



Randomized Trial of Polymer-Free Sirolimus- and Probucol-Eluting Stents Versus Durable Polymer Zotarolimus-Eluting Stents

5-Year Results of the ISAR-TEST-5 Trial

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ABSTRACT

OBJECTIVES The aim of this study was to evaluate the late clinical performance of a polymer-free sirolimus- and probucol-eluting stent compared with a new-generation durable polymer-based zotarolimus-eluting stent.

BACKGROUND It was previously shown that polymer-free sirolimus- and probucol-eluting stents were noninferior to zotarolimus-eluting stents at 12 months. However, long-term follow-up of these devices is critical to evaluate late comparative efficacy.

METHODS In a clinical trial with minimal exclusion criteria, 3,002 patients were randomly assigned to treatment with polymer-free sirolimus- and probucol-eluting stents versus zotarolimus-eluting stents. The primary endpoint was the combined incidence of cardiac death, target vessel-related myocardial infarction, or target lesion revascularization.

RESULTS At 5 years, there was no difference in the incidence of the primary endpoint between sirolimus- and probucol-eluting stents and zotarolimus-eluting stents (23.8% vs. 24.2%, respectively; hazard ratio: 0.98; 95% confidence interval: 0.84 to 1.15; $p = 0.80$). The rates of the individual components of the primary endpoint were also comparable in both groups. The incidence of definite or probable stent thrombosis was low in both groups (1.3% vs. 1.6%, respectively; hazard ratio: 0.86; 95% confidence interval: 0.46 to 1.62; $p = 0.64$). The rates of any death, myocardial infarction, and revascularization were similar in both groups. Results were consistent across pre-specified subgroups of age, sex, diabetes, and vessel size.

CONCLUSIONS Long-term outcomes of patients treated with polymer-free sirolimus- and probucol-eluting stents compared with a new-generation durable polymer-based zotarolimus-eluting stent were similar. Rates of stent thrombosis were low and comparable in both treatment groups, with few events beyond 12 months. (Efficacy Study of Rapamycin- vs. Zotarolimus-Eluting Stents to Reduce Coronary Restenosis [ISAR-TEST-5]; [NCT00598533](https://doi.org/10.1016/j.jcin.2016.01.009)) (J Am Coll Cardiol Intv 2016;9:784–92) © 2016 by the American College of Cardiology Foundation.

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Polymer coatings are important components of drug-eluting stent (DES) technology, controlling the release kinetics of the active drug, the critical determinant of antirestenotic efficacy (1). Furthermore, there is ongoing debate over potential beneficial antithrombogenic effects of polymer coatings (2,3). At the same time, it is well recognized that inflammatory reaction to durable polymer coatings plays an important causative role in the process of delayed arterial healing after DES implantation (4,5). This pathophysiological condition likely underlies a spectrum of late adverse events, including late stent thrombosis, delayed late luminal loss, and de novo in-stent atherosclerosis (6). Therefore, great efforts have been made to create polymer coatings with higher biocompatibility in new-generation permanent polymer DES (7). The new-generation zotarolimus-eluting stent represents a potential forward step in DES therapy. A 3-component durable polymer combines hydrophilic surface elements with a hydrophobic core and offers potentially improved biocompatibility, with enhanced drug-release kinetics.

Probucol is an antioxidant with efficacy as a systemic agent in preventing restenosis after coronary intervention (8–10). In addition, when used as a component of a stent coating matrix, its high lipophilicity means that it can retard the release of sirolimus, enhancing its antirestenotic efficacy (11). 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 (12). However, despite encouraging clinical data at short- to medium-term follow-up, the late performance of these stents remains poorly delineated. Against this background, we performed 5-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.

METHODS

STUDY POPULATION, DEVICE DESCRIPTION, AND STUDY PROTOCOL. Full details of the study population, methods, endpoints, and primary analysis have been previously reported (12). In brief, between February 2008 and August 2009, patients older than 18 years of age with ischemic symptoms or evidence of myocardial ischemia (inducible or spontaneous) in the presence of $\geq 50\%$ de novo stenosis located in native coronary vessels were considered eligible, provided that written informed consent from patients

or their legally authorized representatives for participation in the study was obtained. Patients with target lesions located in the left main stem, cardiogenic shock, malignancies or other comorbid conditions with life expectancy less than 12 months or that may result in protocol noncompliance, known allergy to the study medications (probucol, sirolimus, and zotarolimus), or pregnancy (present, suspected, or planned) were considered ineligible for the study. The study was conducted in accordance with the provisions of the Declaration of Helsinki and with the International Conference on Harmonization Good Clinical Practices. The trial protocol was approved by the institutional ethics committee of the 2 participating centers: Deutsches Herzzentrum München and I. Medizinische Klinik, Klinikum Rechts der Isar, both in Munich, Germany.

