, Massachusetts) (4,5). This concern is particularly relevant for patients with STEMI, who, compared to patients with stable coronary artery disease, have greater rates of ST due to heightened platelet activation and the presence of thrombus (6,7).

To overcome the safety concerns with first-generation DES, newer devices have been developed that use novel stent materials, designs, and delivery systems with enhanced biocompatible polymers, and new antiproliferative agents compared to their predecessors. However, studies performed so far comparing second-generation DES with first-generation DES or BMS in patients with STEMI have not been powered to detect significant differences in the occurrence of death, MI, or ST (8,9). Moreover, previous meta-analyses have compared pooled PES and SES versus BMS, thus leaving undetermined whether there are stent-related differences between these two devices or whether second-generation DES have improved outcomes compared to first-generation DES (or BMS) (10,11).

Network meta-analyses and mixed treated comparisons are novel research methods capable of comparing different treatments using a common reference treatment, and their role in clinical research has been established (12). Accordingly, we performed an updated contemporary, comprehensive network meta-analysis to investigate whether there are major differences in safety and efficacy among first-generation DES, second-generation DES, and BMS in patients with STEMI undergoing primary PCI.

Abbreviations and Acronyms

BMS = bare-metal stent(s)
CoCr-EES = cobalt-chromium everolimus-eluting stent(s)
DES = drug-eluting stent(s)
PES = paclitaxel-eluting stent(s)
PCI = percutaneous coronary intervention
PC-ZES = phosphorylcholine-based zotarolimus-eluting stent(s)
PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-analyses
RCT = randomized controlled trial
SES = sirolimus-eluting stent(s)
StThr = stent thrombosis
STEMI = ST-segment elevation acute myocardial infarction
TVR = target vessel revascularizations

Methods

Objectives, definitions, and study design. In this network meta-analysis we compared the safety and efficacy of U.S. Food and Drug Administration (FDA)-approved DES and BMS in patients with STEMI. We restricted our analyses to FDA-approved DES as these are the devices with the widest use in the setting of STEMI. Thus, the DES studied in the present report were SES, PES (both Express and Liberté platforms), cobalt-chromium everolimus-eluting stents (CoCr-EES) (Xience, Abbott Vascular, Santa Clara, California), and phosphorylcholine-based zotarolimus-eluting stents (PC-ZES) (Endeavor, Medtronic, Santa Rosa, California).

As fewer studies with data at 2 years compared to 1 year have been reported for second-generation DES, we specified that the primary analyses for the present report be performed at 1-year follow-up. Safety endpoints included death, cardiac death, MI, death or MI, cardiac death or MI, and definite or definite/probable ST according to Academic Research Consortium (ARC) criteria. ST was further stratified as early (≤30 days) and late (31 days to 1 year). The efficacy endpoint was TVR.

The present review was performed according to Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statements (13).

Data source and study selection. We searched for randomized controlled trials (RCTs) relevant to this meta-analysis in MEDLINE, PubMed, Cochrane Collaboration database, Embase, TCTMD.com, Clinical Trials.gov, Clinical Trials Results.org, and CardioSource.com, and in abstracts and presentations from major cardiovascular meetings using the keywords ST-segment elevation myocardial infarction, drug-eluting stent, everolimus-eluting stent, paclitaxel-eluting stent, sirolimus-eluting stent, zotarolimus-eluting stent, and bare metal stent. RCTs comparing 2 or 3 different DES or DES with BMS were identified and included in the meta-analysis. Two investigators (T.P. and D.D.R.) independently reviewed the titles, abstracts, and studies to determine whether they met inclusion criteria. Conflicts between reviewers were resolved by consensus. No language, publication date, or publication status restrictions were imposed. The most updated or most inclusive data for

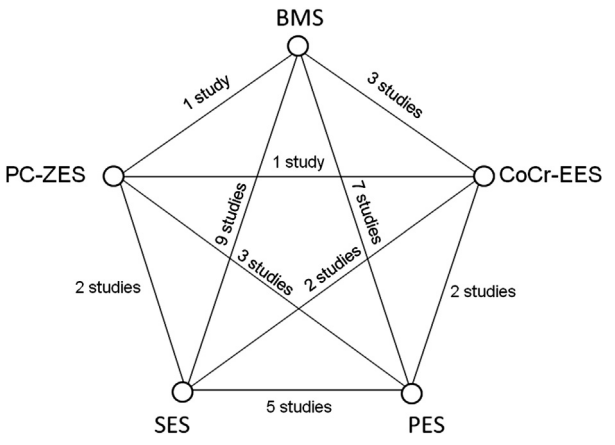

Figure 1 Evidence Network Among Stents Included in the Meta-Analysis

CoCr-EES = cobalt-chromium everolimus-eluting stent(s); PES = paclitaxel-eluting stent(s); SES = sirolimus-eluting stent(s); BMS = bare-metal stent(s); PC-ZES = phosphorylcholine polymer-based zotarolimus-eluting stent(s).

