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A Polymer-Based, Paclitaxel-Eluting Stent in Patients with Coronary Artery Disease

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ABSTRACT

BACKGROUND

Restenosis after coronary stenting necessitates repeated percutaneous or surgical revascularization procedures. The delivery of paclitaxel to the site of vascular injury may reduce the incidence of neointimal hyperplasia and restenosis.

METHODS

At 73 U.S. centers, we enrolled 1314 patients who were receiving a stent in a single, previously untreated coronary-artery stenosis (vessel diameter, 2.5 to 3.75 mm; lesion length, 10 to 28 mm) in a prospective, randomized, double-blind study. A total of 652 patients were randomly assigned to receive a bare-metal stent, and 662 to receive an identical-appearing, slow-release, polymer-based, paclitaxel-eluting stent. Angiographic follow-up was prespecified at nine months in 732 patients.

RESULTS

In terms of base-line characteristics, the two groups were well matched. Diabetes mellitus was present in 24.2 percent of patients; the mean reference-vessel diameter was 2.75 mm, and the mean lesion length was 13.4 mm. A mean of 1.08 stents (length, 21.8 mm) were implanted per patient. The rate of ischemia-driven target-vessel revascularization at nine months was reduced from 12.0 percent with the implantation of a bare-metal stent to 4.7 percent with the implantation of a paclitaxel-eluting stent (relative risk, 0.39; 95 percent confidence interval, 0.26 to 0.59; $P < 0.001$). Target-lesion revascularization was required in 3.0 percent of the group that received a paclitaxel-eluting stent, as compared with 11.3 percent of the group that received a bare-metal stent (relative risk, 0.27; 95 percent confidence interval, 0.16 to 0.43; $P < 0.001$). The rate of angiographic restenosis was reduced from 26.6 percent to 7.9 percent with the paclitaxel-eluting stent (relative risk, 0.30; 95 percent confidence interval, 0.19 to 0.46; $P < 0.001$). The nine-month composite rates of death from cardiac causes or myocardial infarction (4.7 percent and 4.3 percent, respectively) and stent thrombosis (0.6 percent and 0.8 percent, respectively) were similar in the group that received a paclitaxel-eluting stent and the group that received a bare-metal stent.

CONCLUSIONS

As compared with bare-metal stents, the slow-release, polymer-based, paclitaxel-eluting stent is safe and markedly reduces the rates of clinical and angiographic restenosis at nine months.

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THE IMPLANTATION OF CORONARY stents reduces the risk of periprocedural complications and restenosis more than does balloon angioplasty alone.^{1,2} Nonetheless, clinical and angiographic restenosis still occurs in a substantial proportion of patients, often necessitating repeated revascularization procedures, decreasing the quality of life, and increasing health care expenditures.^{3,4} The principal cause of restenosis after coronary stenting is neointimal hyperplasia resulting from the proliferation and migration of smooth-muscle cells and extracellular matrix production.⁵ Numerous systemic pharmacologic and adjunctive device-based approaches have been ineffective at further lowering the risk of restenosis after stenting.⁶ Recently, the site-specific delivery of agents capable of interrupting cellular replication has shown promise in inhibiting neointimal hyperplasia.⁷ In particular, the polymer-based, sirolimus-eluting stent has proved to be safe and effective in reducing the risk of restenosis in previously untreated lesions of native coronary arteries.^{8,9}

Paclitaxel, a lipophilic molecule derived from the Pacific yew tree *Taxus brevifolia*, is capable of inhibiting cellular division, motility, activation, secretory processes, and signal transduction.¹⁰⁻¹⁵ The vascular compatibility and efficacy of paclitaxel in reducing neointimal hyperplasia after balloon- and stent-mediated injury have been shown in *in vitro* and *in vivo* studies.¹⁶⁻²¹ The potential for a slow-release, polymer-based, paclitaxel-eluting stent to reduce the risk of restenosis after the treatment of short, focal atherosclerotic lesions in humans has been demonstrated in small-to-moderate-sized studies.^{22,23} We therefore performed a large-scale, prospective, double-blind, randomized, multicenter trial to examine the safety and efficacy of such a stent in reducing the risk of clinical and angiographic restenosis in a broad population of patients and lesions.

METHODS

STUDY POPULATION AND PROTOCOL

Patients who were at least 18 years of age, had stable or unstable angina or provokable ischemia, and were undergoing percutaneous coronary intervention for a single, previously untreated lesion in a native coronary artery were considered for enrollment. Clinical exclusion criteria included previous or planned use of intravascular brachytherapy in the target vessel or of any drug-eluting stent; myocardial infarction within 72 hours before enrollment; a left

ventricular ejection fraction of less than 25 percent; hemorrhagic diatheses; contraindications or allergy to aspirin, thienopyridines, paclitaxel, or stainless steel; a history of anaphylaxis in response to iodinated contrast medium; use of paclitaxel within 12 months before study entry or current use of colchicine; a serum creatinine level of more than 2.0 mg per deciliter (177 μ mol per liter), a leukocyte count of less than 3500 per cubic millimeter, or a platelet count of less than 100,000 per cubic millimeter; a recent positive pregnancy test, breast-feeding, or the possibility of a future pregnancy; coexisting conditions that limited life expectancy to less than 24 months or that could affect a patient's compliance with the protocol; and current participation in other investigational trials. The study was approved by the institutional review board at each participating center, and consecutive, eligible patients provided written informed consent.

Before undergoing catheterization, patients received 325 mg of aspirin and a 300-mg oral dose of clopidogrel, a base-line electrocardiogram was obtained, and creatine kinase and isoenzyme levels were measured. Angiographic eligibility for inclusion was then assessed: patients had to have a single target lesion with a reference-vessel diameter on visual examination of 2.5 to 3.75 mm and a lesion length of 10 to 28 mm that could be covered by a single study stent. Angiographic exclusion criteria included a left main or ostial target lesion, moderate or severe calcification of the target vessel or lesion, tortuosity or angulation, bifurcation of the target lesion (defined by a side branch measuring more than 2.0 mm in diameter with more than 50 percent stenosis), an occluded target lesion (Thrombolysis in Myocardial Infarction grade 0 or 1 flow), or thrombus. Patients were also excluded if the use of atherectomy or cutting balloon was planned before stenting. Enrollment was permitted after the successful treatment of one additional nonstudy lesion in a nonstudy vessel before randomization.

