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Sirolimus-Eluting Stents versus Standard Stents in Patients with Stenosis in a Native Coronary Artery

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ABSTRACT

BACKGROUND

Preliminary reports of studies involving simple coronary lesions indicate that a sirolimus-eluting stent significantly reduces the risk of restenosis after percutaneous coronary revascularization.

METHODS

We conducted a randomized, double-blind trial comparing a sirolimus-eluting stent with a standard stent in 1058 patients at 53 centers in the United States who had a newly diagnosed lesion in a native coronary artery. The coronary disease in these patients was complex because of the frequent presence of diabetes (in 26 percent of patients), the high percentage of patients with longer lesions (mean, 14.4 mm), and small vessels (mean, 2.80 mm). The primary end point was failure of the target vessel (a composite of death from cardiac causes, myocardial infarction, and repeated percutaneous or surgical revascularization of the target vessel) within 270 days.

RESULTS

The rate of failure of the target vessel was reduced from 21.0 percent with a standard stent to 8.6 percent with a sirolimus-eluting stent ($P < 0.001$) — a reduction that was driven largely by a decrease in the frequency of the need for revascularization of the target lesion (16.6 percent in the standard-stent group vs. 4.1 percent in the sirolimus-stent group, $P < 0.001$). The frequency of neointimal hyperplasia within the stent was also decreased in the group that received sirolimus-eluting stents, as assessed by both angiography and intravascular ultrasonography. Subgroup analyses revealed a reduction in the rates of angiographic restenosis and target-lesion revascularization in all subgroups examined.

CONCLUSIONS

In this randomized clinical trial involving patients with complex coronary lesions, the use of a sirolimus-eluting stent had a consistent treatment effect, reducing the rates of restenosis and associated clinical events in all subgroups analyzed.

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THE DEMONSTRATED CLINICAL USEFULNESS of the implantation of a coronary stent as the preferred method of percutaneous revascularization is due to improved procedural safety as compared with balloon angioplasty and reduced rates of restenosis.¹⁻⁷ But despite the use of coronary stents, the frequency of restenosis may be more than 30 percent in several subgroups of patients, including subgroups with diabetes mellitus, small coronary vessels, and long lesions.⁸⁻¹⁵

During the past two decades, attempts to reduce restenosis after angioplasty with the use of locally delivered or systemic pharmaceutical agents have been largely unsuccessful.¹⁶⁻¹⁹ Recently, sirolimus (rapamycin), a cytostatic macrocyclic lactone with both antiinflammatory and antiproliferative properties,²⁰⁻²² delivered from a polymer-encapsulated stent was shown in small registry studies and randomized clinical trials to reduce the risk of restenosis in patients who were at low risk for restenosis.²³⁻²⁵ We conducted a study to determine the clinical usefulness of the sirolimus-eluting stent in patients with more challenging coronary stenoses.

METHODS

STUDY DESIGN AND ELIGIBILITY

This randomized, double-blind study complied with the provisions of the Declaration of Helsinki regarding investigation in humans and was approved by the Food and Drug Administration. The study was approved by the institutional review boards at all 53 investigational sites, and written informed consent was obtained from all patients.

Eligible patients had a history of stable or unstable angina and signs of myocardial ischemia. A single newly diagnosed target lesion in a native coronary artery resulting in stenosis of 51 to 99 percent of the luminal diameter and measuring 15 to 30 mm in length (as estimated visually on angiography) was treated. Major criteria for exclusion were recent myocardial infarction (within the previous 48 hours); an ejection fraction of less than 25 percent; a target lesion in an ostium, a bifurcation, or an "unprotected" left main coronary artery or in a vessel with thrombus or severe calcification; and treatment of nontarget lesions in the same or a different coronary vessel during the index procedure.

Before the index procedure, an automated telephone randomization system was used to randomly assign eligible patients in a double-blind manner to treatment with a sirolimus-eluting stent or a stand-

ard stent (Bx Velocity, Cordis) in a 1:1 ratio at each site. Randomization blocks were created and were stratified according to the clinical center and the presence or absence of diabetes mellitus.

CORONARY-STENT PROCEDURE

Before and after the index procedure, all patients received oral aspirin (325 mg daily) and oral clopidogrel (a loading dose of 300 to 375 mg 24 hours before the procedure and then 75 mg daily for three months). During the procedure, intravenous heparin boluses were administered. The use of intravenous glycoprotein IIb/IIIa inhibitors was at the discretion of the physician. Lesions were treated with the use of standard interventional techniques, including mandated balloon dilation before the placement of the stent. One or two stents of the assigned type were used to treat the target lesion. The sirolimus-eluting stents and the standard stents (available in lengths of 8 mm and 18 mm and in diameters of 2.5 mm, 3.0 mm, and 3.5 mm) were identical in appearance. The sirolimus-eluting stents contained 140 μ g of sirolimus per square centimeter of stent-surface area within a copolymer matrix that was 5 to 10 μ m thick and was designed to release approximately 80 percent of the total dose of sirolimus in 30 days. Both the physician and the patient were unaware of the treatment-group assignment.

