Comparison of an Everolimus-Eluting Stent and a Paclitaxel-Eluting Stent in Patients With Coronary Artery Disease

A Randomized Trial

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Context A thin, cobalt-chromium stent eluting the antiproliferative agent everolimus from a nonadhesive, durable fluoropolymer has shown promise in preliminary studies in improving clinical and angiographic outcomes in patients with coronary artery disease.

Objective To evaluate the safety and efficacy of an everolimus-eluting stent compared with a widely used paclitaxel-eluting stent.

Design, Setting, and Patients The SPIRIT III trial, a prospective, randomized, single-blind, controlled trial enrolling patients at 65 academic and community-based US institutions between June 22, 2005, and March 15, 2006. Patients were 1002 men and women undergoing percutaneous coronary intervention in lesions 28 mm or less in length and with reference vessel diameter between 2.5 and 3.75 mm. Angiographic follow-up was prespecified at 8 months in 564 patients and completed in 436 patients. Clinical follow-up was performed at 1, 6, 9, and 12 months.

Interventions Patients were randomized 2:1 to receive the everolimus-eluting stent (n=669) or the paclitaxel-eluting stent (n=333).

Main Outcome Measures The primary end point was noninferiority or superiority of angiographic in-segment late loss. The major secondary end point was noninferiority assessment of target vessel failure events (cardiac death, myocardial infarction, or target vessel revascularization) at 9 months. An additional secondary end point was evaluation of major adverse cardiac events (cardiac death, myocardial infarction, or target lesion revascularization) at 9 and 12 months.

Results Angiographic in-segment late loss was significantly less in the everolimus-eluting stent group compared with the paclitaxel group (mean, 0.14 [SD, 0.41] mm vs 0.28 [SD, 0.48] mm; difference, –0.14 [95% CI, –0.23 to –0.05]; $P \leq .004$). The everolimus stent was noninferior to the paclitaxel stent for target vessel failure at 9 months (7.2% vs 9.0%, respectively; difference, –1.9% [95% CI, –5.6% to 1.8%]; relative risk, 0.79 [95% CI, 0.51 to 1.23]; $P < .001$). The everolimus stent compared with the paclitaxel stent resulted in significant reductions in composite major adverse cardiac events both at 9 months (4.6% vs 8.1%; relative risk, 0.56 [95% CI, 0.34 to 0.94]; $P = .03$) and at 1 year (6.0% vs 10.3%; relative risk, 0.58 [95% CI, 0.37 to 0.90]; $P = .02$), due to fewer myocardial infarctions and target lesion revascularization procedures.

Conclusions In this large-scale, prospective randomized trial, an everolimus-eluting stent compared with a paclitaxel-eluting stent resulted in reduced angiographic late loss, noninferior rates of target vessel failure, and fewer major adverse cardiac events during 1 year of follow-up.

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BY ENLARGING THE ARTERIAL lumen and sealing dissection planes, stent implantation relieves coronary flow obstruction at the site of atherosclerotic disease. However, injury to the tunica media results in excessive neointimal hyperplasia in approximately 20% to 30% of patients treated with bare-metal stents, which results in recurrent ischemia often necessitating rehospitalization for repeat percutaneous coronary intervention or coronary artery bypass graft surgery.[1] Drug-eluting stents combine the mechanical scaffolding properties of metallic stents with the site-specific delivery of an antiproliferative agent designed to inhibit vascular responses to arterial injury, thereby reducing restenosis. The polymer-regulated, site-specific delivery of paclitaxel and sirolimus have been shown to inhibit tissue growth after coronary stent implantation and to improve long-term event-free survival compared with bare-metal stents.[2,3] However, restenosis still occurs, and the incidence of stent thrombosis, especially after

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the first year of implantation, is increased with these drug-eluting stents compared with their bare-metal counterparts,[4,5] likely due to delayed and incomplete endothelialization.[6,7]

Newer drug-eluting stents are being designed with the goal of enhanced safety, efficacy, or both compared with previous devices. Everolimus, a semisynthetic macrolide immunosuppressant, is an analogue of rapamycin, which binds to cytosolic FKBP12 and subsequently to the mammalian target of rapamycin, thereby blocking the stimulatory effects of growth factors and cytokines, which are released after vascular injury. As a result, cell cycle progression is blocked between the G1 and S phases, inhibiting smooth muscle cell proliferation.[8]

Everolimus has been shown to prevent cardiac allograft vasculopathy,[9] which histologically resembles the neointimal hyperplasia that develops after coronary stent implantation.[10] An everolimus-eluting stent has been designed in which the drug is released from a thin (7.8-μm), nonadhesive, durable, biocompatible fluoropolymer coated onto a low-profile (0.0032-in [0.0813-mm] strut thickness), flexible cobalt-chromium stent. Preclinical studies have shown more rapid endothelialization with this stent compared with sirolimus-eluting and paclitaxel-eluting stents.[11] Following favorable results with this device in 1 small and 1 moderate-sized randomized study in Europe,[12,13] the large-scale SPIRIT III trial was performed to evaluate the everolimus-eluting stent in comparison to a widely used paclitaxel-eluting stent in patients with coronary artery disease.

METHODS

Study Population, Device Description, and Protocol

SPIRIT III was a prospective, multicenter, randomized, single-blind, controlled clinical trial in which 1002 patients with either 1 or 2 de novo native coronary artery lesions (maximum 1 lesion per epicardial coronary artery) were randomized in a 2:1 ratio to receive the polymer-based everolimus-eluting stent (XIENCE V; Abbott Vascular, Santa Clara, California) or the polymer-based paclitaxel-eluting stent (TAXUS EXPRESS2; Boston Scientific, Natick, Massachusetts). Patients aged 18 years or older with stable or unstable angina or inducible ischemia undergoing percutaneous coronary intervention were considered for enrollment.

