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Comparison of Titanium-Nitride-Oxide–Coated Stents With Zotarolimus-Eluting Stents for Coronary Revascularization

A Randomized Controlled Trial

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Objectives This study sought to compare the efficacy of passive stent coating with titanium-nitride-oxide (TiNO) with drug-eluting stents releasing zotarolimus (ZES) (Endeavor, Medtronic, Minneapolis, Minnesota).

Background Stent coating with TiNO has been shown to reduce restenosis compared with bare-metal stents in experimental and clinical studies.

Methods In an assessor-blind noninferiority study, 302 patients undergoing percutaneous coronary intervention were randomized to treatment with TiNO or ZES. The primary endpoint was in-stent late loss at 6 to 8 months, and analysis was by intention to treat.

Results Both groups were well balanced with respect to baseline clinical and angiographic characteristics. The TiNO group failed to reach the pre-specified noninferiority margin for the primary endpoint (in-stent late loss: 0.64 ± 0.61 mm vs. 0.47 ± 0.48 mm, difference: 0.16, upper 1-sided 95% confidence interval [CI]: 0.26; $p_{noninferiority} = 0.54$), and subsequent superiority testing was in favor of ZES ($p_{superiority} = 0.02$). In-segment binary restenosis was lower with ZES (11.1%) than with TiNO (20.5%; $p_{superiority} = 0.04$). A stratified analysis of the primary endpoint found particularly pronounced differences between stents among diabetic versus nondiabetic patients (0.90 ± 0.69 mm vs. 0.39 ± 0.38 mm; $p_{interaction} = 0.04$). Clinical outcomes showed a similar rate of death (0.7% vs. 0.7%; $p = 1.00$), myocardial infarction (5.3% vs. 6.7%; $p = 0.60$), and major adverse cardiac events (21.1% vs. 18.0%, hazard ratio: 1.19, 95% CI: 0.71 to 2.00; $p = 0.50$) at 1 year. There were no differences in rates of definite or probable stent thrombosis (0.7% vs. 0%; $p = 0.51$) at 1 year.

Conclusions Compared with TiNO, ZES was superior with regard to late loss and binary restenosis. The concept of passive stent coating with TiNO remains inferior to drug-eluting stent technology in reducing restenosis. ([TIDE] Randomized Trial Comparing Titan Stent With Zotarolimus-Eluting Stent: NCT00492908) (J Am Coll Cardiol Intv 2011;4:672–82) © 2011 by the American College of Cardiology Foundation

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Early generation drug-eluting stents (DES) have successfully addressed the problem of restenosis inherent to bare-metal stents but have been associated with an increased risk of very late stent thrombosis (1–5). Efforts to resolve the problem of very late stent thrombosis include newer generation DES with drug release from more biocompatible polymers and passive stent coatings, which mitigate the proinflammatory and thrombotic response to stent-mediated arterial injury in the absence of drug release (6–9). The newer generation Endeavor stent (Medtronic, Minneapolis, Minnesota) releases zotarolimus, a sirolimus analog, from the biocompatible phosphorylcholine polymer applied to a cobalt chromium alloy, thin-strut stent surface (10). Although angiographic studies revealed a somewhat higher late loss with zotarolimus-eluting stents (ZES) than the Taxus paclitaxel-eluting stent (Boston Scientific, Natick, Massachusetts), ZES showed similar clinical efficacy as paclitaxel-eluting stents in the large-scale ENDEAVOR IV (Randomized, Controlled Trial of the Medtronic Endeavor Drug-Eluting Coronary Stent System Versus the Taxus Paclitaxel-Eluting Coronary Stent System in De Novo Native Coronary Artery Lesions) and ZEST (Comparison of the Efficacy and Safety of Zotarolimus-Eluting Stent With Sirolimus-Eluting and Paclitaxel-Eluting Stent for Coronary Lesions) trials (7,11,12). During long-term follow-up, the incidence of very late stent thrombosis was exceedingly low and significantly lower than with paclitaxel-eluting stents (13).

Passive stent coating with titanium-nitride-oxide (TiNO) has been shown to diminish platelet adhesion and fibrinogen binding in vitro and to reduce neointimal hyperplasia in the porcine restenosis model (14). Moreover, TiNO was found to be superior in terms of late loss, restenosis, and target lesion revascularization (TLR) compared with bare-metal stents in a randomized clinical trial (9). We therefore hypothesized that passive stent coating with TiNO would provide similar efficacy in terms of neointimal hyperplasia suppression as a DES releasing zotarolimus. The present study was designed to compare the angiographic outcome between TiNO-coated stents (Titan2 stent, Hexacath, Rueil-Malmaison, France) and ZES (Endeavor) in a randomized, assessor-blind, noninferiority trial.

Methods

Patient population. Patients who were at least 18 years of age with stable or unstable angina pectoris or non–ST-segment elevation myocardial infarction and signs of myocardial ischemia were eligible if they had at least 1 lesion with a diameter stenosis of 50% or more that was suitable for coronary stent implantation in a vessel with a reference vessel diameter ranging from 2.25 to 4.0 mm. The following exclusion criteria were applied: patients unable to provide informed consent; participation in another trial before reaching the primary endpoint; and patients with known intolerance to aspirin, clopidogrel, heparin, stainless steel, titanium, zotarolimus, or contrast material. The study complied with the Declaration of Helsinki and was approved by the institutional review boards of all participating institutions. Written informed consent was obtained from all patients. The study was an investigator-initiated study and there was no industry involvement in the design, conduct, financial support, or analysis of the study.

Study design and procedures. The study was a randomized assessor-blind, noninferiority trial performed in 3 institutions in Switzerland. Randomization was performed after diagnostic angiography and before percutaneous coronary intervention. Sequentially numbered, sealed, opaque, tamper-proof security envelopes (Envelock Safety Envelopes, Plasto-Sac Ltd., Yavne, Israel) were used, which were independently monitored by an academic clinical trials unit. The allocation schedule was based on computer-generated random numbers, stratified according to trial center and catheter laboratory, and blocked, with block sizes of 2, 4, and 6 varying randomly. Patients were assigned on a 1:1 basis to treatment with a TiNO-coated stent (Titan 2) or ZES (Endeavor).

