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Biodegradable Polymer Biolimus-Eluting Stents Versus Durable Polymer Everolimus-Eluting Stents in Patients With Coronary Artery Disease

Final 5-Year Report From the COMPARE II Trial (Abluminal Biodegradable Polymer Biolimus-Eluting Stent Versus Durable Polymer Everolimus-Eluting Stent)

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ABSTRACT

OBJECTIVES This analysis investigates the 5-year outcomes of the biodegradable polymer biolimus-eluting stent (BP-BES) and durable polymer everolimus-eluting stent (DP-EES) in an all-comers population undergoing percutaneous coronary intervention.

BACKGROUND Recent 1- and 3-year results from randomized trials have indicated similar safety and efficacy outcomes of BP-BES and DP-EES. Whether benefits of the biodegradable polymer device arise over longer follow-up is unknown. Moreover, in-depth, prospective, long-term follow-up data on metallic drug-eluting stents with durable or biodegradable polymers are scarce.

METHODS The COMPARE II trial (Abluminal Biodegradable Polymer Biolimus-Eluting Stent Versus Durable Polymer Everolimus-Eluting Stent) was a prospective, randomized, multicenter, all-comers trial in which 2,707 patients were randomly allocated (2:1) to BP-BES or DP-EES. The pre-specified endpoint at 5 years was major adverse cardiac events, a composite of cardiac death, nonfatal myocardial infarction, or target vessel revascularization.

RESULTS Five-year follow-up was available in 2,657 patients (98%). At 5 years, major adverse cardiac events occurred in 310 patients (17.3%) in the BP-BES group and 142 patients (15.6%) in the DP-EES group ($p = 0.26$). The rate of the combined safety endpoint all-cause death or myocardial infarction was 15.0% in the BP-BES group versus 14.8% in the DP-EES group ($p = 0.90$), whereas the efficacy measure target vessel revascularization was 10.6% versus 9.0% ($p = 0.18$), respectively. Interestingly, definite stent thrombosis rates did not differ between groups (1.5% for BP-BES vs. 0.9% for DP-EES; $p = 0.17$).

CONCLUSIONS The 5-year analysis comparing biodegradable polymer-coated BES and the durable polymer-coated EES confirms the initial early- and mid-term results regarding similar safety and efficacy outcomes in this all-comers percutaneous coronary intervention population. (J Am Coll Cardiol Intv 2017;10:1215–21)

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ABBREVIATIONS AND ACRONYMS

BES = biolimus-eluting stent(s)

BP-BES = biodegradable polymer biolimus-eluting stent(s)

DES = drug-eluting stent(s)

DP-EES = durable polymer everolimus-eluting stent(s)

EES = everolimus-eluting stent(s)

MACE = major adverse cardiac event(s)

MI = myocardial infarction

PCI = percutaneous coronary intervention

SES = sirolimus-eluting stent(s)

STEMI = ST-segment elevation myocardial infarction

TVR = target vessel revascularization

Different approaches have been applied to address the risk of very late adverse events such as stent thrombosis in patients treated with permanent polymer drug-eluting coronary devices. One innovation was to replace the permanent polymer responsible for the drug release of the drug-eluting stent (DES) platform with a biodegradable polymer, because durable polymers of first-generation DES have been linked to enduring inflammatory response at implantation site that might lead to delayed re-endothelialization, late-acquired malapposition, and neointimal proliferation (1-3).

Early results from randomized trials have underlined the safety benefits of biodegradable polymer-coated DES when compared with first-generation DES in terms of a significant reduction in very late stent thrombosis events and associated composite clinical outcomes, including the primary endpoint cardiac death, myocardial infarction (MI), and clinically indicated target vessel revascularization (TVR) (4).

The purpose of the COMPARE II (Abluminal Biodegradable Polymer Biolimus-Eluting Stent Versus Durable Polymer Everolimus-Eluting Stent; NCT01233453) trial was to compare the biodegradable polymer-coated biolimus-eluting stent (BP-BES) (Nobori, Terumo, Tokyo, Japan) to the newer-generation durable polymer-coated everolimus-eluting stent (DP-EES) (Xience V or Prime, Abbott Vascular, Santa Clara, California, or Promus, Boston Scientific, Natick, Massachusetts) in an all-comers percutaneous coronary intervention (PCI) population. Initial early- and mid-term reports from the COMPARE II and NEXT (NOBORI Biolimus-Eluting Versus XIENCE/PROMUS Everolimus-eluting Stent Trial) trials showed similar outcomes of BP-BES compared with DP-EES up to 3 years (5-7). However, potential benefits of the BP-BES are expected over a long-term period. The present analysis displays the final 5-year results of the COMPARE II trial.