Clinical exclusion criteria included percutaneous intervention in the target vessel either prior to or planned within 9 months after the index procedure; intervention in a nontarget vessel within 90 days prior to or planned within 9 months after the index procedure; prior coronary brachytherapy at any time; acute or recent myocardial infarction with elevated cardiac biomarker levels; left ventricular ejection fraction less than 30%; prior or planned organ transplantation; current or planned chemotherapy for malignancy; known immunologic or autoimmune disease or prescribed immunosuppressive medication; use of chronic anticoagulation; contraindications or allergy to aspirin, heparin, and bivalirudin, thienopyridines, everolimus, cobalt, chromium, nickel, tungsten, acrylic, or fluoropolymers, or to iodinated contrast that cannot be premedicated; elective surgery planned within 9 months after the procedure, necessitating antiplatelet agent discontinuation; platelet count less than 100 000 cells/μL or greater than 700 000 cells/μL, white blood cell count less than 3000 cells/μL, serum creatinine level greater than 2.5 mg/dL (to convert to μmol/L, multiply by 88.4), or dialysis or liver disease; recent major bleeding, hemorrhagic diathesis, or objection to blood transfusions; stroke or transient ischemic attack within 6 months; comorbid conditions that limit life expectancy to less than 1 year or that could affect protocol compliance; positive pregnancy test result, lactation, or planned pregnancy within 1 year after enrollment; and participation in another investigational study that has not yet reached its primary end point. The study was approved by the institutional review board at each participating center, and consecutive, eligible patients signed written informed consent.

Prior to catheterization, an electrocardiogram was performed, creatine phosphokinase and isoenzyme levels were measured, and 300 mg or more of aspirin was administered. A 300-mg or greater oral dose of clopidogrel was recommended preprocedure and required in all cases within 1 hour after stent implantation. Procedural anticoagulation was achieved with either unfractionated heparin or bivalirudin per standard of care, and use of glycoprotein IIb/IIIa inhibitors was per operator discretion. Angiographic eligibility was assessed following mandatory predilatation. The reference vessel diameter of all study lesions was required to be between 2.5 mm and 3.75 mm, and the lesion length was required to be 28 mm or less, both by visual assessment, representing the on-label lesion dimensions for which the paclitaxel-eluting stent has been approved by the US Food and Drug Administration (FDA) for use in the United States. Other angiographic exclusion criteria included ostial or left main lesions; bifurcation lesions with either side branch more than 50% stenosed or more than 2 mm in diameter or requiring predilatation; excessive proximal tortuosity, lesion angulation or calcification, or thrombus; lesion located within a bypass graft conduit; diameter stenosis less than 50% or 100%; or the presence of lesions with greater than 40% stenosis within the target vessel or likelihood that additional percutaneous intervention would be required within 9 months.

Following confirmation of angiographic eligibility, telephone randomization was performed in randomly alternating blocks of 3 and 6 patients using an automated voice response system, stratified by the presence of diabetes, planned dual-vessel treatment, and study site. For this trial everolimus-eluting stents were available in 2.5-, 3.0-, and 3.5-mm diameters, and in 8-, 18-, and 28-mm lengths. The full range of US-manufactured paclitaxel-eluting stents were available, ranging from 2.5 to 3.5 mm in diameter and from 8 to 32 mm in length. An appropriate-length stent was selected sufficient to cover approximately 3 mm of nondiseased tissue on either side of the lesion. In patients receiving multiple

stents for a single lesion, 1 to 4 mm of stent overlap was recommended. Additional study stents were permitted for edge dissections greater than type C or otherwise suboptimal results, and postdilation was at operator discretion.

Following the procedure, an electrocardiogram was performed and cardiac enzyme levels were measured. The protocol recommended that patients receive aspirin (≥80 mg/d) indefinitely and clopidogrel (75 mg/d) for a minimum of 6 months. Clinical follow-up was scheduled at 30 (±7) days, 180 (±14) days, 240 (±28) days, 270 (±14) days, 365 (±28) days, and then yearly (±28 days) through 5 years. Although the operators were by necessity unblinded during the stent implantation procedure, the patient and staff involved in follow-up assessments remained blinded through the follow-up period, with a standardized follow-up interview script used to reduce bias. Protocol-specified angiographic follow-up was scheduled at 240 (±28) days in the first 564 patients enrolled. Among these patients, intravascular ultrasound immediately following stent implantation and at follow-up was intended in 240 patients at selected sites.

