Circulation

ORIGINAL RESEARCH ARTICLE

Ten-Year Clinical Outcomes From a Trial of Three Limus-Eluting Stents With Different Polymer Coatings in Patients With Coronary Artery Disease

Results From the ISAR-TEST 4 Randomized Trial

Editorial, see p 334

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BACKGROUND: New-generation drug-eluting stents offer the potential for enhanced late outcomes in comparison with early generation drug-eluting stents. However, assessment of extended long-term outcomes for these devices is lacking, especially regarding the comparison between new-generation drug-eluting stents with biodegradable or permanent polymers. The aim of this study is to compare the efficacy and safety of biodegradable polymer-based sirolimus-eluting stents (BP-SES; Yukon Choice PC) versus permanent polymer-based everolimus-eluting stents (PP-EES; Xience) versus early generation permanent polymer-based sirolimus-eluting stents (PP-SES; Cypher) at 10-year follow-up.

METHODS: Overall, 2603 patients were randomized to treatment with BP-SES (n=1299), PP-EES (n=652), or PP-SES (n=652). The primary end point of this analysis was major adverse cardiac event, the composite of death, myocardial infarction, or target lesion revascularization. The main secondary end point of interest was definite/probable stent thrombosis. Follow-up at 10 years was available in 83% of the study patients.

RESULTS: The 10-year incidence of major adverse cardiac event (BP-SES 47.7% versus PP-EES 46.0% versus PP-SES 54.9%, *P*=0.003) and mortality (BP-SES 31.8% versus PP-EES 30.3% versus PP-SES 37.2%, *P*=0.02) was different among the groups. Definite/probable stent thrombosis was not significantly different among the groups (BP-SES 1.8% versus PP-EES 2.5% versus PP-SES 3.7%, *P*=0.09). Definite stent thrombosis was significantly different among the groups (BP-SES 1.1% versus PP-EES 0.8% versus PP-SES 2.4%, *P*=0.03). There were no significant differences between BP-SES and PP-EES.

CONCLUSIONS: In this unique long-term outcome analysis, BP-SES and PP-EES showed comparable clinical outcomes out to 10 years. PP-SES had higher rates of major adverse cardiac events and definite stent thrombosis.

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ORIGINAL RESEARCH ARTICLE

Clinical Perspective

What Is New?

- In this unique long-term outcome analysis, we were able to show superiority of biodegradable polymer-based sirolimus-eluting stents (Yukon Choice PC) and permanent polymer-based everolimus-eluting stents (Xience) versus early generation permanent polymer-based sirolimus-eluting stents (Cypher), with increasing treatment effect over a 10-year follow-up.

What Are the Clinical Implications?

- The absence of significant differences between biodegradable polymer-based sirolimus-eluting stents and permanent polymer-based everolimus-eluting stents over a 10-year time horizon means that meaningful clinical differences between the devices are unlikely to exist.
- Sustained accrual of events with early generation DES means that intensified secondary prevention and surveillance of patients treated with these devices are warranted.

The development of drug-eluting stents (DES) represented a significant milestone in the battle against restenosis after percutaneous coronary intervention.[1] Early generation DES offered improved efficacy compared with bare-metal stents. Worldwide, millions of patients were treated with early generation DES between 2003 and 2011. However, the high antirestenotic efficacy of early generation DES occurred at the collateral cost of late adverse events, including late/very late stent thrombosis and late target lesion revascularization, which continue to occur years after implantation.[2,3]

New-generation DES with improved stent designs and more biocompatible biodegradable or permanent polymers offer the potential of enhanced late clinical outcomes compared with early generation DES. Although clinical outcomes out to 5 years were favorable regarding the occurrence of very late stent thrombosis,[4–6] long-term data failed to show a significant advantage of new-generation DES in terms of late clinical events, especially those not related to thrombotic events.[7–9] Moreover, although the benefit of new-generation DES—particularly with biodegradable polymer—is expected to occur over time, currently available data on clinical outcome beyond 5 years are scant. Indeed, extended long-term follow-up data, up to 10 years, of new-generation DES with different polymer coating strategies remain a notable scientific gap.

In the present analysis, we report the 10-year outcomes from patients enrolled in the ISAR-TEST 4 trial (Intracoronary Stenting and Angiographic Results: Test Efficacy of 3 Limus-Eluting Stents) and randomly allocated to treatment with either biodegradable polymer-based sirolimus-eluting stents (BP-SES) versus permanent polymer-based everolimus-eluting stents (PP-EES) versus permanent polymer-based sirolimus-eluting stents (PP-SES).

METHODS

The data, analytic methods, and study materials will be made available to other researchers for purposes of reproducing the results or replicating the procedure. The data are available from the corresponding author on reasonable request.

Between September 2007 and August 2008, patients >18 years of age with ischemic symptoms or evidence of myocardial ischemia (inducible or spontaneous) in the presence of ≥50% de novo stenosis located in native coronary vessels were enrolled at 2 centers in Munich, Germany, provided that written informed consent by the patient or her or his legally authorized representative for participation in the study was obtained. Patients with a target lesion located in the left main stem or in cardiogenic shock were considered ineligible for the study. Full details of the study population, methods, end points, and primary analysis have been previously reported.[7,10] Patients were randomly allocated to receive a new-generation BP-SES (Yukon Choice PC, Translumina, Hechingen, Germany and Translumina Therapeutics, Dehradoon, India), a new-PP-EES (Xience, Abbott Vascular, Abbott Park, IL) or an early generation PP-SES (Cypher, Cordis Corporation, Miami Lakes, FL) in a 2:1:1 allocation. Description of stent platforms and elution characteristics have been reported elsewhere.[7,11,12] The aim of the current study was to compare outcomes of patients treated with BP-SES versus PP-EES versus PP-SES after 10-year follow-up.