DATA COLLECTION, FOLLOW-UP, AND CORE LABORATORY ANALYSES

All data were submitted to a data coordinating center (the Cardiovascular Data Analysis Center, Harvard Clinical Research Institute, Harvard Medical School, Boston), and the investigators had full access to the data. The investigators also initiated, performed, and reviewed all analyses and made the decisions about publication. Clinical follow-up information was obtained for all patients by the research coordinators at each site at 30, 90, 180, and 270 days. All clinical end points were adjudicated by an independent clinical-events committee that was unaware of the treatment-group assignments. A separate data and safety monitoring board that was not affiliated with the study sponsor or the investigators reviewed all data periodically to identify potential safety issues (all complications, including death, stent thrombosis, and myocardial infarction) and to review the conduct of the study (the pace of enrollment, patients' eligibility, and compliance with data collection). The monitoring board did not perform an interim analysis with regard to the pri-

primary efficacy end point at nine months, since enrollment was completed before the nine-month primary end point was reached in the first patient.

Coronary angiograms, obtained at base line, at the completion of the stenting procedure, and at 240 days of follow-up, were submitted to the angiographic core laboratory (Brigham and Women's Angiographic Core Laboratory, Boston) and were analyzed with the use of a computer-based system (Medis). "Binary" restenosis was defined as stenosis of more than 50 percent of the luminal diameter in the target lesion. Late luminal loss was defined as the difference between the minimal luminal diameter at the completion of the stenting procedure and that measured during follow-up. Quantitative angiographic measurements of the target lesion were obtained in the "in-stent" zone (including only the stented segment) and in the "in-segment" zone (including the stented segment as well as the margins 5 mm proximal and distal to the stent).

Intravascular ultrasonographic examinations were performed after the index stenting procedure and at 240 days in a subgroup of 250 consecutive patients at 17 centers. With the use of intravascular ultrasonography, qualitative assessments and quantitative determinations of the areas and volumes of the vessels, stents, and lumens were made by the intravascular ultrasonography core laboratory (Cardiovascular Core Analysis Laboratory, Stanford University, Stanford, Calif.).

STUDY END POINTS

The primary end point of this study was failure of the target vessel, defined as the occurrence of any of the following within 270 days after the index procedure: death from cardiac causes, Q-wave or non-Q-wave myocardial infarction, or revascularization of the target vessel (emergency or elective coronary-artery bypass grafting [CABG] or repeated percutaneous transluminal coronary angioplasty [PTCA]).

The secondary clinical end points included death from any cause, revascularization of the target lesion (clinically driven CABG or repeated PTCA due to restenosis or closure of the target lesion), and stent thrombosis. All major adverse events were determined for the in-hospital period, for the out-of-hospital period, and cumulatively for the 270 days after the placement of the stent.

STATISTICAL ANALYSIS

The planned sample size of 1100 patients provided 80 percent statistical power to detect a 40 percent

reduction in the rate of the primary end point at 270 days (from 15 percent with the standard stent to 9 percent with the sirolimus-eluting stent) with a 5 percent false positive rate (two-sided). We prespecified that the effectiveness analysis and the safety evaluation were to be based on data from all patients who underwent randomization except those who were withdrawn before they received the assigned treatment (as described below). The differences between the treatment groups were evaluated with the use of analysis of variance or with Wilcoxon rank-sum scores for the continuous variables, when appropriate. The Cochran–Mantel–Haenszel statistic, with control for the clinical center, was used for the analysis of categorical variables. The rate of survival free of target-vessel failure during the 270-day follow-up period was analyzed with the use of the

Table 1. Characteristics of the Patients and the Lesions.*

Characteristic	All Patients (N=1058)	Sirolimus-Stent Group (N=533)	Standard-Stent Group (N=525)
Age (yr)	62.3±11.1	62.1±11.2	62.4±11.0
Male sex (%)	71	73	70
Diabetes mellitus (%)	26	25	28
Hyperlipidemia (%)†	74	73	75
Hypertension (%)	68	68	68
Current smoker (%)	20	18	22
Previous myocardial infarction (%)	31	28	33
Angina pectoris (%)			
Exertional angina	58	59	59
Angina while at rest	23	23	23
Unstable angina‡	53	53	54
Target artery (%)			
Left anterior descending coronary artery	44	44	43
Right coronary artery	31	30	32
Left circumflex coronary artery	25	25	24
Multivessel disease (%)	42	41	42
ACC–AHA class (%)			
A	8	7	8
B1	36	34	38
B2	33	33	34
C	23	26	21
Diameter of reference vessel (mm)	2.80±0.47	2.79±0.45	2.81±0.49
Length of lesion (mm)	14.4±5.8	14.4±5.8	14.4±5.8

* Plus–minus values are means ±SD. There were no significant differences between the treatment groups. ACC denotes American College of Cardiology, and AHA American Heart Association.

† Hyperlipidemia was defined as a low-density lipoprotein cholesterol level above 130 mg per deciliter (3.4 mmol per liter).

‡ Unstable angina was defined according to the Braunwald classification.

actuarial life-table method, and the difference between survival curves was assessed with the log-rank test. To identify factors that might be related to angiographic restenosis and revascularization of the target lesion, logistic-regression models were used. All statistical analyses were performed with the use of SAS software (version 6.12, SAS Institute), and all reported P values are two-sided.

RESULTS

CHARACTERISTICS OF THE PATIENTS AND THE LESIONS

Between February 2001 and August 2001, 1101 patients gave written informed consent and were randomly assigned to one of the two treatment groups. After randomization, 43 patients (4 percent of all patients, 23 in the sirolimus-stent group and 20 in the standard-stent group) were withdrawn from the study and did not receive the assigned treatment. The reasons for withdrawal were the unavailability of the assigned type of stent at the center (in the cases of 4 patients) and the discovery of criteria for exclusion that became apparent only after pretreatment angiography (in 39 patients). The final patient cohort included 1058 patients — 533 in the sirolimus-stent group and 525 in the standard-stent group.