Patients who met all of the inclusion criteria and none of the exclusion criteria were randomized in the order in which they qualified. Patients were assigned to receive polymer-free sirolimus- and probucol-eluting stents or permanent polymer zotarolimus-eluting stents in a 2:1 allocation. The polymer-free stent platform consists of a pre-mounted, sand-blasted, 316L stainless steel microporous stent coated with a mixture of sirolimus, probucol, and shellac resin (a biocompatible resin widely used in the coating of medical tablets). The permanent polymer zotarolimus-eluting stent (Resolute; Medtronic Cardiovascular, Santa Clara, California) consists of a thin-strut stainless steel stent platform (Driver). The polymer coating system (BioLinx) consists of 3 different polymers: a hydrophobic C10 polymer, a hydrophilic C19 polymer, and polyvinylpyrrolidinone. Further detailed descriptions of stent platforms and elution characteristics of both stents have been reported previously (7,11,13,14). The aim of the present study was to compare outcomes of patients treated with polymer-free sirolimus- and probucol-eluting stents versus permanent polymer zotarolimus-eluting stents after 5-year clinical follow-up.

ENDPOINTS AND DEFINITIONS. The primary endpoint of this study was the device-oriented composite of cardiac death, myocardial infarction (MI) related to the target vessel, or target lesion revascularization at 60 months post-index intervention. Secondary endpoints were cardiac death, MI related to the target vessel, target lesion revascularization, all-cause mortality, any MI, any revascularization, target vessel revascularization, and the incidence of definite or probable stent thrombosis (by

ABBREVIATIONS AND ACRONYMS

CI	= confidence interval
CK	= creatine kinase
DES	= drug-eluting stent(s)
HR	= hazard ratio
MI	= myocardial infarction
ULN	= upper limit of normal

Academic Research Consortium definition) at 60 months. MI related to procedure was defined as either an increase in creatine kinase (CK)-MB (or CK) ≥ 3 times the upper limit of normal (ULN) and at least 50% higher than the most recent pre-percutaneous coronary intervention levels or the development of new electrocardiographic changes consistent with MI and CK-MB (or CK) elevation higher than the ULN at 2 measurements for patients undergoing DES implantation in the setting of stable angina pectoris or non-ST-segment elevation acute coronary syndrome and falling or normal CK-MB (or CK) levels. Recurrent chest pain lasting more than 30 min with either new electrocardiographic changes consistent with second MI or next CK-MB (or CK) level at least 8 to 12 h after percutaneous coronary intervention elevated at least 50% higher than the previous level was considered procedure-related MI for patients presenting with non-ST-segment elevation acute coronary syndromes and elevated CK-MB (or CK) levels prior to percutaneous coronary intervention. Bypass surgery-related MI was considered either CK-MB elevation ≥ 10 times the ULN and at least 50% higher than the most recent pre-surgery levels or CK-MB elevation ≥ 5 times the ULN and at least 50% higher than the most recent pre-surgery levels in addition to new abnormal Q waves on electrocardiography. Spontaneous MI was defined as any CK-MB increase with or without the development of Q waves on electrocardiography. Detailed definitions of endpoints have been previously reported (12).

FOLLOW-UP AND ANALYSIS. Patients were systematically evaluated at 1, 12, 24, and 60 months by telephone call or office visit. Repeat coronary angiography was scheduled for 6 to 8 months, according to the trial protocol. Additional analyses at long-term follow-up (beyond 12 months) may be regarded as post hoc analysis. All events were adjudicated and classified by an event adjudication committee blinded to the treatment groups.

STATISTICAL ANALYSIS. Continuous data are presented as mean \pm SD or median (interquartile range). Categorical data are presented as counts or proportions. Data distribution was tested for normality using the Kolmogorov-Smirnov test for goodness of fit. For patient-level data, differences between groups were checked for significance using the Student *t* test or 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 using generalized estimating equations for data not normally distributed to address inpatient correlation in patients who underwent multiple-lesion intervention (15).

Event-free survival was assessed using the Kaplan-Meier method. Hazard ratios (HRs), confidence intervals (CIs), 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 was also performed for pre-specified subsets of interest: old and young patients (above and at or below the median age), men and women, patients with and those without diabetes, and small and large vessels (below and at or above the median value). Interaction between treatment effect and these covariates was assessed using Cox proportional hazards models. S-PLUS version 4.5 (Insightful Corporation, Seattle, Washington) was used for statistical analysis.

RESULTS

PATIENTS. A total of 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. As shown in Table 1, the groups were well matched in terms of baseline patient and lesion characteristics. Minimal luminal diameter post-procedure ($p = 0.04$) and total stent length ($p = 0.01$) were marginally higher in the zotarolimus-eluting stent group.

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 and 37.8% in the zotarolimus-eluting group ($p = 0.26$). Five-year follow-up was complete in all but 306 patients (10.2%), without any significant difference between the 2 study groups (206 patients [10.3%] in the sirolimus- and probucol-eluting stent group and 100 patients [10.0%] in the zotarolimus-eluting stent group, $p = 0.94$).