The primary end point of this analysis was major adverse cardiac event, the composite of death, myocardial infarction, or target lesion revascularization. The main secondary end point of interest was definite/probable stent thrombosis. Stent thrombosis was classified according to the Academic Research Consortium criteria.[13]

Follow-Up and Analysis

Patients were systematically evaluated at 1 and 12 months and annually out to 120 months. Extended follow-up was performed in the setting of routine care by either telephone calls or office visits in the 2 participating centers. The study was conducted in accordance with the provisions of the Declaration of Helsinki and with the International Conference on Harmonization Good Clinical Practices. All patients had given their written informed consent to the trial protocol. Analysis of data from extended follow-up, which was not prespecified within the study protocol, was approved by the institutional ethics committee responsible for the participating centers. Additional written informed consent from patients was waived because of the routine availability of patient follow-up data. All events were adjudicated and classified by an event adjudication committee blinded to the treatment groups.

Statistical Analysis

Continuous data are presented as mean (±SD) or median (25th–75th percentiles). Categorical data are presented as

counts and proportions (%). Unless otherwise stated, differences among groups regarding baseline, angiographic, and procedural data were checked for significance using ANOVA test (continuous data) and χ^2 or Fisher exact test (categorical variables). Survival was analyzed according to Kaplan–Meier methods, and hazard ratios were calculated using Cox proportional hazards model after checking for fulfillment of the proportional hazards assumption by the method of Grambsch and Therneau.[14] The analysis of myocardial infarction, target lesion revascularization, and stent thrombosis also accounted for the competing risk of death. The analysis of the primary end point accounted for the presence of multiple group comparisons by choosing a CI of 0.983 instead of 0.95. Because the analysis of the additional end point was only of an exploratory nature, it did not account for multiple group comparisons. Patient age, sex, and diabetes mellitus status were prespecified subgroups of interest for analysis of the primary outcome. Overall, the *P* value for interaction was obtained by entering an interaction term between the treatment groups and the variable defining the subgroup into the Cox proportional hazards model. All analyses were by intention to treat using all patients randomized in the study. In view of the absence of crossover, additional per protocol analysis was of no relevance to the current study. Statistical analysis was performed by using the R 3.5.1 Statistical Package (R Foundation for Statistical Computing). For the competing risk analysis in particular, the cmprsk package was used. For among-group comparisons regarding the primary end point, the statistical significance was set at an adjusted 2-sided *P* value <0.017 (accounting for 3-group comparisons). For all other comparisons, a 2-sided *P* value <0.05 was considered to indicate statistical significance.

RESULTS

A total of 2603 patients were randomized to receive BP-SES (n=1299), PP-EES (n=652), or PP-SES (n=652). The study enrolled a large proportion of patients with advanced age; there was a high prevalence of diabetes mellitus and multivessel disease. More than one third of the study population presented with acute coronary syndrome. Baseline patient and lesion characteristics according to the 3 treatment groups were well balanced and are shown in Table 1.

Median follow-up interval of the entire study cohort was 10.6 years (25th–75th percentiles: 9.4–11.4 years). Ten-year clinical follow-up was not available in 450 patients (17.3%) without difference among the 3 groups (BP-SES 228 patients [17.6%] versus PP-EES 116 patients [17.8%] versus PP-SES 106 patients [16.3%], *P*=0.72). In patients without complete follow-up out to 10 years, median follow-up interval was 5.9 years (25th–75th percentiles: 4.0–7.3 years). The last follow-up contact was an office visit in 32.8% and a telephone interview in 67.2% of the patients, respectively, without difference among the 3 groups (*P*=0.26). Detailed patient follow-up data are displayed in Figure I in the online-only Data Supplement.

At last follow-up contact, aspirin was prescribed in 89.5% of the overall study cohort. There was no difference among the 3 study groups concerning aspirin therapy (BP-SES 89.7% versus PP-EES 88.4% versus PP-SES 90.0%, *P*=0.59). P2Y12 inhibitors were prescribed in 10.3% of the overall study cohort. There was no difference among the 3 study groups concerning P2Y12 inhibitor therapy (BP-SES 9.2% versus PP-EES 11.9% versus PP-SES 10.8%, *P*=0.58). Clopidogrel was the most frequently prescribed P2Y12 inhibitor (clopidogrel 8.9% versus prasugrel 0.6% versus ticagrelor 0.9%). Dual antiplatelet therapy was prescribed in 7.8% of the overall study cohort.

Clinical results are summarized in Table 2. At 10 years, the incidence of the primary end point was significantly different across the treatment groups (BP-SES 47.7% versus PP-EES 46.0% versus PP-SES 54.9%, *P*=0.003). Both new-generation DES showed significantly lower event rates compared with early generation DES (BP-SES versus PP-SES: hazard ratio, 0.82; 98.3% CI, 0.69–0.96; PP-EES versus PP-SES: hazard ratio, 0.79; 98.3% CI, 0.65–0.96). Event rates of new-generation BP-SES compared with new-generation PP-EES were similar (BP-SES versus PP-EES: hazard ratio, 1.04; 98.3% CI, 0.87–1.24) (Figure, A). Kaplan–Meier curves and the results of landmark analysis from 0 to 5 and 5 to 10 years according to the primary end point are displayed in Figure IIA in the online-only Data Supplement.

The results concerning the primary end point were consistent across the prespecified subgroups of age ($P_{interaction}$=0.85), sex ($P_{interaction}$=0.64), and diabetes mellitus status ($P_{interaction}$=0.75). Hazard ratios regarding the comparison of BP-SES versus PP-SES, PP-EES versus PP-SES, and BP-SES versus PP-SES across the prespecified subgroups are displayed in Figure III in the online-only Data Supplement.