METHODS

The COMPARE II trial is an investigator-initiated, multicenter, open-label, randomized, all-comers trial that assigned patients undergoing PCI in a 2:1 fashion to either biolimus-eluting stents (BES) (316L stainless steel stent with 120-μm strut thickness coated abluminally with biodegradable polymer poly-lactic acid, eluting the drug Biolimus A9/Nobori, Terumo) or everolimus-eluting stents (EES) (cobalt or platinum chromium metallic stent with a strut thickness of 81 μm coated with a durable fluoropolymer, eluting the drug everolimus/Xience V or Xience Prime, Abbot Vascular, or Promus, Boston Scientific, respectively). Patients were followed for 5 years after index procedure. A detailed description of study and procedural methodologies has been published previously (6).

The study complied with the CONSORT 2010 Statement of Declaration of Helsinki and was approved by all the institutional ethics committees of all participating centers. Patients were evaluated at 1, 6, 12, 24, 36, and 60 months at the outpatient clinic or by post, e-mail, or telephone regarding medication regime and adverse events; whenever required, general practitioners, medical specialists, or hospitals were contacted to collect further information. The study protocol-pre-specified composite endpoint at 5 years was major adverse cardiac events (MACE) defined as cardiac death, nonfatal MI, or TVR.

STATISTICAL ANALYSIS. The study was designed as a noninferiority trial at 1 year (6). The current analysis at 5-year follow-up, including subgroup analysis across clinically relevant subgroups, was pre-specified as secondary endpoint per protocol. Categorical variables are presented as numbers and percentages, and were compared with the Fisher exact test, due to the low prevalence of some baseline variables. Continuous variables were expressed as mean ± SD or median (interquartile range). Continuous variables were compared using the Wilcoxon rank sum test. All analyses were performed according to the intention-to-treat principle. Time to the respective endpoint was analyzed according to the Kaplan-Meier method and the log-rank test was applied to compare the incidence of endpoints between groups. The landmark analysis used the 1-year landmark, thus patients who had experienced the event of interest during the first year following index procedure were excluded from analysis.

All p values were 2-sided, and a p value of <0.05 was regarded as statistically significant. SAS version 8.02 (SAS Institute, Cary, North Carolina) was used for analysis.

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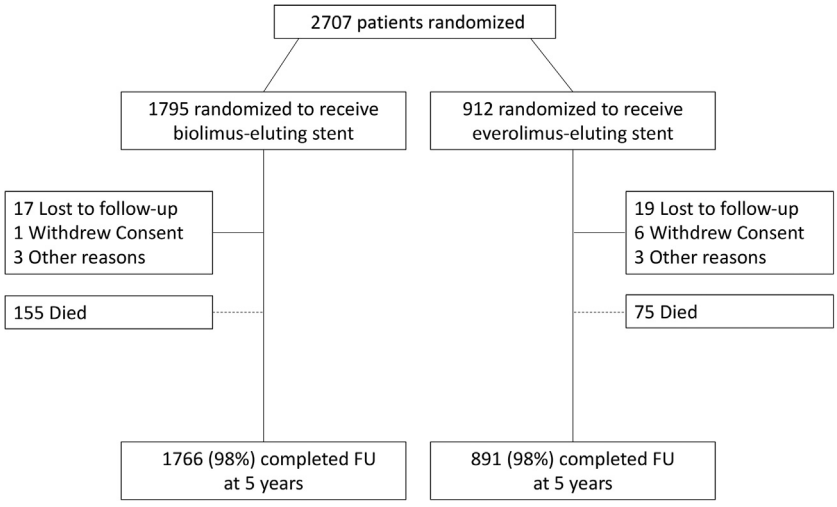
FIGURE 1 Study Flow Chart



FU = follow-up.