The groups were well matched, with no significant differences in the frequency of cardiac risk factors (Table 1). Among all patients, the mean age was 62 years; 71 percent were men, 31 percent had had

a previous myocardial infarction, and 26 percent had diabetes. Cardiac symptoms included exertional angina in 58 percent of patients, angina while at rest in 23 percent, and unstable angina (Braunwald class I, II, or III) in 53 percent. The majority (56 percent) of treated lesions were class B2 or C according to the American College of Cardiology–American Heart Association classification, the average reference-vessel diameter was 2.80 mm, and the mean lesion length was 14.4 mm.

PROCEDURAL FACTORS

There were no differences between the groups in the rate of use of conventional interventions; glycoprotein IIb/IIIa inhibitors were given to 60 percent of patients, the maximal balloon-inflation pressure after stenting was 15 atm, and the mean (\pm SD) ratio of the stent length to the lesion length was 1.6 ± 0.6 . An average of 1.4 stents were implanted per target lesion, with overlapping stents in 28 percent of patients.

QUANTITATIVE CORONARY ANGIOGRAPHY

The dimensions of the lesion at base line were similar in the two groups (Table 2). Follow-up angiographic data were available for 350 patients in the sirolimus-stent group (86 percent of the patients assigned to undergo angiographic follow-up) and 353 in the standard-stent group (85 percent of the patients assigned to undergo angiographic follow-up). Table 2 shows that at follow-up, the minimal luminal diameter, stenosis as a percentage of the lu-

Table 2. Results of Quantitative Coronary Angiography.*

Variable	In-Stent Zone			In-Segment Zone		
	Sirolimus Stent	Standard Stent	P Value	Sirolimus Stent	Standard Stent	P Value
Minimal luminal diameter (mm)						
Before procedure	0.98 \pm 0.40	0.97 \pm 0.38	0.68	0.99 \pm 0.40	0.97 \pm 0.38	0.68
After procedure	2.67 \pm 0.40	2.68 \pm 0.42	0.98	2.38 \pm 0.45	2.40 \pm 0.46	0.63
At 240 days	2.50 \pm 0.58	1.69 \pm 0.79	<0.001	2.15 \pm 0.61	1.60 \pm 0.72	<0.001
Stenosis (% of luminal diameter)						
Before procedure	65.1 \pm 12.6	65.6 \pm 12.1	0.46	65.1 \pm 12.6	65.6 \pm 12.1	0.46
After procedure	5.4 \pm 8.2	6.0 \pm 7.9	0.22	16.1 \pm 9.7	16.2 \pm 8.5	0.80
At 240 days	10.4 \pm 16.5	40.1 \pm 25.3	<0.001	23.6 \pm 16.4	43.2 \pm 22.4	<0.001
Late luminal loss (mm) †	0.17 \pm 0.45	1.00 \pm 0.70	<0.001	0.24 \pm 0.47	0.81 \pm 0.67	<0.001
Restenosis (% of patients) ‡	3.2	35.4	<0.001	8.9	36.3	<0.001

* Plus–minus values are means \pm SD.

† Late luminal loss was defined as the difference between the minimal luminal diameter immediately after the placement of the stent and the minimal luminal diameter at 240 days. The data are for the 701 patients for whom both postprocedural and follow-up measurements of the minimal luminal diameter were available.

‡ Restenosis was defined as stenosis of 50 percent of the luminal diameter on the 240-day follow-up angiogram.

minimal diameter, and the late luminal loss in both the in-stent zone and the in-segment zone were all improved with the sirolimus stent as compared with the standard stent ($P < 0.001$ for all comparisons). The frequency of binary in-stent restenosis (stenosis of at least 50 percent of the luminal diameter) was 3.2 percent in the sirolimus-stent group and 35.4 percent in the standard-stent group ($P < 0.001$), and the frequency of in-segment restenosis was 8.9 percent in the sirolimus-stent group and 36.3 percent in the standard-stent group ($P < 0.001$). The higher rate of in-segment restenosis in the sirolimus-stent group was due to a smaller reduction in late luminal loss in the in-segment zone than in the in-stent zone and a higher rate of restenosis at the proximal margin of the stent than at the distal margin or in the body of the stent.

INTRAVASCULAR ULTRASONOGRAPHY

The use of sirolimus-eluting stents, as compared with the use of standard stents, resulted in reductions in the neointimal volume in the in-stent zone (4.4 mm^3 vs. 57.6 mm^3 , $P < 0.001$) and in the in-stent obstruction as a percentage of volume (3.1 percent vs. 33.4 percent, $P < 0.001$).

CLINICAL OUTCOMES

Major adverse cardiac events are listed in Table 3. In-hospital events occurred at a similar frequency in the two groups (including death, myocardial infarction, and repeated revascularization); the proportion of patients with any in-hospital major adverse event was 2.4 percent in the sirolimus-stent group and 1.5 percent in the standard-stent group ($P = 0.38$). There was a lower rate of out-of-hospital adverse events during the 270 days of follow-up in the sirolimus-stent group than in the standard-stent group; reductions included those in the number of patients with non-Q-wave myocardial infarction (from 7 to 1, $P = 0.04$), the number requiring revascularization of the target lesion (from 87 to 21, $P < 0.001$), and the number with any major adverse event (from 93 to 26, $P < 0.001$). Similarly, the number of patients reaching the primary clinical end point, failure of the target vessel within 270 days, was reduced by 58 percent with sirolimus stents (from 110 to 46, $P < 0.001$). The rate of survival free of target-vessel failure for 270 days increased from 78.6 percent with a standard stent to 91.1 percent with a sirolimus stent ($P < 0.001$) (Fig. 1).

