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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 (A Trial of Everolimus-Eluting Stents and Paclitaxel Stents for Coronary Revascularization in Daily Practice)

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ABSTRACT

OBJECTIVES This study sought to report the 5-year outcomes of everolimus-eluting stents (EES) and paclitaxel-eluting stents (PES) in an all-comers population undergoing percutaneous coronary intervention (PCI).

BACKGROUND The medium-term 1 and 2-year results of the prospective randomized COMPARE trial (A Trial of Everolimus-Eluting Stents and Paclitaxel-Eluting Stents for Coronary Revascularization in Daily Practice) showed superior clinical outcomes with EES compared with PES in an all-comers PCI population. Whether this benefit is sustained over longer-term follow-up is unknown. Furthermore, systematic long-term follow-up data on these metallic drug eluting stents with durable polymers are scarce.

METHODS We randomly assigned 1,800 patients undergoing PCI to EES or PES. The pre-specified composite primary endpoint was death, myocardial infarction (MI), or target vessel revascularization (TVR).

RESULTS Follow-up at 5 years was completed in 1,791 (99.5%) patients. Treatment with EES compared with PES led to a relative risk reduction of the primary endpoint by 27% (18.4% vs. 25.1%, $p = 0.0005$), driven by lower rates of MI (7.0% vs. 11.5%, $p = 0.001$) and TVR (7.4% vs. 11.4%, $p = 0.003$), but not with mortality (9.0% vs. 10.3%, relative risk 0.88, $p = 0.36$). Moreover, patients treated with EES compared with PES had lower rates of definite/probable stent thrombosis at 5 years (3.1% vs. 5.9%, $p = 0.005$). The hazard curves for TVR, MI, and stent thrombosis diverge over the first 3 years and, subsequently, progress in parallel.

CONCLUSIONS The early- and medium-term superiority of EES over PES measured both by safety and efficacy endpoints is sustained at 5 years in this all-comer population. (A Trial of Everolimus-Eluting Stents and Paclitaxel-Eluting Stents for Coronary Revascularization in Daily Practice [COMPARE]; NCT01016041) (J Am Coll Cardiol Intv 2015;8:1157–65) © 2015 by the American College of Cardiology Foundation. Published by Elsevier. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

The introduction of drug-eluting stents (DES) significantly reduced restenosis after percutaneous coronary interventions (PCI), thereby decreasing the need for repeated interventions (1). However, the better efficacy of first-generation DES (reduced stent restenosis) compared with bare-metal stents was offset by a poorer safety profile (increased stent thrombosis [ST]) thus decreasing net clinical

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ABBREVIATIONS AND ACRONYMS

DAPT = dual antiplatelet therapy

DES = drug-eluting stent(s)

EES = everolimus-eluting stent(s)

MI = myocardial infarction

PCI = percutaneous coronary intervention

PES = paclitaxel-eluting stent(s)

RRR = relative risk reduction

ST = stent thrombosis

TLR = target lesion revascularization

TVR = target vessel revascularization

benefit (2). Newer-generation DES were designed to improve both the efficacy and safety profile. Several studies showed that the newer-generation everolimus-eluting stent (EES) XIENCE-V (Abbott Vascular, Santa Clara, California) was superior to the first-generation paclitaxel-eluting stent (PES) TAXUS EXPRESS2 (Boston Scientific, Natick, Massachusetts) (3–5). However, as a result of strict inclusion and exclusion criteria, mainly low-risk patient and lesion characteristics were studied, thereby making extrapolation of these conclusions to real-life practice problematic. Furthermore, follow-up was generally limited to 3 years (6), and recent data suggest that longer follow-up of 5 years or more is needed to truly evaluate the effect of different DES. In 3 recently reported comparative stent trials, the results and conclusions at 1 year differed from those at 4- and 5-year follow-up (7–9).

TABLE 1 Baseline Patient and Lesion Characteristics

	Everolimus-Eluting Stent (n = 897)	Paclitaxel-Eluting Stent (n = 903)
Age, median, yrs	62.9	63.6
Men	619 (69)	654 (72)
Diabetes mellitus*	153 (17)	172 (19)
Chronic renal failure†	25 (3)	24 (3)
Hypertension	417 (46)	447 (50)
Hypercholesterolemia	477 (53)	451 (50)
Current smoker	295 (33)	262 (29)
Family history of CAD	399 (44)	403 (45)
History of myocardial infarction	136 (15)	159 (18)
History of percutaneous coronary intervention	117 (13)	123 (14)
History of coronary artery bypass surgery	60 (7)	53 (6)
Stable angina pectoris	331 (37)	349 (39)
Acute coronary syndrome	541 (60)	534 (59)
Unstable angina	107 (12)	105 (12)
Non-ST-segment elevation myocardial infarction	194 (22)	217 (24)
ST-segment elevation myocardial infarction	240 (27)	212 (23)
Multivessel treatment	244 (27)	239 (26)
Treated lesions per patient, n ± SD	1.4 ± 0.7	1.4 ± 0.7
Lesion length ≥20 mm	290 (32)	263 (29)
Number of lesions	1,286	1,294
Number of stents per lesion, mean ± SD	1.7 ± 0.9	1.6 ± 0.9
Total stent length per lesion, median (IQR)	28 (18–46)	28 (18–44)
Direct stenting	432 (34)	451 (35)
Type B2 or C lesion	950 (74)	955 (74)
Bifurcation lesion	223 (17)	237 (18)
Thrombus present	310 (3)	314 (24)
Chronic total occlusion	39 (3)	53 (4)

Values are n (%) except as noted. *Diabetes was defined as treatment by diet or drugs for previously diagnosed diabetes. †Chronic renal failure was defined as serum creatinine of >130 μmol/l or on dialysis.

