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TAXUS Liberté Attenuates the Risk of Restenosis in Patients With Medically Treated Diabetes Mellitus

Results From the TAXUS ATLAS Program

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Objectives The aim of this study was to assess the relative efficacy and safety of the second-generation TAXUS Liberté paclitaxel-eluting stent (PES) in patients with and without diabetes mellitus.

Background Diabetic patients suffer from accelerated atherosclerosis and increased risk of restenosis after coronary interventions; however, prior data suggest that PES might blunt this effect, providing equal benefit in diabetic and nondiabetic patients.

Methods A pooled analysis of all 4 TAXUS ATLAS studies was conducted that included 413 diabetic and 1,116 nondiabetic subjects treated with the TAXUS Liberté stent for de novo coronary lesions. Angiographic and intravascular ultrasound outcomes at 9 months and clinical outcomes at 9 and 12 months were compared in patients with and without diabetes. Propensity score and multivariate adjustments were performed to correct for baseline differences.

Results In-stent angiographic restenosis (13.0% vs. 9.6%, $p = 0.12$), late luminal loss (0.40 mm vs. 0.38 mm, $p = 0.58$), and intimal hyperplasia (14.8% vs. 13.4%, $p = 0.29$) were similar for diabetic and nondiabetic subjects. After propensity adjustment, 12-month target lesion revascularization rates were similar for diabetic and nondiabetic subjects (6.4% vs. 4.7%, $p = 0.18$), with no differences in mortality, myocardial infarction, or stent thrombosis. However, the rate of target vessel revascularization (TVR) was higher for diabetic subjects due to increased TVR outside the target lesion (TVR Remote).

Conclusions Similar clinical, angiographic, and intravascular ultrasound outcomes were observed for both diabetic and nondiabetic subjects treated with TAXUS Liberté, suggesting that this PES attenuates the effect of diabetes on restenosis after percutaneous coronary intervention, yielding comparable efficacy and safety in diabetic and nondiabetic patients. (TAXUS ATLAS; NCT00371709, NCT00371423, NCT00371748, and NCT00371475) (J Am Coll Cardiol Intv 2009;2:240–52) © 2009 by the American College of Cardiology Foundation

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There is an increased prevalence of atherosclerosis in patients with diabetes mellitus (1). Diabetic patients thus tend to have more advanced coronary artery disease compared with nondiabetic patients, with greater plaque burden, and longer lesions in smaller (or more diffusely diseased) vessels (2–5). Patients with diabetes are also more likely to develop restenosis after treatment with bare metal stents and are at greater risk for myocardial infarction (MI) and stent thrombosis compared with those without diabetes (6–9). The use of drug-eluting stents, including the TAXUS (Boston Scientific, Natick, Massachusetts) paclitaxel-eluting stent (PES) and the CYPHER (Cordis, Miami, Florida) sirolimus-eluting stent (SES), has resulted in significantly lower rates of restenosis as compared with bare metal stents (10–15). However, the relative efficacy and safety of drug-eluting stents in diabetic versus nondiabetic patients has not been well studied. In this regard, in vitro studies have suggested a selective benefit of paclitaxel in suppressing the neointimal hyperplasia in a diabetic model (16). This study examines whether that observation is supported clinically from data for diabetic versus nondiabetic patients treated with the second-generation, thin-strut PES, TAXUS Liberté.

The TAXUS Liberté stent, designed specifically to improve deliverability and conformability and provide more homogeneous drug distribution, has recently been evaluated in 4 prospective, controlled studies enrolling patients with de novo coronary lesions: TAXUS ATLAS (17), TAXUS ATLAS Direct Stent (18), TAXUS ATLAS Long Lesion (19), and TAXUS ATLAS Small Vessel (19). In the TAXUS ATLAS study, the TAXUS Liberté PES was shown to be similarly effective to the TAXUS Express PES in reducing restenosis and the need for repeat revascularization in an overall sample containing both diabetic and nondiabetic patients (17). The current integrated analysis was undertaken to compare the angiographic, intravascular ultrasound, and clinical outcomes in medically treated diabetic patients treated with the TAXUS Liberté stent in all 4 TAXUS ATLAS studies with those of the nondiabetic cohort in the same studies. The objective of this analysis was to evaluate the effect of the TAXUS Liberté PES on neointima development and the need for repeat revascularization in patients with and without diabetes.

Methods

Device description. The TAXUS Liberté stent (Boston Scientific Corporation, Natick, Massachusetts) consists of a balloon-expandable Liberté stent with a biostable poly(styrene-b-isobutylene-b-styrene) polymer coating that contains 1 $\mu g/mm^2$ of paclitaxel in a slow-release formulation. Drug-dosing and release kinetics are virtually identical to that of the TAXUS Express PES, but the different stent geometry and thinner strut (0.0038 inch/0.096 mm vs. 0.0052 inch/0.132 mm) design allows for enhanced deliverability and more uniform wall coverage.

Patient selection, procedure, and follow-up. The study protocols were approved by local ethics review committees for included studies, and all patients provided written informed consent. Trials are registered on the National Institutes of Health website (identifiers NCT00371709, NCT00371423, NCT00371748, and NCT00371475) (20).

Subjects were pooled from the 4 TAXUS ATLAS studies. A summary of the individual TAXUS ATLAS study designs is presented in Table 1. Eligibility criteria and procedural requirements were the same in all 4 studies (17–19). After stent implantation, all patients were prescribed thienopyridine therapy for a minimum of 6 months. Aspirin therapy was mandated for at least 9 months and was recommended indefinitely.

Abbreviations and Acronyms

%DS = percent diameter stenosis
CI = confidence interval
HR = hazard ratio
MACE = major adverse cardiac events
MI = myocardial infarction
MLD = minimum lumen diameter
PES = paclitaxel-eluting stent(s)
RVD = reference vessel diameter
TLR = target lesion revascularization
TVR = target vessel revascularization

Diabetic subjects were identified as those treated with at least 1 hypoglycemic agent (oral or insulin) at the time of enrollment. By this criterion, the 1,529 subjects enrolled in the 4 TAXUS ATLAS trials were divided into 2 groups: 413 patients with medically treated diabetes and 1,116 without diabetes (Table 1). Clinical follow-up was at 1, 4, 9, and 12 months. Quantitative coronary angiography at 9-month follow-up was planned for all patients in the Direct Stent, Long Lesion, and Small Vessel studies plus 543 randomly selected patients in TAXUS ATLAS trial. Intravascular ultrasound analysis was prespecified for randomly selected patients in 3 studies—TAXUS ATLAS, Direct Stent, and Long Lesion—for a total intravascular ultrasound cohort of 624 patients. Patient follow-up through 12-months is outlined in Figure 1.