Abbreviations and Acronyms

CI = confidence interval
CK = creatine kinase
DES = drug-eluting stent(s)
IQR = interquartile range
TiNO = titanium-nitride-oxide
TLR = target lesion revascularization
ZES = zotarolimus-eluting stent(s)

TiNO-coated stents were available in diameters of 2.25 to 4.0 mm and in lengths of 7 to 28 mm. ZES were available in diameters of 2.25 to 4.0 mm and in lengths of 8 to 30 mm. Balloon angioplasty and coronary stent implantation were performed using standard techniques; direct stenting was allowed and performed at the discretion of the investigator. Full lesion coverage was attempted by implanting 1 or several stents. Crossover to a nonstudy stent was allowed to complete the procedure successfully, in the event that the assigned study stent could not be implanted. In case more than 1 lesion was treated in a given patient in the same session or in a staged procedure during the index hospitalization, the remaining lesions were still treated with the originally assigned study stent.

All patients were treated with at least 100 mg of acetylsalicylic acid and 300 to 600 mg of clopidogrel bisulfate before or at the time of the procedure. During percutaneous coronary intervention, unfractionated heparin in a dose of at least 5,000 IU or 70 to 100 IU/kg was administered to maintain an activated clotting time >250 s. The use of glycoprotein IIb/IIIa antagonists was left to the discretion of the operator. Creatine kinase (CK), CK-myocardial band, and troponin were assessed 6 h after the procedure and either at 18 h after the procedure or at hospital discharge, whichever came first. A 12-lead electrocardiogram was obtained before and within 24 h after the procedure or for any suspicion of

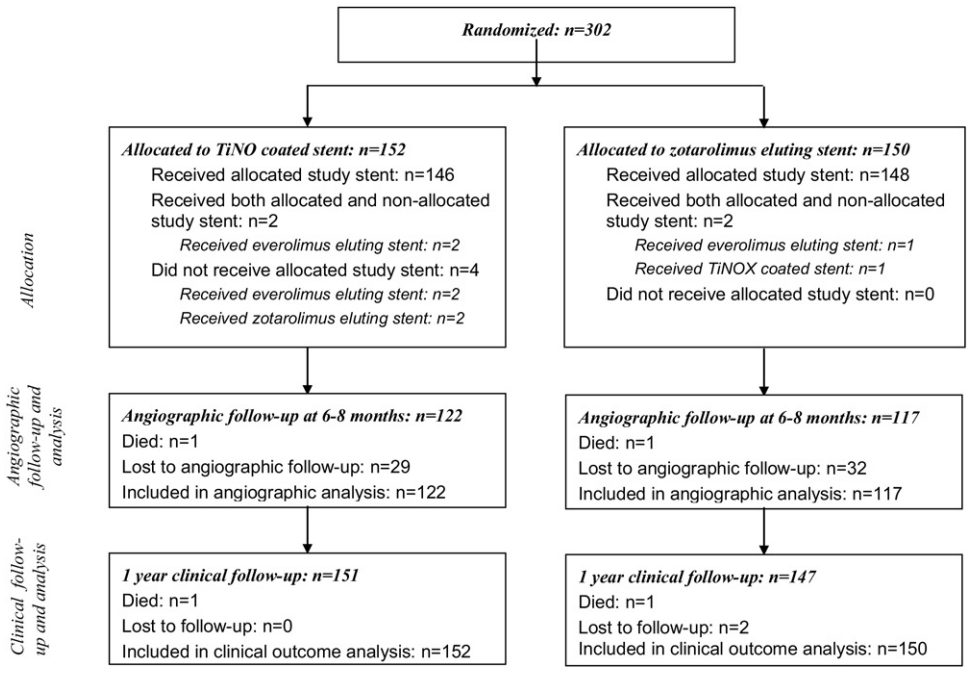

Figure 1. Patient and Lesion Flow

Patient and lesion flow according to CONSORT (Consolidated Standards for Reporting of Trials) (16). TiNO = titanium-nitride-oxide.

acute ischemia. In case of elevated cardiac enzymes after the procedure, CK, CK-myocardial band, and troponin measurements were continued every 8 h until the peak of the biomarkers had been conclusively defined. All patients were discharged on acetylsalicylic acid 100 mg daily indefinitely and clopidogrel bisulfate 75 mg daily for an intended duration of 3 months.

Quantitative coronary angiography. Coronary angiograms were digitally recorded at baseline, immediately after the procedure, and at follow-up and were assessed at the angiographic core laboratory of Bern University Hospital. Readers of angiograms were blinded to the assigned study stent. The projections that best showed the stenosis were used for all analyses. Measurements were performed on the cineangiograms after maximum vasodilation with nitroglycerin and the contrast-filled, nontapered catheter tip was used for calibration (≥6-F guiding catheter). Digital angiograms were analyzed with the help of an automated edge-detection system (QAngio XA, Version 7/1/14.Zero, Medis Medical Imaging Systems, Leiden, the Netherlands). Quantitative measurements included the diameter of the reference vessel, the minimal luminal diameter, percent diameter stenosis (difference between reference vessel diameter and minimal luminal diameter/reference diameter × 100), and late lumen loss (difference between minimal lumen diameter after the procedure and minimal lumen diameter at follow-up). Binary restenosis was defined as stenosis of 50% or greater of the minimal lumen diameter in the target lesion

Table 1. Baseline Clinical Characteristics

	TiNO-Coated Stent (n = 152)	ZES (n = 150)
Age, yrs	65.9 ± 9.0	63.4 ± 10.5
Male	124 (81.6)	118 (78.7)
Cardiac risk factors		
Diabetes mellitus	30 (19.7)	28 (18.7)
Insulin-requiring diabetes	7 (4.6)	10 (6.7)
Hypertension	105 (69.1)	113 (75.3)
Hypercholesterolemia	115 (75.7)	122 (81.3)
Current smoking	53 (34.9)	43 (28.7)
Family history of CAD	45 (29.6)	47 (31.3)
Past medical history		
Myocardial infarction	42 (27.6)	32 (21.3)
PCI	39 (25.7)	38 (25.3)
With drug-eluting stent	18 (11.8)	22 (14.7)
Previous CABG	12 (7.9)	4 (2.7)
Clinical characteristics		
Stable coronary artery disease	88 (57.9)	71 (47.3)
Unstable angina	14 (9.2)	16 (10.7)
Non–ST-segment elevation myocardial infarction	50 (32.9)	63 (42.0)
Left ventricular ejection fraction	56.5 ± 10.6	57.8 ± 10.1
Multivessel disease	36 (23.7)	38 (25.3)
Small vessel disease, RVD ≤2.75 mm	81 (53.3)	74 (49.3)
Long lesions, >20 mm	33 (21.7)	42 (28.0)
Average number of lesions per patient	1.5 ± 0.7	1.5 ± 0.7

Values are mean ± SD or n (%).

