ORIGINAL ARTICLE

Polymer-based or Polymer-free Stents in Patients at High Bleeding Risk

S. Windecker, A. Latib, E. Kedhi, A.J. Kirtane, D.E. Kandzari, R. Mehran, M.J. Price, A. Abizaid, D.I. Simon, S.G. Worthley, A. Zaman, M. Hudec, P. Poliacikova, A.K.. Abdul Ghapar, K. Selvaraj, I. Petrov, D. Mylotte, E. Pinar, R. Moreno, F. Fabbiocchi, S. Pasupati, H.-S. Kim, A. Aminian, C. Tie, A. Wlodarczak, S.-H. Hur, S.O. Marx, I. Jankovic, S. Brar, L. Bousquette, M. Liu, and G.W. Stone, for the ONYX ONE Investigators*

ABSTRACT

BACKGROUND

Polymer-free drug-coated stents provide superior clinical outcomes to bare-metal stents in patients at high bleeding risk who undergo percutaneous coronary intervention (PCI) and are treated with 1 month of dual antiplatelet therapy. Data on the use of polymer-based drug-eluting stents, as compared with polymer-free drug-coated stents, in such patients are limited.

METHODS

In an international, randomized, single-blind trial, we compared polymer-based zotarolimus-eluting stents with polymer-free umirolimus–coated stents in patients at high bleeding risk. After PCI, patients were treated with 1 month of dual antiplatelet therapy, followed by single antiplatelet therapy. The primary outcome was a safety composite of death from cardiac causes, myocardial infarction, or stent thrombosis at 1 year. The principal secondary outcome was target-lesion failure, an effectiveness composite of death from cardiac causes, target-vessel myocardial infarction, or clinically indicated target-lesion revascularization. Both outcomes were powered for noninferiority.

RESULTS

A total of 1996 patients at high bleeding risk were randomly assigned in a 1:1 ratio to receive zotarolimus-eluting stents (1003 patients) or polymer-free drug-coated stents (993 patients). At 1 year, the primary outcome was observed in 169 of 988 patients (17.1%) in the zotarolimus-eluting stent group and in 164 of 969 (16.9%) in the polymer-free drug-coated stent group (risk difference, 0.2 percentage points; upper boundary of the one-sided 97.5% confidence interval [CI], 3.5; noninferiority margin, 4.1; P=0.01 for noninferiority). The principal secondary outcome was observed in 174 patients (17.6%) in the zotarolimus-eluting stent group and in 169 (17.4%) in the polymer-free drug-coated stent group (risk difference, 0.2 percentage points; upper boundary of the one-sided 97.5% CI, 3.5; noninferiority margin, 4.4; P=0.007 for noninferiority).

CONCLUSIONS

Among patients at high bleeding risk who received 1 month of dual antiplatelet therapy after PCI, use of polymer-based zotarolimus-eluting stents was noninferior to use of polymer-free drug-coated stents with regard to safety and effectiveness composite outcomes. (Funded by Medtronic; ONYX ONE ClinicalTrials.gov number, NCT03344653.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Windecker at the Department of Cardiology, Inselspital, Bern University Hospital, University of Bern, Freiburgstr., CH-3010 Bern, Switzerland, or at stephan.windecker@insel.ch.

*A complete list of the ONYX ONE investigators is provided in the Supplementary Appendix, available at NEJM.org.

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Contemporary drug-eluting stents are the standard of care for patients undergoing percutaneous coronary intervention (PCI).[1,2] Nearly one third of patients treated with PCI are considered to be at high bleeding risk and are frequently excluded from stent trials.[3,4] Short durations of dual antiplatelet therapy were used during the bare-metal stent era and have been evaluated[5] in a few trials comparing bare-metal stents with drug-eluting stents[6,7] in patients at high bleeding risk.[8]

In the LEADERS FREE trial, a polymer-free umirolimus-coated stent was shown to be superior in safety and effectiveness to a bare-metal stent in patients at high bleeding risk who received 1 month of dual antiplatelet therapy.[9] However, data on a direct comparison between polymer-free drug-coated stents and drug-eluting stents are limited. Polymer-based zotarolimus-eluting stents have been shown to be safe and effective in a large, "all-comer" population of patients (i.e., a trial population that had minimal exclusion criteria).[10,11] A post hoc analysis of trials of the zotarolimus-eluting stent suggested that 1 month of dual antiplatelet therapy may be safe after PCI.[12] We designed a randomized trial to compare the safety and effectiveness of the polymer-based zotarolimus-eluting stent with the polymer-free umirolimus-coated stent in patients at high bleeding risk receiving 1 month of dual antiplatelet therapy after PCI.[13]

Methods

Trial Design and Oversight

ONYX ONE was a randomized, single-blind trial, the design of which has been described previously.[13] Patients were enrolled at 84 centers in Asia, Oceania, and Europe (see the Supplementary Appendix, available with the full text of this article at NEJM.org). Local ethics review boards approved the protocol (available at NEJM.org), all the patients provided written informed consent, and the trial adhered to the principles of the Declaration of Helsinki.