CAD = coronary artery disease.

The prospective randomized COMPARE trial (A Trial of Everolimus-Eluting Stents and Paclitaxel-Eluting Stents for Coronary Revascularization in Daily Practice) was an investigator-initiated all-comers study designed to compare the second-generation PES TAXUS LIBERTÉ with the second-generation EES XIENCE-V in real-life practice. The results at 1 year showed superiority of EES over PES with regard to both efficacy and safety endpoints, driven by lower rates of myocardial infarction (MI), ST and target vessel revascularization (TVR) (10). These clinical benefits of EES over PES were maintained at 2 years, driven by lower rates of ST and TVR (11). Whether the documented benefit of EES is maintained at later follow-up has not been addressed. Therefore, we report the final 5-year results of the COMPARE trial.

METHODS

The study design has been reported elsewhere (10). Briefly, the COMPARE trial was a prospective, randomized, single-blinded, single-center trial comparing PES (TAXUS LIBERTÉ) and EES (XIENCE-V). Consecutive patients aged 18 years or older referred to Maasstad Ziekenhuis, Rotterdam, the Netherlands, for elective or emergent percutaneous coronary intervention were eligible for enrollment. Major exclusion criteria were contraindications to dual antiplatelet therapy (DAPT) or planned major surgery within 30 days necessitating DAPT interruption. The study was approved by the institutional ethics committee of the Maasstad Ziekenhuis, Rotterdam, the Netherlands, and registered in the Dutch Central Committee on Research Involving Human Subjects (CCMO trial no. NL15206.101.06) and in ClinicalTrials.gov (NCT01016041). All patients provided written informed consent.

PCI was performed according to standard techniques, and patients were assigned on a 1:1 basis to EES or PES. Procedural details, including pre-and periprocedural pharmacotherapy, have been previously reported (10). Patients were discharged from hospital on aspirin 100 mg daily indefinitely and clopidogrel 75 mg daily for 12 months.

Clinical follow-up was performed at hospital discharge and at 1, 6, and 12 months. Study monitors collected data by visits, phone calls, and postal questionnaires annually up to 5 years. Reported adverse events and hospitalizations were monitored. Data processing and adjudication of adverse events were done in a blinded fashion by an independent core laboratory and the Clinical Events Committee masked to treatment assignment (Cardialysis, Rotterdam, the Netherlands).

The pre-specified patient-oriented primary endpoint of the COMPARE trial was a composite of death, nonfatal MI, and TVR at 5 years. The secondary device-specific endpoint was a composite of major adverse cardiac events (cardiac death, nonfatal MI, and clinically driven target lesion revascularization [TLR]). Definition of endpoints are presented elsewhere (10).

STATISTICAL ANALYSIS. All analyses were performed by intention to treat. Categorical outcomes were compared with the chi-square test or Fisher exact test, and continuous variables with the Wilcoxon rank sum test. The time to the endpoints was assessed according to the method of Kaplan-Meier, and the log-rank test. Relative risk with 95% confidence intervals were calculated using the normal approximation to the binomial distribution. All p values were 2-sided, and a p value <0.05 was considered to indicate statistical significance. Analyses were performed using SAS version 8.02 (SAS Institute, Cary, North Carolina).

RESULTS

PATIENTS AND PROCEDURES. Between February 2007 and September 2008, we enrolled 1,800 patients of whom 897 patients were randomized to EES and 903 patients to PES. Baseline patient and lesion characteristics between EES and PES groups were well matched (Table 1). No significant differences in DAPT adherence between groups was observed at 1, 6, 12, 24, 36, and 60 months follow-up (respectively for EES: 91%, 91%, 70%, 11%, 13%, and 12%, for PES: 92%, 91%, 70%, 15%, 14%, and 12%) with the exception at 2 years (15% for PES vs. 11% for EES, p = 0.02). Follow-up at 5 years was completed in 1,791 (99.5%) comprising 892 patients assigned to EES and 899 assigned to PES (Figure 1).

CLINICAL OUTCOMES. The clinical outcomes at 5 years are presented in Table 2. The primary endpoint (death, MI, TVR) was significantly lower in patients treated with EES compared with PES (18.4% vs. 25.1%, p = 0.001), which was mainly driven by lower rates of MI and TVR in the EES group (7.0% vs. 11.5%, p = 0.001, and 7.4% vs. 11.4%, p = 0.003, respectively). All-cause mortality did not differ between groups (9.0% vs. 10.3%, p = 0.36). The hazard curves of the primary endpoint seem to diverge over the complete follow-up period, whereas the hazard curves for the individual endpoints MI and TVR seem to progress in a parallel manner after 3 and 2 years, respectively (Figure 2).