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Table 1. Summary of TAXUS ATLAS Clinical Study Designs

Parameter	TAXUS ATLAS	TAXUS ATLAS Direct Stent	TAXUS ATLAS Small Vessel	TAXUS ATLAS Long Lesion
Study design	Prospective, multicenter, single-arm, historically-controlled	Prospective, multicenter, single-arm, historically-controlled	Prospective, multicenter, single-arm, historically-controlled	Prospective, multicenter, single-arm, historically-controlled
Primary end point	9-month TVR	9-month % diameter stenosis, analysis segment	9-month % diameter stenosis, analysis segment	9-month % diameter stenosis, analysis segment
No. of investigative sites	61 (North America and Asia Pacific)	24 (North America and Asia Pacific)	23 (North America and Asia Pacific)	24 (North America and Asia Pacific)
Lesion criteria	De novo, multiple lesions, treatable with single stent (treatment of 1 nontarget lesion in nontarget vessel allowed)	De novo, multiple lesions, treatable with single stent (treatment of 1 nontarget lesion in nontarget vessel allowed)	De novo, multiple lesions, treatable with single stent (treatment of 1 nontarget lesion in nontarget vessel allowed)	De novo, multiple lesions, treatable with single stent (treatment of 1 nontarget lesion in nontarget vessel allowed)
RVD criteria	2.5–4.0 mm	2.5–4.0 mm	2.2–2.5 mm	2.7–4.0 mm
Lesion length	≥10 and ≤28 mm	≥10 and ≤28 mm	≥10 and ≤28 mm	≥26 and ≤34 mm
Post-procedure antiplatelet therapy	Aspirin: 9 months*; clopidogrel or ticlopidine: 6 months	Aspirin: 9 months*; clopidogrel or ticlopidine: 6 months	Aspirin: 9 months*; clopidogrel or ticlopidine: 6 months	Aspirin: 9 months*; clopidogrel or ticlopidine: 6 months
Diabetic subjects	220	56	95	42
Nondiabetic subjects	651	191	166	108

*Aspirin use recommended indefinitely.
RVD = reference vessel diameter; TVR = target vessel revascularization.

Quantitative coronary angiographic and intravascular ultrasound analyses. Quantitative coronary angiographic analyses were performed by the same core laboratory (Brigham and Women's Hospital, Boston, Massachusetts) for all studies. Standard image acquisition was performed at the clinical sites with 2 or more angiographic projections of the stenosis, and all procedural and follow-up angiograms were reviewed with standard morphologic criteria (21,22). With the contrast-filled injection catheter as the calibration source, quantitative coronary angiography was performed with a validated automated edge detection algorithm (MEDIS CMS, Version 5.0, Leiden, the Netherlands) (22). A 5-mm segment of reference diameter proximal and distal to the stenosis was used to calculate the average reference vessel diameter (RVD) at baseline, after stent implantation. Minimal lumen diameter (MLD) was measured at these same time points within the stent (in-stent analysis), within the 5-mm proximal and distal edges of the stent and within the segment between the proximal and distal reference vessel (in-segment analysis). Angiographic percent diameter stenosis (% DS) was defined as: $(1-[MLD/RVD]) \times 100$. Binary angiographic restenosis was defined as the incidence of % DS ≥50% at the qualifying angiographic follow-up. Late loss was defined as MLD immediately after the procedure minus MLD at 9-month follow-up. Restenosis patterns were qualitatively assessed with the Mehran classification system (23). Lesion length was defined as the axial extent of the lesion that contained a shoulder-to-shoulder lumen reduction by ≥20%. Angiographic follow-up was performed 9 months (±14 days) after the index procedure unless earlier angiography was required clinically.

Volumetric intravascular ultrasound analyses were performed by the same core laboratory (Washington Hospital Center, Washington DC) for all studies. Detailed methods have been previously described (24). Images were obtained immediately after stent implantation and at 9-month follow-up in patients designated for intravascular ultrasound follow-up. Images with technically inadequate quality, inconsistent pullback speed, and incomplete visualization of the vascular interface were not analyzed.

The angiographic and intravascular ultrasound Core Laboratories were blinded to all clinical characteristics, including the diabetic status.

Definitions. Major adverse cardiac events (MACE) and stent thromboses were adjudicated by an independent Clinical Events Committee. The clinical and angiographic end point definitions were identical for all TAXUS ATLAS studies (17,18). Stent thrombosis adjudicated by the Academic Research Consortium definite/probable definition is also reported (25).

Statistical methodology. All end points were analyzed with the intent-to-treat analysis set. Homogeneity tests were performed to justify pooling across the 4 TAXUS ATLAS studies. The Breslow-Day test was used for binary data and 2-way analysis of variance was employed for continuous variables. Values of $p > 0.05$ (the lowest p value was 0.31) suggested that the treatment effect between the diabetic and nondiabetic patients across studies is homogeneous and that all 4 TAXUS ATLAS studies can be pooled together.

Baseline, post-procedure, and follow-up data are summarized with descriptive statistics, with data presented as proportions (%, count/sample size) or mean ± SD. The Student *t* test was used for comparing continuous variables.

