Randomized trial of paclitaxel- and sirolimus-eluting stents in small coronary vessels

Julinda Mehilli¹, Alban Dibra¹, Adnan Kastrati¹*, Jürgen Pache¹, Josef Dirschinger², and Albert Schömig¹,² for the Intracoronary Drug-Eluting Stenting to Abrogate Restenosis in Small Arteries (ISAR-SMART 3) Study Investigators

¹Deutsches Herzcentrum, Technische Universität, Lazaretstr. 36, 80636 Munich, Germany; and ²Medizinische Klinik rechts der Isar, Technische Universität, Munich, Germany

Received 12 December 2005; revised 24 December 2005; accepted 28 December 2005; online publish-ahead-of-print 9 January 2006

KEYWORDS
Coronary artery disease;
Drug-eluting stents;
Paclitaxel;
Restenosis;
Sirolimus

Aims Sirolimus- and paclitaxel-eluting stents effectively reduce restenosis in small coronary vessels. The relative efficacy of these drug-eluting stents in this high-risk subset is not known.

Methods and results A total of 360 patients undergoing percutaneous coronary intervention for de novo lesions in native coronary vessels with a diameter of <2.80 mm received randomly paclitaxel-eluting stents (n = 180) or sirolimus-eluting stents (n = 180). The primary endpoint was in-stent late luminal loss. Secondary endpoints were angiographic restenosis and need of target lesion revascularization. The study intended to show that the paclitaxel-eluting stent is not inferior to the sirolimus-eluting stent with respect to the primary endpoint. The non-inferiority margin was set at 0.16 mm. Follow-up angiography was performed in 87% of the patients. In-stent late luminal loss in the paclitaxel-eluting stent group was 0.32 mm (upper 95% boundary, 0.42 mm), which was greater than that in the sirolimus-eluting stent group, failing to show the non-inferiority of the paclitaxel-eluting stent to the sirolimus-eluting stent (P > 0.99). Angiographic restenosis was found in 19.0% of the lesions in the paclitaxel-eluting stent group and 11.4% of the lesions in the sirolimus-eluting stent group (P = 0.047). Target lesion revascularization was performed in 14.7% of the lesions treated with paclitaxel-eluting stents and 6.6% of the lesions treated with sirolimus-eluting stents (P = 0.008).

Conclusion The paclitaxel-eluting stent is associated with a greater late luminal loss and is less effective in reducing restenosis in small coronary vessels than the sirolimus-eluting stent.

Percutaneous coronary interventions constitute a major treatment strategy for patients with ischaemic heart disease, and coronary stenting is the most frequently used form of percutaneous interventions.¹ Although the use of bare metal stents has reduced restenosis in coronary vessels with a diameter ≥3 mm when compared with plain balloon angioplasty,²,³ most of the dedicated randomized studies have failed to show a better outcome with stents in vessels with a smaller reference diameter.⁴⁻⁸ In spite of refinements in stent design and periprocedural therapy, the risk of restenosis after bare metal stenting in this setting remains high.⁹,¹⁰ Nowadays, percutaneous coronary interventions in small vessels account for 35–67% of interventional procedures performed in patients with coronary artery disease¹¹ and, when bare metal stents are used, restenosis will be detected in >35% of the treated patients and a repeat revascularization procedure will be required in >20% of them.¹²,¹³,¹⁴

Several randomized trials have shown that stents eluting antiproliferative drugs, with sirolimus- and paclitaxel-eluting stents, the only devices approved by Federal Drug Administration (FDA) so far, are highly effective in reducing restenosis when compared with bare metal stents.¹²⁻¹⁸ Subgroup analysis from these trials have shown that the efficacy of either sirolimus- or paclitaxel-eluting stents extends also to those patients who undergo coronary stenting in small-size vessels.¹²⁻¹⁴ In addition, a randomized study of sirolimus-eluting stents and bare metal stents for small coronary arteries reported an 82% reduction in the relative risk of restenosis with sirolimus-eluting stents,¹¹ providing further evidence on the role of drug-eluting stents as an effective treatment strategy for coronary arteries with a small reference diameter.¹⁹

