

CLINICAL RESEARCH

Interventional Cardiology

Clinical Outcomes With Bioabsorbable Polymer- Versus Durable Polymer-Based Drug-Eluting and Bare-Metal Stents

Evidence From a Comprehensive Network Meta-Analysis

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Objectives

This study sought to investigate the relative safety and efficacy of bioabsorbable polymer (BP)-based biolimus-eluting stents (BES) versus durable-polymer (DP)-drug-eluting stents (DES) and bare-metal stents (BMS) by means of a network meta-analysis.

Background

Studies have suggested that BP-BES might reduce the risk of stent thrombosis (ST) and late adverse outcomes compared with first-generation DES. However, the relative safety and efficacy of BP-BES versus newer-generation DES coated with more biocompatible DP have not been investigated in depth.

Methods

Randomized controlled trials comparing BP-BES versus currently U.S.-approved DES or BMS were searched through MEDLINE, EMBASE, and Cochrane databases. Information on study design, inclusion and exclusion criteria, sample characteristics, and clinical outcomes was extracted.

Results

Data from 89 trials including 85,490 patients were analyzed. At 1-year follow-up, BP-BES were associated with lower rates of cardiac death/myocardial infarction (MI), MI, and target vessel revascularization (TVR) than BMS and lower rates of TVR than fast-release zotarolimus-eluting stents. The BP-BES had similar rates of cardiac death/MI, MI, and TVR compared with other second-generation DP-DES but higher rates of 1-year ST than cobalt-chromium everolimus-eluting stents (CoCr-EES). The BP-BES were associated with improved late outcomes compared with BMS and paclitaxel-eluting stents, considering the latest follow-up data available, with nonsignificantly different outcomes compared with other DP-DES although higher rates of definite ST compared with CoCr-EES.

Conclusions

In this large-scale network meta-analysis, BP-BES were associated with superior clinical outcomes compared with BMS and first-generation DES and similar rates of cardiac death/MI, MI, and TVR compared with second-generation DP-DES but higher rates of definite ST than CoCr-EES. (J Am Coll Cardiol 2014;63:299–307) © 2014 by the American College of Cardiology Foundation

Although first-generation Cypher (Cordis Corporation, Johnson and Johnson, Warren, New Jersey) sirolimus-eluting stents (SES) and Taxus (Boston Scientific, Natick, Massachusetts) paclitaxel-eluting stents (PES) have reduced the risk of restenosis and target vessel revascularization (TVR)

compared with bare-metal stents (BMS) (1,2), concern has been raised over their ongoing propensity for very late stent

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**Abbreviations
and Acronyms**

BP = bioabsorbable polymers
BES = biolimus-eluting stent(s)
CI = credible interval
CoCr-EES = cobalt-chromium everolimus-eluting stent(s)
DP = durable polymers
OR = odds ratio
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
SES = sirolimus-eluting stent(s)
ST = stent thrombosis
TVR = target vessel revascularizations

thrombosis (ST) (3). Human autopsy studies have identified the durable polymers (DP) of these first-generation drug-eluting stents (DES) as possible triggers for chronic vessel inflammation, delayed hypersensitivity reactions, and chronic fibrin deposition, resulting in impaired stent strut endothelialization, delayed arterial healing, altered flow dynamics, and an increased risk of very late ST (4,5).

To improve DES safety, second-generation DES have been developed with more biocompatible DPs, or bioabsorbable polymers (BP), which are eventually bioresorbed, rendering the stent surface more similar to BMS and free of a chronic inflammatory stimulus. Some studies have shown that BP-based DES are more effective than BMS (6) and, by reducing the risk of very late ST, perhaps safer than

first-generation DES (7). However, second-generation fluorinated DP-based cobalt-chromium everolimus-eluting stents (CoCr-EES) (Xience V and Promus, Boston Scientific) and platinum chromium everolimus-eluting stents (PtCr-EES) (Promus Element, Boston Scientific) have been associated with lower rates of early, late, and very late ST compared with first-generation DES and even BMS (8), challenging the notion that BP are required to minimize the risk of ST.

The relative safety and efficacy of BP-based DES and other second-generation DP-DES have been incompletely characterized. Studies comparing these new devices have in general been insufficiently powered to determine significant differences in individual components of safety (death, cardiac death, myocardial infarction [MI], and ST) and efficacy (TVR) (9). Network meta-analyses and mixed treated comparisons are novel research methods capable of comparing different treatments with a common reference treatment, and their role in clinical research has been established (10). Accordingly, we performed an updated, contemporary, comprehensive network meta-analysis to investigate whether there are major differences in safety and efficacy between BP-based DES, other first- and second-generation DES, and BMS.