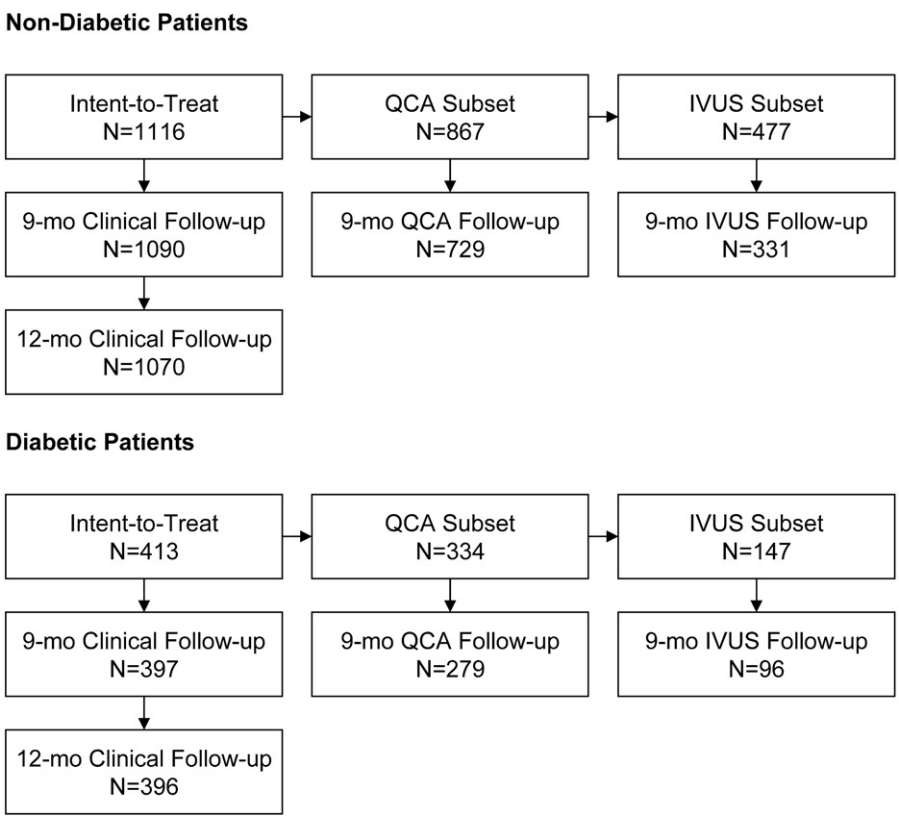

Figure 1. Patient Flow Through 9- and 12-Month Follow-Up

Patient flow of all diabetic and nondiabetic subjects enrolled in the TAXUS ATLAS, Direct Stent, Long Lesion, and Small Vessel Studies. mo = month; QCA = quantitative coronary angiography; IVUS = intravascular ultrasound.

The chi-square test or Fisher exact test, as appropriate, was used for comparing 2 proportions. Kaplan-Meier product-limit method and log-rank test were used to assess time-to-event end points between the 2 groups.

Due to significant differences in baseline characteristics between diabetic and nondiabetic patients, clinical, angiographic, and intravascular ultrasound outcomes were adjusted with propensity score analysis. In addition, 1-year clinical outcomes were also adjusted with multivariate modeling, to confirm the results of the propensity analysis.

Propensity score analysis (26–29) is used to balance 2 nonrandomized groups on the basis of observed covariates in order to equalize the baseline differences associated with a treatment or disease state and give a more accurate estimate of the effect of the treatment or the disease (30). Use of this propensity score allows for adjustment of baseline differences (other than the presence of diabetes) between the diabetic and nondiabetic groups. Propensity score analysis was performed with a hierarchical logistic regression model with a stepwise selection process and an entry/exit criterion of 0.10. The logistic regression model creates a score on the basis of the propensity that a patient belongs to 1 of the 2 groups being compared. The propensity score for the likelihood of belonging to the diabetic group ordered patients of the 2 analysis sets into quintiles. Each quintile contained patients with similar scores and more balanced baseline characteristics, thus allowing for more like-to-like comparisons between the 2 groups and adjustment of the outcomes. All demographic data and lesion characteristics listed in Table 2 and the following procedural characteristics were considered for adjustment: pre-procedure Thrombolysis in Myocardial Infarction flow; nontarget lesion treated; maximum balloon/artery ratio; maximum overall pressure; glycoprotein IIb/IIIa inhibitor use during index procedure; and pre-procedure aspirin and thienopyridine use.

Multivariate adjustment was also performed for 1-year clinical outcomes, with the same variables that were considered for propensity score adjustment. In addition, event-free survival estimates/diabetic status were produced by stratification of multivariate Cox regression models in a 2-stage multivariate analysis.

Multivariate analyses were used to determine predictors of 12-month mortality, MI, target vessel revascularization (TVR), TVR Remote, and target lesion revascularization (TLR) in all subjects. All characteristics listed in the

Table 2. Baseline Demographic Data

	Nondiabetic (n = 1,116)	Diabetic (n = 413)	p Value
Male, n (%)	794 (71.1)	242 (58.6)	<0.001
Age (yrs)	62.2 ± 10.9	62.4 ± 10.3	0.74
Cardiac history, n (%)			
Percutaneous coronary intervention	336 (30.1)	157 (38.0)	0.003
Coronary artery bypass graft	71 (6.4)	39 (9.4)	0.04
Previous MI	325 (29.1)	122 (29.5)	0.87
Congestive heart failure	39 (3.5)	37 (9.0)	<0.001
Stable angina	687 (61.6)	239 (57.9)	0.19
Unstable angina	347 (31.1)	132 (32.0)	0.75
Silent ischemia	81 (7.3)	42 (10.2)	0.06
Risk factors and comorbidities, n (%)			
Current smoking	269 (24.1)	78 (18.9)	0.03
Hyperlipidemia requiring medication	835 (74.8)	358 (86.7)	<0.001
Hypertension requiring medication	745 (66.8)	358 (86.7)	<0.001
Renal disease	38 (3.4)	27 (6.5)	0.007
Baseline lesion characteristics by quantitative coronary angiography			
Target vessel LAD (%)	42.8 (478/1,116)	39.7 (163/411)	0.27
RVD (mm)	2.67 ± 0.53 (1,116)	2.55 ± 0.56 (411)	<0.001
MLD (mm)	0.84 ± 0.34 (1,116)	0.81 ± 0.35 (411)	0.10
% diameter stenosis	68.34 ± 11.54 (1,116)	68.29 ± 11.35 (411)	0.94
Lesion length (mm)	15.7 ± 7.8 (1,116)	16.4 ± 7.7 (410)	0.14
Eccentric lesions (%)	49.0 (547/1,116)	44.0 (181/411)	0.08
Bend ≥45° (%)	29.5 (329/1,116)	28.0 (115/411)	0.57
Calcification (%)	30.7 (343/1,116)	28.8 (118/410)	0.46
Tortuosity (%)	14.2 (159/1,116)	13.1 (54/411)	0.58
Branch vessel disease (%)	11.3 (125/1,107)	11.9 (49/411)	0.73
Total occlusion (%)	0.8 (9/1,115)	1.0 (4/411)	0.76
Thrombus (%)	3.8 (42/1,116)	3.2 (13/411)	0.58
Ulceration (%)	6.1 (68/1,116)	5.1 (21/411)	0.47
Modified ACC/AHA type B2 or C lesion (%)	76.3 (851/1,116)	76.2 (313/411)	0.97

Numbers shown are mean ± SD (n) or % (n/N).
ACC = American College of Cardiology; AHA = American Heart Association; LAD = left anterior descending coronary artery; MLD = minimum lumen diameter; MI = myocardial infarction; RVD = Reference Vessel Diameter.

preceding text along with diabetes were considered. A 2-stage multivariate analysis was conducted for each outcome with the Cox regression model. In the first stage, the predictors were determined by stepwise selection with an entry and exit criterion for each candidate of $p \leq 0.05$. In the second stage, a multivariate model was created only considering the variables found to be significant predictors in the first stage for each outcome.

