

## Predictive Factors of Restenosis After Coronary Implantation of Sirolimus- or Paclitaxel-Eluting Stents

Adnan Kastrati, MD; Alban Dibra, MD; Julinda Mehilli, MD; Sandra Mayer, RN; Susanne Pinieck, RN; Jürgen Pache, MD; Josef Dirschinger, MD; Albert Schömig, MD

**Background**—The efficacy of drug-eluting stents in reducing restenosis risk has not been uniform across patient subsets. Identifying predictive factors of restenosis may help improve outcomes after percutaneous coronary interventions.

**Methods and Results**—All patients who underwent successful implantation of sirolimus- or paclitaxel-eluting stents in native vessels for de novo lesions between August 2002 and December 2004 were eligible for this study. All data were prospectively collected. Angiographic restenosis was defined as diameter stenosis  $\geq 50\%$  at follow-up in the in-segment area. Target lesion revascularization was defined as any revascularization procedure involving the target lesion. Included in this study were 1845 patients with 2093 target lesions. Multivariable analysis showed that vessel size, final diameter stenosis, and drug-eluting stent type were the strongest predictors of restenosis. A 0.5-mm decrease in vessel size was associated with adjusted odds ratios (ORs) of 1.74 (95% CI, 1.31 to 2.32) for angiographic restenosis and 1.65 (95% CI, 1.22 to 2.23) for target lesion revascularization. A 5% increase in final diameter stenosis was associated with adjusted ORs of 1.30 (95% CI, 1.15 to 1.47) for angiographic restenosis and 1.18 (95% CI, 1.03 to 1.35) for target lesion revascularization. Compared with paclitaxel-eluting stent, sirolimus-eluting stent was associated with adjusted ORs of 0.60 (95% CI, 0.44 to 0.81) for angiographic restenosis and 0.67 (95% CI, 0.49 to 0.91) for target lesion revascularization.

**Conclusions**—Vessel size and drug-eluting stent type are the most important predictors of angiographic and clinical restenosis, with drug-eluting stent type having a particular impact on restenosis of small coronary vessels. (*Circulation*. 2006;113:2293-2300.)

**Key Words:** angioplasty ■ predictive factors ■ restenosis ■ stents

Although bare metal stents have been associated with improved outcomes among patients undergoing percutaneous coronary interventions, their efficacy has been limited by the development of in-stent restenosis as a result of neointimal proliferation.<sup>1-3</sup> Studies have shown that restenosis rates are different in various patient subsets and that specific clinical and angiographic characteristics such as vessel size, diabetes mellitus, and stent type are predictive of a higher risk of restenosis and repeated revascularization procedures after stent implantation.<sup>4-9</sup>

### Editorial p 2262 Clinical Perspective p 2300

Drug-eluting stents, which release controlled amounts of antiproliferative agents targeting the suppression of neointimal formation at the local level, constitute the most effective tool currently available to deal with the problem of restenosis.<sup>10,11</sup> Sirolimus-eluting and paclitaxel-eluting stents, the 2 drug-eluting stents most extensively studied so far, have markedly altered the outcome of patients undergoing coronary angioplasty, mainly because of their effect on the reduction of restenosis. Thanks to their better efficacy,

sirolimus-eluting and paclitaxel-eluting stents are being used increasingly during percutaneous coronary interventions. However, the efficacy of these drug-eluting stents, albeit to a lesser degree than that of bare metal stents, has not been uniform across different patient populations, which suggests that specific characteristics still confer an increased risk of restenosis after drug-eluting stent placement.<sup>12-15</sup>

Identification of those clinical and angiographic characteristics that may predict the risk of restenosis and repeated revascularization procedures in the new era of drug-eluting stents may be of particular interest, because it may assist in the improvement of existing or the development of new tools and strategies to eliminate restenosis. Therefore, we addressed this issue in a large series of consecutive patients who underwent implantation of either sirolimus-eluting or paclitaxel-eluting stent(s) and were followed up both angiographically and clinically.

### Methods

#### Study Patients

Those eligible for this study included all consecutive patients presenting with symptomatic coronary artery disease between Au-

Received November 15, 2005; revision received February 10, 2006; accepted February 24, 2006.

From Deutsches Herzzentrum (A.K., A.D., J.M., S.M. S.P., J.P., A.S.) and First Medizinische Klinik rechts der Isar (J.D., A.S.), Technische Universität, Munich, Germany.

Correspondence to Adnan Kastrati, MD, Deutsches Herzzentrum, Lazarettstrasse 36, 80636 Munich, Germany. E-mail [kastrati@dhh.mhn.de](mailto:kastrati@dhh.mhn.de)

© 2006 American Heart Association, Inc.

*Circulation* is available at <http://www.circulationaha.org>

DOI: 10.1161/CIRCULATIONAHA.105.601823

gust 2002 and December 2004 who underwent successful implantation of a sirolimus-eluting or paclitaxel-eluting stent for de novo lesions located in native coronary vessels in 2 tertiary centers, Deutsches Herzzentrum and First Medizinische Klinik rechts der Isar, both in Munich, Germany. Patients with acute ST-segment-elevation myocardial infarction or target lesion located in the left main trunk were excluded. From August 2002 to June 2003, the sirolimus-eluting stent was the only drug-eluting stent approved for use. Thereafter, assignment to sirolimus- or paclitaxel-eluting stent was done in the settings of randomized trials comparing these drug-eluting stents. All patients received the same drug-eluting stent if >1 lesion per patient was treated, and patients gave informed consent for the angiographic follow-up study at 6 to 8 months after intervention and for clinical follow-up study at 1, 6 to 8, and 9 months after intervention. Both clinical and angiographic follow-up study protocols were approved by the institutional ethics committee.

### Stent Placement and Adjunct Drug Therapy

Patients underwent implantation of sirolimus-eluting stents (Cypher; Cordis, Johnson & Johnson, Miami Lakes, Fla) or paclitaxel-eluting stents (Taxus; Boston Scientific, Boston, Mass). Sirolimus-eluting stents were available in 2.25- to 3.5-mm diameters and 8- to 33-mm lengths. Paclitaxel-eluting stents were available in 2.25- to 3.5-mm diameters and 8- to 32-mm lengths.

