JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. ■, NO. ■, 2018

Ultrathin Bioresorbable Polymer Sirolimus-Eluting Stents Versus Thin Durable Polymer Everolimus-Eluting Stents After Myocardial Infarction

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ABSTRACT

BACKGROUND Coronary drug-eluting stent development has introduced new metal alloys, changes in stent architecture, and bioresorbable polymers. Whether these advancements improve long-term clinical safety and efficacy has been inconsistent in prior studies.

OBJECTIVES The authors sought to compare late-term clinical outcomes among patients treated with an ultrathin strut (60 μm) bioresorbable polymer sirolimus-eluting stent (BP SES) and a thin strut (81 μm) durable polymer everolimus-eluting stent (DP EES) in a large randomized trial.

METHODS BIOFLOW V (Biotronik Prospective Randomized Multicenter Study to Assess the Safety and Effectiveness of the Orsiro Sirolimus Eluting Coronary Stent System in the Treatment of Subjects with Up to Three De Novo or Restenotic Coronary Artery Lesions V) was an international randomized trial comparing coronary revascularization with BP SES and DP EES regarding the primary endpoint of 12-month target lesion failure (TLF). Analysis of pre-specified 2-year clinical outcomes was performed.

RESULTS Among 1,334 patients randomized to treatment with BP SES (884 patients) or DP EES (450 patients), the 2-year TLF rate was 7.5% for BP SES and 11.9% for DP EES (−4.33% treatment difference; 95% confidence interval: −8.16% to −0.91%; p = 0.015), driven by differences in target vessel myocardial infarction (MI) (5.3% vs. 9.5%; p = 0.01) and ischemia-driven target lesion revascularization (2.6% vs. 4.9%; p = 0.04). Rates of cardiac death or MI were 7.0% versus 10.4% for BP SES and DP EES, respectively (p = 0.047). Late/very late definite stent thrombosis was statistically lower for BP SES compared with DP EES (0.1% vs. 1.0%; p = 0.045).

CONCLUSIONS In a large randomized trial, significant differences in both TLF and target vessel–related MI persisted through 2 years, favoring treatment with BP SES over DP EES. Significantly lower cumulative target lesion revascularization and late/very late stent thrombosis were also observed with BP SES. (Safety and Effectiveness of the Orsiro Sirolimus Eluting Coronary Stent System in Subjects With Coronary Artery Lesions [BIOFLOW-V]; NCT02389946) (J Am Coll Cardiol 2018;■:■–■) © 2018 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ISSN 0735-1097 https://doi.org/10.1016/j.jacc.2018.09.019

ABBREVIATIONS AND ACRONYMS

BP SES = bioresorbable polymer sirolimus-eluting stent

CI = confidence interval

CK-MB = creatine kinase-myocardial band

CMH = Cochran-Mantel-Haenszel

DES = drug-eluting stent(s)

DP EES = durable polymer everolimus-eluting stent

MACE = major adverse cardiac events

MI = myocardial infarction

RR = relative risk

TLF = target lesion failure

TLR = target lesion revascularization

The persistence of adverse events associated with both first-generation and contemporary-generation permanent polymer drug-eluting stents (DES) has motivated iterative developments in stent technology that have included new metal alloys, changes in stent architecture, and bioresorbable polymers. Bioresorbable polymer DES were developed with the intent to control antiproliferative drug release during simultaneous (or subsequent) dissolution of the polymer material, thereby eliminating the stimulus for chronic inflammation that may be associated with impaired healing, progressive neointimal proliferation, and neoatherosclerosis (1-6).

The BIOFLOW V trial (Biotronik Prospective Randomized Multicenter Study to Assess the Safety and Effectiveness of the Orsiro Sirolimus Eluting Coronary Stent System in the Treatment of Subjects with Up to Three De Novo or Restenotic Coronary Artery Lesions V) was an international, randomized study comparing clinical outcomes among patients undergoing percutaneous coronary revascularization with an ultrathin-strut (60 μm) bioresorbable polymer sirolimus-eluting stent (BP SES) (Orsiro, Biotronik, Bülach, Switzerland) or contemporary thin-strut (81 μm) durable polymer everolimus-eluting stent (DP EES) (Xience, Abbott Vascular, Santa Clara, California) (7). At 1 year, significant differences were observed favoring treatment with BP SES regarding the primary endpoint of target lesion failure (TLF) (6.0% vs. 10.0%; p = 0.04) and target vessel-related myocardial infarction (MI) (5.0% vs. 8.0%; p = 0.02) (8). Further, in a pooled analysis with 2 additional randomized trials comparing these stents (9,10), the Bayesian posterior probability of noninferiority for BP SES was 100%, and the posterior probability of superiority was 97%.

Whether late-term outcomes differ between alternative bioresorbable and permanent polymer DES has been inconsistently demonstrated in previous studies. Specific to the BIOFLOW V trial, a focus of attention is directed to whether benefits observed at 1 year with BP SES versus DP EES are sustained over longer duration, and might differences emerge regarding other clinical endpoints. To this purpose, we report the pre-specified 2-year safety and efficacy outcomes among patients treated with BP SES and DP EES in the BIOFLOW V trial.

METHODS

STUDY DESIGN AND PATIENT POPULATION. Detailed descriptions of the study design, inclusion and exclusion criteria, methods, and 1-year results of the BIOFLOW V trial have been previously reported (7,8). Briefly, BIOFLOW V (NCT02389946) is a prospective, 2:1 randomized, single-blinded multicenter trial comparing BP SES and DP EES in patients undergoing elective and urgent percutaneous coronary intervention of ≤3 de novo native coronary artery lesions in a maximum of 2 native target vessels. Hemodynamically stable non-ST-segment elevation MI and acute coronary syndrome patients were eligible for enrollment. Angiographic inclusion criteria included a reference vessel diameter between 2.25 and 4.0 mm with lesion length ≤36 mm by visual estimation. Major angiographic exclusions included chronic total occlusions, bifurcations involving a side branch with diameter >2.0 mm, bypass graft stenoses, and DES in-stent restenosis. Calcified lesions requiring atherectomy were permitted following instances of inadequate angioplasty balloon predilation. Patients with recent (<72 h) ST-segment elevation MI, left ventricular ejection fraction <30%, active stent thrombosis, creatinine clearance <30 ml/min, any prior percutaneous coronary intervention within 30 months or within 9 months involving the target vessel, and those unlikely to adhere to dual antiplatelet therapy were also excluded. The study was approved by the institutional review board or ethics committee at each enrolling site, and consecutive, eligible patients signed written informed consent before the interventional procedure.

from Biotronik through the Baim Institute for Clinical Research, for aid with the design of the study. Dr. Doros has been a consultant to Pfizer, Sarepta, Novartis, Softworld, and Lipocine. Dr. Cutlip has received contracted research to his institution from Medtronic and Boston Scientific. Dr. Waksman has received consultant fees from Abbott Vascular, Amgen, Biosensors, Biotronik, Boston Scientific, Corindus, Lifetech Medical, Medtronic, and Philips Volcano; has served on advisory boards for Abbott Vascular, Amgen, Boston Scientific, Medtronic, and Philips Volcano; has received grant support from Abbott Vascular, Biosensors, Biotronik, Boston Scientific, and Edwards Lifesciences; and has served on speakers bureaus for AstraZeneca. Drs. Garcia and Bennett have received research grants from Abbott Vascular and Biotronik AG; and speaking fees from Abbott Vascular, Biotronik AG, Boston Scientific and Terumo. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received September 9, 2018; revised manuscript received September 18, 2018, accepted September 18, 2018.