Differences were considered to be statistically significant when the p value was <0.05.

Results

Baseline characteristics and procedural outcomes. Baseline demographic data and angiographic lesion characteristics are shown in Table 2. Subjects with medically treated diabetes were more likely to be women and to have a history of previous revascularization (both percutaneous coronary intervention and coronary artery bypass graft surgery), congestive heart failure, hyperlipidemia, hypertension, and chronic renal insufficiency but were less likely to be smokers. Diabetic subjects had smaller angiographic reference diameter and smaller final implanted stent size. All other baseline clinical and angiographic lesion characteristics were matched between the 2 groups (Table 2). Procedural characteristics and antiplatelet use are shown in Table 3. Use of dual antiplatelet therapy was similar between diabetic and nondiabetic patients pre-procedure, at discharge, and at 9-month follow-up. However, diabetic patients had significantly higher dual antiplatelet therapy use at 1 year compared with nondiabetic patients.

Angiographic end points at 9 months. There were no significant differences in 9-month in-stent angiographic outcomes, regardless of propensity-adjustment. Late loss was

Table 3. Procedural Characteristics and Use of Antiplatelet Therapy

	Nondiabetic (n = 1,116)	Diabetic (n = 413)	p Value
Procedural characteristics			
Procedure time (min)	49.0 ± 25.7 (1,112)	46.9 ± 25.8 (411)	0.16
Pre-dilation (%)	83.1 (927/1,116)	85.7 (354/413)	0.21
Maximum pressure (atm)	15.7 ± 3.3 (1,115)	15.9 ± 3.2 (413)	0.36
Maximum stent size (mm)	3.1 ± 0.6 (1,116)	2.9 ± 0.6 (413)	<0.001
Post-dilation (%)	50.8 (567/1,116)	45.5 (188/413)	0.07
Use of dual antiplatelet therapy*			
Pre-procedure	99.1 (1,106/1116)	99.5 (411/413)	0.53
Discharge	99.6 (1,109/1,113)	100.0 (413/413)	0.58
9 months	61.7 (673/1,090)	63.0 (250/397)	0.67
1 yr	52.2 (565/1,083)	57.9 (231/399)	0.0499

Numbers shown are mean ± SD (n) or % (n/N).
*Aspirin and thienopyridine (clopidogrel or ticlopidine).

similar for diabetic and nondiabetic subjects and nearly identical after propensity score adjustment (Table 4). In addition, the distribution curves of late loss for diabetic and nondiabetic subjects were virtually superimposable (Fig. 2). Binary in-stent restenosis rate and in-stent % DS, whether adjusted or unadjusted, were not statistically different between diabetic and nondiabetic patients. The pattern of in-stent restenosis was also similar between the 2 groups with <2% of the study sample presenting with proliferative hyperplasia or total occlusion at follow-up regardless of diabetic status (Fig. 3).

In-segment late loss was similar for the 2 patient groups regardless of adjustment. There was a trend toward higher rates of in-segment binary restenosis in subjects with diabetes; however, after propensity score adjustment the rates were similar for the 2 groups. In-segment % DS was significantly increased in patients with diabetes; this difference became nonsignificant after propensity score adjustment. Edge analysis was used to evaluate the difference in the in-segment % DS between the 2 groups. Although there were no differences in % DS or restenosis rates at the proximal edge between the 2 groups, both % DS and restenosis at the distal edge were significantly increased in diabetic compared with nondiabetic subjects (Fig. 4).

Intravascular ultrasound end points at 9 months. A total of 427 patients (68% of the intravascular ultrasound cohort) completed 9-month intravascular ultrasound follow-up (Fig. 1), and 413 of these patients had analyzable films. The TAXUS Liberté stent suppressed neointima growth similarly in diabetic and nondiabetic subjects with similar % intimal hyperplasia in both groups (Table 4). Intima-free length of the stent was also similar for the 2 groups. Unadjusted and adjusted results were concordant.

Clinical efficacy of TAXUS Liberté in diabetic subjects at 9 and 12 months. Clinical follow-up at 9 and 12 months demonstrated a higher rate of overall TVR for diabetic subjects as compared with nondiabetic subjects, a difference that re-

Table 4. Angiographic and Intravascular Ultrasound Results at 9 Months

	Unadjusted Values			Propensity Score-Adjusted Values		
	Nondiabetic (n = 1,116)	Diabetic (n = 413)	p Value	Nondiabetic (n = 1,116)	Diabetic (n = 413)	p Value
In-stent measures						
Late loss*	0.38 ± 0.50 (724)	0.40 ± 0.53 (276)	0.58	0.37	0.38	0.80
% diameter stenosis*	20.63 ± 19.51 (726)	23.25 ± 21.47 (276)	0.07	20.5	21.5	0.49
Restenosis (%)*	9.6 (70/726)	13.0 (36/276)	0.12	9.7	9.6	0.99
% intimal hyperplasia†	13.4 ± 10.7 (321)	14.8 ± 12.4 (91)	0.29	13.8	14.6	0.59
% intima-free length†	33.0 ± 32.7 (321)	27.1 ± 28.1 (92)	0.12	34.3	27.0	0.08
In-segment measures						
Late loss*	0.24 ± 0.46 (727)	0.26 ± 0.49 (278)	0.46	0.22	0.25	0.54
% diameter stenosis*	28.47 ± 17.22 (729)	32.12 ± 18.98 (278)	0.004	28.5	30.2	0.20
Restenosis (%)*	12.6 (92/729)	16.9 (47/278)	0.08	12.9	12.5	0.85

Numbers shown are mean ± SD (n) or % (n/N). *Quantitative coronary angiography. †Intravascular ultrasound.

