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## Sirolimus-Eluting and Paclitaxel-Eluting Stents for Coronary Revascularization

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### ABSTRACT

#### BACKGROUND

Sirolimus-eluting stents and paclitaxel-eluting stents, as compared with bare-metal stents, reduce the risk of restenosis. It is unclear whether there are differences in safety and efficacy between the two types of drug-eluting stents.

#### METHODS

We conducted a randomized, controlled, single-blind trial comparing sirolimus-eluting stents with paclitaxel-eluting stents in 1012 patients undergoing percutaneous coronary intervention. The primary end point was a composite of major adverse cardiac events (death from cardiac causes, myocardial infarction, and ischemia-driven revascularization of the target lesion) by nine months. Follow-up angiography was completed in 540 of 1012 patients (53.4 percent).

#### RESULTS

The two groups had similar baseline clinical and angiographic characteristics. The rate of major adverse cardiac events at nine months was 6.2 percent in the sirolimus-stent group and 10.8 percent in the paclitaxel-stent group (hazard ratio, 0.56; 95 percent confidence interval, 0.36 to 0.86;  $P=0.009$ ). The difference was driven by a lower rate of target-lesion revascularization in the sirolimus-stent group than in the paclitaxel-stent group (4.8 percent vs. 8.3 percent; hazard ratio, 0.56; 95 percent confidence interval, 0.34 to 0.93;  $P=0.03$ ). Rates of death from cardiac causes were 0.6 percent in the sirolimus-stent group and 1.6 percent in the paclitaxel-stent group ( $P=0.15$ ); the rates of myocardial infarction were 2.8 percent and 3.5 percent, respectively ( $P=0.49$ ); and the rates of angiographic restenosis were 6.6 percent and 11.7 percent, respectively ( $P=0.02$ ).

#### CONCLUSIONS

As compared with paclitaxel-eluting stents, the use of sirolimus-eluting stents results in fewer major adverse cardiac events, primarily by decreasing the rates of clinical and angiographic restenosis.

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**T**HE USE OF DRUG-ELUTING STENTS that deliver site-specific, controlled release of therapeutic agents<sup>1-10</sup> has significantly reduced the problem of restenosis inherent to bare-metal stents.<sup>11-16</sup> As compared with a bare-metal stent, a polymer-encapsulated stent releasing sirolimus reduced the rate of angiographic and clinical restenosis in several randomized trials.<sup>1,2,5,7,9</sup> Similarly, a polymer-based, paclitaxel-eluting stent consistently reduced the rate of restenosis and the need for repeated revascularization procedures, as compared with a bare-metal stent.<sup>3,4,10</sup> A recent meta-analysis of trials of drug-eluting stents confirmed that sirolimus-eluting stents and paclitaxel-eluting stents reduced the rate of restenosis.<sup>17</sup> The rates of death and myocardial infarction were similar to those with bare-metal stents, attesting to the safety of these devices.

Although the therapeutic benefit of sirolimus stents and paclitaxel stents over bare-metal stents is well established, there may be differences between the two devices.<sup>18</sup> We therefore conducted a randomized, controlled, partially blinded trial comparing the safety and efficacy of the sirolimus and paclitaxel stents in patients undergoing percutaneous coronary intervention.

## METHODS

### STUDY POPULATION

Patients with either stable angina or an acute coronary syndrome were eligible to participate if they had at least one lesion with stenosis of at least 50 percent in a vessel with a reference diameter between 2.25 and 4.00 mm that was suitable for stent implantation. The time from the onset of symptoms to treatment was less than 24 hours in patients classified as having a myocardial infarction characterized by ST-segment elevation. There were no limitations on the number of lesions or vessels or on the length of the lesions. Exclusion criteria were allergy to antiplatelet drugs, heparin, stainless steel, contrast agents, sirolimus, or paclitaxel; participation in another coronary-device study; and terminal illness.

The study complied with the Declaration of Helsinki regarding investigation in humans and was approved by the institutional ethics committees at the University Hospital Bern and the University Hospital Zurich, both in Switzerland. All patients provided written informed consent. There was no

industry involvement in the design, conduct, financial support, or analysis of the study.

### RANDOMIZATION, STENT IMPLANTATION, AND ADJUNCT DRUG THERAPY

Randomization was performed after the diagnostic angiography and before percutaneous coronary intervention. Sealed, opaque, sequentially numbered allocation envelopes were used. The allocation schedule was based on computer-generated random numbers, stratified according to trial center and blocked, with block sizes of 6 and 10 varying randomly. Patients were assigned on a 1:1 basis to treatment with a polymer-based, sirolimus-eluting stent (Cypher; Cordis, Johnson & Johnson) or a polymer-based, slow-release, paclitaxel-eluting stent (Taxus, Boston Scientific). Sirolimus-eluting stents were available in diameters of 2.25 to 3.50 mm and in lengths of 8 to 33 mm. Paclitaxel-eluting stents were available in diameters of 2.25 to 3.50 mm and in lengths of 8 to 32 mm.