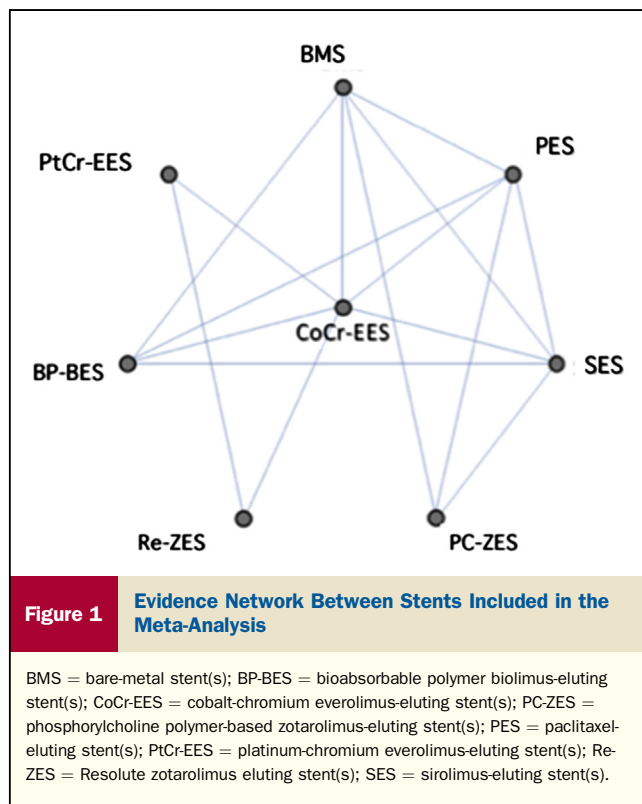
Methods

Objectives, definitions, and study design. Because in-depth comparisons in clinical outcomes between first-generation DP-DES, second-generation DP-DES, and BMS have already been reported (8,11), the primary objective

of this meta-analysis was to compare BP-based DES with the other types of stents. Biolimus-eluting stents (BES) (Biomatrix [Biosensors International, Singapore] and Nobori [Terumo Corporation, Tokyo, Japan]) are the BP-based DES that have been most extensively investigated and are currently the most widely used; therefore, we only included studies using these BP-DES. As DES comparators, we considered only U.S. Food and Drug Administration-approved stents, because these are the devices with the most robust demonstration of safety and efficacy. Therefore, stents considered in this meta-analysis were BP-BES, SES, PES, CoCr-EES, PtCr-EES, phosphorylcholine polymer-based fast-release zotarolimus-eluting stents (PC-ZES) (Endeavor, Medtronic, Minneapolis, Minnesota), and C10/C19/PVP polymer based slow-release ZES (Resolute, Medtronic). We were interested in examining the comparative outcomes at 1-year follow-up (the time period when the greatest amount of follow-up data are available) and beyond 1-year, with the latest follow-up data reported from each study. Safety endpoints included death, cardiac death, MI, death or MI, cardiac death or MI, and ST according to the definite and definite/probable criteria of the Academic Research Consortium (12). Stent thrombosis was further stratified as early (≤ 30 days), late (31 days to 1 year), or very late (beyond 1 year). The efficacy endpoint was TVR. The present review was performed according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statements (13).

Data source and study selection. Relevant randomized controlled trials (RCTs) to include in this meta-analysis were searched through MEDLINE/PubMed; the Cochrane Collaboration database; the EMBASE, TCTMD, ClinicalTrials.gov, Clinical Trial Results, and American College of Cardiology CardioSource online databases; and abstracts and presentations from major cardiovascular meetings, with the key words: drug-eluting stent, biolimus-eluting stent, everolimus-eluting stent, paclitaxel-eluting stent, sirolimus-eluting stent, zotarolimus-eluting stent, and bare-metal stent. The 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 the 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 a given study were chosen for abstraction. 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 posterior median odds ratios (ORs) with 95% Bayesian credible intervals (CIs) by means of network meta-analysis with a random-effect model with WinBUGS (version 1.4.3, MRC Biostatistics



Unit, Cambridge, United Kingdom). We relied on Bayesian inference with Monte Carlo Markov Chain simulations with Gibbs sampling for all computations, including the network estimates (combining direct and indirect evidence), as well as the ORs and absolute risk estimates. Each analysis was based on non-informative priors for effect sizes and precision. Convergence and lack of auto-correlation 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. 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 $<25\%$, $25\% \leq I^2 \leq 50\%$, and $>50\%$, respectively, representing mild, moderate, and severe inconsistency. 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 the length of follow-up reported by each trial, we also determined hazard ratios for event rates/100 patient-years between different stent types by means of a weighted Poisson regression analysis.