At 10-year follow-up, 1827 patients (70.2%) were alive. Mortality rates were significantly different among the 3 groups (BP-SES 31.8% versus PP-EES 30.3% versus PP-SES 37.2%, *P*=0.02). Both new-generation DES showed significantly lower mortality rates compared with early-generation DES (BP-SES versus PP-SES: hazard ratio, 0.82; 95% CI, 0.70–0.97; PP-EES versus PP-SES: hazard ratio, 0.78; 95% CI, 0.64–0.95). Mortality rates of patients receiving new-generation BP-SES were similar with that of patients receiving new-generation PP-EES (BP-SES versus PP-EES: hazard ratio, 1.05; 95% CI, 0.88–1.26). Kaplan–Meier curves are displayed in Figure, B. Kaplan–Meier curves and the results of landmark analysis from 0 to 5 and 5 to 10 years are displayed in Figure 2B in the online-only Data Supplement.

Fewer cardiac deaths occurred with both new-generation DES compared with early generation DES (BP-SES 19.9% versus PP-EES 18.2% versus PP-SES 23.0%, *P*=0.12), although this difference was not significant.

Table 1. Baseline Patient and Lesion Characteristics, by Treatment Group

Characteristics	BP-SES	PP-EES	PP-SES	*P* Value
Patients	(n=1299)	(n=652)	(n=652)	
Age, y, mean±SD	66.7±11.1	66.7±10.3	66.8±11.1	0.96
Male sex	978 (75.3)	507 (77.8)	495 (75.8)	0.48
Diabetes mellitus	376 (28.9)	184 (28.2)	193 (29.6)	0.86
Insulin dependent	108 (8.3)	60 (9.2)	62 (9.5)	0.63
Arterial hypertension	897 (69.1)	442 (67.8)	439 (67.3)	0.43
Hyperlipidemia	868 (66.8)	423 (64.9)	423 (64.9)	0.58
Current smoker	202 (15.6)	101 (15.5)	114 (17.5)	0.50
Prior myocardial infarction	372 (28.6)	191 (29.3)	182 (27.9)	0.86
Prior coronary artery bypass grafting	129 (9.9)	69 (10.6)	60 (9.2)	0.71
Clinical presentation				0.37
ST-segment elevation myocardial infarction	167 (12.9)	70 (10.7)	70 (10.7)	
Non-ST-segment elevation acute coronary syndrome	374 (28.8)	199 (30.5)	180 (27.6)	
Stable angina	758 (58.4)	383 (58.7)	402 (61.7)	
Ejection fraction, %	53.1±11.9	53.4±11.7	53.8±12.1	0.57
Multilesion intervention	375 (28.9)	174 (26.7)	166 (25.6)	0.25
1-vessel disease	175 (13.5)	95 (14.6)	83 (12.7)	
2-vessel disease	357 (27.5)	182 (27.9)	189 (29.0)	
3-vessel disease	767 (60.1)	375 (59.1)	380 (58.3)	
Multivessel disease	1124 (86.5)	557 (85.4)	557 (87.3)	0.62
Lesions	(n=1683)	(n=850)	(n=839)	
Target-vessel location				0.88
Left anterior descending artery	753 (44.7)	372 (43.8)	376 (44.8)	
Left circumflex artery	454 (27.0)	223 (26.2)	230 (27.4)	
Right coronary artery	476 (28.3)	255 (30.0)	233 (27.8)	
Chronic total occlusion	89 (5.3)	36 (4.2)	50 (6.0)	0.27
Bifurcation	421 (25.0)	185 (21.8)	198 (23.6)	0.19
Ostial	267 (15.9)	158 (18.6)	146 (17.4)	0.21
Complex morphology (B2/C)	1225 (72.8)	604 (71.1)	614 (73.2)	0.56
Lesion length, mm	14.8±8.8	15.2±8.9	14.8±8.2	0.55
Vessel size, mm	2.79±0.52	2.80±0.45	2.80±0.48	0.89
Minimum lumen diameter, mm				
Before procedure	0.98±0.51	0.99±0.49	0.97±0.51	0.78
Post procedure	2.58±0.50	2.59±0.44	2.59±0.45	0.69
Percent stenosis, %				
Before procedure	65.0±16.0	64.8±16.0	65.4±16.1	0.79
After procedure	23.2±11.7	23.6±11.4	23.3±10.8	0.76

Values are n (%) or mean (±SD) unless otherwise indicated. BP-SES indicates biodegradable polymer-based sirolimus-eluting stent; PP-EES permanent polymer-based everolimus-eluting stent; and PP-SES, permanent polymer-based-sirolimus-eluting stent.

The incidence of myocardial infarction at 10 years was low and comparable among the 3 groups (BP-SES 7.7% versus PP-EES 7.9% versus PP-SES 9.1%, *P*=0.85). Both new-generation BP-SES and PP-EES showed numerically lower event rates compared with early generation DES without statistical difference (BP-SES versus PP-SES: hazard ratio, 0.90; 95% CI, 0.64–1.28; PP-EES versus PP-SES: hazard ratio, 0.92; 95% CI, 0.62–1.38). New-generation BP-SES compared with new-generation PP-EES showed comparable results (BP-SES versus PP-EES: hazard ratio, 0.98; 95% CI, 0.69–1.4).