Recent studies have shown that in various patient subsets, sirolimus-eluting stents are associated with lower restenosis rates and reduced need of repeat revascularization procedures compared with paclitaxel-eluting stents.²⁰⁻²³ At present, there is no direct evidence on the relative efficacy in the prevention of restenosis of these drug-eluting stents.
Drug-eluting stents in small vessels

after implantation in small coronary vessels. Comparisons of data from subgroup analyses of different trials have suggested that there might be differences in the capacity to prevent restenosis between sirolimus- and paclitaxel-eluting stents in this subset. However, indirect comparisons are subject to many limitations and, consequently, conclusions based on their results may be erroneous. Therefore, reliable guidance on the selection of the most effective drug-eluting stent for treatment of lesions in coronary vessels with a small reference diameter can be provided only from a head-to-head comparison between these devices.

We report the results of a prospective, randomized trial that compared the sirolimus-eluting stent with the paclitaxel-eluting stent in patients undergoing stenting in small coronary vessels.

Methods

Patients

Study participants were enrolled in two centres, Deutsches Herzzentrum and Medizinische Klinik rechts der Isar, Munich, Germany. To be eligible for this study, participants should have angina pectoris and/or a positive stress test in the presence of angiographically significant stenosis in native coronary vessels with a reference diameter of <2.8 mm by visual estimation. Exclusion criteria included acute myocardial infarction (within 48 h), target lesion located in left main trunk, in-stent restenosis, pregnancy, contra-indications to ramipril, paclitaxel, aspirin, clopidogrel, stainless steel, and lack of consent to participate in the study. Also, patients with diabetes mellitus were excluded as they were enrolled in another study comparing paclitaxel- and sirolimus-eluting stents. Study protocol was approved by the Institutional Ethics Committee and all participants provided written informed consent.

Randomization, interventions, and adjunct drug therapy

All patients were pre-treated with a loading dose of 600 mg clopidogrel for at least 2 h before coronary angiography. After the guide wire had crossed the lesion, patients were randomly assigned to treatment with paclitaxel-eluting stent (TaxusTM, Boston Scientific) or sirolimus-eluting stent (CypherTM, Cordis, Johnson & Johnson). Sealed, opaque envelopes containing a computer-generated random sequence were used for the randomization. Study participants were enrolled in two centres, Deutsches Herzzentrum and Medizinische Klinik rechts der Isar, Munich, Germany. To be eligible for this study, participants should have angina pectoris and/or a positive stress test in the presence of angiographically significant stenosis in native coronary vessels with a reference diameter of <2.8 mm by visual estimation. Exclusion criteria included acute myocardial infarction (within 48 h), target lesion located in left main trunk, in-stent restenosis, pregnancy, contra-indications to ramipril, paclitaxel, aspirin, clopidogrel, stainless steel, and lack of consent to participate in the study. Also, patients with diabetes mellitus were excluded as they were enrolled in another study comparing paclitaxel- and sirolimus-eluting stents. Study protocol was approved by the Institutional Ethics Committee and all participants provided written informed consent.

Follow-up protocol

Patients remained at hospital for at least 48 h after randomization. During this period, electrocardiogram (ECG) was recorded and blood was collected for determination of creatine kinase (CK) and its MB isoenzyme levels, before randomization and every 8 h for the first 24 h after randomization and daily afterwards. Study protocol mandated a phone interview after 30 days for the assessment of clinical status. All patients were asked to return for coronary angiography between 6 and 8 months after randomization or earlier if they had angina symptoms. Another phone interview was scheduled at 1 year after index intervention. Patients who complained of symptoms corresponding to angina pectoris were requested to present to the outpatient clinic for a complete clinical, electrocardiographic, and laboratory check-up; if necessary, an angiographic study was performed. Relevant data were entered into a computer database by specialized personnel. All data were verified against source documentation and all adverse clinical events were adjudicated by an Event Adjudication Committee blinded to the patients’ treatment assignments.

