

ORIGINAL ARTICLE

Paclitaxel-Eluting versus Everolimus-Eluting Coronary Stents in Diabetes

Upendra Kaul, M.D., Sripal Bangalore, M.D., M.H.A., Ashok Seth, M.D.,
Priyadarshini Arambam, M.Sc., Rajpal K. Abhaichand, M.D.,
Tejas M. Patel, M.D., Darshan Banker, M.D., Atul Abhyankar, M.D.,
Ajit S. Mullasari, M.D., Sanjay Shah, M.D., Rajneesh Jain, M.D.,
Premchand R. Kumar, M.D., and C.G. Bahuleyan, M.D.,
for the TUXEDO–India Investigators*

ABSTRACT

BACKGROUND

The choice of drug-eluting stent in the treatment of patients with diabetes mellitus and coronary artery disease who are undergoing percutaneous coronary intervention (PCI) has been debated. Previous studies comparing paclitaxel-eluting stents with stents eluting rapamycin (now called sirolimus) or its analogues (everolimus or zotarolimus) have produced contradictory results, ranging from equivalence between stent types to superiority of everolimus-eluting stents.

METHODS

We randomly assigned 1830 patients with diabetes mellitus and coronary artery disease who were undergoing PCI to receive either a paclitaxel-eluting stent or an everolimus-eluting stent. We used a noninferiority trial design with a noninferiority margin of 4 percentage points for the upper boundary of the 95% confidence interval of the risk difference. The primary end point was target-vessel failure, which was defined as a composite of cardiac death, target-vessel myocardial infarction, or ischemia-driven target-vessel revascularization at the 1-year follow-up.

RESULTS

At 1 year, paclitaxel-eluting stents did not meet the criterion for noninferiority to everolimus-eluting stents with respect to the primary end point (rate of target-vessel failure, 5.6% vs. 2.9%; risk difference, 2.7 percentage points [95% confidence interval, 0.8 to 4.5]; relative risk, 1.89 [95% confidence interval, 1.20 to 2.99]; $P=0.38$ for noninferiority). There was a significantly higher 1-year rate in the paclitaxel-eluting stent group than in the everolimus-eluting stent group of target-vessel failure ($P=0.005$), spontaneous myocardial infarction (3.2% vs. 1.2%, $P=0.004$), stent thrombosis (2.1% vs. 0.4%, $P=0.002$), target-vessel revascularization (3.4% vs. 1.2%, $P=0.002$), and target-lesion revascularization (3.4% vs. 1.2%, $P=0.002$).

CONCLUSIONS

In patients with diabetes mellitus and coronary artery disease undergoing PCI, paclitaxel-eluting stents were not shown to be noninferior to everolimus-eluting stents, and they resulted in higher rates of target-vessel failure, myocardial infarction, stent thrombosis, and target-vessel revascularization at 1 year. (Funded by Boston Scientific; TUXEDO–India Clinical Trials Registry–India number, CTRI/2011/06/001830).

From the Fortis Escorts Heart Institute (U.K., A.S., P.A.) and Dharma Vira Heart Centre, Sir Ganga Ram Hospital (R.J.), New Delhi, L.R.G. Naidu Cardiology Research Institute and Clinic, G. Kuppuswamy Naidu Memorial Hospital, Coimbatore (R.K.A.), SAL Hospital and Medical Institute (T.M.P.) and Apex Heart Institute (S.S.), Ahmedabad, Bankers Heart Institute, Vadodara (D.B.), Shree B.D. Mehta Mahavir Heart Institute, Surat (A.A.), Institute of Cardiovascular Diseases, the Madras Medical Mission, Chennai (A.S.M.), Krishna Institute of Medical Sciences, Secunderabad (P.R.K.), and the Ananthapuri Hospitals and Research Institute, Trivandrum (C.G.B.) — all in India; and New York University School of Medicine, New York (S.B.). Address reprint requests to Dr. Kaul at the Fortis Escorts Heart Institute, New Delhi 110025 India, or at kaul.upendra@gmail.com.

*The investigators, institutions, and research organizations participating in the Taxus Element versus Xience Prime in a Diabetic Population (TUXEDO)–India Trial are listed in the Supplementary Appendix, available at NEJM.org.

This article was published on October 14, 2015, and updated on July 28, 2016, at NEJM.org.

N Engl J Med 2015;373:1709-19.

DOI: 10.1056/NEJMoa1510188

Copyright © 2015 Massachusetts Medical Society.

DIABETES MELLITUS IS A HIGHLY PREVALENT medical condition globally and is frequently associated with symptomatic coronary artery disease necessitating percutaneous coronary intervention (PCI).¹ There is, however, controversy regarding the choice of a drug-eluting stent in patients with diabetes. Fundamental to this debate is the finding that there is attenuation of the mammalian target of rapamycin (mTOR) signaling pathway in patients with type 2 diabetes, which suggests that stents eluting rapamycin (now called sirolimus) or its analogues (everolimus or zotarolimus) — often termed “limus-eluting” stents — could be less effective in this cohort, potentially making paclitaxel-eluting stents an attractive option.²

It is generally accepted that paclitaxel-eluting stents are inferior to limus-eluting stents in most patients with coronary artery disease. One exception is patients with diabetes, for whom subgroup analyses from large randomized trials, small to medium-sized trials, pooled analyses, and registries have shown paclitaxel-eluting stents to have efficacy and safety similar to those of limus-eluting stents.³⁻⁵ Everolimus-eluting stents have been shown to be superior to paclitaxel-eluting stents with respect to both angiographic and clinical end points in most patients, but the results in the population with diabetes have been variable.^{6,7} However, previous randomized trials were typically not sufficiently powered to assess the clinical outcomes associated with various drug-eluting stents among patients with diabetes. We therefore performed a prospective, randomized trial to compare paclitaxel-eluting stents with everolimus-eluting stents in patients with diabetes.