All patients received a loading dose of 600 mg clopidogrel for at least 2 hours before coronary angiography and an intravenous bolus of 500 mg aspirin. After the intervention, the protocol-mandated antiplatelet therapy consisted of aspirin 100 mg twice a day indefinitely and clopidogrel 75 mg twice a day until discharge and 75 mg/d for at least 6 months. Other medicaments such as  $\beta$ -blockers, statins, and angiotensin-converting enzyme inhibitors were given as appropriate.

### Coronary Angiography Evaluation and Definitions

Qualitative and quantitative evaluation of the angiograms was performed by the core laboratory of the Deutsches Herzzentrum. The operators who performed the evaluation were unaware of the study in which the patients were participating and the stent type used. Two coronary lesions were defined as independent lesions when they were situated in 2 different coronary segments. The modified American College of Cardiology/American Heart Association grading system (type A, B1, B2, and C) was used to characterize lesion morphology.<sup>16</sup> Calcified lesions were defined in the presence of moderate or severe calcifications as previously described.<sup>17</sup> Bifurcation lesions were defined as lesions requiring placement of stents in both component branches. Overlapping stents were defined in the presence of  $\geq 5$ -mm overlapping.

Digital angiograms were analyzed offline with the use of an automated edge-detection system (CMS; Medis Medical Imaging Systems). All measurements were performed on cineangiograms recorded after intracoronary nitroglycerin administration. The same single, worst-view projection was used at all time points. The contrast-filled nontapered catheter tip was used for calibration. The reference diameter was measured by interpolation. The angiographic parameters obtained were reference diameter, lesion length, minimal lumen diameter, diameter stenosis, maximal balloon pressure, maximal balloon diameter (using actual measurement of maximal balloon size), and length of the stented segment. Binary angiographic restenosis was defined as diameter stenosis  $\geq 50\%$  in the in-segment area (including the stent area and 5-mm segments proximal and distal to the stent edges). Target lesion revascularization (clinical restenosis) was defined as any revascularization procedure, percutaneous or surgical, involving the target lesion and performed in the presence of angiographic restenosis accompanied by symptoms or signs of ischemia. The procedure was considered successful if residual stenosis was  $<30\%$  with TIMI flow grade 3.

### Statistical Analysis

Continuous variables are expressed as mean $\pm$ SD; categorical variables, as proportions. We assessed differences between the 2 groups

of patients with and without restenosis using the *t* test for continuous data and  $\chi^2$  test for categorical data. The main analysis tested the association of any risk factor with outcomes of interest (binary angiographic restenosis and target lesion revascularization). The significant predictive factors were obtained by multivariate analysis. We used generalized estimating equations to address the intrapatient correlation in patients who underwent multilesion intervention.<sup>18,19</sup> Adjusted odds ratios (ORs) were calculated with the use of generalized estimating equation models. We used a tree-based modeling technique of predictors for angiographic restenosis and target lesion revascularization.<sup>20</sup> For this purpose, classification and regression trees (CARTs) for each of the above-mentioned outcomes were developed. The CART model was constructed using only independent correlates of the specific outcome as determined by generalized estimating equations. Subtrees beyond the first 2 levels were snipped off for the sake of clarity. All probability values shown are 2 sided, and the level of statistical significance was set at 0.05. Analyses were performed with the S-Plus statistical package (Mathsoft Inc, Seattle, Wash).

The authors had full access to the data and take responsibility for their integrity. All authors have read and agree to the manuscript as written.

### Results

We included 1845 patients with 2093 lesions in this study. Overall, 1030 patients received sirolimus-eluting stents in 1151 lesions, and 815 patients received paclitaxel-eluting stents in 942 lesions. Early stent thrombosis during the first 30 days after the procedure occurred in 9 patients: 3 patients (0.3%) who received sirolimus-eluting stents and 6 patients (0.7%) who received paclitaxel-eluting stents ( $P=0.17$ ). Follow-up angiography was performed in 1495 patients (81.0%) and 1703 lesions (81.4%) an average of  $193\pm 63$  days after the index procedure. Follow-up angiography was not performed in 350 patients. For 35 patients (18 of the 1030 patients [1.7%] who received sirolimus-eluting stents and 17 of the 815 patients [2.1%] who received paclitaxel-eluting stents), the reason was death before the scheduled follow-up angiography. Death was of cardiac origin in 29 patients (sudden cardiac death in 9 patients [2 patients with sirolimus-eluting stents, 7 patients with paclitaxel-eluting stents], myocardial infarction in 4 patients [3 patients with sirolimus-eluting stents, 1 patient with paclitaxel-eluting stents], and progressive congestive heart failure in 16 patients [10 patients with sirolimus-eluting stents, 6 patients with paclitaxel-eluting stents]); 2 deaths were related to sepsis (1 patient with sirolimus-eluting stents, 1 patient with paclitaxel-eluting stents); 1 death was a result of stroke (paclitaxel-eluting stent group); 1 death resulted from massive bleeding (paclitaxel-eluting stent group); 1 death was caused by carcinoma (sirolimus-eluting stent group); and 1 death was a suicide (sirolimus-eluting stent group). The remaining patients declined to undergo the procedure. There were no differences in baseline characteristics between patients with and those without follow-up angiography except for age and sex; patients with follow-up angiography were younger ( $65.6\pm 10.3$  versus  $67.3\pm 10.9$  years;  $P=0.004$ ) and more frequently men (79% versus 73%;  $P=0.02$ ) compared with those without follow-up angiography. In addition, 12% of the patients with follow-up angiography and 10% of the patients without follow-up angiography had multiple lesion intervention ( $P=0.15$ ).