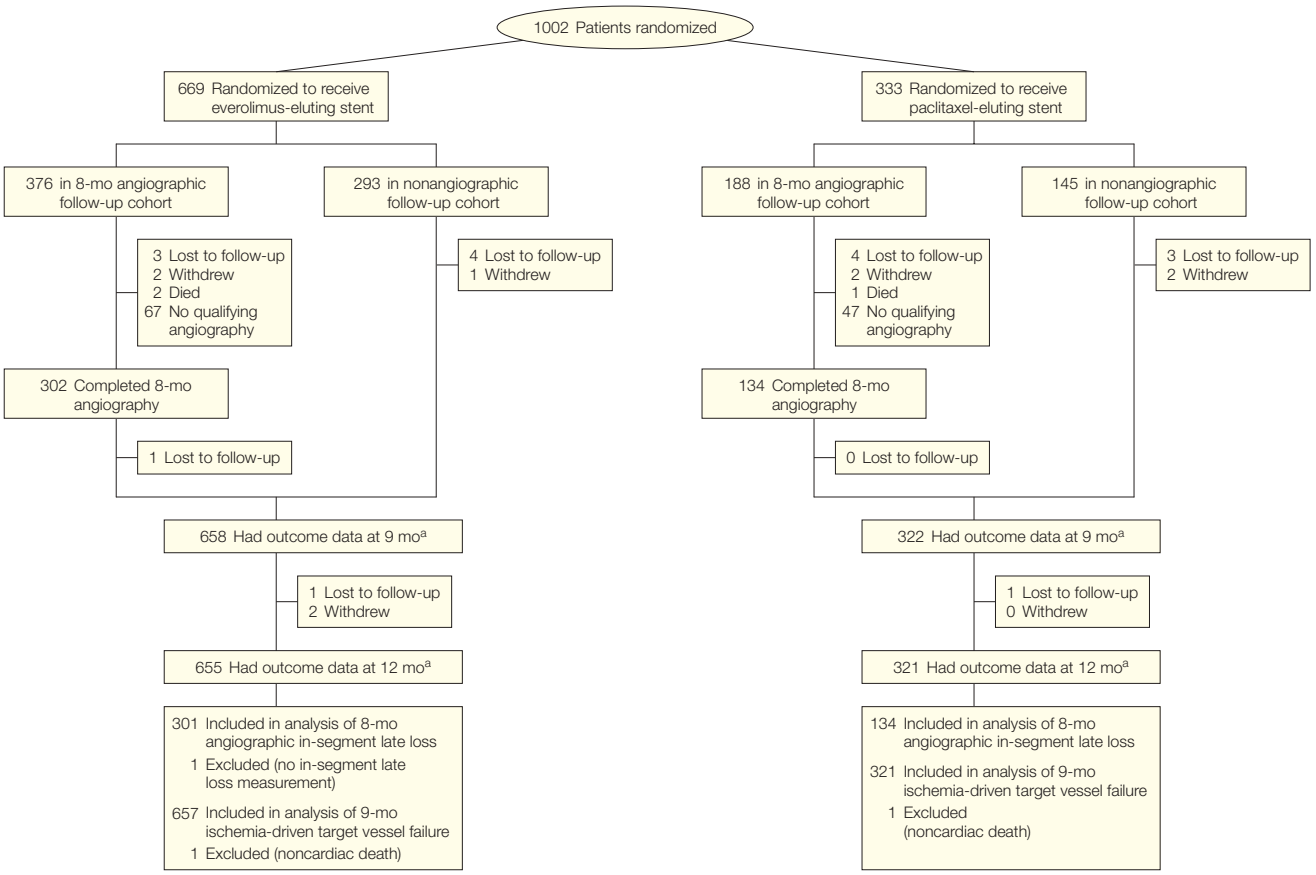
Data Management

Independent study monitors verified 100% of case report form data on-site. Data were stored in a database maintained by Abbott Vascular. All major adverse cardiac events were adjudicated by an independent committee blinded to treatment allocation after review of original source documentation. A second clinical events committee blinded to randomization performed a post hoc adjudication of stent thrombosis using the Academic Research Consortium definitions.[14] A data and safety monitoring board periodically reviewed blinded safety data, each time recommending that the study continue without modification. Independent core angiographic and intravascular ultrasound analyses were performed by technicians blinded to treatment assignment and clinical outcomes using validated methods as previously described.[15,16]

End Points and Definitions

The primary end point was in-segment late loss at 240 days (defined as the difference in the minimal luminal diameter assessed immediately after the pro-

Figure 1. Patient Flow and Follow-up in the SPIRIT III Trial



Prior to the 1-year follow-up period, 14 of 669 patients (2.1%) randomized to receive the everolimus-eluting stent either withdrew (n=5) or were lost to follow-up (n=9), and 12 of 333 patients (3.6%) randomized to receive the paclitaxel-eluting stent either withdrew (n=4) or were lost to follow-up (n=8).
[a]Nine-month follow-up was performed at 270 (±14) days; 12-month follow-up, at 365 (±28) days.

Table 1. Baseline Characteristics of the Study Population

Characteristic	Everolimus-Eluting Stent	Paclitaxel-Eluting Stent
Demographics, No./total (%)	669	332
Age, mean (SD), y	63.2 (10.5)	62.8 (10.2)
Men	469/669 (70.1)	218/332 (65.7)
Hypertension	510/669 (76.2)	245/331 (74.0)
Hypercholesterolemia	489/659 (74.2)	233/326 (71.5)
Diabetes mellitus		
Any	198/669 (29.6)	92/330 (27.9)
Requiring insulin	52/669 (7.8)	18/330 (5.5)
Current smoker	154/659 (23.4)	73/324 (22.5)
Prior myocardial infarction	130/652 (19.9)	59/327 (18.0)
Unstable angina	123/657 (18.7)	82/327 (25.1)
Target vessel, No./total (%)	772	383
Left anterior descending	317/768 (41.3)	164/382 (42.9)
Left circumflex	212/768 (27.6)	108/382 (28.3)
Right coronary	238/768 (31.0)	109/382 (28.5)
Left main, protected	1/768 (0.1)	1/382 (0.3)
Target lesion, mean (SD)	772	383
Reference vessel diameter, mm	2.77 (0.45)	2.76 (0.46)
Minimal luminal diameter, mm	0.82 (0.41)	0.83 (0.40)
Diameter stenosis, %	70.0 (13.3)	69.4 (13.6)
Lesion length, mm	14.7 (5.6)	14.7 (5.7)

cedure and at angiographic follow-up, measured within the margins, 5 mm proximal and 5 mm distal to the stent). To avoid interlesion clustering of restenosis in patients receiving stents for multiple lesions[17] (which would have required correction with multilevel generalized estimating equations), the protocol specified that for patients in whom 2 lesions were treated a single lesion (the analysis lesion) would be randomly selected by computer for analysis of late loss. All randomized lesions were included in the analyses for all other angiographic end points.

The major secondary end point was ischemia-driven target vessel failure at 270 days, defined as the composite of cardiac death (death in which a cardiac cause could not be excluded), myocardial infarction (Q-wave or non–Q-wave), and ischemia-driven target vessel revascularization by either percutaneous coronary intervention or bypass graft surgery. Target vessel (or lesion) revascularization was considered to be ischemia-driven if associated with a positive functional study result, a target vessel (or lesion) diameter stenosis of 50% or greater by core laboratory quantitative analysis with ischemic symptoms, or a target vessel (or lesion) diameter stenosis of 70% or greater with or without documented ischemia.

An additional prespecified secondary end point included major adverse cardiac events at 9 months and 1 year, defined as the composite of cardiac death, myocardial infarction, or ischemia-driven target lesion revascularization. Myocardial infarction was defined either as the development of new pathologic Q waves 0.4 seconds or longer in duration in 2 or more contiguous leads or as an elevation of creatine phosphokinase levels to more than 2 times normal with positive levels of creatine phosphokinase MB. Stent thrombosis was prospectively defined by protocol as an acute coronary syndrome with angiographic evidence of thrombus within or adjacent to a previously treated target lesion or, in the absence of angiography, as any unexplained death or acute myocardial infarction with ST-segment elevation or new Q waves in the distribution of the target lesion occurring within 30 days. Binary restenosis was defined as 50% or greater diameter stenosis of the treated lesion at angiographic follow-up. Other angiographic and intravascular ultrasound parameters were defined as previously described.[15,16]

Statistical Methods

The trial was powered for noninferiority for both the primary end point of in-segment late loss at 8 months among patients in the angiographic follow-up cohort, as well as the major secondary end point of ischemia-driven target vessel failure at 9 months in all enrolled patients. As agreed on with FDA, noninferiority for in-segment late loss would be declared if the upper limit of the 1-sided 97.5% confidence interval (CI) of the difference did not exceed a delta of 0.195 mm from the observed in-segment late lumen loss in the paclitaxel-eluting stent group, equivalent to a 1-sided test with $\alpha = .025$. Assuming a mean late loss of 0.24 (SD, 0.47) mm for both stents, with angiographic follow-up performed in 338 everolimus-eluting stent and 169 paclitaxel-eluting stent analysis lesions, the trial had 99% power to demonstrate noninferiority for in-segment late loss. Sequential superiority testing was prespecified if noninferiority for late loss was met. Noninferiority for ischemia-driven target vessel failure was declared if the upper limit of the 1-sided 95% CI of the difference did not exceed a delta of 5.5% from the observed paclitaxel-eluting stent control event rate. Assuming a target vessel failure rate of 9.4% for both stents, with 9-month clinical follow-up performed in 660 patients randomized to receive the everolimus-eluting stent and 330 to receive the paclitaxel-eluting stent, the trial had 89% power to demonstrate noninferiority for target vessel failure. Noninferiority for the prespecified powered primary as well as the major secondary end points had to be met for the trial to be considered successful, and as such both are considered coprimary end points.