METHODS

STUDY DESIGN

The Taxus Element versus Xience Prime in a Diabetic Population (TUXEDO)—India study is an investigator-initiated, multicenter, randomized clinical trial. The trial protocol, which is available with the full text of this article at NEJM.org, was designed by the principal investigator (the first author). The trial was funded by Boston Scientific, the manufacturer of the paclitaxel-eluting stent (Taxus Element). A commitment to ensure consistent availability of the everolimus-eluting stent (Xience Prime) for the trial was provided by Abbott Vascular, the manufacturer

of the stent. Neither manufacturer participated in the design or conduct of the trial or had access to the data. The institutional review board at each participating center approved the study. The data were gathered and analyzed by a contract research organization (Max Neeman International) that was appointed by the principal investigator. The principal investigator had full access to the data, prepared the first draft of the manuscript, made the decision to submit the manuscript for publication, and vouches for the completeness, authenticity, integrity, and reliability of the data, as well as for the fidelity of this report to the trial protocol.

STUDY ELIGIBILITY AND PROCEDURES

Patients were considered to be eligible if they had diabetes mellitus and either symptomatic coronary artery disease or silent ischemia. The angiographic criteria required for eligibility included lesions 34 mm or less in length and a reference-vessel diameter between 2.25 mm and 4.0 mm (determined by visual estimation from angiograms). The full list of eligibility criteria is provided in Table S1 in the Supplementary Appendix, available at NEJM.org. Written informed consent was obtained from the patients after angiography but before randomization or PCI.

With the use of an interactive Web-based response system, eligible patients were randomly assigned in a 1:1 ratio to receive either a paclitaxel-eluting stent or an everolimus-eluting stent. Randomization was performed in randomly alternating blocks of eight patients. Multiple lesions in a patient were treated with the same type of stent. The characteristics of the two stents are summarized in Table S2 in the Supplementary Appendix.

All patients received oral aspirin (350 mg) and a loading dose of clopidogrel (600 mg), prasugrel (60 mg), or ticagrelor (180 mg) before the index procedure. Patients continued to take aspirin (75 to 150 mg daily) plus clopidogrel (at least 75 mg daily), prasugrel (10 mg daily), or ticagrelor (90 mg twice daily) for at least 12 months after stent implantation. The choice of the second antiplatelet drug and the specifics of the performance of the PCI procedure were at the discretion of the on-site investigator. Guideline-based medical management for secondary prevention of vascular events was recommended for all patients.⁸

Routine follow-up angiography was discour-

aged unless it was clinically indicated. The staff performing the PCI were by necessity aware of the type of stent being implanted during the procedure; however, the patient and the follow-up team were unaware of the randomized group assignment, and a standardized follow-up protocol was implemented to reduce the risk of bias. The clinical follow-up assessments were scheduled at 30 days, 180 days, 1 year, and 2 years after the index procedure. The follow-up assessments at 180 days and 1 year were required to be on site. The 30-day and 2-year follow-up assessments could be performed over the telephone.

Patient data were recorded on electronic case-report forms. All serious adverse events were adjudicated by the members of the clinical event adjudication committee. The members of the data and safety monitoring committee periodically reviewed the safety data and recommended that the trial should continue.

STUDY END POINTS

The primary end point was target-vessel failure at 1 year; target-vessel failure was defined as a composite of cardiac death, target-vessel myocardial infarction, or ischemia-driven target-vessel revascularization. The secondary end points were ischemia-driven target-lesion revascularization, target-vessel revascularization, the composite of cardiac death or target-vessel myocardial infarction, major adverse cardiac events (a composite of cardiac death, myocardial infarction, or ischemia-driven target-lesion revascularization), myocardial infarction (Q-wave and non-Q-wave), cardiac death, noncardiac death, death from any cause, cardiac death or myocardial infarction, all death or myocardial infarction, and Academic Research Consortium–defined stent thrombosis.⁹ The procedural end points were the rate of technical success and the rate of clinical procedural success. Definitions of all trial end points are provided in the Supplementary Appendix.

STATISTICAL ANALYSIS

The trial was powered to detect noninferiority with respect to the primary end point of target-vessel failure at 1 year. On the basis of available data from the Clinical Evaluation of the Xience V Everolimus Eluting Coronary Stent System in the Treatment of Patients with De Novo Native Coronary Artery Lesions (SPIRIT) IV trial,¹⁰ we assumed a 1-year rate of target-vessel failure of 8.4% with each stent. Assuming this event rate,

a 10% attrition rate, and a noninferiority margin (delta) of 4 percentage points for the upper boundary of the 95% confidence interval of the absolute difference in incidence rates, we calculated that with 915 patients in each group (1830 patients in total), the study would have at least 90% power to show the noninferiority of the paclitaxel-eluting stent to the everolimus-eluting stent, at a one-sided 5% significance level.