Table 1 Randomized Controlled Trials Included in the Network Meta-Analysis

Study (Ref. #), Year	Primary Endpoint	Design	Rand Ratio	Maximal Length of Follow-Up	Stent Comparators (n)	Results of the Primary Endpoint
BASKET PROVE, 2010†	Cardiac death and MI at 2 yrs	Multicenter, superiority	1:1:1	2 yrs	CoCr-EES/SES/BMS 2,314 (774/775/765)	Superiority not demonstrated
COMPARE, 2010*	Death, MI, TVR at 1 yr	Single center, superiority	1:1	2 yrs	CoCr-EES/PES 1,800 (897/903)	CoCr-EES superior to PES
Diaz de Llera et al. (3), 2007	Death, MI, TLR at 1 yr	Single center, superiority	1:1	1 yr	BMS/SES 114 (54/60)	SES superior to BMS
EXAMINATION, 2011	Death, MI, any revascularization at 1 yr	Multicenter, superiority	1:1	1 yr	CoCr-EES/BMS 1,504 (751/747)	Superiority not demonstrated
GRACIA-3, 2010	In-segment binary restenosis, myocardial flow at 1 yr	Multicenter, noninferiority	1:1	1 yr	BMS/PES 419 (210/209)	BMS noninferior to PES
HAMUU, 2006	Death, MI, late lumen loss, TVR at 1 yr	Single center, superiority	1:1	1 yr	BMS/PES 164 (82/82)	PES superior to BMS
HORIZONS-AMI, 2009	1. TLR; 2. Death, MI, stroke, or ST at 1 yr	Multicenter, superiority (TLR) Noninferiority (Death, MI, stroke, ST)	3:1	3 yrs	BMS/PES 3,006 (2,257/749)	PES superior for TLR and noninferior for clinical endpoints
Juwana et al. (8), 2009	Late lumen loss at 9 months	Single center, superiority	1:1	1 yr	PES/SES 397 (196/201)	SES superior to PES
KOMER, 2011	Cardiac death, MI, ischemia driven TLR at 1 yr	Multicenter, safety study	1:1:1	18 months	PES/SES/PC-ZES 611 (202/204/205)	PC-ZES as safe as SES and PES
MISSION, 2008	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, 2008	Death, MI, clinically driven TVR at 8 months	Multicenter, superiority	1:1	3 yrs	BMS/SES 744 (372/372)	SES superior to BMS
Pasceri et al. (12), 2003	Death, MI, recurrent ischemia at 1 yr	Single center	1:1	1 yr	BMS/SES 65 (33/32)	No significant differences among stents
PASEO, 2009	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, 2008	Cardiac death, MI, TLR at 2 yrs	2-center, superiority	1:1	5 yrs	BMS/PES 619 (310/309)	Superiority not demonstrated
PRODIGY, 2012†	Death, MI, cerebrovascular accident at 2 yrs	Multicenter, superiority of 24-month vs. 6-month DAPT	1:1:1:1	2 yrs	BMS/EES/PES/PC-ZES 2,013 (502/499/498/500)	Superiority not demonstrated
PROSIT, 2008	Death, MI, TVR, ST at 1 yr	Multicenter, superiority	1:1	3 yrs	PES/SES 308 (154/154)	Superiority not demonstrated
SELECTION, 2007	Neointimal proliferation by IVUS at 7 months	Single-center, superiority	1:1	7 months	BMS/PES 76 (39/37)	PES superior to BMS
SESAMI, 2007	Binary restenosis at 1 yr	Single-center, superiority	1:1	5 yrs	BMS/SES 320 (160/160)	SES superior to BMS
STRATEGY, 2007	Death, MI, stroke, binary restenosis at 8 months	2-center, superiority	1:1	2 yrs	BMS/SES 175 (87/88)	SES superior to BMS
TYPHOON, 2006	TVF† at 1 yr	Multicenter, superiority	1:1	4 yrs	BMS/SES 712 (355/357)	SES superior to BMS
XAMI, 2012	Cardiac death, MI, TVR at 1 yr	Multicenter, Non inferiority	2:1	1 yr	EES/SES 625 (404/221)	EES noninferior to SES
ZEST-AMI, 2009	Death, MI, and ischemia-driven TVR at 1 yr	Multicenter, safety study	1:1:1	1 yr	PES/SES/PC-ZES 328 (110/110/108)	No significant differences among stents

*Data refer to the entire trial. †TVF was defined as cardiac death, target vessel MI, or TVR.

BMS = bare-metal stent stent(s); CoCr-EES = cobalt-chromium everolimus-eluting stent(s); DAPT = dual antiplatelet therapy; DES = drug-eluting stent(s); EES = everolimus-eluting stent(s); IVUS = intravascular ultrasound; MI = myocardial infarction; PC-ZES = phosphorylcholine polymer based zotarolimus-eluting stent(s); PES = paclitaxel-eluting stent(s); Rand = randomization; SES = sirolimus-eluting stent(s); ST = stent thrombosis; TLR = target lesion revascularization; TVF = target vessel failure.

a given study was chosen for abstraction. We also included subgroups of patients with STEMI enrolled in large RCTs (with more than 1,000 patients), provided that stent randomization was stratified by STEMI status to ensure equal distribution of baseline variables. For those trials, data were provided directly by the principal investigators (8,14,15). Internal validity of RCTs was assessed by evaluating concealment of allocation, blind adjudication of clinical events, and inclusion of all randomized patients in the analysis according to the intention-to-treat principle.

