

ORIGINAL ARTICLE

Paclitaxel-Eluting or Sirolimus-Eluting Stents to Prevent Restenosis in Diabetic Patients

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ABSTRACT

BACKGROUND

Drug-eluting stents are highly effective in reducing the rate of in-stent restenosis. It is not known whether there are differences in the effectiveness of currently approved drug-eluting stents in the high-risk subgroup of patients with diabetes mellitus.

METHODS

We enrolled 250 patients with diabetes and coronary artery disease: 125 were randomly assigned to receive paclitaxel-eluting stents, and 125 to receive sirolimus-eluting stents. The primary end point was in-segment late luminal loss. Secondary end points were angiographic restenosis (defined as in-segment stenosis of at least 50 percent at follow-up angiography) and the need for revascularization of the target lesion during a nine-month follow-up period. The study was designed to show noninferiority of the paclitaxel stent as compared with the sirolimus stent, defined as a difference in the extent of in-segment late luminal loss of no more than 0.16 mm.

RESULTS

The extent of in-segment late luminal loss was 0.24 mm (95 percent confidence interval, 0.09 to 0.39) greater in the paclitaxel-stent group than in the sirolimus-stent group ($P=0.002$). In-segment restenosis was identified on follow-up angiography in 16.5 percent of the patients in the paclitaxel-stent group and 6.9 percent of the patients in the sirolimus-stent group ($P=0.03$). Target-lesion revascularization was performed in 12.0 percent of the patients in the paclitaxel-stent group and 6.4 percent of the patients in the sirolimus-stent group ($P=0.13$).

CONCLUSIONS

In patients with diabetes mellitus and coronary artery disease, use of the sirolimus-eluting stent is associated with a decrease in the extent of late luminal loss, as compared with use of the paclitaxel-eluting stent, suggesting a reduced risk of restenosis.

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*The Intracoronary Stenting and Angiographic Results: Do Diabetic Patients Derive Similar Benefit from Paclitaxel-Eluting and Sirolimus-Eluting Stents (ISAR-DIABETES) study investigators are listed in the Appendix.

N Engl J Med 2005;353:663-70.

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CORONARY ARTERY DISEASE IS A MAJOR cause of complications and death among patients with diabetes mellitus.¹ In particular, patients with diabetes are prone to a diffuse and rapidly progressive form of atherosclerosis, which increases their likelihood of requiring revascularization.²⁻⁴ Percutaneous coronary intervention and aortocoronary bypass surgery are recommended revascularization strategies for such patients. However, because of the increased risk of restenosis after percutaneous coronary interventions in these patients,⁵⁻⁷ aortocoronary bypass surgery has been considered to be the preferred revascularization strategy for many.^{8,9}

Drug-eluting stents markedly reduce the incidence of restenosis as compared with bare-metal stents, both in patients without diabetes and in those with diabetes.¹⁰⁻¹⁷ However, no data are available on the relative efficacy of particular drug-eluting stents in patients with diabetes. This issue has important implications for the selection of the most effective therapy in this high-risk group of patients. We therefore designed a prospective, randomized trial to compare paclitaxel- and sirolimus-eluting stents in patients with diabetes and coronary artery disease.

METHODS

PATIENTS

Enrollment of participants began on June 11, 2003, and was completed on March 15, 2004. Two German centers participated in the trial: Deutsches Herzzentrum and First Medizinische Klinik rechts der Isar, both in Munich. Patients were considered eligible if they had diabetes mellitus, presented with angina pectoris or had a positive stress test or met both criteria, and had clinically significant angiographic stenosis in a native coronary vessel. Exclusion criteria included acute ST-segment-elevation myocardial infarction; a target lesion in the left main trunk; in-stent restenosis; any contraindication to the use of aspirin, heparin, or clopidogrel; and lack of consent to participate in the study. The study protocol was approved by the institutional ethics committees at both participating centers. All patients gave written informed consent.