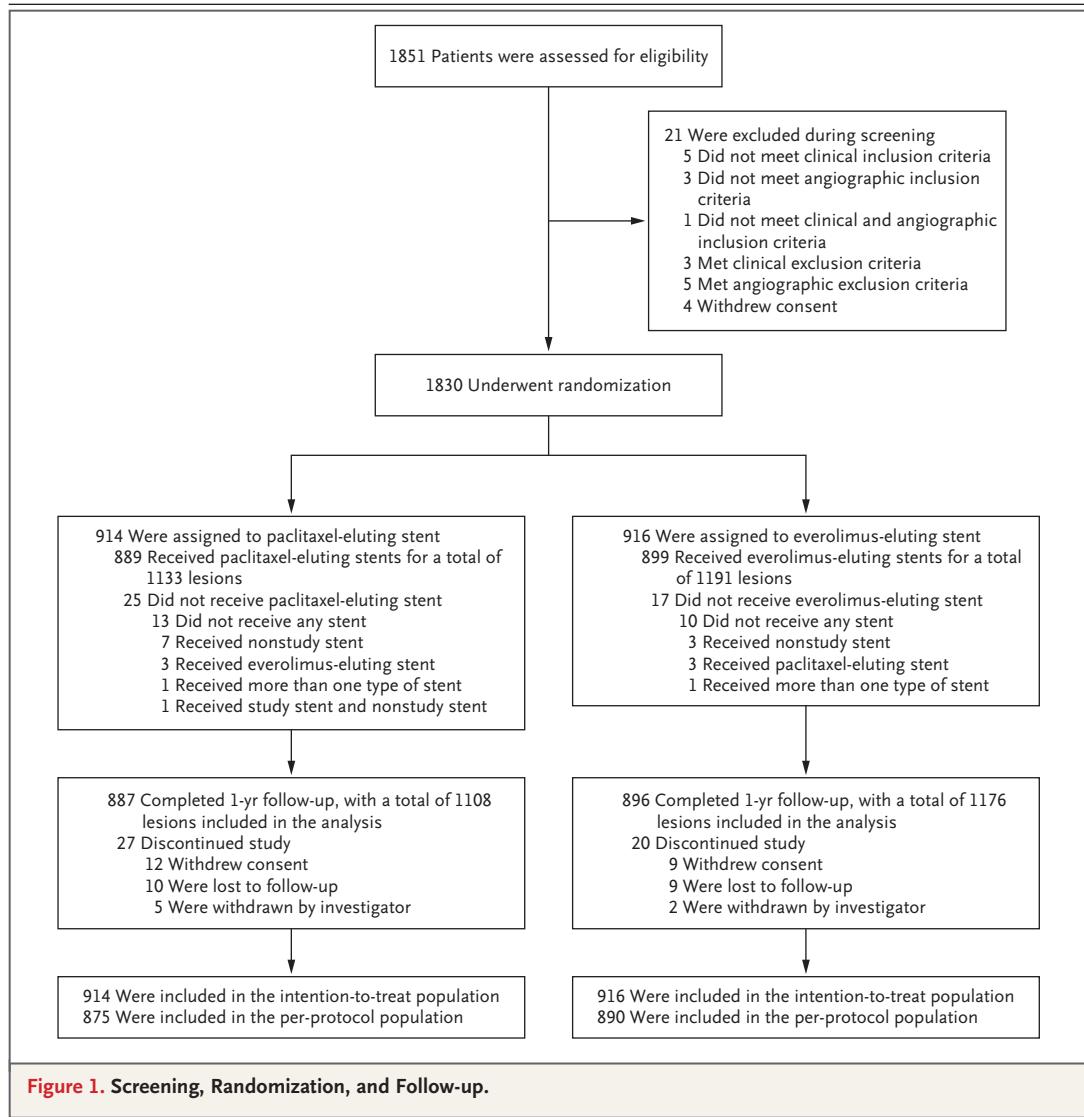
All data are presented for the intention-to-treat population, which included all patients who underwent randomization, regardless of whether a study stent was implanted. For the per-protocol analyses, all patients who underwent randomization, had the assigned study stent implanted, and had 1-year follow-up data available were included.

Categorical variables were compared with the use of the chi-square test or Fisher's exact test; Student's t-test was used for comparison of continuous variables. Relative risks and risk differences were calculated for the primary end point, and 95% confidence intervals were constructed. A two-group Farrington–Manning test was used for testing the hypothesis of noninferiority with respect to the proportion of patients with target-vessel failure, with the use of a one-sided P value for noninferiority of 0.05. For testing the superiority of the everolimus-eluting stent to the paclitaxel-eluting stent, a two-sided alpha level of 0.05 was used. Kaplan–Meier survival estimate curves for time-to-event variables were generated for each group and were compared with the use of a log-rank test. Hazard ratios and the corresponding 95% confidence intervals were also calculated. The consistency of treatment effects in prespecified subgroups was assessed with the use of logistic regression with tests for interaction. All statistical analyses were performed with the use of SAS software, version 9.3 (SAS Institute).

RESULTS

BASELINE CHARACTERISTICS

Between June 23, 2011, and March 12, 2014, a total of 1851 patients with diabetes, at 46 sites, gave written consent for participation in the study (Fig. 1). Of these, 21 patients were not included in the trial because they did not meet an inclusion criterion, met an exclusion criterion, or withdrew consent; the remaining 1830 patients were randomly assigned to receive a paclitaxel-eluting



stent (914 patients) or an everolimus-eluting stent (916 patients). After randomization, 42 patients did not receive the assigned stent, for reasons shown in Figure 1. A total of 1788 patients received the study stent; 889 patients received a paclitaxel-eluting stent, and 899 patients received an everolimus-eluting stent.

The treatment groups were well matched with regard to the patients' baseline characteristics (Table 1). At admission, acute coronary syndrome (unstable angina or non–ST-segment elevation myocardial infarction) was present in 974 patients (53.2%), chronic stable angina in 521 (28.5%), post–ST-segment elevation myocardial infarction in 212 (11.6%), and asymptomatic ischemia in 123 (6.7%).