Statistical analysis. Dichotomous outcome variables at specific time points were compared with odds ratios (OR) with 95% credible intervals (CIs) by means of network meta-analysis with a random-effect model using WinBUGS version 1.4.3 software (MRC Biostatistics Unit, Cambridge, United Kingdom). Each analysis was based on non-informative priors for effect sizes and precision. Convergence and lack of autocorrelation were checked and confirmed after a 50,000-simulation burn-in phase, and, finally, direct probability statements were based on an additional 100,000-simulation phase. Calculation of the probability that each stent had the lowest rate of clinical events was performed using Bayesian Markov chain Monte Carlo modeling. Sensitivity analyses were performed by repeating the main computations using a fixed effect method. Model fit was appraised by computing and comparing estimates for deviance and deviance information criterion. Pair-wise inconsistency and inconsistency between direct and indirect effect estimates were assessed with the I^2 statistic, with values of <25%, 25% $\leq I^2 \leq$50%, and >50% representing mild, moderate, and severe inconsistency, respectively. Extent of small study effects/publication bias was assessed by visual inspection of funnel plots. In addition, to investigate whether there might be differences in clinical outcomes beyond 1 year, given the variability in length of follow-up reported by each trial, we also determined hazard ratios (HR) and event rates per 100 patient years for each stent by means of a weighted Poisson regression analysis.

Results

The flow diagram of the study analysis is shown in Online Figure 1. Of 620 potentially relevant articles initially screened, 22 trials met inclusion criteria and were included in the final meta-analysis consisting of a total of 12,453 randomized patients. Three of those trials did not report ST according to ARC criteria, and therefore, 19 trials were available for the ST endpoint. The evidence network is shown in Figure 1. The 22 RCTs included in the meta-analysis and their relative references are displayed in Online Table 1. Major characteristics of the included trials are listed in Table 1. The major inclusion and exclusion criteria and internal validity assessment for each trial are reported in Online Table 2. The clinical characteristics of patients enrolled in the RCTs included in the meta-analysis are reported in Online Table 3.

1-year clinical outcomes. Twenty-two studies with 12,453 patients contributed to the analysis of the 1-year mortality,

Table 2 Differences in Clinical Outcomes Among Different Stent Types at 1-Year and Long-Term Follow-Up

Stent Type	1-yr Death/MI OR (95% CI)	Long-Term Death/MI HR (95% CI)	1-yr Cardiac Death/MI OR (95% CI)	Long-Term Cardiac Death/MI HR (95% CI)
PES vs. BMS	0.77 (0.60–1.00)	0.93 (0.77–1.16)	0.87 (0.65–1.16)	0.98 (0.79–1.20)
SES vs. BMS	0.88 (0.69–1.10)	0.86 (0.71–1.05)	**0.70 (0.49–0.98)**	0.78 (0.61–1.05)
PC-ZES vs. BMS	0.91 (0.58–1.42)	0.96 (0.62–1.40)	0.86 (0.50–1.49)	0.93 (0.59–1.45)
CoCr-EES vs. BMS	**0.65 (0.46–0.90)**	**0.69 (0.53–0.91)**	**0.63 (0.42–0.92)**	**0.70 (0.50–0.96)**
SES vs. PES	1.14 (0.84–1.54)	0.91 (0.73–1.17)	0.80 (0.54–1.20)	0.80 (0.60–1.08)
PC-ZES vs. PES	1.20 (0.73–1.89)	1.03 (0.66–1.53)	1.00 (0.57–1.71)	0.95 (0.60–1.50)
CoCR-EES vs. PES	0.85 (0.57–1.22)	**0.73 (0.54–0.98)**	0.73 (0.47–1.08)	0.72 (0.51–1.00)
PC-ZES vs. SES	1.04 (0.66–1.63)	1.11 (0.71–1.75)	1.24 (0.68–2.24)	1.19 (0.71–1.99)
CoCr-EES vs. SES	0.74 (0.51–1.05)	0.80 (0.59–1.12)	0.91 (0.56–1.42)	0.90 (0.60–1.31)
CoCr-EES vs. PC-ZES	0.71 (0.42–1.16)	0.72 (0.47–1.14)	0.73 (0.40–1.30)	0.75 (0.46–1.25)
	1-yr MI OR (95% CI)	**Long-Term MI HR (95% CI)**	**1-yr TVR OR (95% CI)**	**Long-Term TVR HR (95% CI)**
PES vs. BMS	0.81 (0.60–1.13)	1.03 (0.78–1.40)	**0.56 (0.42–0.73)**	**0.65 (0.48–0.81)**
SES vs. BMS	0.74 (0.53–1.06)	0.91 (0.65–1.23)	**0.35 (0.26–0.46)**	**0.47 (0.35–0.60)**
PC-ZES vs. BMS	0.58 (0.31–1.03)	0.68 (0.36–1.24)	0.60 (0.34–1.05)	0.67 (0.40–1.16)
CoCr-EES vs. BMS	**0.55 (0.34–0.93)**	0.66 (0.44–1.05)	**0.45 (0.29–0.66)**	**0.43 (0.28–0.62)**
SES vs. PES	0.93 (0.60–1.36)	0.87 (0.60–1.25)	**0.63 (0.45–0.88)**	0.74 (0.54–1.01)
PC-ZES vs. PES	0.73 (0.38–1.27)	0.67 (0.35–1.19)	1.08 (0.60–1.94)	1.05 (0.61–1.86)
CoCR-EES vs. PES	0.67 (0.39–1.14)	0.64 (0.41–1.01)	0.80 (0.50–1.25)	0.67 (0.44–1.02)
PC-ZES vs. SES	0.79 (0.43–1.42)	0.75 (0.40–1.41)	1.71 (0.94–3.16)	1.43 (0.78–2.57)
CoCr-EES vs. SES	0.74 (0.43–1.31)	0.72 (0.47–1.24)	1.28 (0.80–2.00)	0.91 (0.59–1.39)
CoCr-EES vs. PC-ZES	0.92 (0.47–1.94)	0.99 (0.48–1.96)	0.74 (0.38–1.43)	0.64 (0.33–1.18)