**TABLE 1. Baseline Demographic and Clinical Characteristics of the Groups With Follow-Up Angiogram**

Characteristic	Angiographic Restenosis		<i>P</i>	
	Yes (n=211)	No (n=1284)	Univariate	Multivariate
Age, y	67.1±10.3	65.3±10.2	0.02	0.11
Women, n (%)	56 (27)	258 (20)	0.03	0.04
Diabetes mellitus, n (%)	58 (28)	362 (28)	0.83	0.62
Insulin-treated diabetes mellitus, n (%)	18 (9)	122 (10)	0.65	0.35
Current smoker, n (%)	27 (13)	183 (14)	0.57	0.55
Arterial hypertension, n (%)	130 (62)	750 (58)	0.38	0.80
Hypercholesterolemia, n (%)	163 (77)	955 (74)	0.37	0.73
Unstable angina, n (%)	56 (27)	357 (28)	0.70	0.40
Previous myocardial infarction, n (%)	89 (42)	488 (38)	0.25	0.45
Previous aortocoronary bypass surgery, n (%)	32 (15)	116 (94)	0.006	0.01
Previous percutaneous coronary intervention, n (%)	140 (66)	826 (64)	0.57	0.30
Multivessel disease, n (%)	180 (85)	1061 (83)	0.34	0.93
Left ventricular ejection fraction, %	55.2±13.0	55.5±12.4	0.75	0.71

Angiographic restenosis was detected in 222 lesions (13.0%). At follow-up angiography, 1.2% of those treated with sirolimus-eluting stent(s) and 2.4% of lesions treated with paclitaxel-eluting stent(s) were found to be totally occluded ( $P=0.05$ ). Target lesion revascularization was performed in 192 lesions (9.2%) an average of  $160\pm 62$  days after the index procedure.

### Univariate Analysis

This analysis identified several factors associated with a higher risk of restenosis. Age, female sex, and previous aortocoronary bypass surgery (Table 1), as well as lesion complexity, chronic occlusion, vessel size, and initial diameter stenosis (Table 2), correlated with angiographic restenosis. As shown in Table 3, there were significant differences between the groups with and without restenosis at follow-up angiography with respect to most of the procedural characteristics.

Among clinical factors, only previous aortocoronary bypass surgery was associated with a higher risk of target lesion revascularization (Table 4). With respect to baseline angiographic lesion characteristics, chronic occlusion ( $P=0.002$ ), vessel size ( $P<0.001$ ), and initial diameter stenosis ( $P=0.009$ ) were significantly associated with target lesion revascularization (Table 5). With respect to procedural characteristics, maximal balloon diameter ( $P=0.03$ ), type of drug-eluting stent ( $P=0.003$ ), presence of overlapping stents ( $P=0.02$ ), and final diameter stenosis ( $P=0.002$ ) significantly correlated with the likelihood of reintervention (Table 6).

### Multivariable Analysis

We entered into the multivariable model all the baseline clinical, angiographic, and procedural characteristics shown in Tables 1 through 3. After adjustment, female sex and a history of aortocoronary bypass surgery were independently

**TABLE 2. Baseline Angiographic Characteristics of the Lesions With Follow-Up Angiogram**

Characteristic	Angiographic Restenosis		<i>P</i>	
	Yes (n=222)	No (n=1481)	Univariate	Multivariate
Target vessel, n (%)			0.93	0.88
Left anterior descending coronary artery	100 (45)	687 (46)		
Left circumflex coronary artery	63 (28)	411 (28)		
Right coronary artery	59 (27)	383 (26)		
Complex (type B2/C) lesion, n (%)	179 (81)	1100 (74)	0.04	0.30
Chronic occlusion, n (%)	32 (14)	92 (6)	<0.001	0.02
Calcified lesion, n (%)	45 (20)	277 (19)	0.58	0.60
Thrombus-containing lesion, n (%)	4 (2)	45 (3)	0.30	0.38
Bifurcation lesion, n (%)	20 (9)	174 (12)	0.23	0.47
Vessel size, mm	2.51±0.44	2.67±0.49	<0.001	<0.001
Lesion length, mm	14.4±9.1	13.3±7.4	0.06	0.78
Initial diameter stenosis, %	63.5±16.6	60.1±14.9	0.002	0.46

**TABLE 3. Procedural Characteristics of the Lesions With Follow-Up Angiogram**

Characteristic	Angiographic Restenosis		P	
	Yes (n=222)	No (n=1481)	Univariate	Multivariate
Maximal balloon pressure, atm	14.8±3.2	14.4±2.9	0.06	0.04
Maximal balloon diameter, mm	2.94±0.46	3.06±0.48	<0.001	0.31
Type of drug-eluting stent, n (%)			<0.001	<0.001
Sirolimus-eluting stent	99 (44.6)	847 (57.2)		
Paclitaxel-eluting stent	123 (55.4)	634 (42.8)		
Overlapping stents, n (%)	20 (9)	87 (6)	0.07	0.31
Length of stented segment, mm	24.4±10.2	22.4±9.0	0.003	0.33
Final diameter stenosis, %	9.7±7.6	7.7±6.7	<0.001	<0.001

associated with a higher risk of angiographic restenosis (Table 1). Among baseline angiographic parameters, chronic occlusions and vessel size were independent predictors of angiographic restenosis (Table 2). A 0.5-mm decrease in vessel size was associated with an adjusted OR of 1.74 (95% CI, 1.31 to 2.32). Among procedural characteristics that independently predicted angiographic restenosis were maximal balloon pressure, drug-eluting stent type, and final diameter stenosis (Table 3). With regard to angiographic restenosis, the use of sirolimus-eluting stent(s) was associated with an adjusted OR of 0.60 (95% CI, 0.44 to 0.81), whereas there was an OR of 1.30 (95% CI, 1.15 to 1.47) for each 5% increase in final diameter stenosis.

