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

Adnan Kastrati, MD
Julinda Mehilli, MD
Nicolas von Beckerath, MD
Alban Dibra, MD
Jörg Hausleiter, MD
Jürgen Pache, MD
Helmut Schühlen, MD
Claus Schmitt, MD
Josef Dirschinger, MD
Albert Schömig, MD
for the ISAR-DESIRE Study Investigators

Restenosis affects 20% to 40% of de novo coronary lesions treated with bare metal stents. Although it is often considered a benign process, recent data indicate that in-stent restenosis has a negative impact on long-term survival of patients treated with coronary stents. Another problem associated with in-stent restenosis is the difficulty of finding appropriate treatment modalities to reduce the excessive risk of recurrence. Plain balloon angioplasty is the first-line treatment option for in-stent restenosis, yet its results have often been disappointing with a recurrence rate above 40%. Repeated use of bare stents appears to further exacerbate the risk of recurrence. Alternative interventional options, including rotational atherectomy, excimer laser angioplasty, directional coronary atherectomy, and cutting balloon, have not provided additional benefits. Although brachytherapy is currently the treatment approach most supported by evidence for in-stent restenosis, the context of this trial demonstrates the superiority of drug-eluting stents in preventing restenosis.

Context In patients with de novo coronary lesions, drug-eluting stents have drastically reduced restenosis risk compared with bare metal stents and conventional balloon angioplasty. It is less clear whether drug-eluting stents are superior to conventional balloon angioplasty for the treatment of patients with in-stent restenosis.

Objectives To assess if drug-eluting stents are a more effective treatment of in-stent restenosis than conventional balloon angioplasty, and to assess the relative merits of 2 drug-eluting stents, a sirolimus-eluting stent and a paclitaxel-eluting stent.

Design, Setting, and Participants Randomized, open-label, active-controlled trial conducted among 300 patients with angiographically significant in-stent restenosis in 2 tertiary German centers from June 1, 2003, to October 20, 2003.

Interventions After pretreatment with 600 mg of clopidogrel for at least 2 hours before intervention, all patients were randomly assigned to 1 of 3 treatment groups: sirolimus stent, paclitaxel stent, or balloon angioplasty (100 patients in each group).

Main Outcome Measures Primary end point: angiographic restenosis (diameter stenosis ≥50%) at 6-month follow-up angiography based on “in-segment” analysis. Primary analysis was comparison between stent groups and balloon angioplasty groups; a secondary analysis compared sirolimus and paclitaxel stents.

Results Follow-up angiography was performed in 275 (92%) of 300 patients. The incidence of angiographic restenosis was 44.6% (41/92) in the balloon angioplasty group, 14.3% (13/91) in the sirolimus stent group (P = .001 vs balloon angioplasty), and 21.7% (20/92) in the paclitaxel stent group (P = .001 vs balloon angioplasty). When compared with balloon angioplasty, receiving a sirolimus stent had a relative risk (RR) of angiographic restenosis of 0.32 (95% confidence interval [CI], 0.18–0.56); a paclitaxel stent had an RR of 0.49 (95% CI, 0.31–0.76). The incidence of target vessel revascularization was 33.0% (33/100) in the balloon angioplasty group, 8.0% (8/100) in the sirolimus stent group (P < .001 vs balloon angioplasty), and 19.0% (19/100) in the paclitaxel stent group (P = .02 vs balloon angioplasty). The secondary analysis showed a trend toward a lower rate of angiographic restenosis (P = .19) and a significantly lower rate of target vessel revascularization (P = .02) among sirolimus stent patients compared with paclitaxel stent patients.

Conclusions In patients with in-stent restenosis, a strategy based on sirolimus- or paclitaxel-eluting stents is superior to conventional balloon angioplasty for the prevention of recurrent restenosis. Sirolimus-eluting stents may be superior to paclitaxel-eluting stents for treatment of this disorder.