PROCEDURAL AND ANGIOGRAPHIC OUTCOMES

The total number of stents per patient and per lesion was significantly lower in the paclitaxel-eluting stent group than in the everolimus-eluting stent group (Table S3 in the Supplementary Appendix). The maximum stent diameter per lesion was significantly higher in the paclitaxel-eluting stent group than in the everolimus-eluting stent group ($P=0.008$). The extent of stenosis (percentage of the diameter) was significantly higher with paclitaxel-eluting stents than with everolimus-eluting stents immediately after the procedure ($P=0.01$). The concomitant medications in the two groups are outlined in Table S4 in the Supplementary Appendix.

Table 1. Patient and Target-Lesion Characteristics at Baseline.*

Characteristic	Paclitaxel-Eluting Stents (N=914)	Everolimus-Eluting Stents (N=916)
Patients		
Age — yr	58.40±9.21	58.34±9.12
Body-mass index†	25.77±4.02	25.87±4.25
Male sex — no. (%)	681 (74.5)	696 (76.0)
Hypertension — no. (%)	613 (67.1)	604 (65.9)
Hypercholesterolemia — no. (%)‡	702 (76.8)	710 (77.5)
Current smoker — no. (%)	128 (14.0)	145 (15.8)
Insulin-requiring diabetes — no. (%)	365 (39.9)	382 (41.7)
Glycated hemoglobin — %§	8.40±1.84	8.18±1.66
Duration of diabetes — yr	6.75±7.09	6.14±6.69
Previous myocardial infarction — no. (%)	376 (41.1)	366 (40.0)
Previous percutaneous coronary intervention — no. (%)	77 (8.4)	68 (7.4)
Previous coronary-artery bypass graft surgery — no. (%)	14 (1.5)	18 (2.0)
Left ventricular ejection fraction — %	54.70±12.27	54.81±11.85
Left ventricular ejection fraction <40% — no. (%)	87 (9.5)	80 (8.7)
Clinical presentation at admission — no. (%)		
Acute coronary syndrome: unstable angina or non-STEMI	495 (54.2)	479 (52.3)
Chronic stable angina	268 (29.3)	253 (27.6)
Post-STEMI	94 (10.3)	118 (12.9)
Asymptomatic ischemia	57 (6.2)	66 (7.2)
Target lesions to be treated — no. (%)¶		
One	688 (75.3)	656 (71.6)
Two	182 (19.9)	209 (22.8)
Three	27 (3.0)	39 (4.3)
Target lesions per patient§	1.26±0.50	1.32±0.55
Target-lesion stenosis — no. (%)		
50–70%	98 (10.7)	85 (9.3)
71–90%	646 (70.7)	660 (72.1)
91–99%	243 (26.6)	273 (29.8)
Target lesions		
Total no. of lesions	1133	1191
Location of lesions — no. of lesions (%)		
Left anterior descending	548 (48.4)	555 (46.6)
Left circumflex	260 (22.9)	313 (26.3)
Right	325 (28.7)	322 (27.0)
Reference-vessel diameter — mm§	2.90±0.36	2.87±0.36
Diameter stenosis — %	87.26±8.61	87.54±8.43
Lesion length — mm	20.13±7.60	20.12±7.71

* Plus–minus values are means ±SD. Data are shown for the intention-to-treat population. STEMI denotes ST-segment elevation myocardial infarction.

† The body-mass index is the weight in kilograms divided by the square of the height in meters.

‡ Hypercholesterolemia was considered to be present if the triglyceride level was greater than 150 mg per deciliter (1.7 mmol per liter), low-density lipoprotein cholesterol greater than 130 mg per deciliter (3.4 mmol per liter), and high-density lipoprotein cholesterol less than 40 mg per deciliter (1.0 mmol per liter).

§ The difference between treatment groups was significant (P<0.05).

¶ Numbers do not sum to the total numbers of patients because 29 patients did not receive stents.

|| One lesion in the everolimus-eluting stent group was excluded because it was in the left main coronary artery (a protocol violation).

CLINICAL OUTCOMES

A total of 1783 patients (97.4%) completed the 1-year follow-up. In the intention-to-treat analysis, paclitaxel-eluting stents did not meet the criterion for noninferiority to everolimus-eluting stents with respect to target-vessel failure at 1 year (5.6% vs. 2.9%; risk difference, 2.7 percentage points [95% confidence interval {CI}, 0.8 to 4.5]; relative risk, 1.89 [95% CI, 1.20 to 2.99]; $P=0.38$ for noninferiority) (Table 2). In a test of superiority, everolimus-eluting stents were superior to paclitaxel-eluting stents with respect to the primary end point of the 1-year rate of target-vessel failure (relative risk, 0.53; 95% CI, 0.33 to 0.83; $P=0.005$).

At 1 year, patients assigned to receive a paclitaxel-eluting stent had significantly higher rates of ischemia-driven target-vessel revascularization and target-lesion revascularization than did patients assigned to receive an everolimus-eluting stent (3.4% vs. 1.2% for both end points, $P=0.002$), as well as significantly higher rates of spontaneous myocardial infarction (3.2% vs. 1.2%, $P=0.004$), stent thrombosis (2.1% vs. 0.4%, $P=0.002$), the composite of cardiac death or target-vessel myocardial infarction (4.0% vs. 2.3%, $P=0.03$), and major adverse cardiac events (5.9% vs. 3.4%, $P=0.01$) (Table 2 and Fig. 2). There was no significant difference between the treatment groups with respect to the other outcomes. The rates of technical success and procedural success were similar in the two groups.