CABG = coronary artery bypass grafting; CAD = coronary artery disease; PCI = percutaneous coronary intervention; RVD = reference vessel diameter; TiNO = titanium-nitride-oxide; ZES = zotarolimus-eluting stent(s).

Table 2. Procedural Results

	TiNO-Coated Stent (n = 229)	ZES (n = 222)	Difference	
			Estimate (95% CI)	p Value
Pre-procedural results				
Lesion length, mm	13.1 ± 8.1	14.2 ± 8.9	−1.2 (−2.8 to 0.5)	0.17
RVD, mm	2.88 ± 0.47	2.90 ± 0.53	−0.03 (−0.13 to 0.07)	0.53
Minimal lumen diameter, mm	0.85 ± 0.49	0.82 ± 0.53	0.03 (−0.07 to 0.12)	0.60
Stenosis, % lumen diameter	71.0 ± 15.3	72.2 ± 16.4	−1.2 (−4.2 to 1.9)	0.45
Procedural results				
Number of study stents per lesion	1.28 ± 0.55	1.17 ± 0.45	0.11 (0.01 to 0.21)	0.03
Maximal stent diameter per lesion, mm	3.02 ± 0.46	3.01 ± 0.50	0.00 (−0.09 to 0.09)	1.00
Total stent length per lesion, mm	19.3 ± 11.1	19.6 ± 10.0	−0.3 (−2.4 to 1.8)	0.76
Direct stenting	76 (33.2)	66 (29.7)	3.5 (−5.4 to 12.3)	0.44
Implantation of study stent	221 (96.5)	219 (98.7)	−2.1 (−5.1 to 0.8)	0.16
Device success	213 (93.0)	210 (94.6)	−1.6 (−6.8 to 3.6)	0.55
Lesion success	219 (95.6)	213 (96.0)	−0.3 (−4.1 to 3.5)	0.87
Minimal lumen diameter, mm				
In-stent	2.60 ± 0.45	2.64 ± 0.49	−0.05 (−0.13 to 0.04)	0.31
In-segment	2.31 ± 0.54	2.34 ± 0.55	−0.03 (−0.14 to 0.07)	0.54
Diameter stenosis, %				
In-stent	10.35 ± 6.07	9.80 ± 5.11	0.54 (−0.54 to 1.58)	0.33
In-segment	18.65 ± 8.25	17.94 ± 8.20	0.70 (−0.84 to 2.24)	0.37
Acute gain, mm				
In-stent	1.75 ± 0.51	1.83 ± 0.56	−0.07 (−0.17 to 0.03)	0.17
In-segment	1.46 ± 0.57	1.52 ± 0.57	−0.06 (−0.17 to 0.04)	0.26

Values are mean ± SD or n (%).
CI = confidence interval; other abbreviations as in Table 1.

at angiographic follow-up. All angiographic measurements of the target lesion were obtained in the stented area, within the margins 5 mm proximal and distal to each stent edge (in-stent), and over the entire segment (in-segment).

Study endpoints and definitions. Adverse events were assessed at 1, 6, and 12 months. All patients were asked to return for an angiographic follow-up study at 6 to 8 months. An independent clinical event committee whose members

Table 3. Angiographic Follow-Up Results (Primary Outcome)

	TiNO-Coated Stent (n = 186)	ZES (n = 172)	Difference	
			Estimate (95% CI)	p Value
Reference vessel diameter, mm	2.81 (0.45)	2.85 (0.54)	−0.05 (−0.16 to 0.06)	0.36
Minimal lumen diameter, mm				
In-stent	1.93 ± 0.75	2.16 ± 0.69	−0.23 (−0.39 to −0.06)	0.01
In-segment	1.80 ± 0.71	2.00 ± 0.67	−0.19 (−0.35 to −0.03)	0.02
Diameter stenosis, %				
In-stent	31.86 ± 22.71	24.62 ± 18.23	6.57 (1.79 to 11.35)	0.01
In-segment	35.49 ± 21.21	29.07 ± 16.72	6.03 (1.64 to 10.42)	0.01
Late loss, mm				
In-stent*	0.64 ± 0.61	0.47 ± 0.48	0.16 (0.03 to 0.28)	0.02
In-segment	0.48 ± 0.55	0.36 ± 0.44	0.12 (0.00 to 0.23)	0.04
Binary restenosis				
In-stent	36 (19.4)	18 (10.5)	8.9 (−0.40 to 18.16)	0.06
In-segment	38 (20.5)	19 (11.1)	9.43 (0.23 to 18.63)	0.04

Values are n (%) or mean ± SD. The 95% CI and p values are 2-sided, from superiority testing. *Noninferiority testing for difference in means of in-stent late luminal loss: Difference = 0.16, upper 1-sided 95% CI = 0.26, noninferiority margin = 0.15, 1-sided p value = 0.54.
Abbreviations as in Tables 1 and 2.

were unaware of the patient's treatment assignment adjudicated all clinical endpoints. The primary endpoint of the study was in-stent late loss at 6 to 8 months after stent implantation as assessed by quantitative coronary angiography. Secondary angiographic endpoints included in-segment late loss as well as in-stent and in-segment binary restenosis, minimal luminal diameter, and percent diameter stenosis. Secondary clinical endpoints included: death; cardiac death; myocardial infarction; clinically and nonclinically indicated TLR; and the composite of cardiac death, myocardial infarction, or clinically indicated target lesion revascularization at 30 days, 6 months, and 1 year.