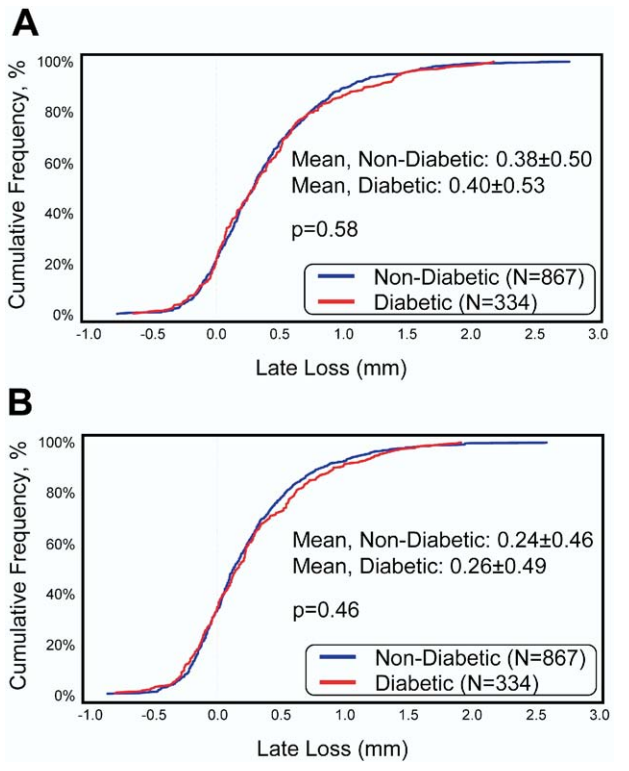

Figure 2. Cumulative Frequency Distribution of 9-Month In-Stent and In-Segment Late Loss by Quantitative Coronary Angiography

Subjects with and without diabetes treated with the TAXUS Liberté Stent in the TAXUS ATLAS studies. **(A)** In-stent; and **(B)** in-segment. Intent-to-treat, angiographic subset (n = 1,201; diabetic: 334; nondiabetic: 867).

mained statistically significant after propensity adjustment (Table 5). The 9- and 12-month rates of both TLR and remote TVR were also significantly higher for diabetic subjects versus nondiabetic subjects. However, after propensity adjustment (Table 5), the TLR rates were similar between the 2 cohorts with a trend toward a higher rate of remote TVR (in the target vessel but outside the target lesion) in the diabetic cohort. The results at 12-month follow-up were corroborated by multivariate adjustment (Fig. 5) demonstrating that the diabetic subjects had significantly increased risk of TVR, driven by a higher risk of TVR Remote (non-TLR TVR); however, the risk of TLR was comparable for the 2 groups.

Safety of TAXUS Liberté in diabetic subjects at 12 months. Subjects with diabetes had comparable rates of all-cause mortality, cardiac death, and MI at 9 and 12 months compared with nondiabetic subjects (Table 5). The rates of stent thrombosis by protocol and Academic Research Consortium definition were also similar between the 2 groups (Table 5). Unadjusted/protocol stent thrombosis rates at 12 months were concordant with those after multivariate (hazard ratio [HR]: 1.37; 95% confidence interval [CI]: 0.34 to 5.5; p = 0.66) and propensity score adjustment (Table 5).

Multivariate predictors of clinical outcomes at 12 months. Multivariate analysis was performed for numerous clinical and procedural variables to determine the risk factors for overall mortality, cardiac mortality, MI, TVR, TLR, and remote TVR (Table 6). Diabetes was not found to be a risk factor for death, MI, or TLR 12 months after TAXUS Liberté stent implantation. However, the presence of diabetes remained a predictor of repeat TVR (HR: 1.77; 95% CI: 1.24 to 2.52; p = 0.002) and remote (nontarget lesion) TVR (HR: 1.71; 95% CI: 1.03 to 2.82; p = 0.04) at 12 months.

Discussion

This study has a number of important findings that pertain to medically treated diabetic patients treated with the second-generation TAXUS Liberté PES. First, angiographic and intravascular ultrasound analyses both demonstrate that this stent reduces neointimal proliferation in diabetic subjects to a level that is comparable to that seen in nondiabetic subjects. Second, when restenosis develops, its pattern is dominated by focal restenosis in both diabetic and nondiabetic subjects. Third, these angiographic and intravascular ultrasound findings are accompanied by rates of clinical restenosis of the target lesion (TLR) that are similar for diabetic and nondiabetic subjects. Fourth, the increased rates of overall TVR and MACE seen in diabetic subjects are driven predominantly by TVR Remote (i.e., TVR outside the stented lesion) rather than events driven within the stented segment. Fifth, at 12-month follow-up, no increase in the likelihood of stent thrombosis, MI, or death exists with this stent in diabetic subjects.

The active ingredient in the TAXUS Liberté stent, paclitaxel, effectively blocks smooth muscle cell proliferation and migration through multiple mechanisms, including stabilization of microtubules to cause G1 arrest (31–33) and inhibition of the Ras/mitogen-activated protein kinase pathway (16,34). When these pathways are affected, the alternative pro-survival mechanism for the smooth muscle cell is through modulation of the AKT-dependent mTOR (35–37) and/or FoxO3a signaling pathways. The ability to not promote activation of AKT under the hyperglycemic state typically seen in the diabetic metabolic state (16), and to strongly inhibit insulin-dependent AKT phosphorylation (35,36), allows paclitaxel to maintain its inhibition of restenosis in diabetic models.

The current study supports the translation of these in vitro findings to the clinical realm by showing that paclitaxel can provide a similarly low degree of neointimal proliferation in diabetic subjects and nondiabetic subjects. Indeed, the angiographic in-stent parameters of late luminal loss and % DS were found to be very similar in diabetic and nondiabetic patients

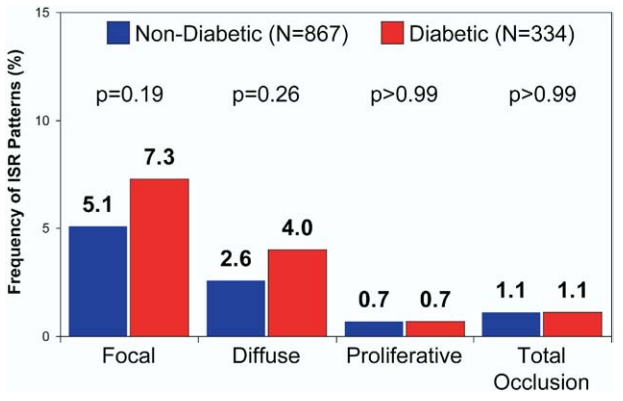

Figure 3. ISR Patterns in Diabetic and Nondiabetic Patients

The frequency of individual patterns of in-stent restenosis (ISR) in subjects with and without diabetes treated with the TAXUS Liberté Stent in TAXUS ATLAS studies. Intent-to-treat, angiographic subset (n = 1,201; diabetic: 334; nondiabetic: 867).