RESULTS

In total, 2,707 patients (4,025 lesions) undergoing PCI were randomized 2:1 to BP-BES (1,795 patients with 2,638 treated lesions) or DP-EES (912 patients with 1,387 treated lesions) (Figure 1). Clinical follow-up was available for 1,776 patients in the BP-BES group (98%) and 891 patients in the DP-EES group (98%). Detailed characteristics for baseline clinical, angiographic, and procedural features have been previously presented (6). Table 1 summarizes the main patient baseline and lesion characteristics, which were well-balanced between groups. In brief, the prevalence of diabetes was 22%. Overall, 58% presented with an acute coronary syndrome. The complexity of coronary lesions was comparable between groups and is described according to the American Heart Association/American College of Cardiology classification.

CLINICAL OUTCOMES. Five-year event rates are detailed in Table 2. The pre-specified composite outcome of MACE (cardiac death, nonfatal MI, or TVR) was similar between groups and occurred in 310 patients (17.3%) in the BP-BES group and 142 patients (15.6%) in the EES group (relative risk: 1.11 [95% confidence interval: 0.92 to 1.33]; p = 0.26). Other safety and efficacy endpoints including stent thrombosis, cardiac death, or MI as well as the device-oriented endpoint target lesion failure were similar between groups.

TABLE 1 Baseline Patient and Lesion Characteristics

	BES (n = 1,795)	EES (n = 912)	p Value
Age (yrs)	63.0 ± 11.1	62.7 ± 11.0	0.37
Male	74.4 (1,336/1,795)	74.3 (678/912)	0.96
Diabetes mellitus	21.8 (391/1,795)	21.6 (197/912)	0.92
Hypertension	54.8 (983/1,795)	56.3 (513/912)	0.49
Current smoker	30.8 (553/1,794)	27.4 (250/912)	0.07
Previous MI	20.3 (362/1,785)	18.8 (170/906)	0.36
Previous PCI	17.8 (320/1,795)	17.0 (155/912)	0.63
Previous CABG	5.9 (105/1,795)	5.7 (52/912)	0.93
Stable angina	38.9 (699/1,795)	38.9 (355/912)	1.00
Silent ischemia	3.2 (57/1,795)	3.3 (30/912)	0.91
ACS	57.9 (1039/1,795)	57.8 (527/912)	0.97
Unstable angina	10.8 (194/1,795)	9.7 (88/912)	0.39
Non-ST-segment elevation MI	26.4 (474/1,795)	26.5 (242/912)	0.96
ST-segment elevation MI	20.7 (371/1,795)	21.6 (197/912)	0.58
Multivessel treatment	25.2 (452/1,795)	25.2 (230/912)	1.00
Number of lesions treated per patient	1.5 ± 0.8	1.5 ± 0.9	0.36
At least 1 lesion length ≥20 mm	29.4 (403/1,373)	32.7 (224/686)	0.13
At least 1 RVD <2.75 mm	37.9 (513/1,355)	37.2 (253/680)	0.81
Number of lesions	2,638	1,387	
Lesion length (mm)	16.8 ± 9.8	17.7 ± 10.6	0.03
Reference vessel diameter (mm)	2.9 ± 0.4	2.9 ± 0.5	0.63
Stents per lesion	1.4 ± 0.8	1.4 ± 0.8	0.98
Type B2 lesion	33.3 (879/2,638)	32.4 (449/1,387)	0.55
Type C lesion	30.4 (801/2,638)	30.9 (428/1,387)	0.75
Bifurcation lesion	6.4 (169/2,638)	6.5 (90/1,387)	0.95
Thrombus present	21.2 (560/2,638)	21.2 (294/1,387)	1.00
Chronic total occlusion	3.0 (79/2,638)	2.7 (38/1,387)	0.69

Values are mean ± SD or % (n/N assessed).

ACS = acute coronary syndrome; BES = biolimus-eluting stent(s); CABG = coronary artery bypass grafting; EES = everolimus-eluting stent(s); MI = myocardial infarction; PCI = percutaneous coronary intervention; RVD = reference vessel diameter.