Results

Evidence network. The flow diagram of the study analysis is shown in [Online Figure 1](#). Of 2,784 potentially relevant

articles initially screened, 89 trials met the inclusion criteria and were included in the final meta-analysis, comprising a total of 85,490 randomized patients ([Online Table 1](#)). The major characteristics of the included trials appear in [Online Table 2](#). The evidence network is shown in [Figure 1](#). The major inclusion and exclusion criteria and internal validity assessment for each trial are reported in [Online Table 3](#). The clinical characteristics of patients enrolled in the RCTs included in the meta-analysis are reported in [Online Table 4](#).

1-year clinical outcomes. Eighty-two studies with 70,127 patients contributed to the analysis of 1-year mortality, 70 studies with 61,887 patients contributed to the analysis of 1-year cardiac mortality; 83 studies with 73,267 patients contributed to the analysis of 1-year MI; 64 studies with 78,720 patients contributed to the analysis of 1-year definite ST; and 64 studies with 73,176 patients contributed to the analysis of 1-year definite/probable ST. As shown in [Online Table 5](#), no significant differences in 1-year rates of mortality or cardiac mortality were apparent between BP-BES and the other stent types. However, BP-BES were associated with significantly lower 1-year rates of cardiac death/MI ([Fig. 2A](#)), MI ([Fig. 2B](#)), and TVR ([Fig. 2C](#)) than BMS and significantly lower 1-year rates of TVR than PC-ZES ([Fig. 2C](#)). Of note, BP-BES had significantly higher 1-year rates of definite ST compared with CoCr-EES ([Fig. 2D](#)). When the broader definition of definite/probable ST was considered, BP-BES was associated with significantly lower rates of 1-year definite/probable ST than BMS ([Fig. 2E](#)), with nonsignificant differences compared with other DES. Differences in 1-year rates of mortality, MI, TVR, and ST between other stent types are reported in [Online Tables 5 to 7](#).

Long-term (>1 year) clinical outcomes. The latest follow-up available for each study is reported in [Online Table 2](#). Data beyond 1 year were present in 44 studies with 50,815 patients for late mortality; in 43 studies with 50,643 patients for late cardiac mortality; in 46 studies with 50,836 patients for late MI; in 38 studies with 49,552 patients for late definite ST; and in 40 studies with 47,695 patients for late definite/probable ST. No significant differences in long-term mortality or cardiac mortality were apparent between any of the stent types ([Online Table 5](#)). As seen in [Figures 3A to 3E](#), BP-BES were associated, by Poisson regression analysis, with significantly lower rates of cardiac death/MI, MI, and TVR/100 patient-years compared with both BMS and PES and lower rates of long-term TVR than PC-ZES. In contrast, BP-BES were associated with significantly higher rates of long-term definite ST than CoCr-EES ([Fig. 3D](#)). When the broader definition of definite/probable ST was considered, BP-BES were associated with a lower risk of long-term definite/probable ST than BMS and PES, with nonsignificantly different rates when compared with other stent types ([Fig. 3E](#)). Differences in long-term mortality, MI, TVR, and ST between other stent types are reported in [Online Tables 5 to 7](#).