Clinical events were assessed during hospital stay and 30 days, 6, 12, and 24 months after the index procedure with planned annual follow-up through 5 years. Surveillance angiography in absence of clinical indication was not performed per protocol.

DATA MANAGEMENT. All data were submitted to a central data coordinating facility (Baim Institute for Clinical Research, Boston, Massachusetts). An independent clinical events committee (Baim Institute for Clinical Research,) adjudicated all primary and secondary clinical endpoints blinded to stent type. Further, an independent core laboratory (MedStar Cardiovascular Research Network, Angiographic Core Laboratory, Washington, DC) performed all related angiographic assessments. Biotronik funded the study and participated in site selection and management. An independent group was responsible for study and site management, monitoring and data collection. The authors (D.E.K., G.D., D.E.C., R.W.) had unrestricted access to the data and are responsible for the analyses and drafting of the manuscript.

STUDY ENDPOINTS. The primary endpoint assessment at 2 years was TLF, defined as the composite of cardiac death, target vessel-related MI, or ischemia-driven target lesion revascularization (TLR). Additional pre-specified endpoints include major adverse cardiac events (MACE: all-cause death, MI, or ischemia-driven TLR); target vessel failure (cardiac death, target vessel-related MI, or ischemia-driven target vessel revascularization); the individual components of the composite endpoints; and definite or probable stent thrombosis according to Academic Research Consortium (ARC) criteria (11).

Periprocedural MI was defined according to the modified ARC criteria (11) as a creatine kinase-myocardial band (CK-MB) or troponin measured within 48 h of the interventional procedure elevated >3 times above the upper limit of normal. Spontaneous MI was defined as any CK-MB or troponin elevation above the upper normal limit with associated ischemic symptoms, new electrocardiographic abnormalities suggestive of ischemia, and/or new development of imaging evidence of infarction or regional wall motion abnormalities. Ischemia-driven revascularization was identified as any repeat revascularization of the target lesion or target vessel associated with either: 1) ischemic symptoms and/or an abnormal functional study and a ≥50% coronary stenosis by quantitative angiography; or 2) any revascularization of a ≥70% diameter stenosis. Cardiac death was considered any death due to any proximate cardiac cause, unwitnessed death, or death of unknown etiology.

STATISTICAL ANALYSES. All analyses were performed in the intention-to-treat population, which consisted of all the patients who underwent randomization, regardless of the treatment received. Kaplan-Meier estimates were also used to construct survival curves for time-to-event variables that were compared by means of the log-rank test as well as all endpoints collected over the 0- to 2-year period (Online Appendix).

Baseline characteristics of study patients were summarized in terms of frequencies and percentages for categorical variables and by means with standard deviations for continuous variables. Treatment differences on dichotomous variables were evaluated using Fisher's exact tests. Categorical variables were compared between treatments using the Cochran-Mantel-Haenszel (CMH) Modified Ridit Scores (12), that is, CMH of general association for nominal variables and CMH of row mean score for ordinal variables. Continuous variables were compared between treatments using 2-sample *t*-tests. Additional analyses, including summaries, were conducted using SAS (version 9.4), unless otherwise noted. Proportions were calculated using known nonmissing values. A p value of 0.05 was established as the level of statistical significance.

RESULTS

Among 1,334 patients randomized to treatment with BP SES (884 patients) or DP EES (450 patients), clinical follow-up was complete for 95.9% (n = 848) and 95.1% (n = 428) of patients treated with BP SES and DP EES, respectively. As reported previously, both groups had similar baseline clinical and angiographic characteristics (**Table 1**). There were no significant differences in target lesion length, vessel diameter, or lesion characteristics, with modest, but statistically significant, differences regarding total stent length, number of stents, and prevalence of overlapping stents (**Table 1**).

At 2 years, the significant differences observed at 1 year favoring BP SES regarding composite endpoints of TLF, target vessel failure, and MACE were maintained (**Table 2**, Online Appendix). Specifically, TLF was significantly lower among patients treated with BP SES (7.5% vs. 11.9%; p = 0.015, Kaplan-Meier estimates) (**Table 2, Figure 1**), representing a modest increase in the absolute difference in event rates compared with 1-year events (4.3% at 2 years vs. 3.4% at 1 year). The difference in TLF was driven principally by a significant difference in target vessel-related MI (5.3% vs. 9.5%; p = 0.01) (**Table 2**) in addition to significantly lower ischemia-driven TLR in

TABLE 1 Baseline Clinical, Angiographic, and Procedural Characteristics

	BP SES (n = 884 Subjects n = 1,051 Lesions)	DP EES (n = 450 Subjects n = 561 Lesions)
Age, yrs	64.5 ± 10.3	64.6 ± 10.7
Female	25.3 (224/884)	27.1 (122/450)
Hypertension	79.7 (696/873)	80.5 (354/440)
Hyperlipidemia	78.9 (695/881)	82.4 (370/449)
Diabetes mellitus	34.0 (300/883)	37.0 (166/449)
Insulin-requiring	10.4 (92/883)	11.1 (50/449)
Prior myocardial infarction	27.4 (238/869)	25.9 (115/444)
Prior stroke or TIA	5.5 (49/884)	4.5 (20/448)
Renal disease	7.9 (70/883)	7.6 (34/450)
Prior coronary revascularization	41.0 (360/877)	37.1 (165/445)
Prior PCI	36.8 (323/877)	33.0 (147/445)
Prior CABG	7.1 (62/877)	5.2 (23/445)
Current tobacco use	23.6 (209/884)	22.7 (102/450)
Clinical presentation		
Documented silent ischemia	12.3 (109/884)	13.6 (61/449)
Stable angina	48.4 (428/884)	47.4 (213/449)
Unstable angina	39.3 (347/884)	39.0 (175/449)
Acute coronary syndrome*	51.4 (454/884)	49.6 (223/450)
Target lesion vessel, no./total no. of target lesions		
Left anterior descending	41.0 (431/1,051)	41.2 (231/561)
Left circumflex	26.5 (279/1,051)	26.0 (146/561)
Right	32.4 (341/1,051)	32.8 (184/561)
Angiographic complexity		
Reference vessel diameter, mm	2.59 ± 0.54	2.60 ± 0.58
Lesion length, mm	13.3 ± 7.6	13.2 ± 7.7
Bifurcation lesion	14.8 (156/1,051)	15.0 (84/561)
Thrombus	1.0 (11/1,051)	0.9 (5/561)
Calcification, moderate/severe	24.0 (252/1,051)	26.7 (150/561)
Vessel tortuosity, moderate/severe	58.8 (618/1,051)	61.5 (345/561)
ACC/AHA lesion class B2/C	72.6 (763/1,051)	75.9 (426/561)
Number of target lesions/patient†	1.2 ± 0.4	1.3 ± 0.5
Number of stents/patient†	1.3 ± 0.7	1.5 ± 0.9
Total study stent length, mm†‡	26.8 ± 14.7	29.5 ± 17.5
Patients with overlapping stents†	9.4 (83/884)	15.0 (67/448)
Stent length/lesion	20.8 ± 9.1	21.8 ± 10.5