TABLE 2 Events at 5 Years

	BES (n = 1,795)	EES (n = 912)	Relative Risk (BES/EES) (95% CI)	p Value
MACE*	17.3 (310)	15.6 (142)	1.11 (0.92–1.33)	0.26
All-cause death	8.6 (155)	8.2 (75)	1.05 (0.81–1.37)	0.72
Cardiac death	4.6 (82)	3.9 (36)	1.16 (0.79–1.70)	0.45
Myocardial infarction	7.6 (137)	7.0 (64)	1.09 (0.82–1.45)	0.56
Any revascularization	15.8 (283)	15.2 (139)	1.03 (0.86–1.25)	0.72
Target vessel revascularization (all)	10.6 (191)	9.0 (82)	1.18 (0.93–1.51)	0.18
Target vessel revascularization (CD)	9.1 (164)	8.1 (74)	1.13 (0.87–1.46)	0.37
Target lesion revascularization (all)	7.9 (142)	7.1 (65)	1.11 (0.95–1.47)	0.47
Target lesion revascularization (CD)	6.4 (115)	5.4 (49)	1.19 (0.74–1.55)	0.29
Definite stent thrombosis	1.5 (27)	0.9 (8)	1.71 (0.78–3.76)	0.17
Early definite stent thrombosis	0.6 (11)	0.3 (3)	1.86 (0.52–6.66)	0.33
Late definite stent thrombosis	0.1 (2)	0.1 (1)	1.02 (0.09–11.19)	0.99
Very late definite stent thrombosis	0.8 (14)	0.4 (4)	1.78 (0.59–5.39)	0.30
Def. or prob. stent thrombosis	1.7 (30)	1.6 (15)	1.02 (0.55–1.88)	0.96
Early def. or prob. stent thrombosis	0.6 (11)	0.8 (7)	0.80 (0.31–2.05)	0.64
Late def. or prob. stent thrombosis	0.2 (3)	0.2 (2)	0.76 (0.13–4.55)	0.77
Very late def. or prob. stent thrombosis	0.9 (16)	0.7 (6)	1.35 (0.53–3.45)	0.52
All-cause death or myocardial infarction	15.0 (269)	14.8 (135)	1.01 (0.84–1.23)	0.90
Target lesion failure†	13.4 (240)	11.5 (105)	1.16 (0.94–1.44)	0.17
Target vessel failure‡	15.2 (272)	12.9 (118)	1.17 (0.96–1.43)	0.12
POCE§	24.6 (441)	24.1 (220)	1.02 (0.88–1.17)	0.80

Values are % (n assessed). Lower and upper limits of the risk ratio represent the 95% confidence interval (CI). *A composite of cardiac death, nonfatal MI, and target vessel revascularization. †A composite of cardiac death, nonfatal target vessel–related MI, and clinically driven target lesion revascularization. ‡Defined as a composite of cardiac death, nonfatal target vessel–related MI, and clinically driven target vessel revascularization. §Defined as all-cause mortality, any MI, any repeat revascularization.

CD = clinically driven; def. or prob. = definite or probable; MACE = major adverse cardiac event(s); MI = myocardial infarction; POCE = patient-oriented composite endpoint; other abbreviations as in Table 1.

The Kaplan-Meier time-to-event curve for the endpoint MACE is shown in Figure 2.

The 1-year landmark analysis showed no significant differences in incremental event rates between 1 and 5-year follow-up (Table 3).

The comparable clinical outcome between stent groups regarding the efficacy endpoint TVR held true over a wide range of subgroups with the exception of the ST-segment elevation MI (STEMI) subgroup, in which DP-EES had significantly lower rates of TVR compared with BP-BES (p for interaction = 0.04) (Figure 3). Of note, no differences were observed regarding dual antiplatelet therapy adherence between groups through the 5-year follow-up (data not shown).

DISCUSSION

The present analysis is the first to our knowledge to report 5-year outcomes comparing biodegradable polymer and exclusively second-generation DES. The principle finding of the current analysis is that biodegradable polymer-coated BES showed a similar safety and efficacy profile at 5 years compared with the gold standard durable polymer-coated EES (Xience or Promus). Moreover, landmark analysis did not indicate any benefit of BP-BES over DP-EES in terms of safety or efficacy beyond the first treatment year. The pre-specified endpoint MACE and the efficacy measures target lesion revascularization and TVR were similar between groups at 5 years.

DES with biodegradable polymer have been developed to combine the best of both worlds, that is, the efficacy of DES and the late safety associated with bare-metal stents. However, no benefit in safety measures, including cardiac death, MI, or stent thrombosis, was observed in patients treated with BP-BES compared with DP-EES. By contrast, although differences were not statistically significant, and the trial was not powered to detect differences in single outcomes such as cardiac death, MI, and stent thrombosis, we observed consistently numerically lower rates of these safety measures in the DP-EES group.