Statistically significant comparisons are in **bold**.

CI = credible interval; OR = odds ratio; other abbreviations as in Table 1.

MI, and TVR endpoints; 17 studies with 10,755 patients contributed to the analysis of 1-year cardiac mortality; 17 studies with 10,826 patients contributed to the analysis of 1-year definite ST; and 17 studies with 11,188 patients contributed to the analysis of 1-year definite/probable ST. As shown in Online Table 4, there was no significant difference in the risk of mortality or cardiac mortality among the different stent types at 1-year follow-up. However, CoCr-EES were associated with significantly lower rates of 1-year composite death or MI and 1-year composite cardiac death or MI than BMS, whereas SES were associated with significantly lower rates of composite cardiac death or MI than BMS (Table 2, Fig. 2A). In addition, CoCr-EES were associated with significantly lower rates of 1-year MI than BMS (Table 2, Fig. 2B) and significantly lower rates of definite or definite/probable ST than both BMS and PES (Table 3, Fig. 2C). SES, PES, and CoCr-EES, but not PC-ZES, were associated with significantly lower rates of TVR at 1-year follow-up than BMS, with SES also showing significantly lower rates of 1-year TVR than PES (Table 2, Fig. 2D). No other significant differences were apparent among the various DES. At 1-year follow-up, according to Bayesian Markov chain Monte Carlo modeling, CoCr-EES had a 59% probability of having the lowest rate of cardiac death/MI, a 56% probability of having the lowest rate of MI, and a 63% probability of having the lowest rate of definite ST, whereas SES had an 82% probability of having the lowest rates of TVR (Table 4).

Long-term (>1 year) clinical outcomes. The latest follow-up available for each study is reported in Table 1, and event rates per 100 patient years for different stent types are shown in Table 4. As seen in Tables 2 and 3 and in Figure 3, by Poisson regression analysis, CoCr-EES were associated with significantly lower rates of cardiac death/MI, MI, definite and definite/probable ST per 100 patient years than BMS and lower rates of cardiac death/MI than PES, whereas SES were associated with significantly lower rates of cardiac death/MI than BMS. CoCr-EES had a 65% probability of having the lowest rate of cardiac death/MI, a 50% probability of having the lowest rate of MI, a 75% probability of having the lowest rate of definite ST, and a 64% probability of having the lowest rates of TVR (Table 4).

Early and late ST. Significant differences in definite and definite/probable ST among different stent types were already apparent at 30 days. Specifically, CoCr-EES were associated with significantly lower rates of early definite and definite/probable ST than BMS and lower rates of early definite/probable ST than PES (Table 3). No significant differences in late ST were apparent among different type of stents.

Additional analyses. Sensitivity analysis based on fixed effect models did not significantly change the results of the meta-analysis (Online Table 5). Moreover, after excluding studies with uncertain risk of bias (Online Table 6), those performed in Asia (Online Table 7) and those using bivalirudin as anticoagulant therapy in a significant proportion of patients (HORIZONS-AMI trial) (Online Table 8), CoCr-EES remained associated with significantly lower rates of 1-year cardiac death/MI, MI, definite ST and definite/probable ST than BMS and significantly lower rates of definite ST than PES.