SUBGROUP ANALYSES

We performed logistic-regression analyses with interaction testing to determine whether the higher rate of target-vessel failure at 1 year (the primary end point) with paclitaxel-eluting stents, as compared with everolimus-eluting stents, was consistent across prespecified subgroups (Fig. 3). There was no significant interaction between stent type and target-vessel failure in subgroups of patients categorized according to age, sex, insulin therapy requirement, glycated hemoglobin level, angina status, lesion length, number of treated lesions, lesion type, reference-vessel diameter, target vessel, or duration of diabetes. A significant interaction between estimated glomerular filtration rate and stent type was found with respect to target-vessel failure ($P=0.047$ for the interaction). The rate of target-vessel failure

was consistently higher with paclitaxel-eluting stents than with everolimus-eluting stents in all 12 prespecified subgroups and in post hoc subgroups based on the number of diseased vessels (Table S5 in the Supplementary Appendix); the exception was the subgroup of patients with an estimated glomerular filtration rate of 60 ml per minute or less (rate of target-vessel failure, 7.1% with paclitaxel-eluting stents and 7.3% with everolimus-eluting stents; relative risk, 0.97; 95% CI, 0.46 to 2.07).

We performed per-protocol analyses that included the 1765 patients who received the assigned stent and for whom 1-year follow-up data were available. The results of these analyses were largely similar to the results of the intention-to-treat analyses (Fig. S1 and S2 and Tables S6 and S7 in the Supplementary Appendix).

DISCUSSION

In this trial comparing paclitaxel-eluting stents and everolimus-eluting stents in patients with diabetes, the paclitaxel-eluting stent was not noninferior to the everolimus-eluting stent with respect to the primary outcome of target-vessel failure. The results for secondary outcomes were consistent with the result of the primary outcome, with higher rates in the paclitaxel-eluting stent group than in the everolimus-eluting stent group of myocardial infarction, stent thrombosis, target-vessel revascularization, target-lesion revascularization, the composite of cardiac death or target-vessel myocardial infarction, and major adverse cardiac events.

Controversy regarding the efficacy and safety of paclitaxel versus sirolimus analogues in drug-eluting stents that are implanted in patients with diabetes has existed since the era of first-generation drug-eluting stents. In patients who do not have diabetes, the superiority of sirolimus-eluting stents over paclitaxel-eluting stents has been consistently reported for clinical outcomes, but the data for patients who have diabetes are controversial, with several studies reporting similar clinical outcomes with paclitaxel-eluting stents and sirolimus-eluting stents.³⁻⁵

This controversy has lingered in the era of newer-generation drug-eluting stents. A pooled analysis of four trials showed substantially lower rates of death, myocardial infarction, stent

Table 2. Clinical Outcomes at 1-Year Follow-up.*

Outcome	Paclitaxel-Eluting Stents (N=914)	Everolimus-Eluting Stents (N=916)	P Value†
	<i>no. of patients (%)</i>		
Target-vessel failure‡§	51 (5.6)	27 (2.9)	0.005
Death			
All	23 (2.5)	21 (2.3)	0.75
Cardiac	16 (1.8)	16 (1.7)	1.00
Noncardiac	7 (0.8)	5 (0.5)	0.56
Myocardial infarction			
Spontaneous	29 (3.2)	11 (1.2)	0.004
Target-vessel	26 (2.8)	5 (0.5)	<0.001
Non-target-vessel	5 (0.5)	6 (0.7)	0.77
Q-wave	8 (0.9)	1 (0.1)	0.02
Non-Q-wave	22 (2.4)	10 (1.1)	0.03
Periprocedural	32 (3.5)	29 (3.2)	0.69
Death or myocardial infarction	47 (5.1)	31 (3.4)	0.06
Cardiac death or myocardial infarction	40 (4.4)	26 (2.8)	0.08
Cardiac death or target-vessel myocardial infarction	37 (4.0)	21 (2.3)	0.03
Stent thrombosis			
Academic Research Consortium definition	19 (2.1)	4 (0.4)	0.002
Acute thrombosis, <24 hr after procedure	1 (0.1)	0	—
Subacute thrombosis, 24 hr to 30 days after procedure	10 (1.1)	1 (0.1)	0.006
Late thrombosis, >30 days after procedure	8 (0.9)	3 (0.3)	0.13
Definite	14 (1.5)	3 (0.3)	0.007
Probable	5 (0.5)	1 (0.1)	0.12
Target-vessel revascularization§	31 (3.4)	11 (1.2)	0.002
Target-lesion revascularization§	31 (3.4)	11 (1.2)	0.002
Major adverse cardiac events§¶	54 (5.9)	31 (3.4)	0.01
Technical success	896 (98.0)	904 (98.7)	0.27
Procedural success**	892 (97.6)	902 (98.5)	0.18

* Percentages are crude rates and are from the intention-to-treat analysis.

† P values were calculated with the use of a chi-square or Fisher's exact test.