Percutaneous coronary intervention was performed according to standard techniques. No mixture of drug-eluting stents was permitted except in the case of an inability to insert the assigned study stent, when crossover to another stent was allowed.

Before or at the time of the procedure, patients received at least 100 mg of aspirin, a 300-mg loading dose of clopidogrel, and unfractionated heparin (70 to 100 U per kilogram of body weight). Glycoprotein IIb/IIIa antagonists were used at the operator's discretion. A 12-lead electrocardiogram was obtained after the procedure and before discharge. Levels of creatine kinase, its MB isoenzyme, and troponin I were assessed 8 to 16 hours and again 18 to 24 hours after the procedure. At the time of discharge, all patients were receiving 100 mg of aspirin once daily for an indefinite period, as well as 75 mg of clopidogrel daily for 12 months.

### STUDY END POINTS AND DEFINITIONS

Adverse events were assessed in the hospital and at one, six, and nine months. An independent clinical-events committee whose members were unaware of the patients' treatment assignments adjudicated all clinical end points. An independent data and safety monitoring board reviewed the data periodically to identify safety issues, but there were no formal stopping rules. All patients were asked to return for an angiographic follow-up study at eight months.

The prespecified primary end point was a composite of major adverse cardiac events (death from cardiac causes, myocardial infarction, and ischemia-driven revascularization of the target lesion) by nine months. Secondary end points included ischemia-driven revascularization of the target lesion, target-vessel revascularization, and target-vessel failure (defined as a composite of death from cardiac causes, myocardial infarction, and ischemia-driven target-vessel revascularization).

The diagnosis of myocardial infarction was based on the presence of new Q waves in at least two contiguous leads and an elevated creatine kinase MB fraction. In the absence of pathologic Q waves, the diagnosis of myocardial infarction was based on an increase in the creatine kinase level to more than twice the upper limit of the normal range with an elevated level of creatine kinase MB or troponin I.

Target-lesion revascularization was defined as revascularization for a stenosis within the stent or within the 5-mm borders adjacent to the stent. Revascularization of the target lesion and vessel was considered to be driven by ischemia if the stenosis of any target lesion or vessel was at least 50 percent of the diameter of the vessel on the basis of quantitative coronary angiography in the presence of ischemic signs or symptoms or if the stenosis was at least 70 percent of the diameter of the vessel even in the absence of ischemic signs or symptoms. We specified post hoc an alternative definition of the primary end point: a composite of death from cardiac causes, myocardial infarction, and clinically driven revascularization of the target lesion with stenoses of at least 50 percent in the presence of ischemic signs or symptoms; revascularization events were disregarded if ischemic signs or symptoms were absent.

The principal secondary end point of the angiographic substudy was late luminal loss within the stent as well as within the 5-mm margins proximal and distal to the stent ("in segment"). Other angiographic end points were late luminal loss within the stent ("in stent"), in-stent and in-segment stenosis, and in-stent and in-segment binary restenosis (described below).

Successful stenting was defined as a final stenosis of less than 50 percent of the vessel diameter after implantation of the study stent, and treatment success was defined as a final stenosis of less than 50 percent of the vessel diameter with the use of any percutaneous intervention. Stent thrombosis

was diagnosed as an acute coronary syndrome with angiographic documentation of either occlusion of the target lesion or thrombus within the previously stented segment.

#### QUANTITATIVE CORONARY ANGIOGRAPHY

Coronary angiograms were digitally recorded at baseline, immediately after the procedure, and at follow-up and were assessed at the angiographic core laboratory of the University Hospital Bern. Angiogram readers were unaware of the type of stent implanted. The projection that best showed the stenosis was used for all analyses. Patients received nitroglycerin before angiography, and measurements were performed on cineangiograms. The contrast-filled, nontapered tip of the catheter was used for calibration. Digital angiograms were analyzed with the use of an automated edge-detection system (CAAS II, Pie Medical Imaging). The intraobserver and interobserver reliabilities of the quantitative measurements have been reported previously.<sup>19</sup>

Quantitative measurements included the diameter of the reference vessel, the minimal luminal diameter, the extent of stenosis (defined as the diameter of the reference vessel minus the minimal luminal diameter, divided by the reference diameter and multiplied by 100), and late luminal loss (the difference between the minimal luminal diameter after the procedure and the minimal luminal diameter at follow-up). Binary restenosis was defined as stenosis of at least 50 percent of the minimal luminal diameter in the target lesion at angiographic follow-up. All angiographic measurements of the target lesion were obtained in the stented area and within the margins 5 mm proximal and distal to each stent edge.