Categorical variables were compared by Fisher exact test. Continuous variables are presented as mean (SD) and were compared by *t* test. The statistical analysis plan prespecified that all primary and secondary analyses

would be performed in the intent-to-treat population, consisting of all patients randomized in the study, regardless of the treatment actually received. However, patients lost to follow-up in whom no event had occurred prior to the follow-up windows were not included in the denominator for calculations of binary end points. Survival curves using all available follow-up data were also constructed for time-to-event variables using Kaplan-Meier estimates and compared by log-rank test. Superiority testing was performed after demonstration of noninferiority for the primary and major secondary end points[18] and for all other secondary end points using a 2-sided $\alpha = .05$. All statistical analyses were performed using SAS version 9.1.3 (SAS Institute Inc, Cary, North Carolina).

RESULTS

Patients and Enrollment

Between June 22, 2005, and March 15, 2006, 1002 patients were enrolled at 65 US sites and randomized to receive the everolimus-eluting stent (n=669) or the paclitaxel-eluting stent (n=333) (FIGURE 1). One patient in the paclitaxel group did not sign informed consent; thus, his or her data are unavailable. Baseline characteristics of the patients were well matched between the 2 groups (TABLE 1), except for slightly more unstable angina in the paclitaxel group ($P = .02$). The mean number of lesions stented was 1.2 (SD, 0.4) in each group; 2 lesions were treated in 15.4% of patients in each group, whereas the remainder had 1 lesion treated. Lesion characteristics as measured by quantitative coronary angiography were also similar between the 2 groups (Table 1).

Procedural Results and Angiographic Outcomes

As shown in TABLE 2, the total stent length per lesion was slightly greater in the everolimus group, likely due to the fewer stent lengths available for accurate lesion matching. Conversely, implantation pressure was slightly less in the group receiving everolimus stents. Other procedural variables were well matched between the groups. Acute postprocedure angiographic measures were also not significantly different between the 2 groups.

Angiographic follow-up at 8 months was completed in 77% of eligible patients (Figure 1). The primary end point of in-segment late loss in the analysis lesion was significantly less in the everolimus group compared with the paclitaxel group (0.14 [SD, 0.41] mm [n=301 lesions] vs 0.28 [SD, 0.48] mm [n=134 lesions]; difference, –0.14 [95% CI, –0.23 to –0.05]; $P_{\text{noninferiority}} < .001$; $P_{\text{superiority}} = .004$). In-stent late loss in the analysis lesion was also significantly less in the everolimus group (0.16 [SD, 0.41] mm vs 0.31 [SD, 0.55] mm; difference, –0.15 [95% CI, –0.25 to –0.04]; $P_{\text{noninferiority}} < .001$; $P_{\text{superiority}} = .006$). Similar results were found when all lesions were considered (Table 2). As a result, strong trends were present toward a reduction in binary in-stent and in-segment restenosis with the everolimus stent compared with the paclitaxel stent (Table 2). No aneurysms were present at 8 months in either group.

Intravascular Ultrasound Findings

Volumetric intravascular ultrasound data were available at 8 months in 101

Table 2. Procedural Results and Angiographic Outcomes

Result/Outcome	Everolimus-Eluting Stent	Paclitaxel-Eluting Stent	*P* Value
Procedural variables, mean (SD)			
No. of patients	669	332	
No. of stents per patient	1.3 (0.6)	1.3 (0.5)	.27
No. of stents per lesion	1.2 (0.4)	1.1 (0.3)	.07
Maximum stent diameter per lesion, mm	3.0 (0.4)	3.0 (0.4)	>.99
Maximum stent to reference vessel diameter ratio	1.1 (0.1)	1.1 (0.1)	.56
Total stent length per lesion, mm	22.8 (8.4)	21.6 (7.8)	.02
Total stent to lesion length ratio	1.6 (0.5)	1.5 (0.5)	.01
Maximum pressure, atm	14.8 (2.9)	15.1 (2.6)	.049
Glycoprotein IIb/IIIa inhibitors used, No./total (%)	184/669 (27.5)	82/332 (24.7)	.36
Postprocedural angiographic results, mean (SD)			
No. of lesions	772	383	
Minimal luminal diameter, mm			
In-stent	2.71 (0.43)	2.74 (0.41)	.38
In-segment	2.37 (0.45)	2.36 (0.45)	.73
Diameter stenosis, %			
In-stent	0.3 (8.9)	–0.2 (9.9)	.37
In-segment	13.5 (7.6)	14.4 (7.1)	.06
Acute gain, mm			
In-stent	1.89 (0.48)	1.91 (0.47)	.56
In-segment	1.54 (0.51)	1.53 (0.50)	.62
8-mo angiographic follow-up, mean (SD)[a]			
No. of lesions	344	158	
Reference vessel diameter, mm	2.77 (0.43)	2.78 (0.42)	.84
Minimal luminal diameter, mm			
In-stent	2.56 (0.53)	2.45 (0.65)	.07
In-segment	2.22 (0.53)	2.12 (0.60)	.08
Diameter stenosis, %			
In-stent	5.9 (16.4)	10.3 (21.4)	.02
In-segment	18.8 (14.4)	22.8 (16.4)	.008
Late loss, mm			
In-stent	0.16 (0.41)	0.30 (0.53)	.002
In-segment	0.14 (0.39)	0.26 (0.46)	.003
Binary restenosis, No./total (%)			
In-stent	8/343 (2.3)	9/158 (5.7)	.06
In-segment	16/344 (4.7)	14/158 (8.9)	.07

[a] Analysis of all lesions.

lesions in the everolimus group and 41 in the paclitaxel group. The everolimus stent compared with the paclitaxel stent resulted in significantly less neointimal hyperplasia (10.13 [SD, 11.46] mm^3 vs 20.87 [SD, 31.51] mm^3, $P=.04$) and percent volume obstruction (6.9% [SD, 6.4%] vs 11.2% [SD, 9.9%], $P=.01$). Paired immediate postprocedure and follow-up intravascular ultrasound studies were available in 90 lesions in the everolimus group and 43 in the paclitaxel group. Comparing the everolimus and paclitaxel stents, there were no significant differences detected in the rates of incomplete stent apposition either at the completion of the procedure (34.4% vs 25.6%, respectively; $P=.33$) or at 8 months (25.6% vs 16.3%, $P=.27$). Late acquired incomplete stent apposition was infrequent in both groups (1.1% vs 2.3%, $P=.54$).