treated with this second-generation PES. Despite slightly smaller reference vessels at baseline in the diabetic patients, their in-stent binary restenosis rates were comparable to those of nondiabetic subjects and the pattern of restenosis at the time of repeat revascularization for both groups was predominantly focal in nature, a pattern easier to treat than proliferative or diffuse restenosis (23). Angiographic findings were corroborated by intravascular ultrasound results, which demonstrated that the in-stent intimal hyperplasia was similar between diabetic and nondiabetic subjects, further supporting that this PES can inhibit neointimal growth even in the diabetic state. This is consistent with a recent meta-analysis of the TAXUS IV, V de novo, and VI trials that also shows comparable suppression of neointimal hyperplasia by quantitative intravascular ultrasound analysis in diabetic subjects and nondiabetic subjects with the first generation PES TAXUS Express (38).

Whereas there were no significant differences between diabetic and nondiabetic patients in any in-stent measures, % DS in the analysis segment was significantly increased in patients with diabetes, driven by a greater % DS at the distal edge. The increased rate of distal edge restenosis in diabetic patients as compared with nondiabetic subjects might be caused by more pronounced restenotic response within the injured vessel segments that remained uncovered by the PES or more rapid disease progression outside the stent in patients with diabetes. However, in-segment % DS was not significantly different between groups after propensity score adjustment. Similarly, the unadjusted TLR rates were higher in the diabetic cohort, which presented with smaller diameter vessels, slightly longer lesions, increased comorbidities, and more edge restenosis than the nondiabetic cohort. Importantly, no significant difference in the likelihood of TLR remained after propensity score or multivariate adjustment correcting for baseline differences between the 2 groups. These findings corroborate the results from a meta-analysis of 5 TAXUS Express randomized studies that demonstrated TLR reduction for the first-generation PES compared with bare metal stents in cohorts with diabetes (HR: 0.42; 95% CI: 0.30 to 0.60) and without diabetes (HR: 0.47; 95% CI: 0.38 to 0.59) (15).

The higher MACE rate seen in the diabetic cohort was accounted for by the increased TVR Remote (non-TLR) in diabetic subjects. Because diabetes is a systemic disease, pro-

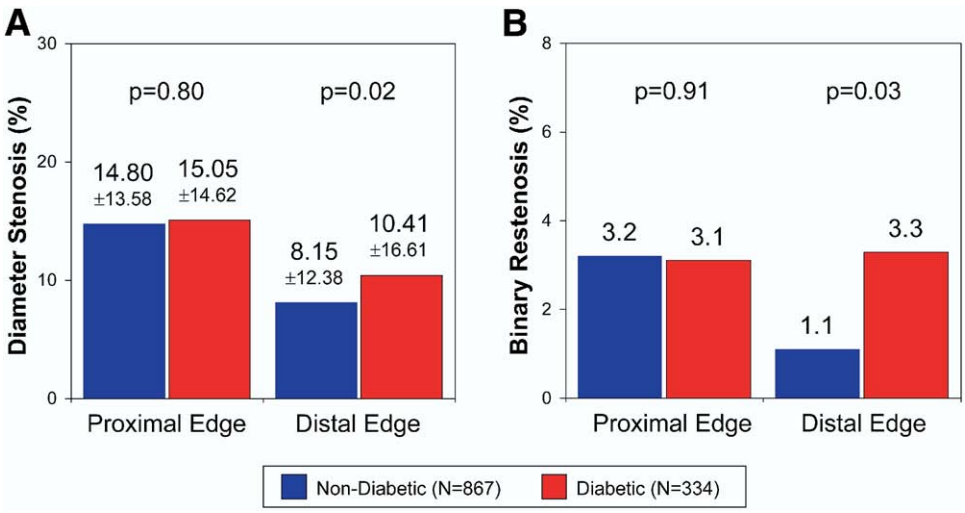

Figure 4. Angiographic Edge Analysis

Frequency of percent diameter stenosis **(A)** and binary restenosis **(B)** 5 mm proximal and distal to each stent edge in subjects with and without diabetes mellitus treated with the TAXUS Liberté Stent in TAXUS ATLAS studies. Intent-to-treat, angiographic subset (n = 1,201; diabetic: 334; nondiabetic: 867).

Table 5. Clinical Outcomes at 9 and 12 Months

	Unadjusted Values			Propensity Score Adjusted Values		
	Nondiabetic (n = 1,116)	Diabetic (n = 413)	p value	Nondiabetic (n = 1,116)	Diabetic (n = 413)	p value
9 months, % (n/N)						
MACE	9.7 (107/1,108)	14.0 (57/407)	0.02	9.9	12.6	0.16
Cardiac death or MI	4.2 (46/1,108)	3.4 (14/407)	0.53	4.1	3.5	0.63
Cardiac death	0.8 (9/1,108)	0.5 (2/407)	0.74	0.7	0.4	0.29
MI	3.4 (38/1,108)	3.4 (14/407)	0.99	3.4	3.5	0.96
Q-wave MI	0.6 (7/1,108)	0.5 (2/407)	>0.99	0.6	0.6	0.99
Non–Q-wave MI	2.8 (31/1,108)	2.9 (12/407)	0.88	2.9	2.9	0.95
TVR overall*	6.5 (72/1,108)	11.8 (48/407)	<0.001	6.7	10.1	0.04
TLR	4.5 (50/1,108)	7.4 (30/407)	0.03	4.6	6.1	0.26
TVR-remote	3.1 (34/1,108)	5.7 (23/407)	0.02	3.2	5.1	0.10
All death	1.1 (12/1,108)	1.0 (4/408)	>0.99	1.0	0.9	0.83
Stent thrombosis						
Per protocol	0.5 (6/1,102)	0.5 (2/404)	>0.99	0.5	0.6	0.90
Definite/probable†	0.7 (8/1,102)	0.5 (2/404)	>0.99	0.7	0.6	0.82
12 months, % (n/N)						
MACE at 1 yr	10.7 (117/1,096)	15.9 (64/403)	0.006	10.9	14.1	0.12
Cardiac death or MI	4.3 (47/1,096)	4.0 (16/403)	0.79	4.3	4.1	0.87
Cardiac death	0.8 (9/1,096)	0.7 (3/403)	>0.99	0.7	0.7	0.88
MI	3.6 (39/1,096)	3.7 (15/403)	0.88	3.6	3.7	0.90
Q-wave MI	0.6 (7/1,096)	0.5 (2/403)	>0.99	0.6	0.6	0.98
Non–Q-wave MI	2.9 (32/1,096)	3.2 (13/403)	0.76	3.0	3.2	0.89
TVR overall*	7.4 (81/1,096)	13.2 (53/403)	<0.001	7.6	11.0	0.04
TLR	4.9 (54/1,096)	8.2 (33/403)	0.02	4.7	6.4	0.18
TVR-remote	3.7 (41/1,096)	6.5 (26/403)	0.02	3.4	5.6	0.08
All death	1.3 (14/1,097)	1.7 (7/406)	0.51	1.2	1.6	0.59
Stent thrombosis	0.6 (6/1,087)	0.8 (3/399)	0.71	0.5	0.8	0.58