In the multivariable model of target lesion revascularization, only 1 clinical variable, a history of aortocoronary bypass surgery, was independently associated with a higher risk (Table 4). Among baseline angiographic parameters, calcified lesion, vessel size, and initial diameter stenosis were independent predictors of target lesion revascularization (Table 5). A 0.5-mm decrease in vessel size was associated with an adjusted OR of 1.65 (95% CI, 1.22 to 2.23). Among procedural characteristics that independently predicted target

lesion revascularization were drug-eluting stent type and final diameter stenosis (Table 6). With regard to target lesion revascularization, the use of sirolimus-eluting stent(s) was associated with an adjusted OR of 0.67 (95% CI, 0.49 to 0.91), whereas there was an OR of 1.18 (95% CI, 1.03 to 1.35) for each 5% increase in final diameter stenosis.

### CART Analysis

The results of CART analysis are shown in Figures 1 and 2. The strongest predictors of restenosis were vessel size, drug-eluting stent type, and final diameter stenosis. The analysis shows that the type of drug-eluting stent was important only for small vessels (smaller than the median value of 2.6 mm). The incidence of target lesion revascularization was as low as 6.6% when larger vessels were treated, achieving a final diameter stenosis <8.3% and as high as 15.6% when paclitaxel-eluting stents were placed in small vessels. More specifically, the incidence of target lesion revascularization in small vessels was 7.8% after placement of sirolimus-eluting stent(s) and 15.6% after placement of paclitaxel-eluting stent(s); the incidence of target lesion revascularization in larger vessels was 7.2% for both sirolimus- and paclitaxel-eluting stents.

**TABLE 4. Baseline Demographic and Clinical Characteristics of the Patients**

Characteristic	Target Lesion Revascularization		P	
	Yes (n=174)	No (n=1671)	Univariate	Multivariate
Age, y	66.9±10.3	65.8±10.4	0.21	0.50
Women, n (%)	46 (26)	362 (22)	0.15	0.33
Diabetes mellitus, n (%)	50 (29)	477 (29)	0.96	0.79
Insulin-treated diabetes mellitus, n (%)	16 (9)	166 (10)	0.76	0.27
Current smoker, n (%)	22 (13)	236 (14)	0.59	0.82
Arterial hypertension, n (%)	110 (63)	992 (59)	0.32	0.38
Hypercholesterolemia, n (%)	132 (76)	1228 (74)	0.50	0.72
Unstable angina, n (%)	53 (31)	472 (28)	0.53	0.91
Previous myocardial infarction, n (%)	75 (43)	632 (38)	0.17	0.28
Previous aortocoronary bypass surgery, n (%)	29 (17)	154 (9)	0.002	0.004
Previous percutaneous coronary intervention, n (%)	112 (64)	1041 (62)	0.59	0.81
Multivessel disease, n (%)	148 (85)	1392 (83)	0.55	0.68
Left ventricular ejection fraction, %	56.0±12.1	55.1±12.8	0.37	0.23



**TABLE 5. Baseline Angiographic Characteristics of the Lesions**

Characteristic	Target Lesion Revascularization		P	
	Yes (n=192)	No (n=1901)	Univariate	Multivariate
Target vessel, n (%)			0.41	0.78
Left anterior descending coronary artery	95 (50)	880 (46)		
Left circumflex coronary artery	55 (28)	552 (28)		
Right coronary artery	42 (22)	499 (26)		
Complex (type B2/C) lesions, n (%)	152 (79)	1436 (76)	0.26	0.82
Chronic occlusion, n (%)	25 (13)	129 (7)	0.002	0.46
Calcified lesion, n (%)	28 (15)	382 (20)	0.07	0.04
Thrombus-containing lesion, n (%)	6 (3)	54 (3)	0.82	0.30
Bifurcation lesion, n (%)	27 (14)	202 (11)	0.15	0.28
Vessel size, mm	2.53±0.50	2.67±0.49	<0.001	<0.001
Lesion length, mm	13.5±8.1	13.6±7.6	0.83	0.42
Initial diameter stenosis, %	63.0±15.7	60.0±15.1	0.009	0.04

### Discussion

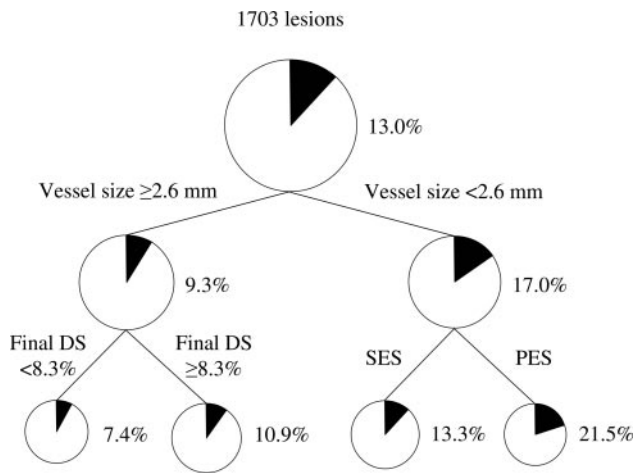
In the present study, we analyzed the predictors of angiographic and clinical restenosis in a series of consecutive patients who underwent implantation of either sirolimus-eluting or paclitaxel-eluting stents. This is the largest number of patients with follow-up angiography studied so far. Overall rates of lesion-based angiographic and clinical restenosis were 13.0% and 9.2%, respectively, further supporting the efficacy of this new technology. Our main results can be summarized as follows: In the era of drug-eluting stents, clinical characteristics play a less relevant role in the prediction of restenosis, and in particular, the presence of diabetes mellitus is not associated with an increased risk; in contrast, vessel size, type of drug-eluting stent, and final angiographic result are strong independent predictors of both angiographic and clinical restenosis.

