JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 76, NO. 2, 2020

10-Year Outcomes From a Randomized Trial of Polymer-Free Versus Durable Polymer Drug-Eluting Coronary Stents

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ABSTRACT

BACKGROUND Outcome data after extended long-term follow-up of patients with coronary artery disease treated with drug-eluting stents (DES) in randomized clinical trials are scant.

OBJECTIVES Performance differences among devices may be expected to emerge over time depending on whether stenting is done with polymer-free or durable polymer DES. This study assessed the 10-year outcomes of patients enrolled in the ISAR-TEST-5 (Test Efficacy of Sirolimus- and Probucol-Eluting Versus Zotarolimus-Eluting Stents) trial.

METHODS A total of 3,002 patients were randomized to treatment with either polymer-free sirolimus- and probucol-eluting stents (n = 2,002) or durable polymer zotarolimus-eluting stents (n = 1,000). The primary endpoint was the composite of cardiac death, target vessel–related myocardial infarction, or target lesion revascularization (a device-oriented composite endpoint [DOCE]). Additional endpoints of interest were the patient-oriented composite endpoint (POCE), including all-cause death, any myocardial infarction, or any revascularization; individual components of the composite endpoints; and definite or probable stent thrombosis.

RESULTS The median age of the patients at randomization was 67.8 years. At 10 years, 63.9% of patients were alive. The rates of DOCE and POCE were high in both groups with no difference in the incidence between polymer-free sirolimus- and probucol-eluting stents and durable polymer zotarolimus-eluting stents (DOCE: 43.8% vs. 43.0%, respectively; hazard ratio: 1.01; 95% confidence interval [CI]: 0.89 to 1.14; p = 0.90; POCE: 66.2% vs. 67.7%, respectively; hazard ratio: 0.94; 95% CI: 0.86 to 1.04; p = 0.22). The rates of the individual components of the composite endpoints were comparable in both groups. The incidence of definite/probable stent thrombosis over 10 years was low and comparable in both groups (1.6% vs. 1.9%; hazard ratio: 0.85; 95% CI: 0.46 to 1.54; p = 0.58).

CONCLUSIONS At 10 years, there were no measurable differences in outcomes between patients treated with polymer-free versus durable polymer DES. The incidence of stent thrombosis was low and comparable in both groups. High overall adverse clinical event rates were observed during extended follow-up. (Test Efficacy of Sirolimus- and Probucol-Eluting Versus Zotarolimus-Eluting Stents [ISAR-TEST-5]; NCT00598533) (J Am Coll Cardiol 2020;76:146–58)

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ISSN 0735-1097 https://doi.org/10.1016/j.jacc.2020.05.026

The time horizon of follow-up in randomized clinical trials of patients with coronary artery disease treated with stent implantation is limited. In historical trials with predicate devices, stent failure was expected to occur within 12 months, and due to logistical and funding challenges, only a few trials incorporated additional follow-up out to 3 and sometimes 5 years (1). Data for extended long-term follow-up beyond this time point are scant, despite the fact that most patients enrolled in clinical trials are in middle age, a significant proportion of whom will have a long life expectancy with the implanted device (2–6).

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Current-generation drug-eluting stents (DES) were an important development in medical device technology and considerably improved clinical outcomes for patients compared with bare-metal stents and early-generation DES (1). Indeed, clinical practice guidelines recommend the use of DES across the spectrum of patients with coronary artery disease requiring intervention (7). Concern exists, however, about the potential adverse long-term impact of durable polymer coatings, which have been the most common type of coatings used to control drug release. In fact, autopsy studies and studies of patients presenting with acute stent failure suggest that delayed arterial healing and accelerated in-stent atherosclerosis may be widespread months and years after stenting, caused, at least partly, by an inflammatory reaction to polymer coatings (8,9). Against this background, polymer-free stent technology has been developed and shows promising results. However, due in part to the relatively low incidence of stent thrombosis, large-scale trials with extended follow-up are necessary to assess whether these technologies improve clinical outcomes.

We previously showed that a polymer-free sirolimus- and probucol-eluting stent was noninferior to a new-generation durable polymer-based zotarolimus-eluting stent with respect to clinical outcomes at 12 months (10). Against this background, we report extended 10-year follow-up of patients enrolled in the ISAR-TEST-5 (Intracoronary Stenting and Angiographic Results: Test Efficacy of Sirolimus- and Probucol- and Zotarolimus-Eluting Stents) randomized trial, which is the largest clinical trial of patients treated with polymer-free DES.

ABBREVIATIONS AND ACRONYMS

CI = confidence interval

DES = drug-eluting stent(s)

DOCE = device-oriented composite endpoint

PCI = percutaneous coronary intervention

POCE = patient-oriented outcome

METHODS

STUDY POPULATION, DEVICE DESCRIPTION, AND STUDY PROTOCOL. Patients older than 18 years 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 considered eligible, provided that written informed consent for participation in the study was obtained from the patient or her/his legally authorized representative. Patients with a target lesion located in the left main stem, cardiogenic shock, malignancies, or other comorbid conditions with a life expectancy of <12 months or that may result in protocol noncompliance; known allergy to the study medications (probucol, sirolimus, zotarolimus); or pregnancy (present, suspected, or planned) were considered ineligible for the study. The trial protocol was approved by the institutional ethics committee of the 2 participating centers: Deutsches Herzzentrum München and 1. Medizinische Klinik, Klinikum rechts der Isar, both in Munich, Germany. Full details of the study population, methods, endpoints, and primary analysis have been previously reported (10).

Patients who met all of the inclusion criteria and none of the exclusion criteria were randomized in the order that they qualified. Patients were assigned to receive polymer-free sirolimus- and probucol-eluting stents or durable polymer zotarolimus-eluting stents in a 2:1 allocation.

from Boston Scientific and Edwards; and has received grants from Amgen, not related to the current work. Dr. Koppara has received grants and speaker fees from Abbott Vascular, not related to the current work. Dr. Wiebe has received a lecture fee from AstraZeneca, not related to the current work. Dr. Schunkert has received honoraria from AstraZeneca, Bayer Vital, Merck Sharp & Dohme, Novartis, Servier, Sanofi, Boehringer Ingelheim, Daiichi-Sankyo, Amgen, and Pfizer; and has received consulting fees from AstraZeneca, Amgen, and Merck Sharp & Dohme, not related to the current work. Dr. Byrne has received lecture fees/honoraria from B. Braun Melsungen AG and Biotronik; and has received grants to the institution of prior employment from CeloNova Biosciences, not related to the current work. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC* author instructions page.