Regarding antirestenotic efficacy, target lesion revascularization rates at 10 years were comparable in all 3 groups (BP-SES 20.3% versus PP-EES 18.2% versus PP-SES 22.5%, *P*=0.15). Both new-generation

Table 2. Clinical Outcomes Out to 10 Years, Hazard Ratios, by Treatment Group

Event	BP-SES (n=1299)	PP-EES (n=652)	PP-SES (n=652)	Overall *P* Value	BP-SES vs PP-SES	PP-EES vs PP-SES	BP-SES vs PP-EES
Major adverse cardiac event	575 (47.7)	279 (46.0)	336 (54.9)	0.003	0.82 (0.69–0.96)	0.79 (0.65–0.96)	1.04 (0.87–1.24)
All-cause death	374 (31.8)	179 (30.3)	223 (37.2)	0.02	0.82 (0.70–0.97)	0.78 (0.64–0.95)	1.05 (0.88–1.26)
Myocardial infarction	88 (7.7)	45 (7.9)	49 (9.1)	0.85	0.90 (0.64–1.28)	0.92 (0.62–1.38)	0.98 (0.69–1.41)
Target lesion revascularization	225 (20.3)	103 (18.2)	129 (22.5)	0.15	0.85 (0.69–1.06)	0.78 (0.60–1.00)	1.10 (0.87–1.38)
Definite/probable stent thrombosis	20 (1.8)	14 (2.5)	20 (3.7)	0.09	0.50 (0.27–0.93)	0.70 (0.35–1.39)	0.71 (0.36–1.41)
Definite stent thrombosis	12 (1.1)	5 (0.8)	14 (2.4)	0.03	0.43 (0.20–0.92)	0.36 (0.13–0.99)	1.20 (0.42–3.42)
Probable stent thrombosis	8 (0.7)	9 (1.6)	6 (1.3)	0.23	0.67 (0.23–1.90)	1.52 (0.54–4.26)	0.44 (0.17–1.15)

Data are shown as number (Kaplan–Meier estimates as percentages), hazard ratios (98.3% CI for major adverse cardiac event analysis and 95% CI for the analysis of other events) are derived from Cox proportional hazard models, and *P* values are derived from Cox proportional hazard models. In the analysis of myocardial infarction, target lesion revascularization, and stent thrombosis, the competing risk of death was also accounted for. BP-SES indicates biodegradable polymer-based sirolimus-eluting stent; PP-EES permanent polymer-based everolimus-eluting stent; and PP-SES, permanent polymer-based sirolimus-eluting stent.

BP-SES and PP-EES showed numerically lower event rates compared with early generation DES without statistical difference (BP-SES versus PP-SES: hazard ratio, 0.85; 95% CI, 0.69–1.06; PP-EES versus PP-SES: hazard ratio, 0.78; 95% CI, 0.60–1.00). New-generation BP-SES compared with new-generation PP-EES showed

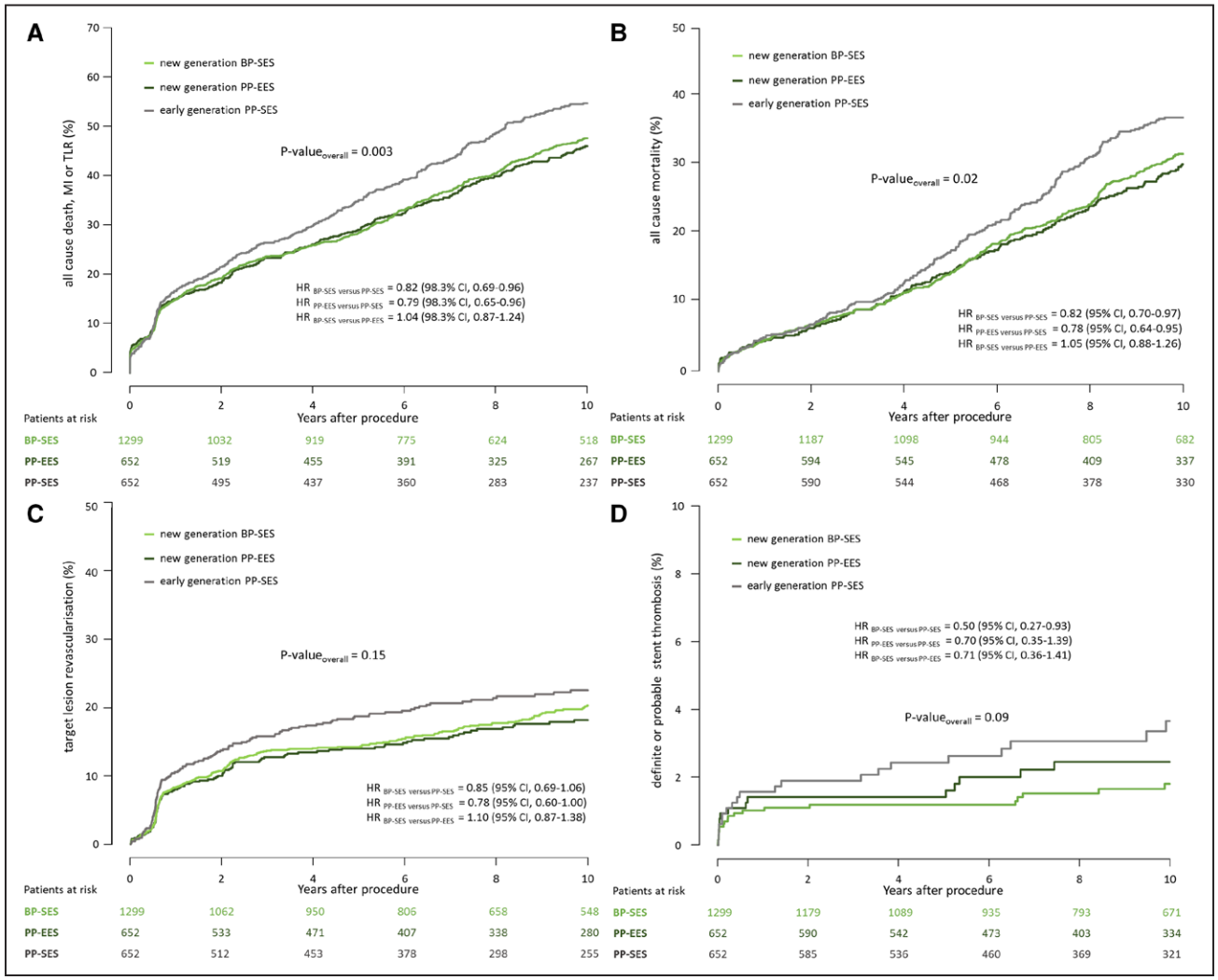

Figure. Comparison of clinical outcomes at 10 years in patients treated with new-generation BP-SES versus new-generation PP-EES versus early generation SES.