Drug-eluting stents represent a major advance in cardiology. The improved outcomes with respect to angiographic and clinical restenosis associated with their use have been shown in several randomized trials that have included patients with various clinical and angiographic characteristics. Although angiographic and clinical restenosis rates with drug-eluting stents are markedly lower compared with bare

metal stents, the reported benefit has not been homogeneous across various clinical and angiographic subgroups and with different drug-eluting stents. Consequently, investigators have suggested that several factors may confer a higher risk of restenosis after drug-eluting stent implantation. One of these factors is the reference diameter of the treated vessel, which has been long been regarded as an important predictor of restenosis.<sup>21</sup> In the Sirolimus-Coated Bx Velocity Balloon-Expandable Stent in the Treatment of Patients With De Novo Coronary Artery Lesions (SIRIUS) trial, rates of angiographic restenosis were 17.6% in small vessels and 1.9% in large vessels.<sup>22</sup> With respect to target lesion revascularization rates, they were 6.3% in the subgroup with a vessel size <2.75 mm compared with 1.9% in the subgroup with vessels size ≥2.75 mm.<sup>13</sup> Similarly, in Treatment of De Novo Coronary Disease Using a Single Paclitaxel-Eluting Stent (TAXUS V) trial, the subgroup with small vessels had an angiographic restenosis rate of 31.2%, and the subgroup with large vessels had a restenosis rate of 3.5%.<sup>15</sup> Target lesion revascularization rates in the respective vessel size groups were 10.4% and 0%.<sup>15</sup> In our study, the subgroup of vessels with reference diameter ≥2.6 mm had a significant reduction in the odds of angiographic restenosis and clinical restenosis

**TABLE 6. Procedural Characteristics**

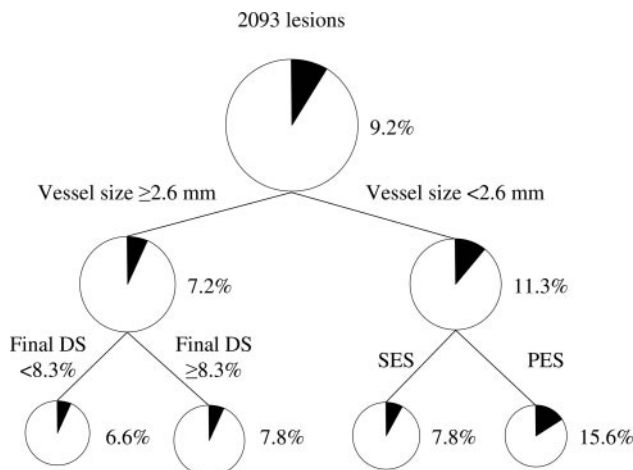
Characteristic	Target Lesion Revascularization		P	
	Yes (n=192)	No (n=1901)	Univariate	Multivariate
Maximal balloon pressure, atm	14.6±3.0	14.5±2.9	0.55	0.43
Maximal balloon diameter, mm	2.97±0.49	3.05±0.47	0.03	0.08
Type of drug-eluting stent, n (%)			0.003	0.01
Sirolimus-eluting stent	86 (44.8)	1065 (56.0)		
Paclitaxel-eluting stent	106 (55.2)	836 (44.0)		
Overlapping stents, n (%)	19 (10)	108 (6)	0.02	0.33
Length of stented segment, mm	23.8±9.7	22.7±9.0	0.12	0.34
Final diameter stenosis, %	9.4±8.2	7.9±6.6	0.002	0.02



**Figure 1.** CART model showing the most important variables influencing the likelihood of angiographic restenosis. The global area of the pie represents the size of the subgroup relative to the whole group; solid area, the proportion of lesions with restenosis. Shown cutoff values are median values of the variable. DS indicates diameter stenosis; SES, sirolimus-eluting stents; and PES, paclitaxel-eluting stents.

compared with the subgroup with reference diameter <2.6 mm. These results provide strong support for the role of vessel size as an important predictor of restenosis in the drug-eluting stent era.

Diabetes mellitus has traditionally been considered a major risk factor for the development of restenosis after coronary angioplasty with or without stenting.<sup>5,23</sup> However, data from recent studies of drug-eluting stents have not consistently related diabetes mellitus with increased rates of restenosis and repeated revascularization procedures. In the subgroup of diabetic patients treated with sirolimus-eluting stents from the SIRIUS trial, angiographic restenosis rates were 17.6% among patients with diabetes mellitus and 6.0% among patients without diabetes mellitus.<sup>24</sup> Lemos et al<sup>25</sup> found in



**Figure 2.** CART model showing the most important variables influencing the likelihood of target lesion revascularization. The global area of the pie represents the size of the subgroup relative to the whole group; solid area, the proportion of lesions with restenosis. Shown cutoff values are median values of the variable. Abbreviations as in Figure 1.

238 registry patients treated with sirolimus-eluting stents that diabetic patients more frequently developed angiographic restenosis compared with their nondiabetic counterparts. In contrast, Kuchulakanti et al<sup>26</sup> found no difference in target lesion revascularization rates between 403 patients with diabetes mellitus and 750 patients without diabetes mellitus. Similarly, in the studies of Berenguer et al<sup>27</sup> and Migliorini et al,<sup>28</sup> diabetes mellitus was not an independent predictor of angiographic and clinical restenosis. Comparable rates of angiographic restenosis rates also were found among patients with (6.4%) and without (8.4%) diabetes mellitus in the diabetes substudy of TAXUS IV trial.<sup>29</sup> However, all the above-mentioned studies have analyzed only patients treated with a particular drug-eluting stent and have had different population sizes and angiographic follow-up rates. In our study, the presence of diabetes mellitus was not associated with an increased risk for angiographic and clinical restenosis in both the univariate and multivariate analyses. Yang et al<sup>30</sup> also did not find an increased risk of restenosis among 226 diabetic patients compared with 560 nondiabetic patients treated with sirolimus-eluting and paclitaxel-eluting stents. It is possible that the high efficacy of these drug-eluting stents has eliminated the propensity of diabetic patients to develop a more pronounced response to balloon and stent injury, leading to more neointimal proliferation, lumen renarrowing, and ultimately increased restenosis and the need for repeated revascularization procedures.