RANDOMIZATION AND STENT IMPLANTATION

Randomization was performed by telephone and was stratified according to the presence or absence of medically treated diabetes mellitus and vessel size (less than 3.0 mm vs. 3.0 mm or more). Patients were assigned in equal proportions in a double-blind fashion with the use of random serial numbers to treatment with either the slow-release, polymer-based, paclitaxel-eluting stent (TAXUS, Boston Scientific) or a visually indistinguishable bare-metal

stent (EXPRESS, Boston Scientific). Unfractionated heparin was administered according to standard practice, and the use of glycoprotein IIb/IIIa inhibitors was at the operator's discretion. After mandatory dilation with the use of a balloon:artery ratio of 1:1, an appropriate-sized stent (approximately 2 to 4 mm longer than the lesion, with a ratio of stent diameter to distal reference-vessel diameter of 1 to 1.1:1) was implanted at a pressure of at least 12 atm. Stents were available in lengths of 16, 24, and 32 mm and in diameters of 2.5, 3.0, and 3.5 mm. Additional study stents could be implanted in the event of edge dissections of types B through E or otherwise suboptimal results, and the use of dilation after stent implantation was at the operator's discretion.

A postprocedural electrocardiogram was obtained, and cardiac enzymes were measured every 8 hours for 24 hours. Patients took 325 mg of aspirin daily indefinitely and 75 mg of clopidogrel daily for six months. Clinical follow-up was scheduled at one, four, and nine months and yearly thereafter for five years.

DATA MANAGEMENT

Independent study monitors verified 100 percent of the data on site from case-report forms. Data were maintained in a computerized data base by PAREXEL International, and the investigators had unrestricted access to the data. All major adverse cardiac events were reviewed and adjudicated by an independent committee whose members were unaware of patients' treatment allocation. A data and safety monitoring committee periodically reviewed blinded safety data, each time recommending that the study continue without modification. An independent analysis was performed at the angiographic core laboratory by a technician who was unaware of patients' clinical outcomes, using validated quantitative methods.²⁴ Measures were reported separately within the stent, within 5 mm proximal and distal to each edge, and over the entire segment that was analyzed (the "analysis segment"). The manuscript was prepared by the principal investigator and revised after the other coauthors reviewed it.

END POINTS AND DEFINITIONS

The primary end point was the nine-month incidence of ischemia-driven target-vessel revascularization, as adjudicated by the independent clinical-events committee. Target-vessel revascularization was considered to be driven by ischemia if the stenosis of the target vessel was at least 50 percent of

Table 1. Base-Line Clinical and Angiographic Characteristics.*

Characteristic	Paclitaxel-Eluting Stent (N=662)	Bare-Metal Stent (N=652)
Age (yr)	62.8±11.2	62.1±10.9
Male sex (% of patients)	71.8	72.4
Diabetes mellitus (% of patients)		
Requiring medication	23.4	25.0
Requiring insulin	7.7	8.3
Hypertension requiring medication (% of patients)	70.5	69.0
Hyperlipidemia requiring medication (% of patients)	65.0	65.6
Current smoking (% of patients)	23.4	20.1
Prior myocardial infarction (% of patients)	30.5	29.9
Unstable angina (% of patients)	35.8	32.7
Left ventricular ejection fraction (%)	55.2±10.0	55.5±10.5
Target-lesion coronary artery (% of patients)		
Left anterior descending	40.0	41.4
Left circumflex	28.9	26.6
Right	31.1	32.0
Reference-vessel diameter (% of patients)†		
≥3.0 mm	77.3	76.4
<3.0 mm	22.7	23.6
Lesion length (mm)	13.4±6.3	13.4±6.2
Reference-vessel diameter (mm)	2.75±0.47	2.75±0.49
Minimal luminal diameter (mm)	0.92±0.33	0.95±0.34
Stenosis (% of luminal diameter)	66.5±10.7	65.6±10.7
Intervention in nonstudy lesion in nonstudy vessel before randomization (% of patients)	20.8	17.8

* Plus-minus values are means ±SD. There were no significant differences between groups.

† Values were visually estimated by the operator; other angiographic measures are quantitative and were made in the core laboratory.

the luminal diameter on the basis of a quantitative analysis, with either electrocardiographic changes while the patient was at rest or a functional study indicating ischemia in the distribution of the target vessel, or if there was stenosis of at least 70 percent in conjunction with recurrent symptoms alone. Target-lesion revascularization was defined as repeated revascularization for ischemia owing to stenosis of at least 50 percent of the luminal diameter anywhere within the stent or within the 5-mm borders proximal or distal to the stent.

Myocardial infarction after the intervention was defined as either the development of pathologic Q waves lasting at least 0.4 second in at least two contiguous leads with an elevated creatine kinase MB fraction level or, in the absence of pathologic Q waves, an elevation in creatine kinase levels to more than twice the upper limit of normal with an

elevated creatine kinase MB level. A creatine kinase level more than five times the upper limit of normal was required to diagnose a myocardial infarction after bypass surgery.

Major adverse cardiac events were defined as death from cardiac causes (if the cause of death was undetermined, it was categorized as cardiac), myocardial infarction, or ischemia-driven target-vessel revascularization. Target-vessel failure was defined as death, myocardial infarction, or ischemia-driven revascularization related to the target vessel. If an adverse event could not conclusively be attributed to a non-target vessel, the event was considered a target-vessel failure.