Network meta-analyses have indicated an excess risk of biodegradable polymer DES with regard to MI or stent thrombosis when compared with DP-EES, though these analyses were restricted due to limited follow-up duration and heterogeneity of devices in the BP-DES group (8-10). Of note, whereas the meta-analyses by Kang et al. (8) and Navarese et al. (10) included BP-BES trials using the Biosensors BioMatrix device (Biosensors International, Singapore), which is similar to the Nobori stent, the meta-analysis of Bangalore et al. (9) also included trials using a sirolimus-eluting stent (SES) with biodegradable polymer (Yukon Choice PC, Translumina, Hechingen, Germany).

In the present study, the 5-year definite stent thrombosis rate in the DP-EES group is 0.9%, thus, within the range of previously reported DP-EES all-comers trials, such as the SORT OUT IV (Randomized Clinical Comparison of the Xience V and the Cypher Coronary Stents in Non-selected Patients With Coronary Heart Disease) trial (0.4%) and COMPARE I trial (A Trial of Everolimus-Eluting Stents and Paclitaxel Stents for Coronary Revascularization in Daily Practice) (1.8%) (7,11). By contrast, 5-year clinical outcome data do not exist for Nobori BP-DES. However, 5-year data on other biodegradable polymer DES can be derived from the ISAR-TEST 4 (Intracoronary Stenting and Angiographic Results: Test Efficacy of 3 Limus-Eluting Stents) and LEADERS (Limus Eluted From a Durable Versus Erodable Stent Coating) trials (4,12). In the ISAR-TEST 4 trial, the definite stent thrombosis rate at 5 years was 0.7%, whereas in the LEADERS trial, it was 2.6%. Moreover, the LEADERS trial, as well as a pooled long-term follow-up analysis of 3 randomized trials—including the ISAR-TEST 4 trial—showed a significant reduction in very late stent thrombosis with biodegradable polymer DES compared with first-generation durable polymer SES

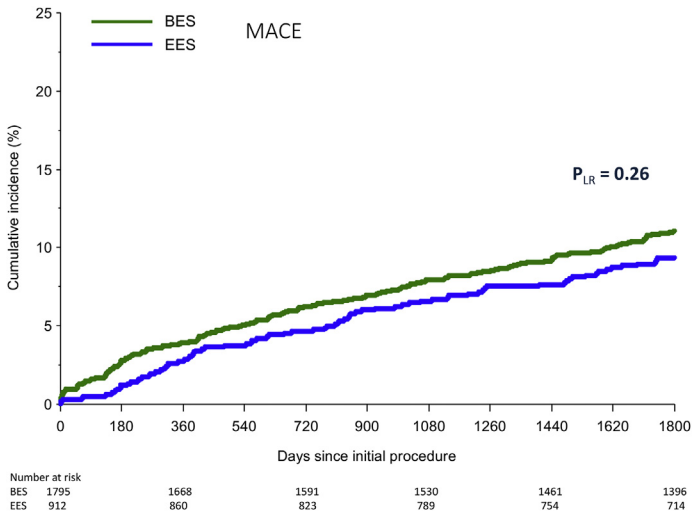
(13). Importantly, the biodegradable polymer DES used in this study is not the same, but similar to, the stent used in the LEADERS trial (Biomatrix, Biosensor) and different to the one used in the ISAR-TEST 4 trial (Yukon Choice PC), thus limiting further interstudy comparability.

Of note, subgroup analysis showed lower rates of TVR in STEMI patients treated with DP-EES compared with BP-BES. This result should be viewed as hypothesis generating. Long-term data on biodegradable polymer DES for treatment of STEMI are scarce. A recent pooled analysis showed superior clinical outcomes at 4 years of biodegradable polymer DES when compared to first-generation DES in STEMI (14). In this line, the COMFORTABLE AMI (Comparison of Biolimus Eluted From an Erodible Stent Coating With Bare Metal Stents in Acute ST-Elevation Myocardial Infarction) trial showed at 2 years superior outcomes with BP-BES compared with bare-metal stents in STEMI, with a planned study follow-up of 5 years (15). However, there are no long-term comparative data on STEMI between biodegradable polymer DES and current-generation durable polymer DES.