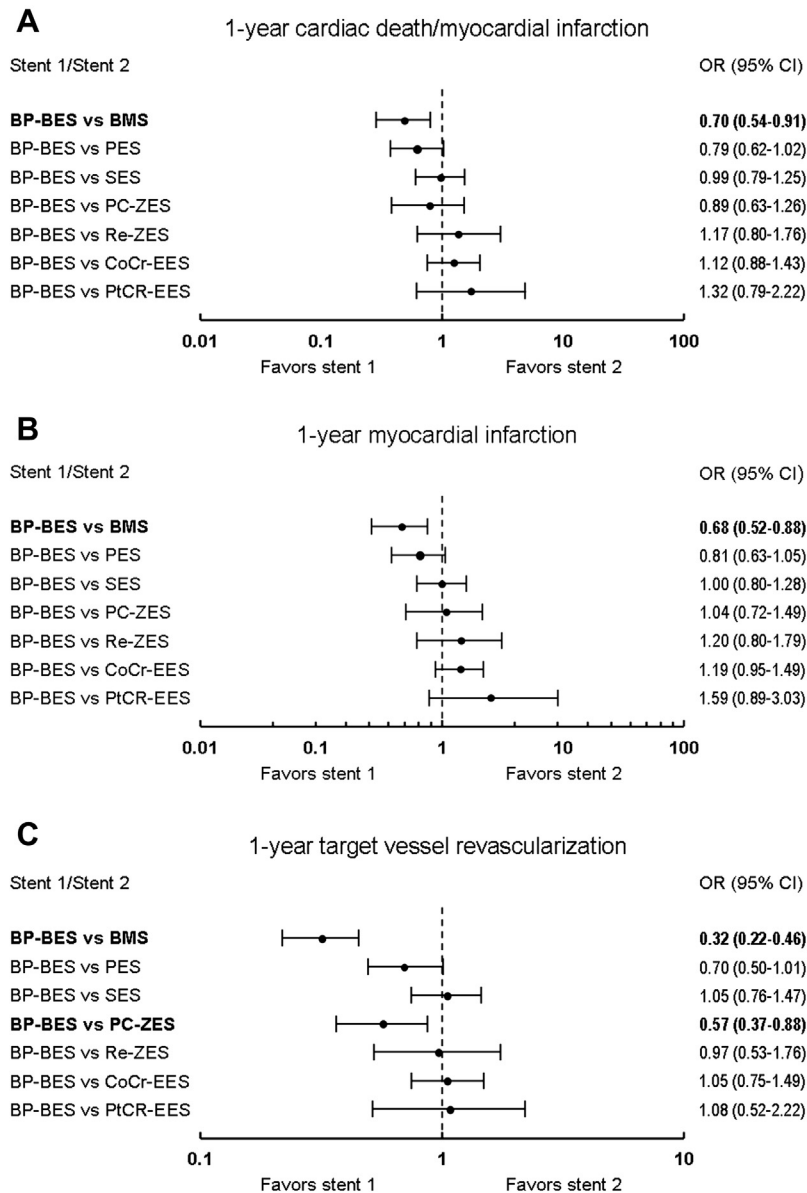


Figure 2 1-Year Pooled ORs and 95% CIs of BES Versus Other Stent Types

One-year pooled odds ratio (OR) and 95% credible intervals (CIs) of BES versus other stent types determined by the network meta-analysis for (A) cardiac death or myocardial infarction; (B) myocardial infarction; (C) target vessel revascularization; (D) definite stent thrombosis; and (E) definite/probable stent thrombosis. Abbreviations as in Figure 1. Continued on the next page.

Early, late, and very late ST. As shown in Online Table 7 and Online Figure 2, significant time-related differences in definite and definite/probable ST were apparent between the different stent types. In general CoCr-EES were associated with the lowest rates of definite ST in the early (≤ 30 days) and late (between 30 days and 1 year) periods. In the very late period (>1 year), PES and SES had higher rates of definite ST than other stent types. The BP-BES, CoCr-EES, and PC-ZES had lower very late definite ST rates than BMS. No significant

differences were present between BP-BES and other second-generation DES in the risk of very late definite ST. Of note, all slow-release limus-eluting stents were associated with lower rates of early definite probable ST compared with BMS.

Additional analyses. Sensitivity analysis on the basis of fixed effect models or performed after excluding studies enrolling patients with diabetes or studies performed in Asia did not significantly change the results of the meta-analysis (Online Tables 8 to 10). Visual inspection of funnel plots