Stent thrombosis was defined as an acute coronary syndrome with angiographic documentation of either vessel occlusion or thrombus within or adjacent to a previously successfully stented vessel or, in the absence of angiographic confirmation, either acute myocardial infarction in the distribution of the treated vessel or death from cardiac causes within 30 days. Binary restenosis was defined as stenosis of at least 50 percent of the luminal diameter of the treated lesion.

STATISTICAL ANALYSIS

Using a two-sided test for differences in independent binomial proportions with an alpha level of 0.05 and allowing for a 10 percent rate of attrition, we calculated that 1172 patients would have to undergo randomization for the study to have 85 percent power to detect a reduction in the primary end point of ischemia-driven target-vessel revascularization from an anticipated 15 percent after bare-metal stenting to 9 percent with the paclitaxel-eluting stent, a 40 percent relative reduction. The protocol also prespecified that a minimum of 216 patients would be randomly assigned to receive a 32-mm stent, which became available only in the latter part of the study. An additional 154 patients whose lesions were longer than 24 mm therefore underwent randomization, bringing the total number enrolled to 1326 patients.

The principal secondary end point was the extent of stenosis of the target lesion at nine months. The protocol initially prespecified that follow-up angiography be performed in the first 536 consecutive patients enrolled — a number that, assuming a 25 percent rate of attrition, afforded the study 80 percent power to demonstrate a 17 percent reduction in mean (\pm SD) stenosis, from 27.2 to 22.5 \pm 16.7 percent. To make possible adequate angiographic evaluation of long lesions, the angiographic cohort was expanded by 196 consecutive patients who were receiving 24- or 32-mm stents, resulting in a total of 732 patients in the follow-up angiographic cohort.

Categorical variables were compared by means of the likelihood-ratio chi-square test or Fisher's exact test. Continuous variables are presented as means \pm SD or medians with interquartile ranges and were compared with the use of Student's t-test or the Wilcoxon two-sample test. The influence of base-line variables on nine-month categorical end points was evaluated with logistic regression with the use of Wald's chi-square test. This analysis included all base-line clinical and angiographic fea-

Table 2. Stent Implantation and Procedural Results.*

Variable	Paclitaxel-Eluting Stent (N=662)	Bare-Metal Stent (N=652)	P Value
Stents (in study vessel) per patient			
0 (% of patients)	0.6	0.6	1.00
1 (% of patients)	91.5	92.2	0.69
2 (% of patients)	7.6	6.3	0.39
\geq 3 (% of patients)	0.3	0.9	0.18
Mean no.	1.08 \pm 0.29	1.09 \pm 0.36	0.74
Stent diameter			
2.5 mm (% of patients)	20.7	21.1	0.86
3.0 mm (% of patients)	49.8	47.0	0.46
3.5 mm (% of patients)	29.5	31.9	0.35
Maximal diameter of device (mm)	3.1 \pm 0.4	3.2 \pm 0.4	0.30
Maximal balloon:artery ratio	1.2 \pm 0.2	1.2 \pm 0.2	0.25
Stent length			
16 mm (% of patients)	62.8	63.6	0.77
24 mm (% of patients)	20.1	20.6	0.81
32 mm (% of patients)	17.1	15.8	0.60
Mean (mm)	21.9 \pm 8.1	21.7 \pm 8.8	0.68
Stent:lesion length ratio			0.67
Median	1.58	1.60	
Interquartile range	1.29–2.10	1.29–2.11	
Maximal pressure (atm)	14.8 \pm 2.8	15.1 \pm 2.8	0.06
Use of glycoprotein IIb/IIIa inhibitors (% of patients)	57.7	56.7	0.74
Use of intravascular ultrasonography (% of patients)	22.8	23.9	0.65
Final reference-vessel diameter (mm)	2.80 \pm 0.49	2.83 \pm 0.48	0.39
Final minimal luminal diameter (mm)			
Analysis segment	2.26 \pm 0.48	2.29 \pm 0.50	0.46
In stent	2.66 \pm 0.43	2.67 \pm 0.41	0.68
Final stenosis (% of luminal diameter)			
Analysis segment	19.1 \pm 9.5	19.1 \pm 10.0	0.95
In stent	4.2 \pm 10.7	4.9 \pm 11.6	0.49
Acute gain (mm)			
Analysis segment	1.32 \pm 0.46	1.32 \pm 0.51	0.96
In stent	1.72 \pm 0.44	1.70 \pm 0.46	0.63

* Plus-minus values are means \pm SD.

tures, treatment assignment, and procedural variables, and the results are expressed as odds ratios with 95 percent confidence intervals. The statistical-analysis plan prespecified that the primary intention-to-treat population would consist of all patients in whom an attempt was made to implant a study stent. All P values are two-sided.

RESULTS

ENROLLMENT AND BASE-LINE CHARACTERISTICS
 Between March 29 and July 8, 2002, 1326 patients at 73 U.S. centers were assigned to receive either a paclitaxel-eluting stent (667 patients) or a bare-metal stent (659 patients). Twelve patients (0.9 percent) were subsequently excluded because the appropriate stent size was not available for three patients, the guide wire or pre-dilation balloon could not be successfully passed in three, complications occurred

before stenting in three, the lesion was reevaluated before stenting and determined to meet exclusion criteria in two, and withdrawal of consent by one. The population included in the analysis therefore consisted of 1314 patients: 662 were assigned to receive paclitaxel-eluting stents, and 652 to receive the bare-metal stents. The base-line characteristics of the two groups were well matched (Table 1).

PROCEDURAL OUTCOMES

The number of stents implanted per patient, the mean length and diameter of the stents, and other deployment and implantation variables were similar in the two groups (Table 2). The initial angiographic results were also similar in the two cohorts.

CLINICAL OUTCOMES

As shown in Table 3, implantation of the paclitaxel-eluting stent, as compared with the bare-metal stent,

Table 3. Clinical Outcomes at Nine Months.