DEVICE-ORIENTED OUTCOMES AT 5 YEARS. The results of 5-year follow-up are shown in Table 2. Regarding the primary endpoint, the composite

of cardiac death, MI related to the target vessel, and target lesion revascularization, there was no difference between sirolimus- and probucol-eluting stents and zotarolimus-eluting stents (23.8% vs. 24.2%, respectively; HR, 0.98; 95% CI: 0.84 to 1.15; $p = 0.80$). **Figure 1A** shows survival analysis curves for the occurrence of the primary endpoint. Adjusted results for multivessel disease and total stented length were comparable (HR, 1.01; 95% CI: 0.86 to 1.19). Patients with multivessel disease had a 2-fold higher risk for cardiac death, MI related to the target vessel, or target lesion revascularization (HR, 2.01; 95% CI: 1.55 to 2.60).

In terms of individual components of the primary endpoint, the sirolimus- and probucol-eluting stent in comparison with the zotarolimus-eluting stent showed similar rates of cardiac death or MI related to the target vessel (11.8% vs. 12.2%, respectively; HR, 0.96; 95% CI: 0.77 to 1.21; $p = 0.73$) (**Figure 1B**), cardiac death (9.3% vs. 9.4%, respectively; HR, 0.99; 95% CI: 0.76 to 1.28; $p = 0.93$), and MI related to the target vessel (3.3% vs. 4.0%, respectively; HR, 0.80; 95% CI: 0.53 to 1.19; $p = 0.27$); rates of target lesion revascularization were also similar in both groups (14.7% vs. 14.7%, respectively; HR, 1.00; 95% CI: 0.82 to 1.23; $p = 0.98$) (**Figure 1C**).

In terms of safety endpoints, the sirolimus- and probucol-eluting stent in comparison with the zotarolimus-eluting stent showed similar rates definite or probable stent thrombosis (1.3% vs. 1.6%, respectively; HR, 0.86; 95% CI, 0.46 to 1.62; $p = 0.64$) (**Figure 2**). Detailed outcomes for definite, probable,

TABLE 1 Selected Baseline Patient and Procedural Characteristics

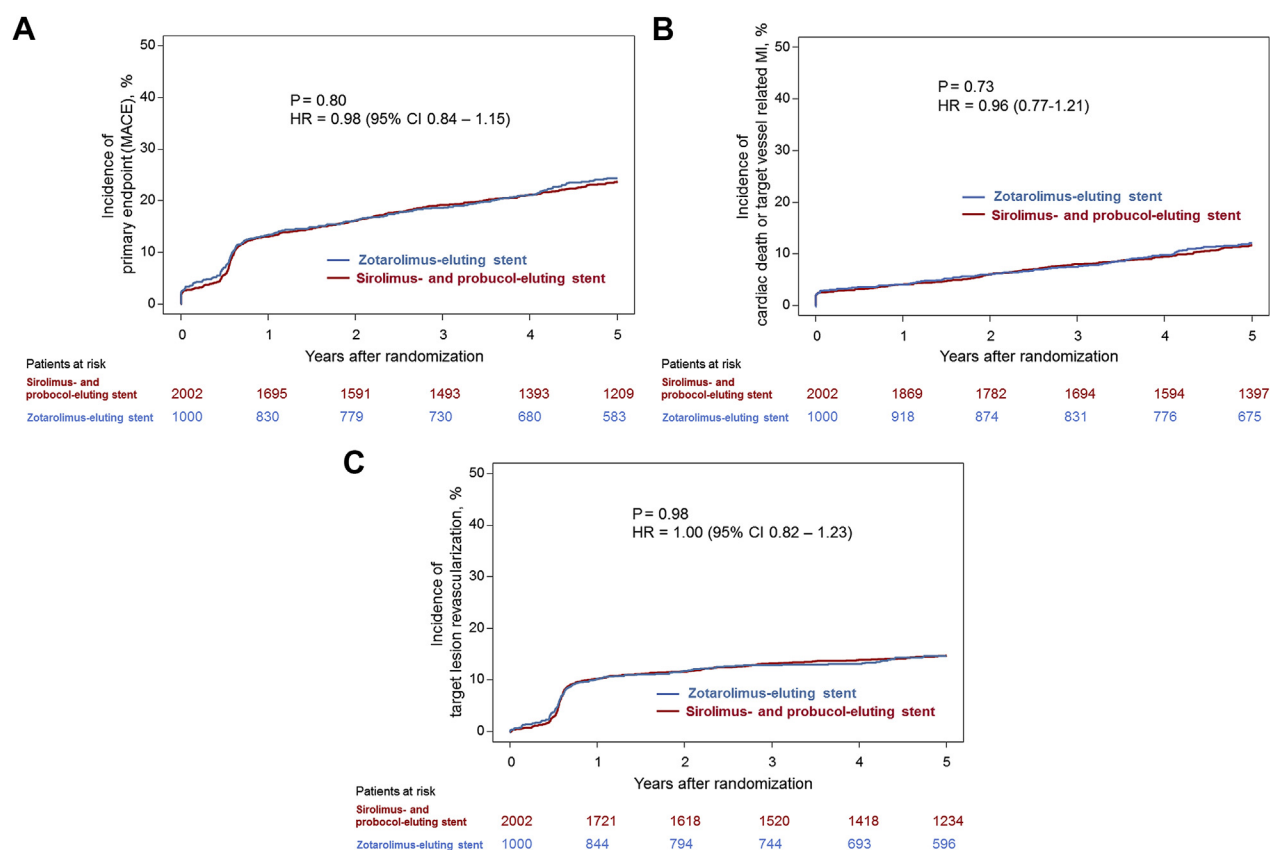
	Sirolimus- and Probucol-Eluting Stent(s)	Zotarolimus-Eluting Stent(s)	p Value
Patient characteristics	(n = 2,002)	(n = 1,000)	
Age (yrs)	67.7 ± 11.2	68.1 ± 10.8	0.30
Female	470 (23.5)	237 (23.7)	0.89
Diabetes mellitus	575 (28.7)	295 (29.5)	0.66
Insulin-dependent	197 (9.8)	109 (10.9)	0.37
Hypertension	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
Lesion characteristics	(n = 2,912)	(n = 1,479)	
Target vessel			0.55
Left anterior descending coronary artery	1,315 (45.2)	666 (45.0)	
Left circumflex coronary artery	711 (24.4)	386 (26.1)	
Right 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 luminal diameter, pre (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 (%)	12.1 ± 7.4	11.7 ± 8.2	0.23