Values are mean ± SD or % (n/N). Shown are data for patients who were randomized to receive a study stent. *Acute coronary syndrome defined as subjects with unstable angina or any elevated cardiac enzymes at baseline (any pre-procedure creatine kinase [CK], CK-MB, or troponin out of normal range). †Statistically significant differences between groups. Target-lesion characteristics as assessed by an independent angiographic core laboratory. ‡The length of the individual study stents summed per patient.

ACC/AHA = American College of Cardiology/American Heart Association; BP SES = bioresorbable polymer sirolimus-eluting stent; CABG = coronary artery bypass grafting; DP EES = durable polymer everolimus-eluting stent; PCI = percutaneous coronary intervention; TIA = transient ischemic attack.

the BP SES cohort (2.6% vs. 4.9%; p = 0.04, Kaplan-Meier estimates) (Table 2, Figure 1). Between 1 and 2 years, a significant difference in ischemia-driven TLR emerged between BP SES and DP EES (0.7% vs. 2.6%; p = 0.01) (Figure 2). In multivariable analysis, treatment with BP SES favored most pre-specified subgroups regarding the 2-year occurrence of TLF with no significant interactions observed other than age (Figure 3).

The incidence of cardiac death or MI was also lower in the BP SES group versus DP EES (7.0% vs. 10.4%; p = 0.047). As previously reported, the difference in target vessel-related MI at 1 year was principally driven by differences in periprocedural MI, in addition to a trend toward lower spontaneous MI (30 days to 1 year) with BP SES (8). In a landmark analysis of target vessel-related MI beyond 30 days of index revascularization through 2 years, a significantly higher event rate was observed among DP EES-treated patients (0.8% vs. 2.7%; p = 0.01) (Figure 2). Overall, approximately one-third of all late MI events (>30 days) were related to stent thrombosis. Over the entire 2-year period, cumulative rates of both Q-wave (0.1% vs. 1.5%; p = 0.01) and non-Q-wave (5.2% vs. 8.6%; p = 0.02) target vessel-related MI were also higher with DP EES.

Multivariable analyses of 2-year occurrence of TLF, target vessel-related MI, and ischemia-driven TLR were performed. For each endpoint analysis, no clinical, angiographic, or procedural characteristic that differed between groups was identified as a predictor of adverse outcome (Online Appendix).

Adherence to dual antiplatelet therapy at 2 years was approximately 45% in the entire study population and did not statistically differ between treatment groups (45.6% BP SES vs. 45.1% DP EES; p = 0.88). The cumulative incidence of definite and definite/probable stent thrombosis was numerically, but not statistically, lower among patients treated with BP SES (0.5% vs. 1.2%; p = 0.17) (Table 3, Online Appendix). However, combined late and very late rates of both definite and definite/probable stent thrombosis were significantly lower in the BP SES cohort (0.1% vs. 1.0%; p = 0.045 for both comparisons).

DISCUSSION

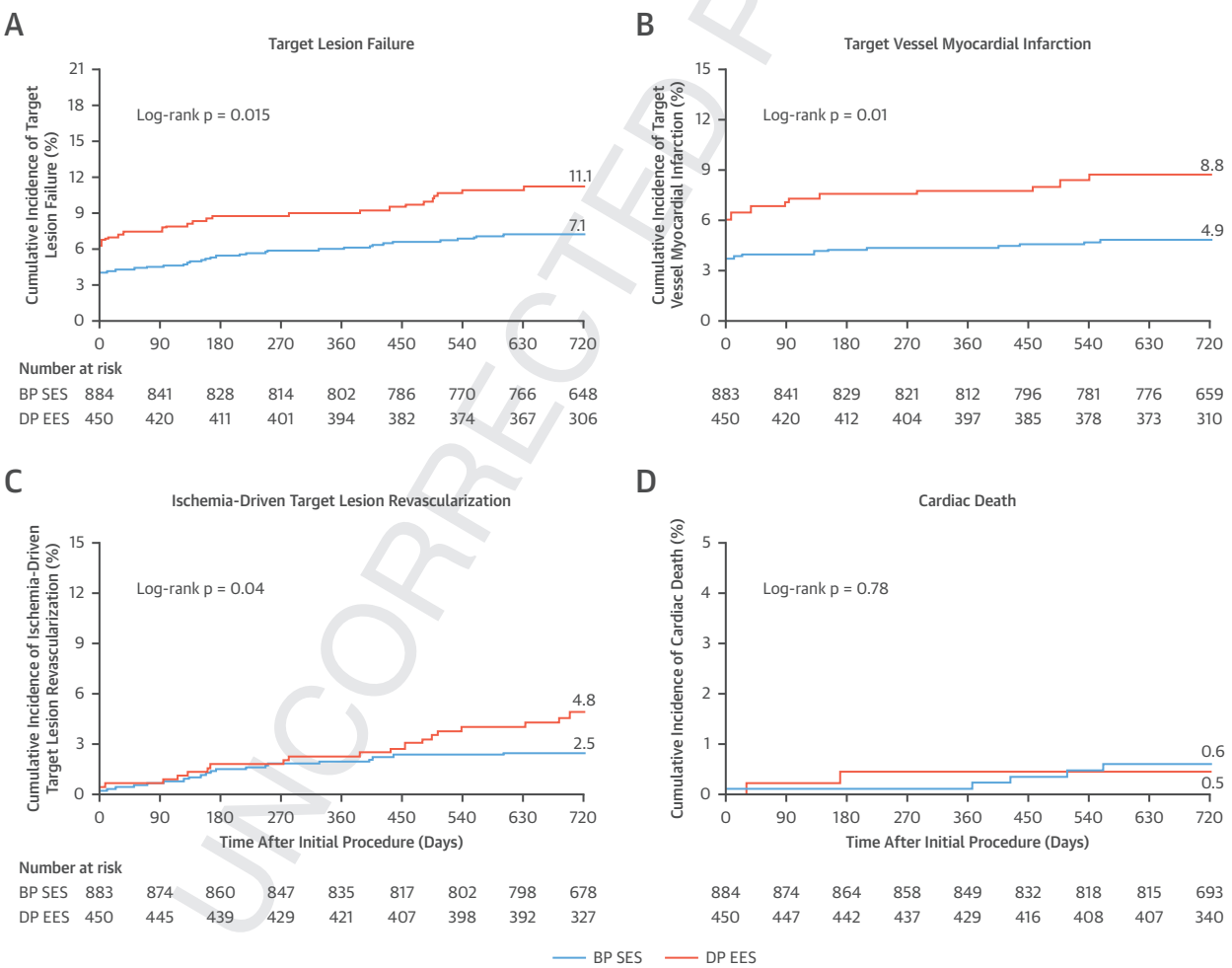
DES design and composition have evolved with specific focus to resolve existing limitations of contemporary stent technology related to late-term safety and efficacy. Until recently, clinical adoption of BP DES has been driven by several previous comparative trials mostly showing clinical parity—but not superiority—to permanent polymer DES (13-18). In the randomized BIOFLOW V trial, however, the occurrence of TLF and target vessel-related MI was significantly lower at 1 year among patients treated with an ultrathin-strut BP SES compared with DP EES (8). The present analysis extends insight to the durability of late-term comparative outcomes with this specific BP SES, further revealing differences in additional safety and efficacy endpoints. Specifically, significant