Manuscript received March 23, 2020; revised manuscript received May 10, 2020, accepted May 10, 2020.

TABLE 1 Selected Baseline Patient and Procedural Characteristics

	Polymer-Free Sirolimus- and Probucol-Eluting Stent	Durable Polymer Zotarolimus-Eluting Stent	p Value
Patients	2,002	1,000	
Age, yrs	67.7 ± 11.2	68.1 ± 10.8	0.30
Female	470 (23.5)	237 (23.7)	0.89
Diabetes mellitus	575 (28.7)	295 (29.5)	0.66
Insulin-dependent	197 (9.8)	109 (10.9)	0.37
Hypertension	1,336 (66.7)	666 (66.6)	0.94
Hyperlipidemia	1,257 (62.8)	650 (65.0)	0.24
Current smoker	357 (17.8)	166 (16.6)	0.40
Prior myocardial infarction	586 (29.3)	299 (29.9)	0.72
Prior bypass surgery	188 (9.4)	96 (9.6)	0.85
Multivessel disease	1,658 (82.3)	855 (85.5)	0.06
Clinical presentation			0.60
Acute myocardial infarction	215 (10.7)	96 (9.6)	
Unstable angina	596 (29.8)	325 (32.5)	
Stable angina	1,191 (59.5)	579 (57.9)	
Ejection fraction, %*	52.6 ± 11.9	52.4 ± 11.4	0.74
Lesions	2,912	1,479	
Target vessel			0.55
Left anterior descending	1,315 (45.2)	666 (45.0)	
Left circumflex right	711 (24.4)	386 (26.1)	
Coronary artery	886 (30.4)	427 (28.9)	
Chronic total occlusion	174 (6.0)	76 (5.1)	0.28
Bifurcation	798 (27.4)	427 (28.9)	0.39
Ostial	583 (20.0)	305 (20.6)	0.66
Complex morphology (B2/C)	2,164 (74.3)	1,088 (73.6)	0.63
Lesion length, mm	16.4 ± 9.6	16.9 ± 10.0	0.09
Vessel size, mm	2.78 ± 0.50	2.80 ± 0.50	0.23
Minimal lumen diameter, pre-procedure, mm	0.91 ± 0.50	0.90 ± 0.50	0.48
Stented length, mm	25.9 ± 12.2	26.8 ± 12.4	0.01
% Diameter stenosis, post-procedure	12.1 ± 7.4	11.7 ± 8.2	0.23

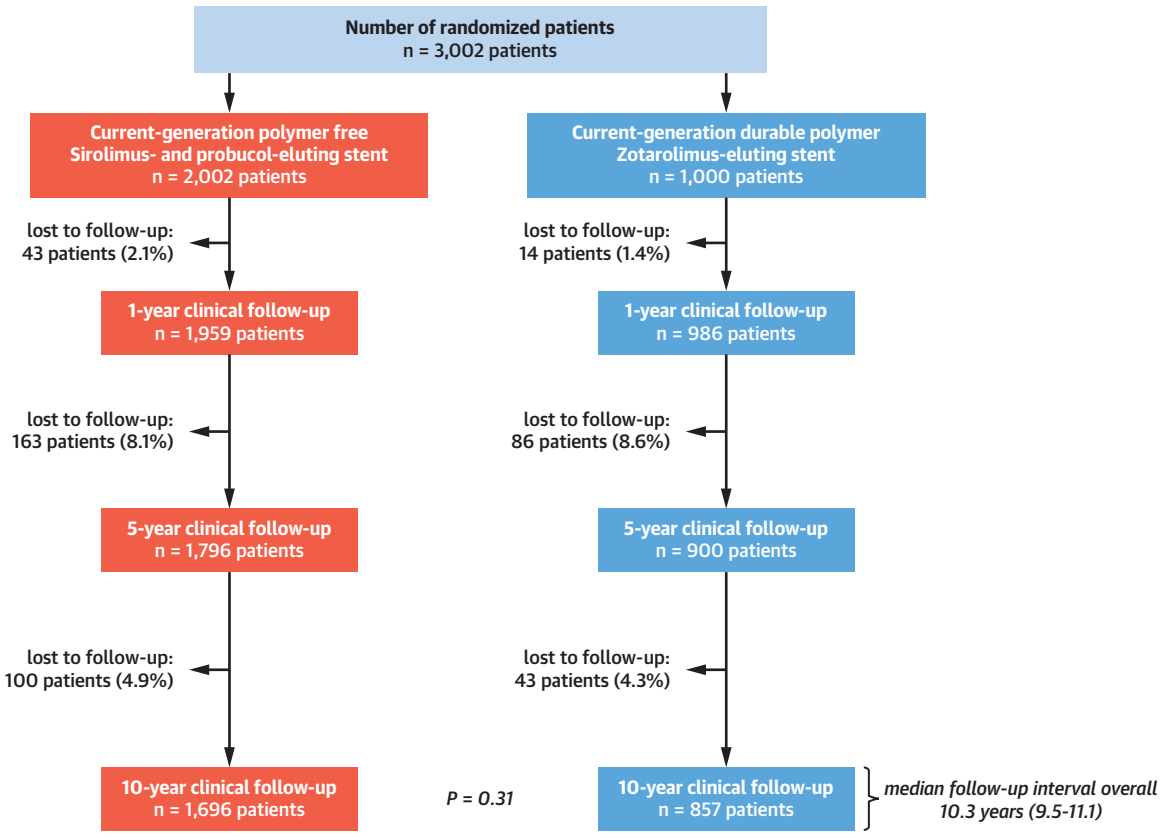
Values are n, mean ± SD, or n (%). *Data available for 2,604 (86.7%) patients.