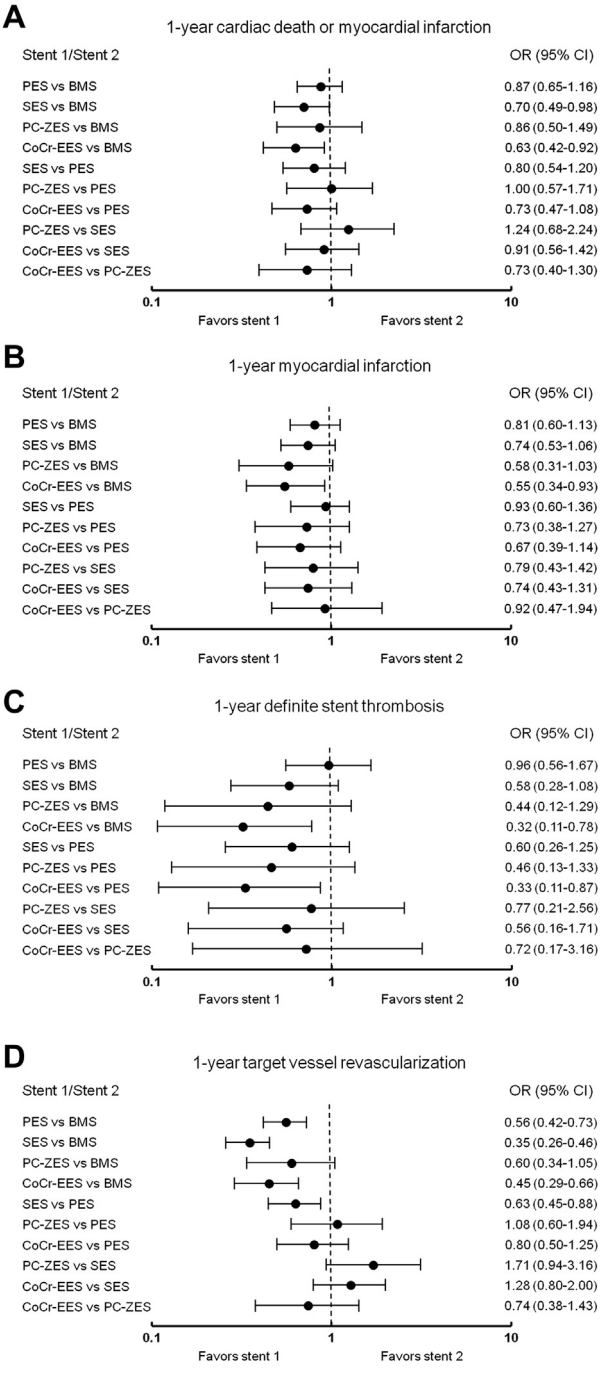

Figure 2 **1-Year Pooled Odds Ratio and 95% Credible Intervals**

OR and 95% CI were determined by network meta-analysis for cardiac death **(A)** or myocardial infarction (MI) **(B)**, definite stent thrombosis **(C)**, and target vessel revascularization (TVR) **(D)**. Abbreviations are as in Figure 1.

Table 3 Time-Related Differences Among Different Stent Types for the Risk of Definite and Definite/Probable Stent Thrombosis

Stent Type	Early Definite ST OR (95% CI)	Late Definite ST OR (95% CI)	1-yr Definite ST OR (95% CI)	Long-Term Definite ST HR (95% CI)
PES vs. BMS	0.82 (0.39–1.62)	1.84 (0.24–357.81)	0.96 (0.56–1.67)	1.25 (0.80–1.99)
SES vs. BMS	0.47 (0.16–1.04)	0.68 (0.00–22.15)	0.58 (0.28–1.08)	0.92 (0.52–1.56)
PC-ZES vs. BMS	0.39 (0.08–1.43)	0.42 (0.00–35.87)	0.44 (0.12–1.29)	0.68 (0.23–1.84)
CoCr-EES vs. BMS	**0.26 (0.07–0.80)**	0.57 (0.01–38.90)	**0.32 (0.11–0.78)**	**0.39 (0.17–0.90)**
SES vs. PES	0.57 (0.19–1.39)	0.37 (0.00–7.94)	0.60 (0.26–1.25)	0.73 (0.37–1.37)
PC-ZES vs. PES	0.48 (0.10–1.70)	0.21 (0.00–6.14)	0.46 (0.13–1.33)	0.55 (0.18–1.45)
CoCr-EES vs. PES	0.32 (0.08–1.08)	0.29 (0.00–8.48)	**0.33 (0.11–0.87)**	**0.31 (0.13–0.76)**
PC-ZES vs. SES	0.84 (0.18–3.59)	NA	0.77 (0.21–2.56)	0.73 (0.24–2.18)
CoCr-EES vs. SES	0.56 (0.13–2.48)	NA	0.56 (0.16–1.71)	0.43 (0.16–1.17)
CoCr-EES vs. PC-ZES	0.67 (0.11–3.99)	NA	0.72 (0.17–3.16)	0.55 (0.18–2.16)
	Early Definite/Probable ST OR (95% CI)	**Late Definite/Probable ST OR (95% CI)**	**1-yr Definite/Probable ST OR (95% CI)**	**Long-Term Definite/Probable ST HR (95% CI)**
PES vs. BMS	0.75 (0.42–1.28)	1.23 (0.28–9.68)	0.82 (0.53–1.22)	1.25 (0.81–1.92)
SES vs. BMS	0.60 (0.28–1.20)	0.61 (0.04–4.00)	0.73 (0.41–1.22)	0.93 (0.56–1.49)
PC-ZES vs. BMS	0.45 (0.15–1.12)	0.26 (0.00–4.95)	0.47 (0.19–1.04)	0.68 (0.21–1.80)
CoCr-EES vs. BMS	**0.28 (0.12–0.61)**	0.73 (0.11–6.46)	**0.36 (0.18–0.66)**	**0.41 (0.16–0.88)**
SES vs. PES	0.80 (0.36–1.68)	0.49 (0.01–4.33)	0.90 (0.47–1.62)	0.73 (0.39–1.33)
PC-ZES vs. PES	0.59 (0.21–1.48)	0.21 (0.00–3.33)	0.57 (0.24–1.28)	0.53 (0.17–1.43)
CoCr-EES vs. PES	**0.38 (0.15–0.83)**	0.59 (0.08–3.51)	**0.44 (0.22–0.83)**	**0.32 (0.12–0.71)**
PC-ZES vs. SES	0.74 (0.25–2.06)	0.43 (0.01–21.37)	0.64 (0.25–1.52)	0.75 (0.22–2.11)
CoCr-EES vs. SES	0.47 (0.16–1.28)	1.21 (0.09–41.89)	0.49 (0.22–1.10)	0.44 (0.16–1.10)
CoCr-EES vs. PC-ZES	0.62 (0.20–2.17)	NA	0.77 (0.29–2.08)	0.59 (0.17–2.32)