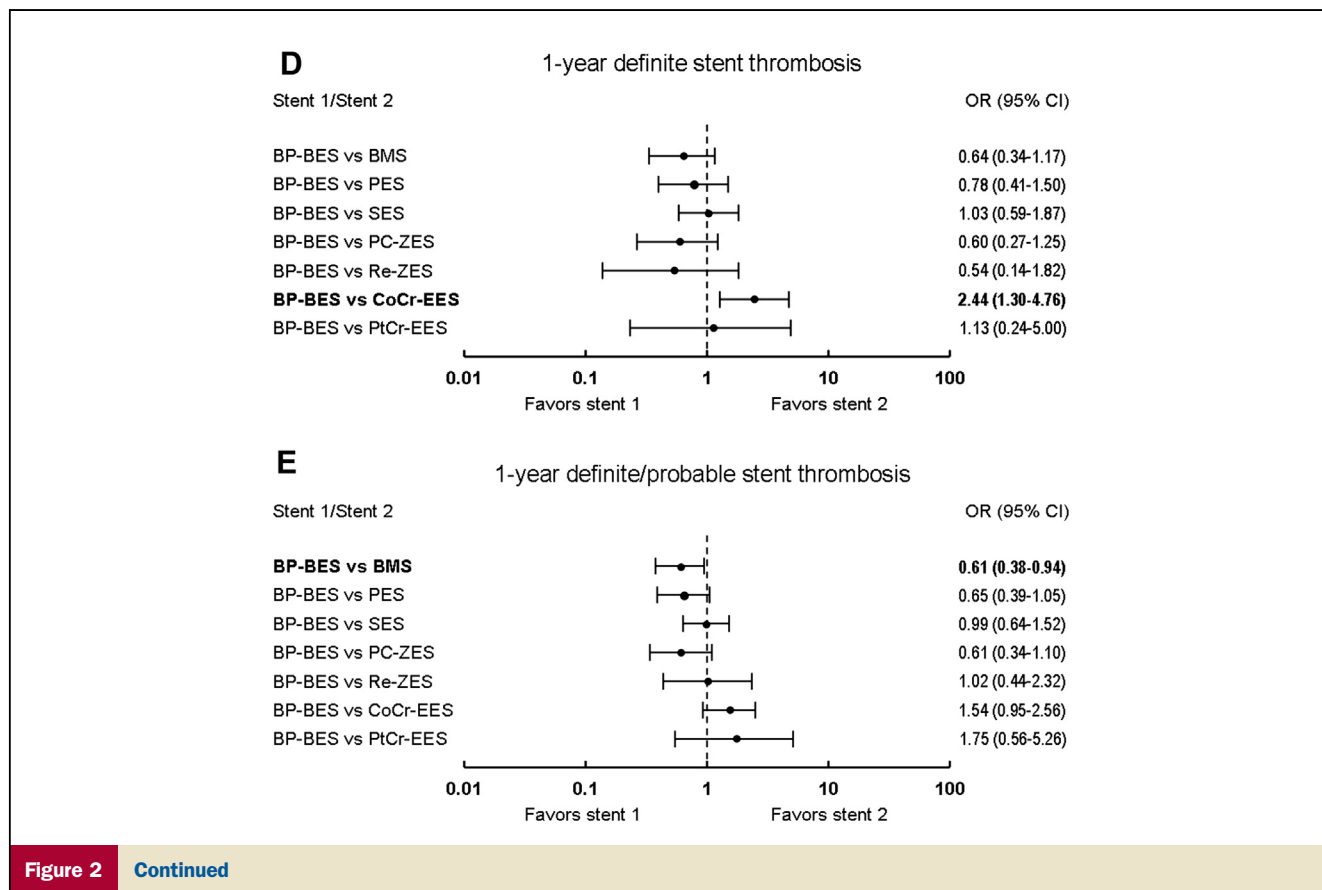


Figure 2 Continued

did not suggest any small study effects or publication bias (Online Fig. 3). Only mild or moderate statistical heterogeneity was found for all pair-wise analyses. Direct and indirect estimates were consistent for all main analyses ($I^2 < 25\%$).

Discussion

The BP-based DES and second-generation DES coated with biocompatible DP have been shown to be safer and more effective than both BMS and first-generation DES (7,8,11). However, few studies have compared BP-BES versus second-generation DP-DES (9), and therefore their relative safety and efficacy remains undetermined. The present report is the largest and most comprehensive study to date comparing the safety and efficacy profile of BP-based BES with other stent types, including first-generation DES, second-generation DES, and BMS. The principal findings are: 1) BP-BES were associated with significantly lower 1-year rates of cardiac death/MI, MI, and TVR than BMS, lower 1-year rates of TVR than PC-ZES, and improved long-term outcomes compared with BMS and PES; 2) although there were no significant differences in the risk of cardiac death/MI, MI, and TVR between BP-BES and other second-generation DES (CoCr-EES, PtCr-EES, and slow-release zotarolimus-eluting stent), BP-BES

were associated with higher rates of 1-year and long-term definite ST compared with CoCr-EES; and 3) significant time-related differences in ST were apparent between different stent types, with CoCr-EES being associated with the lowest rates of ST in the early and late periods, and PES and SES having the highest risk of very late ST.