RANDOMIZATION, INTERVENTIONS, AND ADJUNCT DRUG THERAPY

All patients received a loading dose of 600 mg of clopidogrel at least two hours before undergoing

coronary angiography.^{18,19} After the guide wire had crossed the lesion, patients were randomly assigned to receive a paclitaxel-eluting stent (Taxus, Boston Scientific) or a sirolimus-eluting stent (Cypher; Cordis, Johnson & Johnson) with the use of sealed envelopes containing a computer-generated randomization sequence. The same randomly assigned stent had to be implanted in all lesions in patients who required stenting in multiple lesions; the use of more than one stent per lesion was also allowed.

Periprocedural antithrombotic therapy consisted of intravenously administered aspirin and heparin; abciximab (ReoPro, Lilly) was given only to patients with acute coronary syndromes. After the intervention, the protocol mandated the use of antiplatelet therapy consisting of 100 mg of aspirin twice a day indefinitely as well as 75 mg of clopidogrel twice a day until discharge, followed by a dose of 75 mg a day for at least six months.

FOLLOW-UP PROTOCOL

After undergoing stenting, all patients remained in the hospital for at least 48 hours. Electrocardiography was performed and blood was collected for the measurement of creatine kinase and its MB isoenzyme before stenting, every 8 hours for the first 24 hours after the procedure, and daily thereafter during hospitalization. A telephone interview was conducted after 30 days to assess each patient's clinical status. All patients were asked to return for coronary angiography between six and eight months after the procedure, or earlier if anginal symptoms occurred. Telephone interviews were repeated nine months after the intervention. Relevant data were collected and entered into a computerized database by specialized personnel at the clinical data-management center. All data were verified with the use of hospital records or the records of family physicians, and all adverse clinical events were adjudicated by an events committee whose members were unaware of patients' treatment assignments.

QUANTITATIVE CORONARY ANGIOGRAPHY

Baseline, postprocedural, and follow-up coronary angiograms were digitally recorded and assessed off-line in the quantitative angiographic core laboratory (Deutsches Herzzentrum) with an automated edge-detection system (CMS version 5.1.4.1, Medis Medical Imaging Systems) by experienced personnel unaware of the type of stent implanted. The complexity of the lesions was defined according to the modified grading system of the Ameri-

can College of Cardiology–American Heart Association.²⁰ The morphologic appearance of in-stent restenosis at follow-up angiography was classified according to the system proposed by Mehran et al.²¹ All measurements were performed on cineangiograms recorded after the intracoronary administration of nitroglycerin. The same single, worst-view projection was used at all times. The contrast-filled nontapered catheter tip was used for calibration. The reference diameter was determined by interpolation.

The variables that were measured included the reference diameter of the vessel, the minimal diameter of the lumen, the extent of stenosis (the difference between the reference diameter and the minimal luminal diameter, divided by the reference diameter and multiplied by 100), late luminal loss (the difference between the minimal luminal diameter at the end of the procedure and the minimal luminal diameter at follow-up), and net luminal gain (the difference between the minimal luminal diameter at follow-up and the minimal luminal diameter before the procedure). Quantitative analysis was used to evaluate the stented area (“in stent”) and the area that included the stented segment as well as the 5-mm margins proximal and distal to the stent (“in segment”).

STUDY END POINTS, DEFINITIONS, AND DESIGN

The primary end point of the study was in-segment late luminal loss on follow-up angiography. Secondary end points were angiographic restenosis (defined as in-segment stenosis of at least 50 percent on follow-up angiography) and the need for revascularization of the target lesion owing to narrowing of the lumen in the presence of symptoms or objective signs of ischemia during the nine-month follow-up interval.