FIGURE 1 Study Flow Chart

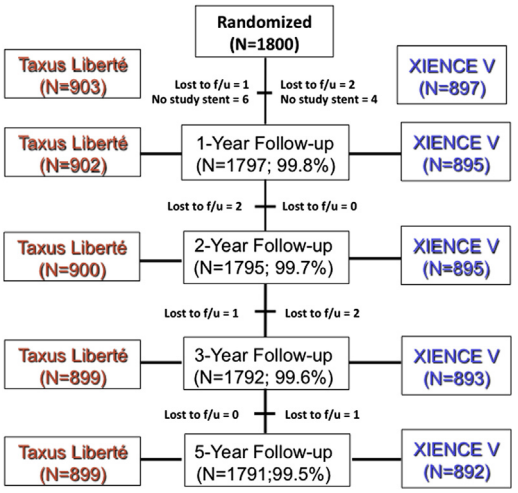


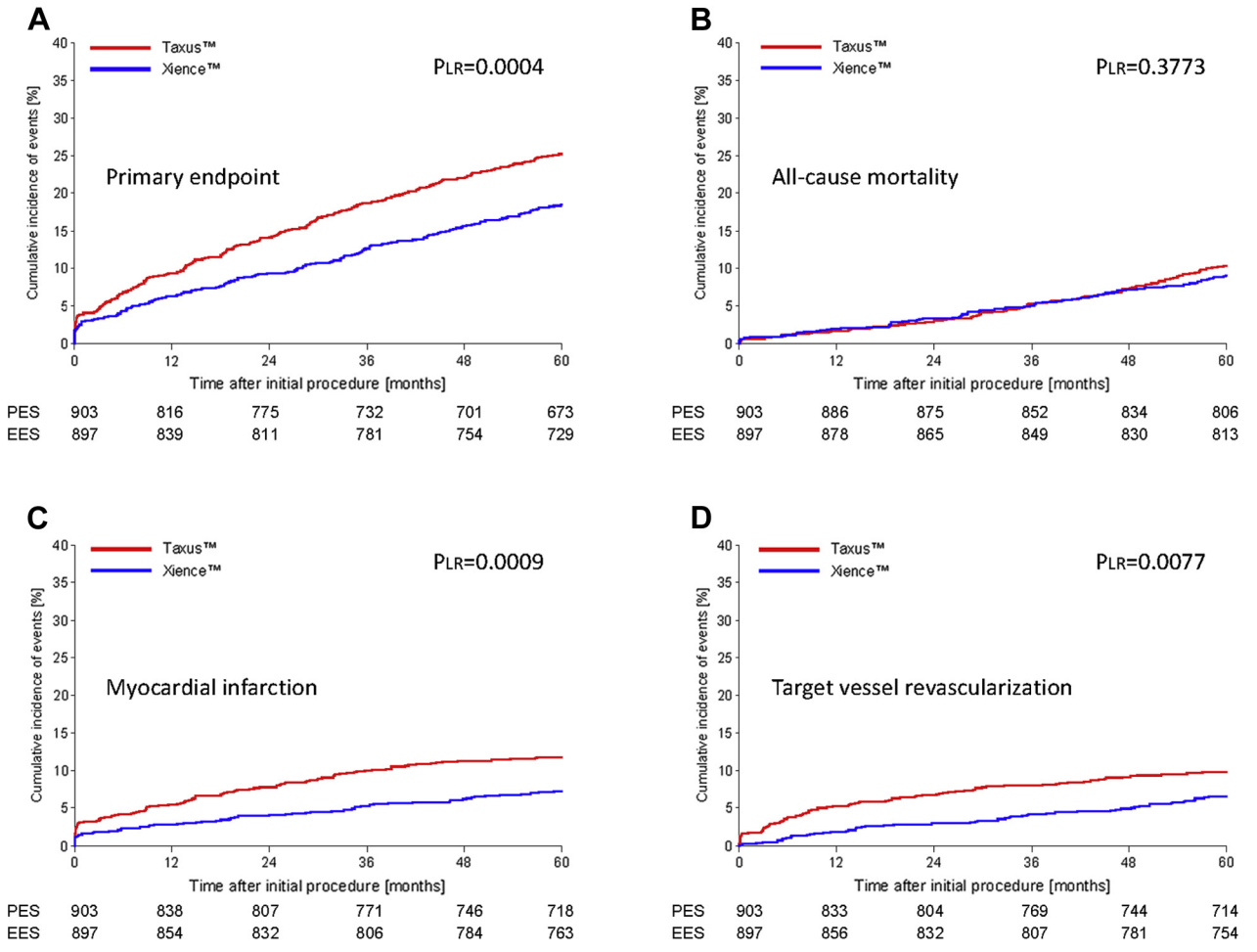
TABLE 2 Events at 5 Years

Events	EES (n = 897)	PES (n = 903)	RR (EES/PES)	Lower Limit RR	Upper Limit RR	p Value
Death	81 (9.0)	93 (10.3)	0.88	0.66	1.16	0.36
Cardiac death	40 (4.5)	42 (4.7)	0.96	0.63	1.46	0.85
MI	63 (7.0)	104 (11.5)	0.61	0.45	0.82	<0.01
Q-wave	19 (2.1)	23 (2.5)	0.83	0.46	0.82	<0.01
Non-Q-wave	44 (4.9)	85 (9.4)	0.52	0.37	0.74	<0.01
Death or MI	131 (14.6)	182 (20.2)	0.72	0.59	0.88	<0.01
Cardiac death or MI	92 (10.3)	135 (15.0)	0.69	0.54	0.88	<0.01
TVR, clinically driven	60 (6.7)	97 (10.7)	0.62	0.46	0.85	<0.01
Percutaneous	48 (5.4)	77 (8.5)	0.63	0.44	0.89	<0.01
Surgical	12 (1.3)	24 (2.7)	0.50	0.25	1.00	0.05
TVR, any	66 (7.4)	103 (11.4)	0.65	0.48	0.87	<0.01
Percutaneous	54 (6.0)	83 (9.2)	0.66	0.47	0.91	0.01
Surgical	12 (1.3)	24 (2.7)	0.50	0.25	1.00	0.05
TLR, clinically driven	45 (5.0)	75 (8.3)	0.60	0.42	0.86	0.01
Percutaneous	36 (4.0)	59 (6.5)	0.61	0.41	0.92	0.02
Surgical	9 (1.0)	19 (2.1)	0.48	0.22	1.05	0.06
TLR, any	56 (6.2)	86 (9.5)	0.66	0.47	0.91	<0.01
Percutaneous	47 (5.2)	70 (7.8)	0.68	0.47	0.97	0.03
Surgical	9 (1.0)	19 (2.1)	0.48	0.22	1.05	0.06
Non-TVR	74 (8.2)	70 (7.8)	1.06	0.78	1.46	0.70
Primary endpoint	165 (18.4)	227 (25.1)	0.73	0.61	0.87	<0.01
Secondary endpoint	112 (12.5)	164 (18.2)	0.69	0.55	0.86	<0.01
Target lesion failure	102 (11.4)	144 (15.9)	0.71	0.56	0.90	<0.01
Target vessel failure	113 (12.6)	161 (17.8)	0.71	0.57	0.88	<0.01
ST, definite and probable	28 (3.12)	53 (5.9)	0.53	0.34	0.83	<0.01
Early ST	2 (0.2)	15 (1.7)	0.13	0.03	0.59	<0.01
Late ST	3 (0.3)	8 (0.9)	0.38	0.10	1.42	0.13
Very late ST	23 (2.6)	31 (3.4)	0.75	0.44	1.27	0.28
Definite ST	20 (2.2)	36 (4.0)	0.56	0.33	0.96	0.03

Values are n (%) except as noted.

EES = everolimus-eluting stent; PES = paclitaxel-eluting stent; MI = myocardial infarction; RR = relative risk; ST = stent thrombosis; TLR = target lesion revascularization; TVR = target vessel revascularization.