Kaplan–Meier curves for (**A**) primary end point, (**B**) all-cause mortality, (**C**) target lesion revascularization, and (**D**) definite/probable stent thrombosis. The primary end point is the composite of all-cause death, myocardial infarction (MI) or target lesion revascularization (TLR). BP-SES indicates biodegradable polymer sirolimus-eluting stent; HR, hazard ratio; PP-EES, permanent polymer everolimus-eluting stent; and PP-SES, permanent polymer sirolimus-eluting stent.

comparable results (BP-SES versus PP-EES: hazard ratio, 1.10; 95% CI, 0.87–1.38). Kaplan–Meier curves of the incidence of target lesion revascularization are displayed in Figure, C.

Regarding safety outcomes, definite/probable stent thrombosis was comparable among the groups (BP-SES 1.8% versus PP-EES 2.5% versus PP-SES 3.7%, *P*=0.09). Both new-generation BP-SES and PP-EES showed numerically lower event rates compared with early generation DES without statistical difference (BP-SES versus PP-SES: hazard ratio, 0.49; 95% CI, 0.27–0.92; PP-EES versus PP-SES: hazard ratio, 0.69; 95% CI, 0.35–1.36). New-generation BP-SES compared with new-generation PP-EES showed comparable results (BP-SES versus PP-EES: hazard ratio, 0.72; 95% CI, 0.36–1.42). Kaplan–Meier curves of the incidence of definite/probable stent thrombosis are displayed in Figure, D. Kaplan–Meier curves and the results of landmark analysis from 0 to 5 and 5 to 10 years for definite/probable stent thrombosis are displayed in Figure IIC in the online-only Data Supplement.

DISCUSSION

The current article represents the first report of long-term randomized trial data out to 10 years, comparing treatment with new-generation DES, sirolimus-eluting stents with biodegradable polymer or everolimus-eluting stents with permanent polymer versus early generation sirolimus-eluting stents with permanent polymer. The major findings of this study are: (1) new-generation DES are superior to early generation DES in terms of clinical outcomes, (2) the favorable outcome after new-generation DES is driven by increasing event rates over time in patients treated with early generation DES, and (3) both BP-SES and PP-EES showed comparable clinical outcomes out to 10 years.

Early generation DES technology showed an excess of adverse events attributable to very late stent thrombosis that continues to accrue at a constant rate after stent implantation.[2,9,15] Autopsy studies suggest a delay in healing of the stented arterial segment as the underlying issue.[16] This is in line with intravascular imaging studies, which found that delayed healing and subsequently neoatherosclerosis are frequently responsible for late adverse events after percutaneous coronary intervention.[17,18] This latter phenomenon is reported to occur more frequently and earlier in DES.[19] Although the etiology of delayed healing after percutaneous coronary intervention with DES is undoubtedly multifactorial, device-related inflammatory reaction and endothelial dysfunction followed by neoatherosclerosis after stent implantation might play a central role.[20,21] New-generation DES incorporated improvements in backbone alloy, strut thickness, antiproliferative drug, dosage and release kinetics, as well as more biocompatible polymers. These improvements translated into enhanced clinical safety and efficacy in comparison with early generation DES.[5,22] However, data beyond 5 years are currently not available to further investigate whether the implantation of new-generation DES results in persistent attenuation of clinical events.

Our findings show that at 10 years, a difference is observed in definite stent thrombosis between patients treated with new-generation DES compared with early generation DES. This is in line with previous randomized trials, which showed a significant reduction of very late stent thrombosis with new-generation DES, reported for both biodegradable polymer-based and permanent polymer-based DES.[4,6,9] A limitation of several long-term follow-up data with biodegradable polymer DES is that early generation DES was the only comparator stent.[6,9,23]

The rate of definite/probable stent thrombosis with the PP-SES was low in our trial (3.7%) compared with some but not all trials. For example, in the SIRIUS trial (Sirolimus-Eluting Stent in De-Novo Native Coronary Lesions), at final reported 5-year follow-up, the rate of definite/probable stent thrombosis was 1.2%.[24] In contrast, higher rates were seen in the SORT-OUT II trial (Danish Organization on Randomized Trials With Clinical Outcome) (definite stent thrombosis 5.3%) and the SIRTAX trial (Sirolimus-Eluting Versus Paclitaxel-Eluting Stents for Coronary Revascularization) (definite stent thrombosis 5.6%) at 10 years.[2,15] Reasons for the differences across trials are difficult to ascertain and may be because of the baseline risk of patients, medical treatment received, and methods used for follow-up and adjudication.

The main finding of the current study is a significant reduction in overall major adverse cardiac events after new-generation DES compared with early generation DES. Although the superiority of new-generation DES in this trial derives from numerically lower event rates of both safety and efficacy end points, the difference is driven by significantly lower all-cause mortality after implantation of new-generation DES. A number of prior trials showed the advantage of new-generation DES over early generation SES, which was previously the benchmark device among early generation DES. For example, although the LEADERS trial (Limus Eluted From a Durable Versus Erodible Stent Coating) did not show superiority for the biodegradable polymer biolimus-eluting stent for the primary end point of cardiac death, myocardial infarction, or clinically indicated target vessel revascularization at 5 years, a significant reduction was seen for the patient-oriented composite end point.[6] The current results are also in line with 5-year data from the SORT OUT IV trial (Scandinavian Organization for Randomized Trials With Clinical Outcome), reporting superiority of

new-generation EES compared with early generation SES in terms of major adverse cardiac events.[4] The improved outcome in the SORT OUT IV trial, however, was mainly driven by a lower risk of very late stent thrombosis.