The definition of cardiac death included any death due to immediate cardiac cause (e.g., myocardial infarction, low-output failure, fatal arrhythmia); procedure-related deaths, including those related to concomitant treatment; unwitnessed death; and death of unknown cause. Myocardial infarction was defined using the electrocardiographic criteria of the Minnesota Code Manual, or as an elevation of CK levels to more than 2 times the upper limit of normal with positive levels of CK-myocardial band or troponin. TLR was defined as any repeat PCI within the stent or within the 5-mm borders adjacent to the stent, or bypass surgery of the target vessel. Revascularization of the target lesion and vessel was regarded as clinically indicated if the stenosis on any target lesion or vessel was at least 50% of the diameter of the vessel on the basis of quantitative coronary angiography in the presence of recurrent angina or objective signs of ischemia, or if the stenosis was at least 70% of the diameter of the vessel even in the absence of ischemic signs and symptoms. Stent thrombosis was defined according to the Academic Research Consortium definition as definite, probable, or possible (15).

Statistical analysis. This was a noninferiority trial, which was powered for noninferiority on the primary endpoint in-stent late lumen loss at 6 to 8 months. Based on angiographic outcomes reported for the ENDEAVOR II (Randomized Controlled Trial to Evaluate the Safety and Efficacy of the Medtronic AVE ABT-578 Eluting Driver Coronary Stent in De Novo Native Coronary Artery Lesions) trial (11) and the TINOX (Randomized Comparison of a Titanium-Nitride-Oxide–Coated Stent With a Stainless Steel Stent for Coronary Revascularization) study (9), we postulated the following in-stent late lumen loss values: ZES 0.61 ± 0.46 mm; TiNO 0.55 ± 0.63 mm. Assuming a noninferiority margin of 0.15 mm as the acceptable difference between TiNO and ZES to claim TiNO noninferiority to ZES, an average number of 1.5 lesions per patient, a design factor of 1.1 to take into account the correlation of lesions within patients, and a 1-sided type-1 error of 0.05, we estimated that 234 patients (117 patients in each group) will yield >80% power to detect noninferiority. To account for patients not undergoing repeat angiography 6 to 8 months after the procedure (typically 20% to 25% of the overall patient population), we pre-specified a total enrollment of 300 patients.

Baseline clinical characteristics, pre-procedural, procedural, and follow-up angiographic results (including the primary endpoint in-stent late lumen loss) are reported as mean ± SD for continuous variables and absolute numbers and percentages for categorical variables. For the angio-

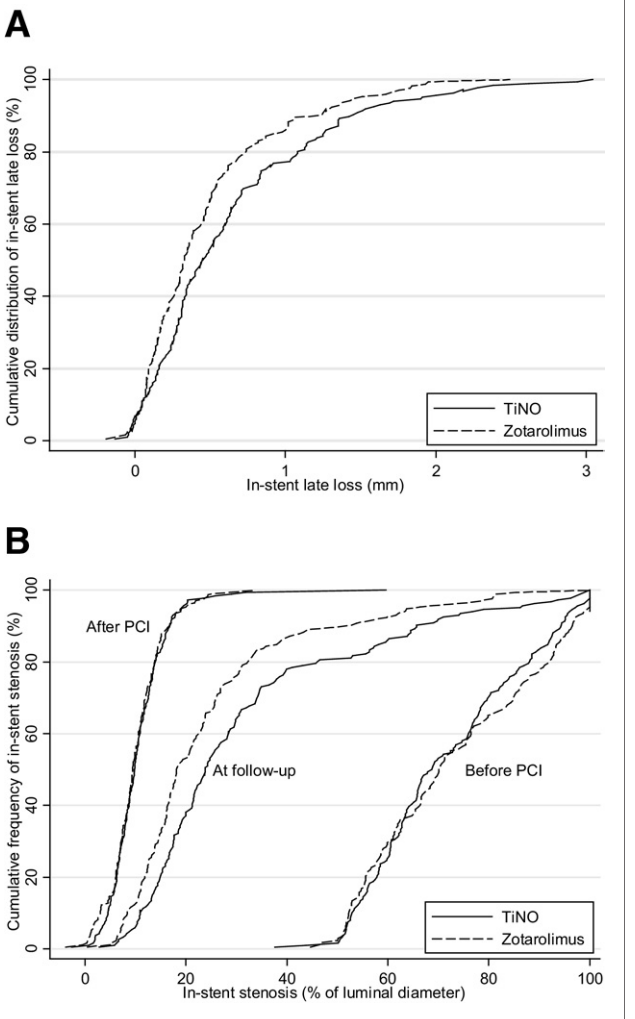

Figure 2. Cumulative Distribution of In-Stent Late Loss and Cumulative Frequency Distribution of In-Stent Percent Diameter Stenosis

(A) Cumulative distribution of in-stent late loss shown separately for the 2 stent types. The cumulative distribution curve of in-stent late loss is shifted to the right for titanium-nitride-oxide (TiNO) relative to zotarolimus-eluting stent (ZES), indicating that neointimal hyperplasia was more effectively reduced with ZES. **(B)** Cumulative frequency distribution curves of percent in-stent diameter stenosis shown separately for the stent types. There was no difference in measurements before and immediately after the procedure between the 2 stent types. At follow-up angiography, the cumulative distribution curve of percent in-stent diameter stenosis is shifted to the right for TiNO compared with ZES, indicating that in-stent diameter stenosis was more effectively reduced with ZES. TiNO = **continuous lines;** ZES = **dotted lines**.

graphic results, the differences (including 95% confidence interval [CI] and p value) between the 2 treatment groups were calculated using multilevel mixed-effects linear or logistic models that allowed for correlation of multiple lesions within patients. Stratified analyses were performed for the primary outcome according to the presence or absence of diabetes, lesions located in the left anterior descending artery, multivessel intervention, small vessel disease, long lesions, and age (>65 years vs. ≤65 years). To determine whether there was an interaction between treatment group and these characteristics, we used a likelihood-ratio test. We used the Mantel-Cox model and the corresponding log-rank test for between-group comparison of clinical outcomes occurring up to 1 month, up to 6 months, and up to 1 year. The duration of clopidogrel prescription between both treatment groups was compared using the Wilcoxon rank sum test. All patients who underwent randomization were included in the analysis in the groups to which they were originally allocated to (intention-to-treat principle). Analyses of angiographic outcomes were restricted to lesions from patients who attended follow-up angiography at 6 to 8 months (±2 months). In a sensitivity analysis, only the first lesion of each patient was analyzed on angiographic outcomes. Analyses were performed by a statistician (A.L.) who was blinded to the allocated treatment. No adjustments were made for multiple comparisons in secondary analyses; all p values and 95% CI are 2-sided. All analyses were done in Stata (version 11.0, StataCorp, College Station, Texas).