TABLE 2 2-Year Clinical Outcomes

	BP SES (N = 884)	DP EES (N = 450)	Difference, % (95% CI)	p Value
Target-lesion failure	7.5 (62/823)	11.9 (49/413)	−4.33 (−8.16 to −0.91)	0.015
Cardiac death	0.6 (5/817)	0.5 (2/407)	0.12 (−1.21 to 1.01)	1.00
Target-vessel myocardial infarction	5.3 (43/816)	9.5 (39/410)	−4.24 (−7.73 to −1.21)	0.01
Ischemia-driven target lesion revascularization	2.6 (21/816)	4.9 (20/407)	−2.34 (−5.04 to −0.17)	0.04
Death from any cause	1.9 (16/828)	2.2 (9/414)	−0.24 (−2.29 to 1.32)	0.83
Cardiac death or any myocardial infarction	7.0 (58/823)	10.4 (43/412)	−3.39 (−7.06 to −0.14)	0.047
Major adverse clinical events composite	9.8 (82/835)	13.6 (57/419)	−3.78 (−7.84 to −0.10)	0.046
Target-vessel failure	8.7 (72/823)	13.8 (57/414)	−5.02 (−9.07 to −1.35)	0.01
Ischemia-driven target vessel revascularization	4.4 (36/816)	7.6 (31/409)	−3.17 (−6.38 to −0.44)	0.02

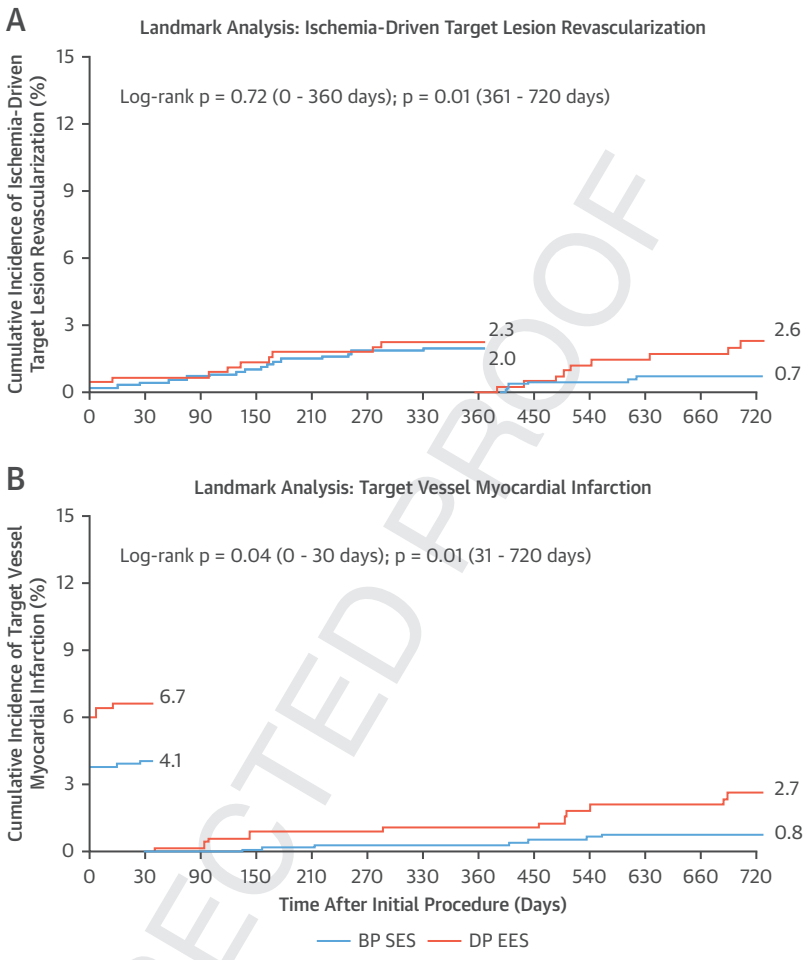
Values are % (n/N) unless otherwise indicated.
CI = confidence interval; other abbreviations as in Table 1.

FIGURE 1 Kaplan-Meier Rates of TLF and Component Endpoints at 2-Year Follow-Up Q3



Kaplan-Meier survival curves comparing BP SES and DP EES for **(A)** target lesion failure, comprising cardiac death, target vessel myocardial infarction, or ischemia-driven target lesion revascularization; **(B)** target vessel myocardial infarction; **(C)** ischemia-driven target lesion revascularization; and **(D)** cardiac death. BP SES = bioresorbable polymer sirolimus-eluting stent; DP EES = durable polymer everolimus-eluting stent; TLF = target lesion failure.