Quantitative coronary angiography evaluation

Angiographic studies performed at baseline, post-procedurally, and at follow-up were digitally recorded and sent for assessment to the Quantitative Angiographic Core Laboratory (Deutsches Herzzentrum, Munich, Germany). Digital angiograms were analysed offline with the use of an automated edge detection system (QCA-CMS, Medis Medical Imaging Systems, Nuenen, the Netherlands) by experienced personnel unaware of the stent type used. The complexity of the lesions was defined according to the modified American College of Cardiology/American Heart Association grading system. The pattern of in-stent restenosis at follow-up angiography was classified according to the system proposed by Mehran et al. All measurements were performed on cineangiograms recorded after intracoronary nitroglycerine administration. The same projections were used at all time points. The contrast-filled non-tapered catheter tip was used for calibration. The following angiographic quantitative parameters were measured: reference diameter of the vessel, minimal luminal diameter, percent diameter stenosis (difference between the reference diameter and minimal luminal diameter divided by the reference diameter and multiplied by 100), and late luminal loss (difference between minimal luminal diameter at the end of the procedure and minimal luminal diameter at follow-up). 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 areas proximal and distal to the stent (‘in-segment’ analysis).

Study endpoints and definitions

The primary endpoint of the study was in-stent late luminal loss at follow-up angiography. Secondary endpoints were binary angiographic restenosis (in-segment diameter stenosis of at least 50% at follow-up angiography) and target lesion revascularization due to luminal renarrowing in the presence of symptoms or objective signs of ischaemia at 1-year follow-up.

The diagnosis of myocardial infarction during the follow-up required the presence of new Q-waves in the electrocardiogram and/or an elevation of CK or its MB isoenzyme at least three times the upper limit of normal in at least two blood samples.

Although it was an open-label study design with both operators and patients knowing about the drug-eluting stent that was implanted, the assessment of both angiographic and clinical outcomes was done by assessors blinded to the study treatment arm.

Statistical analysis

The objective of the study was to assess the non-inferiority of the paclitaxel-eluting stent to the sirolimus-eluting stent. Sample size calculation was based on a margin of non-inferiority for in-stent late luminal loss set at 0.16 mm. This threshold would have allowed for preservation of 80% of reduction in late lumen loss observed previously with sirolimus-eluting stent compared with bare metal stent. This conservative approach was chosen in view of the reduced accommodation potential of small vessels. With a power of 90% and a one-sided α level of 0.05, 149 patients per group were needed to conclude non-inferiority of the paclitaxel-eluting stent to the sirolimus-eluting stent. Expecting that up to 20% of the patients would not present for follow-up coronary angiography, we included 360 patients in the study. Analysis relative to the sample size calculation was performed with nQuery Advisor.
version 4.0 (Statistical Solutions, Cork, Ireland) according to the method described by O’Brien and Muller.30 The data are presented as means ± SD; medians, with 25th and 75th percentiles; or counts or percentages. The non-inferiority hypothesis was assessed statistically with EquivTest™ (Statistical Solutions, Cork, Ireland) according to the method described by Chow and Liu.31 According to the null hypothesis, the difference in late luminal loss between the paclitaxel- and the sirolimus-eluting stents would be ≥0.16 (i.e. the sirolimus-eluting stent is superior to the paclitaxel-eluting stent). According to the alternative hypothesis, the difference in late luminal loss between the paclitaxel- and the sirolimus-eluting stents would be <0.16 mm (i.e. the paclitaxel-eluting stent is not inferior to the sirolimus-eluting stent). If the null hypothesis could not be rejected, as made clear by D’Agostino et al.,32 this would imply that the sirolimus-eluting stent would be superior to the paclitaxel-eluting stent with respect to the primary endpoint. According to Snapinn33 and European Agency for the Evaluation of Medicinal Products (EMEA),34 both non-inferiority and superiority can be assessed in the same clinical trial without statistical penalty.

The differences between the groups were assessed using a two-sided χ² square test or Fisher’s exact test for categorical data, and Student’s t-test for comparing continuous data. The relative risk and its 95% confidence interval were computed for outcome measures. A P-value of <0.05 was considered statistically significant.