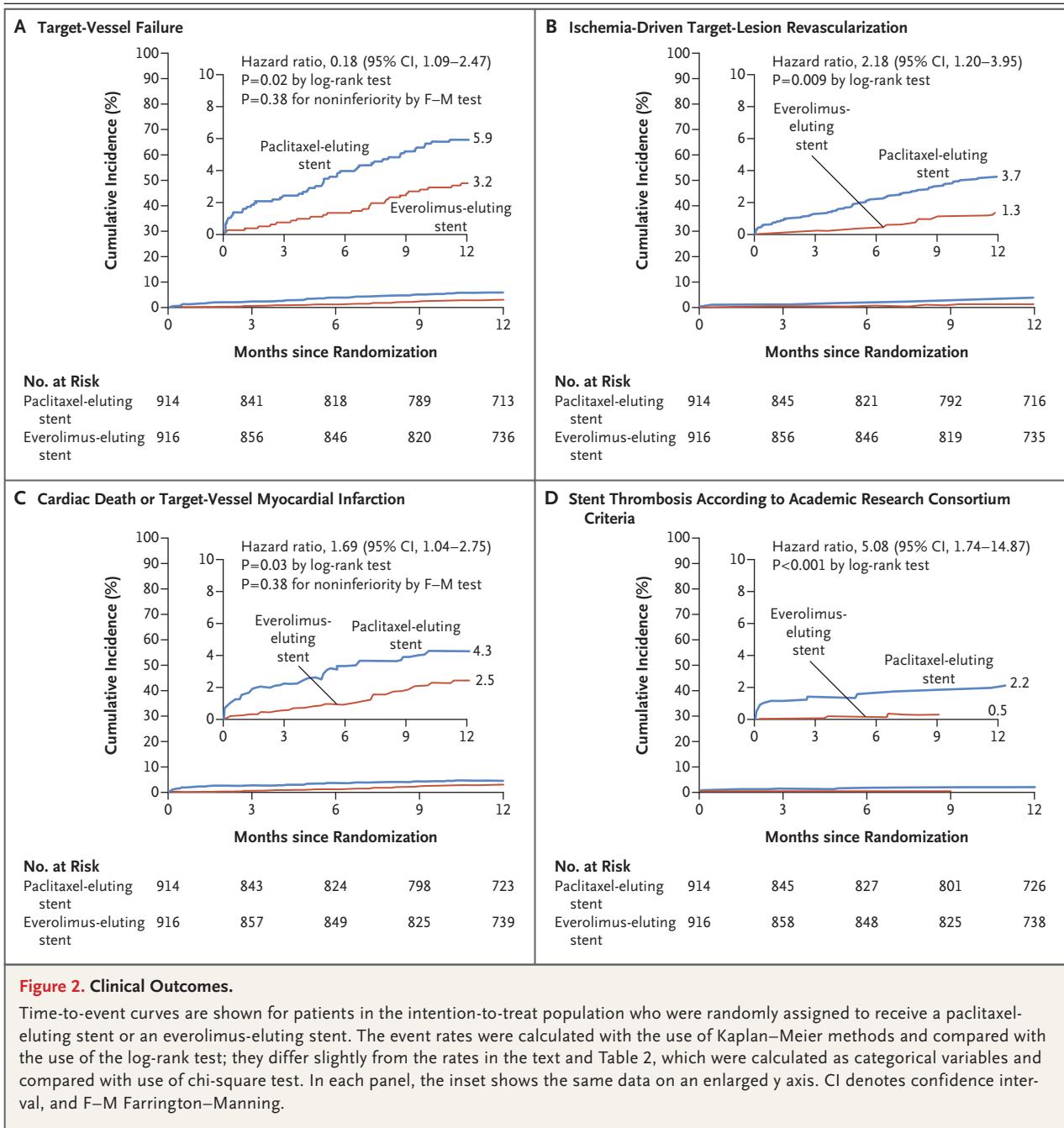
‡ Target-vessel failure was defined as any ischemia-driven target-vessel revascularization, target-vessel myocardial infarction (Q-wave and non-Q-wave), or cardiac death. The relative risk of failure was 1.89 (95% confidence interval [CI], 1.20 to 2.99). The risk difference was 2.7 percentage points (95% CI, 0.8 to 4.5) (P=0.38 for noninferiority at the 4-percentage-point margin).

§ All events are ischemia-driven events.

¶ Major adverse cardiac events was a composite end point of cardiac death, myocardial infarction, or target-lesion revascularization.

|| Technical success was defined as the successful delivery and deployment of the study stent to the target vessel, without balloon rupture or stent embolization.

** Clinical procedural success was defined as a mean lesion diameter stenosis of less than 30% in two near-orthogonal projections with a Thrombolysis in Myocardial Infarction flow grade of 3 (normal coronary blood flow), as visually assessed by the physician, without the occurrence of in-hospital myocardial infarction, target-vessel revascularization, or cardiac death.



thrombosis, and ischemia-driven target-lesion revascularization with everolimus-eluting stents than with paclitaxel-eluting stents among patients without diabetes. However, among 1869 patients with diabetes, there was no significant difference with regard to any efficacy or safety outcome.⁶ In contrast, in a meta-analysis of 42 randomized studies that compared various stents and included 22,844 patient-years of follow-up of

patients with diabetes, everolimus-eluting stents, as compared with other drug-eluting stents and bare metal stents, were found to be the most efficacious and safe stents, and they had a high probability of being associated with the lowest rate of restenosis, myocardial infarction, and stent thrombosis.⁷ The discordance in the results between these meta-analyses is possibly a result of differences among the studies that were in-