FIGURE 2 Kaplan-Meier Cumulative Event Curves for the Primary Endpoint



Kaplan-Meier cumulative event curves for the primary endpoint **(A)**, all-cause death **(B)**, myocardial infarction **(C)**, and target vessel revascularization **(D)**. At the **bottom** of each graph is a table with the number at risk. **Red lines** indicate paclitaxel-eluting stent (PES). **Blue lines** indicate everolimus-eluting stent (EES). f/u = follow-up; PLR = p value according to the log-rank test.

The device-oriented secondary endpoint (cardiac death, MI, clinically driven TLR) at 5 years occurred in 12.5% of patients treated with EES and 18.2% treated with PES (p = 0.0008), driven by reduced rates of MI and clinically driven TLR (5.0% vs. 8.3%, p = 0.005) in the EES group without a significant difference in cardiac mortality between groups (4.5% vs. 4.7%, p = 0.85).

The Academic Research Consortium definite or probable ST rate was significantly lower in the EES group (3.1% vs. 5.9%, p = 0.005), driven by a significant reduction in early ST (0.2% vs. 1.7%, p = 0.002) (Table 2). Rates of Academic Research Consortium late and very late definite or probable ST were numerically, but not statistically, lower in the EES group (0.5% vs. 0.9%, p = 0.25, and 2.6% vs. 3.4%, p = 0.28, respectively).

In the 1-year landmark analysis, the primary endpoint was reached by fewer patients in the EES group compared with patients treated with PES (12.9% vs. 17.4%, p = 0.011) (Table 3). However, the rates of the individual endpoints all-cause death (7.2% vs. 8.8%, p = 0.22), MI (4.4% vs. 6.4%, p = 0.07), TVR (5.0% vs. 5.8%, p = 0.52), and definite or probable ST (2.5% vs. 3.4%, p = 0.26) were numerically lower in the EES group without reaching significance in the 1- to 5-year follow-up period (Figure 3).