Observations in relation to mortality in the current article deserve more detailed considerations. First, new-generation DES were associated with a 18% to 22% relative risk reduction of mortality, which is only in part explained by a 30% to 50% relative risk reduction of stent thrombosis. Although numerically higher rates of target lesion revascularization and myocardial infarction might have contributed to some extent to this finding, which is also reflected in numerically higher rates of cardiac mortality, there is still no clear explanation for higher mortality rates with early generation DES. Second, overall mortality rates in the current study are higher than previously reported in trials with 10-year follow-up, which typically had mortality rates ranging from 24% to 27%.[2,15] A potential explanation for these observations could be the higher mean age and the higher proportion of patients with diabetes mellitus in the current study. Although it stands to reason that advanced age at enrollment might result in higher overall mortality during follow-up compared with other trials, a higher proportion of older patients and those with diabetes mellitus may potentially contribute to a higher risk of clinically unapparent device-related events, such as silent myocardial infraction. This might explain the clear difference in overall survival among the treatment groups.

An important finding was that the comparative efficacy of the 2 new-generation DES outcomes at 10 years does not seem to be impacted by whether the polymer is of a biodegradable or permanent nature. This finding is consistent with and extends observations from a number of clinical trials, which showed comparable results between biodegradable polymer DES versus new-generation permanent polymer DES at time points out to 3 to 5 years.[7,25–27] The low and comparable incidence of adverse events with both new-generation DES between 5 and 10 years is noteworthy. This suggests that the improvement in polymer biocompatibility with new-generation permanent polymer DES may have resulted in extended safety and efficacy outcomes that are comparable to that of DES, where no polymer remains behind over the long term.

LIMITATIONS

A number of important limitations of the current article need to be considered. The most important limitation of the current study is the incomplete ascertainment at 10 years, with 17% of the patients having a median follow-up of 5.9 years. This issue is even more problematic considering that we failed to assess the vital status of the latter patients because of the lack of a central national death registry in Germany.

Second, the current report is a post hoc analysis; hence, the findings need to be interpreted with caution. The comparative efficacy of the DES investigated in the present study should be considered in the context of differences among the 3 study DES regarding not just polymer coating but also stent backbone, drug type, and dose. Moreover, the classification of stents into specific groups according to the time course of development (eg, early and new generation) is necessarily arbitrary. Additionally, further alterations of biodegradable polymer-based DES technology have replaced stainless steel backbones with thin-strut cobalt chrome. These devices' potential additional benefits should be addressed by analysis of extended follow-up of patients treated with these devices.

Third, although this study is 1 of the largest randomized controlled trials dedicated to DES versus DES comparisons, the power is reduced when considering 3-group comparison. For example, although the rate of target lesion revascularization was lower with both new-generation DES in our analysis, the difference compared with early generation DES was not statistically significant. Fourth, the ISAR-TEST 4 trial protocol included planned angiographic follow-up at 6 to 8 months for all patients. The influence on the rate of clinical events during follow-up should be considered, although its impact is likely to decrease with the accrual of additional years of follow-up. Finally, in this study, we focused on all-cause mortality instead of cardiac death, which was originally part of the primary end point of the trial. However, this is in line with the recent updated recommendation of the Academic Research Consortium on end points in coronary intervention trials.[28]

CONCLUSIONS

In this unique long-term outcome analysis, BP-SES and PP-EES showed comparable clinical outcomes out to 10 years. PP-SES had higher rates of major adverse cardiac events and definite stent thrombosis.