Results

Figure 1 summarizes the trial profile and patient flow (16). Between June 2007 and September 2008, 302 patients with 451 lesions were randomly assigned to treatment with either TiNO (152 patients, 229 lesions) or ZES (150 patients, 222 lesions). One hundred forty-six patients allocated to TiNO (96.1%) and 148 patients allocated to ZES (98.7%) received at least 1 allocated study stent. No patient allocated to TiNO and 2 patients allocated to ZES (1.3%) were lost to follow-up or withdrew consent before reaching 12 months. Baseline clinical characteristics are shown in Table 1 and are similar in both groups. Procedural characteristics including number of treated lesions, the distribution of lesion location, and rate of direct stenting, as well as lesion and stent length were similar among patients treated with TiNO and ZES (Table 2). More stents per lesion were implanted in the TiNO group than in the ZES group (1.3 vs. 1.2; p = 0.03). Implantation of the allocated study stent occurred with similar frequency in both groups (96.5% vs. 98.7%; p = 0.16). Device and lesion success were comparable for the 2 devices as were the angiographic lesion measurements before and after stent implantation (Table 2). Median length of clopidogrel prescription was 4.0

	TiNO coated stent [n=186 lesions]		Zotarolimus eluting stent [n=172 lesions]		Difference	
	Number of patients	Mean (SD)	Number of patients	Mean (SD)	Estimate (95% CI)	P-value for interaction*
Overall	122	0.64 (0.61)	117	0.47 (0.48)	0.16 (0.03 to 0.28)	
Diabetes mellitus						
Yes	20	0.90 (0.69)	17	0.39 (0.38)	0.50 (0.21 to 0.79)	0.04
No	102	0.59 (0.58)	100	0.49 (0.50)	0.10 (-0.04 to 0.23)	
Left anterior descending						
Yes	53	0.54 (0.51)	47	0.43 (0.46)	0.11 (-0.05 to 0.28)	0.47
No	69	0.71 (0.66)	70	0.50 (0.49)	0.19 (0.02 to 0.36)	
Multivessel intervention						
Yes	29	0.52 (0.51)	32	0.38 (0.41)	0.14 (-0.05 to 0.32)	0.93
No	93	0.71 (0.64)	85	0.55 (0.52)	0.15 (-0.01 to 0.32)	
Small vessel disease						
Yes	65	0.67 (0.62)	62	0.44 (0.49)	0.22 (0.05 to 0.40)	0.23
No	57	0.60 (0.58)	55	0.53 (0.45)	0.07 (-0.11 to 0.25)	
Long lesions						
Yes	25	0.71 (0.64)	33	0.54 (0.58)	0.18 (-0.11 to 0.48)	0.92
No	97	0.62 (0.60)	84	0.44 (0.42)	0.17 (0.03 to 0.31)	
Age > 65 years						
Yes	62	0.71 (0.66)	51	0.44 (0.51)	0.25 (0.04 to 0.45)	0.16
No	60	0.56 (0.54)	66	0.50 (0.45)	0.07 (-0.09 to 0.22)	

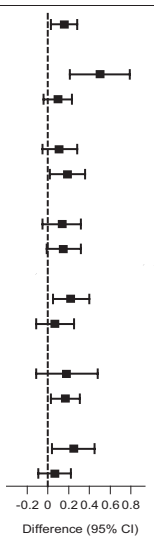

Figure 3. Stratified Analyses for Primary Outcome

Subgroup analysis of the primary endpoint, in-stent late loss, among patients randomized to treatment with TiNO or ZES. *p values for interaction between treatment group and corresponding stratification factor. CI = confidence interval; other abbreviations as in Figures 1 and 2.