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Drug-eluting stents have emerged as the most successful strategy in the primary prevention of restenosis. Randomized clinical trials including patients with de novo lesions have shown that sirolimus and paclitaxel stents lead to a marked reduction of restenosis with incidences below the limit of 10%. Although no data are available from head-to-head comparisons, findings from recent studies suggest that sirolimus and paclitaxel stents may have equivalent efficacy for treatment of de novo lesions. Observational studies have reported encouraging results with the use of drug-eluting stents in in-stent restenosis lesions. However, plain balloon angioplasty currently represents the most common form of therapy used in patients with in-stent restenosis, and no randomized trials have addressed the issue of whether drug-eluting stents provide advantages over plain angioplasty. In addition, the particularly high risk for recurrence associated with in-stent restenosis lesions is more demanding and may render better evidence of subtle differences in performance between various drug-eluting stents.

The primary objective of this trial was to assess whether 2 different drug-eluting stents approved by the US Food and Drug Administration are more effective for treatment of in-stent restenosis lesions than conventional balloon angioplasty. The secondary objective of this trial was to assess the relative merits of 2 drug-eluting stents—a sirolimus-eluting stent and a paclitaxel-eluting stent—in the prevention of recurrences in patients with in-stent restenosis.

**METHODS**

**Patients**

Eligible patients had angina pectoris and/or a positive stress test and presented with angiographically significant in-stent restenosis (lumen narrowing of ≥50% at a previously stented segment) in native coronary vessels. Acute myocardial infarction; in-stent restenosis lesions in the left main coronary artery; lesions created by restenosis of drug-eluting stents; and known allergy to sirolimus, paclitaxel, heparin, aspirin, or clopidogrel were pre-specified exclusion criteria. The study protocol was approved by the institutional ethics committee, and all patients gave written informed consent for participation in this trial.

**Randomization, Interventions, and Adjunct Drug Therapy**

From June 1, 2003, to October 20, 2003, 300 patients were enrolled and randomly assigned to receive a sirolimus stent (n = 100), a paclitaxel stent (n = 100), or balloon angioplasty (n = 100) (Figure 1). All patients received a loading dose of 600 mg of clopidogrel at least 2 hours before coronary angiography. Eligible patients who did not meet any exclusion criteria were enrolled in the study immediately after coronary angiography. Randomization was done according to a computer-generated random sequence with a block size of 30. Sealed envelopes in the catheterization laboratories of the 2 participating hospitals, Deutsches Herz-Zentrum and I. Medizinische Klinik rechts der Isar, both in Munich, Germany, included the treatment arm to which the patients were assigned: sirolimus-eluting stent (Cypher, Cordis Corporation, Miami Lakes, Fla), paclitaxel-eluting stent (Taxus, Boston Scientific Corporation, Natick, Mass), or balloon angioplasty. Sirolimus stents were available in diameters of 2.25 mm, 2.5 mm, 2.75 mm, 3.0 mm, and 3.5 mm, and in lengths of 8 mm, 13 mm, 18 mm, 23 mm, 28 mm, and 33 mm. Paclitaxel stents were available in diameters of 2.25 mm, 2.5 mm, 2.75 mm, 3.0 mm, and 3.5 mm, and in lengths of 8 mm, 12 mm, 16 mm, 20 mm, 24 mm, 28 mm, and 32 mm.

Both balloon angioplasty and stenting procedures were performed according to standard techniques. The number and length of stents to be implanted were left to the operator’s discretion, but the recommendation was to fully cover the restenotic lesion. Among patients assigned to receive balloon angioplasty, the use of stents was strongly discouraged. However, operators were allowed to use only bare stents to cover large (≥5 mm) dissections created after balloon angioplasty outside the previously stented area. The operators were to decide whether to perform direct stenting or stenting after predilatation.