Outcome	Paclitaxel-Eluting Stent (N=662)	Bare-Metal Stent (N=652)	Relative Risk (95% CI)*	P Value
	<i>percent</i>			
Death from cardiac causes	1.4	1.1	1.27 (0.47–3.38)	0.80
Myocardial infarction	3.5	3.7	0.94 (0.54–1.66)	0.88
Q-wave	0.8	0.3	2.46 (0.48–12.60)	0.45
Non-Q-wave	2.7	3.4	0.81 (0.44–1.49)	0.52
Stent thrombosis	0.6	0.8	0.79 (0.21–2.92)	0.75
In hospital	0	0.3	—	0.25
Up to 1 mo after discharge	0.3	0.3	0.98 (0.14–6.97)	1.00
>1–6 mo	0.3	0.2	1.97 (0.68–5.73)	1.00
>6–9 mo	0	0	—	—
Target-lesion revascularization	3.0	11.3	0.27 (0.16–0.43)	<0.001
Percutaneous coronary intervention	2.4	8.7	0.28 (0.16–0.48)	<0.001
Coronary-artery bypass grafting	0.6	3.1	0.20 (0.07–0.57)	<0.001
Target-vessel revascularization†	4.7	12.0	0.39 (0.26–0.59)	<0.001
Percutaneous coronary intervention	3.6	9.0	0.40 (0.25–0.64)	<0.001
Coronary-artery bypass grafting	1.1	3.4	0.31 (0.13–0.33)	0.005
Within 1 mo	0	0.3	—	0.25
>1–9 mo	4.7	11.7	0.40 (0.27–0.60)	<0.001
Major adverse cardiac events‡	8.5	15.0	0.56 (0.41–0.77)	<0.001
Within 1 mo	2.9	2.5	1.17 (0.61–2.25)	0.73
>1–9 mo	5.7	12.7	0.45 (0.31–0.65)	<0.001
Target-vessel failure§	7.6	14.4	0.52 (0.38–0.73)	<0.001
Within 1 mo	2.6	2.5	1.05 (0.53–2.05)	1.00
>1–9 mo	5.1	12.1	0.42 (0.29–0.62)	<0.001

* CI denotes confidence interval.

† Patients undergoing both percutaneous coronary intervention and coronary-artery bypass grafting during follow-up are counted as having a single target-vessel revascularization event.

‡ Major adverse cardiac events were death from cardiac causes, myocardial infarction, or ischemia-driven target-vessel revascularization.

§ Target-vessel failure was defined by death, myocardial infarction, or ischemia-driven revascularization related to the target vessel.

Table 4. Angiographic Measures at Nine Months.*

Variable	Paclitaxel-Eluting Stent (N=292)	Bare-Metal Stent (N=267)	Relative Risk (95% CI)	P Value
Reference-vessel diameter (mm)	2.75±0.46	2.77±0.47	—	0.69
Minimal luminal diameter (mm)				
Analysis segment	2.03±0.55	1.68±0.61	—	<0.001
Proximal edge	2.58±0.60	2.51±0.60	—	0.20
In stent	2.26±0.58	1.75±0.65	—	<0.001
Distal edge	2.34±0.51	2.25±0.54	—	0.04
Stenosis (% of luminal diameter)				
Analysis segment	26.3±15.5	39.8±18.5	—	<0.001
Proximal edge	13.2±13.4	16.1±15.0	—	0.02
In stent	17.4±17.7	37.2±19.8	—	<0.001
Distal edge	7.6±12.0	11.8±13.1	—	<0.001
Late loss (mm)				
Analysis segment	0.23±0.44	0.61±0.57	—	<0.001
Proximal edge	0.15±0.42	0.27±0.49	—	0.002
In stent	0.39±0.50	0.92±0.58	—	<0.001
Distal edge	0.05±0.40	0.17±0.44	—	<0.001
Loss index (mm)†				
Analysis segment	0.17±0.38	0.48±0.49	—	<0.001
In stent	0.23±0.32	0.56±0.37	—	<0.001
Binary-restenosis rate (%)‡				
Analysis segment	7.9	26.6	0.30 (0.19–0.46)	<0.001
Proximal edge	2.7	3.4	0.81 (0.32–2.08)	0.81
In stent	5.5	24.4	0.23 (0.13–0.38)	<0.001
Distal edge	0.7	1.9	0.37 (0.07–1.87)	0.27
Pattern of restenosis (%)§¶				
Focal	3.4	7.5	0.46 (0.22–0.96)	0.04
Diffuse	1.0	14.3	0.07 (0.02–0.23)	<0.001
Proliferative	0.3	1.9	0.18 (0.02–1.55)	0.11
Total occlusion	0.7	0.8	0.91 (0.13–6.44)	1.00
Length of restenosed lesion (mm)¶	9.75±5.08	15.30±8.21	—	0.01

* Plus–minus values are means ±SD. The analysis included 559 patients who underwent follow-up angiography at nine months as prespecified in the protocol. CI denotes confidence interval.

† Loss index was determined by dividing late loss by acute gain.

‡ Binary restenosis was defined as stenosis of at least 50 percent of the luminal diameter of the treated lesion.

§ The pattern of restenosis was defined according to the classification of Mehran et al.²⁵

¶ Data were not available for one patient who received a paclitaxel-eluting stent.

reduced the primary end point of the risk of target-vessel revascularization at nine months by 61 percent and lowered the risk of target-lesion revascularization by 73 percent, a consequence of significant reductions in the rates of both percutaneous coronary intervention and coronary-artery bypass grafting. Multivariate analysis showed that randomization to the group receiving a paclitaxel-eluting stent was an independent predictor of freedom from target-vessel revascularization (odds ratio, 0.34; 95 percent confidence interval, 0.22 to 0.54; $P < 0.001$). The rates of death, myocardial infarction, and stent thrombosis were low and similar in the two groups. Thus, at the end of the nine-month follow-up period, the rates of target-vessel failure and major ad-

verse cardiac events were significantly lower after the receipt of a paclitaxel-eluting stent than after the receipt of a bare-metal stent (Table 3).