Stent thrombosis was infrequent, and the rate was similar in the two treatment groups. There were

Table 3. Major Adverse Cardiac Events in the Hospital and outside of the Hospital during 270 Days of Follow-up.*

Variable	Sirolimus-Stent Group (N=533)	Standard-Stent Group (N=525)	P Value
	<i>no. of patients (%)</i>		
In-hospital events			
Death	1 (0.2)	0	
Myocardial infarction	12 (2.3)	8 (1.5)	
Q-wave	2 (0.4)	0	
Non-Q-wave	10 (1.9)	8 (1.5)	
Target-lesion revascularization	1 (0.2)	0	
CABG	0	0	
PTCA	1 (0.2)	0	
Any major adverse cardiac event	13 (2.4)	8 (1.5)	
Out-of-hospital events			
Death	4 (0.8)	3 (0.6)	
Myocardial infarction	3 (0.6)	9 (1.7)	
Q-wave	2 (0.4)	2 (0.4)	
Non-Q-wave	1 (0.2)	7 (1.3)	0.04
Target-lesion revascularization	21 (3.9)	87 (16.6)	<0.001
CABG	3 (0.6)	8 (1.5)	
PTCA	19 (3.6)	83 (15.8)	<0.001
Any major adverse cardiac event	26 (4.9)	93 (17.7)	<0.001
Cumulative to 270 days			
Death	5 (0.9)	3 (0.6)	
Myocardial infarction	15 (2.8)	17 (3.2)	
Q-wave	4 (0.8)	2 (0.4)	
Non-Q-wave	11 (2.1)	15 (2.9)	
Target-lesion revascularization	22 (4.1)	87 (16.6)	<0.001
CABG	3 (0.6)	8 (1.5)	
PTCA	20 (3.8)	83 (15.8)	<0.001
Any major adverse cardiac event	38 (7.1)	99 (18.9)	<0.001
Target-vessel failure	46 (8.6)	110 (21.0)	<0.001
Stent thrombosis	2 (0.4)	4 (0.8)	

* P values are given only for significant differences. The total numbers of patients who underwent target-lesion revascularization may not equal the number who underwent coronary-artery bypass grafting (CABG) plus the number who underwent percutaneous transluminal coronary angioplasty (PTCA), because some patients underwent both procedures; the numbers given for any major adverse cardiac event in the cumulative analysis do not equal the numbers given for in-hospital events plus out-of-hospital events, because some patients had more than one event.

no acute stent thromboses (occurring less than 24 hours after placement of the stent), there was one case of subacute stent thrombosis (occurring between 1 and 30 days after placement) in each group, and there were four late stent thromboses (occurring between 31 and 270 days after placement) — one in the sirolimus-stent group and three in the standard-stent group. The cumulative frequency of stent

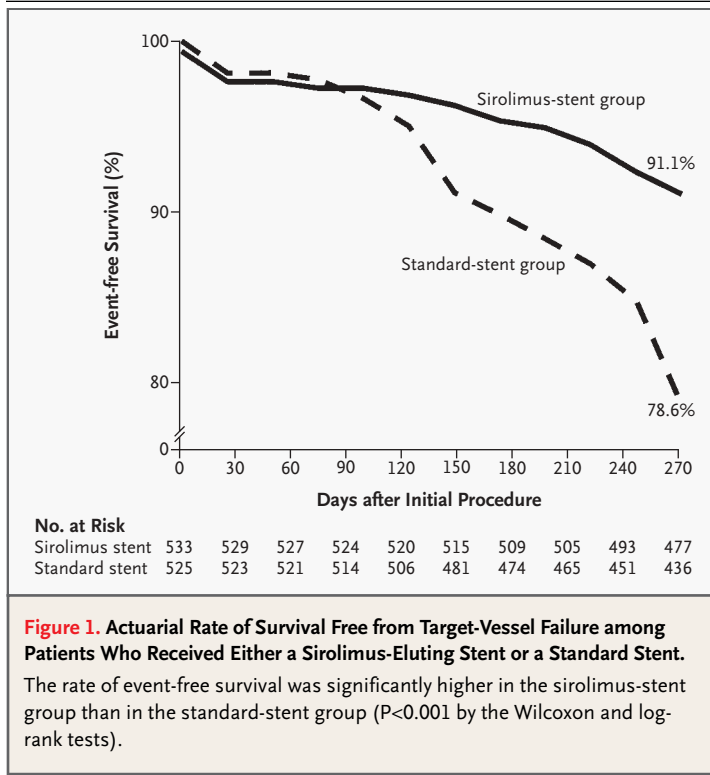


Figure 1. Actuarial Rate of Survival Free from Target-Vessel Failure among Patients Who Received Either a Sirolimus-Eluting Stent or a Standard Stent.
The rate of event-free survival was significantly higher in the sirolimus-stent group than in the standard-stent group ($P < 0.001$ by the Wilcoxon and log-rank tests).

thrombosis was 0.4 percent in the sirolimus-stent group and 0.8 percent in the standard-stent group.