The concept of biodegradable polymer-coated DES is based on the potential benefits in safety beyond the first treatment year after drug elution and polymer breakdown, leaving merely the bare-metal stent platform in the vessel. Indeed, when compared with first-generation SES with durable polymer, implantation of biodegradable polymer DES has been allied with more complete re-endothelialization as well as preserved endothelium-dependent vasomotion (1,16,17). However, a recent randomized comparison of BP-BES (Nobori) and DP-EES (Xience) based on intravascular optical coherence tomography analysis reported similar stent coverage and apposition at 6 to 8 months (18). This result supports the increased safety measures observed with DP-EES in this and other randomized studies, as well as in meta-analyses (8,19,20). In this line, the prospect of BP-DES to demonstrate clinical benefits is hampered by the excellent outcomes of the DP-EES.

The present results regarding the Nobori BP-BES cannot be generalized to other stent systems using biodegradable polymers because the performance of a device depends on interaction between the drug and its elution characteristics, the biodegradable polymer properties, and the stent platform. Further research is warranted to determine whether other biodegradable polymer technologies with faster polymer resorption and newer thin-strut stent platforms are adding advantages in safety and efficacy outcomes when compared with current-generation thin-strut DES with durable polymer.

FIGURE 2 Kaplan-Meier Cumulative Event Curve for MACE



P_{LR} indicates p value using the log-rank test. BES = biolimus-eluting stent(s); EES = everolimus-eluting stent(s); MACE = major adverse cardiac event(s).

Finally, at 5 years, approximately one-fourth of all the PCI patients reached the patient-oriented composite endpoint (death, MI, or any revascularization), with more than one-half of these events being attributable to target lesion failures. This fact signposts the importance of further efforts in improving treatment options in this patient population.

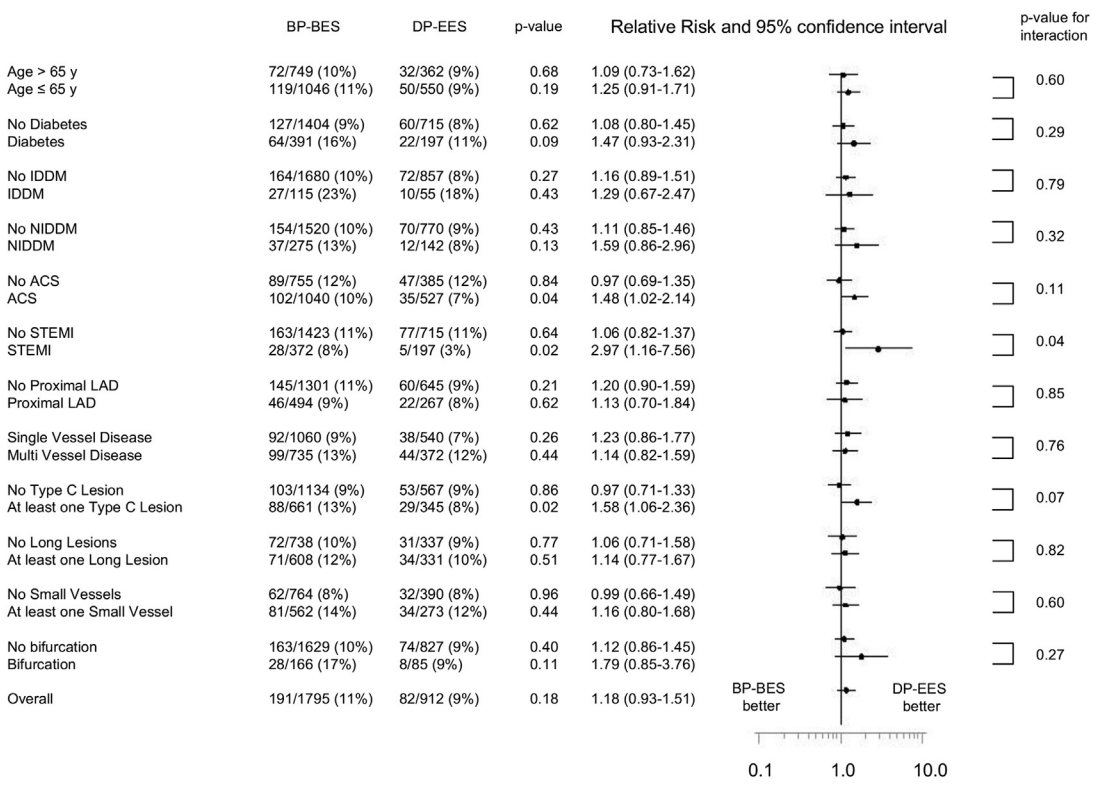
TABLE 3 Adverse Events Occurring Between 1 and 5 Years