The diagnosis of diabetes mellitus was considered confirmed in all patients receiving active treatment with an oral hypoglycemic agent or insulin; for patients with a diagnosis of diabetes who were receiving dietary therapy alone, enrollment in the trial required the documentation of an abnormal blood glucose level after an overnight fast or an abnormal glucose-tolerance test.²² The diagnosis of myocardial infarction during follow-up required the presence of new Q waves on the electrocardiogram or an elevation of creatine kinase or its MB isoen-

zyme to at least three times the upper limit of the normal range in at least two blood samples (some patients met both criteria).²³

STATISTICAL ANALYSIS

The objective of the study was to assess whether the outcome of treatment with the paclitaxel-eluting stent was not inferior to the outcome of treatment with the sirolimus-eluting stent. Calculation of the sample size was based on a margin of noninferiority for in-segment late luminal loss of 0.16 mm. This value is equal to 35 percent of an assumed mean (\pm SD) late luminal loss of 0.46 ± 0.45 mm in diabetic patients after the implantation of a sirolimus stent, as found in an analysis of a series of diabetic patients treated with sirolimus stents at participating centers in the 10 months that preceded the initiation of the study.

Using a one-sided α level of 0.05, we estimated that 99 patients per group were needed to demonstrate noninferiority of the paclitaxel stent with a statistical power of 80 percent. Expecting that up to 20 percent of the patients would not return for follow-up coronary angiography, we included 250 patients in the study. Sample size was calculated with the use of nQuery Advisor (version 4.0, Statistical Solutions) according to the method of O’Brien and Muller.²⁴

Analyses related to angiographic measures were conducted according to the number of patients available for each analyses. All other analyses were conducted according to the intention-to-treat principle. For patients with multilesion interventions, only the data pertaining to the first treated lesion were included in the analysis. The noninferiority hypothesis was assessed statistically with EquivTest (Statistical Solutions) according to the method of Chow and Liu.²⁵ The differences between the groups were assessed with a two-sided chi-square test or Fisher’s exact test for categorical data and Student’s t-test for continuous data. The relative risk and its 95 percent confidence interval were computed for outcome measures. The differences in quantitative angiographic results at follow-up between the two study groups were also assessed after adjustment for baseline characteristics by means of multiple linear regression analysis (continuous dependent variables) or multiple logistic-regression analysis (dichotomous dependent variables). All P values were two-sided, and a P val-

ue of less than 0.05 was considered to indicate statistical significance.

RESULTS

A total of 250 patients were enrolled in the study and randomly assigned to receive either a paclitaxel stent or a sirolimus stent. Table 1 shows the baseline demographic, clinical, and angiographic characteristics of the study population. The procedural characteristics are shown in Table 2. Implantation of the randomly assigned stent was successful in all patients. In 12.0 percent of patients, more than one lesion was treated. There was only one case of

early stent thrombosis: in one patient in the paclitaxel-stent group, the stent became occluded five hours after the index procedure.

ANGIOGRAPHIC RESULTS

Follow-up angiography was performed in 103 patients (82.4 percent) in the paclitaxel-stent group and 102 patients (81.6 percent) in the sirolimus-stent group. Patients who did not undergo follow-up angiography did not differ significantly from those who did with respect to the baseline characteristics shown in Table 1. Five of the 22 patients who did not undergo follow-up angiography in the paclitaxel-stent group died during the nine-month follow-up period, as did 4 of the 23 such patients in the sirolimus-stent group. No other adverse events were observed among these patients, and none required rehospitalization during follow-up.

The median duration of angiographic follow-up was 196 days (10th and 90th percentiles, 92 and 236) in the paclitaxel-stent group and 196 days (10th and 90th percentiles, 91 and 238) in the sirolimus-stent group ($P=0.94$). Table 3 shows the results of the quantitative analysis of follow-up angiograms. The mean difference in in-segment late luminal loss between the paclitaxel-stent group and the sirolimus-stent group was 0.24 mm (95 percent confidence interval, 0.09 to 0.39), a result failing to show the noninferiority of the paclitaxel stent and instead demonstrating the statistical superiority of the sirolimus stent ($P=0.002$) (Fig. 1). This difference remained significant after adjustment for the baseline characteristics of the patients ($P=0.001$) (Table 3). Figure 2 shows the cumulative rates of in-segment stenosis at follow-up angiography.