SUBGROUP ANALYSES, MULTIVARIABLE ANALYSES, AND ASSESSMENTS OF TREATMENT EFFECTS

Among the 279 patients with diabetes (26 percent of the total study population; 131 patients in the sirolimus-stent group and 148 in the standard-stent group), the absolute frequency of in-segment restenosis and the absolute frequency of target-lesion revascularization were higher than those among patients without diabetes in both treatment groups, but the relative reductions after the placement of a sirolimus stent were of similar magnitude (the rate of in-segment restenosis was reduced from 50.5 percent to 17.6 percent, $P < 0.001$; and the rate of target-lesion revascularization was reduced from 22.3 percent to 6.9 percent, $P < 0.001$).

Among the third of the patient population with the smallest vessels (averaging 2.32 mm in diameter in the sirolimus-stent group and 2.29 mm in the standard-stent group), there was less (albeit still significant) improvement with sirolimus stents in both the rate of in-segment restenosis (18.4 percent, vs.

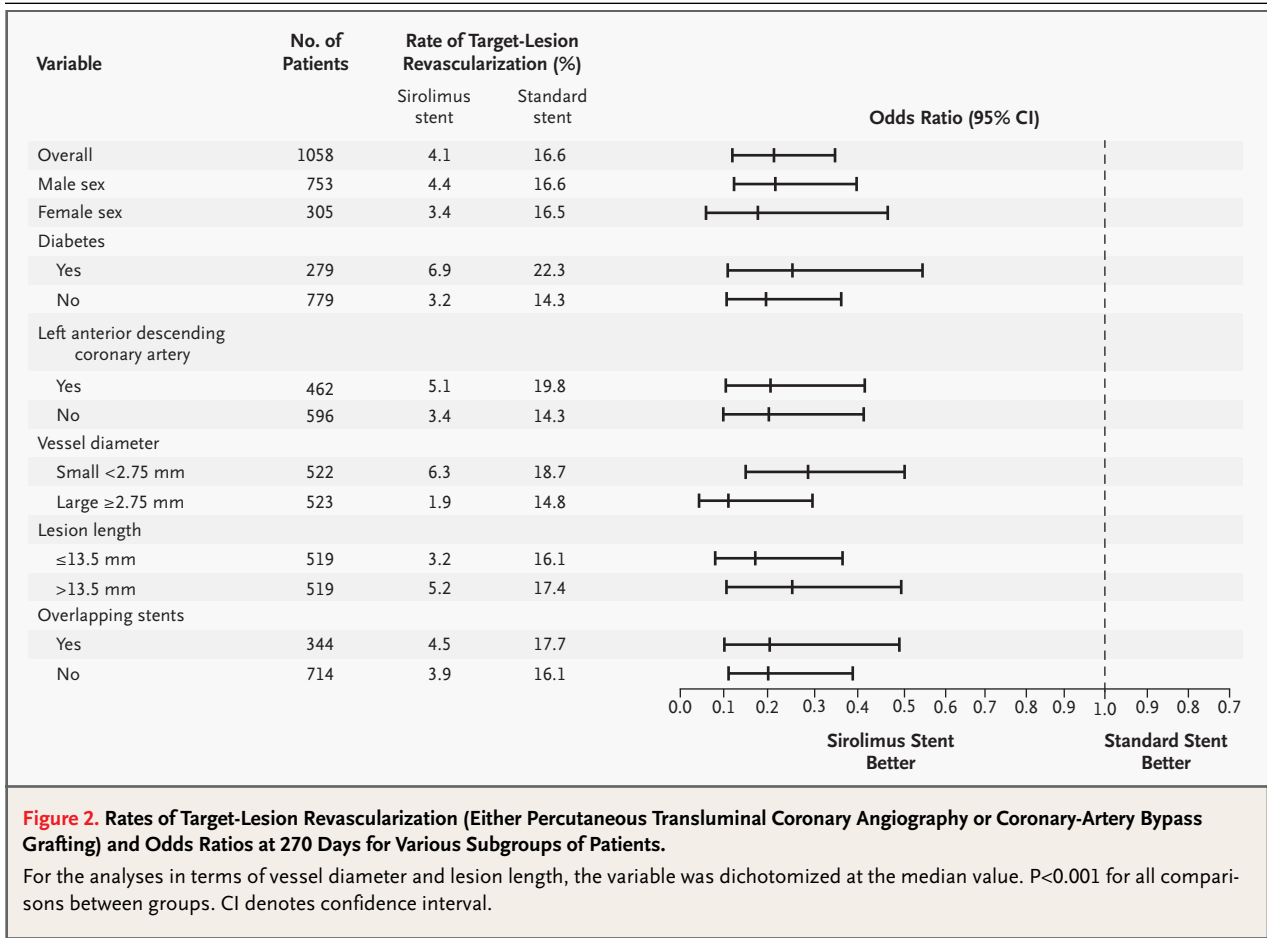
42.9 percent in the standard-stent group; $P < 0.001$) and the rate of target-lesion revascularization (7.3 percent vs. 20.6 percent, $P < 0.001$). Among the patients with the smallest vessels who received sirolimus stents, the restenosis was usually located at the proximal margin of the stent.

In addition to reducing the overall frequency of angiographic restenosis, the use of sirolimus stents altered the patterns of post-stenting restenosis. The mean length of a restenotic lesion was 9.1 ± 5.8 mm after the placement of a sirolimus stent, as compared with 14.8 ± 7.4 mm after the placement of a standard stent ($P < 0.001$), with a diffuse pattern (a lesion length of more than 10 mm) in 58 percent of cases after the placement of a standard stent, as compared with only 13 percent of cases after the placement of a sirolimus stent ($P < 0.001$).