The polymer-free sirolimus- and probucol-eluting stents consist of a pre-mounted, sand-blasted, 316L stainless steel microporous thin strut (87-μm) stent, which is coated with a mixture of sirolimus, probucol, and shellac resin (a biocompatible resin widely used in the coating of medical tablets). This coating strategy is currently available in 2 devices: ISAR VIVO (Translumina Therapeutics, Dehradoon, India; Translumina, Hechingen, Germany; and Coroflex ISAR, B. Braun Melsungen, Berlin, Germany). The durable polymer zotarolimus-eluting stent (Resolute, Medtronic Cardiovascular, Santa Rosa, California) consists of a cobalt-chrome, thin-strut (91-μm) stent platform. The polymer coating system consists of 3 different polymers: a hydrophobic C10 polymer, a hydrophilic C19 polymer, and polyvinylpyrrolidone. Further detailed descriptions of stent platforms and elution characteristics of both stents have been reported previously (11–14). The aim of the current study was to compare the outcomes of patients treated with polymer-free sirolimus- and probucol-eluting stents versus durable polymer zotarolimus-eluting stent after extended clinical follow-up out to 10 years.

ENDPOINTS AND DEFINITIONS. The primary endpoint of this study was the composite of cardiac death, myocardial infarction related to the target vessel, or target lesion revascularization (device-oriented composite endpoint [DOCE]) at 10 years. Additional endpoints of interest were the composite of all-cause death, any myocardial infarction, or any revascularization (patient-oriented composite endpoint); individual components of the composite endpoints; and the incidence of definite or probable stent thrombosis (by the Academic Research Consortium definition) at 10 years. Detailed descriptions of the study endpoints and definitions have been reported previously (10).

FOLLOW-UP AND ANALYSIS. Patients were systematically evaluated at 1 and 12 months and annually out to 10 years. Extended follow-up was performed in the

FIGURE 1 Study Flow Chart and Follow-Up at 1, 5, and 10 Years



The p value is derived from Cox proportional hazard methods and refers to completeness of 10-year follow-up in patients treated with polymer-free sirolimus- and probucol-eluting versus durable polymer zotarolimus-eluting stents. The overall follow-up interval is shown as median (25th to 75th percentiles).

setting of routine care by either telephone calls or office visit 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 Harmonisation Good Clinical Practices. All patients provided written informed consent for participation in the clinical trial. Analysis of data from extended follow-up, which was not prespecified in the trial protocol, was approved by the institutional ethics committee responsible for the participating centers. Additional written informed consent from patients was waived. All events were adjudicated and classified by an event adjudication committee blinded to treatment allocation.

STATISTICAL ANALYSIS. Continuous data are presented as mean ± SD or median (25th to 75th percentiles). Categorical data are presented as count or proportion (percentage). Data distribution was tested for normality by using the Kolmogorov-Smirnov test for goodness of fit. For patient-level data, differences between groups were checked for significance using Student's *t*-test or the Wilcoxon rank sum test (continuous data) or the chi-square or Fisher exact test when the expected cell value was <5 (categorical variables). For lesion-level data, differences between groups were checked for significance by using generalized estimating equations for non-normally distributed data to address intrapatient correlation in patients who underwent multilesion intervention (15).

Event-free survival was assessed with the methods of Kaplan-Meier. Hazard ratios, confidence intervals, and p values were calculated from univariate Cox proportional hazards models. The proportional hazards assumption was checked by the method of Grambsch and Therneau (16) and was fulfilled in all cases in which we used Cox proportional hazards models. The analysis of primary and secondary endpoints was planned to be performed on an intention-to-treat basis (17). Analysis of the primary outcome

FIGURE 2 Device-Oriented Outcomes at 10 Years

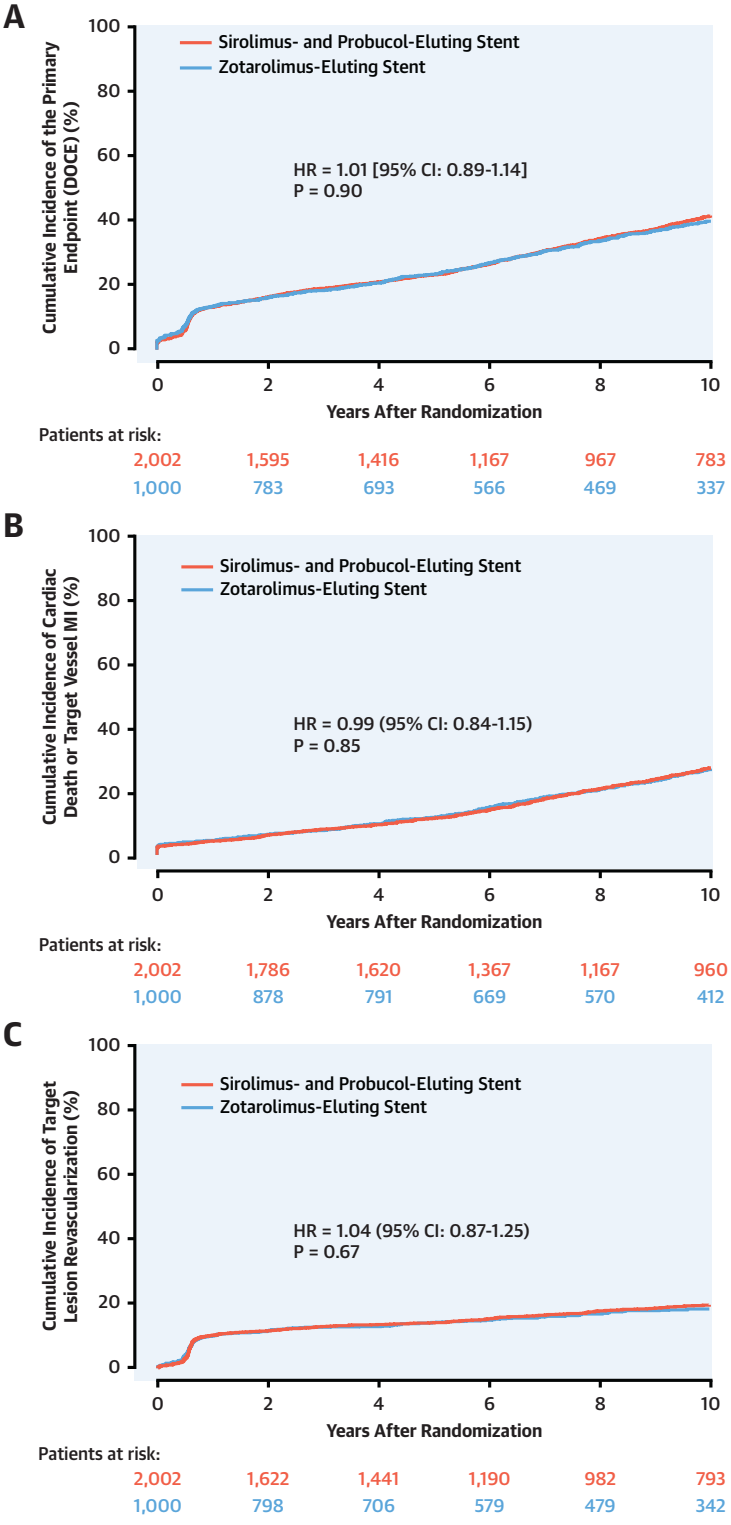


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TABLE 2 Clinical Results at 10 Years