Results

A total of 360 patients were enrolled in this study and randomly assigned to receive paclitaxel- or sirolimus-eluting stents. Table 1 shows the baseline demographic and clinical characteristics. The angiographic and procedural characteristics are shown in Tables 2 and 3, respectively. No significant differences with respect to these characteristics were found between the two stent groups. Implantation of the randomly assigned stent was successful in all patients. Regarding post-discharge concomitant drug therapy, all patients were given aspirin indefinitely and clopidogrel for at least 6 months; ACE-inhibitors were given to 83% of the patients were given aspirin indefinitely and clopidogrel for at least 6 months; ACE-inhibitors were given to 83% of the patients.

Restenosis

Follow-up angiography was performed in 154 patients (86%) in the paclitaxel-stent group and 159 patients (88%) in the sirolimus-stent group (P = 0.43; Figure 1). Median angiographic follow-up interval was 196 days (25th and 75th percentiles were 162 and 203 days, respectively) in the sirolimus-stent group and 196 days (25th and 75th percentiles are 179 and 206 days, respectively) in the sirolimus-stent group (P = 0.29). In total, 174 lesions in the paclitaxel-stent group and 176 lesions in the sirolimus-stent group had follow-up angiography. Table 4 shows the results of the quantitative analysis performed on follow-up angiograms. The difference in in-stent late luminal loss between the paclitaxel- and the sirolimus-eluting stent groups was 0.32 mm (upper 95% boundary, 0.42 mm) failing to show the non-inferiority of the paclitaxel stent (P > 0.99), consequently showing the superiority of the sirolimus-eluting stent (P < 0.001; Figure 2). To avoid a potential impact of interlesion dependence in patients with multileesion interventions, the analysis regarding the primary endpoint was repeated including only one lesion at random per patient. This analysis demonstrated a difference of 0.30 mm in in-stent late luminal loss between the paclitaxel- and the sirolimus-eluting stent groups.

Other indexes of quantitative coronary angiography were better with sirolimus-eluting stents (Table 4). Angiographic restenosis was found in 33 of the 174 lesions (19.0%) in the paclitaxel-eluting stent group and 20 of the 176 lesions (11.4%) in the sirolimus-eluting stent group (relative risk associated with paclitaxel stent, 1.67; 95% confidence interval, 1.00–2.79; P = 0.047). With respect to the pattern of restenosis at follow-up angiography, 23 patients in the paclitaxel-stent group presented pattern I of in-stent restenosis, three patients presented type II, two patients presented type III, and the other five patients presented type IV of in-stent restenosis. In the sirolimus-stent group, 16 patients presented pattern I of in-stent restenosis, one patient presented type III, and the other three type IV of in-stent restenosis.

We used cut-off points that divided the population in three subgroups according to vessel size. In the lower tertile (vessel size <2.24 mm), the restenosis rates were 28.3% for the paclitaxel stent and 10.4% for the sirolimus stent (P = 0.02), in the middle tertile (vessel size between 2.24 and 2.57 mm), the restenosis rates were 14.8% for the paclitaxel stent and 12.1% for the sirolimus stent.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Paclitaxel-eluting stent (n = 180)</th>
<th>Sirolimus-eluting stent (n = 180)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>65.7 ± 10.4</td>
<td>67.4 ± 10.9</td>
<td>0.12</td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>45 (25)</td>
<td>55 (31)</td>
<td>0.24</td>
</tr>
<tr>
<td>Current smoker, n (%)</td>
<td>22 (12)</td>
<td>27 (15)</td>
<td>0.44</td>
</tr>
<tr>
<td>Arterial hypertension, n (%)</td>
<td>120 (67)</td>
<td>116 (64)</td>
<td>0.66</td>
</tr>
<tr>
<td>Hypercholesterolemia, n (%)</td>
<td>99 (55)</td>
<td>100 (56)</td>
<td>0.92</td>
</tr>
<tr>
<td>Unstable angina, n (%)</td>
<td>63 (35)</td>
<td>49 (27)</td>
<td>0.11</td>
</tr>
<tr>
<td>Prior myocardial infarction, n (%)</td>
<td>56 (31)</td>
<td>53 (29)</td>
<td>0.73</td>
</tr>
<tr>
<td>Prior aortocoronary bypass surgery, n (%)</td>
<td>29 (16)</td>
<td>20 (11)</td>
<td>0.17</td>
</tr>
<tr>
<td>Left ventricular ejection fraction (%)</td>
<td>56.4 ± 12.3</td>
<td>56.2 ± 12.8</td>
<td>0.89</td>
</tr>
<tr>
<td>Multivessel disease, n (%)</td>
<td>146 (81)</td>
<td>144 (80)</td>
<td>0.79</td>
</tr>
</tbody>
</table>