The association of known risk factors for restenosis with the treatment effect of the sirolimus stent on either angiographic or clinical restenosis was evaluated with the use of multivariable logistic-regression modeling of the rate of in-segment restenosis within 240 days and the rate of target-lesion revascularization within 270 days. In the model of in-segment restenosis, diabetes was significantly associated with an increased risk of restenosis (odds ratio, 2.39; $P < 0.001$), as were the diameter of the reference vessel (odds ratio per 1-mm decrement, 0.54; $P = 0.001$) and the length of the lesion (odds ratio per 1-mm increment, 1.02; $P = 0.01$).

Similarly, in the model of target-lesion revascularization, diabetes was significantly associated with an increased risk of restenosis (odds ratio, 1.65; $P = 0.03$), as were the diameter of the reference vessel (odds ratio per 1-mm decrement, 0.37; $P < 0.001$) and the length of the lesion (odds ratio per 1-mm increment, 1.05; $P < 0.001$). According to both of these models, assignment to the sirolimus-stent group was associated with a significant reduction in the risk of restenosis (odds ratio for in-segment restenosis, 0.24; odds ratio for target-lesion revascularization, 0.17; $P < 0.001$ for both comparisons).

Figure 2 shows the consistent beneficial effect of sirolimus-eluting stents on the risk of target-lesion revascularization in important clinical and angiographic subgroups, including those defined according to sex, the presence or absence of diabetes, whether or not the lesion was located in the left anterior descending artery, the size of the vessel, the length of the lesion, and the presence or absence of overlapping stents.



DISCUSSION

In comparison with previous studies of sirolimus-eluting stents,²³⁻²⁵ our trial enrolled patients with more challenging conditions, including a higher frequency of cardiac risk factors (especially diabetes), more complex lesion morphology, and longer lesions. Nevertheless, the suppression of in-stent neointimal hyperplasia was again demonstrated after the placement of sirolimus-eluting stents, both on angiography (an 83 percent reduction in late luminal loss and a 91 percent reduction in the rate of in-stent restenosis) and on intravascular ultrasonography (a 92 percent reduction in neointimal volume). Moreover, the clinical manifestations of excessive neointimal hyperplasia were similarly improved, with a 77 percent reduction in the rate of out-of-hospital target-lesion revascularization and an 85 percent reduction in the rate of out-of-hospital

non-Q-wave myocardial infarction. There were no untoward angiographic complications (e.g., late aneurysms), and the rates of adverse clinical events (including stent thromboses) were not significantly higher in the sirolimus-stent group than in the standard-stent group.

The subgroup analyses indicated that after the placement of a sirolimus stent, the exposed margins of stents that did not cover the entire region of balloon injury were the primary sites of restenosis, which occurred predominantly at the proximal stent margin in smaller vessels. Thus, we would recommend the use of a technique including predilation with shorter balloons, the use of longer single stents in order to cover the entire zone of balloon injury, and dilation after stenting (as needed) with short, high-pressure balloons within the stented regions.

In addition to the reduction in the frequency of restenosis, the pattern of post-stenting restenosis

differed with sirolimus-eluting stents: whereas restenotic lesions in standard stents were diffuse, those in sirolimus-eluting stents were focal.²⁶ Such focal post-stenting lesions may typically be treated successfully with the use of simple balloon angioplasty,^{27,28} minimizing the need for subsequent vascular brachytherapy.^{29,30} Both patients with diabetes and those with lesions in smaller vessels have higher absolute rates of restenosis, although the relative reduction in the rate of restenosis is preserved. Most important, the sirolimus-eluting stent was found to have a consistent treatment effect in analyses of a broad range of subgroups of patients and lesions.

To determine the ultimate clinical usefulness of sirolimus-eluting stents, additional clinical trials are required that involve patients with disease in a bifurcation, chronic total occlusions, saphenous-vein graft disease, restenosis after stenting, failure of vascular brachytherapy, lesions in the left main coronary artery, and multivessel disease. The findings in two-year follow-up examinations in a cohort of 45 patients who were treated with sirolimus-eluting stents are encouraging, indicating that the angiographic and clinical efficacy are maintained.³¹ However, the long-term safety and durability of this very potent site-specific therapy require further substantiation in larger cohorts of patients.

A clinically efficacious drug-eluting stent system requires a meticulous integration of the stent design, drug-carrier vehicle, and therapeutic agent. Preliminary stent-based results with paclitaxel, a well-described chemotherapeutic agent that suppresses microtubule dynamics,³²⁻³⁴ delivered through a polymer-matrix formulation, have also shown promise.³⁵ The results of our clinical trial demonstrate that the sirolimus-eluting stent has achieved the delicate balance of preserved safety and improved efficacy and thus has the potential to alter the course of coronary therapy in the future.