ANGIOGRAPHIC RESULTS

Follow-up angiography at nine months was completed in 559 of the 732 prespecified patients (76.4 percent), including 442 of the 536 patients (82.5 percent) from the original prespecified angiographic cohort and 117 of the 196 patients (59.7 percent) from the extended long-lesion cohort, from whom consent for angiographic follow-up had not initially been obtained. There were no significant base-line clinical or angiographic differences between patients in whom follow-up angiography was sched-

uled and those in whom it was not scheduled, except that the lesion was significantly longer in patients in the follow-up angiographic cohort (mean, 14.4±6.9 vs. 12.1±5.1 mm; P<0.001). Among patients in the angiographic follow-up cohort, diabetes mellitus was present in 27.7 percent of those who received a paclitaxel-eluting stent and 23.8 percent of those who received a bare-metal stent (P=0.24), and the mean lesion length was 14.4±6.7 and 14.4±7.1 mm, respectively (P=0.94).

Quantitative follow-up data were available for 559 patients. As compared with those who received a bare-metal stent, patients who received a paclitaxel-eluting stent had a significantly smaller amount of late loss and a lower loss index, resulting in greater luminal dimensions and a smaller degree of stenosis at follow-up, both within the stented segment and at its edges (Table 4 and Fig. 1). The use of a paclitaxel-eluting stent reduced the risk of binary restenosis by 77 percent within the stent and by 70 percent in the analysis segment.

Multivariate analysis showed that randomization to the group that received a paclitaxel-eluting stent was an independent predictor of freedom from restenosis (odds ratio, 0.16; 95 percent confidence interval, 0.08 to 0.30; P<0.001).

The relative reduction in the risk of restenosis with the paclitaxel-eluting stent, as compared with the bare-metal stent, was independent of diabetes mellitus status, epicardial-vessel location, and the length and diameter of the lesion or stent (Fig. 2). Among patients with restenosis, those treated with the paclitaxel-eluting stent were much less likely than those who received a bare-metal stent to have a diffuse or proliferative pattern of hyperplasia, and they had a significantly shorter restenosed segment (Table 4). Aneurysms were present at nine months in two patients (0.7 percent) in each group; only one of these aneurysms (in a patient who received a bare-metal stent) developed during the nine-month follow-up period.

Among patients in the angiographic cohort who completed follow-up angiography, the rate of target-lesion revascularization was reduced from 14.6 percent with the bare-metal stent to 3.8 percent with the paclitaxel-eluting stent (P<0.001). Among patients who did not undergo angiographic follow-up, the rate of target-lesion revascularization was reduced from 9.2 percent with the bare-metal stent to 2.4 percent with the paclitaxel-eluting stent (P<0.001).

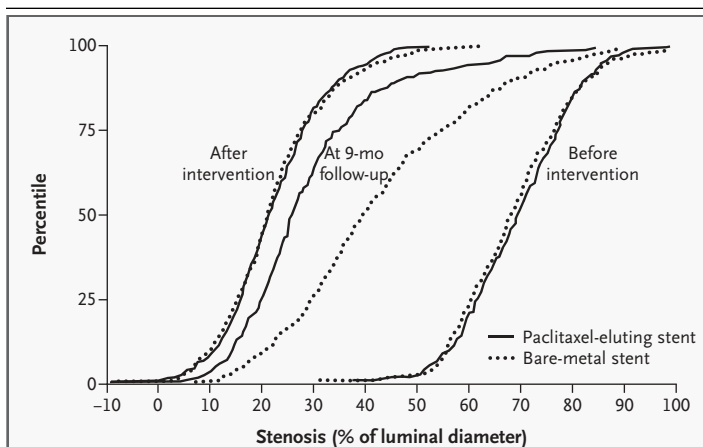


Figure 1. Cumulative Distribution Curves (Paired-Lesion Analysis) for Percent Stenosis of the Luminal Diameter in the Group That Received a Paclitaxel-Eluting Stent and the Group That Received a Bare-Metal Stent before and Immediately after the Intervention and at Nine Months.

At nine months, the mean degree of stenosis in the group that received a paclitaxel-eluting stent was 13.5 percentage points less than the value in the group that received a bare-metal stent (95 percent confidence interval, -16.3 to -10.7; P<0.001).

DISCUSSION

In this prospective, randomized, double-blind study, the implantation of a slow-release, polymer-based, paclitaxel-eluting stent markedly reduced the risk of clinical and angiographic restenosis as compared with the implantation of a bare-metal stent, in patients with a wide range of previously untreated coronary lesions. Despite the relatively low rate of restenosis in the control group, the biologic potency of the paclitaxel-eluting stent was evidenced by a 70 percent relative reduction in the risk of angiographic restenosis, with a corresponding 73 percent reduction in the risk of target-lesion revascularization. In addition to reducing the need for repeated percutaneous coronary intervention, the paclitaxel-eluting stent also reduced the need for coronary-artery bypass grafting. Notably, target-lesion revascularization was required in only 3.8 percent of patients assigned to receive a paclitaxel-eluting stent who underwent protocol-specified angiographic follow-up, and the rate was also significantly reduced among patients who received a paclitaxel-eluting stent who did not undergo routine angiographic follow-up.