All patients received intravenous aspirin (500 mg) and heparin (140 U/kg of body weight) during the procedure. Postinterventional antiplatelet therapy consisted of aspirin (100 mg twice daily indefinitely) and clopidogrel (75 mg twice daily until discharge and once daily for ≥6 months). Other medications, including statins, β-blockers, and angiotensin-converting enzyme inhibitors, were given if considered necessary by the attending physician.

**Follow-up Protocol**

Patients stayed in hospital for at least 48 hours after randomization. During the in-hospital period, electrocardiograms were recorded and blood was collected for determination of creatine kinase (CK) and its MB isoenzyme before randomization and every 8 hours for the first 24 hours after randomization and daily afterward. Patients were contacted by phone after 30 days (±7 days) to assess their clinical status. All patients were asked to return for coronary angiography between 6 and 8
months after randomization or earlier if they had anginal symptoms. Telephone interviews were repeated at 9 months (±1 month) and 12 months (±1 month). All patients reporting symptoms of chest pain were requested to come to the outpatient clinic for clinical, electrocardiographic, laboratory, and, eventually, angiographic assessment. Relevant data were collected and entered into a computer database by specialized personnel of the Clinical Data Management Center. All data were verified against source documentation and an events committee blinded to the treatment groups adjudicated all adverse clinical events.

**Quantitative Coronary Angiography Evaluation**

Coronary angiograms at baseline after completion of the procedure and at follow-up were digitally recorded and sent for assessment to the Quantitative Angiographic Core Laboratory (Deutsches Herzzentrum, Munich, Germany). Angiographic readers were wholly unaware of the stent model used and study allocation. Digital angiograms were analyzed with use of an automated edge detection system (CMS, Medis Medical Imaging Systems, Nuenen, the Netherlands). In-stent restenosis patterns at baseline were defined angiographically according to the system proposed by Mehran et al.14

All measurements were performed on cineangiograms recorded after intracoronary nitroglycerin administration. The same projections were used at all time points. The contrast-filled montaged catheter tip was used for calibration. Quantitative parameters measured included the reference diameter of the vessel, the minimal lumen diameter, percent diameter stenosis (difference between the reference diameter and minimal lumen diameter/reference diameter × 100), late lumen loss (difference between minimal lumen diameter at the end of the procedure and minimal lumen diameter at follow-up), and net lumen gain (difference between minimal lumen diameter at follow-up and minimal lumen diameter before the procedure). For patients assigned to the stent arms, quantitative analysis was performed in the “in-stent” area (“in-stent” analysis) and in the “in-segment” area including the stented segment as well as both 5-mm margins proximal and distal to the drug-eluting stent implanted during the index procedure (“in-segment” analysis).

**Study End Points and Definitions**

The primary end point of the study was binary angiographic restenosis defined as a diameter stenosis of 50% or greater at follow-up angiography on the basis of the “in-segment” analysis. Secondary end points were net lumen gain (a continuous quantitative angiographic parameter), target vessel revascularization due to restenosis, and the combined incidence of death or myocardial infarction during 1 year of follow-up. Two types of analyses were planned to be done by protocol: the primary analysis consisting of separate comparisons of the sirolimus and paclitaxel stent arms on one side with the angioplasty arm on the other side, and a comparison between the 2 stent arms, sirolimus and paclitaxel, with each other.

The diagnosis of myocardial infarction during the follow-up was established whenever new Q-waves appeared in the electrocardiogram and/or the CK-MB value rose to 3 or more times the upper limit of normal. Target vessel revascularization was defined as any repeat percutaneous coronary intervention or aortocoronary bypass surgery involving the target vessel due to lumen renarrowing associated with symptoms or objective signs of ischemia.

**Statistical Analysis**

To calculate sample size, we assumed an angiographic restenosis rate of 40% in the angioplasty arm and 20% in both the sirolimus stent and paclitaxel stent arms and incorporated the method appropriate for more than 2 groups described by Lachin.15 We intended to give 80% power to the study and chose an α level of .025 (the usual α level of .05 corrected for the 2 planned comparisons in the primary analysis according to the Bonferroni method). A sample size of 85 patients in each group was calculated. We included 100 patients in each group to accommodate for possible losses to follow-up angiography. All analyses relative to the sample size calculation were performed with nQuery Advisor, Version 4.0 (Statistical Solutions, Cork, Ireland).