#### STATISTICAL ANALYSIS

On the basis of results from RAVEL (the Randomized Study with the Sirolimus-Coated Bx Velocity Balloon-Expandable Stent in the Treatment of Patients with de Novo Native Coronary Artery Lesions)<sup>1</sup> and the TAXUS II trial,<sup>4</sup> we assumed an incidence of major adverse cardiac events of 6 percent in the sirolimus-stent group and of 12 percent in the paclitaxel-stent group. Enrollment of 1010 patients would provide the study with a statistical power of 90 percent to detect this difference with a two-sided significance level of 0.05. All enrolled patients were included in the analysis of primary

**Table 1. Baseline Clinical Characteristics.\***

Characteristic	Sirolimus Stent (503 Patients)	Paclitaxel Stent (509 Patients)
Age — yr	62±11	62±12
Male sex — no. (%)	382 (75.9)	399 (78.4)
Diabetes mellitus — no. (%)	108 (21.5)	93 (18.3)
Hypertension — no. (%)	302 (60.0)	317 (62.3)
Hyperlipidemia — no. (%)	305 (60.6)	290 (57.0)
Current smoking — no. (%)	184 (36.6)	181 (35.6)
Previous myocardial infarction — no. (%)	145 (28.8)	151 (29.7)
Stable angina pectoris — no. (%)	246 (48.9)	246 (48.3)
Acute coronary syndromes — no. (%)	257 (51.1)	263 (51.7)
Unstable angina — no. (%)	28 (5.6)	30 (5.9)
Non-ST-segment elevation MI — no. (%)	112 (22.3)	123 (24.2)
ST-segment elevation MI — no. (%)	117 (23.3)	110 (21.6)
Time from onset of symptoms of MI to percutaneous coronary intervention — no. (%)†		
<24 hr	192 (38.2)	180 (35.4)
24–72 hr	29 (5.8)	39 (7.7)
>72 hr	8 (1.6)	14 (2.8)
Glycoprotein IIb/IIIa antagonists — no. (%)	171 (34.0)	147 (28.9)
Distal-embolization-protection devices — no. (%)	33 (6.6)	31 (6.1)
Multivessel disease — no. (%)	300 (59.6)	301 (59.1)
Left ventricular ejection fraction	0.57±0.12	0.57±0.12

\* Plus-minus values are means ±SD. There were no significant differences between groups. MI denotes myocardial infarction.

† Percentages refer to all patients and not only to patients with myocardial infarction.

and secondary clinical outcomes according to the intention-to-treat principle. We used a Cox proportional-hazards model to compare clinical outcomes between the groups. We assessed the assumptions of the Cox model statistically on the basis of Schoenfeld residuals and graphically using log-log plots and found them to be approximately satisfied for all variables. We prespecified stratified analyses of the primary outcome at nine months according to the presence or absence of two characteristics: diabetes and an acute coronary syndrome.

Analyses of outcomes of the angiographic substudy were not based on the intention-to-treat principle but were restricted to patients who returned for follow-up angiography. A patient could have had more than one lesion in which a stent was implanted. Therefore, in the analysis of the quantita-

tive angiographic data, we used maximum-likelihood logistic and linear-regression models based on robust standard errors that allowed the correlation of multiple lesions within a patient to compare the characteristics of lesions between groups at baseline and follow-up.

Trial data were held by the trial-coordination center at the University Hospital Bern. Analyses were performed with the use of Stata software by an analyst who was unaware of the type of stent implanted. No adjustments were made for multiple comparisons in secondary analyses. All P values are two-sided. As principal investigator, Dr. Windecker had full access to the data and vouches for the data and the analysis.

## RESULTS

Between April 2003 and May 2004, 1012 patients (1401 lesions) were enrolled; 503 patients (693 lesions) were randomly assigned to receive a sirolimus-eluting stent, and 509 patients (708 lesions) to receive a paclitaxel-eluting stent. A total of 98.4 percent of lesions were located in a native coronary artery. The groups had similar baseline clinical and angiographic characteristics (Tables 1 and 2). Procedural characteristics, including the number of lesions per patient, the number of stents per lesion, the length and diameter of the stents, and the rate of direct stenting, were also similar in the two groups (Table 2). The rates of stenting success and treatment success were similar for the two types of stents.

## CLINICAL OUTCOME

Major adverse cardiac events during follow-up are listed in Table 3. At one month, there was no trend favoring either group for any of the clinical end points.

The primary end point (death from cardiac causes, myocardial infarction, or ischemia-driven target-lesion revascularization at nine months) occurred in 6.2 percent of patients receiving sirolimus stents and 10.8 percent of patients receiving paclitaxel stents (hazard ratio, 0.56; 95 percent confidence interval, 0.36 to 0.86;  $P=0.009$ ) (Fig. 1 and Table 3). This difference was driven by a 44 percent reduction in the relative risk of target-lesion revascularization in favor of the sirolimus stent (4.8 percent vs. 8.3 percent; hazard ratio, 0.56; 95 percent confidence interval, 0.34 to 0.93;  $P=0.03$ ). Analysis of the alternative definition of the primary end point,