	BES	EES	Relative Risk (BES/EES) (95% CI)	p Value
MACE*	12.1 (201)	11.3 (97)	1.07 (0.85-1.34)	0.60
All-cause death	7.3 (128)	7.3 (66)	0.99 (0.74-1.32)	0.94
Cardiac death	3.8 (67)	3.2 (29)	1.18 (0.77-1.81)	0.51
Myocardial infarction	5.0 (86)	4.7 (41)	1.07 (0.75-1.54)	0.77
Target vessel revascularization (all)	7.1 (121)	6.5 (57)	1.09 (0.81-1.48)	0.62
Target lesion revascularization (all)	5.3 (91)	4.9 (43)	1.08 (0.76-1.54)	0.71
Definite stent thrombosis	0.8 (14)	0.4 (4)	1.79 (0.59-5.42)	0.45
Def. or prob. stent thrombosis	0.9 (16)	0.7 (6)	1.36 (0.53-3.46)	0.65
Target lesion failure†	9.5 (161)	8.2 (71)	1.16 (0.89-1.52)	0.28
Target vessel failure‡	10.8 (182)	9.2 (80)	1.17 (0.91-1.50)	0.24
POCE§	17.8 (291)	18.2 (153)	0.98 (0.82-1.16)	0.78

Values are % (n assessed). Lower and upper limits of the risk ratio represent the 95% confidence interval. Only patients who were event-free at 1 year for the outcome of interest were entered into the landmark analysis. *A composite of cardiac death, nonfatal MI, and target vessel revascularization. †A composite of cardiac death, nonfatal target vessel-related MI. and clinically driven target lesion revascularization. ‡Defined as a composite of cardiac death, nonfatal target vessel related-MI, and clinically driven target vessel revascularization. §Defined as all-cause mortality, any MI, any repeat revascularization.

Abbreviations as in Tables 1 and 2.

FIGURE 3 Post Hoc Subgroup Analysis for TVR



ACS = acute coronary syndrome; BP-BES = biodegradable polymer biolimus-eluting stent(s); DP-EES = durable polymer everolimus-eluting stent(s); IDDM = insulin-dependent diabetes mellitus; LAD = left anterior descending coronary artery; NIDDM = noninsulin-dependent diabetes mellitus; STEMI = ST-segment elevation myocardial infarction; TVR = target vessel revascularization.

STUDY LIMITATIONS. Although designed as an all-comers study, only 26% of patients undergoing percutaneous interventions were enrolled in the study, so selection bias cannot be ruled out. The power of the present study was attenuated by the lower than expected event rates of the primary endpoints used for sample size calculation (6). Secondly, we report on a secondary endpoint, and testing of the primary endpoint at multiple time points other than the specified 1-year primary endpoint is subject to the perils of multiple testing.

CONCLUSIONS

This final 5-year analysis of the COMPARE II trial confirms the early- and mid-term results of similar safety and efficacy outcomes of the BP-BES and the DP-EES. In view of the similar clinical outcomes, BP-BES do not indicate any benefits, in particular towards reduction of very late adverse events, thus challenging the concept of biodegradable polymer coating. Whether newer-generation biodegradable polymer stent platforms support proof of concept of the biodegradable polymer technology needs to be investigated.

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PERSPECTIVES

WHAT IS KNOWN? Initial long-term results indicated reduced very late stent thrombosis rates of biodegradable polymer DES when compared with first-generation DES with durable polymer. However, whether biodegradable polymer technology adds benefits at long-term follow-up when compared with current generation durable polymer DES is unknown.

WHAT IS NEW? The early- and mid-term results of similar safety and efficacy outcomes of the biodegradable polymer-coated BES (Nobori) and the durable polymer-coated EES (Xience or Promus) were confirmed at this 5-year analysis. Interestingly, no benefit toward very late adverse events including stent thrombosis was seen in the biodegradable polymer BES group, thus challenging the concept of biodegradable polymer coating.

WHAT IS NEXT? Future studies will further investigate whether biodegradable polymer technology used with newer-generation stent platforms can improve DES safety and efficacy when compared with best-in-class durable polymer DES.

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KEY WORDS biodegradable polymer-coated stent(s), biolimus-eluting stent(s), everolimus-eluting stent(s), Nobori, Promus, Xience

APPENDIX For a list of participating centers and investigators, please see the online version of this article.