All analyses were done on the basis of the intention-to-treat principle, ie, the
analyses were based on all randomized patients, as randomized. Because most of the quantitative angiographic data were not normally distributed, continuous data are presented as median (interquartile range [IQR]). Categorical data are presented as counts or proportions (percentage). Baseline clinical and angiographic characteristics as well as procedural variables were checked for statistically significant differences with analysis of variance (continuous data) or contingency table analysis (categorical data). Differences between groups in outcome variables were assessed using the $\chi^2$ test or Fisher exact test (whenever an expected cell value was <5) for categorical data, and the Kruskal-Wallis rank sum test and Wilcoxon rank sum test for continuous data. The relative risk (RR) and its 95% confidence interval (CI) were computed for outcome measures. A $P$ value of <.025 was considered statistically significant. Statistical software S-PLUS, version 4.5 (S-PLUS, Insightful Corp, Seattle, Wash) was used for all analyses.

**RESULTS**

Baseline demographic, clinical, and angiographic characteristics are shown in Table 1, and procedural characteristics are shown in Table 2. A higher balloon pressure was used in the 2 stent groups compared with the balloon angioplasty group. In addition, final results were better in the 2 stent groups as shown by a bigger minimal lumen diameter and a smaller diameter stenosis at the end of procedure. Operators were unable to place a stent in 3 patients of the sirolimus stent group and in 2 patients of the paclitaxel stent group. A single stent was implanted in 92 patients of the sirolimus stent group and in 89 patients of the paclitaxel stent group, and 2 stents were placed in 5 patients of the sirolimus stent group and in 9 patients of the paclitaxel stent group. The median total length of stents implanted in each patient was 23.0 mm (IQR, 18.0-33.0 mm) in the sirolimus stent group and 20.0 mm (IQR, 16.0-26.0 mm) in the paclitaxel stent group (P = .60). Operators used bare metal stents in only 4 of the 100 patients assigned to the balloon angioplasty group. No patient experienced vessel closure during the first 30 days after randomization.

### Angiographic Results

Angiographic follow-up was performed after a median of 197 days (IQR, 176-203 days) in 92% of the patients (Figure 1). Table 3 shows the results of the quantitative analysis performed on follow-up angiograms. The primary end point of the trial—the incidence of angiographic restenosis (Figure 2)—was noted in 44.6% in the