**Table 2. Baseline Characteristics of Lesions and Procedural Results.\***

Characteristic	Sirolimus Stent (693 Lesions)	Paclitaxel Stent (708 Lesions)
Target-lesion coronary artery — no. (%)		
Left main	13 (1.9)	10 (1.4)
Left anterior descending	326 (47.0)	325 (45.9)
Left circumflex	135 (19.5)	133 (18.8)
Right	208 (30.0)	228 (32.2)
Bypass graft	11 (1.6)	12 (1.7)
ACC–AHA lesion class — no. (%)		
A	131 (18.9)	153 (21.6)
B1	300 (43.3)	307 (43.4)
B2	173 (25.0)	155 (21.9)
C	89 (12.8)	93 (13.1)
Approximate duration of total occlusion — no. (%)		
<3 mo	129 (18.6)	108 (15.3)
≥3 mo	8 (1.2)	17 (2.4)
Thrombus present — no. (%)	163 (23.5)	155 (21.9)
Bifurcated lesion — no. (%)†	61 (8.8)	56 (7.9)
Ostial lesion — no. (%)	48 (6.9)	58 (8.2)
Calcification — no. (%)		
None or mild	439 (63.3)	480 (67.8)
Moderate	232 (33.5)	200 (28.2)
Severe	22 (3.2)	28 (4.0)
Before procedure		
Lesion length — mm	11.8±6.8	12.4±7.2
Diameter of reference vessel — mm	2.82±0.40	2.82±0.43
Minimal luminal diameter — mm	0.52±0.45	0.53±0.43
Stenosis — % of luminal diameter	81.7±15.1	81.5±14.5
During procedure		
No. of lesions treated per patient	1.4±0.6	1.4±0.6
No. of stents per lesion‡	1.1±0.4	1.2±0.5
Maximal stent diameter — mm	2.9±0.4	2.9±0.5
Length of stent per lesion — mm	18.7±10.3	19.0±10.7
Maximal pressure — atm§	14.4±3.2	14.1±2.9
Direct stenting — no. (%)	222 (32.0)	235 (33.2)
Successful implantation — no. (%)	686 (99.0)	698 (98.6)
Treatment success — no. (%)	689 (99.4)	701 (99.0)
Intraprocedural complications — no. (%)	14 (2.0)	14 (2.0)
Immediately after procedure		
Final minimal luminal diameter — mm		
In stent	2.65±0.37	2.68±0.39
In segment	2.56±0.41	2.60±0.44
Final stenosis — % of luminal diameter		
In stent	7.2±4.7	6.8±5.5
In segment	8.8±7.2	8.4±6.6
Acute gain — mm		
In stent	2.13±0.52	2.15±0.51
In segment	2.08±0.53	2.08±0.56

\* Plus–minus values are means ±SD. ACC denotes American College of Cardiology, and AHA American Heart Association.

† Bifurcated lesions required double wiring.

‡ P=0.09 for the comparison between groups.

§ P=0.04 for the comparison between groups.

**Table 3. Clinical Events during Follow-up.**

Event	Sirolimus Stent (503 Patients)	Paclitaxel Stent (509 Patients)	Hazard Ratio (95% CI)*	P Value
	<i>no. of patients (%)</i>			
<b>Events at 1 mo</b>				
Death	0	4 (0.8)	0.11 (0.01–2.08)	0.12
Death from cardiac causes	0	4 (0.8)	0.11 (0.01–2.08)	0.12
Myocardial infarction	12 (2.4)	13 (2.6)	0.93 (0.43–2.04)	0.86
Q-wave	6 (1.2)	4 (0.8)	1.52 (0.43–5.37)	0.52
Non-Q-wave	6 (1.2)	9 (1.8)	0.67 (0.24–1.89)	0.45
Target-lesion revascularization	11 (2.2)	10 (2.0)	1.11 (0.47–2.62)	0.81
Percutaneous	11 (2.2)	9 (1.8)	1.23 (0.51–2.98)	0.64
Surgical	0	2 (0.4)	0.20 (0.01–4.21)	0.50
Target-vessel revascularization	12 (2.4)	10 (2.0)	1.22 (0.53–2.81)	0.65
Percutaneous	12 (2.4)	9 (1.8)	1.35 (0.57–3.20)	0.50
Surgical	0	2 (0.4)	0.20 (0.01–4.21)	0.50
Stent thrombosis	9 (1.8)	7 (1.4)	1.30 (0.48–3.49)	0.60
Major adverse cardiac events	15 (3.0)	19 (3.7)	0.80 (0.41–1.57)	0.51
Target-vessel failure	15 (3.0)	19 (3.7)	0.80 (0.41–1.57)	0.51
<b>Events at 9 mo</b>				
Death	5 (1.0)	11 (2.2)	0.45 (0.16–1.31)	0.14
Death from cardiac causes	3 (0.6)	8 (1.6)	0.38 (0.10–1.42)	0.15
Myocardial infarction	14 (2.8)	18 (3.5)	0.78 (0.39–1.57)	0.49
Q-wave	6 (1.2)	5 (1.0)	1.21 (0.37–4.00)	0.75
Non-Q-wave	8 (1.6)	13 (2.6)	0.62 (0.26–1.50)	0.28
Target-lesion revascularization	24 (4.8)	42 (8.3)	0.56 (0.34–0.93)	0.03
Percutaneous	22 (4.4)	36 (7.1)	0.61 (0.36–1.03)	0.06
Surgical	3 (0.6)	9 (1.8)	0.33 (0.10–1.22)	0.10
Target-vessel revascularization	30 (6.0)	47 (9.2)	0.63 (0.40–1.00)	0.05
Percutaneous	28 (5.6)	41 (8.1)	0.68 (0.42–1.10)	0.11
Surgical	3 (0.6)	9 (1.8)	0.33 (0.10–1.22)	0.10
Stent thrombosis	10 (2.0)	8 (1.6)	1.26 (0.50–3.20)	0.62
Primary end point†	31 (6.2)	55 (10.8)	0.56 (0.36–0.86)	0.009
Alternatively defined primary end point‡	29 (5.8)	49 (9.6)	0.59 (0.37–0.93)	0.02
Target-vessel failure	35 (7.0)	59 (11.6)	0.58 (0.38–0.89)	0.01