	Polymer-Free Sirolimus- and Probucol-Eluting Stent	Durable Polymer Zotarolimus-Eluting Stent	Hazard Ratio (95% CI)	p Value
Device-oriented outcomes				
Cardiac death, MI related to target vessel, or target lesion revascularization	765 (43.8)	370 (43.0)	1.01 (0.89–1.14)	0.90
Cardiac death or MI related to target vessel	488 (29.2)	242 (29.3)	0.99 (0.84–1.15)	0.85
Cardiac death	438 (26.7)	217 (26.9)	0.99 (0.84–1.16)	0.86
MI related to target vessel	69 (3.8)	41 (4.4)	0.83 (0.57–1.23)	0.35
Target lesion revascularization	371 (21.9)	175 (20.6)	1.04 (0.87–1.25)	0.67
Patient-oriented outcomes				
All-cause death, any MI, or any revascularization	1,263 (66.2)	649 (67.7)	0.94 (0.86–1.04)	0.22
All-cause death or any MI	703 (38.3)	370 (40.0)	0.89 (0.82–1.06)	0.29
All-cause death	637 (35.0)	343 (37.3)	0.91 (0.80–1.04)	0.16
Any MI	103 (5.7)	52 (5.8)	0.98 (0.70–1.37)	0.91
Any revascularization	826 (45.9)	415 (47.0)	0.96 (0.86–1.09)	0.56

Values are n (%) by Kaplan-Meier analysis; hazard ratios and p values were calculated from Cox proportional hazard models.
CI = confidence interval; MI = myocardial infarction.

was also performed for pre-specified subsets of interest: old and young patients (above and at or below the median age), men and women, diabetic and nondiabetic patients, and small and large vessels (below and at or above the median value). The interaction between treatment effect and these covariates was assessed with Cox proportional hazards models. Statistical software R, version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria), was used for analysis.

RESULTS

PATIENTS. Between February 2008 and August 2009, 3,002 patients were enrolled and randomized to receive either polymer-free sirolimus- and probucol-eluting (n = 2,002) or durable polymer zotarolimus-eluting (n = 1,000) stents. The study enrolled a high proportion of patients with advanced age and multivessel disease. More than one-quarter of the study population had diabetes mellitus at baseline. More than 40% of patients presented with an acute coronary syndrome. Baseline patient characteristics according to the treatment groups were well balanced and are shown in Table 1.

The total number of treated lesions was 4,391 (sirolimus- and probucol-eluting stent, n = 2,912; zotarolimus-eluting stent, n = 1,479). More than 1 lesion was treated in 35.7% of patients in the sirolimus- and probucol-eluting stent group versus 37.8% in the zotarolimus-eluting group (p = 0.26). Baseline lesion and procedural characteristics according to the treatment groups are shown in Table 1.

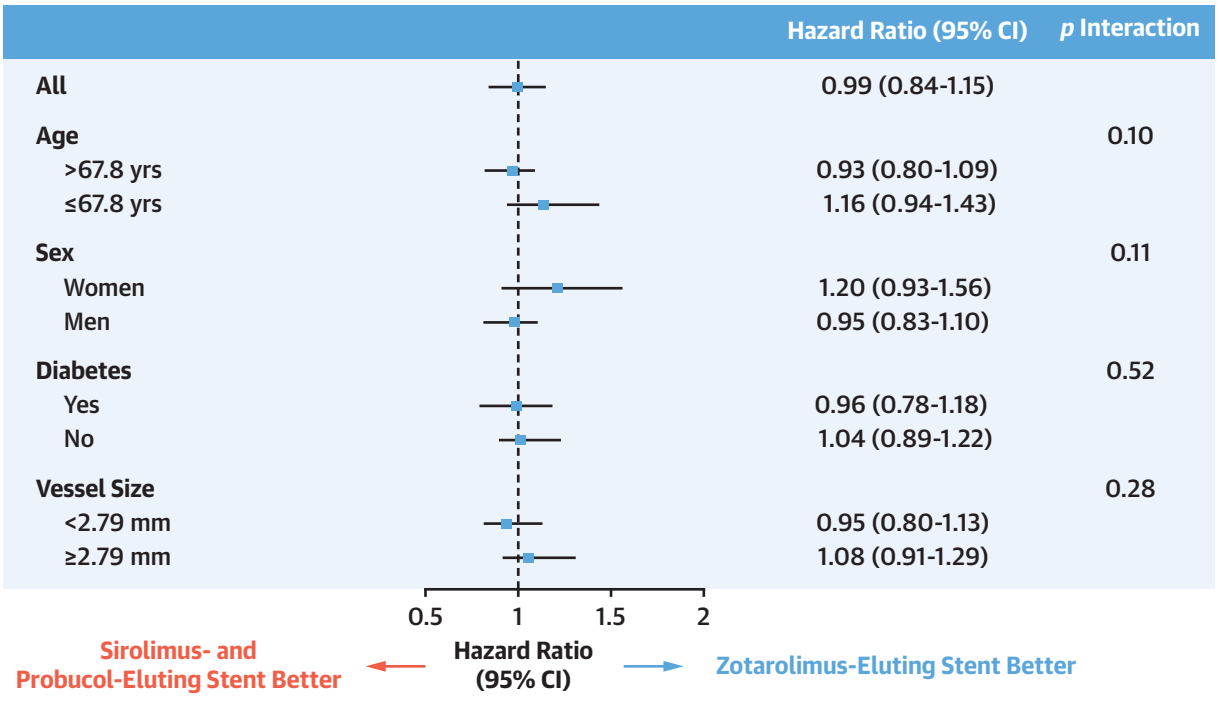
The 10-year follow-up was complete for all but 449 patients (14.9%). The median follow-up interval was 10.3 years (9.5 to 11.1 years). Between 5 and 10 years post-procedure, 143 patients (4.8%) were lost to follow-up. Concerning the completeness of follow-up, there was no significant difference between the 2 study groups: 306 (15.2%) patients in the sirolimus- and probucol-eluting stent group and 143 (14.3%) patients in the zotarolimus-eluting stent group (p = 0.31). The study flow chart and detailed follow-up results are displayed in Figure 1.