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Table 4. Clinical Outcomes

	TiNO-Coated Stent (n = 152)	ZES (n = 150)	Hazard Ratio (95% CI)	p Value
Events at 30 days				
Death	0	1 (0.7)	0.33 (0.01–8.01)	0.50*
Cardiac death	0	0	—	—
Myocardial infarction	5 (3.3)	5 (3.3)	0.99 (0.28–3.48)	0.98
Q-wave	1 (0.7)	1 (0.7)	0.99 (0.06–15.90)	1.00*
Non–Q-wave	4 (2.6)	4 (2.7)	0.98 (0.24–4.00)	0.98
Clinically indicated TLR	1 (0.7)	0	2.96 (0.12–72.11)	0.51*
Percutaneous	1 (0.7)	0	2.96 (0.12–72.11)	0.51*
Surgical	0	0	—	—
Any TLR	1 (0.7)	0	2.96 (0.12–72.11)	0.51*
Percutaneous	1 (0.7)	0	2.96 (0.12–72.11)	0.51*
Surgical	0	0	—	—
Clinically indicated TVR	1 (0.7)	0	2.96 (0.12–72.11)	0.51*
Percutaneous	1 (0.7)	0	2.96 (0.12–72.11)	0.51*
Surgical	0	0	—	—
Any TVR	1 (0.7)	0	2.96 (0.12–72.11)	0.51*
Percutaneous	1 (0.7)	0	2.96 (0.12–72.11)	0.51*
Surgical	0	0	—	—
Any repeat revascularization	1 (0.7)	0	2.96 (0.12–72.11)	0.51*
Percutaneous	1 (0.7)	0	2.96 (0.12–72.11)	0.51*
Surgical	0	0	—	—
Death or MI	5 (3.3)	6 (4.0)	0.82 (0.25–2.74)	0.75
Cardiac death or MI	5 (3.3)	5 (3.3)	0.99 (0.28–3.48)	0.98
Cardiac death, MI, or clinically indicated TLR	5 (3.3)	5 (3.3)	0.99 (0.28–3.48)	0.98
MACE (cardiac death, MI, or clinically indicated TVR)	5 (3.3)	5 (3.3)	0.99 (0.28–3.48)	0.98
Events at 6 months				
Death	1 (0.7)	1 (0.7)	0.98 (0.06–15.80)	1.00*
Cardiac death	0	0	—	—
Myocardial infarction	6 (4.0)	6 (4.0)	0.99 (0.31–3.11)	0.98
Q-wave	1 (0.7)	1 (0.7)	0.99 (0.06–15.90)	1.00*
Non–Q-wave	5 (3.3)	5 (3.3)	0.98 (0.28–3.44)	0.98
Clinically indicated TLR	6 (4.0)	1 (0.7)	5.96 (0.72–49.50)	0.06
Percutaneous	5 (3.3)	1 (0.7)	4.96 (0.58–42.51)	0.10
Surgical	1 (0.7)	0	2.96 (0.12–72.11)	0.51*
Any TLR	6 (4.0)	1 (0.7)	5.96 (0.72–49.50)	0.06
Percutaneous	5 (3.3)	1 (0.7)	4.96 (0.58–42.51)	0.10
Surgical	1 (0.7)	0	2.96 (0.12–72.11)	0.51*
Clinically indicated TVR	7 (4.6)	2 (1.3)	3.51 (0.73–16.94)	0.10
Percutaneous	6 (4.0)	2 (1.3)	3.00 (0.60–14.90)	0.16
Surgical	1 (0.7)	0	2.96 (0.12–72.11)	0.51*
Any TVR	7 (4.6)	2 (1.3)	3.51 (0.73–16.94)	0.10
Percutaneous	6 (4.0)	2 (1.3)	3.00 (0.60–14.90)	0.16
Surgical	1 (0.7)	0	2.96 (0.12–72.11)	0.51*
Any repeat revascularization	9 (5.9)	3 (2.0)	3.00 (0.81–11.08)	0.08
Percutaneous	8 (5.3)	3 (2.0)	2.66 (0.70–10.02)	0.13
Surgical	1 (0.7)	0	2.96 (0.12–72.11)	0.51*
Death or MI	7 (4.6)	7 (4.7)	0.98 (0.34–2.85)	0.98
Cardiac death or MI	6 (4.0)	6 (4.0)	0.99 (0.31–3.11)	0.98
Cardiac death, MI, or clinically indicated TLR	10 (6.6)	7 (4.7)	1.41 (0.53–3.75)	0.49
MACE (cardiac death, MI, or clinically indicated TVR)*	11 (7.2)	8 (5.3)	1.36 (0.54–3.41)	0.51

Continued on next page

Table 4. Continued

	TiNO-Coated Stent (n = 152)	ZES (n = 150)	Hazard Ratio (95% CI)	p Value
Events at 1 yr				
Death	1 (0.7)	1 (0.7)	0.98 (0.06–15.80)	1.00*
Cardiac death	0	0	—	—
Myocardial infarction	8 (5.3)	10 (6.7)	0.78 (0.30–1.99)	0.60
Q-wave	1 (0.7)	1 (0.7)	0.99 (0.06–15.90)	1.00*
Non–Q-wave	7 (4.6)	9 (6.0)	0.76 (0.28–2.04)	0.58
Clinically indicated TLR	22 (14.5)	13 (8.7)	1.74 (0.87–3.46)	0.11
Percutaneous	21 (13.8)	11 (7.3)	1.95 (0.94–4.07)	0.07
Surgical	2 (1.3)	2 (1.3)	0.98 (0.14–6.93)	1.00*
Any TLR	26 (17.1)	17 (11.3)	1.57 (0.85–2.90)	0.15
Percutaneous	24 (15.8)	15 (10.0)	1.64 (0.86–3.13)	0.13
Surgical	3 (2.0)	2 (1.3)	1.46 (0.24–8.77)	0.66
Clinically indicated TVR	27 (17.8)	20 (13.3)	1.39 (0.78–2.50)	0.27
Percutaneous	26 (17.1)	17 (11.3)	1.57 (0.85–2.91)	0.15
Surgical	2 (1.3)	3 (2.0)	0.65 (0.11–3.89)	0.63
Any TVR	31 (20.4)	23 (15.3)	1.39 (0.81–2.39)	0.24
Percutaneous	29 (19.1)	20 (13.3)	1.50 (0.84–2.65)	0.17
Surgical	3 (2.0)	3 (2.0)	0.97 (0.20–4.83)	0.97
Any repeat revascularization	41 (20.4)	30 (15.3)	1.42 (0.89–2.29)	0.14
Percutaneous	39 (25.7)	28 (18.7)	1.45 (0.89–2.36)	0.14
Surgical	3 (2.0)	3 (2.0)	0.97 (0.20–4.83)	0.97
Death or MI	9 (5.9)	11 (7.3)	0.80 (0.33–1.94)	0.62
Cardiac death or MI	8 (5.3)	10 (6.7)	0.78 (0.30–1.99)	0.60
Cardiac death, MI, or clinically indicated TLR	27 (17.8)	21 (14.0)	1.29 (0.73–2.29)	0.39
MACE (cardiac death, MI, or clinically indicated TVR)	32 (21.1)	27 (18.0)	1.19 (0.71–2.00)	0.50

Values are presented as n (%). Hazard ratios are from Mantel-Cox model. p values are 2-sided from superiority testing using a log-rank test. Note that a continuity correction of 0.5 was used in case of 0 events in 1 group. *Fisher exact test.

MACE = major adverse cardiac event(s); MI = myocardial infarction; TLR = target lesion revascularization; TVR = target vessel revascularization; other abbreviations as in Tables 1 and 2.

months in patients treated with TiNO (interquartile range [IQR]: 3.0 to 10.6 months) and 7.0 months in patients treated with ZES (IQR: 3.1 to 12.0 months; p value for difference = 0.06).