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

TABLE 2 Clinical Results at 5 Years

Outcome	Sirolimus- and Probucol-Eluting Stent(s) (n = 2,002)	Zotarolimus-Eluting Stent(s) (n = 1,000)	HR (95% CI)	p Value
Device-oriented outcomes				
Cardiac death, MI related to target vessel, or target lesion revascularization	455 (23.8)	228 (24.2)	0.98 (0.84-1.15)	0.80
Cardiac death or MI related to target vessel	221 (11.8)	113 (12.2)	0.96 (0.77-1.21)	0.73
Cardiac death	171 (9.3)	85 (9.4)	0.99 (0.76-1.28)	0.93
MI related to target vessel	61 (3.3)	38 (4.0)	0.80 (0.53-1.19)	0.27
Target lesion revascularization	279 (14.7)	137 (14.7)	1.00 (0.82-1.23)	0.98
Patient-oriented outcomes				
All-cause death, any MI, or any revascularization	972 (49.4)	513 (52.3)	0.92 (0.83-1.03)	0.13
All-cause death or any MI	389 (20.0)	216 (22.3)	0.89 (0.75-1.05)	0.16
All-cause death	328 (17.0)	187 (19.4)	0.86 (0.72-1.03)	0.10
Any MI	84 (4.3)	46 (4.8)	0.91 (0.63-1.30)	0.60
Any revascularization	722 (38.1)	364 (39.0)	0.96 (0.85-1.09)	0.57
Target vessel revascularization	415 (22.0)	205 (22.0)	0.99 (0.84-1.17)	0.90

Values are n (%) by Kaplan-Meier analysis. HRs and p values were calculated using Cox proportional hazard methods.
CI = confidence interval; HR = hazard ratio; MI = myocardial infarction.

FIGURE 1 Time-to-Event Curves

Time-to-event curves for the 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 (HRs) and p values are derived from Cox proportional hazard methods. CI = confidence interval.

and possible stent thrombosis are displayed in [Table 3](#).

There was no evidence of an interaction between treatment effect and each of the pre-specified subgroups of age, sex, diabetes, and vessel size ([Figure 3](#)).

PATIENT-ORIENTED OUTCOMES AT 5 YEARS.

Regarding the composite endpoint of death, any MI, or any revascularization, there was no difference between sirolimus- and probucol-eluting stents and zotarolimus-eluting stents (49.4% vs. 52.3%, respectively; HR, 0.92; 95% CI: 0.83 to 1.03; p = 0.13) ([Figure 4A](#)).

The sirolimus- and probucol-eluting stent in comparison with the zotarolimus-eluting stent showed similar rates of all-cause death or any MI (20.0% vs. 22.3%, respectively; HR, 0.89; 95% CI: 0.75 to 1.05; p = 0.16) ([Figure 4B](#)), all-cause death (17.0% vs. 19.4%, respectively; HR, 0.86; 95% CI: 0.72 to 1.03; p = 0.10),

any MI (4.3% vs. 4.8%, respectively; HR, 0.91; 95% CI: 0.63 to 1.30; p = 0.60), any revascularization (38.1% vs. 39.0%, respectively; HR, 0.96; 95% CI: 0.85 to 1.09; p = 0.57) ([Figure 4C](#)), and target vessel revascularization (22.0% vs. 22.0%, respectively; HR, 0.99; 95% CI: 0.84 to 1.17; p = 0.90).