The 5-year reduction in the primary endpoint with EES compared with PES was consistent in all tested subgroups. There was no significant interaction between treatment assignment and analyzed subgroups present, although there were borderline

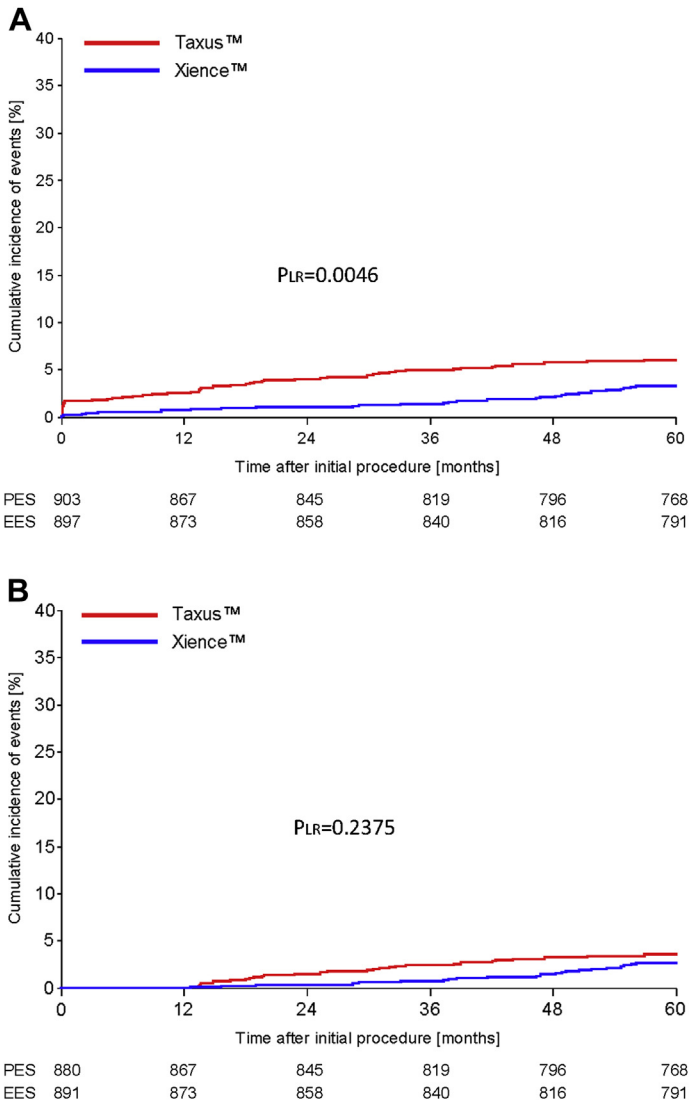
TABLE 3 Outcome Differences Between 1 Year and 5 Years

Outcome	Patients With Events Between 1 and 5 Yrs Who Were Event-Free at 1 Yr		RR (EES/PES)	95% CI	p Value
	EES	PES			
Primary endpoint	12.9 (108)	17.4 (142)	0.74	0.59–0.93	0.01
Death	7.2 (63)	8.8 (78)	0.82	0.59–1.12	0.22
Cardiac death	3.3 (29)	3.6 (32)	0.92	0.56–1.50	0.80
MI	4.4 (38)	6.4 (55)	0.68	0.45–1.01	0.07
Death and MI	10.4 (89)	14.2 (119)	0.73	0.57–0.95	0.02
TVR, all	5.0 (44)	5.8 (49)	0.87	0.59–1.29	0.52
TVR, clinically driven	4.6 (40)	5.4 (46)	0.84	0.56–1.28	0.44
TLR, all	4.4 (39)	4.6 (39)	0.97	0.63–1.50	0.91
TLR, clinically driven	3.5 (31)	3.8 (33)	0.92	0.57–1.48	0.80
TLF	7.3 (62)	8.9 (74)	0.82	0.59–1.13	0.25
TVF	7.9 (67)	10.5 (86)	0.76	0.56–1.03	0.09
ST, definite and probable	2.5 (22)	3.4 (30)	0.72	0.42–1.25	0.26
ST, definite	1.8 (16)	2.0 (18)	0.88	0.45–1.72	0.73

Values are n (%) except as noted.

CI = confidence interval; TLF = target lesion failure; TVF = target vessel failure; other abbreviations as in Table 2.

FIGURE 3 Kaplan-Meier Cumulative Event Curves for ST



Kaplan-Meier curve cumulative event curves for definite and probable stent thrombosis (ST) during complete follow-up **(A)**; and definite and probable ST after 1-year landmark analysis **(B)**. Probable and definite ST as defined by the Academic Research Consortium. **Red lines** indicate PES. **Blue lines** indicate EES. Abbreviations as in Figure 2.

interactions in patients treated for multivessel disease or female sex (Figure 4).