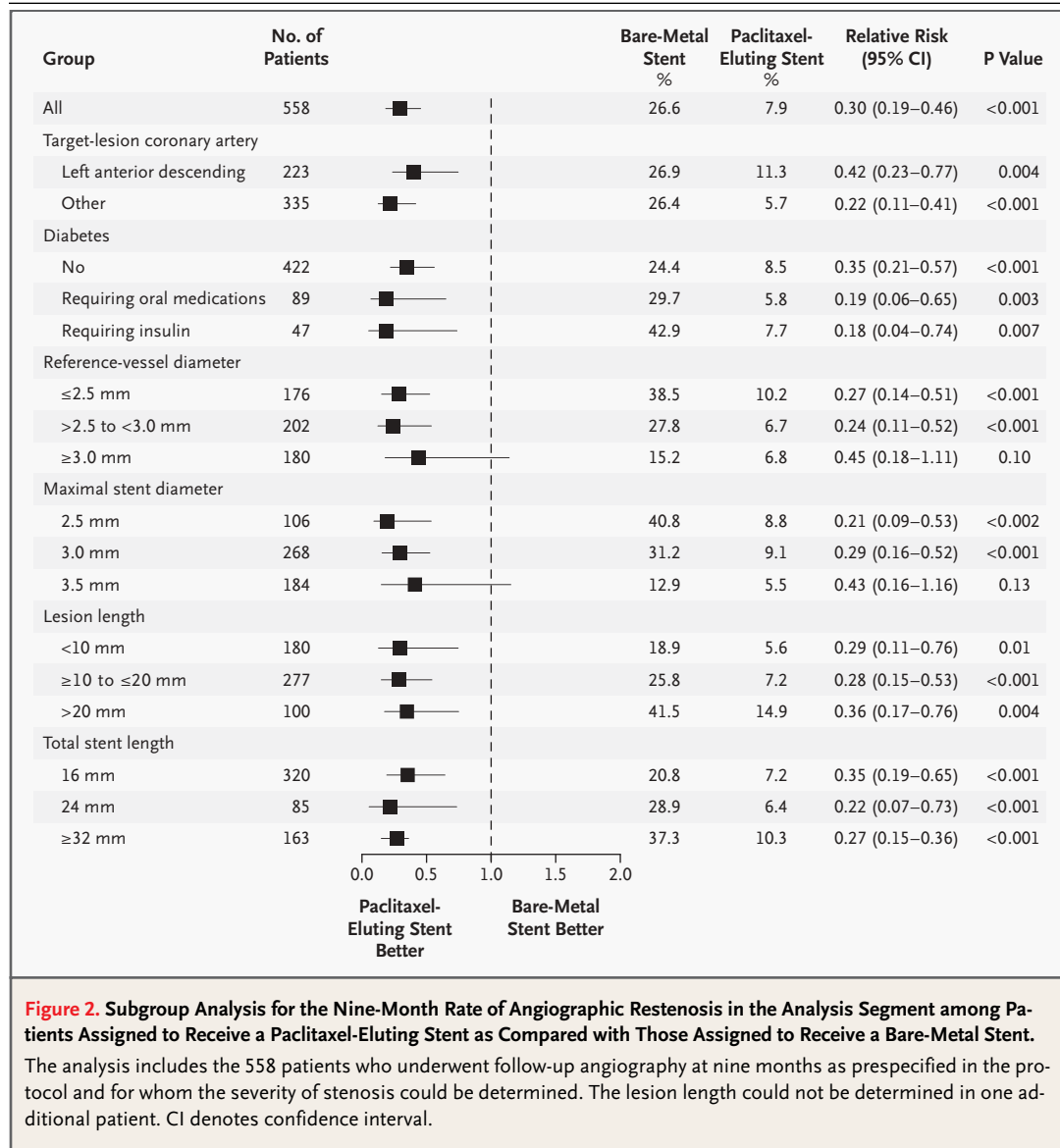


Figure 2. Subgroup Analysis for the Nine-Month Rate of Angiographic Restenosis in the Analysis Segment among Patients Assigned to Receive a Paclitaxel-Eluting Stent as Compared with Those Assigned to Receive a Bare-Metal Stent.

The analysis includes the 558 patients who underwent follow-up angiography at nine months as prespecified in the protocol and for whom the severity of stenosis could be determined. The lesion length could not be determined in one additional patient. CI denotes confidence interval.

The paclitaxel-eluting stent effectively reduced the risk of restenosis in a broad range of lesions and patients undergoing percutaneous intervention. The three principal determinants of restenosis after coronary-stent implantation are diabetes mellitus status, the reference-vessel diameter, and the lesion length (or the length of the implanted stent).²⁶⁻³⁰ We found that the risk of restenosis was increased by approximately 50 percent among diabetic patients who received a bare-metal stent as compared with those without diabetes who received such a stent. In contrast, the risk of restenosis was reduced by more than 80 percent among patients with dia-

betes who received a paclitaxel-eluting stent, so that these patients and patients without diabetes had similar rates of angiographic recurrence after the receipt of such a stent. The marked efficacy of site-specific paclitaxel delivery in reducing the risk of restenosis among patients with diabetes may be explained by paclitaxel's ability to disrupt microtubules, leading to inhibition of signal-transduction pathways regulated by insulin that mediate growth, differentiation, and stress responses.³¹ The rates of restenosis after the implantation of a bare-metal stent in small coronary arteries (no more than 2.5 mm in diameter) and long lesions (longer than

20 mm) were also increased, by 38.5 percent and 41.5 percent, respectively. The benefits of the paclitaxel-eluting stent were particularly evident in these subtypes of lesions, which had the greatest absolute reductions in the risk of restenosis.

The ability of the paclitaxel-eluting stent to reduce the extent of neointimal hyperplasia was evident both within the stent and at the proximal and distal margins of the stent. Moreover, when restenosis did occur after the implantation of a paclitaxel-eluting stent, the pattern was much more likely to be focal than diffuse or proliferative, potentially translating into easier subsequent management.²⁵

Use of the paclitaxel-eluting stent was safe, with no excess risks apparent. Stent thrombosis was infrequent in both groups, and no late stent thromboses occurred after clopidogrel was discontinued at six months. The rates of death from cardiac causes and myocardial infarction over the nine-month follow-up period were also low and were not significantly different between the two groups. Aneurysms did not develop during the nine-month follow-up period in any patient who received a paclitaxel-eluting stent.