ARTICLE INFORMATION

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REFERENCES

1. Byrne RA, Stone GW, Ormiston J, Kastrati A. Coronary balloon angioplasty, stents, and scaffolds. *Lancet*. 2017;390:781–792. doi: 10.1016/S0140-6736(17)31927-X
2. Galløe AM, Kelbæk H, Thuesen L, Hansen HS, Ravkilde J, Hansen PR, Christiansen EH, Abildgaard U, Stephansen G, Lassen JF, Engstrøm T, Jensen JS, Jeppesen JL, Bligaard N; SORT OUT II Investigators. 10-year clinical outcome after randomization to treatment by sirolimus- or paclitaxel-eluting coronary stents. *J Am Coll Cardiol*. 2017;69:616–624. doi: 10.1016/j.jacc.2016.11.055
3. Kimura T, Morimoto T, Nakagawa Y, Kawai K, Miyazaki S, Muramatsu T, Shiode N, Namura M, Sone T, Oshima S, Nishikawa H, Hiasa Y, Hayashi Y, Nobuyoshi M, Mitudo K; j-Cypher Registry Investigators. Very late stent thrombosis and late target lesion revascularization after sirolimus-eluting stent implantation: five-year outcome of the j-Cypher Registry. *Circulation*. 2012;125:584–591. doi: 10.1161/CIRCULATIONAHA.111.046599
4. Jensen LO, Thayssen P, Christiansen EH, Maeng M, Ravkilde J, Hansen KN, Hansen HS, Krusell L, Kaltoft A, Tilsted HH, Berencsi K, Junker A, Lassen JF; SORT OUT IV Investigators. Safety and efficacy of everolimus- versus sirolimus-eluting stents: 5-year results from SORT OUT IV. *J Am Coll Cardiol*. 2016;67:751–762. doi: 10.1016/j.jacc.2015.11.051
5. Räber L, Magro M, Stefanini GG, Kalesan B, van Domburg RT, Onuma Y, Wenaweser P, Daemen J, Meier B, Jüni P, Serruys PW, Windecker S. Very late coronary stent thrombosis of a newer-generation everolimus-eluting stent compared with early-generation drug-eluting stents: a prospective cohort study. *Circulation*. 2012;125:1110–1121. doi: 10.1161/CIRCULATIONAHA.111.058560
6. Serruys PW, Farooq V, Kalesan B, de Vries T, Buszman P, Linke A, Ischinger T, Klauss V, Eberli F, Wijns W, Morice MC, Di Mario C, Corti R, Antoni D, Sohn HY, Eerdmans P, Rademaker-Havinga T, van Es GA, Meier B, Jüni P, Windecker S. Improved safety and reduction in stent thrombosis associated with biodegradable polymer-based biolimus-eluting stents versus durable polymer-based sirolimus-eluting stents in patients with coronary artery disease: final 5-year report of the LEADERS (Limus Eluted From A Durable Versus ERodable Stent Coating) randomized, noninferiority trial. *JACC Cardiovasc Interv*. 2013;6:777–789. doi: 10.1016/j.jcin.2013.04.011
7. Kufner S, Byrne RA, Valeskini M, Schulz S, Ibrahim T, Hoppmann P, Schneider S, Laugwitz KL, Schunkert H, Kastrati A; Intracoronary Stenting and Angiographic Results: Test Efficacy of 3 Limus-Eluting Stents (ISAR-TEST4) Investigators. Five-year outcomes from a trial of three limus-eluting stents with different polymer coatings in patients with coronary artery disease: final results from the ISAR-TEST 4 randomised trial. *EuroIntervention*. 2016;11:1372–1379. doi: 10.4244/EIJY14M11_02
8. Shiomi H, Kozuma K, Morimoto T, Igarashi K, Kadota K, Tanabe K, Morino Y, Akasaka T, Abe M, Suwa S, Muramatsu T, Kobayashi M, Dai K, Nakao K, Uematsu M, Tarutani Y, Fujii K, Simonton CA, Kimura T; RESET Investigators. Long-term clinical outcomes after everolimus- and sirolimus-eluting coronary stent implantation: final 3-year follow-up of the Randomized Evaluation of Sirolimus-Eluting Versus Everolimus-Eluting Stent Trial. *Circ Cardiovasc Interv*. 2014;7:343–354. doi: 10.1161/CIRCINTERVENTIONS.113.001322
9. Stefanini GG, Kalesan B, Serruys PW, Heg D, Buszman P, Linke A, Ischinger T, Klauss V, Eberli F, Wijns W, Morice MC, Di Mario C, Corti R, Antoni D, Sohn HY, Eerdmans P, van Es GA, Meier B, Windecker S, Jüni P. Long-term clinical outcomes of biodegradable polymer biolimus-eluting stents versus durable polymer sirolimus-eluting stents in patients with coronary artery disease (LEADERS): 4 year follow-up of a randomised non-inferiority trial. *Lancet*. 2011;378:1940–1948. doi: 10.1016/S0140-6736(11)61672-3
10. Byrne RA, Kastrati A, Kufner S, Massberg S, Birkmeier KA, Laugwitz KL, Schulz S, Pache J, Fusaro M, Seyfarth M, Schömig A, Mehilli J; Intracoronary Stenting and Angiographic Results: Test Efficacy of 3 Limus-Eluting Stents (ISAR-TEST-4) Investigators. 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;30:2441–2449. doi: 10.1093/eurheartj/ehp352
11. Beijk MA, Piek JJ. XIENCE V everolimus-eluting coronary stent system: a novel second generation drug-eluting stent. *Expert Rev Med Devices*. 2007;4:11–21. doi: 10.1586/17434440.4.1.11
12. Sousa JE, Costa MA, Abizaid A, Abizaid AS, Feres F, Pinto IM, Seixas AC, Staico R, Mattos LA, Sousa AG, Falotico R, Jaeger J, Popma JJ, Serruys PW. Lack of neointimal proliferation after implantation of sirolimus-coated stents in human coronary arteries: a quantitative coronary angiography and three-dimensional intravascular ultrasound study. *Circulation*. 2001;103:192–195.
13. Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van Es GA, Steg PG, Morel MA, Mauri L, Vranckx P, McFadden E, Lansky A, Hamon M, Krucoff MW, Serruys PW; Academic Research Consortium. Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation*. 2007;115:2344–2351. doi: 10.1161/CIRCULATIONAHA.106.685313
14. Grambsch PM, Therneau TM. Proportional hazards tests and diagnostics based on weighted residuals. *Biometrika*. 1994;81:515–526.
15. Yamaji K, Räber L, Zanchin T, Spitzer E, Zanchin C, Pilgrim T, Stortecky S, Moschovitis A, Billinger M, Schönenberger C, Eberli F, Jüni P, Lüscher TF, Heg D, Windecker S. Ten-year clinical outcomes of first-generation drug-eluting stents: the sirolimus-eluting vs. paclitaxel-eluting stents for coronary revascularization (SIRTAX) VERY LATE trial. *Eur Heart J*. 2016;37:3386–3395. doi: 10.1093/eurheartj/ehw343
16. Nakazawa G, Finn AV, Vorpahl M, Ladich ER, Kolodgie FD, Virmani R. Coronary responses and differential mechanisms of late stent thrombosis attributed to first-generation sirolimus- and paclitaxel-eluting stents. *J Am Coll Cardiol*. 2011;57:390–398. doi: 10.1016/j.jacc.2010.05.066
17. Otsuka F, Byrne RA, Yahagi K, Mori H, Ladich E, Fowler DR, Kutys R, Xhepa E, Kastrati A, Virmani R, Joner M. Neoatherosclerosis: overview of histopathologic findings and implications for intravascular imaging assessment. *Eur Heart J*. 2015;36:2147–2159. doi: 10.1093/eurheartj/ehv205
18. Adriaenssens T, Joner M, Godschalk TC, Malik N, Alfonso F, Xhepa E, De Cock D, Komukai K, Tada T, Cuesta J, Sirbu V, Feldman LJ, Neumann FJ, Goodall AH, Heestermans T, Buysschaert I, Hlinomaz O, Belmans A, Desmet W, Ten Berg JM, Gershlick AH, Massberg S, Kastrati A, Guagliumi G, Byrne RA; Prevention of Late Stent Thrombosis by an Interdisciplinary Global European Effort (PRESTIGE) Investigators. Optical coherence tomography findings in patients with coronary stent thrombosis: a report of the PRESTIGE Consortium (Prevention of Late Stent Thrombosis by an Interdisciplinary Global European Effort). *Circulation*. 2017;136:1007–1021. doi: 10.1161/CIRCULATIONAHA.117.026788
19. Joner M, Koppara T, Byrne RA, Castellanos MI, Lewerich J, Novotny J, Guagliumi G, Xhepa E, Adriaenssens T, Godschalk TC, Malik N, Alfonso F, Tada T, Neumann FJ, Desmet W, Ten Berg JM, Gershlick AH, Feldman LJ, Massberg S, Kastrati A; Prevention of PRESTIGE Investigators. Neoatherosclerosis in patients with coronary stent thrombosis: findings from optical coherence tomography imaging (a report of the PRESTIGE Consortium). *JACC Cardiovasc Interv*. 2018;11:1340–1350. doi: 10.1016/j.jcin.2018.02.029
20. Nakazawa G, Otsuka F, Nakano M, Vorpahl M, Yazdani SK, Ladich E, Kolodgie FD, Finn AV, Virmani R. The pathology of neoatherosclerosis in human coronary implants bare-metal and drug-eluting stents. *J Am Coll Cardiol*. 2011;57:1314–1322. doi: 10.1016/j.jacc.2011.01.011
21. Byrne RA, Joner M, Kastrati A. Polymer coatings and delayed arterial healing following drug-eluting stent implantation. *Minerva Cardioangiol*. 2009;57:567–584.
22. Tada T, Byrne RA, Simunovic I, King LA, Cassese S, Joner M, Fusaro M, Schneider S, Schulz S, Ibrahim T, Ott I, Massberg S, Laugwitz KL, Kastrati A. Risk of stent thrombosis among bare-metal stents, first-generation drug-eluting stents, and second-generation drug-eluting stents: results from a registry of 18,334 patients. *JACC Cardiovasc Interv*. 2013;6:1267–1274. doi: 10.1016/j.jcin.2013.06.015
23. Stefanini GG, Byrne RA, Serruys PW, de Waha A, Meier B, Massberg S, Jüni P, Schömig A, Windecker S, Kastrati A. Biodegradable polymer drug-eluting stents reduce the risk of stent thrombosis at 4 years