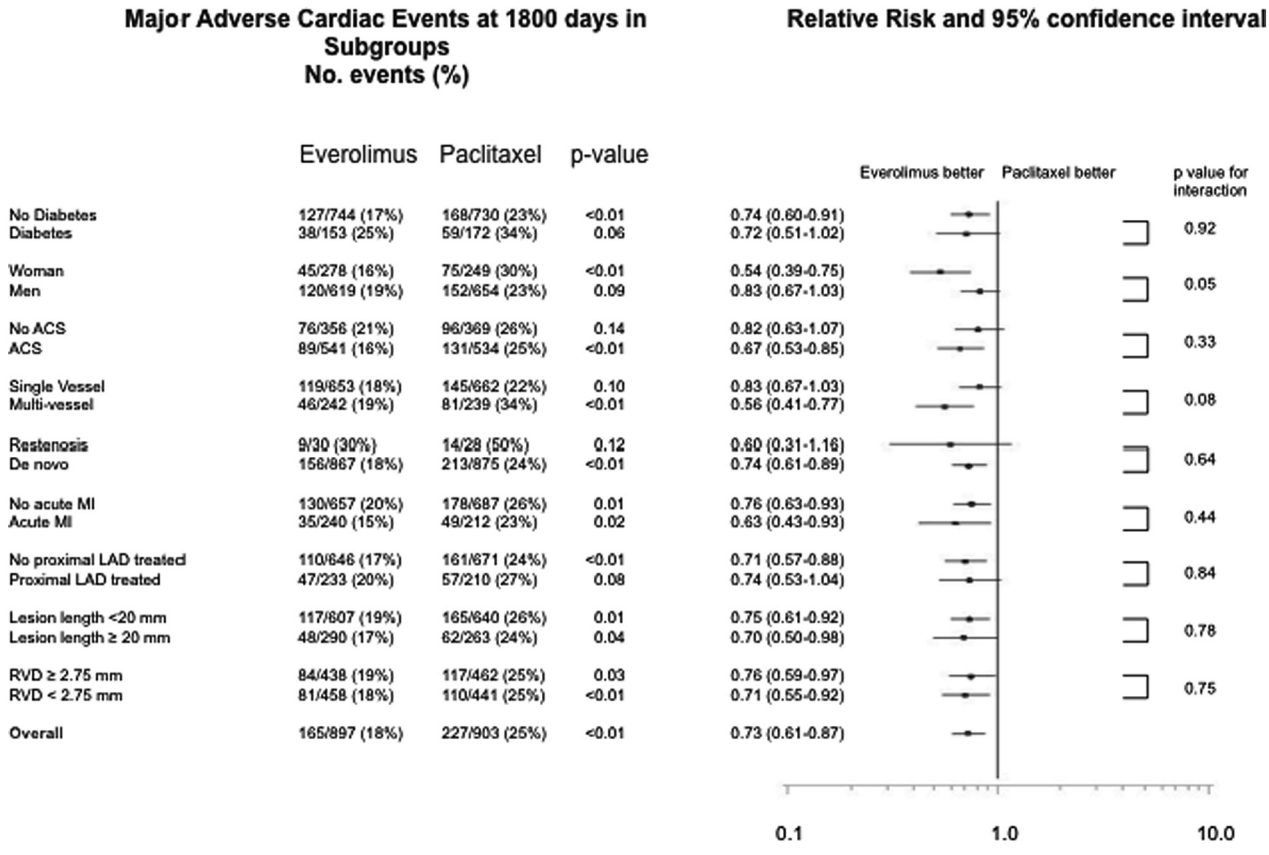
DISCUSSION

This final 5-year report from the COMPARE trial represents the largest study comparing EES to PES in an all-comers cohort with the longest follow-up to date. The results confirm the sustained clinical benefit of EES over PES at 5 years with a 27% relative risk reduction (RRR) in the composite primary endpoint. This risk reduction was mainly driven by fewer TVRs and MI in the EES group. The magnitude of risk reduction in the EES group with regard to the primary endpoint is similar to the previously reported risk reduction of 29% of the endpoint target vessel failure documented in the 3-year pooled analysis of the SPIRIT (A Clinical Evaluation of the XIENCE V Everolimus Eluting Coronary Stent System) II, SPIRIT III, and SPIRIT IV trials (6).

Treatment with EES led to a 39% risk reduction of the safety endpoint MI at 5 years, with differences between groups most apparent during the first 2 years of follow-up. During the first 30 days, the reduction of MI might partly reflect the observed lower rate of early ST in the EES group. Additionally, differences in stent and polymer design leading to less side branch compromise and better stent apposition with EES might further contribute to the observed lower 30-day MI rate (5). Nevertheless, the hazard curves for MI continue to diverge beyond 30 days and up to 3 years, which suggests that additional factors, such as a better biocompatibility and antithrombotic properties of the fluoropolymer in EES, may contribute to this observed reduction in late MI.

Interestingly, TVR hazard curves diverge up to 2 years, which might reflect the better overall antiproliferative profile of EES. However, the hazard curves for TVR and definite and probable ST seem to

FIGURE 4 Post-Hoc Subgroup Analysis



Results of a post-hoc subgroup analysis performed with 9 clinical or angiographic variables. ACS = acute coronary syndrome; LAD = left anterior descending coronary artery; MI = myocardial infarction; RVD = reference vessel diameter.

converge slightly between 4- and 5-year follow-up. Whether this resembles a play of chance or has a pathophysiological cause indicating a catch-up of neoatherosclerosis in the EES group at very late follow-up remains unknown (12-14).