The trial was funded by Medtronic, and the protocol was developed jointly by the executive committee and the sponsor (Table S1 in the Supplementary Appendix). Investigators at each site gathered the data, which were stored and analyzed by the sponsor. All the statistical analyses were performed by the sponsor and validated independently by the Baim Institute for Clinical Research. The sponsor was responsible for site selection, data monitoring, and overall clinical-trial management. An external, independent data and safety monitoring board and clinical-events committee assessed safety and performed event adjudication. Source document monitoring was performed in 100% of patient records. An independent angiographic core laboratory evaluated all baseline and event angiograms. The Cardiovascular Research Foundation oversaw the data and safety monitoring board, the clinical-events committee, and the angiographic core laboratory.

The first draft of the manuscript was written by the first author. All the authors had full access to the data, revised the manuscript, supported the decision to submit the manuscript for publication, and vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

Patient Population

Eligible patients had coronary artery disease and a clinical indication for PCI. In addition, patients were classified as being at high bleeding risk or were otherwise a candidate for short-term prophylaxis for stent thrombosis (1 month of either dual antiplatelet therapy or single antiplatelet therapy plus an anticoagulant drug). Complete inclusion and exclusion criteria, including the criteria defining high bleeding risk, are listed in Table S2.

Trial Procedures

Patients were randomly assigned in a 1:1 ratio to receive either the durable-polymer, slow-release zotarolimus-eluting Resolute Onyx stent (Medtronic) or the polymer-free umirolimus-coated BioFreedom stent (BioSensors Interventional Technologies) after it was confirmed on coronary angiography that one or more target lesions were eligible for implantation with either type of stent (see the Supplementary Appendix). Randomization was performed with the use of an interactive voice- or Web-response system and was stratified according to trial site, diabetes status, and myocardial infarction at time of presentation, with a block size of four. Although the interventional cardiologists were aware of the trial-group assignments, the patients, referring physicians, and personnel conducting patient follow-up, including the members of the clinical-events committee, were unaware of the group assignments.

Operators were instructed to implant the assigned stent type during the index procedure

and any subsequent staged procedures. If the assigned trial stent could not be placed, the comparator device was to be used. A clinically indicated planned staged procedure was allowed within 1 month after the index procedure.

Before the procedure, a loading dose of 250 to 500 mg of aspirin was recommended in patients who had not been taking aspirin; oral $P2Y_{12}$ inhibitor pretreatment and loading doses were administered according to the local standard of care. During the index procedure, heparin or bivalirudin was administered according to standard practice, and the use of glycoprotein IIb/IIIa blockers was according to the discretion of the operator.

After the procedure, patients were given a prescription for 1 month of dual antiplatelet therapy that included a daily dose (75 to 100 mg) of aspirin and a $P2Y_{12}$ inhibitor. Patients who were treated with oral anticoagulants could receive single or dual antiplatelet therapy during this period. After 1 month, patients were given a prescription for single antiplatelet therapy (either aspirin or a $P2Y_{12}$ inhibitor, at the discretion of the physician). Additional information regarding antithrombotic therapy is provided in the Supplementary Appendix. After the index procedure, patients were followed up at 1 month (in an office visit) and at 2, 6, and 12 months (in an office visit or by telephone).

TRIAL OUTCOMES

The primary outcome was a safety composite of death from cardiac causes, myocardial infarction, or definite or probable stent thrombosis at 1 year. The principal secondary outcome was an effectiveness outcome of target-lesion failure (a composite of death from cardiac causes, target-vessel myocardial infarction, or clinically indicated target-lesion revascularization) at 1 year. Other secondary outcomes included the components of the primary outcome and the principal secondary outcome as well as major adverse cardiac events, stroke, and bleeding events. A detailed list of all outcomes and their definitions is provided in the Supplementary Appendix. Myocardial infarction was defined according to the Third Universal Definition of Myocardial Infarction.[14] Bleeding was defined according to Bleeding Academic Research Consortium (BARC) criteria (see the End Point Definitions section in the Supplementary Appendix). BARC types range from 0 to 5, with higher values indicating greater severity of bleeding.

STATISTICAL ANALYSIS

On the basis of the results in the LEADERS FREE trial,[9] we assumed that 9.4% of the patients in each group would have a primary-outcome event. A noninferiority margin of 4.1 percentage points was chosen, which represented 44% of the expected percentage of patients with an event. We calculated that a sample of 900 patients in each group would provide the trial with more than 90% power to show noninferiority on the basis of the Farrington–Manning test at a one-sided type I error of 0.05. Under an assumption that 10% of the patients would be lost to follow-up, a total sample of 2000 patients was deemed to be sufficient to evaluate the primary outcome. If noninferiority regarding the primary outcome was established, a conditional test for superiority would be performed.

If the zotarolimus-eluting stent was noninferior to the polymer-free drug-coated stent in the analysis of the primary outcome, the principal secondary outcome of target-lesion failure at 1 year would be tested for noninferiority. In the LEADERS FREE trial, 11% of the patients were estimated to have target-lesion failure, on the basis of the reported components of target-lesion failure in that trial.[9] We selected a noninferiority margin of 4.4 percentage points, which represented 40% of the expected percentage of patients with an event. If noninferiority regarding the principal secondary outcome was met, a conditional test for superiority would be performed.