DISCUSSION

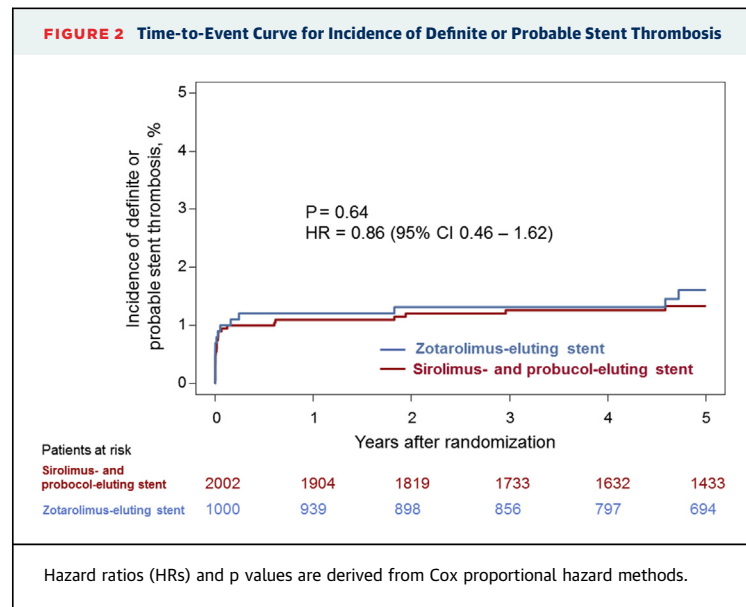
The main findings of our study were that in a large-scale randomized controlled trial, the primary composite outcome measure of cardiac death, target vessel-related MI, or target lesion revascularization occurred with equal frequency at 5 years in patients randomized to treatment with a polymer-free probucol- and sirolimus-eluting stent in comparison with a durable polymer zotarolimus-eluting stent. Moreover, durability of efficacy was high,

and incident late safety events, including stent thrombosis, were low and comparable in both groups beyond 1 year. In addition, at long-term follow-up, patient-oriented outcome events such as all-cause death, any MI, or any revascularization tended to outweigh more device-specific events such as target lesion revascularization or stent thrombosis.

A number of studies showed that first-generation DES technology was associated with a small but significant excess of late stent thrombosis in comparison with bare-metal stents. Moreover, autopsy studies suggested that the underlying issue was a delay in healing of the stented arterial segment (18). This pathophysiological process also underlies a small-magnitude delayed loss of antirestenotic efficacy (19,20) and a possible increase in de novo in-stent atherosclerosis (neoatherosclerosis) with DES devices (6). Although the cause of this delayed healing is multifactorial, autopsy and pre-clinical studies suggest that inflammatory reaction to polymer coatings plays a central role (4).

Although the development of polymer-free DES technology represents a clinical need, polymer coatings are critically important to facilitate loading and controlled elution of antirestenotic drugs, which is in turn intrinsically linked to the efficacy of the DES in preventing restenosis. In fact, all current U.S. Food and Drug Administration-approved DES incorporate a durable polymer matrix coating. Earlier investigations suggested that polymer-free DES showed clinical efficacy that was not as high as that of durable polymer stents (21,22). This results from a drug-release profile that is too rapid in the early days after stent implantation and a failure to optimally suppress neointimal hyperplasia. Probucol is an antioxidant with proven efficacy as a systemic drug in randomized trials for preventing restenosis after coronary intervention (9,10). However when used as a component of a DES coating, its high lipophilicity means that it can retard the release of a partner drug, enhancing its antirestenotic efficacy. We previously reported that a polymer-free sirolimus- and probucol-eluting stent was noninferior to a new-generation durable polymer-based zotarolimus-eluting stent with respect to angiographic outcomes at 6 to 8 months and clinical outcomes at 12 months (11). However, durability of efficacy and evaluation of potential late clinical benefit can be evaluated only after long-term clinical follow-up.

In this respect, the results of the present study are important because they represent the first long-term report of a large-scale clinical trial of a polymer-free DES. The data demonstrate sustained clinical



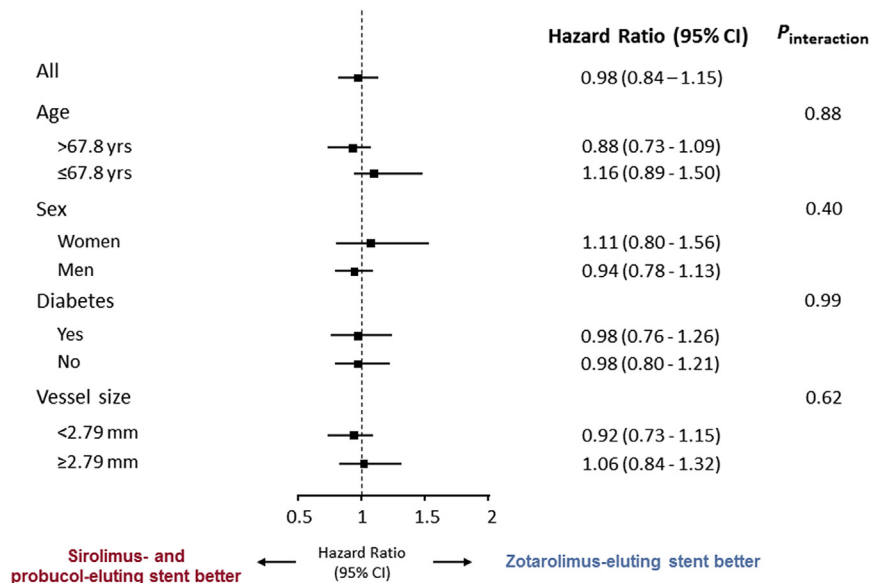
efficacy comparable with that of leading durable polymer stents. Against this, however, the present study failed to demonstrate a reduction in late adverse events, including stent thrombosis and MI related to the target vessel. This may be because the trial was considerably underpowered to detect differences in these events. In contrast, the rates of stent thrombosis events were low and numerically similar in both groups, with no signal of difference beyond 1 year. Indeed, the low event rates in the control group highlight the improvement in durable polymer technology with more biocompatible components, better stent backbones, and thinner matrix coatings, which may translate into improved late performance of these devices. Indeed, the results of our study are in line with those a recent trial reporting low rates of stent thrombosis at 5 years with the zotarolimus-eluting stent (2.8% vs. 1.6% in the present trial) (23). Long-term follow-up of other ongoing clinical trials with polymer-free DES technology will shed additional light on the comparative efficacy of both