\* Hazard ratios and P values are from the Cox proportional-hazards model. CI denotes confidence interval.

† The prespecified primary end point was a composite of major adverse cardiac events (death from cardiac causes, myocardial infarction, and ischemia-driven target-lesion revascularization).

‡ The alternative primary end point, defined post hoc, was a composite of death from cardiac causes, myocardial infarction, and clinically driven target-lesion revascularization.

which included clinically driven rather than ischemia-driven revascularization of the target lesion, yielded similar results (5.8 percent in the sirolimus-stent group, as compared with 9.6 percent in the paclitaxel-stent group; hazard ratio, 0.59; 95 percent confidence interval, 0.37 to 0.93; P=0.02).

In a stratified analysis of the primary end point,

the difference between sirolimus and paclitaxel stents was more pronounced among the 201 patients with diabetes (hazard ratio, 0.31; 95 percent confidence interval, 0.12 to 0.78) than among the 811 patients without diabetes (hazard ratio, 0.66; 95 percent confidence interval, 0.40 to 1.09), but confidence intervals were wide, and the result of

a test of interaction was not significant ( $P$  for interaction=0.13). Conversely, the difference between the sirolimus and paclitaxel stents appeared less pronounced among the 520 patients presenting with an acute coronary syndrome (hazard ratio, 0.84; 95 percent confidence interval, 0.46 to 1.51) than among the 492 patients presenting without an acute coronary syndrome (hazard ratio, 0.34; 95 percent confidence interval, 0.17 to 0.68). Here, the test of interaction reached borderline significance ( $P=0.05$ ).

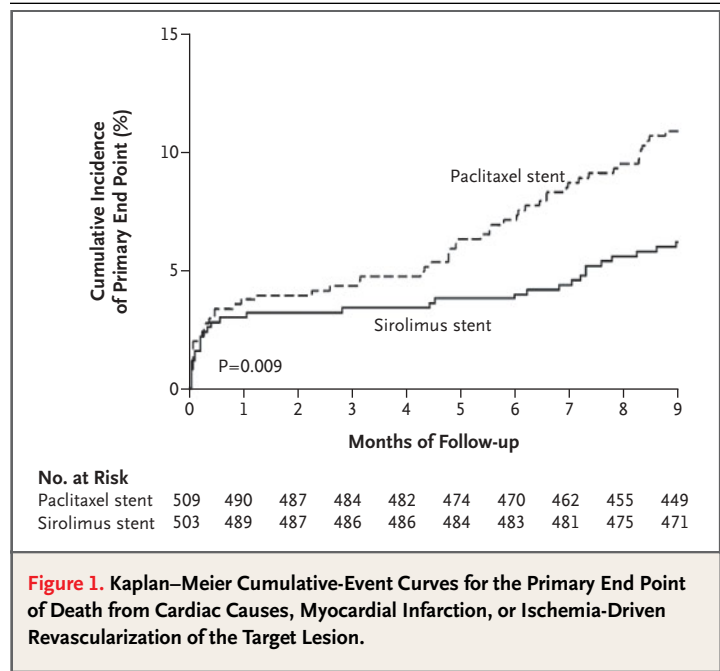
The rates of death and myocardial infarction were low and the estimates of hazard ratios imprecise (Table 3). The cumulative frequency of stent thrombosis was 2.0 percent with the sirolimus stent and 1.6 percent with the paclitaxel stent (hazard ratio, 1.26; 95 percent confidence interval, 0.50 to 3.20;  $P=0.62$ ), and the rates of acute, subacute, and late stent thrombosis were similar in the two groups. The rates of antithrombotic treatment were similar in the two groups during the nine months of the study.

#### ANGIOGRAPHIC RESULTS

Angiographic measurements of lesions before and after stent implantation were similar in the sirolimus-stent and paclitaxel-stent groups (Table 2). Angiographic follow-up at eight months was completed in 540 of 1012 patients (53.4 percent), who had 723 of the 1401 lesions (51.6 percent) (Table 4). A total of 267 patients in the sirolimus-stent group (53.1 percent) and 273 patients in the paclitaxel-stent group (53.6 percent) underwent follow-up angiography ( $P=0.86$ ).