Studies have shown that permanent polymers coating first-generation DES are associated with chronic inflammation and delayed arterial healing, which might be responsible for the higher rates of very late ST observed with first-generation DES compared with BMS (4,5). These findings prompted the development of safer DPs as well as BPs. The theoretical advantage of BP-DES is to eliminate the potential for polymer-related triggers for late and very late ST. Among BP-based DES, BP-BES has received the most extensive investigation. Several RCTs have investigated the safety and efficacy of BP-BES compared with SES (14,15), BMS (6), and more recently with CoCr-EES (9). However, all these studies were powered for non-inferiority for composite endpoints and were not sized sufficiently to reveal potential differences in low-frequency endpoints such as cardiac mortality, MI, and ST. With more than 85,000 randomized patients, our study has sufficient power to reveal important safety and efficacy differences between BP-based DES and other stent types.

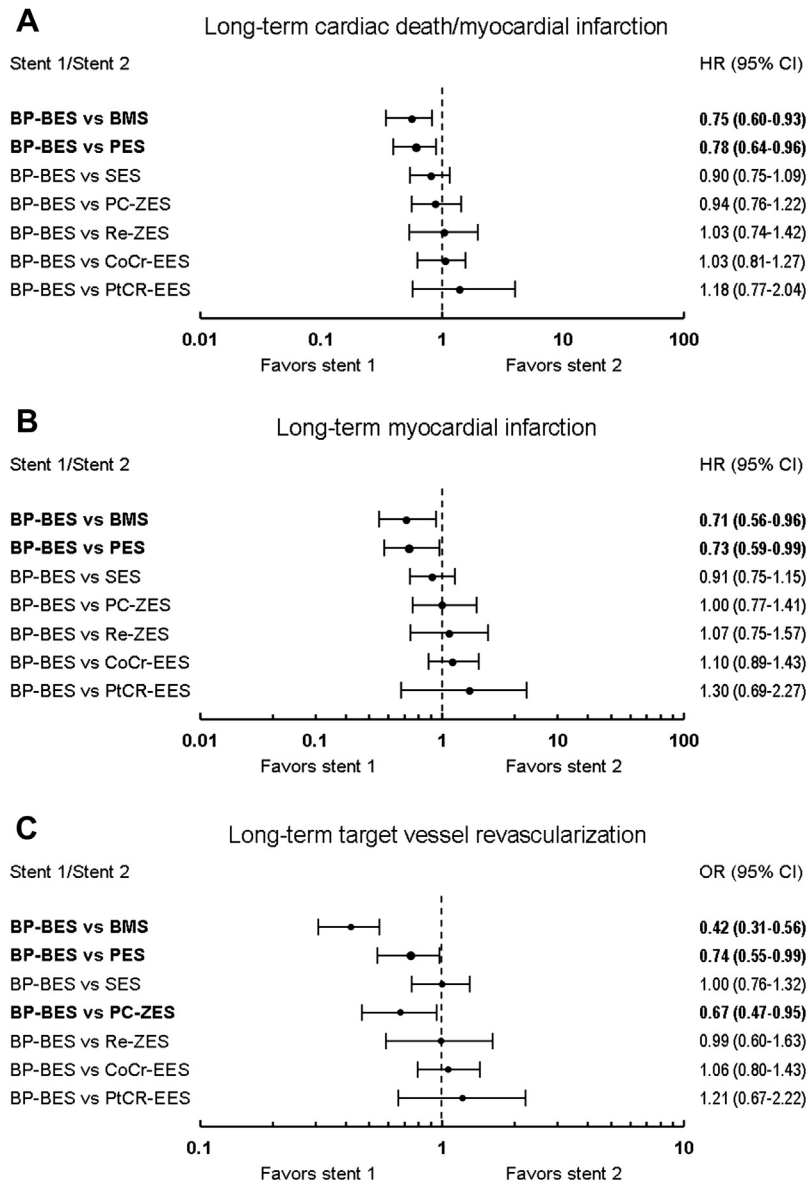


Figure 3 Pooled HR and 95% CIs/100 Patient-Years of BES Versus Other Stent Types

Pooled hazard ratio (HR) and 95% CIs/100 patient-years of BES versus other stent types determined by Poisson's regression analysis for (A) cardiac death or myocardial infarction; (B) myocardial infarction; (C) target vessel revascularization (TVR); (D) definite stent thrombosis; and (E) definite/probable stent thrombosis. Abbreviations as in Figure 1. Continued on the next page.