Data presented as proportions (%, count/sample size). *Patients with both a target lesion revascularization (TLR) and a target vessel revascularization (TVR)-remote are only counted once in the per-patient analysis of overall TVR. †Academic Research Consortium definition (25).
MACE = major adverse cardiac events; MI = myocardial infarction.

gression of atherosclerosis or formation of new lesions remote from the index treated lesion is expected, as is the inability of focal treatment by a drug-eluting stent to reduce progressive disease beyond the treated vessel segment. In patients treated with the paclitaxel-eluting TAXUS Liberté stent, diabetes thus remained a significant risk factor for repeat TVR at 1 year due to revascularization outside the target lesion.

In a meta-analysis of 5 TAXUS Express randomized studies with a follow-up 4 years after stenting, diabetic patients treated with the TAXUS Express stent compared with those receiving bare metal stents demonstrated similar rates of all-cause mortality (8.4% TAXUS vs. 10.3% bare metal stent, p = 0.61), Q-wave MI (0.5% TAXUS vs. 1.5% bare metal stent, p = 0.26), and Academic Research Consortium definite/probable stent thrombosis (2.2% TAXUS vs. 1.4% bare metal stent, p = 0.74) and thus demonstrated a similar safety profile (15). The present study demonstrates that patients with and without diabetes had similar rates of death, MI, and stent thrombosis at 1 year after TAXUS Liberté PES implantation. This suggests a similar safety profile for the TAXUS Liberté stent in diabetic and nondiabetic patients. Although diabetes has been recognized as a cardiovascular risk factor (30) and higher rates of death and MI can be anticipated in diabetic patients with longer follow-up beyond 1 year, the current analysis did not identify any incremental risk of using PES in patients with diabetes at 1 year.

Study limitations. The TAXUS ATLAS, Direct Stent, Long Lesion, and Small Vessel studies are prospective studies evaluating the TAXUS Liberté stent in patients with strict inclusion/exclusion criteria; because patients enrolled in these trials were carefully selected, the results might only apply to the types of patients and lesions included in these 4 studies. Assessment of diabetic status in these subjects was also not ideal, because plasma glucose, hemoglobin A1c, and glucose-tolerance data were not obtained. Biological indicators of diabetic status might have detected more