The results for the primary outcome were based on a modified intention-to-treat population that excluded patients who withdrew from the trial or were lost to follow-up. A sensitivity analysis was performed with the use of multiple imputation to account for missing data, including data for the patients who were lost to follow-up or withdrew from the trial. Additional analyses were performed in the per-protocol and as-treated populations; definitions of all the analysis populations are provided in the Supplementary Appendix. The 95% confidence intervals presented in this article have not been adjusted for multiple comparisons, and therefore inferences drawn from these intervals may not be reproducible. In a post hoc analysis, the upper boundary of the one-sided 97.5% confidence interval, which corresponds to a one-sided type I error of 0.025 for the primary analysis results, was also calculated.

Categorical data are reported as percentages

(counts divided by the number of patients who could be evaluated) and were compared with the use of Fisher's exact test. Continuous data are reported as means with standard deviations and were tested with the use of two-sample Student's t-tests; rates are based on all the patients who underwent randomization and had data that could be evaluated. For prespecified subgroup analyses, the interaction term between treatment groups and subgroups was evaluated with the use of logistic regression. Cumulative-incidence curves with Kaplan–Meier estimates were generated. Post hoc landmark analyses were performed with the use of cutoffs at 30 days, which corresponded to the planned date of discontinuation of dual antiplatelet therapy. All the statistical analyses were performed with the use of SAS software, version 9.4 or higher (SAS Institute).

RESULTS

PATIENTS

Of 3239 patients enrolled in the trial, 1996 patients underwent randomization between November 1, 2017, and September 28, 2018; a total of 1003 patients were assigned to the zotarolimus-eluting stent and 993 were assigned to the polymer-free drug-coated stent (Fig. S1). A total of 15 patients (1.5%) assigned to the zotarolimus-eluting stent group and 24 (2.4%) patients assigned to the polymer-free drug-coated stent group were lost to follow-up or withdrew consent. The remaining patients (988 in the zotarolimus-eluting stent group and 969 in the polymer-free drug-coated stent group) were included in the modified intention-to-treat analyses at 1 year.

Patients had a mean (±SD) age of 74±10 years, frequently had diabetes (770 of 1996 patients [38.6%]), and commonly presented with acute coronary syndromes (982 of 1902 patients [51.6%]) (Table 1). The mean number of high-bleeding-risk criteria per patient was 1.6; a total of 921 of 1995 patients (46.2%) met 2 or more criteria. The most common high-bleeding-risk qualifying features were an age of 75 years or older and oral anticoagulation use (Table 2).

PROCEDURAL CHARACTERISTICS

Vascular access was predominantly radial in each group, and the number of vessels and lesions treated was similar in the two groups (Tables S3 and S4). Most patients had complex lesions. A total of 2 patients assigned to the zotarolimus-eluting stent crossed over to receive the polymer-free drug-coated stent, and 40 patients assigned to the polymer-free drug-coated stent crossed over to receive the zotarolimus-eluting stent (reasons are presented in Table S5). The immediate change in the dimension of the vessel (often called acute gain) was greater and the percentage of the vessel diameter with residual stenosis was lower after treatment with the zotarolimus-eluting stent than with the polymer-free drug-coated stent. Device success occurred in 1158 of 1248 lesions (92.8%) in patients in the zotarolimus-eluting stent group and in 1109 of 1237 lesions (89.7%) in patients in the polymer-free drug-coated stent group (difference, 3.1 percentage points; 95% confidence interval [CI], 0.9 to 5.4).

The timing of the discontinuation of dual antiplatelet therapy was similar in the two groups. At 30 days, dual antiplatelet therapy had been prescribed in 899 of 980 patients (91.7%) in the zotarolimus-eluting stent group and in 901 of 966 patients (93.3%) in the polymer-free drug-coated stent group (Fig. S2). At 2 months, 57 of 969 patients (5.9%) in the zotarolimus-eluting stent group and 66 of 954 patients (6.9%) in the polymer-free drug-coated stent group were taking dual antiplatelet therapy; at 1 year, 53 of 899 patients (5.9%) and 75 of 897 patients (8.4%), respectively, were taking dual antiplatelet therapy. Single antiplatelet agent therapy at 1 year consisted of aspirin in 451 of 899 patients (50.2%) in the zotarolimus-eluting stent group and in 447 of 897 patients (49.8%) in the polymer-free drug-coated stent group and consisted of a $P2Y_{12}$ inhibitor in 349 patients (38.8%) and 333 patients (37.1%), respectively (Tables S6 through S10).

PRIMARY AND PRINCIPAL SECONDARY OUTCOMES

At 1 year, the primary outcome — a composite of death from cardiac causes, myocardial infarction, or stent thrombosis — had occurred in 169 of 988 patients (17.1%) in the zotarolimus-eluting stent group and in 164 of 969 patients (16.9%) in the polymer-free drug-coated stent group (risk difference, 0.2 percentage points; upper boundary of the one-sided 95% CI, 3.0; upper boundary of the one-sided 97.5% CI, 3.5; P=0.01 for noninferiority) (Table 3). Cumulative-incidence curves for the primary outcome and its components are shown in Figure 1.