The main finding of this study is that BP-BES were associated with improved outcomes compared with BMS and first-generation DES (especially PES) and similar rates of death, cardiac death, cardiac death/MI, MI, and TVR compared with other second-generation DES but with higher rates of 1-year and long-term definite ST compared with CoCr-EES. The increased risk for definite ST with BP-BES compared with CoCr-EES was apparent both in the early period (before 30 days) and the late period (between 30 days and 1 year). Conversely, a nonsignificant

trend was present for a reduced rate of very late ST (beyond 1 year) with BP-BES compared with CoCr-EES (OR: 2.46), although the confidence interval around this point estimate was wide due to insufficient data, and this trend did not offset the significant reduction in early and late ST with CoCr-EES. Similar results were apparent when the less-specific definition of definite/probable ST was considered, but the precision of the point estimate was reduced.

These data demonstrate that use of BP might not be associated with the lowest risk of ST, especially within the

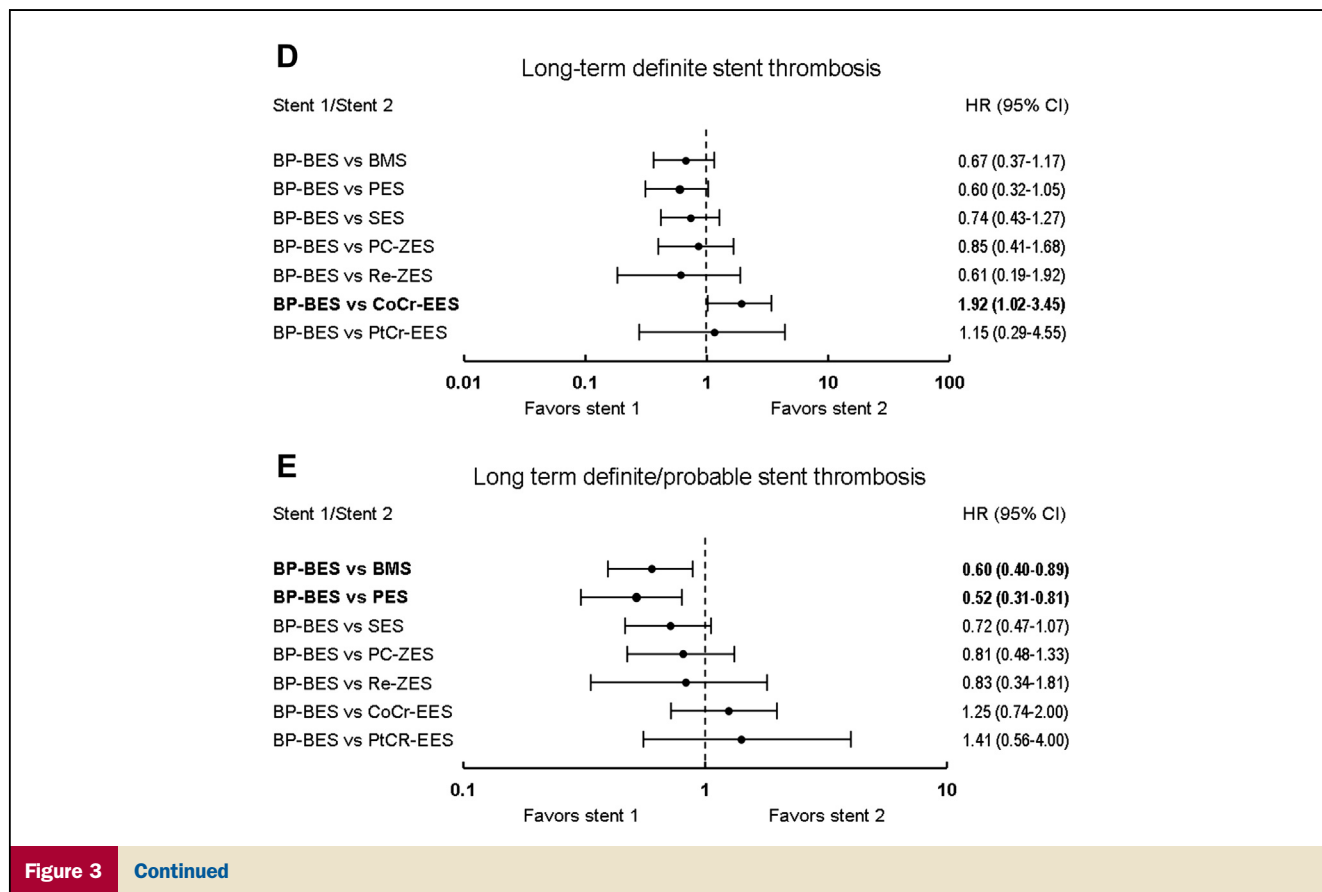


Figure 3 Continued

first year after stent implantation. Polymers requiring active bioresorption have historically been associated with greater rates of inflammation than DP (16,17). Conversely, in vitro studies have shown that the durable fluorinated co-polymer coating CoCr-EES and PtCr-EES is less thrombogenic and causes less platelet activation compared with other polymers (18,19) or even an uncoated metallic stent surface (20). The results of the present study are consistent with the hypothesis that any potential advantages of BP-based DES over biocompatible DP-based stents might not emerge until the late follow-up period after biodegradation of the polymer. However, prior studies have shown that most ST episodes occur within the first 30 days after implantation (21,22). Thus, large-scale studies will be required to determine whether the potential late benefits of a BP can more than offset the early benefits of a thromboresistant DP. In this regard, the extent to which the DP provides clinically important thromboresistant properties in the very late period is undetermined. Moreover, although polylactic acid (the BP used in the Biomatrix and Nobori stents [Terumo Corporation] in the present report) induces relatively low levels of inflammation, other BP might theoretically be more inert and/or completely resorb faster (e.g., in 3 months compared with 6 to 9 months in the current BP-BES), permitting the late benefits of BP-DES to emerge at an earlier time period (23).