DEVICE-ORIENTED OUTCOMES AT 10 YEARS. The results of 10-year follow-up are shown in Table 2. Regarding the primary endpoint, there was no difference between sirolimus- and probucol-eluting stent and zotarolimus-eluting stent (43.8% vs. 43.0% respectively; hazard ratio: 1.01; 95% confidence interval [CI]: 0.89 to 1.14; p = 0.90). Figure 2A shows survival analysis curves for the occurrence of the primary endpoint. There was no evidence of interaction between treatment effect and each of the pre-specified subgroups of age, sex, diabetes, and

FIGURE 2 Continued

Time-to-event curves for incidence of **(A)** the primary composite endpoint of cardiac death, myocardial infarction related to the target vessel, or target lesion revascularization; **(B)** the composite of cardiac death or myocardial infarction related to the target vessel; and **(C)** target lesion revascularization. Hazard ratios and p values are derived from Cox proportional hazard models. CI = confidence interval; DOCE = device-oriented composite endpoint; HR = hazard ratio.

FIGURE 3 Treatment Effect for Sirolimus- and Probucol-Eluting Versus Zotarolimus-Eluting Stents for the Primary Endpoint in the Overall Study Population and in Pre-Specified Subgroups



The p values for interaction are derived from Cox proportional hazard models. CI = confidence interval.

vessel size. Details concerning subgroup analysis are displayed in Figure 3.

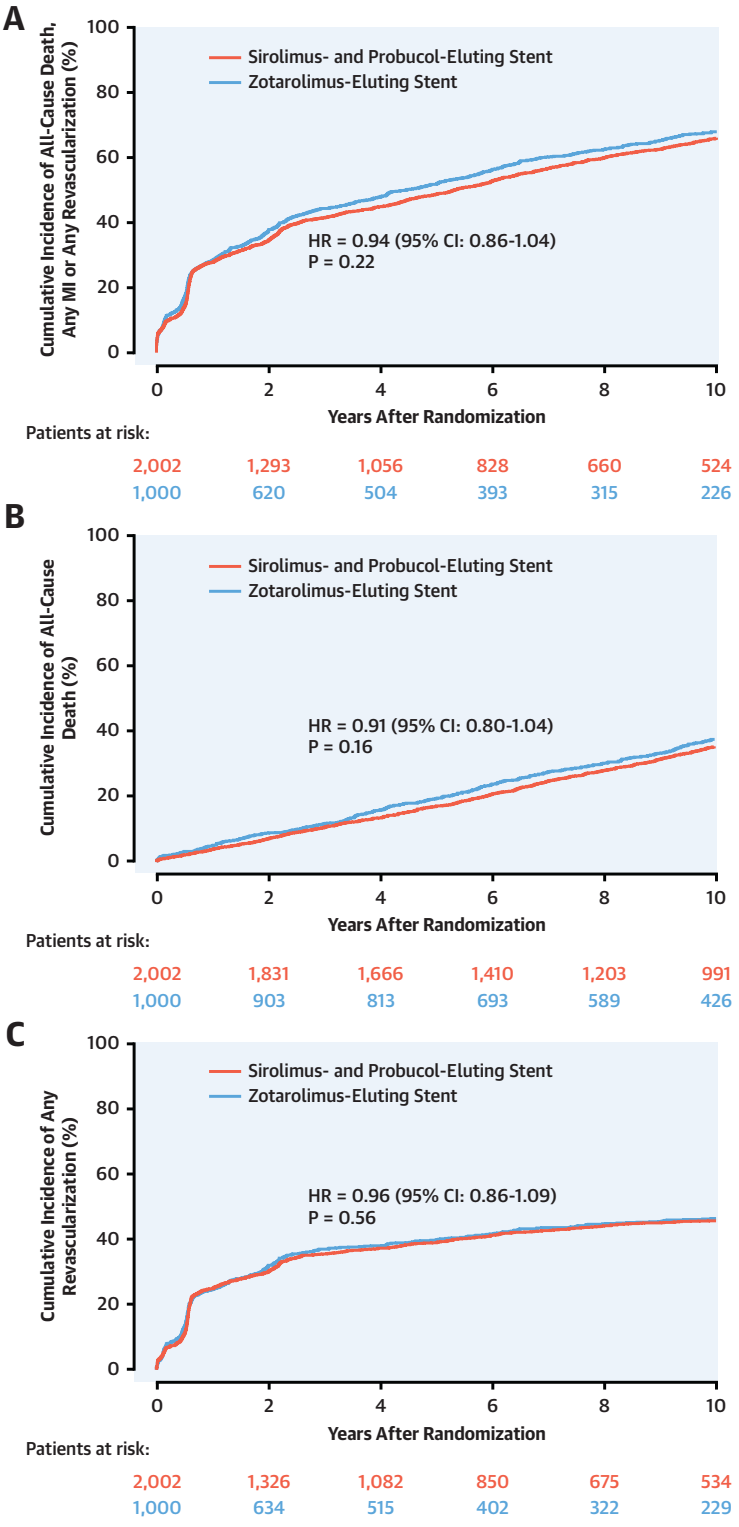
In terms of individual components of the primary endpoint, the sirolimus- and probucol-eluting stent compared with the zotarolimus-eluting stent showed similar rates of cardiac death or myocardial infarction related to the target vessel (29.2% vs. 29.3% respectively; hazard ratio: 0.99; 95% CI: 0.84 to 1.15; p = 0.85) (Figure 2B), cardiac death (26.7% vs. 26.9%, respectively; hazard ratio: 0.99; 95% CI: 0.84 to 1.16; p = 0.86), or myocardial infarction related to the target vessel (3.8% vs. 4.4%, respectively; hazard ratio: 0.83; 95% CI: 0.57 to 1.23; p = 0.35); rates of target lesion revascularization were also similar in both groups (21.9% vs. 20.6%, respectively; hazard ratio: 1.04; 95% CI: 0.87 to 1.25; p = 0.67) (Figure 2C).