The overall definite and probable ST rate remained significantly lower in the EES group compared with the PES group at 5 years with a RRR of 47%. As previously reported, the rates of early ST were significantly lower in the EES group (RRR: 87%). The rate of late ST was numerically lower in the EES group without reaching statistical significance (RRR: 50%). The 5-year follow-up demonstrates that the very late ST rate was numerically lower, but not significantly different, in the EES group compared with PES, with an overall risk reduction of 25%. In contrast to the recently published 4-year results from the PROTECT trial (Randomized Study Comparing Endeavor With Cypher Stents) (7), we observed a consistently lower ST rate with EES throughout the 5-year follow-up, though in the 1-year landmark analysis, the ST curves seem to converge between 4- and 5-year follow-up (Figure 3B). Whether this observation is true and consistent beyond 5 years remains uncertain because of the modest sample size of the study and the fact that follow-up was limited to 5 years. However, our results emphasize again the importance of long-term follow-up of randomized controlled trials in DES.

Because groups were well matched with regard to patient, lesion, and procedure characteristics, the observed effects are most likely due to the specific features of the EES system compared with PES. It has been speculated that differences in the stent platform including metallic platform (material, geometry, strut thickness, deliverability), polymer (composition, thickness, biocompatibility, thrombogenicity, proinflammatory potential), and antiproliferative drug (molecular composition, biological actions, doses, release kinetics) might all contribute to the observed differences between the devices. Moreover, more

TABLE 4 Patient Characteristics With EES and Definite Or Probable Very Late ST

	Event Data						Index Data										
Patient #	Def/Prob ST	Event Type	Days After Index	$P2Y_{12}$ Type	On DAPT	Antithrombotic Agent	Age (yrs)	Sex	DM	Smoking*	Index Procedure	Vessel	Lesion Type	Total Stent Length	Post-Dilation	Bif Treatment	Vessel Disease
0015	Prob	NSTEMI	1,405	Clop	No	Clop	60	F	2, NIDDM	Yes/yes	STEMI	RCX	B2	18	Yes	Yes	2
0353	Def	STEMI	933	No	No	ASA	55	M	2, NIDDM	Yes/yes	STEMI	RCA	B1	23	No	No	2
0555	Def	STEMI	871	No	No	ASA	53	M	No	No	STEMI	RCA	C	28	No	Yes	3
0593	Def	NSTEMI	1,134	No	No	ASA	34	F	No	Yes/yes	STEMI	LAD	C†	92	Yes	No	2
0650	Def	NSTEMI	380	No	No	ASA	62	F	No	Ex	NSTEMI	RCA	C†	46	No	No	2
0736	Prob	NSTEMI	1,410	No	No	ASA+OAC	69	F	2, NIDDM	Ex	SAP	RCX	C	58	No	No	2
0738	Def	STEMI	854	No	No	ASA+OAC	68	M	No	Yes/yes	NSTEMI	LAD	B1†	12	No	No	1
0773	Def	NSTEMI	1,241	Clop	Yes	ASA+Clop	48	M	2, NIDDM	Ex	UAP	LAD	C	97	Yes	Yes	1
0803	Def	STEMI	711	Clop	Yes	ASA+Clop	56	M	No	Yes/yes	STEMI	RCX	C‡	64	Yes	Yes	3
0808	Prob	NSTEMI	544	Clop	Yes	ASA+Clop	74	M	2, IDDM	Yes/yes	NSTEMI	Graft	C	54	No	No	3
0831	Def	Dyspnea	1,393	N	No	ASA+OAC	68	F	No	Ex	SAP	RCX	B2†	36	No	No	3
0883	Def	STEMI	1,516	N	No	ASA	55	M	No	Yes/yes	STEMI	LAD	B2	33	Yes	Yes	1
0965	Prob	NSTEMI	1,599	Clop	Yes	ASA+Clop	64	F	No	Yes/ukn	NSTEMI	LAD	B1	23	Yes	No	1
1083	Def	STEMI	1,647	N	No	ASA	57	M	No	Yes/no	SAP	RCA	B1	43	Yes	No	3
1231	Def	STEMI	1,249	N	No	N	75	M	No	No	SAP	RCA	B2	56	Yes	No	2
1288	Def	NSTEMI	1,554	Clop	Yes	ASA+Clop	57	M	2, IDDM	Ex	NSTEMI	Graft	C	28	Yes	No	3
1318	Prob	NSTEMI	1,669	N	No	ASA	78	M	No	Ex	SAP	RCA	B1	28	Yes	No	3
1331	Prob	Death	1,469	N	No	ASA	72	M	No	Ex	SAP	LAD	C§	59	Yes	Yes	3
1406	Prob	NSTEMI	1,638	Y	Yes	ASA+Dipyr	50	M	No	Yes/yes	SAP	LAD	B2	40	No	No	3
1452	Def	STEMI	1,449	Ukn	Ukn	Ukn	60	M	No	Yes/yes	NSTEMI	LAD	B2	40	Yes	No	1
1484	Def	STEMI	1,317	N	No	ASA	75	F	2, NIDDM	No	SAP	LAD	C§	48	Yes	No	2
1514	Def	STEMI	571	N	No	ASA	48	M	No	No	STEMI	RCA	B2	15	No	No	3
1728	Def	STEMI	1,477	N	No	ASA	57	M	No	Yes/yes	SAP	LAD	B1	15	Yes	Yes	2

*Active smoking at index or at event. †Index lesion in-stent thrombosis or restenosis of Cypher stent. ‡Index procedure in-stent thrombosis of bare-metal stent. §Index lesion very calcified and rotablator procedure.