Clinical Outcomes

At 30 days there tended to be fewer myocardial infarctions among the patients randomized to receive the everolimus stent compared with the paclitaxel stent (7/667 patients [1.0%] vs 9/330 [2.7%], respectively; relative risk, 0.38 [95% CI, 0.14 to 1.02]; $P=.06$), with comparable rates of cardiac death (0% in both groups) and target lesion revascularization (3/667 patients [0.4%] vs 1/330 [0.3%], respectively; relative risk, 1.48 [95% CI, 0.15 to 14.21]; $P>.99$). At 9 months, everolimus stents compared with paclitaxel stents were noninferior for the major secondary end point of ischemia-driven target vessel failure (47/657 patients [7.2%] vs 29/321 [9.0%], respectively; difference, –1.9% [95% CI, –5.6% to 1.8%]; relative risk, 0.79 [95% CI, 0.51 to 1.23]; $P_{\text{noninferiority}}<.001$; $P_{\text{superiority}}=.31$). A nonsignificant trend was also present at 1 year for a 24% reduction in target vessel failure in patients randomized to receive everolimus stents rather than paclitaxel stents (56/653 patients [8.6%] vs 36/320 [11.3%], respectively; relative risk, 0.76 [95% CI, 0.51 to 1.13]; $P=.20$). Use of the everolimus stent compared with the paclitaxel stent resulted in significant reductions in the secondary end point of composite major adverse cardiac events, both at 9 months (30/657 patients [4.6%] vs 26/321 [8.1%]; relative risk, 0.56 [95% CI, 0.34 to 0.94]; $P=.03$) and at 1 year (39/653 patients [6.0%] vs 33/320 [10.3%]; relative risk, 0.58 [95% CI, 0.37 to 0.90]; $P=.02$).

As shown in TABLE 3, there were no significant differences between the everolimus stent and the paclitaxel stent in the 1-year rates of death (all cause, cardiac, or noncardiac) or of myocardial infarction (all, Q-wave, or non–Q-wave). Similarly, there were no significant differences between the 2 devices in the rates of stent thrombosis, either early (≤30 days) or late (>30 days), whether analyzed by the prespecified protocol definition or by post hoc Academic Research Consortium definitions. There were also no statistically significant differences in the rates of target lesion revascularization, target vessel revascularization, or target vessel failure between the 2 stents at 1 year. As shown in FIGURE 2, the difference between the hazard curves for major adverse cardiac events became apparent in the early postprocedural period due to fewer myocardial infarctions with the everolimus stent, and then spread further between 6 and 12 months due to fewer target lesion revascularization procedures with the everolimus stent. Of the 15 and 12 patients in the everolimus and paclitaxel groups who had a protocol-defined ischemic target lesion revascularization event by 1 year, 5 and 4 patients, respectively (33.3% in each group) underwent revascularization solely on the basis of a diameter stenosis greater than 70% demonstrated by quantitative coronary angiography. At 365 days, aspirin was being taken by 94.9% and 92.4%

Table 3. Clinical Outcomes at 1 Year

Outcome	No./Total (%)		*P* Value
	Everolimus-Eluting Stent (n = 655)	Paclitaxel-Eluting Stent (n = 321)	
Death	8/655 (1.2)	4/321 (1.2)	>.99
Cardiac	5/655 (0.8)	3/321 (0.9)	.72
Noncardiac	3/655 (0.5)	1/321 (0.3)	>.99
Myocardial infarction[a]	18/653 (2.8)	13/320 (4.1)	.33
Q-wave	2/653 (0.3)	1/320 (0.3)	>.99
Non–Q-wave	16/653 (2.5)	12/320 (3.8)	.31
Death or myocardial infarction	24/654 (3.7)	16/321 (5.0)	.39
Cardiac death or myocardial infarction[a]	22/653 (3.4)	15/320 (4.7)	.37
Stent thrombosis			
Protocol definition	5/647 (0.8)	2/317 (0.6)	>.99
≤30 d	3/667 (0.4)	0/330 (0)	.55
>30 d	2/646 (0.3)	2/317 (0.6)	.60
ARC			
Definite	5/652 (0.8)	0/319 (0)	.18
Probable	2/652 (0.3)	2/319 (0.6)	.60
Possible	4/652 (0.6)	2/319 (0.6)	>.99
Definite or probable	7/652 (1.1)	2/319 (0.6)	.73
Any	11/652 (1.7)	4/319 (1.3)	.78
Target lesion revascularization	22/655 (3.4)	18/321 (5.6)	.12
Target vessel revascularization	40/655 (6.1)	24/321 (7.5)	.41
Target vessel revascularization remote	20/655 (3.1)	14/321 (4.4)	.35
Major adverse cardiac events[a]	39/653 (6.0)	33/320 (10.3)	.02
Target vessel failure[a]	56/653 (8.6)	36/320 (11.3)	.20