FIGURE 2 Landmark Analysis of TLR and TV MI Through 2 Years

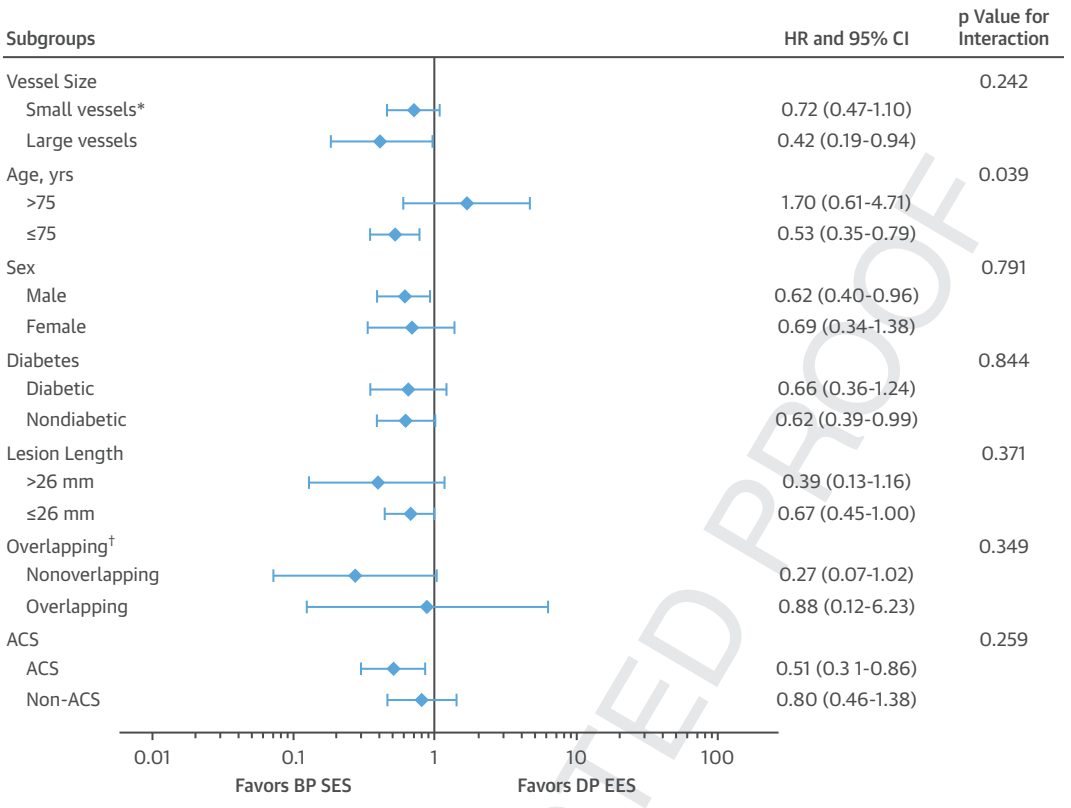


(A) Target lesion revascularization (TLR) from the index revascularization to 1 year and from 1- to 2-year follow-up. **(B)** Target vessel–related myocardial infarction (TV MI) from the index revascularization to 30 days, and from 31 days to 2-year follow-up.

differences in both TLF and target vessel-related MI persisted through 2 years favoring treatment with BP SES over DP EES (**Central Illustration**). In addition, by 2 years, significantly lower ischemia-driven TLR and late/very late stent thrombosis were also observed with BP SES. These results indicate stability in safety and efficacy outcomes beyond the first year of index revascularization with ultrathin-strut BP SES leading to continued and emerging significant differences compared with thin-strut DP EES.

In part a consequence of noninferiority trials, a dilemma presented by current DES studies is the opportunity to differentiate DES relative to infrequent adverse event rates. Because current DES report the most favorable efficacy and safety outcomes to date, endpoint event rates have migrated even lower over the past decade, further limiting the potential to demonstrate incremental benefit with newer stent technologies. Nevertheless, outcomes with current-generation DES have plateaued, presenting the need to reset expectations regarding when and for which endpoints differences may emerge. Although disparities may not occur to the magnitude observed in early studies comparing DES with bare-metal stents, instead DES may be distinguished by meaningful, yet less anticipated endpoints, such as MI rather than late lumen loss or angiographic restenosis. In addition, dedicated longitudinal follow-up in clinical trials

FIGURE 3 Interaction Analysis Between Subgroups and at 2 Years



*Small vessels defined as 2.75 mm or smaller. †Nonoverlapping versus overlapping stents subgroup analysis is only performed on subjects with lesion length >26 mm. ACS = acute coronary syndrome; CI = confidence interval; HR = hazard ratio; other abbreviations as in Figure 1.

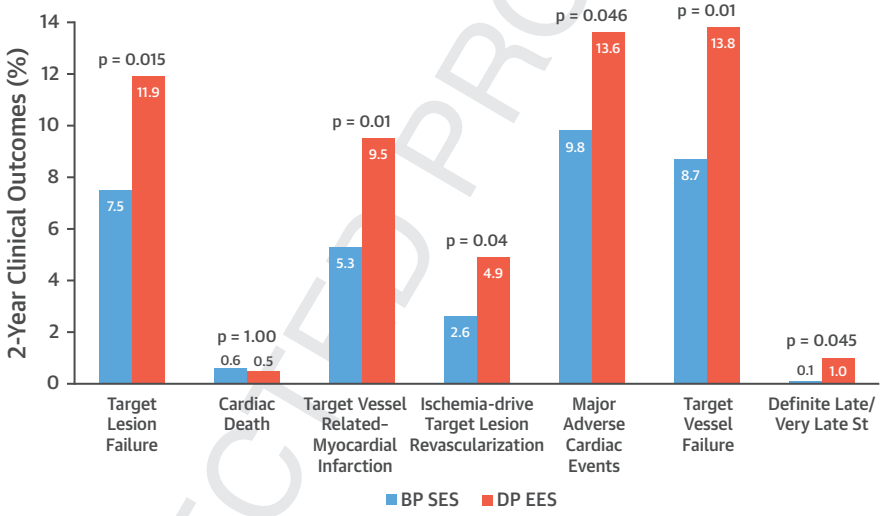
TABLE 3 Stent Thrombosis Events Through 2 Years