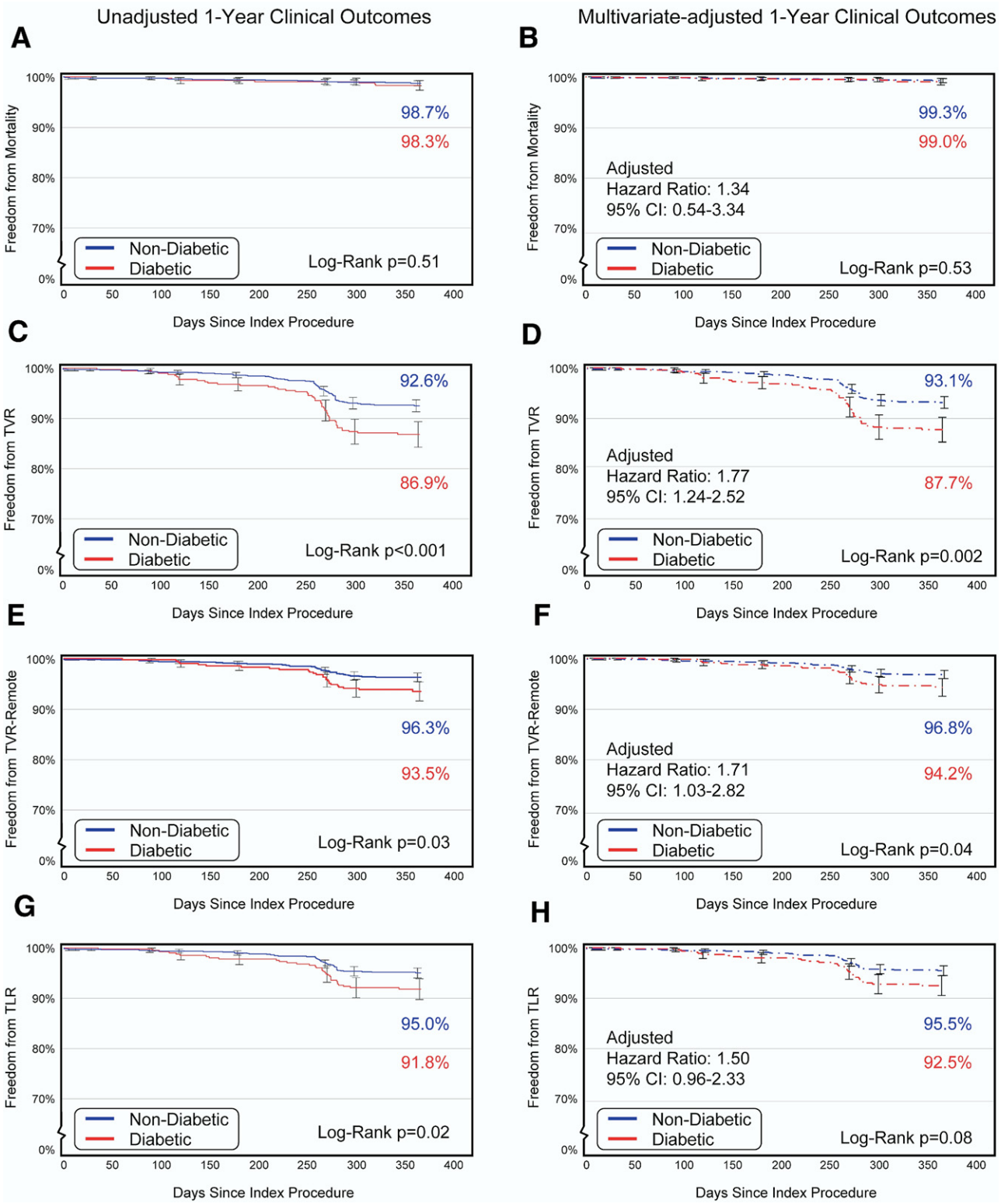

Figure 5. 12-Month Freedom From Adverse Outcomes

Unadjusted **(A, C, E, G)** and multivariate-adjusted **(B, D, F, H)** freedom from all-cause mortality **(A, B)**, target vessel revascularization (TVR) **(C, D),** TVR Remote (non-target lesion revascularization [TLR] TVR) **(E, F)**, and TLR **(G, H)**. Diabetic (n = 413) and nondiabetic (n = 1,116) intent-to-treat subjects treated with the TAXUS Liberté Stent in TAXUS ATLAS studies. Event-free survival ± 1.5 SEM. CI = confidence interval.

Table 6. Multivariate Predictors of Clinical Outcomes at 1 Year

Significant Predictors	Coefficient	SE	Hazard Ratio (95% CI)	p Value
All-cause mortality				
Age at procedure	0.10	0.03	1.11 (1.06–1.17)	<0.001
Smoking, current	1.11	0.52	3.04 (1.11–8.35)	0.03
Post-procedure TIMI flow	−1.61	0.60	0.20 (0.06–0.64)	0.007
Pre-procedure MLD*	−1.45	0.74	0.23 (0.06–1.00)	0.0499
Cardiac mortality				
Age at procedure	0.11	0.03	1.12 (1.05–1.19)	<0.001
Post-procedure TIMI flow	−2.16	0.57	0.12 (0.04–0.36)	<0.001
MI				
Age at procedure	0.03	0.01	1.04 (1.01–1.06)	0.01
Glycoprotein IIb/IIIa inhibitor during procedure	0.73	0.29	2.08 (1.18–3.69)	0.01
Nonstudy stents implanted	1.44	0.73	4.23 (1.02–17.61)	0.047
Unstable angina	0.54	0.28	1.71 (0.99–2.96)	0.06
Post-procedure TIMI flow	−1.95	0.35	0.14 (0.07–0.28)	<0.001
TVR				
Medically treated diabetes	0.57	0.18	1.77 (1.24–2.52)	0.002
Pre-procedure RVD*	−0.72	0.17	0.49 (0.35–0.68)	<0.001
Medication for hyperlipidemia	−0.43	0.20	0.65 (0.44–0.96)	0.03
TLR				
Total length implanted	0.03	0.01	1.03 (1.01–1.05)	0.002
Pre-procedure RVD*	−0.67	0.22	0.51 (0.33–0.78)	0.002
Calcification*	−0.59	0.28	0.55 (0.32–0.95)	0.03
TVR-Remote				
Medically treated diabetes	0.53	0.26	1.71 (1.03–2.82)	0.04
Pre-procedure RVD*	−0.94	0.25	0.39 (0.24–0.64)	<0.001
Medication for hyperlipidemia	−0.66	0.27	0.52 (0.30–0.87)	0.01

Note that negative (−) coefficients with hazard ratios <1.0 indicate variables that are inversely associated with the event. *As determined by quantitative coronary angiography.

CI = confidence interval; MI = myocardial infarction; MLD = minimum lumen diameter; TIMI = Thrombolysis In Myocardial Infarction; TLR = target lesion revascularization; TVR = target vessel revascularization; RVD = reference vessel diameter.

patients with early-stage diabetes than the currently used definition of "treatment with oral hypoglycemic agents or insulin." In addition, because the analysis of diabetic patients was restricted to those receiving medical treatment, the results might not be extrapolative to patients with pre-diabetes or hypoglycemia managed by change in lifestyle or diet. Furthermore, within these constraints, the comparison of the diabetic versus nondiabetic cohort was a post-hoc analysis and might be underpowered to detect differences in low-frequency safety events such as stent thrombosis, death, or MI. In this study, significant differences in baseline characteristics also existed between the 2 cohorts that might be related to diabetes. However, several of these variables are also independent predictors of adverse events after coronary interventions, and metabolic features of the diabetic state confer additional risks that are unique to the diabetic condition. Therefore, propensity score and multivariate adjustment were used to partially compensate for baseline differences. Although this might be suboptimal, it provides a method to adjust for baseline imbalance when randomization is not possible. It is important to note that the intent of reporting propensity- and multivariate-adjusted results is not to suggest "new" rates but rather to ensure more like-to-like comparisons between the 2 patient groups so that a less biased assessment of paclitaxel's ability to inhibit in-stent restenosis in the diabetic metabolic state can be ascertained.

Conclusions

The TAXUS Liberté is a second-generation paclitaxel-eluting stent with reduced stent strut thickness and a better delivery system compared with the first-generation PES. When used for treatment of single simple and complex de novo native coronary lesions, this stent is associated with nearly identical late luminal loss, restenosis, and neointimal hyperplasia in both diabetic and nondiabetic subjects. This was accompanied by similar and low rates of adjusted TLR at 12-month follow-up in both groups and provides clinical evidence that the paclitaxel-eluting TAXUS Liberté stent

blunts any deleterious effect of diabetes on the development of restenosis within the stented segment. The increased need for repeat intervention in diabetic subjects as compared with nondiabetic subjects, however, is due to higher rates of remote TVR likely due to accelerated atherosclerosis in diabetic subjects. The safety profile of the TAXUS Liberté stent is comparable for diabetic and nondiabetic subjects as evident by similar rates of death, MI, and stent thrombosis in the 2 patient subsets. Therefore, the TAXUS Liberté PES is an effective treatment option for de novo coronary lesions in patients with diabetes but has no effect on the development and progression of atherosclerosis beyond the treated lesion.

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Key Words: coronary artery disease ■ diabetes ■ drug-eluting stent ■ paclitaxel.