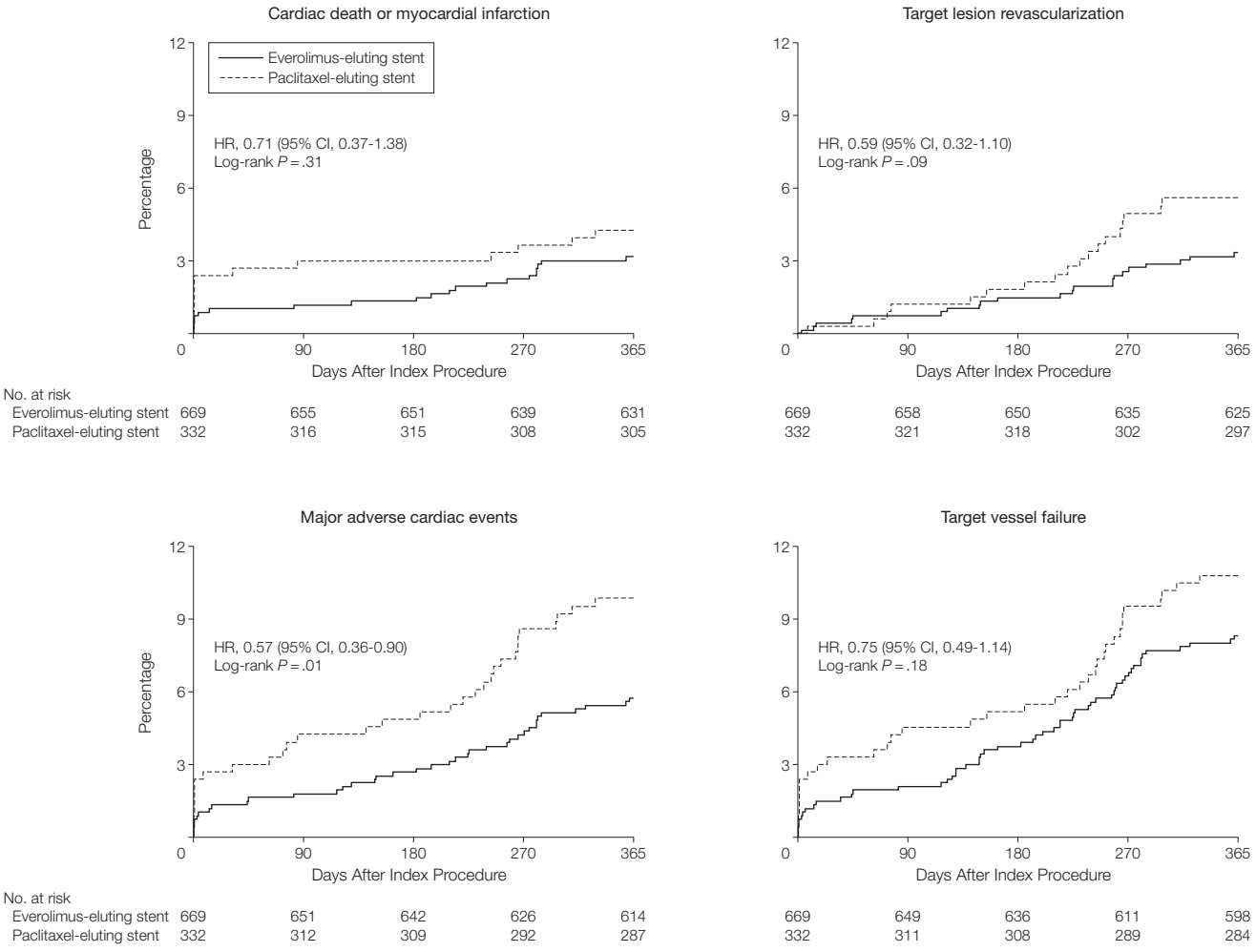
Abbreviations: ARC, Academic Research Consortium.[14]
[a] Per the statistical analysis plan, since the composite target vessel failure and major adverse cardiac event end points included cardiac deaths only, patients with noncardiac deaths were excluded from the denominator.

of patients receiving everolimus stents and paclitaxel stents, respectively (P=.15), and a thienopyridine (clopidogrel or ticlopidine) was being taken by 71.2% and 70.4%, respectively (P=.82).

Subgroup Analysis

A post hoc linear regression analysis with formal interaction testing was performed to explore whether the reduction of the primary end point of in-segment late loss at 8 months with the everolimus stent compared with the paclitaxel stent was consistent across important subgroups (of which diabetes and the number of treated vessels were prespecified). As shown in FIGURE 3, there were no significant interactions between treatment assignment and angiographic outcomes among 7 subgroups, with the exception of age. Logistic regression analysis with interaction testing was also performed to explore whether the reduction in major adverse cardiac events with the everolimus stent compared with the paclitaxel stent present at 1 year was consistent across important subgroups. As shown in FIGURE 4, there were no significant interactions between treatment assignment and outcomes at 1 year among 8 subgroups, with the exception of patients with diabetes. The relative reduction in major adverse cardiac events with everolimus stents compared with paclitaxel stents was comparable in patients both undergoing and not undergoing 8-month follow-up angiography. Among patients in the angiographic follow-up cohort, target lesion revascularization in the everolimus and paclitaxel stent groups was required in 15 of 368 (4.1%) vs 12 of 181 (6.6%) patients, respectively (relative

Figure 2. Time-to-Event Curves for Cardiac Death or Myocardial Infarction, Target Lesion Revascularization, Major Adverse Cardiac Events, and Target Vessel Failure Among Patients Randomized to Receive the Everolimus-Eluting Stent and the Paclitaxel-Eluting Stent



Event rates presented here were calculated by Kaplan-Meier methods and compared with the log-rank test and differ slightly from those in the text and Table 3, which were calculated as categorical variables and compared with the Fisher exact test. In each panel, initial number at risk for the paclitaxel stent differs from the number randomized because 1 patient did not sign informed consent. CI indicates confidence interval; HR, hazard ratio.

risk, 0.61 [95% CI, 0.29 to 1.29]; *P*=.21), whereas in the nonangiographic follow-up cohort the target lesion revascularization rates were 7 of 285 (2.5%) vs 6 of 139 (4.3%), respectively (relative risk, 0.57 [95% CI, 0.19 to 1.66]; *P*=.37).

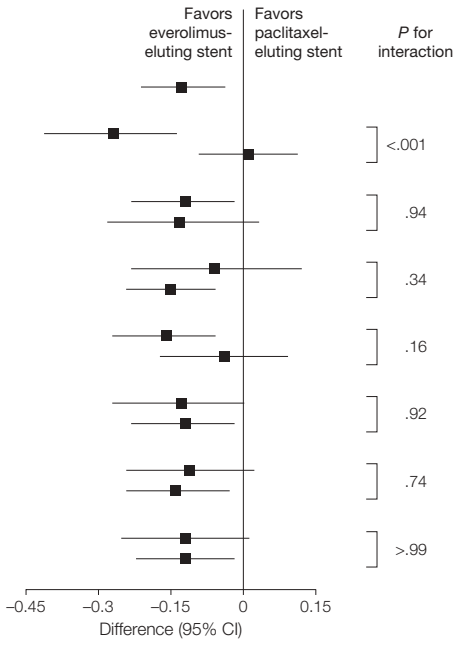
COMMENT

This large-scale, prospective, randomized, single-blind, controlled study demonstrates that an everolimus-eluting stent compared with a widely used paclitaxel-eluting stent results in a significant reduction in angiographic in-segment late loss at 8 months, with noninferior 9-month rates of ischemia-driven target vessel failure. Thus, the 2 prespecified FDA regulatory requirements required for the trial to be considered successful were met. The reduction in late loss was confirmed by the findings from intravascular ultrasound, which demonstrated an approximate 50% reduction in volumetric neointimal hyperplasia. As a result, even though the trial was not powered for a reduction in binary angiographic restenosis, a strong trend was present in this direction favoring the everolimus-eluting stent.

