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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 ($\leq$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