In our study population, we found that the type of drug-eluting stent used was a strong independent predictor of restenosis. This confirms the prediction made by previous studies based on the model relating late lumen loss to angiographic and clinical restenosis that different clinical outcomes may be expected from 2 drug-eluting stents with different extents of late lumen loss.<sup>31–33</sup> Moreover, we showed that differences between the 2 drug-eluting stents used in this study were restricted mainly to small coronary vessels. This finding also has been reported previously in a study analyzing a series of 197 patients treated with these 2 drug-eluting stents in small coronary arteries.<sup>34</sup> Recently, several randomized and nonrandomized studies that have compared sirolimus-eluting with paclitaxel-eluting stents in various subsets of patients with coronary disease have been published.<sup>30,35–42</sup> In 3 randomized studies, angiographic restenosis, target lesion revascularization rates, or both were significantly lower with sirolimus-eluting stents compared with paclitaxel-eluting stents.<sup>36–38</sup> Similar findings also were reported from the nonrandomized prospective study of Yang et al.<sup>30</sup> In 3 other randomized studies,<sup>35,39,40</sup> there were no significant differences between the 2 drug-eluting stents, although in 1 study there was a clear trend toward better outcomes with sirolimus-eluting stents.<sup>40</sup> In the other 2 studies, target vessel revascularization rates were not significantly different between patients treated with either drug-eluting stent despite an absolute difference favoring the sirolimus-eluting stents.<sup>41,42</sup> A recent meta-analysis of 6 randomized trials showed a clear benefit with sirolimus-eluting stents compared with paclitaxel-eluting stents.<sup>43</sup> Several explanations, including differences in pharmacological action between sirolimus and paclitaxel, drug-release kinet-

ics, pattern of drug distribution in the arterial wall, and stent characteristics, have been provided as possible causes of the observed difference in the effectiveness between the sirolimus-eluting and paclitaxel-eluting stents. Our finding that the difference between the sirolimus-eluting and paclitaxel-eluting stents was confined almost exclusively to small vessels (<2.6 mm) might be particularly valuable for the process of stent selection.

The present study also showed that the short-term result of the intervention as reflected by final diameter stenosis is a major factor for restenosis. This is in line with previous findings from studies on bare metal stents<sup>4</sup> and demonstrates that the use of drug-eluting stents does not attenuate the value of optimal acute angiographic results.

### Study Limitations

The large majority of the patients included in this analysis had participated in randomized trials comparing sirolimus-with paclitaxel-eluting stents. However, these stents were not simultaneously available to us; sirolimus-eluting stents were approved earlier for use. Thus, this cohort also includes patients not randomly assigned to a given drug-eluting stent type, and this study lacks the comparative power of specifically designed trials on the relative merits of sirolimus- and paclitaxel-eluting stents.<sup>43</sup> In addition, because of distinct characteristics in stent design and delivery platforms, blinding of stent assignment is impossible even in the framework of a randomized trial. A major limitation of the present study is that it represents the experience gained with only 2 drug-eluting stents, the sirolimus-eluting stent (Cypher) and the paclitaxel-eluting stent (Taxus). Although these stents are currently the most commonly used drug-eluting stents, the findings of the present study cannot be extrapolated to other sirolimus- or paclitaxel-eluting stent platforms in development or other drug-eluting stents coated with different antirestenotic agents. It should also be noted that we used pretreatment with a loading dose of 600 mg clopidogrel. Although no data exist to support an influence of clopidogrel dose in restenosis, we do not know to what extent the present findings can be extrapolated to other clopidogrel pretreatment regimens. Another limitation to be acknowledged is missing follow-up angiographies in 19% of the patients, mainly because of patient refusal. This may reduce the accuracy of angiographic results at follow-up. However, the main findings relative to angiographic restenosis were largely supported by findings relative to clinical restenosis or target lesions revascularization. In addition, angiographic restenosis was defined on the basis of the magnitude of lumen renarrowing in follow-up angiography, but we acknowledge that coronary angiography cannot reliably differentiate between thrombosis and restenosis as causes of lumen renarrowing.

### Conclusions

Vessel size and drug-eluting stent type are the most important predictors of angiographic and clinical restenosis. Drug-eluting stent type has a particular impact on restenosis in small coronary vessels; this finding may facilitate the process of drug-eluting stent selection.

### Disclosures

Dr Kastrati received lecture fees from Bristol-Myers Squibb, Cordis, Glaxo, Lilly, Medtronic, and Sanofi. The other authors report no conflicts of interest.