Notably, the everolimus stent compared with the paclitaxel stent resulted in a significant 42% reduction in major adverse cardiac events at 1 year. As such, the present study is the first pivotal randomized trial to demonstrate enhanced event-free survival with a new stent compared with any of the 3 drug-eluting stents commercially available in the United States for on-label lesions (ie, those for which treatment with drug-eluting stents has been approved by the FDA). As defined in this trial, major adverse cardiac events is a composite measure of safety (cardiac death and myocardial infarction) and stent efficacy (target lesion revascularization), which is more specific to the action of the stent than is target vessel failure (which includes the occurrence of target vessel revascularization remote from the target lesion, which would not be expected to be affected by stent implantation). The reduction in composite major adverse cardiac events with the everolimus stent was attributable to fewer postprocedural non–Q-wave myocardial infarctions and late target lesion revascularizations due to the reduction in restenosis. In this regard the results of SPIRIT III confirm and extend those from the smaller (300 patients) randomized SPIRIT II trial, in which the 1-year rates of major adverse cardiac events (using the same definition) were decreased from 9.2% with a paclitaxel-eluting stent to 2.7% with an everolimus-eluting stent (*P*=.04), also due to fewer cardiac deaths, myocardial infarctions, and target lesion revascularizations.[19] Reduction in procedural-related myonecrosis with the everolimus stent may result from less side-branch compromise due to the thinner polymer (7.8 μm vs 16.0 μm) and total polymer plus stent strut width (89 vs 148 μm) compared with the paclitaxel stent,[20] though detailed angio-

Figure 3. Subgroup Analyses of the Primary End Point of 8-Month Angiographic In-Segment Late Loss Among Patients Randomized to Receive the Everolimus-Eluting Stent vs the Paclitaxel-Eluting Stent

	No. of randomized lesions		In-segment luminal late loss, mean (SD), mm			
	Everolimus-eluting stent	Paclitaxel-eluting stent	Everolimus-eluting stent	Paclitaxel-eluting stent	Difference (95% CI)	*P* for interaction
Angiographic follow-up cohort	343	158	0.14 (0.39)	0.26 (0.46)	–0.13 (–0.21 to 0.04)	
Age						
≥Median (63 y)	171	76	0.12 (0.37)	0.39 (0.55)	–0.27 (–0.41 to 0.14)	<.001
<Median	172	82	0.16 (0.42)	0.15 (0.33)	0.01 (–0.09 to 0.11)	
Sex						
Men	250	108	0.13 (0.34)	0.25 (0.49)	–0.12 (–0.23 to –0.02)	.94
Women	93	50	0.16 (0.51)	0.29 (0.41)	–0.13 (–0.28 to 0.03)	
Diabetes						
Yes	96	31	0.18 (0.51)	0.24 (0.40)	–0.06 (–0.23 to 0.12)	.34
No	247	127	0.12 (0.34)	0.27 (0.48)	–0.15 (–0.24 to –0.06)	
No. of treated vessels						
Single	258	110	0.13 (0.41)	0.30 (0.49)	–0.16 (–0.27 to –0.06)	.16
Dual	85	48	0.14 (0.33)	0.18 (0.39)	–0.04 (–0.17 to 0.09)	
Target vessel						
LAD	135	68	0.13 (0.40)	0.26 (0.49)	–0.13 (–0.27 to 0.00)	.92
Non-LAD	208	90	0.14 (0.39)	0.26 (0.45)	–0.12 (–0.23 to –0.02)	
RVD						
>Median (2.775 mm)	166	88	0.18 (0.38)	0.29 (0.54)	–0.11 (–0.24 to 0.02)	.74
≤Median	177	70	0.10 (0.41)	0.24 (0.36)	–0.14 (–0.24 to –0.03)	
Lesion length						
>Median (13.7 mm)	169	82	0.19 (0.47)	0.31 (0.51)	–0.12 (–0.25 to 0.01)	>.99
≤Median	174	74	0.09 (0.30)	0.21 (0.40)	–0.12 (–0.22 to –0.02)	

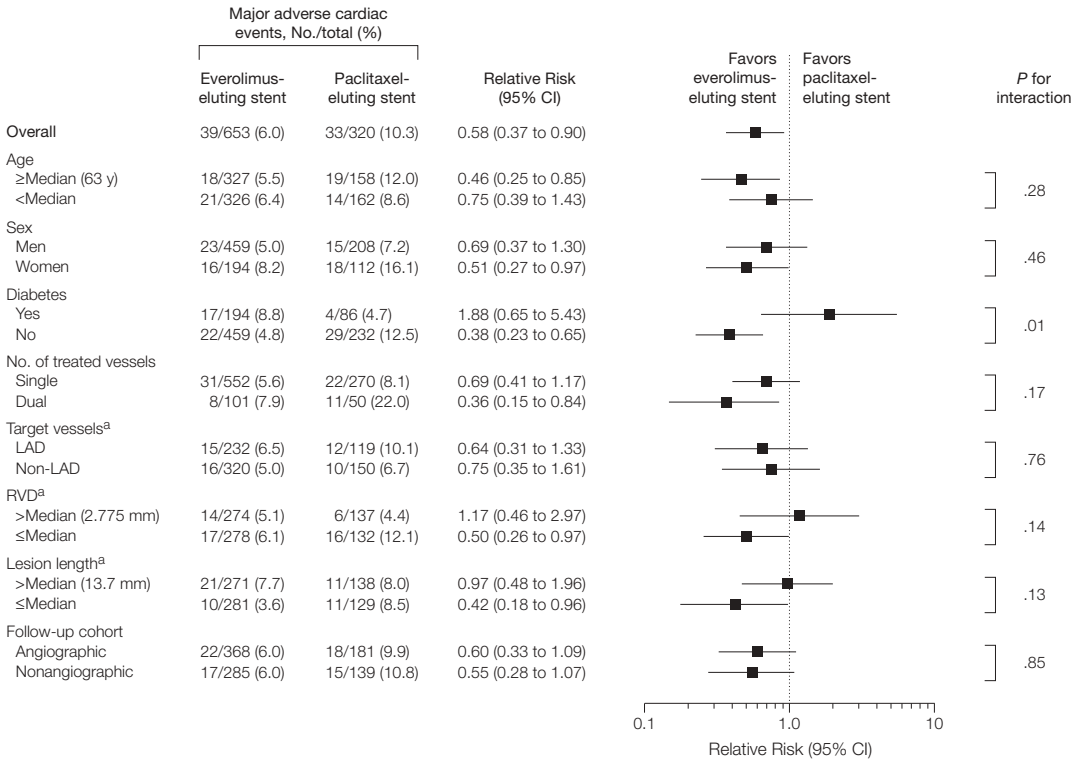


Probability for interaction represents the likelihood for interaction between the variable and the relative treatment effect. CI indicates confidence interval; LAD, left anterior descending; RVD, reference vessel diameter.