Angiographic outcomes. Angiographic follow-up was completed according to protocol in 239 of 302 patients (79.1%) with 358 of 451 lesions (79.4%) at a median follow-up of 7.9 months (IQR: 7.4 to 8.9 months) (Table 3). A total of 122 patients (80.3%) allocated to TiNO and 117 patients (78.0%) allocated to ZES underwent follow-up angiography (p = 0.63). Patients with angiographic follow-up were younger (63.9 vs. 67.6; p = 0.008) and were less frequently diabetic (15.5% vs. 33.3%; p = 0.001) and hypertensive (69.5% vs. 82.5%, p = 0.04). Among patients undergoing angiographic follow-up, clinical baseline characteristics were similar between TiNO and ZES, with the exception of age (65.5 vs. 62.3 years; p = 0.01).

The TiNO group failed to reach the pre-specified non-inferiority margin (difference: 0.16, upper 1-sided 95% CI: 0.26; $p_{noninferiority} = 0.54$) (Table 3). In-stent late loss was significantly lower with ZES than TiNO (0.47 ± 0.48 mm vs. 0.64 ± 0.61 mm; $p_{superiority} = 0.02$). In-segment late loss was also lower with ZES than TiNO (0.36 ± 0.44 mm vs. 0.48 ± 0.55 mm; $p_{superiority} = 0.04$). Consistent results in favor of ZES were observed for measurements of in-stent and in-segment minimal lumen diameter and percent diameter stenosis. As a result, a significant reduction of in-segment binary restenosis was observed with ZES versus TiNO groups (11.1% vs. 20.5%; $p_{superiority} = 0.04$). The cumulative distribution of in-stent late lumen loss for the 2 stent groups is shown in Figure 2A. The cumulative frequencies of in-stent percent diameter stenosis for the 2 stent groups before and after the procedure, and at follow-up angiography are shown in Figure 2B. Figure 3 shows the results of stratified analyses of the primary endpoint. Results were consistent among patients with or without lesions located in the left anterior descending artery, multivessel intervention, and long lesions. Conversely, differences between TiNO and ZES appeared more pronounced among diabetic compared with nondiabetic patients, patients with or without small vessel disease, and patients aged below or above 65 years. However, a p value for interaction reached conventional

levels of significance only in the case of diabetic mellitus ($p = 0.04$).

Clinical outcomes. At 30 days, adverse events were rare, and there were no differences with respect to ischemic and revascularization endpoints among patients randomized to TiNO or ZES (Table 4). At 6 months, revascularization procedures by any definition (clinically indicated TLR, any TLR, clinically indicated target vessel revascularization, any target vessel revascularization, any repeat revascularization procedure) tended to be more common among patients randomized to TiNO than to ZES (Table 4). This trend remained sustained up to 1 year, but there were no differences with respect to death, cardiac death, or myocardial infarction. Similarly, major adverse cardiac events—the composite of cardiac death, myocardial infarction. and clinically indicated target vessel revascularization—showed no significant differences between TiNO and ZES up to 1 year (Fig. 4A). Cumulative incidence curves of clinically indicated TLR began to diverge as early as 4 months after the procedure in favor of ZES (Fig. 4B). Rates of definite, probable, and possible stent thrombosis during the early and late time periods were low and comparable for both stent types (Table 5).

Discussion

In this randomized, assessor-blind, noninferiority trial, compared with ZES, passive stent coating with TiNO failed to reach noninferiority for the primary endpoint, in-stent late lumen loss. The zotarolimus-eluting DES was found superior to TiNO in all angiographic measurements including in-segment binary restenosis at 6 to 8 months. Correspondingly, there was a trend toward fewer repeat revascularization procedures.

Restenosis following percutaneous coronary interventions is the result of a vasculo-proliferative cascade in response to stent-mediated arterial injury (17). Several concepts have been put forward to attenuate neointimal hyperplasia in response to iatrogenic arterial injury associated with stent implantation. Changes in stent strut configuration, thickness, and geometry, as well as primary stent implantation aim to reduce arterial injury and thereby the extent of neointimal hyperplasia (18–20). Passive stent coatings attempt to mitigate the proinflammatory and thrombotic response to stent-mediated arterial injury and, thereby, the impact on the vasculo-proliferative response (14). Finally, active stent coatings with release of antiproliferative drugs or radioactivity directly inhibit smooth muscle cell proliferation and migration, as well as extracellular matrix formation to minimize neointimal hyperplasia (21,22).

The latter concept has proved successful in the form of early generation DES with important reductions in the need for repeat revascularization procedures compared with bare-metal stents (1,2). However, the problem of very late stent thrombosis emerged as a distinct entity particularly among more complex patient and lesion subsets (5). To overcome this limitation, newer generation DES have been developed with thinner struts, more biocompatible polymers, and lower drug concentrations, such as the ZES used in the present study. Passive stent coating with TiNO is an alternative concept. Titanium has improved biocompatibility compared with stainless steel as well as cobalt chromium alloys, owing to higher corrosion resistance and less tissue reactivity. Moreover, TiNO-coated stents resulted in less neointimal hyperplasia in a porcine restenosis model and were superior in terms of restenosis and repeat revascularization in a small randomized clinical study (9,14).