Among patients who were receiving insulin, in-segment late luminal loss averaged 0.72 ± 0.66 mm in the paclitaxel-stent group and 0.41 ± 0.42 mm in the sirolimus-stent group ($P=0.02$). Among patients who were not receiving insulin, in-segment late luminal loss averaged 0.65 ± 0.60 mm in the paclitaxel-stent group and 0.44 ± 0.46 mm in the sirolimus-stent group ($P=0.03$).

In-segment restenosis was found on follow-up angiography in 17 of 103 patients in the paclitaxel-stent group, as compared with 7 of 102 patients in the sirolimus-stent group (16.5 percent vs. 6.9 percent; relative risk, 2.40; 95 percent confidence interval, 1.04 to 5.55; $P=0.03$). With respect to the pattern of restenosis on follow-up angiography, all seven of the patients in the sirolimus-stent group

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

Characteristic	Paclitaxel-Stent Group (N=125)	Sirolimus-Stent Group (N=125)
Age — yr	68.3±9.6	67.7±10.2
Female sex — no. (%)	36 (28.8)	32 (25.6)
Treatment of diabetes — no. (%)		
Dietary therapy alone	24 (19.2)	24 (19.2)
Oral hypoglycemic agents	65 (52.0)	55 (44.0)
Insulin	36 (28.8)	46 (36.8)
Glycosylated hemoglobin — %	7.4±1.6	7.3±1.1
Current smoker — no. (%)	16 (12.8)	16 (12.8)
Arterial hypertension — no. (%)	82 (65.6)	70 (56.0)
Hypercholesterolemia — no. (%)	78 (62.4)	73 (58.4)
Unstable angina — no. (%)	43 (34.4)	56 (44.8)
Prior myocardial infarction — no. (%)	49 (39.2)	39 (31.2)
Prior aortocoronary bypass surgery — no. (%)	13 (10.4)	16 (12.8)
Left ventricular ejection fraction — %	51.7±13.6	50.3±12.7
Target vessel — no. (%)		
Left anterior descending coronary artery	64 (51.2)	58 (46.4)
Left circumflex coronary artery	36 (28.8)	43 (34.4)
Right coronary artery	25 (20.0)	24 (19.2)
Complex (type B2 or C) lesions — no. (%)	92 (73.6)	102 (81.6)
Vessel size — mm	2.75±0.56	2.70±0.50
Lesion length — mm	12.4±7.7	13.8±7.6
Minimal luminal diameter before procedure — mm	1.12±0.40	1.03±0.37†
Stenosis before procedure — % of luminal diameter	59.4±11.9	61.1±13.1

* Plus-minus values are means ±SD.

† $P=0.09$ for the comparison with the paclitaxel-stent group.

presented with pattern I. In the paclitaxel-stent group, 13 patients presented with pattern I, 1 patient with pattern II, 1 patient with pattern III, and 2 patients with pattern IV.

CLINICAL OUTCOMES

All patients completed the nine-month follow-up. Six patients (4.8 percent) in the paclitaxel-stent group and four patients (3.2 percent) in the sirolimus-stent group died during this period (P=0.52). Myocardial infarction occurred in three patients (2.4 percent) in the paclitaxel-stent group and five patients (4.0 percent) in the sirolimus-stent group (P=0.72). Target-lesion revascularization was performed in 15 patients in the paclitaxel-stent group, as compared with 8 patients in the sirolimus-stent group (12.0 percent vs. 6.4 percent; relative risk, 1.89; 95 percent confidence interval, 0.82 to 4.27; P=0.13). Among the patients who underwent target-lesion revascularization, the mean extent of in-segment stenosis at follow-up angiography was 65.0±17.0 percent.

DISCUSSION

In this randomized trial, we compared the efficacy of the sirolimus-eluting stent and the paclitaxel-eluting stent in the prevention of restenosis in patients with diabetes mellitus and coronary artery disease. The paclitaxel stent was associated with a higher rate of in-segment late luminal loss as well as an increased risk of angiographic restenosis. Our study was not sufficiently powered to assess the incidence of clinical restenosis, and we found no significant differences in the rates of clinical end points between the two groups. Nonetheless, our results imply that the sirolimus stent may be preferable to the paclitaxel stent in patients with diabetes who require coronary revascularization.