At 1 year, the principal secondary outcome of target-lesion failure had occurred in 174 patients

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Zotarolimus-Eluting Stent (N=1003)	Polymer-free Drug-Coated Stent (N=993)
Age — yr	74.0±9.5	74.1±9.8
Female sex — no. (%)	326 (32.5)	340 (34.2)
Body-mass index†	27.2±5.0	27.3±5.0
Diabetes — no. (%)	388 (38.7)	382 (38.5)
Insulin treatment — no. (%)	119 (11.9)	117 (11.8)
Hypertension — no. (%)	796 (79.4)	807 (81.3)
Hyperlipidemia — no. (%)	643 (64.1)	619 (62.3)
Current smoker — no./total no. (%)	93/993 (9.4)	108/987 (10.9)
Previous myocardial infarction — no. (%)	264 (26.3)	249 (25.1)
Previous PCI — no. (%)	237 (23.6)	230 (23.2)
Previous coronary-artery bypass grafting — no. (%)	77 (7.7)	66 (6.6)
Previous stroke or transient ischemic attack — no. (%)	135 (13.5)	124 (12.5)
Peripheral vascular disease — no. (%)	106 (10.6)	95 (9.6)
Atrial fibrillation — no. (%)	328 (32.7)	316 (31.8)
Left ventricular ejection fraction ≤35% — no./total no. (%)	82/711 (11.5)	77/703 (11.0)
Silent ischemia — no./total no. (%)	88/967 (9.1)	103/935 (11.0)
Chronic coronary syndrome — no./total no. (%)	368/967 (38.1)	361/935 (38.6)
Acute coronary syndrome — no./total no. (%)	511/967 (52.8)	471/935 (50.4)
Unstable angina — no./total no. (%)	189/967 (19.5)	171/935 (18.3)
NSTEMI — no./total no. (%)	262/967 (27.1)	252/935 (27.0)
STEMI — no./total no. (%)	60/967 (6.2)	48/935 (5.1)

* Plus–minus values are means ±SD. NSTEMI denotes non–ST-segment elevation myocardial infarction, PCI percutaneous coronary intervention, and STEMI ST-segment elevation myocardial infarction.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.

(17.6%) in the zotarolimus-eluting stent group and in 169 patients (17.4%) in the polymer-free drug-coated stent group (risk difference, 0.2 percentage points; upper boundary of the one-sided 95% CI, 3.0; upper boundary of the one-sided 97.5% CI, 3.5; P=0.007 for noninferiority) (Table 3). Cumulative-incidence curves for the principal secondary outcome are shown in Figure 2. Subsequent testing for superiority did not yield significant between-group differences for the primary outcome or the principal secondary outcome.

Noninferiority was confirmed in the as-treated and per-protocol analyses at the one-sided level of 0.05 but was not confirmed at the one-sided level of 0.025 (Tables S11 and S12). Findings were also confirmed in sensitivity analyses that accounted for missing data (Table S13).

ADDITIONAL ANALYSES

The incidence of prespecified secondary outcomes, including subtypes of myocardial infarction, was similar in the two groups (Table 3 and Tables S14 and S15). Bleeding events that met the criteria for BARC grade 2 through 5 occurred in 149 patients (15.1%) in the zotarolimus-eluting stent group and in 133 patients (13.7%) in the polymer-free drug-coated stent group. Stent thrombosis at 1 year occurred in 13 patients (1.3%) in the zotarolimus-eluting stent group and in 20 (2.1%) in the polymer-free drug-coated stent group (Table 3). The risk differences between the two groups with regard to the primary outcome were consistent across prespecified baseline subgroups (Fig. S3).

Post hoc landmark analyses set at 30 days for the primary outcome and the principal secondary

outcome are shown in Table S16. Time-to-event curves with landmark analysis that were analyzed according to the Kaplan–Meier method are shown in Figures S4 through S7. Between 0 and 30 days, the primary outcome occurred in 10.7% of the patients in the zotarolimus-eluting stent group and in 9.6% of those in the polymer-free drug-coated stent group. Between 31 days and 1 year, the comparable percentages were 6.9% and 8.2%, respectively.

DISCUSSION

Among patients at high bleeding risk who were treated with 1 month of dual antiplatelet therapy after PCI, polymer-based zotarolimus-eluting stents were found to be noninferior to polymer-free drug-coated stents at 1 year with regard to both safety (as shown by the composite outcome of death from cardiac causes, myocardial infarction, or stent thrombosis) and effectiveness (as shown by the composite outcome of death from cardiac causes, target-vessel myocardial infarction, or clinically indicated target-lesion revascularization).