### Table 1. Baseline Characteristics*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Sirolimus Stent Group (n = 100)</th>
<th>Paclitaxel Stent Group (n = 100)</th>
<th>Balloon Angioplasty Group (n = 100)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (IQR), y</td>
<td>63.2 (55.5-70.8)</td>
<td>65.4 (57.6-73.9)</td>
<td>64.3 (57.1-72.9)</td>
<td>.27</td>
</tr>
<tr>
<td>Women</td>
<td>22 (22)</td>
<td>21 (21)</td>
<td>22 (22)</td>
<td>.98</td>
</tr>
<tr>
<td>Diabetes</td>
<td>31 (31)</td>
<td>31 (31)</td>
<td>25 (25)</td>
<td>.63</td>
</tr>
<tr>
<td>Current smoker</td>
<td>13 (13)</td>
<td>9 (9)</td>
<td>12 (12)</td>
<td>.65</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>58 (58)</td>
<td>53 (53)</td>
<td>59 (59)</td>
<td>.66</td>
</tr>
<tr>
<td>Arterial hypertension</td>
<td>51 (51)</td>
<td>56 (56)</td>
<td>56 (56)</td>
<td>.71</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>45 (45)</td>
<td>55 (55)</td>
<td>47 (47)</td>
<td>.33</td>
</tr>
<tr>
<td>Previous bypass surgery</td>
<td>13 (13)</td>
<td>15 (15)</td>
<td>12 (12)</td>
<td>.82</td>
</tr>
<tr>
<td>Left ventricular ejection</td>
<td>58.0 (48.0-63.0)</td>
<td>56.0 (48.0-62.0)</td>
<td>57.0 (49.0-63.0)</td>
<td>.91</td>
</tr>
<tr>
<td>Target vessel</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAD</td>
<td>46 (46)</td>
<td>42 (42)</td>
<td>48 (48)</td>
<td>.39</td>
</tr>
<tr>
<td>LCx</td>
<td>20 (20)</td>
<td>31 (31)</td>
<td>26 (26)</td>
<td>.85</td>
</tr>
<tr>
<td>RCA</td>
<td>34 (34)</td>
<td>27 (27)</td>
<td>26 (26)</td>
<td></td>
</tr>
<tr>
<td>In-stent restenosis pattern†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>60 (60)</td>
<td>51 (51)</td>
<td>58 (58)</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>34 (34)</td>
<td>44 (44)</td>
<td>38 (38)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>2 (2)</td>
<td>2 (2)</td>
<td>1 (1)</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>4 (4)</td>
<td>3 (3)</td>
<td>3 (3)</td>
<td></td>
</tr>
<tr>
<td>Vessel size, median (IQR), mm</td>
<td>2.60 (2.23-2.93)</td>
<td>2.60 (2.29-2.91)</td>
<td>2.57 (2.1-2.84)</td>
<td>.25</td>
</tr>
<tr>
<td>Lesion length, median (IQR), mm</td>
<td>12.4 (7.9-18.3)</td>
<td>11.5 (8.4-19.1)</td>
<td>12.3 (9.0-16.7)</td>
<td>.87</td>
</tr>
<tr>
<td>Minimal lumen diameter prior to procedure, median (IQR), mm</td>
<td>0.91 (0.73-1.17)</td>
<td>0.97 (0.75-1.26)</td>
<td>0.95 (0.72-1.21)</td>
<td>.53</td>
</tr>
<tr>
<td>Diameter stenosis prior to procedure, median (IQR), %</td>
<td>63.8 (53.3-71.6)</td>
<td>61.0 (52.2-71.3)</td>
<td>61.8 (52.7-70.8)</td>
<td>.59</td>
</tr>
</tbody>
</table>

*Data shown as number (percentage) of patients unless otherwise indicated.

†Pattern I includes focal (≤10 mm in length); pattern II is in-stent restenosis greater than 10 mm within the stent; pattern III includes in-stent restenosis greater than 10 mm extending outside the stent; and pattern IV is totally occluded in-stent restenosis.

### Table 2. Procedural Characteristics*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Sirolimus Stent Group (n = 100)</th>
<th>Paclitaxel Stent Group (n = 100)</th>
<th>Balloon Angioplasty Group (n = 100)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximal balloon pressure, atm</td>
<td>14.0 (12.0-16.0)</td>
<td>14.0 (12.0-16.0)</td>
<td>14.0 (10.0-16.0)</td>
<td>.05</td>
</tr>
<tr>
<td>Balloon-to-vessel ratio</td>
<td>1.18 (1.10-1.23)</td>
<td>1.17 (1.07-1.27)</td>
<td>1.15 (1.04-1.28)</td>
<td>.54</td>
</tr>
<tr>
<td>Patients who received stent, No. (%)</td>
<td>97 (97)</td>
<td>98 (98)</td>
<td>4 (4)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Minimal lumen diameter after procedure, mm</td>
<td>2.52 (2.23-2.73)</td>
<td>2.56 (2.30-2.92)</td>
<td>2.07 (1.72-2.41)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Diameter stenosis immediately after procedure, %</td>
<td>9.7 (6.0-12.5)</td>
<td>9.0 (5.0-14.2)</td>
<td>19.9 (13.2-29.5)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

*Data shown as median (interquartile range) unless otherwise indicated.