TABLE 3 Stent Thrombosis at 5 Years

Stent Thrombosis	Sirolimus- and Probucol-Eluting Stent(s) (n = 2,002)	Zotarolimus-Eluting Stent(s) (n = 1,000)	HR (95% CI)	p Value
Definite	13 (0.7)	6 (0.7)	1.07 (0.41-2.83)	0.88
Probable	13 (0.7)	9 (0.9)	0.72 (0.31-1.68)	0.44
Possible	12 (0.6)	5 (0.5)	1.19 (0.42-3.37)	0.75
Definite or probable	26 (1.3)	15 (1.6)	0.86 (0.46-1.62)	0.64

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

Abbreviations as in Table 2.

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

p values for interaction are derived from Cox proportional hazard methods. CI = confidence interval; HR = hazard ratio.

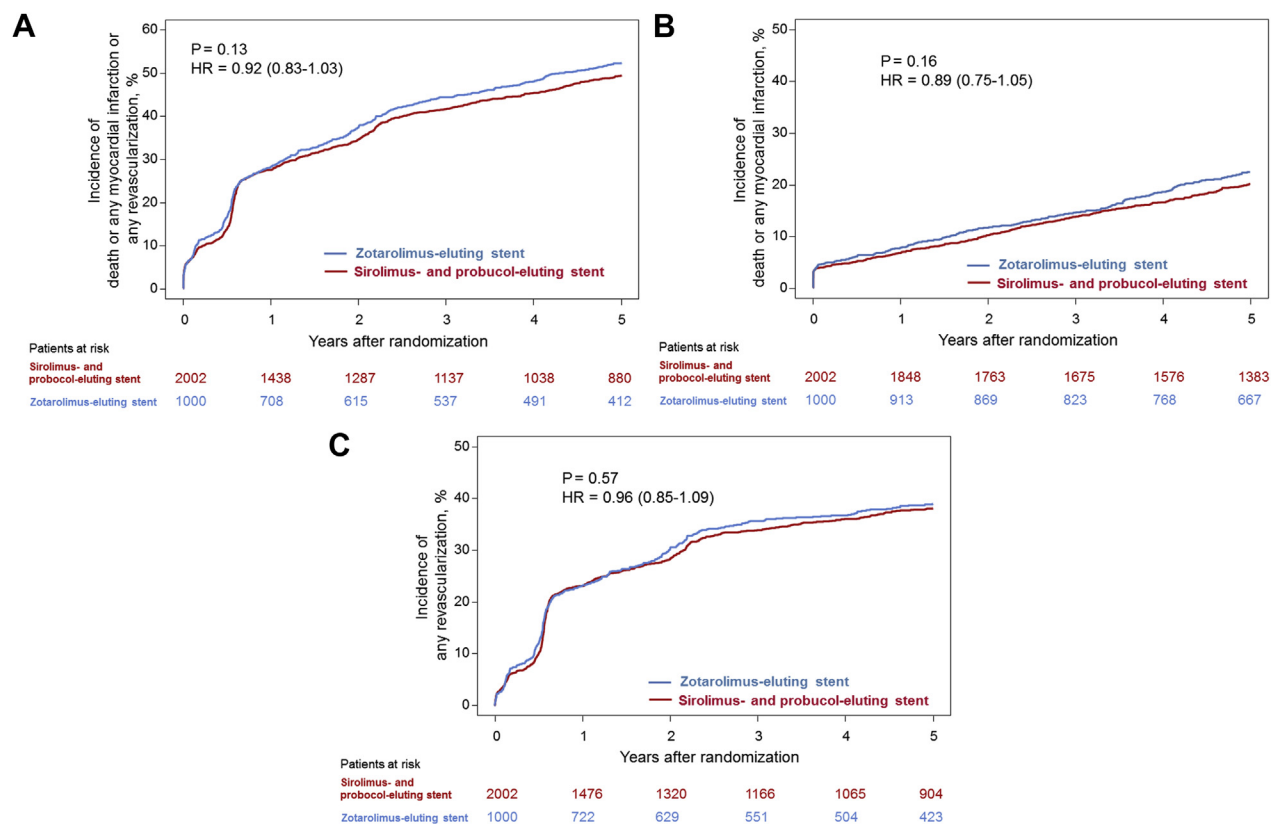
classes of device. In addition, relative differences in the performance of polymer-free and durable polymer stents beyond 5 years remain unknown.