This trial adds to the body of evidence from previous trials involving patients at high bleeding risk.[6,7,9] Features of high bleeding risk are frequent in patients undergoing PCI, and in the past, these patients often received bare-metal stents.[2-4] Current guidelines recommend 3 to 6 months of dual antiplatelet therapy in patients at high bleeding risk after the implantation of drug-eluting stents.[1,15-17] The ZEUS (Zotarolimus-Eluting Endeavor Sprint Stent in Uncertain DES [Drug-Eluting Stent] Candidates) and SENIOR (Short Duration of Dual Antiplatelet Therapy with Synergy II Stent in Patients Older Than 75 Years Undergoing Percutaneous Coronary Revascularization) trials showed that such patients receiving the Endeavor zotarolimus-eluting stent[7] or the bioresorbable polymer-based everolimus-eluting stent[6] with abbreviated dual antiplatelet therapy (1 to 6 months) had better outcomes than patients receiving bare-metal stents. The LEADERS FREE trial showed that polymer-free umirolimus-coated stents were superior to bare-metal stents in terms of both safety and effectiveness in patients at high bleeding risk who were treated with 1 month of dual antiplatelet therapy.[9]

The present trial compared a contemporary, durable, polymer-based, slow-release, zotarolimus-eluting stent with the same polymer-free drug-coated stent that was used in the LEADERS FREE trial in patients at high bleeding risk who were treated with 1 month of dual antiplatelet therapy. The proportion and distribution of features of high bleeding risk were similar in the LEADERS FREE trial and the present trial. More than 90% of patients in the two trial groups in the present trial discontinued dual antiplatelet therapy after 1 month, as required by the protocol. Stent thrombosis and other ischemic events after 30 days were infrequent, and the incidence of these events was similar in the two groups. The present findings show that polymer-based zotarolimus-eluting stents may be safely and effectively used in pa-

Table 2. Criteria for High Bleeding Risk.*

Criterion	Zotarolimus-Eluting Stent (N=1003)	Polymer-free Drug-Coated Stent (N=992)
	number (percent)	
Age ≥75 yr	613 (61.1)	618 (62.3)
Oral anticoagulation therapy planned to continue after PCI	386 (38.5)	383 (38.6)
Hemoglobin <11 g/dl or transfusion within 4 wk before procedure	156 (15.6)	155 (15.6)
Creatinine clearance <40 ml/min	143 (14.3)	154 (15.5)
Non-skin cancer diagnosed or treated within previous 3 yr	85 (8.5)	71 (7.2)
Surgery planned in next 12 mo	56 (5.6)	81 (8.2)
Expected nonadherence to prolonged dual antiplatelet therapy	39 (3.9)	47 (4.7)
Stroke in previous 12 mo	29 (2.9)	32 (3.2)
Hospital admission for major bleeding in previous 12 mo	30 (3.0)	18 (1.8)
NSAID or glucocorticoid use for ≥30 days after PCI	24 (2.4)	23 (2.3)
Previous intracerebral hemorrhage	20 (2.0)	18 (1.8)
Thrombocytopenia†	15 (1.5)	19 (1.9)
Severe chronic liver disease‡	8 (0.8)	12 (1.2)

* Data for one patient in the polymer-free drug-coated stent group were not included in this analysis because the patient underwent randomization before it was determined that no inclusion criteria were met. NSAID denotes nonsteroidal antiinflammatory drug.
† Thrombocytopenia was defined as a platelet count of less than 100,000 per cubic millimeter.
‡ Severe chronic liver disease was defined as variceal hemorrhage, ascites, hepatic encephalopathy, or jaundice.

tients at high bleeding risk who are treated with a duration of dual antiplatelet therapy as short as 1 month. This is noteworthy because more than 50% of the patients in our trial presented with acute coronary syndromes. The trial thus extends earlier results suggesting that bleeding, more than ischemic risk, should determine clinical decision making regarding the duration of dual antiplatelet therapy.[18]

Similar to the results in the LEADERS FREE trial (but at variance with results in other trials,[6,7] which used more conservative definitions of myocardial infarction[19]), the outcomes in this trial were adjudicated according to the Third Universal Definition of Myocardial Infarction.[14] Event rates for the primary outcome were higher in this trial than in the LEADERS FREE trial, which was driven by a greater incidence of periprocedural myocardial infarction in both groups. These higher rates may be due to differences in patient populations but are more likely to be due to differences in ascertainment and adjudication of events between the trials. The vast majority of diagnoses of periprocedural myocardial infarctions in the present trial were based on angiographic findings, without symptoms or electrocardiographic changes, in patients in whom both preprocedural and postprocedural troponin levels were measured (Table S15). Conversely, the rates of death, death from cardiac causes, and stent

Table 3. Primary and Secondary Outcomes (Modified Intention-to-Treat Population).*