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balloon angioplasty group (41 of 92 patients), in 14.3% in the sirolimus stent group (13 of 91 patients, P<.001 vs balloon angioplasty), and in 21.7% in the paclitaxel stent group (20 of 92 patients, P=.001 vs balloon angioplasty). When compared with assignment to receive balloon angioplasty, assignment to the sirolimus stent group was associated with an RR of target vessel revascularization of 0.58 (95% CI, 0.35-0.94) and assignment to the paclitaxel stent groups (20 of 92 patients) was associated with an RR of target vessel revascularization of 0.24 (95% CI, 0.12-0.56) and assignment to the paclitaxel stent group was associated with an RR of 0.50), and assignment to the paclitaxel stent group was associated with an RR of 0.58 (95% CI, 0.35-0.94).

When compared with assignment to receive balloon angioplasty, assignment to the sirolimus stent group was associated with an RR of target vessel revascularization of 0.58 (95% CI, 0.35-0.94) and assignment to the paclitaxel stent groups (20 of 92 patients) was associated with an RR of target vessel revascularization of 0.24 (95% CI, 0.12-0.56) and assignment to the paclitaxel stent group was associated with an RR of 0.50), and assignment to the paclitaxel stent group was associated with an RR of 0.58 (95% CI, 0.35-0.94).

Clinical Outcome

One-year follow-up was completed in all but 5 patients (1.7%): 2 in the sirolimus stent group, 2 in the paclitaxel stent group, and 1 in the balloon angioplasty group. The length of follow-up interval in these 5 patients was between 34 and 210 days (median, 182 days). Table 4 shows the adverse clinical events observed during 1 year. Although there were no differences in mortality and in the incidence of myocardial infarction, the need for target vessel revascularization (a secondary end point of the trial) was significantly lower in the sirolimus and paclitaxel stent groups (Figure 2). When compared with assignment to receive balloon angioplasty, the assignment to the sirolimus stent group was associated with an RR of target vessel revascularization of 0.24 (95% CI, 0.12-0.50), and assignment to the paclitaxel stent group was associated with an RR of 0.58 (95% CI, 0.35-0.94).

Sirolimus-Eluting Stent vs Paclitaxel-Eluting Stent

A secondary analysis was performed to compare measures of restenosis between the 2 drug-eluting stent groups (Table 5). We found either a trend or a significant difference in favor of the sirolimus stent group. When compared with the assignment to the paclitaxel stent group, the assignment to the sirolimus stent group was associated with an RR of angiographic restenosis of 0.32 (95% CI, 0.18-0.56) and assignment to the paclitaxel stent groups (Figure 2). When compared with the assignment to the paclitaxel stent group, the assignment to the sirolimus stent group was associated with an RR of angiographic restenosis of 0.66 (95% CI, 0.35-1.24). One of the 13 patients with restenosis in the sirolimus stent group and 3 of the 20 patients with restenosis in the paclitaxel stent group had total occlusion in follow-up angiography. Three of the 13 patients with restenosis in the sirolimus stent group and 6 of the 20 patients with restenosis in the paclitaxel stent group had diffuse restenosis morphology. Among the patients who received a single drug-eluting stent, the angiographic restenosis rate was 14.1% (12 of 85 patients) in the sirolimus stent group and 22.0% (18 of 82 patients) in the paclitaxel stent group (P=.19). In addition, the incidence of target vessel revascularization was significantly lower in the sirolimus stent group (8.0%, 8 of 100 patients) than in the paclitaxel stent group (19.0%, 19 of 100 patients) (P=.02). When compared with assignment to the paclitaxel stent group, the assignment to the sirolimus stent group was associated with an RR of target vessel revascularization of 0.42 (95% CI, 0.19-0.92).