We chose late luminal loss at follow-up angiography as the primary end point of our trial because it reflects the degree of neointimal proliferation,²⁶ which is the chief cause of restenosis after stent implantation.²⁷ Late loss is the most sensitive measure of the antiproliferative effectiveness of drug-eluting stents,^{28,29} although in-stent late loss may be a more reliable predictor of restenosis than in-segment late loss.²⁹ In a recent trial, a 70 percent reduction in the rate of in-segment late luminal loss with the sirolimus-eluting stent was associated with a 75 percent reduction in the rate of target-

lesion revascularization as compared with the rates with the control bare-metal stent.¹² However, it should be stressed that late luminal loss constitutes only a surrogate for clinical end points. The limitations of surrogate end points have been well described.^{30,31} Our results should be interpreted in this context.

Our calculation of sample size was based on a margin of noninferiority of 0.16 mm for in-segment late luminal loss. This value was selected after an analysis of a series of diabetic patients treated with sirolimus stents at our own institutions. It is also a reasonable margin of difference on the basis of findings in other studies. In the SIRIUS trial, an absolute reduction of 0.57 mm in in-segment late luminal loss was achieved with the use of the sirolimus-eluting stent as compared with the bare-metal stent.¹² Our margin of difference of 0.16 mm represents the preservation of 72 percent of the effect demonstrated by the sirolimus-

Table 2. Procedural Characteristics.*

Characteristic	Paclitaxel-Stent Group (N=125)	Sirolimus-Stent Group (N=125)
Maximal balloon pressure — atm	14.3±2.6	13.7±2.6†
Ratio of balloon to vessel	1.15±0.10	1.15±0.10
Length of stented segment — mm	22.1±9.3	23.8±10.2
No. of stents	1.13±0.36	1.15±0.38
>1 Stent implanted — no. (%)	15 (12.0)	18 (14.4)
Minimal luminal diameter after procedure — mm		
In segment	2.65±0.52	2.59±0.45
In stent	2.67±0.52	2.62±0.46
Proximal margin	2.70±0.54	2.64±0.48
Distal margin	2.66±0.51	2.60±0.46
Stenosis after procedure — % of luminal diameter‡		
In segment	9.2±7.2	7.9±6.3
In stent	8.4±7.7	7.0±6.4
Proximal margin	7.5±7.2	6.4±6.2
Distal margin	8.9±7.0	7.8±6.5
Abciximab therapy — no. (%)	24 (19.2)	25 (20.0)

* Plus-minus values are means ±SD.

† P=0.08 for the comparison with the paclitaxel-stent group.

‡ The extent of stenosis was defined as the difference between the reference diameter and the minimal luminal diameter, divided by the reference diameter and multiplied by 100.

Table 3. Results of Quantitative Angiographic Analysis at Follow-up.*

Characteristic	Paclitaxel-Stent Group (N=103)	Sirolimus-Stent Group (N=102)	P Value	Adjusted P Value†
Late luminal loss — mm				
In segment	0.67±0.62	0.43±0.45	0.002	0.001
In stent	0.46±0.64	0.19±0.44	<0.001	<0.001
Proximal margin	0.26±0.70	0.06±0.57	0.03	
Distal margin	0.49±0.58	0.28±0.46	0.006	
Net luminal gain — mm				
In segment	0.90±0.75	1.12±0.64	0.03	0.003
In stent	1.12±0.77	1.38±0.66	0.01	<0.001
Proximal margin	1.32±0.78	1.50±0.74	0.08	
Distal margin	1.09±0.69	1.27±0.61	0.05	
Minimal luminal diameter — mm				
In segment	2.03±0.78	2.15±0.59	0.23	0.11
In stent	2.25±0.80	2.41±0.62	0.12	0.05
Proximal margin	2.43±0.84	2.53±0.71	0.46	
Distal margin	2.21±0.75	2.29±0.60	0.43	
Stenosis — % of luminal diameter‡				
In segment	31.73±20.87	25.74±15.61	0.02	0.02
In stent	24.22±21.53	16.59±17.22	0.006	0.004
Proximal margin	17.18±23.45	12.63±19.61	0.13	
Distal margin	25.09±20.09	20.74±14.84	0.08	
Angiographic restenosis — no. (%)§				
In segment	17 (16.5)	7 (6.9)	0.03	0.02
In stent	14 (13.6)	5 (4.9)	0.03	0.02
Proximal margin	1 (1.0)	1 (1.0)	1.0	
Distal margin	2 (1.9)	1 (1.0)	0.99	