	BP SES (N = 884)	DP EES (N = 450)	Difference, % (95% CI)	p Value
Definite ST	0.5 (4/814)	1.2 (5/406)	−0.74 (−2.39 to 0.30)	0.17
Probable ST	0.0 (0/812)	0.0 (0/405)	0.00 (−0.94 to 0.47)	–
Definite/probable ST	0.5 (4/814)	1.2 (5/406)	−0.74 (−2.39 to 0.30)	0.17
Early	0.3 (3/878)	0.2 (1/449)	0.12 (−0.93 to 0.80)	1.00
Acute, ≤24 h	0.1 (1/884)	0.0 (0/450)	0.11 (−0.74 to 0.64)	1.00
Subacute, >24 h and ≤30 days	0.2 (2/878)	0.2 (1/449)	0.01 (−1.04 to 0.63)	1.00
Late, >30 days and ≤1 year	0.1 (1/812)	0.5 (2/405)	−0.37 (−1.66 to 0.30)	0.26
Very late, >1 year and ≤2 years	0.0 (0/812)	0.5 (2/405)	−0.49 (−1.78 to 0.10)	0.11
Any late/very late ST	0.4 (3/814)	1.2 (5/406)	−0.86 (−2.50 to 0.14)	0.13
Definite late/very late ST	0.1 (1/812)	1.0 (4/405)	−0.86 (−2.39 to −0.03)	0.045
Possible late/very late ST	0.2 (2/814)	0.2 (1/406)	0.00 (−0.94 to 0.47)	1.00
Probable late/very late ST	0.0 (0/812)	0.0 (0/405)	−0.00 (−1.15 to 0.68)	–
Definite/probable late/very late ST	0.1 (1/812)	1.0 (4/405)	−0.86 (−2.39 to −0.03)	0.045

Values are % (n/N). Stent thrombosis events reported per Academic Research Consortium criteria (11).
ST = stent thrombosis; other abbreviations as in Tables 1 and 2.

CENTRAL ILLUSTRATION **Comparison of an Ultrathin-Strut Bioresorbable Polymer Sirolimus-Eluting Stent and a Thin-Strut Durable Polymer Everolimus-Eluting Stent: Summary of 2-Year Outcomes**

Patients With Coronary Artery Disease That Qualify For Percutaneous Coronary Intervention With Stenting (N = 1334 Randomized)		
Stent model	Bioresorable Polymer Sirolimus-Eluting Stents (BP SES) (N = 884)	Durable Polymer Everolimus-Eluting Stents (DP EES) (N = 450)
Stent material‡§	L-605 Cobalt-Chromium	L-605 Cobalt-Chromium
Antiproliferative drug‖	Sirolimus (1.4 μg/mm^2), >80% eluted in first 90 days	Everolimus (100 μg/cm^2), 100% drug release within 4 months



Kandzari, D.E. et al. J Am Coll Cardiol. 2018;■(■):■–■.

*For 2.25-mm to 3.0-mm diameter stents, thin struts for >3.0-mm diameter stents. †Statistically significant. ‡BP SES Instructions for Use. §DP SES Instructions for Use. ‖Kandzari et al. (8). Target lesion failure includes cardiac death, target vessel-related myocardial infarction, or ischemia-driven target lesion revascularization. Major adverse cardiac events include all-cause death, myocardial infarction (Q-wave or non-Q-wave), and any ischemia-driven target lesion revascularization. Target vessel failure includes cardiac death, target vessel myocardial infarction or ischemia-driven target vessel revascularization. BP SES = bioresorbable polymer sirolimus-eluting stent; DP SES = durable polymer everolimus-eluting stent.

offers greater insight to the effectiveness of DES, and the accrual of events may amplify the ability to distinguish outcomes between therapies. Detailed ascertainment of events over longer duration permits insight not only to annualized estimates of stent thrombosis but also the persistence of late target lesion revascularization that seems constant with existing DES (19-22).

In the BIOFLOW V trial, the significant difference in the 1-year composite TLF endpoint was principally driven by a lower risk of target vessel-related MI associated with BP SES compared with DP EES (8). In particular, a significant difference in procedural-related MI was observed favoring BP SES, yet a trend toward lower spontaneous MI events (>30 days from index revascularization through 1 year) was also identified. Through 2 years, however, both overall and spontaneous target vessel-related MI event rates were significantly lower in the BP SES cohort, including significant differences in both target vessel non-Q-wave MI and Q-wave MI. Further, statistically significant differences in late/very late stent thrombosis emerged also favoring BP SES, with 1 late event

(133 days) and no very late events in the BP SES cohort.

These findings are largely consistent with recent comparative studies of ultrathin-strut DES and contemporary thin-strut DES. Specifically, thinner stent struts may permit accelerated endothelialization, reduce inflammation and arterial injury, and decrease neointimal proliferation and thrombogenicity (23). Thinner strut thickness has also been attributed to reduced side branch coverage that may translate to lower periprocedural MI (23,24). Indeed, the transition of stent design from stainless steel (132 μm to 140 μm) to chromium alloys (81 μm to 91 μm) has been associated with approximate 40% to 80% reductions in both procedural-related and late-term MI (25–29). In the present study, a further 20-μm strut thickness difference between BP SES and DP EES is associated with an approximate 45% reduction in target vessel-related MI. Similar to the BIOFLOW V trial, the BioMime DES (Meril Life Sciences, Vapi, India; 65-μm strut thickness) was associated with significantly lower risk of MI compared with the thin-strut Xience permanent polymer DES in the meriT-V trial (30). In the SORT OUT VII (Sirolimus Eluting ORSIRO Stent Versus Biolimus-eluting NOBORI Stent) trial, definite stent thrombosis at 12 months was significantly lower with the Orsiro BP SES than with a biolimus-eluting bioresorbable polymer drug-eluting stent (0.4% vs. 1.2%; $p = 0.03$) having a strut thickness approximately 2 times greater than the BP SES (Nobori, Terumo Corporation, Japan), although statistical significance did not persist at 2 years (31,32). Altogether, in a meta-analysis of randomized trials comparing ultrathin-strut BP DES with contemporary-generation thin-strut DES (10 trials, $N = 11,658$), revascularization with ultrathin-strut DES was associated with significant reductions in TLF (relative risk [RR]: 0.84; 95% confidence interval [CI]: 0.72 to 0.99) and MI (RR: 0.80; 95% CI: 0.65 to 0.99) and numerically lower stent thrombosis (RR: 0.72; 95% CI: 0.51 to 1.01) (33).

In addition to MI and stent thrombosis events, a lower rate of repeat TLR through 2 years observed with BP SES in this trial also aligns with recent clinical study. Notably, in the BIOFLOW V trial, rates of ischemia-driven TLR at 1 year were similar between stent groups, yet a significant difference in late TLR beyond 1 year favoring BP SES emerged. Similarly, in a landmark analysis of events from 1 to 2 years follow-up in the BIO-RESORT trial, significant differences in both TLF and TLR emerged between 1 and 2 years comparing the BP SES and the durable polymer zotarolimus-eluting stent (Resolute Integrity; Medtronic, Dublin, Ireland; strut thickness 90 μm) (34). These findings from both trials are hypothesis-generating given that lower TLR rates over late-term surveillance may represent additional benefit of very thin-strut stents (35,36) and/or polymer resolution and absence of stimulus for neointimal hyperplasia and atherosclerotic disease progression that has been observed with permanent polymers (1,3,37,38). Nevertheless, inconsistency across comparative trials and over differential time periods is evident. Through 5-year follow-up in the BIOSCIENCE (Sirolimus-eluting Stents With Biodegradable Polymer Versus an Everolimus-eluting Stents) trial, for example, no significant differences in major cardiovascular events were observed between patients randomized to treatment with BP SES or DP SES (39). Such variance between trials is challenging to interpret but may be related in part or entirely to differences in patient and lesion complexity, endpoint definitions, and event adjudication or other unmeasured variables related to trial conduct and/or patient treatment.