graphic study is required to confirm this possibility. Importantly, there were no significant differences in the occurrence of stent thrombosis through 1 year between these 2 devices, though this trial was underpowered to reliably evaluate this event; also, longer-term follow-up is required, because the incremental risk of stent thrombosis with drug-eluting stents may emerge beyond 1 year.[4] The lower rate of target lesion revascularization with the everolimus stent compared with the paclitaxel stent may be directly attributed to the reduction in late loss and smaller follow-up diameter stenosis in the target lesion, as recently described.[21]

The reduction in in-segment late loss with the everolimus stent compared with the paclitaxel stent was consistent across multiple important subgroups except when stratified by age. No significant differences in angiographic outcomes were present between the 2 stents in young patients, whereas assignment to receive the everolimus stent rather than the paclitaxel stent was associated with a marked reduction in late loss in elderly patients. Given the lack of an interaction with reference vessel diameter and lesion length, an explanation underlying this finding is not immediately evident. Of note, no interaction was present between diabetic status and angiographic late loss, signifying a significant reduction in in-segment late loss with the everolimus stent compared with the paclitaxel stent in patients both with and without diabetes. In contrast, a significant interaction was present between diabetes and stent type on the major adverse cardiac event end point, a finding that contributes to the conflicting reports from prior studies examining the relative safety and efficacy of paclitaxel-eluting compared with sirolimus-eluting stents in patients with diabetes.[22-25] However, this difference was driven by the 62% lower rate of major adverse cardiac events in patients with diabetes who were treated with paclitaxel stents compared with patients without diabetes who also were treated with paclitaxel stents, an unlikely finding that may have been due to chance alone. The differences between the 2 devices were also less apparent in larger vessels (which, compared with small vessels, may be able to accommodate more neointimal hyperplasia before the ischemic threshold is reached)[21] and in longer lesions (which, compared with shorter lesions, may have a greater statistical likelihood of restenosis developing in a

Figure 4. Subgroup Analyses of the 1-Year Rates of Major Adverse Cardiac Events Among Patients Randomized to Receive the Everolimus-Eluting Stent vs the Paclitaxel-Eluting Stent



Probability for interaction represents the likelihood for interaction between the variable and the relative treatment effect. CI indicates confidence interval; LAD, left anterior descending; RVD, reference vessel diameter.
[a]Analysis restricted to patients undergoing treatment of a single lesion.

single spot, despite less volumetric neointimal hyperplasia). Moreover, no differences were evident in the beneficial effect of the everolimus stent compared with the paclitaxel stent in reducing the occurrence of major adverse cardiac events as a function of age. All of these subgroup findings should be considered hypothesis-generating, because subgroup analysis is inherently underpowered and statistical adjustments were not made for multiple comparisons leading to possible false-positive findings.[26]

The strengths and limitations of the present investigation should be considered. That composite major adverse cardiac events have now been shown to be reduced with an everolimus stent compared with a paclitaxel stent in 2 consecutive randomized trials performed at different institutions in different geographies (United States vs Europe and Asia Pacific)[19] increases the likelihood that this finding is real. Despite the dilutive effect of including target vessel revascularization in the target vessel failure end point, a trend was also present toward a 24% reduction with the everolimus stent in this composite measure at 1 year. Moreover, the clinical and angiographic outcomes with the paclitaxel stent in the present study were similar or better than those observed in earlier trials with this device in comparable patients and lesions,[2] and as such underperformance of the control stent does not explain this finding. However, while SPIRIT III is the largest completed trial to date investigating an everolimus-eluting stent, major adverse cardiac events were not the primary end point of this study (nor of SPIRIT II), and therefore this conclusion cannot be considered definitive until prospectively verified in an adequately powered randomized trial. The present trial also was underpowered to examine whether an everolimus stent reduces target lesion revascularization, target vessel revascularization, and target vessel failure as well as the occurrence of low-frequency safety events, compared with a paclitaxel stent. That angiographic follow-up was performed in 43.5% of patients in the present trial further raises concern whether the greater late loss with the paclitaxel stent compared with the everolimus stent may have triggered a greater proportion of excess revascularization procedures in the former group (the "oculostenotic reflex"),[27] although such a bias was not apparent in subgroup analysis. Logistic considerations precluded blinding the operator to the stent type, although clinical follow-up assessment, core laboratory, and clinical events committee personnel were blinded to randomization group, and source-documented ischemia or a severe stenosis by quantitative analysis was required to be present for declaration of target lesion or vessel revascularization. The results of the present trial cannot be extended to patient and lesion types excluded from enrollment. Also, complete screening log data are not available, and thus the proportion of patients undergoing percutaneous coronary intervention who were eligible for enrollment in this study is unknown. Finally, the current study was not designed to elicit other potential advantages of the everolimus stent, such as its greater flexibility and deliverability in complex coronary anatomy.

In summary, in this large-scale, prospective randomized trial, an everolimus-eluting stent compared with a paclitaxel-eluting stent in de novo native coronary artery lesions resulted in reduced angiographic late loss, noninferior rates of target vessel failure, and fewer major adverse cardiac events during 1 year of follow-up.

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Independent Statistical Analysis: The accuracy of the data analysis was independently verified by Martin Fahy, MSc, from the Cardiovascular Research Foundation (CRF), an affiliate of Columbia University College of Physicians and Surgeons. (The dean of Columbia University is responsible for this collaboration with the CRF and empowers an active oversight committee to monitor this relationship and the activities of the CRF.) Mr Fahy received the entire raw database and replicated all of the analyses that were reported in the manuscript, and no discrepancies were discovered. The results reported in this article are the results based on this independent analysis. Neither Mr Fahy nor the CRF received any funding for this independent analysis.

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