The results of our trial add to the number of reports of late follow-up from coronary stent trials with minimal exclusion criteria (23-26). In keeping with these other trials, at 5-year follow-up in our study, patient-oriented endpoints—such as all-cause death, any MI, or any revascularization—tended to predominate over more device specific events such as target lesion revascularization or target vessel MI. This observation is in line with longitudinal finding studies such as PROSPECT (Providing Regional Observations to Study Predictors of Events in the Coronary Tree), which showed that at 3-year follow-up after stenting, the origin of adverse cardiac events was at least as likely to be attributable to disease progression in other coronary segments as to recurrent in events in the intervened vessel (27). This in turn highlights the long-term importance of secondary prevention therapies in these patients undergoing coronary stenting over and above lesion-specific revascularization therapies (28,29).

STUDY LIMITATIONS. First, our trial was powered to show noninferiority of the study stent (the probucol- and sirolimus-eluting stent) compared with

the control stent (the zotarolimus-eluting stent) at 12 months. Additional analyses at long-term follow-up may be regarded as post hoc and should be interpreted with caution. Second, the trial was not powered to detect differences in relation to rarely occurring late adverse events. Therefore, failure to detect significant differences does not represent reliable evidence for an absence of difference (30). Third, the inclusion of protocol-mandated surveillance angiography as well as reevaluation of patients at 2 years after stenting according to local practice at the time the study was performed inflates rates of target lesion to a level that is higher than would otherwise be seen in routine clinical care (30). Nevertheless, this is not expected to affect the relative treatment effect observed in the trial. Fourth, the influence of planned staged interventions in patients requiring revascularization in another vessel must be accounted for in interpreting the rates of all revascularization. The study protocol did not provide for a blanking period to exclude events related to these interventions, though random treatment allocation is expected to balance the influence of this factor on any treatment effect. Although both treatment groups received the same recommendation for duration of treatment after stenting, complete data relating to compliance or actual duration of dual antiplatelet

FIGURE 4 Time-to-Event Curves



Time-to-event curves for the incidence of (A) the composite of all-cause death, myocardial infarction, or any revascularization; (B) the composite of all-cause death or myocardial infarction; and (C) all revascularization. Hazard ratios and p values are derived from Cox proportional hazard methods. CI = confidence interval.

therapy received were not available. Data relating to other cardiac medications received were not available.

CONCLUSIONS

In a trial with broad inclusion criteria, long-term outcomes of patients randomized to revascularization with a polymer-free sirolimus- and probucol-eluting stent compared with a new-generation durable polymer-based zotarolimus-eluting stent were similar at 5 years. Rates of late adverse events such as stent thrombosis were low and comparable in both treatment groups with few events beyond 12 months.

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PERSPECTIVES

WHAT IS KNOWN? We previously showed that a polymer-free sirolimus- and probucol-eluting stent was noninferior to a new-generation durable polymer-based zotarolimus-eluting stent at 12 months. However, long-term follow-up of these devices is critical to evaluate late clinical performance.

WHAT IS NEW? At 5 years, outcomes of patients randomized to revascularization with a polymer-free sirolimus- and probucol-eluting stent versus a new-generation durable polymer-based zotarolimus-eluting stent were similar.

WHAT IS NEXT? Long-term follow-up of other ongoing clinical trials with polymer-free DES technology will shed additional light on the comparative efficacy of polymer-free and permanent polymer DES.