* Plus–minus values are means ±SD. Late luminal loss was defined as the difference between the minimal luminal diameter at the end of the procedure and the minimal luminal diameter at follow-up. Net luminal gain was defined as the difference between the minimal luminal diameter at follow-up and the minimal luminal diameter before the procedure.

† P values were obtained after adjustment for the baseline characteristics shown in Table 1.

‡ The extent of stenosis was defined as the difference between the reference diameter and the minimal luminal diameter, divided by the reference diameter and multiplied by 100.

§ If angiographic restenosis was detected concomitantly in the in-stent area and any of the margins, it was counted only as restenosis in the in-stent area.

eluting stent in that trial. A new treatment is considered noninferior to a standard treatment when it retains 50 to 80 percent of the superiority that the standard treatment has shown over placebo.³²

Another issue that requires comment is our observation that the extent of in-segment late luminal loss exceeded the extent of in-stent late luminal loss. This finding differs from the results of most other stenting trials, although a similar result was report-

ed among patients receiving a sirolimus stent in the SIRIUS trial.^{12,16} The phenomenon of greater in-segment late loss may be a consequence of two factors. First, after the procedure, the in-stent minimal luminal diameter (2.65 mm) was nearly identical to the in-segment minimal luminal diameter (2.62 mm) — a result that is somewhat unexpected, especially in diabetic patients with diffuse coronary disease. Second, patients with diabetes have a

distinctive, swiftly progressive form of atherosclerosis, which increases the reactivity of the vascular wall to the injury produced by the procedure at the stent margins as well as the rate of natural progression of disease outside the stent, an effect presumably mitigated within the stent by the antiproliferative properties of sirolimus and paclitaxel.

The incidence ratio of target-lesion revascularization to angiographic restenosis in our study was 78.6 percent. In previous randomized trials comparing drug-eluting stents with bare-metal stents, this ratio ranged from 38 and 46 percent^{12,13} to 85 percent³³ among patients assigned to receive the drug-eluting stent. It is difficult to be certain of the reason for the higher ratio in our study than in several previous trials. The rate of late loss in our trial was also higher than that in other, similar trials, possibly because we limited our study population to patients with diabetes. The higher rate may reflect not only an increased incidence but also increased severity of angiographically evident restenosis, increasing the likelihood of the need for reintervention. In addition, diabetes mellitus is often perceived as a disease that attenuates anginal symptoms even in the presence of clinically significant coronary artery stenosis. This perception may have induced the clinicians to overestimate symptoms and lower their threshold for reintervention in some patients with angiographically evident restenosis in the present trial.

Although the exact mechanism underlying our findings remains unclear, pharmacologic differences between the two drugs, differences in the dose response of patients with diabetes, or differences in the properties of the two drug-delivery stents (such as release kinetics and polymeric coating) may account for the results. A study of another high-risk subgroup of patients (those with in-stent restenosis) also found sirolimus stents to reduce the risk of target-vessel revascularization more effectively than did paclitaxel stents.³⁴ These findings, however, cannot be extrapolated to a patient population with a more favorable risk profile. This issue has recently been investigated in other trials, and preliminary results have been presented.³⁵

In conclusion, we did not establish the noninferiority of paclitaxel-eluting stents to sirolimus-eluting stents in patients with diabetes and coronary artery disease. Instead, we found that the use of the sirolimus-eluting stent in this setting was associated with a decrease in the extent of late luminal loss, suggesting a reduced risk of restenosis.