PATIENT-ORIENTED OUTCOMES AT 10 YEARS. Regarding the composite endpoint of all-cause death, any myocardial infarction, or any revascularization, there was no difference between sirolimus- and probucol-eluting stent and zotarolimus-eluting stent (66.2% vs. 67.7% respectively; hazard ratio: 0.94; 95% CI: 0.86 to 1.04; p = 0.22) (Figure 4A).

In terms of individual components of the patient-oriented composite endpoint, the sirolimus- and probucol-eluting stent in comparison with the zotarolimus-eluting stent showed similar rates of all-cause death or any myocardial infarction (38.3% vs. 40.0%, respectively; hazard ratio: 0.89; 95% CI: 0.82 to 1.06; p = 0.29). At 10 years, 63.9% of patients were alive. There was no difference between sirolimus- and probucol-eluting stent and zotarolimus-eluting stent concerning all-cause death (35.0% vs. 37.3%, respectively; hazard ratio: 0.91; 95% CI: 0.80 to 1.04; p = 0.16) (Figure 4B), any myocardial infarction (5.7% vs. 5.8%, respectively; hazard ratio: 0.98; 95% CI: 0.70 to 1.37; p = 0.91), or any revascularization (45.9% vs. 47.0%, respectively; hazard ratio: 0.96; 95% CI: 0.86 to 1.09; p = 0.56) (Figure 4C). Time-to-event curves of the composite of all-cause death, any myocardial infarction, or any revascularization landmark analysis at 0 to 1, 1 to 5, and 5 to 10 years are displayed in the Central Illustration.

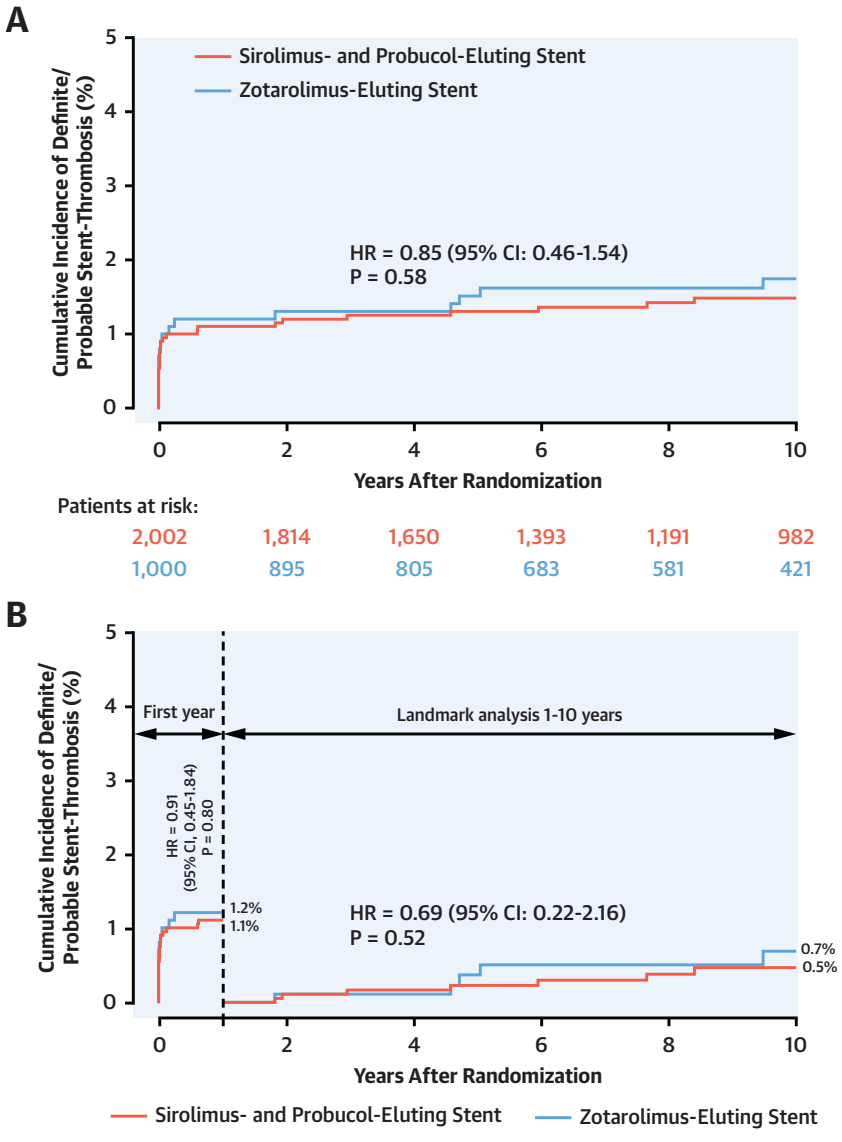
DEFINITE OR PROBABLE STENT THROMBOSIS AT 10 YEARS. In terms of safety endpoints, the sirolimus- and probucol-eluting stent in comparison with the zotarolimus-eluting stent showed comparable rates of definite or probable stent thrombosis (1.6% vs. 1.9%, respectively; hazard ratio: 0.85; 95% CI: 0.46

FIGURE 4 Patient-Oriented Outcomes at 10 Years



Time-to-event curves for the incidence of **(A)** the composite of all-cause death, myocardial infarction, or any revascularization; **(B)** all-cause death; and **(C)** any revascularization. Hazard ratios and p values are derived from Cox proportional hazard models. MI = myocardial infarction; other abbreviations as in Figure 2.