STUDY LIMITATIONS. Although statistical significance was demonstrated across both composite and individual endpoints, the BIOFLOW V study was not designed as a superiority trial, and statistical power is limited for comparison of selected endpoints. Further, whether the benefit observed with BP SES is isolated to a specific design feature or multifactorial remains uncertain. This observation is particularly relevant given that 1-year differences in TLF and MI emerged during a period before complete polymer dissolution, and stent thrombosis and TLR leveled after 1 year in comparison to progression with the durable polymer, thin-strut EES. A class effect among bioresorbable polymer DES also cannot be assumed; in the EVOLVE II trial (The EVOLVE II Clinical Trial To Assess the SYNERGY Stent System for the Treatment of Atherosclerotic Lesion[s]), for example, no significant differences in outcome were observed at 1 year or even late-term follow-up between a bioresorbable polymer and durable polymer everolimus-eluting stents, although differences in strut thickness between these two stent platforms is less distinct (74 μm vs. 81 μm) (18,40). Therefore, the results of the present study suggest a new focus for DES development relative not only to design an ultrathin-strut stent but to further elucidate the contribution of bioresorbable polymers.

CONCLUSIONS

Through 2 year's follow-up in the randomized BIOFLOW V trial, significant differences in both TLF and target vessel-related MI persisted favoring treatment

with an ultrathin-strut BP SES over a contemporary-generation thin-strut DP EES. By 2 years, significantly lower cumulative TLR was also observed with BP SES, driven by significant differences in late TLR between 1 and 2 years compared with DP EES. Finally, significantly lower late/very late stent thrombosis was identified among patients treated with BP SES. Altogether, these findings affirm the durability of late-term comparative outcomes with this specific BP SES, further revealing differences in additional safety and efficacy endpoints. The results not only advance a standard of comparison for new DES but also direct attention to strut thickness and polymer composition as key features for iterative DES development.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Through 2 years' follow-up, differences in both target lesion failure and target vessel-related myocardial infarction favor use of ultrathin bioresorbable polymer sirolimus-eluting coronary stents over contemporary thin strut durable polymer everolimus-eluting stents. Similar advantages extend to rates of cumulative target lesion revascularization and late stent thrombosis.

TRANSLATIONAL OUTLOOK: Longer-term studies are needed to confirm the relative safety and effectiveness of ultrathin strut bioresorbable polymer sirolimus-eluting coronary stents in this and other clinical settings.

REFERENCES

1. Kuriyama N, Kobayashi Y, Nakama T, et al. Late restenosis following sirolimus-eluting stent implantation. J Am Coll Cardiol Intv 2011;4:123–8.

2. Guagliumi G, Sirbu V, Musumeci G, et al. Examination of the in vivo mechanisms of late drug-eluting stent thrombosis. J Am Coll Cardiol Intv 2012;5:12–20.

3. Nakazawa G, Otsuka F, Nakano M, et al. The pathology of neoatherosclerosis in human coronary implants: bare-metal and drug-eluting stents. J Am Coll Cardiol 2011;57:1314–22.

4. Otsuka F, Vorpahl M, Nakano M, et al. Pathology of second-generation everolimus-eluting stents versus first-generation sirolimus- and paclitaxel-eluting stents in humans. Circulation 2014;129:211–23.

5. Otsuka F, Yahagi K, Ladich E, et al. Hypersensitivity reaction in the US Food and Drug Administration–approved second-generation drug-eluting stents: histopathological assessment with ex vivo optical coherence tomography. Circulation 2015;131:322–4.

6. Otsuka F, Byrne RA, Yahagi K, et al. Neoatherosclerosis: overview of histopathologic findings and implications for intravascular imaging assessment. Eur Heart J 2015;36:2147–59.

7. Doros G, Massaro JM, Kandzari D, et al. Rationale and design of the BIOFLOW V study, a prospective randomized multicenter study to assess the safety and effectiveness of the Orsiro sirolimus-eluting coronary stent system in the treatment of subjects with up to three de novo or restenotic coronary artery lesions. Am Heart J 2017;193:35–45.

8. Kandzari DE, Mauri L, Koolen JJ, et al. Ultrathin, bioresorbable polymer sirolimus-eluting stents versus thin, durable polymer everolimus-eluting stents in patients undergoing coronary revascularisation (BIOFLOW V): a randomised trial. Lancet 2017;390:1843–52.

9. Windecker S, Haude M, Neumann FJ, et al. Comparison of a novel biodegradable polymer sirolimus-eluting stent with a durable polymer everolimus-eluting stent: results of the randomized BIOFLOW II trial. Circ Cardiovasc Interv 2015;8:e001441.

10. Saito S. First European DES in Japan: Orsiro with ultrathin strut shows excellent data in clinical studies and bench test. Paper presented at: 81st Annual Scientific Meeting of the Japanese Circulation Society; March 2017; Kanzawa, Japan.

11. Cutlip DE, Windecker S, Mehran R, et al., for the Academic Research Consortium. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation 2007;115:2344–51.

12. van Elteren PH. On the combination of independent two-sample tests of Wilcoxon. Bull Int Stat Inst 1960;37:351–61.

13. Windecker S, Serruys PW, Wandel S, et al. Biolimus-eluting stent with biodegradable polymer versus sirolimus-eluting stent with durable polymer for coronary revascularisation (LEADERS): a randomised non-inferiority trial. Lancet 2008;372:1163–73.

14. Byrne RA, Kastrati A, Kufner S, et al. Randomized, non-inferiority trial of three limus agent-eluting stents with different polymer coatings: the Intracoronary Stenting and Angiographic Results: Test Efficacy of 3 Limus-Eluting Stents (ISAR-TEST-4) trial. Eur Heart J 2009;30:2441–9.

15. Smits PC, Hofma MT, Vazquez N, et al. Abluminal biodegradable polymer biolimus-eluting stent versus durable polymer everolimus-eluting stent (COMPARE II): a randomized, controlled, non-inferiority trial. Lancet 2013;381:651–60.

16. Natsuaki M, Kozuma K, Morimoto T, et al. Biodegradable polymer biolimus-eluting stent versus durable polymer everolimus-eluting stent: a randomized, controlled, noninferiority trial. J Am Coll Cardiol 2013;62:181–90.