Outcome	Zotarolimus-Eluting Stent (N=988)	Polymer-free Drug-Coated Stent (N=969)	Risk Difference (95% CI)	P Value for Noninferiority
	number (percent)		*percentage points*	
Primary outcome: death from cardiac causes, myocardial infarction, or stent thrombosis†	169 (17.1)	164 (16.9)	0.2 (–3.1 to 3.5)	0.01
Principal secondary outcome: target-lesion failure‡	174 (17.6)	169 (17.4)	0.2 (–3.2 to 3.5)	0.007
Target-vessel failure§	177 (17.9)	175 (18.1)	–0.1 (–3.5 to 3.3)	
Death				
Any death	87 (8.8)	72 (7.4)	1.4 (–1.0 to 3.8)	
Death from cardiac causes	44 (4.5)	36 (3.7)	0.7 (–1.0 to 2.5)	
Target-vessel myocardial infarction¶	126 (12.8)	136 (14.0)	–1.3 (–4.3 to 1.7)	
Myocardial infarction¶				
Any myocardial infarction	132 (13.4)	142 (14.7)	–1.3 (–4.4 to 1.8)	
Periprocedural	93 (9.4)	77 (7.9)	1.5 (–1.0 to 4.0)	
Spontaneous	45 (4.6)	69 (7.1)	–2.6 (–4.6 to -0.5)	
Q-wave	12 (1.2)	12 (1.2)	0.0 (–1.0 to 1.0)	
Non–Q-wave	120 (12.1)	132 (13.6)	–1.5 (–4.4 to 1.5)	
Stent thrombosis‖				
Definite or probable	13 (1.3)	20 (2.1)	–0.7 (–1.9 to 0.4)	
Early (≤30 days)	6 (0.6)	13 (1.3)	–0.7 (–1.6 to 0.1)	
Late (31–365 days)	7 (0.7)	7 (0.7)	0.0 (–0.8 to 0.7)	
Definite	9 (0.9)	12 (1.2)	–0.3 (–1.2 to 0.6)	
Probable	4 (0.4)	8 (0.8)	–0.4 (–1.1 to 0.3)	
Stroke**	22 (2.2)	22 (2.3)	0.0 (–1.4 to 1.3)	
Major adverse cardiac event††	215 (21.8)	204 (21.1)	0.7 (–2.9 to 4.3)	
Revascularization				
Clinically indicated target-lesion revascularization	28 (2.8)	39 (4.0)	–1.2 (–2.8 to 0.4)	
Clinically indicated target-vessel revascularization	36 (3.6)	51 (5.3)	–1.6 (–3.4 to 0.2)	
Any revascularization	57 (5.8)	66 (6.8)	–1.0 (–3.2 to 1.1)	

Table 3. (Continued)

Outcome	Zotarolimus-Eluting Stent (N=988)	Polymer-free Drug-Coated Stent (N=969)	Risk Difference (95% CI)	P Value for Noninferiority
	number (percent)		*percentage points*	
Bleeding event, according to BARC type‡‡				
BARC type 1–5	175 (17.7)	158 (16.3)	1.4 (–1.9 to 4.7)	
BARC type 2–5	149 (15.1)	133 (13.7)	1.4 (–1.8 to 4.5)	
BARC type 3–5	48 (4.9)	43 (4.4)	0.4 (–1.4 to 2.3)	

* The modified intention-to-treat population included all patients in the trial who had known values (i.e., patients who had not withdrawn or were lost to follow-up). Percentages indicate patients who had an event up to 365 days after the index procedure. Risk differences may not calculate as expected owing to rounding. The 95% confidence intervals have not been adjusted for multiple comparisons, and therefore inferences drawn from these intervals may not be reproducible.

† The upper boundary of the one-sided 95% confidence interval was 3.0 percentage points, the upper boundary of the one-sided 97.5% confidence interval was 3.5 percentage points, and the noninferiority margin was 4.1 percentage points. The relative risk was 1.01 (upper boundary of the one-sided 95% CI, 1.19; upper boundary of the one-sided 97.5% CI, 1.23). The P value for noninferiority is one-sided and was calculated by the Farrington–Manning test.

‡ The principal secondary outcome of target-lesion failure was a composite of death from cardiac causes, target-vessel myocardial infarction (Q-wave and non–Q-wave), or clinically indicated target-lesion percutaneous or surgical revascularization. The upper boundary of the one-sided 95% confidence interval was 3.0 percentage points, the upper boundary of the one-sided 97.5% confidence interval was 3.5 percentage points, and the noninferiority margin was 4.4 percentage points. The relative risk was 1.01 (upper boundary of the one-sided 95% CI, 1.19; upper boundary of the one-sided 97.5% CI, 1.22). The P value for noninferiority is one-sided and was calculated by the Farrington–Manning test.

§ Target-vessel failure was defined as a composite of death from cardiac causes, target-vessel myocardial infarction, or clinically driven target-vessel revascularization by percutaneous or surgical methods.

¶ Myocardial infarction was assessed according to the Third Universal Definition of Myocardial Infarction.[14]

‖ Stent thrombosis was defined according to the Academic Research Consortium (see the End Point Definitions section in the Supplementary Appendix).

** The definition of stroke is provided in the End Point Definitions section in the Supplementary Appendix.

†† A major adverse cardiac event was defined as death from any cause, myocardial infarction, or clinically driven target-lesion revascularization.

‡‡ Bleeding was defined according to Bleeding Academic Research Consortium (BARC) criteria (see the End Point Definitions section in the Supplementary Appendix). BARC types range from 0 to 5, with higher values indicating greater severity of bleeding.

thrombosis were similar to those in the LEADERS FREE trial. Bleeding was relatively frequent, but the incidence was balanced in the two trial groups.