The safety and efficacy of the slow-release, polymer-based, paclitaxel-eluting stent in our study population cannot be generalized to patients and types of lesions that were excluded from randomization, including lesions resulting from acute myocardial infarction, thrombus-containing lesions, bifurcations, stenoses of the left main coronary artery, heavily calcified stenoses, vessels visually estimated as less than 2.5 mm or greater than 3.75 mm in diameter, diseased saphenous-vein grafts, or le-

sions with in-stent restenosis. The extent to which an injured or unstented margin contributed to the remaining cases of focal restenosis with the paclitaxel-eluting stent cannot be determined with certainty. Moreover, overlapping stents were implanted in relatively few patients in this trial, and thus, further study is required to evaluate the treatment of lesions that are longer than 28 mm, which require at least two stents. Extended follow-up is required to establish the long-term safety of this and other drug-eluting stent devices. All of our patients received clopidogrel for six months in order to maximize the safety of this device (though preclinical studies demonstrated equivalent rates of healing with the use of nonoverlapping bare-metal stents and slow-release, paclitaxel-eluting stents). Though the use of a prolonged course of clopidogrel is consistent with current studies demonstrating an incremental benefit of extended thienopyridine therapy,³² it is unknown whether this duration of treatment is necessary to prevent subacute thrombosis after the implantation of a paclitaxel-eluting stent. Finally, appropriately powered, head-to-head, randomized trials comparing different drug-eluting stent systems are required to evaluate their relative safety and efficacy.

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APPENDIX

Members of the TAXUS-IV Study were as follows: *Executive Committee* — G. Stone (principal investigator), Cardiovascular Research Foundation and Lenox Hill Heart and Vascular Institute, New York; S. Ellis (co-principal investigator), Cleveland Clinic Foundation, Cleveland; P. Teirstein, Scripps Clinic, La Jolla, Calif.; D. Cohen, Beth Israel Deaconess Medical Center, Boston; M. Russell, Boston Scientific, Natick, Mass.; *Data Monitoring* — PAREXEL International, Waltham, Mass.; R. Baldwin (coordinator), Boston Scientific; *Data Management and Biostatistical Analysis* — PAREXEL International: P. Lam (director); M. Cody (coordinator), Boston Scientific; *Clinical Events Adjudication Committee* — Harvard Cardiovascular Research Institute, Boston: D. Cutlip (chair), M. Chauhan, K. Ho, J. Aroesty, J. Kannam; *Data and Safety Monitoring Committee* — B. Gersh (chair), Mayo Clinic, Rochester, Minn.; M. Ohman, University of North Carolina, Chapel Hill, Chapel Hill; T. Ryan, Boston Medical Center, Boston; D. Faxon, University of Chicago, Chicago; D. DeMets, University of Wisconsin, Madison; *Angiographic Core Laboratory* — Brigham and Women's Hospital, Boston: J. Popma (director), J. Shah, A. Wong; *Intravascular Ultrasound Imaging Core Laboratory* — Washington Hospital Center, Washington, D.C.: N. Weissman (director); *Study Sites, Principal Investigators, and Study Coordinators* — Huntsville Hospital, Huntsville, Ala.: W. Strickland, D. McCrackin; *Good Samaritan Regional Medical Center, Phoenix, Ariz.*: N. Laufer, D. Cook; *Scripps Memorial Hospital, La Jolla, Calif.*: M. Buchbinder, S. Costello; *Mercy General Hospital, Sacramento, Calif.*: M. Chang, S. Bordash; *University of California Davis Medical Center, Sacramento*: R. Low, K. Harder; *Good Samaritan Hospital, Los Angeles*: R. Matthews, S. Mullin; *Scripps Clinic, La Jolla, Calif.*: P. Teirstein, E. Anderson; *Stanford Medical Center, Stanford, Calif.*: A. Yeung, P. Tsao; *Columbia Medical Center of Aurora, Aurora, Colo.*: B. Molk, K. Bickett; *Aurora Denver Cardiology, Denver*: B. Molk, K. Bickett; *Connecticut Clinical Research, Bridgeport*: E. Kosinski, M. Capasso; *Washington Hospital Center, Washington, D.C.*: L. Satler, R. Howery; *Christiana Hospital, Newark, Del.*: J. Hopkins, K. Sullivan; *Sarasota Memorial Hospital, Sarasota, Fla.*: S. Culp, J. Selby; *MediQuest Research Group, Ocala, Fla.*: R. Feldman, K. Tighe; *Florida Hospital, Orlando*: J. Greenberg, M. Allan; *St. Vincent's Hospital, Jacksonville, Fla.*: G. Pilcher, A. Dennis; *Piedmont Hospital, Atlanta*: C. Brown, A. Garvitte; *Mercy Hospital Medical Center, Des Moines, Iowa*: M. Tannenbaum, R. Porter; *Mercy Medical Center, Des Moines, Iowa*: M. Tannenbaum, M. Craig; *Northwestern University Medical School, Chicago*: C. Davidson, L. Goodreau; *St. John's Hospital, Springfield, Ill.*: G. Mishkel, P. Warren; *Community Hospital Heart Institution, India-*