in patients undergoing percutaneous coronary intervention: a pooled analysis of individual patient data from the ISAR-TEST 3, ISAR-TEST 4, and LEADERS randomized trials. *Eur Heart J*. 2012;33:1214–1222. doi: 10.1093/eurheartj/ehs086

24. Weisz G, Leon MB, Holmes DR Jr, Kereiakes DJ, Popma JJ, Teirstein PS, Cohen SA, Wang H, Cutlip DE, Moses JW. Five-year follow-up after sirolimus-eluting stent implantation results of the SIRIUS (Sirolimus-Eluting Stent in De-Novo Native Coronary Lesions) trial. *J Am Coll Cardiol*. 2009;53:1488–1497. doi: 10.1016/j.jacc.2009.01.050
25. Natsuaki M, Kozuma K, Morimoto T, Kadota K, Muramatsu T, Nakagawa Y, Akasaka T, Igarashi K, Tanabe K, Morino Y, Ishikawa T, Nishikawa H, Awata M, Abe M, Okada H, Takatsu Y, Ogata N, Kimura K, Urasawa K, Tarutani Y, Shiode N, Kimura T. Final 3-year outcome of a randomized trial comparing second-generation drug-eluting stents using either biodegradable polymer or durable polymer: NOBORI biolimus-eluting versus XIENCE/PROMUS everolimus-eluting stent trial. *Circ Cardiovasc Interv*. 2015;8:e002817
26. Vlachojannis GJ, Puricel S, Natsuaki M, Morimoto T, Smits PC, Kimura T. Biolimus-eluting versus everolimus-eluting stents in coronary artery disease: a pooled analysis from the NEXT (NOBORI biolimus-eluting versus XIENCE/PROMUS everolimus-eluting stent) and COMPARE II (Abluminal biodegradable polymer biolimus-eluting stent versus durable polymer everolimus-eluting stent) randomised trials. *EuroIntervention*. 2017;12:1970–1977. doi: 10.4244/EIJ-D-16-00773
27. Vlachojannis GJ, Smits PC, Hofma SH, Togni M, Vázquez N, Valdés M, Voudris V, Slagboom T, Goy JJ, den Heijer P, van der Ent M. 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). *JACC Cardiovasc Interv*. 2017;10:1215–1221. doi: 10.1016/j.jcin.2017.02.029
28. Garcia-Garcia HM, McFadden EP, Farb A, Mehran R, Stone GW, Spertus J, Onuma Y, Morel MA, van Es GA, Zuckerman B, Fearon WF, Taggart D, Kappetein AP, Krucoff MW, Vranckx P, Windecker S, Cutlip D, Serruys PW; Academic Research Consortium. Standardized end point definitions for coronary intervention trials: the Academic Research Consortium-2 consensus document. *Circulation*. 2018;137:2635–2650. doi: 10.1161/CIRCULATIONAHA.117.029289