These findings should be interpreted in view of several limitations. First, this trial was single-blind because it was not possible for operators to be unaware of the device type. Indeed, we observed more frequent crossover in patients who had been assigned to receive polymer-free drug-coated stents than in those assigned to receive polymer-based zotarolimus-eluting stents, which may have contributed to the observed differences in device success. However, patients and outcome assessors were unaware of the treatment assignments. Second, the trial was powered for noninferiority testing for the primary outcome and the principal secondary outcome but not for superiority testing. The trial was also not powered to examine differences in lower-frequency secondary outcomes such as stent thrombosis and target-lesion revascularization, and these analyses were not adjusted for multiple comparisons. Finally, neither the present trial nor the LEADERS FREE trial had a control group of patients taking dual antiplatelet therapy for 3 or 6 months. Therefore, it is unknown whether patients at high bleeding risk who were selected to undergo PCI would have a superior net clinical benefit with a course of dual antiplatelet therapy longer than 1 month.

In conclusion, among patients at high bleeding risk, a strategy of PCI with a polymer-based zotarolimus-eluting stent followed by 1 month

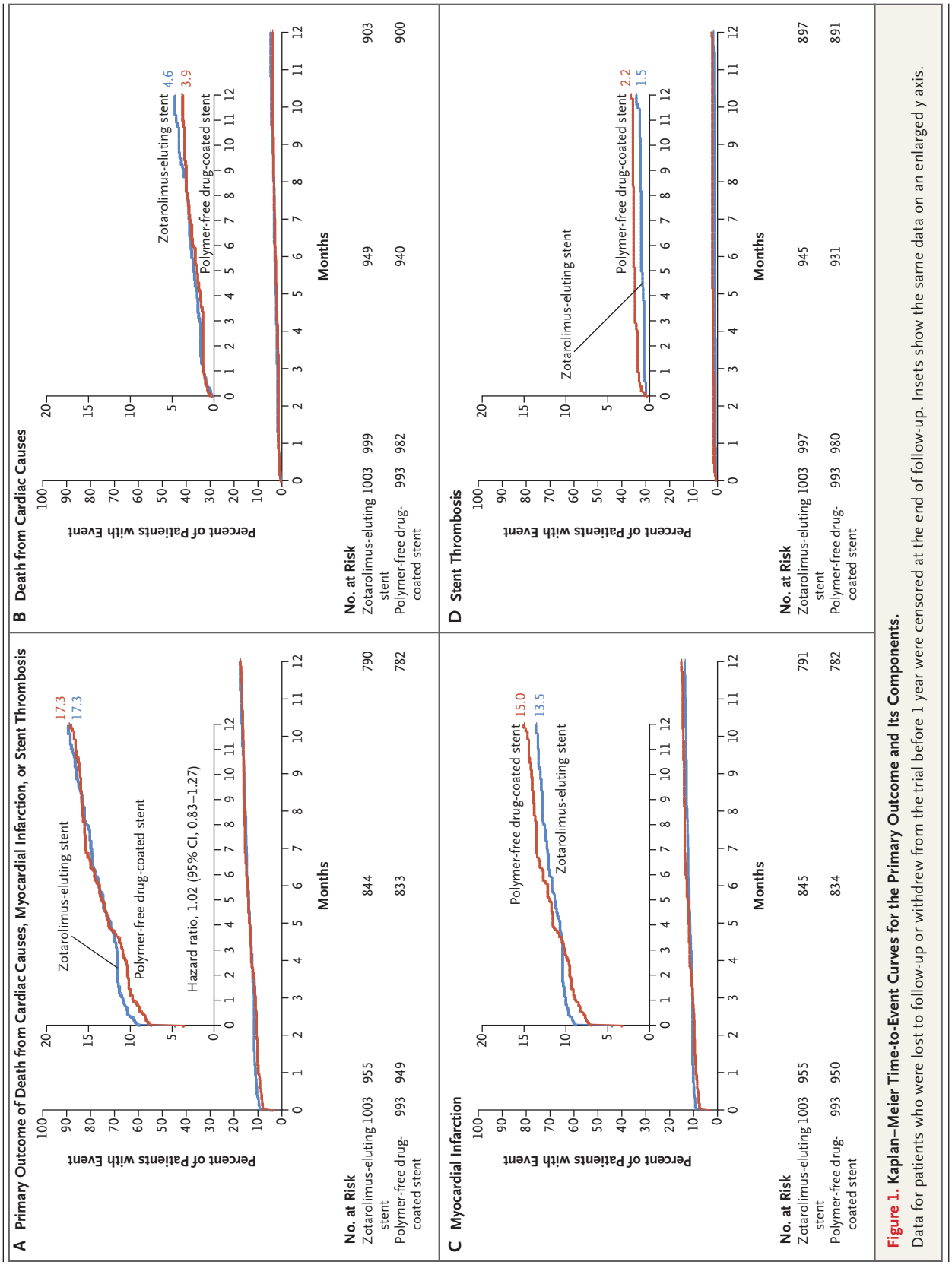
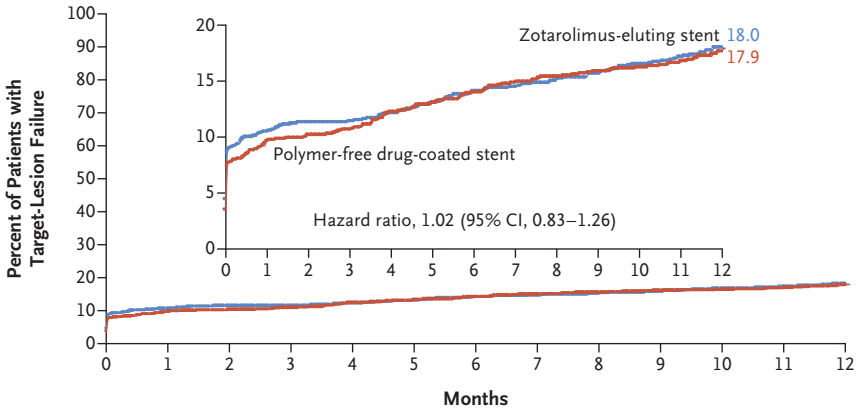