COMMENT

The main finding of this randomized clinical trial was a marked reduction of recurrent restenosis with 2 drug-eluting stents (sirolimus and paclitaxel) in patients with in-stent restenosis. When compared with balloon angioplasty, both stents led to 51% to 68% reduction of the risk of angiographic restenosis and to 42% to 76% reduction of the need for target vessel revascularization. There was no increased risk of late total occlusion with drug-eluting stents.

We chose to use conventional balloon angioplasty as the control because it is currently the most commonly used treatment strategy in this patient population despite its known limitations. Several randomized trials have been published on the value of brachytherapy in patients with in-stent restenosis in native vessels. Recurrent restenosis at 6-month angiographic follow-up was reduced from 44% to 60% in control groups of conventional balloon angioplasty to 22% to 32% in the brachytherapy groups. In contrast to these favorable data, there have been concerning reports on the late total occlusion and the limited durability of the initial benefit achieved by brachytherapy. Among
308 patients enrolled in the brachytherapy arm of different randomized trials, Waksman et al\(^{21}\) found 28 cases (9.1%) of late total occlusion (\(>28\) days after application) of the treated vessel frequently associated with severe ischemic events; this complication occurred much less often in the control patients treated with balloon angioplasty (1.2%). In addition, target vessel revascularization was required 3 times more frequently in the brachytherapy group than in the control group after the first 6 months after randomization.\(^{7}\) Although our trial shows that drug-eluting stents are an effective treatment option for patients with in-stent restenosis, we do not know whether they are superior to brachytherapy, and the lack of a brachytherapy group as a control in this study should be acknowledged as a limitation. Thus, the definitive answer regarding the optimal treatment of in-stent restenosis will come after the completion of ongoing trials that include both brachytherapy and drug-eluting stent arms.

Both measures of restenosis in the 2 drug-eluting stent groups, the incidence of angiographic restenosis and the degree of late lumen loss observed in the sirolimus and paclitaxel stent groups, were higher than the respective values recorded in previously published randomized trials on the value of these devices for de novo lesions.\(^{9,10}\) In our in-stent restenosis patients, we found an incidence of angiographic restenosis of 14.3% and a median late lumen loss of 0.32 mm in the sirolimus stent group. In the biggest randomized trial of the sirolimus stent for de novo lesions, the angiographic restenosis rate was 8.9% and mean late lumen loss was 0.24 mm.\(^{9}\) We also found an incidence of angiographic restenosis of 21.7% and a median late lumen loss of 0.55 mm in the paclitaxel stent group. In the biggest randomized trial of the paclitaxel stent for de novo lesions, the angiographic restenosis rate was 7.9% and mean late lumen loss was 0.39 mm.\(^{10}\) A previous randomized trial has also shown that the results of sirolimus stents in bifurcation lesions are less favorable than those for less complex lesions.\(^{12}\) This may indicate that more challenging lesions may require adjustments in the dose regimen of the antiproliferative drugs and an “individualized” drug-eluting stent platform tailored to lesion and patient characteristics may be preferable in these situations.

Although not part of the primary analysis, the comparison between the sirolimus-eluting stents and paclitaxel-eluting stents may be of particular interest because it suggested that there may be differences between the 2 drug-eluting stents evaluated in their perforations with a particularly high risk for restenosis such as restenotic lesions. Previous publications support the concept that a higher lesion complexity facilitates the distinction in performance between 2 different stents.\(^{24,25}\)

In conclusion, the results of this randomized controlled trial demonstrate that a strategy based on sirolimus- or paclitaxel-eluting stents is superior to conventional balloon angioplasty for the prevention of recurrent restenosis in patients with in-stent restenosis. They also suggest that in this high-risk subset of patients, sirolimus-eluting stents may be superior to paclitaxel-eluting stents.

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### Table 4. Clinical Outcome at 1 Year

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Sirolimus Stent Group (n = 100)</th>
<th>Paclitaxel Stent Group (n = 100)</th>
<th>Balloon Angioplasty Group (n = 100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>2 (2)</td>
<td>2 (2)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Target vessel revascularization</td>
<td>8 (8)*</td>
<td>19 (19)†</td>
<td>33 (33)</td>
</tr>
</tbody>
</table>

*P < .001 vs balloon angioplasty.
†P = .02 vs balloon angioplasty. For all other comparisons, P ≥ .50.