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APPENDIX

The following investigators and institutions participated in the multicenter, randomized, double-blind study of the sirolimus-eluting balloon-expandable stent in the treatment of patients with de novo native coronary-artery lesions (the SIRIUS trial): Sponsor — Cordis, Warren, N.J.; D. Donohoe (medical director), J. Jaeger (program director), E. Keim, L. Lonzetta, L. Reynolds, J. Batiller, C. Hill; Data and Safety Monitoring Board — B. Gersch (chair), Rochester, Minn.; M. Farkouh, New York; R. Bonow, Chicago; R. D'Agostino (biostatistician), Boston; G. Mintz, Washington, D.C.; A. Schwartz, New York; Data Management — Harvard Clinical Research Institute, Boston; Coordination — E. Catapane; Clinical Events Committee — D. Cohen (chair), L. Epstein, J. Kannam, W. Manning, J. Markis; Electrocardiography Core Laboratory — P. Zimetbaum, M. Josephson; Core Angiographic Laboratory — Brigham and Women's Hospital, Boston, J. Popma (director); Core Intravascular Ultrasound Laboratory — Stanford University Medical Center, Stanford, Calif., P. Fitzgerald (director); Clinical Sites — J. Carrozza, P. Rooney, Beth Israel Deaconess Medical Center, Boston; S. Ellis, A. Robakowski, Cleveland Clinic Foundation, Cleveland; J. Douglas, P. Hyde, Emory University Hospital, Atlanta; J. Moses, M. Leon, V. Laroche, Lenox Hill Hospital, New York; P. Teirstein, E. Anderson, Scripps Clinic, La Jolla, Calif.; E. Perin, M. Harlan, Texas Heart Institute, Houston; R. Wilensky, M. Walsh, Hospital of the University of Pennsylvania, Philadelphia; L. Satler, J. Lavoie, Washington Hospital Center, Washington, D.C.; M. Cleman, C. Roberts, Yale University Hospital, New Haven, Conn.; S. DeMaio, L. Rogers, Baylor Medical Center, Dallas; E. Fry, A. Taylor, M. Potrikus, Saint Vincent's Hospital, Indianapolis; A. Yeung, C. McWard, Stanford University Medical Center, Stanford, Calif.; J. Zidar, S. Dickerson, Duke University Medical Center, Durham, N.C.; W. O'Neill, K. Dimick, William Beaumont Hospital, Royal Oak, Mich.; G. Mishkel, J. Daniels, P. Sullivan, Saint John's Hospital, Springfield, Ill.; D. McCormick, L. Mark, B. Connor, Hahnemann Hospital, Philadelphia; D. Roberts, B. Seiler, Sutter Memorial General Hospital, Sacramento, Calif.; D. Holmes, D. Shelstad, Saint Mary's Hospital, Rochester, Minn.; F. Kiernan, D. Murphy, Hartford Hospital, Hartford, Conn.; M. Midei, E. Yaker, Saint Joseph's Hospital, Baltimore; D. Williams, J. Muratori, T. Chaffee, Rhode Island Hospital, Providence; T. Fischell, S. Baskerville, Borgess Medical Center, Kalamazoo, Mich.; S. Oesterle, I. Palacios, C. Cothran, Massachusetts General Hospital, Boston; S. Yakubov, C. Gilliland, P. Vieira, Riverside Methodist Hospital, Columbus, Ohio; D. Kereiakes, R. Lengerich, Christ Hospital—Lindner Center, Cincinnati; C. Davidson, L. Eckman, Northwestern Memorial Hospital, Chicago; C. Brown, K. Reid, Piedmont Hospital, Atlanta; C. Lambert, T. Watts, N. Parker, Health First Institute, Melbourne, Fla.; D. Baim, R. Monboquette, Brigham and Women's Hospital, Boston; A. Raizner, R. Benfield, Methodist Hospital, Houston; B. Cohen, R. Lao, Morristown Memorial Hospital, Morristown, N.J.; N. Laufer, M. Balfour, Good Samaritan Regional Medical Center, Phoenix, Ariz.; S. Raible, B.J. Henahan, Jewish Hospital Heart and Lung Institute, Louisville, Ky.; P. Coleman, A. Nofi, Northern California Medical Association, Santa Rosa; S. Sorenson, K. Robinson, Latter Day Saints Hospital, Salt Lake City; M. Mooney, P. Demmer, Abbott Northwestern Hospital, Minneapolis; T. Feldman, J. Lopez, L. Lofitis, University of Chicago Hospitals, Chicago; J. Lasala, K. Zuchowski, S. Aubuchon, Barnes Jewish Hospital, St. Louis; R. Caputo, C. Lastinger, Saint Joseph's Hospital, Syracuse, N.Y.; C. O'Shaughnessy, T. Julio, L. St. Marie, L. Barr, North Ohio Heart Center, Elyria; H. Madyoon, T. Weaver, Saint Joseph's Medical Center, Stockton, Calif.; J. Midwall, L. Herlan, JFK Memorial Hospital, Atlantis, Fla.; M. Bates, L. Lukhart, Charleston Area Medical Center, Charleston, W.Va.; M. Clark, L. Pennington, Integrus Oklahoma Heart Institute, Okla-