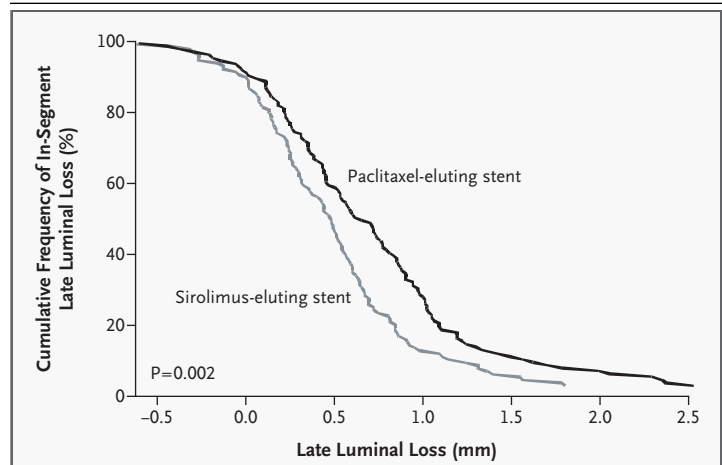


Figure 1. Cumulative Rates of In-Segment Late Luminal Loss at Follow-up Angiography.

Late luminal loss was defined as the difference between the minimal luminal diameter at the end of the procedure and the minimal luminal diameter at follow-up.

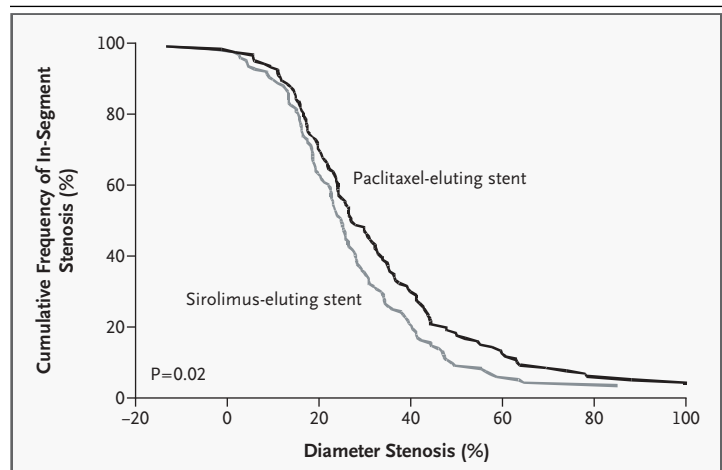


Figure 2. Cumulative Rates of In-Segment Stenosis at Follow-up Angiography.

The extent of stenosis was defined as the difference between the reference diameter and the minimal luminal diameter, divided by the reference diameter and multiplied by 100.

Supported by a grant (KKF 04-03) from Deutsches Herzzentrum, Munich, Germany.

Dr. Kastrati reports having received research grants from Deutsches Herzzentrum and Medtronic as well as lecture fees from Guidant. Dr. Schühlen reports having received lecture fees from Boston Scientific, Guidant, and Lilly. Dr. Schömig reports having received research grants on behalf of the Department of Cardiology from Bristol-Myers Squibb, Guidant, and Lilly.

APPENDIX

The following centers and investigators participated in the ISAR-DIABETES Study: **Steering Committee:** A. Schömig (chair), A. Kastrati (principal investigator); **Event-Adjudication Committee:** J. Dirschinger, H. Schühlen, J. Pache; **Data-Coordinating Center:** J. Mehilli, H. Bollwein, C. Markwardt; **Angiographic Core Laboratory:** A. Dibra, S. Piniak, S. Meier; **Clinical Follow-up Center:** H. Holle, K. Hösl, F. Rodrigues, C. Peterler; **Participating Centers and Investigators:** *Deutsches Herzzentrum, Munich* — J. Pache, C. Schmitt, N. von Beckerath, R. Wessely; *Klinikum rechts der Isar, Munich* — J. Dirschinger, H. Schühlen, M. Seyfarth, M. Karch.

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