Statistically significant comparisons are in **bold**.
HR = hazard ratio; NA = not available or analyzable due to insufficient number of events; other abbreviations as in Table 1.

Visual inspection of funnel plots did not suggest any small-study effects or publication bias (Online Fig. 2). Only mild or moderate statistical inconsistency was found for all pair-wise analyses, with the exception of the CoCr-EES versus PES comparison for 1-year TVR (I^2= 74%); such analysis, however, was limited in scope by the inclusion of only 2 studies. Conversely, no inconsistency was apparent when comparing direct and indirect estimates ($I^2 = 0$ for all main analyses).

Discussion

The present report is the largest and most comprehensive study to date comparing the safety and efficacy profile of different stent types in patients with STEMI undergoing primary PCI. The principal findings are the following: 1) CoCr-EES were associated with significantly lower rates of 1-year cardiac death/MI, MI, definite ST, and definite/probable ST than BMS, whereas SES were associated with significantly lower rates of cardiac death/MI than BMS; 2) the reduction in cardiac death/MI and in ST with CoCr-EES compared to BMS was already apparent at 30 days and was maintained up to 2-year follow-up; 3) CoCr-EES were also associated with significantly lower rates of 1-year definite ST and definite/probable ST and significantly lower rates of cardiac death/MI up to 2-year follow-up than PES; and 3) while SES was associated with the greatest reduction in TVR at 1-year follow-up, CoCr-EES was the most effective stent when follow-up was extended beyond 1 year.

Potentially the most important finding of this study is the significantly lower risk of 1-year cardiac death/MI, MI, and ST with CoCr-EES compared to BMS, a finding not reported to date for any DES in the setting of STEMI. First-generation DES have in fact been shown to reduce TVR compared with BMS in patients with STEMI, with no significant effect on overall cardiac death and MI (3,16). However, first-generation DES have been associated with increased rates of very late ST, raising concerns over the safety of these devices in patients with STEMI (17). Delayed healing with a greater number of uncovered struts, persistent fibrin deposition, late acquired malapposition upon thrombus resolution, stent strut penetration into the necrotic core, and more frequent and rapidly developing neoatherosclerosis may be some of the possible mechanisms associated with the increased risk of late events with first-generation DES in patients with STEMI (18,19).

Although second-generation DES have been developed to improve the safety and efficacy of first-generation DES, no study performed to date has been sufficiently powered to detect significant differences among these devices and first-generation DES or BMS in low-frequency endpoints such as ST, MI, and cardiac death (14,20). With more than 12,000 patients, our study has sufficient power to reveal potentially important safety differences between certain DES and BMS. The observed reduction in ST, MI, and composite cardiac death/MI rates with CoCr-EES compared to BMS is consistent with experimental data suggesting that stents covered by fluorinated polymers are less thrombogenic than

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Table 4 Event Rates per 100 Patient Years and Probability for Each Stent to Be Best at 1 Year and at the Latest Follow-Up Available