*Values with plus or minus symbol are means ± SD.
(P = 0.66), and in the upper tertile (vessel size >2.57 mm), the restenosis rates were 13.2% for the paclitaxel stent and 11.3% for the sirolimus stent (P = 0.75).

Target lesion revascularization was performed in 30 of the 204 lesions (14.7%) of the paclitaxel-eluting stent group and 13 of the 198 lesions (6.6%) of the sirolimus-eluting stent group (relative risk associated with the paclitaxel-eluting stent, 2.24; 95% confidence interval, 1.20–4.17; P = 0.008). With the exception of one patient in the sirolimus-eluting stent group, who underwent coronary artery bypass surgery, in all the other patients revascularization procedures consisted in repeat balloon angioplasties.

**Clinical outcome**

One-year follow-up was completed in all study patients. Four patients (2.2%) in the paclitaxel-eluting stent group and three patients (1.7%) in the sirolimus-eluting stent group died within this period (P > 0.99). Myocardial infarction occurred in six patients (3.3%) of the paclitaxel-eluting stent group and seven patients (3.9%) of the sirolimus-stent group (P = 0.78). The composite of death or myocardial infarction occurred in 10 patients (5.6%) who received paclitaxel-eluting stents and nine patients (5.0%) who received sirolimus-eluting stents (P = 0.81).

**Discussion**

This was a prospective, randomized study, specifically designed to compare the paclitaxel-eluting stent with the sirolimus-eluting group for the reduction of restenosis in small coronary vessels. The results of this study show, however, that the paclitaxel-eluting stent cannot be considered non-inferior to the sirolimus-eluting stent, thus demonstrating the superior efficacy of the sirolimus-eluting stent with respect to the primary endpoint of the study, late luminal loss. In addition, sirolimus-eluting stents were associated with a lower incidence of angiographic restenosis as well as a reduced need of target lesion revascularizations. These results confirm previous findings according to which the impact of a late loss difference between two drug-eluting stents in high-risk subsets may be of critical importance in terms of angiographic and clinical restenosis.35–37

Small vessel diameter has been identified as an important predictor of restenosis after percutaneous coronary interventions.10 In contrast to the well-established superiority of bare metal stents with respect to restenosis reduction in large coronary vessels, their advantage over balloon angioplasty in small vessels remains a matter of controversy,38,39 and in some comparative randomized studies restenosis rates as high as 35.7% have been reported with stenting.4,7 Compared with plain balloon angioplasty, stent deployment abrogates elastic recoil and vessel