ASA = acetylsalicylic acid; Bif = bifurcation; Clop = clopidogrel; DAPT = dual antiplatelet therapy; Def = definite; Dipyr = dipyridamole; DM = diabetes mellitus; Ex = ex-smoker; F = female; IDDM = insulin-dependent diabetes mellitus; LAD = left anterior coronary artery; M = male; NIDDM = non-insulin-dependent diabetes mellitus; NSTEMI = non-ST-segment elevation myocardial infarction; OAC = oral anticoagulant (vitamin K antagonist); Prob = probable; RCA = right coronary artery; RCX = circumflex coronary artery; SAP = stable angina pectoris; STEMI = ST-segment elevation myocardial infarction; UAP = unstable angina pectoris; Ukn = unknown; other abbreviations as in Table 2.

rapid re-endothelialization with EES as documented in animal models might contribute to the present findings because it has been shown that incomplete endothelialization is strongly associated with the risk of ST (15,16). The average annual increment of very late ST between 1 and 5 years was 0.64% in the EES and 0.86% in the PES group. Both very late ST rates are higher when compared with the previously reported very late ST rates in the 5-year SPIRIT III trial paper (average annual increment of 0.12% for EES and 0.25% for PES) and the 3-year pooled analysis of the SPIRIT trials (average annual increment of 0.18% for EES and 0.34% for PES) and various meta-analyses (6,17,18). The observed differences might be explained by the all-comers design of the present study thus including higher-risk patient and lesion characteristics. In fact, only 5 of the 23 very-late ST cases within the COMPARE study would have fulfilled the inclusion and exclusion criteria for enrollment in the SPIRIT trials. Second, in the COMPARE trial, DAPT was stopped after 1 year in 89% to 85% of the patients, whereas in the SPIRIT III trial, DAPT discontinuation after 1 year was about 28% to 29% (19). However, both the SPIRIT and COMPARE trials were underpowered to evaluate differences in ST between the stent platforms. Only in a pooled analysis of the SPIRIT II, III, and IV and COMPARE trials of 6,789 patients with follow-up at 2 years, we could identify that interruption of DAPT beyond 6 months after implantation of EES was safe, whereas the opposite was true for PES (20). Detailed information on patient and lesion characteristics and DAPT usage of patients with very-late ST in the EES group up to 5 years follow-up is given in **Table 4**.

The relative benefits of EES compared with PES in reducing the primary endpoint were consistent across all analyzed subgroups. However, interaction testing was nonsignificant between stent type and analyzed subgroups. Of note, there was a trend for greater absolute benefit in female patients and in patients with multivessel treatment (p for interaction = 0.05 and 0.08, respectively). The former finding potentially reflects the superiority of EES over PES in smaller vessels and more complex lesions, which are more prevalent in the female PCI population compared with the male PCI population. The latter finding, combined with the overall superiority of EES over PES at 5-year follow-up in this trial, raises the possibility that the SYNTAX (TAXUS Drug-Eluting Stent Versus Coronary Artery Bypass Surgery for the Treatment of Narrowed Arteries) trial might have been more favorable for PCI if EES had been used as the comparator to coronary artery bypass graft surgery (21,22).

Finally, the SPIRIT III and SPIRIT IV trials, as well as pooled patient-level analysis consisting of the SPIRIT II, SPIRIT III, SPIRIT IV, and COMPARE trials, have suggested a diminished efficacy of EES compared with PES measured by the endpoint target lesion failure in the diabetic subgroup (4,5,23). However, our stratified analysis shows numerical superior performance of EES compared with PES in patients with diabetes at 5-year follow-up. Additional studies are warranted to delineate the interaction between diabetic state, DES, and vascular response.

STUDY LIMITATIONS. The COMPARE trial was conducted in a single high-volume, tertiary center, and the results might not be applicable in other settings. Furthermore, PES is now seldom used in clinical practice, and these results may have limited relevance, though long-term data are imperative for confirmation of initial results because some other comparative stent trials reported significant changes in outcomes over different study time points. Secondly, the study was underpowered to derive reliable estimates of relatively low-frequency adverse events such as death or ST. Similarly, subgroup analysis is inherently underpowered and should be considered hypothesis generating. Thirdly, 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. Finally, the standard antiplatelet regimen after DES implantation at the time of the study was aspirin and clopidogrel for 12 months. A possible impact on the study results of a longer duration of DAPT or the use of the recent more potent $P2Y_{12}$ receptor inhibitors, such as of prasugrel or ticagrelor, remains unknown.

CONCLUSIONS

At 5 years, treatment with EES compared with PES resulted in sustained clinical benefits. The separation of the hazard curves for TVR, MI, and ST occurred in the first 2 to 3 years. With progression of time, the curves start to run parallel.

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PERSPECTIVES

WHAT IS KNOWN? Long-term data of comparative DES trials are scarce.

WHAT IS NEW? This paper reports that with a follow-up of 5 years, the everolimus-eluting XIENCE stent remains superior in outcome compared with the paclitaxel-eluting TAXUS stent.

WHAT IS NEXT? It also shows an ongoing device-related event rate, which indicates the need for new stent or resorbable scaffold technology to further improve outcome of patients with coronary artery disease treated with PCI.

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