Figure 1. Kaplan–Meier Time-to-Event Curves for the Primary Outcome and Its Components.
Data for patients who were lost to follow-up or withdrew from the trial before 1 year were censored at the end of follow-up. Insets show the same data on an enlarged y axis.



No. at Risk				
Zotarolimus-eluting stent	1003	956	845	787
Polymer-free drug-coated stent	993	949	835	779

Figure 2. Kaplan–Meier Time-to-Event Curves for the Principal Secondary Outcome of Target-Lesion Failure.

Target-lesion failure was defined as a composite of death from cardiac causes, target-vessel myocardial infarction, or clinically indicated target-lesion revascularization. Data for patients who were lost to follow-up or withdrew from the trial before 1 year were censored at the end of follow-up. The inset shows the same data on an enlarged y axis.

of dual antiplatelet therapy was noninferior to a polymer-free drug-coated stent with regard to a composite outcome of death from cardiac causes, myocardial infarction, or stent thrombosis, as well as with regard to target-lesion failure.

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APPENDIX

The authors' full names and academic degrees are as follows: Stephan Windecker, M.D., Azeem Latib, M.D., Elvin Kedhi, M.D., Ph.D., Ajay J. Kirtane, M.D., David E. Kandzari, M.D., Roxana Mehran, M.D., Matthew J. Price, M.D., Alexandre Abizaid, M.D., Daniel I. Simon, M.D., Stephen G. Worthley, M.B., B.S., Ph.D., Azfar Zaman, M.D., Martin Hudec, M.D., Petra Poliacikova, M.D., A. Kahar bin Abdul Ghapar, M.D., Kamaraj Selvaraj, M.D., Ivo Petrov, M.D., Ph.D., Darren Mylotte, M.D., Eduardo Pinar, M.D., Raul Moreno, M.D., Franco Fabbiocchi, M.D., Sanjeevan Pasupati, M.D., Hyo-Soo Kim, M.D., Ph.D., Adel Aminian, M.D., Charles Tie, M.D., Adrian Wlodarczak, M.D., Seung-Ho Hur, M.D., Ph.D., Steven O. Marx, M.D., Ivana Jankovic, M.D., Sandeep Brar, M.D., Lisa Bousquette, M.S., Minglei Liu, Ph.D., and Gregg W. Stone, M.D.

The authors' affiliations are as follows: Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland (S.W.); Montefiore Medical Center (A.L.), Columbia University Irving Medical Center–New York–Presbyterian Hospital (A.J.K., S.O.M.), the Cardiovascular Research Foundation (A.J.K., S.O.M., I.J., G.W.S.), Mount Sinai Medical Center (R. Mehran), and the Zena and Michael A. Wiener Cardiovascular Institute, Icahn School of Medicine at Mount Sinai (G.W.S.) — all in New York; Isala Zwolle, Zwolle, the Netherlands (E.K.); Medical University of Silesia, Katowice (E.K.), and Poland Miedziowe Centrum Zdrowia, Lubin (A.W.) — both in Poland; Piedmont Heart Institute, Atlanta (D.E.K.); the Division of Cardiovascular Diseases, Scripps Clinic, La Jolla (M.J.P.), and Medtronic, Santa Rosa (S.B., L.B., M.L.) — both in California; Instituto Dante Pazzanese de Cardiologia, São Paulo (A. Abizaid); University Hospitals Cleveland Medical Center, Cleveland (D.I.S.); GenesisCare Cardiology, Alexandria, NSW (S.G.W.), and St. Andrew's Hospital, Adelaide, SA (C.T.) — both in Australia; Freeman Hospital and Newcastle University, Newcastle upon Tyne, United Kingdom (A.Z.); Stredoslovensky Ustav Srdcovych a Cievnych Chorob, Banska Bystrica, Slovakia (M.H., P.P.); Hospital Serdang, Kajang, Malaysia (A.K.A.G., K.S.); Acibadem City Clinic, Sofia, Bulgaria (I.P.); Galway University Hospitals–University Hospital Galway, Galway, Ireland (D.M.); Hospital Clínico Universitario Virgen de la Arrixaca, El Palmar (E.P.), and Hospital Universitario La Paz and Hospital La Paz Institute for Health Research, Madrid (R. Moreno) — all in Spain; Centro Cardiologico Monzino IRCCS, Milan (F.F.); Waikato Hospital, Hamilton, New Zealand (S.P.); Seoul National University Hospital, Seoul (H.-S.K.), and Keimyung University Dongsan Medical Center, Daegu (S.-H.H.) — both in South Korea; and Centre Hospitalier Universitaire Charleroi, Charleroi, Belgium (A. Aminian).

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