### Table 2: Angiographic characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Paclitaxel-eluting stent (n = 204)</th>
<th>Sirolimus-eluting stent (n = 198)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target vessel</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left anterior descending coronary artery, n (%)</td>
<td>96 (47)</td>
<td>103 (52)</td>
<td>0.77</td>
</tr>
<tr>
<td>Left circumflex coronary artery, n (%)</td>
<td>69 (34)</td>
<td>62 (31)</td>
<td></td>
</tr>
<tr>
<td>Right coronary artery, n (%)</td>
<td>39 (19)</td>
<td>33 (17)</td>
<td></td>
</tr>
<tr>
<td>Complex (type B2/C) lesions, n (%)</td>
<td>151 (74)</td>
<td>142 (72)</td>
<td>0.60</td>
</tr>
<tr>
<td>Vessel size (mm)</td>
<td>2.40 ± 0.38</td>
<td>2.44 ± 0.34</td>
<td>0.34</td>
</tr>
<tr>
<td>Lesion length (mm)</td>
<td>11.7 ± 6.7</td>
<td>12.9 ± 8.0</td>
<td>0.12</td>
</tr>
<tr>
<td>Minimal luminal diameter prior to procedure (mm)</td>
<td>1.03 ± 0.39</td>
<td>0.99 ± 0.40</td>
<td>0.33</td>
</tr>
<tr>
<td>Diameter stenosis prior to procedure (%)</td>
<td>57.2 ± 14.4</td>
<td>59.4 ± 15.3</td>
<td>0.15</td>
</tr>
</tbody>
</table>

*Data are from a lesion-based analysis. Values with plus or minus symbol are means ± SD.

### Table 3: Procedural characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Paclitaxel-eluting stent (n = 204)</th>
<th>Sirolimus-eluting stent (n = 198)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximal balloon pressure (atm)</td>
<td>14.3 ± 3.1</td>
<td>13.9 ± 2.8</td>
<td>0.15</td>
</tr>
<tr>
<td>Balloon-to-vessel ratio</td>
<td>1.19 ± 0.14</td>
<td>1.19 ± 0.13</td>
<td>0.74</td>
</tr>
<tr>
<td>Length of stented segment (mm)</td>
<td>21.0 ± 7.8</td>
<td>21.4 ± 9.8</td>
<td>0.65</td>
</tr>
<tr>
<td>Number of stents</td>
<td>1.08 ± 0.29</td>
<td>1.08 ± 0.27</td>
<td>0.93</td>
</tr>
<tr>
<td>Minimal luminal diameter after procedure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In-stent (mm)</td>
<td>2.44 ± 0.37</td>
<td>2.44 ± 0.36</td>
<td>0.80</td>
</tr>
<tr>
<td>In-segment (mm)</td>
<td>2.00 ± 0.47</td>
<td>2.04 ± 0.47</td>
<td>0.41</td>
</tr>
<tr>
<td>Diameter stenosis after procedure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In-stent (%)</td>
<td>6.3 ± 7.7</td>
<td>5.6 ± 7.5</td>
<td>0.36</td>
</tr>
<tr>
<td>In-segment (%)</td>
<td>18.5 ± 7.2</td>
<td>16.7 ± 7.7</td>
<td>0.05</td>
</tr>
</tbody>
</table>

*Data are from a lesion-based analysis. Values with plus or minus symbol are means ± SD.
remodelling. However, its long-term success is limited by an increased proliferation of vascular neointima, which results in a greater late luminal loss. Local delivery of drugs that interfere with cell-cycle progression, modifying the healing process after stent injury and leading to decreased neointimal proliferation, has been recognized as the logical therapeutic approach to restenosis. Sirolimus, an immunosuppressive drug that induces cell-cycle arrest in the G1/S phase, and paclitaxel, an antineoplastic drug that induces cell-cycle arrest predominantly in the G2/M phase, are the most extensively studied antiproliferative agents; sirolimus- and paclitaxel-eluting stents are the only drug-eluting stents so far approved for commercial use by FDA.

In the SIRolImUS-coated Bx Velocity balloon-expandable stent in the treatment of patients with de novo coronary artery lesions (SIRIUS) trial, angiographic restenosis in the smallest vessel tertile was significantly lower among patients treated with sirolimus stent as compared with the bare metal stent. In two other randomized studies, which enrolled...
Drug-eluting stents in small vessels