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REFERENCES

- Serruys PW, de Jaegere P, Kiemeneij F, et al. A comparison of balloon-expandable-stent implantation with balloon angioplasty in patients with coronary artery disease. *N Engl J Med* 1994;331:489-95.
- Fischman DL, Leon MB, Baim DS, et al. A randomized comparison of coronary-stent placement and balloon angioplasty in the treatment of coronary artery disease. *N Engl J Med* 1994;331:496-501.
- Al Suwaidi J, Berger PB, Holmes DR Jr. Coronary artery stents. *JAMA* 2000;284:1828-36.
- Peterson ED, Cowper PA, DeLong ER, Zidar JP, Stack RS, Mark DB. Acute and long-term cost implications of coronary stenting. *J Am Coll Cardiol* 1999;33:1610-8.
- Farb A, Sangiorgi G, Carter AJ, et al. Pathology of acute and chronic coronary stenting in humans. *Circulation* 1999;99:44-52.
- Hoffmann R, Mintz GS. Coronary in-stent restenosis—predictors, treatment and prevention. *Eur Heart J* 2000;21:1739-49.
- Babapulle MN, Eisenberg MJ. Coated stents for the prevention of restenosis. *Circulation* 2002;106:2859-66.
- Morice M-C, Serruys PW, Sousa JE, et al. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. *N Engl J Med* 2002;346:1773-80.
- Moses JW, Leon MB, Popma JJ, et al. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. *N Engl J Med* 2003;349:1315-23.
- Roberts RL, Nath J, Friedman MM, Gallin JJ. Effects of taxol on human neutrophils. *J Immunol* 1982;129:2134-41.
- Belotti D, Vergani V, Drudis T, et al. The microtubule-affecting drug paclitaxel has antiangiogenic activity. *Clin Cancer Res* 1996;2:1843-9.
- Jackson JK, Tudan C, Sahl B, Pelech SL, Burt HM. Calcium pyrophosphate dihydrate crystals activate MAP kinase in human neutrophils: inhibition of MAP kinase, oxidase activation and degranulation responses of neutrophils by taxol. *Immunology* 1997;90:502-10.
- Hui A, Min WX, Tang J, Cruz TF. Inhibition of activator protein 1 activity by paclitaxel suppresses interleukin-1-induced collagenase and stromelysin expression by bovine chondrocytes. *Arthritis Rheum* 1998;41:869-76.
- Wang TH, Wang HS, Ichijo H, et al. Microtubule-interfering agents activate c-Jun N-terminal kinase/stress-activated protein kinase through both Ras and apoptosis signal-regulating kinase pathways. *J Biol Chem* 1998;273:4928-36.
- Giannakakou P, Robey R, Fojo T, Blagosklonny MV. Low concentrations of paclitaxel induce cell type-dependent p53, p21 and G1/G2 arrest instead of mitotic arrest: molecular determinants of paclitaxel-induced cytotoxicity. *Oncogene* 2001;20:3806-13.
- Farb A, Heller PF, Shroff S, et al. Pathological analysis of local delivery of paclitaxel via a polymer-coated stent. *Circulation* 2001;104:473-9.
- Sollott SJ, Cheng L, Pauly RR, et al. Taxol inhibits neointimal smooth muscle cell accumulation after angioplasty in the rat. *J Clin Invest* 1995;95:1869-76.
- Axel DI, Kunert W, Goggelmann C, et al. Paclitaxel inhibits arterial smooth muscle cell proliferation and migration in vitro and in vivo using local drug delivery. *Circulation* 1997;96:636-45.
- Herdeg C, Oberhoff M, Baumbach A, et al. Local paclitaxel delivery for the prevention of restenosis: biological effects and efficacy in vivo. *J Am Coll Cardiol* 2000;35:1969-76.
- Oberhoff M, Kunert W, Herdeg C, et al. Inhibition of smooth muscle cell proliferation after local drug delivery of the antimetabolic drug paclitaxel using a porous balloon catheter. *Basic Res Cardiol* 2001;96:275-82.
- Signore PE, Machan LS, Jackson JK, et al. Complete inhibition of intimal hyperplasia by perivascular delivery of paclitaxel in balloon-injured rat carotid arteries. *J Vasc Interv Radiol* 2001;12:79-88.
- Grube E, Silber S, Hauptmann KE, et al. TAXUS I: six- and twelve-month results from a randomized, double-blind trial on a slow-release paclitaxel-eluting stent for de novo coronary lesions. *Circulation* 2003;107:38-42.
- Colombo A, Drzewiecki J, Banning A, et al. Randomized study to assess the effectiveness of slow- and moderate-release polymer-based paclitaxel-eluting stent for coronary artery lesions. *Circulation* 2003;108:788-94.
- van der Zwet PM, Reiber JH. A new approach for the quantification of complex lesion morphology: the gradient field transform: basic principles and validation results. *J Am Coll Cardiol* 1994;24:216-24.
- Mehran R, Dangas G, Abizaid AS, et al. Angiographic patterns of in-stent restenosis: classification and implications for long-term outcome. *Circulation* 1999;100:1872-8.
- Ho KKL, Senerchia C, Rodriguez O, Chauhan MS, Kuntz RE. Predictors of angiographic restenosis after stenting: pooled analysis of 1197 patients with protocol-mandated angiographic follow-up from

- 5 randomized stent trials. *Circulation* 1998; 98:Suppl 1:I-362. abstract.
27. Serruys PW, Kay IP, Disco C, Deshpande NV, de Feyter PJ. Periprocedural quantitative coronary angiography after Palmaz-Schatz stent implantation predicts the restenosis rate at six months: results of a meta-analysis of the Belgian Netherlands Stent Study (BENESTENT) I, BENESTENT II pilot, BENESTENT II and MUSIC trials. *J Am Coll Cardiol* 1999;34:1067-74.
28. Kastrati A, Schomig A, Elezi S, et al. Predictive factors of restenosis after coronary stent placement. *J Am Coll Cardiol* 1997;30:1428-36.
29. Mercado N, Boersma E, Wijns W, et al. Clinical and quantitative coronary angiographic predictors of coronary restenosis: a comparative analysis from the balloon-to-stent era. *J Am Coll Cardiol* 2001;38:645-52.
30. Kasaoka S, Tobis J, Akiyama T, et al. Angiographic and intravascular ultrasound predictors of in-stent restenosis. *J Am Coll Cardiol* 1998;32:1630-5.
31. Mitsuuchi Y, Johnson SW, Selvakumaran M, Williams SJ, Hamilton TC, Testa JR. The phosphatidylinositol 3-kinase/AKT signal transduction pathway plays a critical role in the expression of p21WAF1/CIP1/SDI1 induced by cisplatin and paclitaxel. *Cancer Res* 2000;60:5390-4.
32. Steinhubl SR, Berger PB, Mann JT III, et al. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. *JAMA* 2002;288:2411-20. [Erratum, *JAMA* 2003;289:987.]

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