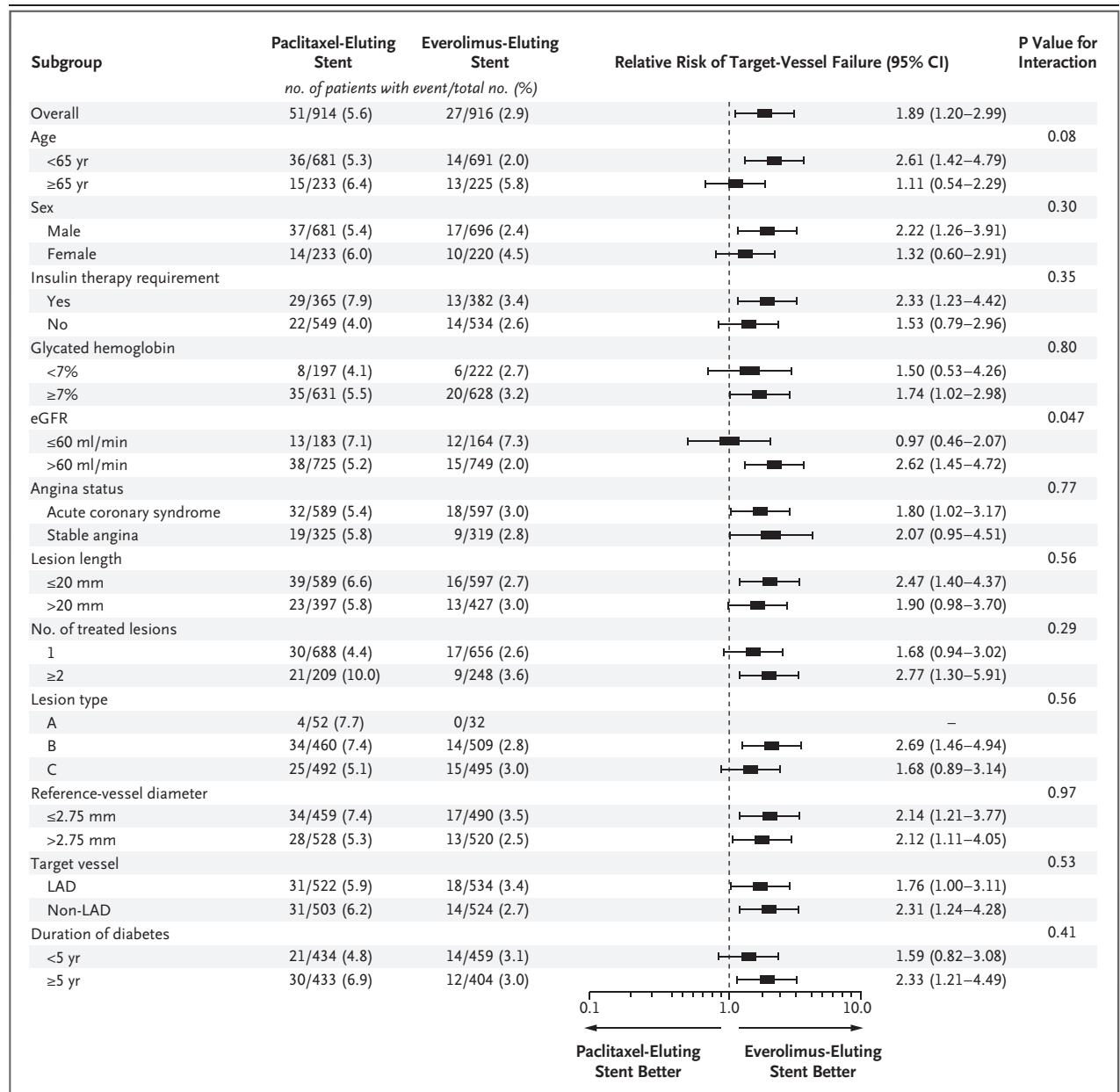


Figure 3. Prespecified Subgroup Analyses of the Primary End Point.

The American College of Cardiology and the American Heart Association classify coronary lesions as type A (simple; very short, concentric lesions), B (moderately complex), or C (very complex, including very long lesions, very tortuous lesions, and chronic total occlusions). The abbreviation eGFR denotes estimated glomerular filtration rate, and LAD left anterior descending artery.

cluded in each analysis and the fact that no single trial was adequately powered to answer the question. The lack of consistent superiority of limus-eluting stents over paclitaxel-eluting stents in studies involving patients with diabetes has led to the question of whether diabetes is the “Achilles’ heel” of limus-eluting stents.¹¹ Various explanations based on the mechanisms

of action of the two drugs in bench-testing models have been proposed to explain this differential effect¹²: limus-eluting stents use the mTOR signaling pathway, which is attenuated in patients with type 2 diabetes, and limus-eluting stents interfere with the process of cellular mitosis, which is regulated by glycosylation-dependent enzymes. The TUXEDO–India trial thus may

serve to resolve a long-standing concern in interventional cardiology.

In a subgroup analysis, the results among patients who required insulin for their diabetes, a group that constituted approximately 40% of the patient population in our study, were no different from the results among patients who did not require insulin. This result differs from the findings of the SPIRIT studies, which showed a trend toward worse outcomes with everolimus-eluting stents than with paclitaxel-eluting stents among patients with diabetes who required insulin.⁶ The only prespecified subgroup in which paclitaxel-eluting stents and everolimus-eluting stents had similar outcomes were patients with an estimated glomerular filtration rate of 60 ml per minute or less. Given the small number of patients in this subgroup and the multiple subgroups examined, this is probably a chance finding, but it should be evaluated in future studies.