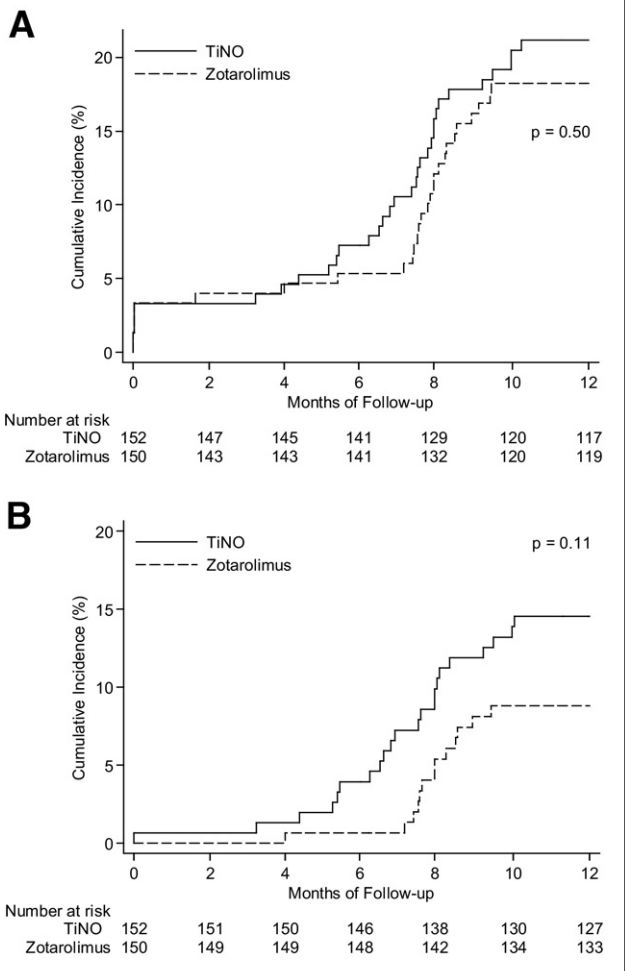

Figure 4. Composite of Cardiac Death, Myocardial Infarction, or Clinically Indicated Target Vessel Revascularization

(A) Kaplan-Meier curves show the cumulative incidence of the composite endpoint of cardiac death, myocardial infarction, and clinically indicated target vessel revascularization up to 12-month follow-up for TiNO and ZES. (B) Kaplan-Meier curves show the cumulative incidence of just clinically indicated target lesion revascularizations up to 12-month follow-up for TiNO and ZES. TiNO = **continuous lines;** ZES = **dotted lines**. Abbreviations as in Figures 1 and 2.

Table 5. Stent Thrombosis

	TiNO-Coated Stent (n = 152)	ZES (n = 150)	Hazard Ratio (95% CI)	p Value
Definite stent thrombosis				
0 to 30 days	1 (0.7)	0	2.96 (0.12–72.11)	0.51*
>30 days to 12 months	0	0	—	—
0 days to 12 months	1 (0.7)	0	2.96 (0.12–72.11)	0.51*
Probable stent thrombosis				
0 to 30 days	0	0	—	—
>30 days to 12 months	0	0	—	—
0 days to 12 months	0	0	—	—
Possible stent thrombosis				
0 to 30 days	0	0	—	—
>30 days to 12 months	0	0	—	—
0 days to 12 months	0	0	—	—
Definite or probable stent thrombosis				
0 to 30 days	1 (0.7)	0	2.96 (0.12–72.11)	0.51*
>30 days to 12 months	0	0	—	—
0 days to 12 months	1 (0.7)	0	2.96 (0.12–72.11)	0.51*

Data are presented as n (%). Hazard ratios are from Mantel-Cox model, and p values are 2-sided from superiority testing using a log-rank test. Note that a continuity correction of 0.5 was used in case of 0 events in 1 group. *Fisher exact test.

Abbreviations as in Tables 1 and 2.

However, the results of the present study indicate that passive stent coating with TiNO remains inferior to current DES technology in reducing late loss and binary restenosis. Compared with previously published data on angiographic outcomes, late loss was lower with ZES in the present study than that observed in the ENDEAVOR trials (ENDEAVOR I [First-in-human study of the Endeavor ABT-578-eluting phosphorylcholine-encapsulated stents system in de novo native coronary artery lesions] (10): 0.61 ± 0.44 mm; ENDEAVOR II (11): 0.61 ± 0.46 mm; ENDEAVOR II CA [Safety of direct stenting with the Endeavor stent: results of the Endeavor II continued access registry] [23]: 0.58 ± 0.58 mm; ENDEAVOR III [Randomized Controlled Trial of the Medtronic Endeavor Drug-Eluting Coronary Stent System Versus the Cypher Sirolimus-Eluting Coronary Stent System in De Novo Native Coronary Artery Lesions] [24]: 0.60 ± 0.48 mm; ENDEAVOR IV [7]: 0.67 ± 0.49 mm). However, CIs overlap widely, indicating that the present results are compatible with previous reports. When restricting the analysis to patients with only 1 lesion, mean late loss was somewhat higher and amounted to 0.56 ± 0.54 mm and 0.67 ± 0.57 mm in ZES and TiNO, respectively. We noted heterogeneity of results for the primary endpoint according to diabetic status. Thus, the difference in late loss between TiNO (0.90 ± 0.69 mm) and ZES (0.39 ± 0.38 mm; p = 0.001) was particularly pronounced among diabetic patients, and a test for interaction reached conventional levels of significance. Diabetic patients are at increased risk of restenosis, and DES have been found particularly effective in this high-risk cohort (25). The differences between passive stent coating using TiNO and DES were more accentuated in diabetic patients in the present study, and therefore, DES remain first-line therapy in this patient population. Differences between the 2 stent platforms were also more pronounced among patients with small vessels and the elderly (age >65 years) favoring ZES. However, a test for interaction failed to reach significance and the findings, therefore, may reflect the play of chance.

Study limitations. The present study was designed for an angiographic endpoint and, therefore, is too small to qualify as a clinical endpoint study. Although late loss was significantly lower with ZES than TiNO, clinical outcomes through 1 year showed similar results in terms of major adverse cardiac events for both stent platforms, and differences in revascularization procedures were likely driven by protocol-mandated angiographic follow-up. Another limitation is the lack of longer-term clinical and angiographic follow-up beyond 1 year. It cannot be excluded that the 2 stent platforms have a differential impact on long-term vessel remodeling. Thus, longitudinal angiographic follow-up series of patients treated with bare-metal stents suggest late improvements in lumen diameter beyond the early period of neointimal proliferation, whereas a late catch-up phenomenon has been observed with early generation DES (26). Notwithstanding, ZES represents a newer generation DES, and long-term clinical follow-up indicates low rates of repeat revascularization up to 3 years (13). Finally, the overall number of patients studied with TiNO is rather small, and therefore, the available evidence is limited as compared to that for established DES platforms.

Conclusions

Compared with TiNO, ZES is superior with regard to late loss and binary restenosis. The concept of passive stent coating with TiNO remains inferior to current DES technology in reducing restenosis.

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Key Words: passive stent coating ■ titanium-nitride-oxide–coated stent(s) ■ zotarolimus-eluting stent(s).