Of note, SES and PES were associated with the highest rates of ST beyond 1 year, significantly higher than with BMS, BP-BES, CoCr-EES, and PC-ZES. Thus, some of the late benefit seen in randomized trials of BP-BES compared with first-generation DES (24) might relate more to the poor safety profile of the comparator stent rather than to specific benefits of the BP itself. This observation reinforces the need for large-scale randomized trials between BP-BES and best-in-class second-generation DES to determine whether meaningful differences are present between these 2 devices. To date, only 1 such study has been performed, the COMPARE II (Comparison of the Everolimus Eluting With the Biolimus A9 Eluting Stent) trial in which 2,707 patients were randomized to BP-BES versus CoCr-EES (9). Unfortunately, the low event rates observed in this trial (one-half of that expected) precluded determining whether the nonsignificant differences in event rates between the 2 stents observed in this trial at 1 year are in fact real (type II error) or whether they would diminish with greater patient recruitment. In addition, longer-term follow-up is required for possible late differences to emerge.

In the present study BP-BES were associated with a significant reduction not only in TVR but also in cardiac death/MI, MI, and ST compared with BMS. This observation has previously been reported with other second-generation

DES (11). The significant reduction in cardiac death and MI is probably due both to the lower risk of early ST and the lower risk of restenosis and TVR compared with BMS, which can present as a MI in up to 20% of patients (25,26). These benefits did not translate to lower rates of death or cardiac death with either BP-BES or second-generation DES but likely reflect the multifactorial causes of death in these patients.

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 studies could have been sampled from the same theoretical population and that similar comparators between different trials have a consistent risk-benefit ratio. Duration of dual antiplatelet therapy in patients treated with DES and BMS differed across trials, thus representing a possible confounding factor. Results were analyzed on aggregate data, and therefore we could not assess whether all baseline characteristics were balanced between the groups (although for the most part they were within each RCT). The observed risk ratios with the PtCr-EES in most cases tracked that of CoCr-EES compared with other stent types, although with wide confidence intervals, likely due to the relatively small number of enrolled patients contributing data to the PtCr-EES. This might explain why significant differences did not emerge for the PtCr-EES despite use of the same polymer, drug, and release kinetics as the CoCr-EES. Finally, follow-up data for CoCr-EES in studies to date are mostly limited to 2 years. Indeed, the advantage of BP-based DES over DP-based DES is expected to emerge in the late follow-up, and therefore whether the observed differences would change with more extended follow-up is unknown.

Conclusions

Our study suggests that stents eluting biolimus from BP are associated with superior clinical outcomes compared with BMS and first-generation DES and similar rates of cardiac death/MI, MI, and TVR compared with second-generation DP-DES but higher rates of definite ST than 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.