REFERENCES

1. Stefanini GG, Holmes DR Jr. Drug-eluting coronary-artery stents. *N Engl J Med* 2013;368:254-65.
2. Chin-Quee SL, Hsu SH, Nguyen-Ehrenreich KL, et al. Endothelial cell recovery, acute thrombogenicity, and monocyte adhesion and activation on fluorinated copolymer and phosphorylcholine polymer stent coatings. *Biomaterials* 2010;31:648-57.
3. Lin JC, Tiong SL, Chen CY. Surface characterization and platelet adhesion studies on fluorocarbons prepared by plasma-induced graft polymerization. *J Biomat Sci Polymer Ed* 2000;11:701-14.
4. Byrne RA, Joner M, Kastrati A. Polymer coatings and delayed arterial healing following drug-eluting stent implantation. *Minerva Cardioangiol* 2009;57:567-84.
5. van der Giessen WJ, Lincoff AM, Schwartz RS, et al. Marked inflammatory sequelae to implantation of biodegradable and nonbiodegradable polymers in porcine coronary arteries. *Circulation* 1996;94:1690-7.
6. Otsuka F, Byrne RA, Yahagi K, et al. Neoatherosclerosis: overview of histopathologic findings and implications for intravascular imaging assessment. *Eur Heart J* 2015;36:2147-59.
7. Meredith IT, Worthley S, Whitbourn R, et al. The next-generation Endeavor Resolute stent: 4-month clinical and angiographic results from the Endeavor Resolute first-in-man trial. *Eurointervention* 2007;3:50-3.
8. Tardif JC, Cote G, Lesperance J, et al. Probucol and multivitamins in the prevention of restenosis after coronary angioplasty. Multivitamins and Probucol Study Group. *N Engl J Med* 1997;337:365-72.
9. Guerra E, Byrne RA, Kastrati A. Pharmacological inhibition of coronary restenosis: systemic and local approaches. *Expert Opin Pharmacother* 2014;15:2155-71.
10. Liu J, Li M, Lu H, et al. Effects of probucol on restenosis after percutaneous coronary intervention: a systematic review and meta-analysis. *PLoS One* 2015;10:e0124021.
11. Byrne RA, Mehili J, Iijima R, et al. A polymer-free dual drug-eluting stent in patients with coronary artery disease: a randomized trial vs. polymer-based drug-eluting stents. *Eur Heart J* 2009;30:923-31.
12. Massberg S, Byrne RA, Kastrati A, et al. Polymer-free sirolimus- and probucol-eluting versus new generation zotarolimus-eluting stents in coronary artery disease: the Intracoronary Stenting and Angiographic Results: Test Efficacy of Sirolimus- and Probucol-Eluting Versus Zotarolimus-eluting Stents (ISAR-TEST 5) trial. *Circulation* 2011;124:624-32.
13. Steigerwald K, Merl S, Kastrati A, et al. The pre-clinical assessment of rapamycin-eluting, durable polymer-free stent coating concepts. *Biomaterials* 2009;30:632-7.
14. Wessely R, Hausleiter J, Michaelis C, et al. Inhibition of neointima formation by a novel drug-eluting stent system that allows for dose-adjustable, multiple, and on-site stent coating. *Arterioscler Thromb Vasc Biol* 2005;25:748-53.
15. Zeger SL, Liang KY. Longitudinal data analysis for discrete and continuous outcomes. *Biometrics* 1986;42:121-30.
16. Grambsch PM, Therneau TM. Proportional hazards tests and diagnostics based on weighted residuals. *Biometrika* 1994;81:515-26.
17. Puggio G, Elbourne DR, Altman DG, Pocock SJ, Evans SJ. Reporting of noninferiority and equivalence randomized trials: an extension of the CONSORT statement. *JAMA* 2006;295:1152-60.
18. 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;57:390-8.
19. Raber L, Wohlwend L, Wigger M, et al. Five-year clinical and angiographic outcomes of a randomized comparison of sirolimus-eluting and paclitaxel-eluting stents: results of the Sirolimus-Eluting Versus Paclitaxel-Eluting Stents for Coronary Revascularization LATE trial. *Circulation* 2011;123:2819-28.
20. Byrne RA, Iijima R, Mehili J, et al. Durability of antirestenotic efficacy in drug-eluting stents with and without permanent polymer. *J Am Coll Cardiol Intv* 2009;2:291-9.
21. Mehili J, Byrne RA, Wiecek A, et al. Randomized trial of three rapamycin-eluting stents with different coating strategies for the reduction of coronary restenosis. *Eur Heart J* 2008;29:1975-82.
22. Gershlick A, De Scheerder I, Chevalier B, et al. Inhibition of restenosis with a paclitaxel-eluting, polymer-free coronary stent: the European Evaluation of Paclitaxel Eluting Stent (ELUTES) trial. *Circulation* 2004;109:487-93.
23. Iqbal J, Serruys PW, Silber S, et al. Comparison of zotarolimus- and everolimus-eluting coronary stents: final 5-year report of the RESOLUTE all-comers trial. *Circ Cardiovasc Interv* 2015;8:e002230.
24. Maeng M, Tilsted HH, Jensen LO, et al. Differential clinical outcomes after 1 year versus 5 years in a randomised comparison of zotarolimus-eluting and sirolimus-eluting coronary stents (the SORT OUT III study): a multicentre, open-label, randomised superiority trial. *Lancet* 2014;383:2047-56.
25. Serruys PW, Farooq V, Kalesan B, et al. 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, non-inferiority trial. *J Am Coll Cardiol Intv* 2013;6:777-89.
26. Kufner S, Byrne RA, Valeskini M, et al. 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;11:1372-137.
27. Stone GW, Maehara A, Lansky AJ, et al. A prospective natural-history study of coronary atherosclerosis. *N Engl J Med* 2011;364:226-35.
28. Smith SC Jr., Benjamin EJ, Bonow RO, et al. AHA/ACC secondary prevention and risk reduction therapy for patients with coronary and other atherosclerotic vascular disease: 2011 update: a guideline from the American Heart Association and American College of Cardiology Foundation. *J Am Coll Cardiol* 2011;58:2432-46.
29. Kumbhani DJ, Fonarow GC, Cannon CP, et al. Temporal trends for secondary prevention measures among patients hospitalized with coronary artery disease. *Am J Med* 2015;128:426.e1-9.
30. Altman DG, Bland JM. Absence of evidence is not evidence of absence. *BMJ* 1995;311:485.

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