patients treated for lesions in coronary vessels with a diameter of 2.6 mm, patients assigned to treatment with sirolimus stent had an 86–96% reduction in the relative risk of restenosis as compared with those assigned to bare metal controls.15,16 More recently, investigators of Sirolimus-Eluting Stent in the Prevention of Restenosis in Small Coronary Arteries (SES-SMART) study reported that the sirolimus-eluting stent was associated with a 9.8% in-segment restenosis rate as compared with the 53.1% restenosis rate with the bare metal control stent, thus corresponding to a 82% relative risk reduction.11 Data from the Treatment of De Novo Coronary Disease Using a Single Paclitaxel-Eluting Stent (TAXUS-IV) trial showed that for vessels with a diameter 2.5–3.0 mm, patients who received a paclitaxel-eluting stent had a 76% reduction in the relative risk of restenosis as compared with those who received a bare metal stent.14 A similar reduction of 73% in the relative risk was also observed in those patients who received a paclitaxel-eluting stent for lesions located in vessels with a reference diameter of <2.5 mm.14 Interestingly, the diameter-related increase in restenosis rate has been less pronounced with paclitaxel-eluting stents as compared with sirolimus-eluting stents in two of the above-mentioned studies.14,44 However, in the most recently published TAXUS-V trial,45 an angiographic restenosis rate of 3.5% was found for 4.0-mm paclitaxel-eluting stents as compared with 31.2% for 2.25-mm paclitaxel-eluting stents. Overall, the results of these studies demonstrate the superior efficacy of sirolimus- and paclitaxel-eluting stents to prevent restenosis in small coronary arteries as compared with bare metal stents. In contrast, they suggest that there might be a difference in the effectiveness of these drug-eluting stents. However, because of the differences between individual studies, no definitive conclusions can be drawn from such an indirect comparison between sirolimus- and paclitaxel-eluting stents.

With an overall restenosis rate of 15.1% and no episodes of subacute stent thrombosis in the entire cohort, our study provides further evidence on the effectiveness and safety of the two currently approved drug-eluting stents in the subset of vessels with a small reference diameter. In contrast, this head-to-head comparison between paclitaxel and sirolimus stent showed that paclitaxel-eluting stent is less effective than the sirolimus-eluting stent to reduce neointimal proliferation after implantation in small coronary vessels. In addition, there was a considerable increase in the relative risk of angiographic restenosis with the paclitaxel-eluting stent. Similarly, there was a clear difference between the two stent types with respect to the need for target lesion revascularization.

We can only speculate on the possible explanations of our findings.46 Although both paclitaxel and sirolimus have been shown to reduce neointimal proliferation, they have distinct mechanisms of actions.47 In addition, some stent characteristics are different between the two drug-eluting stents.25,47 Furthermore, their polymer coatings differ in their composition and design.25 Also, different drug-release kinetics might have contributed to the observed difference in the performance of paclitaxel and sirolimus stents.25,47 Other studies that have enrolled patients with various clinical and angiographic characteristics, including patients with diabetes mellitus, have also shown that sirolimus-eluting stents are associated with less restenosis than paclitaxel-eluting stents.18,20–23

On the basis of the results of this study, it cannot be concluded that the paclitaxel-eluting stent is non-inferior to the sirolimus-eluting stent for the treatment of lesions in small coronary vessels. Conversely, the sirolimus-eluting stent is more effective in suppressing neointimal proliferation, which results in a lower incidence of angiographic restenosis and a reduced need for target lesion revascularization.

Conflict of interest: A.K. reports having received lecture fees from Bristol-Myers Squibb, Cordis, Glaxo, Lilly, Medtronic and Sanofi. Dr R. Wessely reports having received a lecture fee from Lilly. The other authors report no conflicts.

Appendix

The following centres and investigators participated in the Intracoronary Drug-Eluting Stenting to Abrogate Restenosis in Small Arteries (ISAR-SMART 3) Study:

Study organization

Steering committee: A. Schöning (Chairman), A. Kastrati (Principal Investigator), J. Dirschinger.

Event Adjudication Committee: J. Pache, G. Ndreppea, H. Bollwein.

Data Coordinating Centre: J. Mehilli, C. Markwardt, C. Vollmer.

Angiographic Core Laboratory: A. Dibra, S. Pinieck, S. Mayer.


Participating centres and investigators:


Klinikum rechts der Isar, Munich: J. Dirschinger, M. Seyfarth, N. von Beckerath, M. Karch.

References