Patients undergoing angiographic follow-up were younger ( $P<0.001$ ), less likely to have diabetes ( $P=0.04$ ) or hypertension ( $P=0.04$ ), and more likely to be male ( $P=0.004$ ) and to have chest pain ( $P=0.01$ ) than those who did not return for angiographic follow-up. Among patients undergoing angiographic follow-up, most baseline clinical characteristics and the frequency of chest pain were similar in the two groups, but hypertension was significantly more frequent in the paclitaxel-stent group ( $P=0.02$ ).

The mean ( $\pm$ SD) in-segment late luminal loss, the prespecified end point of the angiographic substudy, was  $0.19\pm 0.45$  mm in the sirolimus-stent group and  $0.32\pm 0.55$  mm in the paclitaxel-stent group ( $P=0.001$ ). The rate of in-segment binary restenosis was 6.6 percent in the sirolimus-stent group and 11.7 percent in the paclitaxel-stent group



**Figure 1.** Kaplan–Meier Cumulative-Event Curves for the Primary End Point of Death from Cardiac Causes, Myocardial Infarction, or Ischemia-Driven Revascularization of the Target Lesion.

( $P=0.02$ ). The cumulative frequencies of in-segment stenosis before and after the procedure and at follow-up angiography in the two groups are shown in Figure 2.

#### DISCUSSION

In this randomized, controlled, single-blind trial, the use of sirolimus-eluting stents was associated with a 44 percent decrease in the risk of major adverse cardiac events at nine months, as compared with the use of paclitaxel-eluting stents. The therapeutic benefit of the sirolimus stent was primarily driven by a 44 percent reduction in the need for repeated revascularization of the treated lesion.

The rates of clinical and angiographic restenosis were low for both drug-eluting stents, substantiating the results of previous studies.<sup>1-5,7,9,10</sup> A previous small, randomized trial involving 202 patients found a trend toward a higher rate of major adverse cardiac events at six months with the sirolimus stent than with the paclitaxel stent (6 percent vs. 4 percent; relative risk, 1.5; 95 percent confidence interval, 0.44 to 5.16).<sup>20</sup> Notwithstanding this finding, sirolimus stents have consistently been shown to reduce the extent of late luminal loss, a measure of neointimal hyperplasia, more effectively than paclitaxel stents<sup>1-5,7,9,10,18</sup> — a finding corroborated in the present trial.

**Table 4. Angiographic Results of Follow-up.\***

Variable	Sirolimus Stent (348 Lesions)	Paclitaxel Stent (375 Lesions)	Difference (95% CI)	P Value
Diameter of reference vessel (mm)	2.79±0.43	2.80±0.45	-0.01 (-0.08 to 0.06)	0.74
Minimal luminal diameter (mm)				
Proximal margin	2.64±0.54	2.65±0.65	-0.01 (-0.11 to 0.09)	0.84
In stent	2.53±0.50	2.44±0.66	0.08 (-0.01 to 0.17)	0.07
Distal margin	2.49±0.45	2.49±0.49	0.00 (-0.07 to 0.08)	0.96
In segment	2.37±0.57	2.28±0.73	0.09 (-0.01 to 0.20)	0.07
Stenosis (% of luminal diameter)				
Proximal margin	11.0±12.2	12.7±15.5	-1.7 (-3.9 to 0.5)	0.13
In stent	10.3±12.9	14.0±18.9	-3.4 (-6.3 to -1.3)	0.003
Distal margin	9.1±9.2	9.2±8.08	-0.1 (-1.4 to 1.2)	0.91
In segment	14.9±16.5	19.4±21.7	-4.5 (-7.5 to -1.6)	0.003
Late luminal loss (mm)				
Proximal margin	0.12±0.32	0.16±0.39	-0.05 (-0.10 to 0.01)	0.11
In stent	0.12±0.36	0.25±0.49	-0.13 (-0.19 to -0.06)	<0.001
Distal margin	0.07±0.20	0.08±0.22	-0.01 (-0.04 to 0.02)	0.42
In segment	0.19±0.45	0.32±0.55	-0.13 (-0.21 to -0.05)	0.001
Late-loss index				
In stent	0.06±0.18	0.13±0.28	-0.07 (-0.11 to -0.03)	<0.001
In segment	0.10±0.23	0.17±0.32	-0.07 (-0.12 to -0.03)	0.001
Binary restenosis (%)				
Proximal margin	3.2	4.8	-1.6 (-4.8 to 1.2)	0.29
In stent	3.2	7.5	-4.3 (-7.5 to -1.1)	0.01
Distal margin	1.1	1.1	0.0 (-1.4 to 1.6)	0.92
In segment	6.6	11.7	-5.1 (-9.3 to -1.0)	0.02

\* Plus-minus values are means ±SD. Late luminal loss was defined as the difference between the minimal luminal diameter after the procedure and the minimal luminal diameter at follow-up. Binary restenosis was defined as stenosis of at least 50 percent of the minimal luminal diameter in the target lesion at angiographic follow-up. Late-loss index was determined by dividing late luminal loss by acute gain. CI denotes confidence interval.