### References

1. Al Suwaidi J, Berger PB, Holmes DR Jr. Coronary artery stents. *JAMA*. 2000;284:1828–1836.
2. Brophy JM, Belisle P, Joseph L. Evidence for use of coronary stents: a hierarchical Bayesian meta-analysis. *Ann Intern Med*. 2003;138:777–786.
3. Bauters C, Isner JM. The biology of restenosis. *Prog Cardiovasc Dis*. 1997;40:107–116.
4. Kastrati A, Schömig A, Elezi S, Schühlen H, Dirschinger J, Hadamitzky M, Wehinger A, Hausleiter J, Walter H, Neumann FJ. Predictive factors of restenosis after coronary stent placement. *J Am Coll Cardiol*. 1997;30:1428–1436.
5. Elezi S, Kastrati A, Pache J, Wehinger A, Hadamitzky M, Dirschinger J, Neumann FJ, Schömig A. Diabetes mellitus and the clinical and angiographic outcome after coronary stent placement. *J Am Coll Cardiol*. 1998;32:1866–1873.
6. Kastrati A, Mehili J, Dirschinger J, Pache J, Ulm K, Schühlen H, Seyfarth M, Schmitt C, Blasini R, Neumann F, Schömig A. Restenosis after coronary placement of various stent types. *Am J Cardiol*. 2001;87:34–39.
7. Cutlip DE, Chauhan MS, Baim DS, Ho KK, Popma JJ, Carrozza JP, Cohen DJ, Kuntz RE. Clinical restenosis after coronary stenting: perspectives from multicenter clinical trials. *J Am Coll Cardiol*. 2002;40:2082–2089.
8. Ruygrok PN, Webster MW, de Valk V, van Es GA, Ormiston JA, Morel MA, Serruys PW. Clinical and angiographic factors associated with asymptomatic restenosis after percutaneous coronary intervention. *Circulation*. 2001;104:2289–2294.
9. Mercado N, Boersma E, Wijns W, Gersh BJ, Morillo CA, de Valk V, van Es GA, Grobbee DE, Serruys PW. Clinical and quantitative coronary angiographic predictors of coronary restenosis: a comparative analysis from the balloon-to-stent era. *J Am Coll Cardiol*. 2001;38:645–652.
10. Sousa JE, Serruys PW, Costa MA. New frontiers in cardiology: drug-eluting stents, part II. *Circulation*. 2003;107:2383–2389.
11. 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;364:583–591.
12. Morice MC, Serruys PW, Sousa JE, Fajadet J, Ban Hayashi E, Perin M, Colombo A, Schuler G, Barragan P, Guagliumi G, Molnar F, Falotico R. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. *N Engl J Med*. 2002;346:1773–1780.
13. Moses JW, Leon MB, Popma JJ, Fitzgerald PJ, Holmes DR, O'Shaughnessy C, Caputo RP, Kereiakes DJ, Williams DO, Teirstein PS, Jaeger JL, Kuntz RE. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. *N Engl J Med*. 2003;349:1315–1323.
14. Stone GW, Ellis SG, Cox DA, Hermiller J, O'Shaughnessy C, Mann JT, Turco M, Caputo R, Bergin P, Greenberg J, Popma JJ, Russell ME. A polymer-based, paclitaxel-eluting stent in patients with coronary artery disease. *N Engl J Med*. 2004;350:221–231.
15. Stone GW, Ellis SG, Cannon L, Mann JT, Greenberg JD, Spriggs D, O'Shaughnessy CD, DeMaio S, Hall P, Popma JJ, Koglin J, Russell ME. Comparison of a polymer-based paclitaxel-eluting stent with a bare metal stent in patients with complex coronary artery disease: a randomized controlled trial. *JAMA*. 2005;294:1215–1223.
16. Ellis SG, Vandormael MG, Cowley MJ, DiSciascio G, Deligonul U, Topol EJ, Bulle TM. Coronary morphologic and clinical determinants of procedural outcome with angioplasty for multivessel coronary disease: implications for patient selection: Multivessel Angioplasty Prognosis Study Group. *Circulation*. 1990;82:1193–1202.
17. Mintz GS, Popma JJ, Pichard AD, Kent KM, Satler LF, Chuang YC, Ditrano CJ, Leon MB. Patterns of calcification in coronary artery disease: a statistical analysis of intravascular ultrasound and coronary angiography in 1155 lesions. *Circulation*. 1995;91:1959–1965.
18. Zeger SL, Liang KY. Longitudinal data analysis for discrete and continuous outcomes. *Biometrics*. 1986;42:121–130.
19. Liang KY, Zeger SL. Longitudinal data analysis using generalized linear models. *Biometrika*. 1986;73:13–22.