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REFERENCES

1. Sigwart U, Puel J, Mirkovitch V, Joffre F, Kappenberger L. Intravascular stents to prevent occlusion and restenosis after transluminal angioplasty. *N Engl J Med* 1987;316:701-6.
2. Roubin GS, Cannon AD, Agrawal SK, et al. Intracoronary stenting for acute and threatened closure complicating percutaneous transluminal coronary angioplasty. *Circulation* 1992;85:916-27.
3. 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.
4. 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.
5. Versaci F, Gasparone A, Tomai F, Crea F, Chiariello L, Gioffrè PA. A comparison of coronary-artery stenting with angioplasty for isolated stenosis of the proximal left anterior descending coronary artery. *N Engl J Med* 1997;336:817-22.
6. Rankin JM, Spinelli JJ, Carere RG, et al. Improved clinical outcome after widespread use of coronary-artery stenting in Canada. *N Engl J Med* 1999;341:1957-65.
7. Kimura T, Yokoi H, Nakagawa Y, et al. Three-year follow-up after implantation of metallic coronary-artery stents. *N Engl J Med* 1996;334:561-6.
8. Elezi S, Kastrati A, Neumann FJ, Hadamitzky M, Dirschinger J, Schomig A. Vessel size and long-term outcome after coronary stent placement. *Circulation* 1998;98:1875-80.
9. Dussaillant GR, Mintz GS, Pichard AD, et al. Small stent size and intimal hyperplasia contribute to restenosis: a volumetric intravascular ultrasound analysis. *J Am Coll Cardiol* 1995;26:720-4.
10. Akiyama T, Moussa I, Reimers B, et al. Angiographic and clinical outcome following coronary stenting of small vessels: a comparison with coronary stenting of large vessels. *J Am Coll Cardiol* 1998;32:1610-8.
11. Kastrati A, Elezi S, Dirschinger J, Hadamitzky M, Neumann FJ, Schomig A. Influence of lesion length on restenosis after coronary stent placement. *Am J Cardiol* 1999;83:1617-22.
12. 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.
13. Kobayashi Y, De Gregorio J, Kobayashi N, et al. Stented segment length as an independent predictor of restenosis. *J Am Coll Cardiol* 1999;34:651-9.
14. Elezi S, Kastrati A, Pache J, et al. Diabetes mellitus and the clinical and angiographic outcome after coronary stent placement. *J Am Coll Cardiol* 1998;32:1866-73.
15. Abizaid A, Kornowski R, Mintz GS, et al. The influence of diabetes mellitus on acute and late clinical outcomes following coronary stent implantation. *J Am Coll Cardiol* 1998;32:584-9.
16. de Feyter PJ, Vos J, Rensing BJ. Anti-restenosis trials. *Curr Interv Cardiol Rep* 2000;2:326-31.
17. Holmes DR Jr, Savage M, LaBlanche JM, et al. Results of Prevention of REStenosis with Tranilast and its Outcomes (PRESTO) trial. *Circulation* 2002;106:1243-50.
18. Wilensky RI, Tanguay JF, Ito S, et al. Heparin infusion prior to stenting (HIPS) trial: final results of a prospective, randomized, controlled trial evaluating the effects of local vascular delivery on intimal hyperplasia. *Am Heart J* 2000;139:1061-70.
19. Kutryk MJ, Foley DP, van den Brand M, et al. Local intracoronary administration of antisense oligonucleotide against c-myc for the prevention of in-stent restenosis: results of the randomized investigation by the Thoraxcenter of antisense DNA using local delivery and IVUS after coronary stenting (ITALICS) trial. *J Am Coll Cardiol* 2002;39:281-7.
20. Gallo R, Padurean A, Jayaraman T, et al. Inhibition of intimal thickening after balloon angioplasty in porcine coronary arteries by targeting regulators of the cell cycle. *Circulation* 1999;99:2164-70.
21. Marx SO, Marks AR. Bench to bedside: the development of rapamycin and its application to stent restenosis. *Circulation* 2001;104:852-5.
22. Suzuki T, Kopia G, Hayashi S, et al. Stent-based delivery of sirolimus reduces neointimal formation in a porcine coronary model. *Circulation* 2001;104:1188-93.
23. Sousa JE, Costa MA, Abizaid A, et al. Lack of neointimal proliferation after implantation of sirolimus-coated stents in human coronary arteries: a quantitative coronary angiography and three-dimensional intravascular ultrasound study. *Circulation* 2001;103:192-5.
24. Rensing BJ, Vos J, Smits PC, et al. Coronary restenosis elimination with a sirolimus eluting stent: first European human experience with 6-month angiographic and intravascular ultrasonic follow-up. *Eur Heart J* 2001;22:2125-30.
25. 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.
26. 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.
27. Baim DS, Levine MJ, Leon MB, Levine S, Ellis SG, Schatz RA. Management of restenosis within the Palmaz-Schatz coronary stent (the U.S. multicenter experience). *Am J Cardiol* 1993;71:364-6.
28. Mehran R, Mintz GS, Popma JJ, et al. Mechanisms and results of balloon angioplasty for the treatment of in-stent restenosis. *Am J Cardiol* 1996;78:618-22.
29. Leon MB, Teirstein PS, Moses JW, et al. Localized intracoronary gamma-radiation therapy to inhibit the recurrence of restenosis after stenting. *N Engl J Med* 2001;344:250-6.
30. Waksman R, White RL, Chan RC, et al. Intracoronary gamma-radiation therapy after angioplasty inhibits recurrence in patients with in-stent restenosis. *Circulation* 2000;101:2165-71.
31. Sousa JE, Costa MA, Abizaid AC, et al. Sustained suppression of neo-intimal proliferation by sirolimus-eluting stents: one-year angiographic and intravascular ultrasound follow-up. *Circulation* 2001;104:2007-11.
32. 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.
33. Drachman DE, Edelman ER, Seifert P, et al. Neointimal thickening after stent delivery of paclitaxel: change in composition and arrest of growth over six months. *J Am Coll Cardiol* 2000;36:2325-32.
34. Heldman AW, Cheng L, Jenkins GM, et al. Paclitaxel stent coating inhibits neointimal hyperplasia at 4 weeks in a porcine model of restenosis. *Circulation* 2001;103:2289-95.
35. Park S-J, Shim WH, Ho DS, et al. A paclitaxel-eluting stent for the prevention of coronary restenosis. *N Engl J Med* 2003;348:1537-45.

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