### Table 5. Results of Quantitative Angiographic Analysis at Follow-up in Patients of Drug-Eluting Stent Groups*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Sirolimus Stent Group (n = 91)</th>
<th>Paclitaxel Stent Group (n = 92)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimum lumen diameter</td>
<td>2.45 (2.01 to 2.76)</td>
<td>2.21 (1.80 to 2.60)</td>
<td>.05</td>
</tr>
<tr>
<td>In-stent, mm</td>
<td>2.12 (1.63 to 2.56)</td>
<td>2.02 (1.62 to 2.40)</td>
<td>.23</td>
</tr>
<tr>
<td>In-segment, mm</td>
<td>12.6 (7.3 to 22.8)</td>
<td>19.6 (11.3 to 36.7)</td>
<td>.004</td>
</tr>
<tr>
<td>Diameter stenosis percentage</td>
<td>23.1 (13.2 to 35.5)</td>
<td>26.6 (19.0 to 45.7)</td>
<td>.04</td>
</tr>
<tr>
<td>Late lumen loss</td>
<td>0.10 (−0.12 to 0.38)</td>
<td>0.26 (0.01 to 0.76)</td>
<td>.004</td>
</tr>
<tr>
<td>In-stent, mm</td>
<td>0.32 (0.03 to 0.74)</td>
<td>0.55 (0.23 to 0.90)</td>
<td>.02</td>
</tr>
<tr>
<td>In-segment, mm</td>
<td>1.41 (1.03 to 1.77)</td>
<td>1.20 (0.71 to 1.59)</td>
<td>.02</td>
</tr>
<tr>
<td>Net lumen gain</td>
<td>1.12 (0.76 to 1.54)</td>
<td>1.02 (0.52 to 1.39)</td>
<td>.08</td>
</tr>
<tr>
<td>Restenosis, No. (%) of patients</td>
<td>10 (11.0)</td>
<td>17 (18.5)</td>
<td>.15</td>
</tr>
<tr>
<td>In-stent</td>
<td>13 (14.3)</td>
<td>20 (21.7)</td>
<td>.19</td>
</tr>
</tbody>
</table>

*Data shown as median (interquartile range) unless otherwise indicated.
Author Affiliations: Deutsches Herzzenrum, Technische Universität, Munich, Germany, and Medizinische Klinik rechts der Isar, Technische Universität, Munich, Germany.

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Author Contributions: As principal investigator, Dr Kastrati had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Kastrati, Schömig.
Acquisition of data: Kastrati, Mehlli, von Beckerath, Dibra, Hausleiter, Pache, Schülienn, Schmitt, Dirschinger, Schömig.
Analysis and interpretation of data: Kastrati, Mehlli, Dibra, Schömig.
Drafting of the manuscript: Kastrati, Schömig.
Critical revision of the manuscript for important intellectual content: Mehlli, von Beckerath, Dibra, Hausleiter, Pache, Schülienn, Schmitt, Dirschinger.
Statistical analysis: Kastrati.
Obtained funding: Schömig.
Study supervision: Kastrati, Mehlli, Pache, Schülienn, Dirschinger, Schömig.

Intracoronary Stenting and Angiographic Results: Drug-Eluting Stents for In-Stent Restenosis (ISAR-DESIRE) Study investigators and participating centers: Study Organization Steering Committee: A. Schömig (chairman), A. Kastrati (principal investigator); Data Coordinating Center: J. Mehlli, J. Hausleiter, H. Bollwein, C. Markwardt (Munich); Angiographic Core Laboratory: A. Dibra, S. Piniek, S. Meier (Munich); Clinical Follow-Up Center: H. Holle, K. Hösl, F. Rodrigues, C. Peterler (Munich).

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