20. Classification and regression trees. In: *S-Plus 2000 Guide to Statistics*. Seattle, Wash: Data Analysis Products Division, Mathsoft Inc; 1999: 369–401.
21. Elezi S, Kastrati A, Neumann FJ, Hadamitzky M, Dirschinger J, Schömig A. Vessel size and long-term outcome after coronary stent placement. *Circulation*. 1998;98:1875–1880.
22. Popma JJ, Leon MB, Moses JW, Holmes DR Jr, Cox N, Fitzpatrick M, Douglas J, Lambert C, Mooney M, Yakubov S, Kuntz RE. Quantitative assessment of angiographic restenosis after sirolimus-eluting stent implantation in native coronary arteries. *Circulation*. 2004;110: 3773–3780.
23. Carrozza JP Jr, Kuntz RE, Fishman RF, Baim DS. Restenosis after arterial injury caused by coronary stenting in patients with diabetes mellitus. *Ann Intern Med*. 1993;118:344–349.
24. Moussa I, Leon MB, Baim DS, O'Neill WW, Popma JJ, Buchbinder M, Midwall J, Simonton CA, Keim E, Wang P, Kuntz RE, Moses JW. Impact of sirolimus-eluting stents on outcome in diabetic patients: a SIRIUS (Sirolimus-Coated Bx Velocity Balloon-Expandable Stent in the Treatment of Patients With De Novo Coronary Artery Lesions) substudy. *Circulation*. 2004;109:2273–2278.
25. Lemos PA, Hoyer A, Goedhart D, Arampatzis CA, Saia F, van der Giessen WJ, McFadden E, Sianos G, Smits PC, Hofma SH, de Feyter PJ, van Domburg RT, Serruys PW. Clinical, angiographic, and procedural predictors of angiographic restenosis after sirolimus-eluting stent implantation in complex patients: an evaluation from the Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital (RESEARCH) study. *Circulation*. 2004;109:1366–1370.
26. Kuchulakanti PK, Torguson R, Canos D, Rha SW, Chu WW, Clavijo L, Deible R, Gevorkian N, Suddath WO, Satler LF, Kent KM, Pichard AD, Waksman R. Impact of treatment of coronary artery disease with sirolimus-eluting stents on outcomes of diabetic and nondiabetic patients. *Am J Cardiol*. 2005;96:1100–1106.
27. Berenguer A, Mainar V, Bordes P, Valencia J, Gomez S, Lozano T. Incidence and predictors of restenosis after sirolimus-eluting stent implantation in high-risk patients. *Am Heart J*. 2005;150:536–542.
28. Migliorini A, Shehu M, Carrabba N, Giurlani L, Valenti R, Buonamici P, Dovellini EV, Parodi G, Antoniucci D. Predictors of outcome after sirolimus-eluting stent implantation for complex in-stent restenosis. *Am J Cardiol*. 2005;96:1110–1112.
29. Hermiller JB, Raizner A, Cannon L, Gurbel PA, Kutcher MA, Wong SC, Russell ME, Ellis SG, Mehran R, Stone GW. Outcomes with the polymer-based paclitaxel-eluting TAXUS stent in patients with diabetes mellitus: the TAXUS-IV trial. *J Am Coll Cardiol*. 2005;45:1172–1179.
30. Yang TH, Park SW, Hong MK, Park DW, Park KM, Kim YH, Han KH, Lee CW, Cheong SS, Kim JJ, Park SJ. Impact of diabetes mellitus on angiographic and clinical outcomes in the drug-eluting stents era. *Am J Cardiol*. 2005;96:1389–1392.
31. Mauri L, Orav EJ, Kuntz RE. Late loss in lumen diameter and binary restenosis for drug-eluting stent comparison. *Circulation*. 2005;111: 3435–3442.
32. Mauri L, Orav EJ, Candia SC, Cutlip DE, Kuntz RE. Robustness of late lumen loss in discriminating drug-eluting stents across variable observational and randomized trials. *Circulation*. 2005;112:2833–2839.
33. Kereiakes DJ, Kuntz RE, Mauri L, Krucoff MW. Surrogates, substudies, and real clinical end points in trials of drug-eluting stents. *J Am Coll Cardiol*. 2005;45:1206–1212.
34. Rodriguez-Granillo GA, Valgimigli M, Garcia-Garcia HM, Ong AT, Aoki J, van Mieghem CA, Tsuchida K, Sianos G, McFadden E, van der Giessen WJ, van Domburg R, de Feyter P, Serruys PW. One-year clinical outcome after coronary stenting of very small vessels using 2.25 mm sirolimus- and paclitaxel-eluting stents: a comparison between the RESEARCH and T-SEARCH registries. *J Invasive Cardiol*. 2005;17: 409–412.
35. 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;45:308–311.
36. Kastrati A, Mehili J, von Beckerath N, Dibra A, Hausleiter J, Pache J, Schühlen H, Schmitt C, Dirschinger J, Schömig A. 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;293:165–171.
37. Dibra A, Kastrati A, Mehili J, Pache J, Schühlen H, von Beckerath N, Ulm K, Wessely R, Dirschinger J, Schömig A. Paclitaxel-eluting or sirolimus-eluting stents to prevent restenosis in diabetic patients. *N Engl J Med*. 2005;353:663–670.
38. Windecker S, Remondino A, Eberli FR, Juni P, Raber L, Wenaweser P, Togni M, Billinger M, Tuller D, Seiler C, Roffi M, Corti R, Sutsch G, Maier W, Luscher T, Hess OM, Egger M, Meier B. Sirolimus-eluting and paclitaxel-eluting stents for coronary revascularization. *N Engl J Med*. 2005;353:653–662.
39. Morice MC. Eight-month outcome of the Reality Study: a prospective, randomized, multi-center head-to-head comparison of the sirolimus-eluting stent (Cypher) and the paclitaxel-eluting stent (Taxus). Paper presented at: Scientific Session of the American College of Cardiology; March 2005; Orlando, Fla.
40. de Lezo J, Medina A, Pan M, Romero M, Delgado A, Segura J, Hernandez E, Pavlovic D, Ojeda S, Fernandez-Duenas J, Ariza H, Melian F. Drug-eluting stents for complex lesions: randomized rapamycin versus paclitaxel CORPAL study. *J Am Coll Cardiol*. 2005;45:75A. Abstract.
41. Ong AT, Serruys PW, Aoki J, Hoyer A, van Mieghem CA, Rodriguez-Granillo GA, Valgimigli M, Sonnenschein K, Regar E, van der Ent M, de Jaegere PP, McFadden EP, Sianos G, van der Giessen WJ, de Feyter PJ, van Domburg RT. The unrestricted use of paclitaxel- versus sirolimus-eluting stents for coronary artery disease in an unselected population: one-year results of the Taxus-Stent Evaluated at Rotterdam Cardiology Hospital (T-SEARCH) Registry. *J Am Coll Cardiol*. 2005;45:1135–1141.
42. Kaiser C, Brunner-La Rocca HP, Buser PT, Bonetti PO, Osswald S, Linka A, Bernheim A, Zutter A, Zellweger M, Grize L, Pfisterer ME. Incremental cost-effectiveness of drug-eluting stents compared with a third-generation bare-metal stent in a real-world setting: randomised Basel Stent Kosten Effektivitäts Trial (BASKET). *Lancet*. 2005;366:921–929.
43. Kastrati A, Dibra A, Eberle S, Mehili J, Suarez de Lezo J, Goy JJ, Ulm K, Schömig A. Sirolimus-eluting stents vs paclitaxel-eluting stents in patients with coronary artery disease: meta-analysis of randomized trials. *JAMA*. 2005;294:819–825.

## CLINICAL PERSPECTIVE

The efficacy of drug-eluting stents in reducing restenosis risk has not been uniform across patient subsets. Identifying predictive factors of restenosis may facilitate the decision-making process of the physicians and improve outcomes of patients after percutaneous coronary interventions. We assessed angiographic and clinical restenosis (target lesion revascularization) in 1845 patients who underwent implantation of sirolimus- or paclitaxel-eluting stents in 2093 target lesions. Multivariable analysis showed that vessel size, final diameter stenosis, and drug-eluting stent type were the strongest predictors of restenosis. A 0.5-mm decrease in vessel size was associated with adjusted ORs of 1.74 (95% CI, 1.31 to 2.32) for angiographic restenosis and 1.65 (1.22 to 2.23) for target lesion revascularization. A 5% increase in final diameter stenosis was associated with adjusted ORs of 1.30 (95% CI, 1.15 to 1.47) for angiographic restenosis and 1.18 (95% CI, 1.03 to 1.35) for target lesion revascularization. Sirolimus-eluting stent was associated with adjusted ORs of 0.60 (95% CI, 0.44 to 0.81) for angiographic restenosis and 0.67 (95% CI, 0.49 to 0.91) for target lesion revascularization. Clinical characteristics played a less significant role in the prediction of restenosis. Thus, vessel size and drug-eluting stent type are the most important predictors of angiographic and clinical restenosis. Drug-eluting stent type has a particular impact on restenosis in small coronary vessels; this finding may facilitate the process of drug-eluting stent selection.