FIGURE 5 Definite or Probable Stent Thrombosis at 10 Years



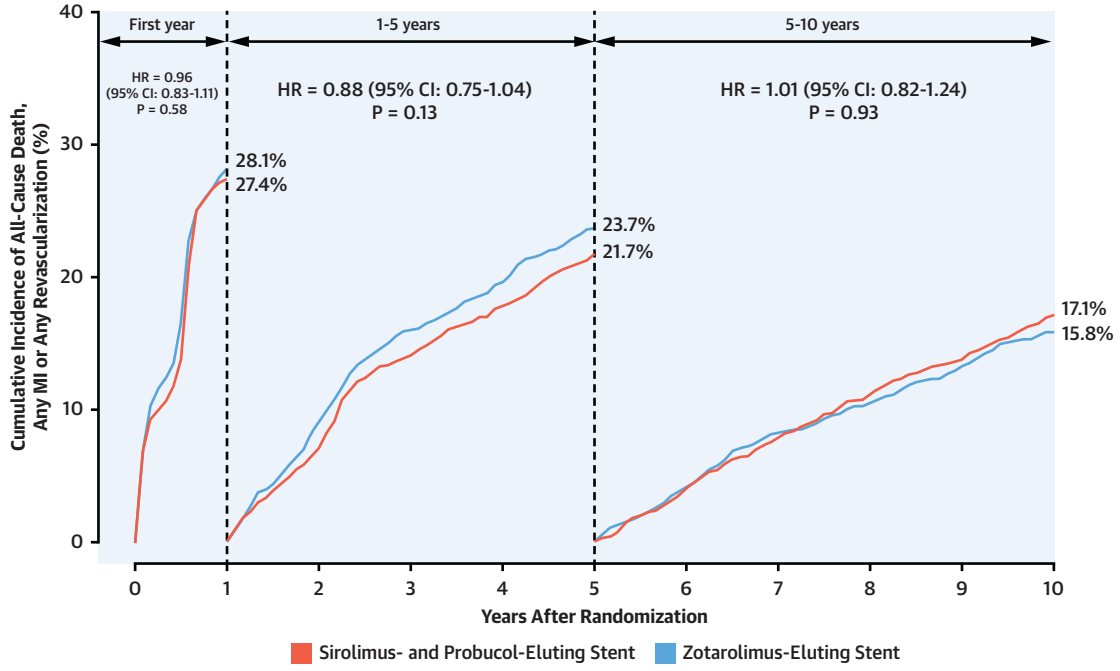
Time-to-event curves for the incidence of **(A)** definite or probable stent thrombosis and **(B)** landmark analysis of the incidence of definite or probable stent thrombosis between 0 and 1 year and 1 and 10 years. Hazard ratios and p values are derived from Cox proportional hazard models. Abbreviations as in Figure 2.

to 1.54; p = 0.58) (Figure 5A). Detailed outcomes regarding definite and probable stent thrombosis are displayed in Table 3. In a landmark analysis, between 1 and 10 years after index percutaneous coronary intervention (PCI), the sirolimus- and probucol-eluting stent compared with the zotarolimus-eluting stent showed comparable and low rates of very late (>1 year after the index PCI) definite/probable stent thrombosis (0.5% vs. 0.7%, respectively; hazard ratio: 0.69; 95% CI: 0.22 to 2.16; p = 0.52) (Figure 5B).

DISCUSSION

The results of the current report detail the cardiovascular outcomes of patients with extended long-term follow-up after PCI in the setting of a randomized clinical trial. This is important because of the broad spectrum of age profiles and life expectancies of patients with coronary artery disease requiring revascularization and the relatively high proportion of patients affected in middle age. In this respect, trials

CENTRAL ILLUSTRATION **Landmark Analysis, Patient-Oriented Outcomes According to Treatment Groups**



Kufner, S. et al. J Am Coll Cardiol. 2020;76(2):146–58.

(A) Combined incidence of the patient-oriented composite endpoint. Landmark analysis at 0 to 1, 1 to 5, and 5 to 10 years with time-to-event curves for the incidence of the composite of all-cause death, any myocardial infarction, or any revascularization. Hazard ratios and p values are derived from Cox proportional hazard models. CI = confidence interval; HR = hazard ratio; MI = myocardial infarction.

with extended follow-up better evaluate the full life-cycle risk of adverse events associated with high-risk medical devices such as coronary stents. In addition, our report represents the first with long-term follow-up of patients treated with durable polymer zotarolimus-eluting stent—which are frequently used in clinical practice—and the first with polymer-free DES-which are hypothesized to have a possible late safety advantage compared with conventional DES.

Our study has a number of important strengths. First, our analysis included extended follow-up out to 10 years and is among the few reports in the literature of trials of coronary stents with >5-year follow-up. Second, we used active rather than passive follow-up methods, which, in our opinion, are more likely to capture events compared with follow-up restricted to analysis of registries of vital status or hospital admission. Third, we incorporated adjudication of patient-oriented and device-oriented outcomes by dedicated study personnel.

The main findings of this study are that at 10 years, treatment with polymer-free probucol- and sirolimus-eluting stent, compared with with a durable polymer zotarolimus-eluting stent, is associated with similar frequency of device- and patient-related adverse events. Second, the incidence of adverse safety events—including myocardial infarction and stent thrombosis—were low and comparable in both groups. In particular, the very low rate of stent thrombosis beyond 1 and out to 10 years (<1% in the 2 study groups) is remarkable and seems to be representative of an improvement in the safety profile of current-generation coronary stents compared with early-generation technologies. This further suggests that differentiating the duration of dual antiplatelet therapy after stenting according to the presence or absence of polymer may not be necessary. Third, the steady rate of patient-related adverse events over time (>65% incidence in both study groups) remains considerable. This is broadly in line with other trials (18-20) and highlights the need for optimization of background medical therapies targeted at retardation of disease progression and the unmet need for novel adjunctive therapies.

The development of DES represented a significant forward step in the battle against restenosis following

TABLE 3 Stent Thrombosis at 10 Years

Stent Thrombosis	Polymer-Free Sirolimus- and Probucol-Eluting Stent	Durable Polymer Zotarolimus-Eluting Stent	Hazard Ratio (95% CI)	p Value
Definite	15 (0.8)	7 (0.8)	1.06 (0.43–2.61)	0.90
Probable	14 (0.8)	10 (1.1)	0.70 (0.31–1.56)	0.38
Possible	20 (1.2)	7 (0.8)	1.41 (0.60–3.33)	0.44
Definite or probable	29 (1.6)	17 (1.9)	0.85 (0.46–1.54)	0.58

Values are n (%) by Kaplan-Meier analysis; hazard ratios and p values were calculated from Cox proportional hazard models.