17. Pilgrim T, Heg D, Roffi M, et al. Ultrathin strut biodegradable polymer sirolimus-eluting stent versus durable polymer everolimus-eluting stent for percutaneous coronary revascularisation (BIOSCIENCE): a randomised, single-blind, non-inferiority trial. Lancet 2014;384:2111–22.

18. Kereiakes DJ, Meredith IT, Windecker S, et al. Efficacy and safety of a novel bioabsorbable polymer-coated, everolimus-eluting coronary stent: the EVOLVE II randomized trial. Circ Cardiovasc Interv 2015;8:e002372.

19. Claessen BE, Beijk MA, Legrand V, et al. Two-year clinical, angiographic, and intravascular ultrasound follow-up of the XIENCE V everolimus-eluting stent in the treatment of patients with de novo native coronary artery lesions. The SPIRIT II trial. Circ Cardiovasc Intervent 2009;2:339–47.

20. Gada H, Kirtane AJ, Newman W, et al. Five-year results of a randomized comparison of XIENCE V everolimus-eluting and TAXUS paclitaxel-eluting stents: final results from the SPIRIT III trial. J Am Coll Cardiol Intv 2013;6:1263–6.

21. Iqbal J, Serruys PW, Silber S, et al. Comparison of zotarolimus- and everolimus-eluting coronary stents. Final 5-year report of the RESOLUTE all-comers trial. Circ Cardiovasc Intervent 2015;8:e002230.

22. Smits PC, Vlachojannis GJ, McFadden EP, et al. Final 5-year follow-up of a randomized controlled trial of everolimus- and paclitaxel-eluting stents for coronary revascularization in daily practice: the COMPARE trial. J Am Coll Cardiol Intv 2015;8:1157–65.

23. Kolandaivelu K, Swaminathan R, Gibson WJ, et al. Stent thrombogenicity early in high- risk interventional settings is driven by stent design and deployment and protected by polymer-drug coatings. Circulation 2011;123:1400–9.

24. Kawamoto H, Panoulas VF, Sato K, et al. Impact of strut width in periprocedural myocardial infarction: a propensity-matched comparison between bioresorbable scaffolds and the first-generation sirolimus-eluting stent. J Am Coll Cardiol Intv 2015;8:900–9.

25. Kandzari DE, Leon MB, Popma JJ, et al., for the ENDEAVOR III Investigators. Comparison of zotarolimus-eluting and sirolimus-eluting stents in patients with native coronary artery disease. J Am Coll Cardiol 2006;48:2440–7.

26. Stone GW, Midei M, Newman W, et al., for the SPIRIT III Investigators. Comparison of an everolimus-eluting stent and a paclitaxel-eluting stent in patients with coronary artery disease: a randomized trial. JAMA 2008;299:1903–13.

27. Leon MB, Mauri L, Popma JJ, et al. A randomized comparison of the Endeavor zotarolimus-eluting stent versus the TAXUS paclitaxel-eluting stent in de novo native coronary lesions. J Am Coll Cardiol 2010;55:543–54.

28. Kandzari DE, Leon MB, Meredith I, Fajadet J, Wijns W, Mauri L. Final 5-year outcomes from the Endeavor zotarolimus-eluting stent clinical trial program. J Am Coll Cardiol Intv 2013;6:504–12.

29. Stone GW, Rizvi A, Newman W, et al., for the SPIRIT IV Investigators. Everolimus-eluting versus paclitaxel-eluting stents in coronary artery disease. N Engl J Med 2010;362:1663–74.

30. Botelho R. Outcomes with a thin-strut PLLA-based sirolimus-eluting stent: Biomime. Paper presented at: TCT 2017; October 31, 2017; Denver CO. Available at: https://www.tctmd.com/slide/outcomes-thin-strut-plla-based-sirolimus-eluting-stent-1-biomime. Accessed August 22, 2018.

31. Jensen LO, Thayssen P, Maeng M, et al. Randomized comparison of a biodegradable polymer ultrathin strut sirolimus-eluting stent with a biodegradable polymer biolimus-eluting stent in patients treated with percutaneous coronary intervention: the SORT OUT VII trial. Circ Cardiovasc Interv 2016;9:e003610.

32. Jensen LO, Maeng M, Raungaard B, et al. Two-year outcome after biodegradable polymer sirolimus- and biolimus-eluting coronary stents (from the randomised SORT OUT VII trial). EuroIntervention 2018;13:1587–90.

33. Bangalore S, Toklu B, Patel N, Feit F, Stone GW. Newer generation ultra-thin strut drug-eluting stents versus older second-generation thicker strut drug-eluting stents for coronary artery disease: a meta-analysis of randomized trials. Circulation 2018 June 26 [E-pub ahead of print].

34. Kok MM, Zocca P, Buiten RA, et al. Two-year clinical outcome of all-comers treated with three highly dissimilar contemporary coronary drug-eluting stents in the randomised BIO-RESORT trial. EuroIntervention 2018;14:915–23.

35. Kastrati A, Mehilli J, Dirschinger J, et al. Intracoronary stenting and angiographic results: strut thickness effect on restenosis outcome (ISAR-STEREO) trial. Circulation 2001;103:2816–21.

36. Pache J, Kastrati A, Mehilli J, et al. Intracoronary stenting and angiographic results: strut thickness effect on restenosis outcome (ISAR-STEREO-2) trial. J Am Coll Cardiol 2003;41:1283–8.

37. Koppara T, Joner M, Bayer G, et al. Histopathological comparison of biodegradable polymer and permanent polymer based sirolimus eluting stents in a porcine model of coronary stent implantation. Thromb Haemost 2012;107:1161–71.

38. Räber L, Wohlwend L, Wigger M, et al. Five-year clinical and angiographic outcomes of a randomized comparison of sirolimus-eluting and paclitaxel-eluting stents: results of the Sirolimus-Eluting Versus Paclitaxel-Eluting Stents for Coronary Revascularization LATE trial. Circulation 2011;123:2819–28.

39. Pilgrim T, Piccolo R, Heg D, et al. Ultrathin-strut, biodegradable-polymer, sirolimus-eluting stents versus thin-strut, durable-polymer, everolimus-eluting stents for percutaneous coronary revascularization: 5-year outcomes of the BIOSCIENCE randomised trial. Lancet 2018;392:737–46.

40. Kereiakes DJ, Meredith I, Windecker S, et al. Three-year results from the EVOLVE II randomized trial: late clinical outcomes with bioresorbable compared to permanent polymer everolimus-eluting stents (abstr). J Am Coll Cardiol 2017;69 Suppl:970.

KEY WORDS bioresorbable polymer, drug-eluting stent, percutaneous coronary intervention, sirolimus

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