In our analysis, the rates of restenosis and late luminal loss in the sirolimus-stent group were similar to those in the SIRIUS (Sirolimus-Eluting Balloon-Expandable Stent in the Treatment of Patients with de Novo Native Coronary-Artery Lesions) trial, the largest previous randomized trial of the sirolimus stent.<sup>2</sup> In contrast, the rates of restenosis and late luminal loss in the paclitaxel-stent group were higher than those observed in the TAXUS IV trial, the largest previous randomized trial of the paclitaxel stent.<sup>10</sup> The reasons for this difference are unclear but may be related to the inclusion in the current trial of patients with more complex conditions and lesions than in the SIRIUS or TAXUS IV

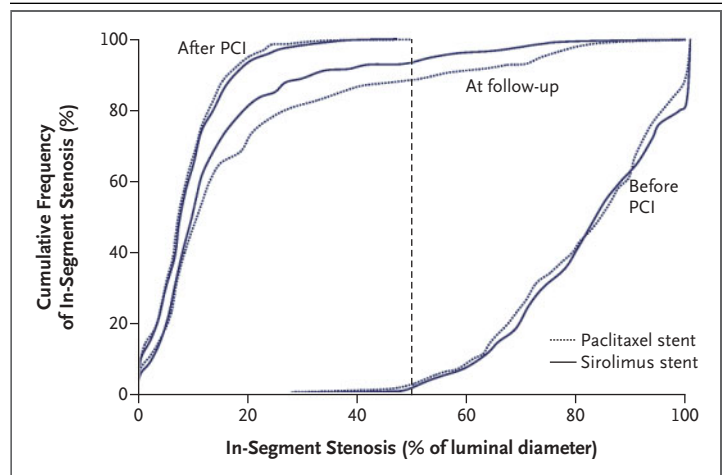
trial. The therapeutic benefit of sirolimus stents appears to be particularly apparent in such patients and lesions, perhaps owing to the increased risk of restenosis. Data from the ISAR-DESIRE (Intracoronary Stenting and Angiographic Results—Drug-Eluting Stents for In-Stent Restenosis) trial<sup>18</sup> involving patients with in-stent restenosis, a subgroup of patients at high risk for restenosis, also indicated that the sirolimus stent was more effective than the paclitaxel stent in suppressing neointimal hyperplasia and reducing the need for repeated revascularization. Patients with diabetes represent another subgroup at increased risk for restenosis, even after the implantation of drug-eluting stents. A pre-

specified, stratified analysis in the present trial indicated that differences in favor of the sirolimus stent were more pronounced in patients with diabetes than in those without diabetes.

The rates of death and myocardial infarction were low in both stent groups. The cumulative incidence of stent thrombosis was similar in the two groups, and there was no significant difference in the rates of antithrombotic treatment. Although the overall rate of stent thrombosis was higher than in previous studies of drug-eluting stents, the rate is in keeping with our own experience of 1.6 percent among 6058 patients treated with bare-metal stents.<sup>21</sup> The higher incidence of stent thrombosis in this trial may have been related to the inclusion of patients with more complex conditions and lesions and a higher prevalence of acute coronary syndromes than in most previous studies.

Routine angiographic follow-up is known to increase the rate of target-lesion revascularization, and the incomplete angiographic follow-up in the present trial may have resulted in an overestimation of differences owing to attrition bias.<sup>22</sup> We consider this possibility unlikely, since the difference in major adverse cardiac events in favor of the sirolimus stent over the paclitaxel stent was already apparent at six months, before the scheduled angiographic follow-up (hazard ratio for major adverse cardiac events at six months, 0.56; 95 percent confidence interval, 0.32 to 0.96;  $P=0.04$ ). In addition, the difference at nine months was significant with the use of an alternative definition of the primary end point, which disregarded target-lesion revascularizations that were driven exclusively by findings on routine angiography.

In conclusion, as compared with polymer-based, paclitaxel-eluting stents, sirolimus-eluting stents resulted in fewer major adverse cardiac events at



**Figure 2. Cumulative Frequency of In-Segment Stenosis.**

The extent of stenosis was defined as the diameter of the reference vessel minus the minimal luminal diameter, divided by the reference diameter and multiplied by 100. There was no significant difference in measurements before and immediately after the procedure between the two groups. At follow-up angiography, the cumulative distribution curve of in-segment stenosis was shifted to the right for the paclitaxel-stent group as compared with the sirolimus-stent group, indicating that in-segment stenosis was more effectively reduced with the sirolimus stent. PCI denotes percutaneous coronary intervention.

nine months, primarily by decreasing the rates of clinical and angiographic restenosis.