	Stent Type				
Event	BMS	PES	SES	PC-ZES	CoCr-EES
Death					
Rate per 100 patient-yrs (95% CI)	3.01 (1.75–5.22)	2.7 (1.49–4.90)	2.50 (1.37–4.57)	3.68 (1.76–8.04)	2.13 (1.11–4.07)
Best at 1 yr	0%	5%	28%	2%	65%
Best at latest follow-up	0%	6%	18%	2%	74%
Cardiac death					
Rate per 100 patient*-yrs (95% CI)	2.03 (1.19–3.47)	1.78 (0.96–3.29)	1.54 (0.83–2.90)	2.81 (1.22–6.32)	1.46 (0.73–2.90)
Best at 1 yr	0%	8%	38%	3%	51%
Best at latest follow-up	0%	7%	35%	2%	56%
MI					
Rate per 100 patient-yrs (95% CI)	3.48 (1.18–3.48)	2.07 (1.13–3.80)	1.70 (0.90–3.22)	1.34 (0.60–2.90)	1.26 (0.62–2.47)
Best at 1 yr	0%	1%	6%	37%	56%
Best at latest follow-up	0%	0%	5%	45%	50%
Cardiac death/MI					
Rate per 100 patient*-yrs (95% CI)	3.69 (2.12–6.45)	3.56 (1.96–6.42)	2.71 (1.47–5.00)	3.33 (1.65–6.79)	2.42 (1.27–4.6)
Best at 1 yr	0%	1%	30%	10%	59%
Best at latest follow-up	0%	0%	25%	10%	65%
Definite stent thrombosis					
Rate per 100 patient-yrs (95% CI)	0.91 (0.54–1.54)	1.26 (0.59–2.53)	0.81 (0.34–1.73)	0.64 (0.11–2.57)	0.35 (0.13–1.03)
Best at 1 yr	0%	0%	7%	30%	63%
Best at latest follow-up	0%	0%	3%	18%	79%
Definite/probable stent thrombosis					
Rate per 100 patient-yrs (95% CI)	1.23 (0.70–2.09)	1.34 (0.67–2.64)	1.11 (0.52–2.33)	0.64 (0.18–1.84)	0.52 (0.22–1.19)
Best at 1 yr	0%	0%	1%	29%	69%
Best at latest follow-up	0%	0%	2%	23%	75%
Target vessel revascularization					
Rate per 100 patient-yrs (95% CI)	4.50 (2.60–7.90)	2.90 (1.60–5.30)	2.10 (1.10–3.90)	2.50 (1.00–5.50)	1.90 (0.90–3.70)
Best at 1 yr	0%	1%	82%	3%	14%
Best at latest follow-up	0%	0%	29%	7%	64%

Abbreviations are as in Table 1.

even BMS (21). Importantly, however, our study did not analyze outcome data from other second-generation DES with durable polymers (e.g., slow-release zotarolimus-eluting stents) or with bioabsorbable polymers, either because data were not available or did not meet the parameters of inclusion in the network. Ongoing and planned trials in patients with stable coronary artery disease and acute coronary syndromes are required to determine the relative safety and efficacy of these devices compared to CoCr-EES, which, based on the present data, should be considered the gold standard for comparative outcomes analyses.

Reocclusion of the infarct-related artery has been associated with increased rates of mortality after STEMI (22), and the significant reduction in cardiac death/MI with CoCr-EES may be attributed to the significant reduction both in ST and TVR compared to BMS. CoCr-EES, in fact, significantly reduced early, 1-year, and 2-year definite ST and definite/probable ST, and 1-year and 2-year TVR compared to BMS. As ST rates in patients with STEMI are significantly higher than in stable patients, the absolute impact of ST on cardiac mortality may be greater in a STEMI cohort (23). This hypothesis is consistent with the findings of the TRITON-TIMI 38 trial in which a 50% reduction in the 30-day rate of ST with prasugrel compared to clopidogrel was associated with a significant reduction in the risk of 30-day cardiac death/MI (24). Moreover, restenosis is not always a benign phenomenon, presenting as acute MI in 3.5% to 19.4% of cases (25), and reinfarction is an independent predictor of mortality in patients with acute coronary syndromes (26).

Another important finding of our meta-analysis is the relative difference in clinical outcomes among first-generation DES. Our data demonstrate that it is inappropriate to consider SES and PES as one category of DES, because significant differences in clinical outcomes are apparent between these two devices. SES, but not PES or PC-ZES, were in fact associated with significantly lower rates of 1-year cardiac death/MI than BMS. Specifically, SES was associated with the greatest reduction in the risk of 1-year TVR among the other stents and with a strong trend toward a reduction in 1-year definite ST compared to BMS, both results likely contributing to the lower rates of cardiac death/MI with SES than with BMS. Although this finding was not apparent in previous meta-analyses comparing first-generation DES with BMS in patients with STEMI (10,11,17), this may be due to pooling SES and PES together in these studies, thus masking possible stent-related differences. Of note, no significant difference in 1-year TVR was apparent between the fast release PC-ZES and BMS.