CI = confidence interval.

coronary intervention (1). Early-generation DES demonstrated a significantly increased risk of very late stent thrombosis compared with bare-metal stents. This seemed to be related to systematically impaired arterial healing after stent implantation compared with bare-metal stents (21). The underlying pathogenic mechanisms appeared to be polymer-related inflammatory reaction and endothelial cell dysfunction, which may predispose to more thrombus formation on uncovered struts and, later on, to accelerated de novo atherosclerosis developing within the stented segment, a condition referred to as neoatherosclerosis (22,23).

Because of these concerns, polymer-free stent technology has been investigated since early in the development of DES technology. Initial investigations suggested inferior clinical efficacy of polymer-free DES compared with durable polymer DES (24,25). This resulted from a poorly controlled and overly rapid drug-release profile in the early days after stent implantation, which is intrinsically linked to impaired suppression of neointimal hyperplasia—the dominant cause of in-stent restenosis. Approaches designed to address inferior efficacy focused on using alternative methods to control release of the active drug or incorporation of a second drug, targeted at another element of the restenotic response cascade. The polymer-free sirolimus- and probucol-eluting stent represents one such approach, and the primary analysis of the present trial showed an antirestenotic efficacy in line with high-performance durable polymer stents (10,26).

The benefit of stents without polymer is expected to accrue with time. However, in many respects, the failure to detect a late advantage with the polymer-free stent—despite following a large number of patients out to 10 years—calls this hypothesis into question. On the other hand, it might be observed that the rate of device-related adverse events (e.g., stent thrombosis) was low and comparable in both groups. This may reflect improvements in the technology studied in both treatment arms—with the absence of polymer in the polymer-free stent group offset by enhanced biocompatibility of the durable polymer coating used on the device in the control group. In addition, although we cannot discount that the absence of differences was due to lack of statistical power and the impact of missing data, meaningful differences between the 2 study devices in relation to stent thrombosis seems unlikely.

Target vessel revascularization rates in both groups are high in comparison with other recent clinical trials, for example the BIONICS (BioNIR Ridaforolimus-Eluting Coronary Stent System in Coronary Stenosis) trial, which also used zotarolimus-eluting stent as a comparator (27). There are 2 main reasons for this. The first relates to increased baseline risk of the enrolled patients in ISAR-TEST-5, and the second relates to the study methodology used. First, ISAR-TEST-5 was conducted at centers where the majority of eligible patients undergoing coronary stenting were enrolled in the trial. In ISAR-TEST-5, 3,002 patients were enrolled at 2 centers over 18 months. In BIONICS, 1,919 patients were enrolled at 76 sites over 17 months. Selection bias for inclusion into the trial was likely lower in ISAR-TEST-5 than in other trials. As evidence of this, the mean age at baseline is considerably higher than in other device trials (approximately 68 years in ISAR-TEST-5 vs. approximately 63 years in BIONICS), and all-cause death at 1 year is significantly higher (3.9% [118 deaths] vs. 1.1% [21 deaths], respectively). Second, the trial protocol in ISAR-TEST-5 planned angiographic follow-up at 6 to 8 months for all patients in ISAR-TEST-5. This is known to inflate the rate of revascularization compared with standard follow-up. In comparison, the BIONICS trial included follow-up angiography at 13 months in 8% of the overall study cohort.

Observations in relation to patient-oriented outcomes in the current report also deserve detailed considerations. In keeping with previous randomized controlled trials, at 10-year follow-up in our study, patient-oriented endpoints—such all-cause mortality, any myocardial infarction, and any revascularization—predominate over device-specific endpoints (18–20). Overall mortality rates—approximately 37% in the current study—are somewhat higher than rates reported in other trials with 10-year follow-up, which typically had mortality rates ranging from 24% to 27% (19,20). This may reflect higher baseline risk of the population enrolled in ISAR-TEST-5, as discussed already. Moreover, the majority of patients (67%) died from cardiac causes. These findings contrast with previous registry-based reports showing that mortality, especially during long-term follow up after

PCI, is mainly driven by noncardiac death, with a temporal switch from predominantly cardiac- to predominantly noncardiac-caused death during long-term follow-up (28). In relation to repeat revascularization, rates of any revascularization are 2-fold higher than rates of target lesion revascularization. Unsurprisingly, and in line with previous observations, these findings suggest that disease progression in other coronary segments is a stronger prognostic factor for late and very late patient-related outcomes than recurrent events in the intervened lesion (29). This emphasizes that improved secondary prevention measures should be an important part of future development and investigation.

STUDY LIMITATIONS. First, this trial was powered to show noninferiority of the study stent (the probucol- and sirolimus-eluting stent) versus the control stent (the zotarolimus-eluting stent) at 12 months. Additional comparisons should be regarded as post hoc and should be interpreted with caution. Second, the comparative efficacy of the DES investigated in the present study should be considered in the context of differences among the study DES regarding not just polymer coating but also stent backbone, alloy, strut thickness, and drug type. Third, the treatment type was not blinded to patients or physicians because of the logistical difficulties involved in blinding. However, assessors adjudicating events were blinded to stent type. Finally, the impact of missing data in relation to long-term follow-up must be considered.

CONCLUSIONS

In this unique long-term analysis out to 10 years, there were no measurable differences in outcomes between patients treated with a polymer-free sirolimus- and probucol-eluting stent and those treated with a new-generation durable polymer zotarolimus-eluting stent. The incidence of stent thrombosis was low and comparable in both groups, suggesting that differentiating duration of dual antiplatelet therapy after stenting according to the presence or absence of polymer may not be necessary. Overall cumulative adverse cardiac event rates were high during 10-year follow-up, highlighting an unmet need for further development of secondary prevention measures in patients undergoing coronary stenting.

ACKNOWLEDGMENTS The authors thank Karin Hoesl and Nonglag Rifatov for their contribution to patient follow-up and data management.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: In patients treated with current-generation DES, stent-related outcomes are similar 10 years after deployment of polymer-free or durable polymer devices.

TRANSLATIONAL OUTLOOK: The continued occurrence of adverse cardiac events even a decade after DES deployment indicates the need for further research to develop more effective secondary prevention strategies.

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KEY WORDS drug-eluting stent, durable polymer, long-term follow-up, polymer free, probucol, randomized controlled trial, sirolimus, zotarolimus