Although paclitaxel-eluting stents are still available worldwide, they have largely been replaced in clinical practice by newer-generation drug-eluting stents. Nevertheless, the results of our trial provide insight into the decade-long debate about the efficacy of drug-eluting stents in patients with diabetes. In addition, the question about the efficacy and safety of everolimus-eluting stents relative to those of paclitaxel-eluting stents in patients with diabetes also has important implications for the translatability of the results from previous randomized trials involving patients with diabetes that were conducted with first-generation stents into modern-day practice of PCI with newer-generation drug-eluting stents. These trials include, in particular, the Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease (FREEDOM) trial¹³ and the Bypass Angioplasty Revascularization Investigation in Type 2 Diabetes (BARI 2D) trial¹⁴. In the FREEDOM trial, which evaluated coro-

nary-artery bypass grafting (CABG) surgery versus PCI with the use of first-generation drug-eluting stents (including paclitaxel-eluting stents) in patients with diabetes, outcomes were superior with CABG, including significantly lower all-cause mortality.¹³ Similarly, in the BARI 2D trial, which involved patients with diabetes who were randomly assigned to receive intensive medical therapy or prompt revascularization (with either CABG or PCI; only 35% of patients received drug-eluting stents, all of which were first-generation stents), there was no benefit of prompt revascularization over medical therapy alone.¹⁴ The results of our study raise the question of whether the results of the FREEDOM and BARI 2D trials would have been different if the trials had been performed with newer-generation drug-eluting stents, especially everolimus-eluting stents.^{15,16}

One limitation of our study is the fact that the event rates were lower than anticipated. This is probably a result of the newer stent design with thinner struts and the use of more potent antiplatelet therapy than in the SPIRIT IV trial, on which our event-rate estimates were based. In addition, we could not perform subgroup analyses based on the Synergy between PCI with Taxus and Cardiac Surgery (SYNTAX) score, because we did not have access to an angiographic core laboratory.¹⁷ Moreover, the study participants were Asian Indians, and the results may not be applicable universally.

In conclusion, our study did not show noninferiority of paclitaxel-eluting stents to everolimus-eluting stents in patients with coronary artery disease and diabetes mellitus. Everolimus-eluting stents were superior to paclitaxel-eluting stents with regard to several end points, including target-vessel failure, myocardial infarction, and stent thrombosis.

Supported by Boston Scientific.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

REFERENCES

1. Aronson D, Edelman ER. Revascularization for coronary artery disease in diabetes mellitus: angioplasty, stents and coronary artery bypass grafting. *Rev Endocr Metab Disord* 2010;11:75-86.
2. Ost A, Svensson K, Ruishalme I, et al. Attenuated mTOR signaling and enhanced autophagy in adipocytes from obese patients with type 2 diabetes. *Mol Med* 2010;16:235-46.
3. Daemen J, Garcia-Garcia HM, Kukreja N, et al. The long-term value of sirolimus- and paclitaxel-eluting stents over bare metal stents in patients with diabetes mellitus. *Eur Heart J* 2007;28:26-32.
4. Ong AT, Aoki J, van Mieghem CA, et al. Comparison of short- (one month) and long- (twelve months) term outcomes of sirolimus- versus paclitaxel-eluting stents in 293 consecutive patients with diabetes mellitus (from the RESEARCH and T-SEARCH registries). *Am J Cardiol* 2005;96:358-62.
5. Stankovic G, Cosgrave J, Chieffo A, et al. Impact of sirolimus-eluting and paclitaxel-eluting stents on outcome in patients with diabetes mellitus and stenting in more than one coronary artery. *Am J Cardiol* 2006;98:362-6.
6. Stone GW, Kedhi E, Kereiakes DJ,

- et al. Differential clinical responses to everolimus-eluting and paclitaxel-eluting coronary stents in patients with and without diabetes mellitus. *Circulation* 2011;124:893-900.
7. Bangalore S, Kumar S, Fusaro M, et al. Outcomes with various drug eluting or bare metal stents in patients with diabetes mellitus: mixed treatment comparison analysis of 22,844 patient years of follow-up from randomised trials. *BMJ* 2012;345:e5170.
 8. Smith SC Jr, Benjamin EJ, Bonow RO, et al. AHA/ACC secondary prevention and risk reduction therapy for patients with coronary and other atherosclerotic vascular disease: 2011 update: a guideline from the American Heart Association and American College of Cardiology Foundation. *Circulation* 2011;124:2458-73.
 9. Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation* 2007;115:2344-51.
 10. Stone GW, Rizvi A, Newman W, et al. Everolimus-eluting versus paclitaxel-eluting stents in coronary artery disease. *N Engl J Med* 2010;362:1663-74.
 11. Kastrati A, Massberg S, Ndrepepa G. Is diabetes the Achilles' heel of limus-eluting stents? *Circulation* 2011;124:869-72.
 12. Wessely R, Schömig A, Kastrati A. Sirolimus and paclitaxel on polymer-based drug-eluting stents: similar but different. *J Am Coll Cardiol* 2006;47:708-14.
 13. Farkouh ME, Domanski M, Sleeper LA, et al. Strategies for multivessel revascularization in patients with diabetes. *N Engl J Med* 2012;367:2375-84.
 14. Frye RL, August P, Brooks MM, et al. A randomized trial of therapies for type 2 diabetes and coronary artery disease. *N Engl J Med* 2009;360:2503-15.
 15. Bangalore S, Blecker S, Hannan EL. Everolimus-eluting stents or bypass surgery for coronary disease. *N Engl J Med* 2015;373:582.
 16. Bangalore S, Guo Y, Samadashvili Z, Blecker S, Xu J, Hannan EL. Everolimus eluting stents versus coronary artery bypass graft surgery for patients with diabetes mellitus and multivessel disease. *Circ Cardiovasc Interv* 2015;8(7):e002626.
 17. Sianos G, Morel MA, Kappetein AP, et al. The SYNTAX Score: an angiographic tool grading the complexity of coronary artery disease. *EuroIntervention* 2005;1:219-27.

Copyright © 2015 Massachusetts Medical Society.