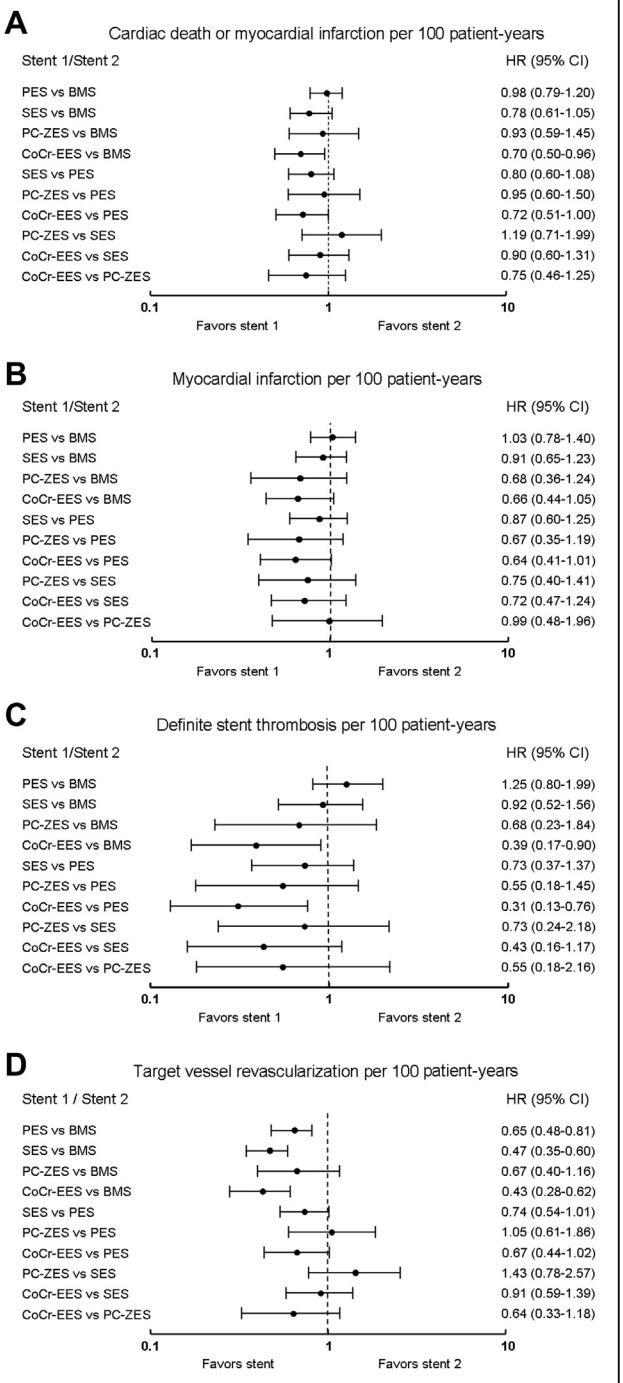

Figure 3 **Pooled Hazard Ratios (HR) and 95% Credible Intervals (CI) per 100 Patient-Years**

HR and 95% CI were determined by Poisson regression analysis for cardiac death **(A)** or MI **(B)**, definite stent thrombosis **(C)**, and TVR **(D)**. Abbreviations as in Figures 1 and 2.

Two prior network meta-analyses suggested lower rates of ST with CoCr-EES than with BMS (27,28). Those studies, however, did not differentiate patients with STEMI and did not report data for cardiac mortality. The present study thus extends the prior findings of reduced ST with CoCr-EES compared to BMS also to patients with STEMI, and further suggests reductions with CoCr-EES in the "hard" endpoints of cardiac death/MI and MI.

Study limitations. A possible confounding factor in the present study is different durations of dual antiplatelet therapy (DAPT) in patients treated with DES and BMS, although DAPT is recommended for at least 1 year in STEMI patients regardless of stent type. Moreover, the differences in ST and cardiac death/MI between CoCr-EES and BMS were already apparent at 30 days, a time period in which both CoCr-EES-treated patients and BMS-treated patients were certainly prescribed DAPT.

Other potential study limitations should be acknowledged. 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 assume that patients enrolled in the studies could have been sampled from the same theoretical population, and that similar comparators among different trials have a consistent risk-benefit ratio. Results were analyzed on aggregate data and therefore we could not assess whether all baseline characteristics were balanced among the groups (although for the most part they were within each RCT). Follow-up data for CoCr-EES in studies to date are limited to 2 years, and therefore, whether the observed differences would remain constant, increase, or diminish with more extended follow-up is unknown. Moreover, due to insufficient statistical power, we could not address whether there might be significant differences in clinical outcomes between the various DES and BMS in the very late period (beyond 1 year), as suggested by a recent meta-analysis for pooled first-generation DES (11). Trials included in the meta-analysis were different in design, inclusion criteria and anticoagulant therapies implemented. However, in sensitivity analyses performed after excluding trials in which bivalirudin was used as anticoagulant therapy, results did not change significantly. Finally, some endpoints (e.g., cardiac death and MI) were based on study-specific definitions which were not uniform across trials, a limitation inherent in most cardiovascular meta-analyses.

Conclusions

In patients with STEMI, steady improvements in outcomes have been realized with the evolution from BMS to first-generation and now second-generation DES, with the most favorable safety and efficacy profile thus far demonstrated with CoCr-EES.

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Key Words: bare-metal stent(s) ■ drug-eluting stent(s) ■ meta-analysis ■ stent thrombosis.

APPENDIX

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