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#### APPENDIX

The following persons contributed to the study: **Author Contributions:** *conception and design* — S. Windecker, A. Remondino, F.R. Eberli, P. Jüni, B. Meier; *analysis and interpretation of data* — S. Windecker, P. Jüni, M. Egger, B. Meier; *drafting of the manuscript* — S. Windecker, P. Jüni, A. Remondino, B. Meier; *critical revision of the manuscript for important intellectual content* — S. Windecker, A. Remondino, F.R. Eberli, P. Jüni, L. Räber, P. Wenaweser, M. Togni, M. Billinger, D. Tüller, C. Seiler, M. Roffi, R. Corti, G. Süttsch, W. Maier, T. Lüscher, O.M. Hess, M. Egger, B. Meier; *final approval of the manuscript* — S. Windecker, A. Remondino, F.R. Eberli, P. Jüni, L. Räber, P. Wenaweser, M. Togni, M. Billinger, D. Tüller, C. Seiler, M. Roffi, R. Corti, G. Süttsch, W. Maier, T. Lüscher, O.M. Hess, M. Egger, B. Meier; *statistical expertise* — S. Windecker, P. Jüni, M. Egger; *obtaining of public funding* — S. Windecker, F.R. Eberli, T. Lüscher, O.M. Hess, B. Meier; *administrative, technical, or logistic support* — S. Windecker, P. Jüni, M. Egger, T. Lüscher, O.M. Hess, B. Meier; *acquisition of data* — S. Windecker, A. Remondino, F.R. Eberli, P. Jüni, L. Räber, P. Wenaweser, M. Togni, M. Billinger, D. Tüller, C. Seiler, M. Roffi, R. Corti, G. Süttsch, W. Maier, T. Lüscher, O.M. Hess, B. Meier; **Data and Safety Monitoring Board:** M. Bertrand (Lille University Heart Institute, Lille, France), P. Urban (La Tour Hospital, Geneva); **Event-Adjudication Committee:** A. Garachemani (Sonnenhof Hospital, Bern, Switzerland) and N. Schwick and A. Wahl (University Hospital Bern, Bern, Switzerland).

## REFERENCES

1. 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.
2. 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.
3. 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.
4. Colombo A, Drzewiecki J, Banning A, et al. Randomized study to assess the effectiveness of slow- and moderate-release polymer-based paclitaxel-eluting stents for coronary artery lesions. *Circulation* 2003;108: 788-94.
5. Schofer J, Schluter M, Gershlick AH, et al. Sirolimus-eluting stents for treatment of patients with long atherosclerotic lesions in small coronary arteries: double-blind, randomised controlled trial (E-SIRIUS). *Lancet* 2003;362:1093-9.
6. 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.
7. Schampaert E, Cohen EA, Schluter M, et al. The Canadian study of the sirolimus-eluting stent in the treatment of patients with long de novo lesions in small native coronary arteries (C-SIRIUS). *J Am Coll Cardiol* 2004; 43:1110-5.
8. Gershlick A, De Scheerder I, Chevalier B, et al. Inhibition of restenosis with a paclitaxel-eluting, polymer-free coronary stent: the European evaluation of paclitaxel Eluting Stent (ELUTES) trial. *Circulation* 2004; 109:487-93.
9. Ardissino D, Cavallini C, Bramucci E, et al. Sirolimus-eluting vs uncoated stents for prevention of restenosis in small coronary arteries: a randomized trial. *JAMA* 2004;292: 2727-34.
10. Stone GW, Ellis SG, Cox DA, et al. A polymer-based, paclitaxel-eluting stent in patients with coronary artery disease. *N Engl J Med* 2004;350:221-31.
11. 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.
12. 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.
13. 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.
14. 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.
15. Brophy JM, Belisle P, Joseph L. Evidence for use of coronary stents: a hierarchical Bayesian meta-analysis. *Ann Intern Med* 2003;138:777-86.
16. Al Suwaidi J, Berger PB, Holmes DR Jr. Coronary artery stents. *JAMA* 2000;284: 1828-36.
17. Babapulle MN, Joseph L, Belisle P, Brophy JM, Eisenberg MJ. A hierarchical Bayesian meta-analysis of randomised clinical trials of drug-eluting stents. *Lancet* 2004;364: 583-91.
18. Kastrati A, Mehilli J, von Beckerath N, et al. Sirolimus-eluting stent or paclitaxel-eluting stent vs balloon angioplasty for prevention of recurrences in patients with coronary in-stent restenosis: a randomized controlled trial. *JAMA* 2005;293:165-71.
19. Togni M, Windecker S, Wenaweser P, et al. Deleterious effect of coronary brachytherapy on vasomotor response to exercise. *Circulation* 2004;110:135-40.
20. Goy JJ, Stauffer JC, Siegenthaler M, Benoit A, Seydoux C. A prospective randomized comparison between paclitaxel and sirolimus stents in the real world of interventional cardiology: the TAXI trial. *J Am Coll Cardiol* 2005;45:308-11.
21. Wenaweser P, Rey C, Eberli FR, et al. Stent thrombosis following bare-metal stent implantation: success of emergency percutaneous coronary intervention and predictors of adverse outcome. *Eur Heart J* 2005; 26:1180-7.
22. Juni P, Altman DG, Egger M. Systematic reviews in health care: assessing the quality of controlled clinical trials. *BMJ* 2001;323: 42-6.

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