Atherosclerosis of small coronary arteries remains a major challenge to revascularization procedures, because coronary artery bypass grafting is limited by high rates of technical failure (1), and percutaneous coronary interventions (PCI) are associated with an increased risk of restenosis and adverse outcome (2). Stent implantation results in arterial injury, initiating a vasculoproliferative cascade with smooth muscle cell proliferation and migration resulting in neointimal hyperplasia. The amount of neointimal hyperplasia is largely independent of vessel size and thus late luminal loss, an angiographic measure of neointimal hyperplasia, is similar across a wide range of vessel diameters (3,4). Accordingly, small vessels are more prone to restenosis than larger vessels, because they are less able to accommodate neointimal tissue without compromising blood flow (5).
Results of randomized trials and observational studies comparing bare-metal stents with balloon angioplasty revealed conflicting results and only modest superiority of bare-metal stents in patients with small-vessel disease (6–9). Drug-eluting stents (DES) with site-specific delivery of therapeutic agents reduce neointimal hyperplasia more effectively and have been shown to improve clinical and angiographic measures of restenosis compared with bare-metal stents (10–12). In direct head-to-head comparisons, sirolimus-eluting stents (SES) consistently showed lower late luminal loss compared with paclitaxel-eluting stents (PES) (13,14). Although late luminal loss has been proposed as a robust marker for discriminating DES (15), its impact on clinical outcomes, such as target lesion revascularization (TLR), remains controversial, particularly in the low range of late loss typical for DES.

The SIRTAX (Sirolimus-Eluting Stent Compared With Paclitaxel-Eluting Stent for Coronary Revascularization) trial was a randomized controlled trial directly comparing the safety and efficacy of SES and PES in an “all comers” population undergoing PCI (14). In the overall population, SES provided lower late luminal loss, which translated into lower rates of clinical and angiographic restenosis. The objective of the present analysis was to evaluate the long-term clinical outcome based on an extended follow-up of 2 years and angiographic result of patients stratified according to vessel size, with the hypothesis that differences in outcome should be particularly pronounced in patients with small-vessel as opposed to large-vessel disease.

### Methods

**Study population.** The SIRTAX trial was a prospective observer-blind randomized controlled study comparing safety and efficacy of SES and PES in 1,012 patients undergoing PCI (14). Eligible patients had a history of stable angina or acute coronary syndrome and presented with at least 1 lesion with a diameter stenosis ≥50% in a vessel with a reference vessel diameter (RVD) between 2.25 and 4.00 mm suitable for stent implantation. There were no limitations on the number of treated lesions and vessels or on lesion length. Prespecified exclusion criteria were known allergy to aspirin, thienopyridines, stainless steel, sirolimus, paclitaxel, or contrast agents; participation in another coronary device study; and terminal illness. The study complied with the Declaration of Helsinki regarding investigations in humans and was approved by the institutional ethics committees at the University Hospitals of Bern and Zurich, Switzerland. All patients provided written informed consent. There was no industry involvement in design, conduct, or analysis of the study.

**Randomization and coronary stent procedure.** Randomization was concealed using sealed, opaque, and sequentially numbered envelopes. The allocation schedule was based on computer-generated random numbers, stratified according to trial center, and blocked, with block lengths of 6 and 10 varied randomly. Patients were randomly assigned on a 1:1 basis to treatment with SES (Cypher, Cordis, Miami Lakes, Florida), or PES (Taxus, Boston Scientific, Natick, Massachusetts). The SES were available in diameters of 2.25 to 3.50 mm and in lengths of 8 to 33 mm. The PES were

### Table 1 Baseline Clinical Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Small Vessels Only</th>
<th></th>
<th>Large Vessels Only</th>
<th></th>
<th>Small and Large Vessels</th>
<th></th>
<th>p Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n</td>
<td>183 (45.4)</td>
<td>94 (50.3)</td>
<td>104 (40.0)</td>
<td>102 (41.8)</td>
<td>30 (50.0)</td>
<td>29 (37.2)</td>
<td>0.12</td>
</tr>
<tr>
<td>Age ≥65 yrs, n (%)</td>
<td>83 (18.6)</td>
<td>45 (24.1)</td>
<td>61 (23.5)</td>
<td>59 (24.2)</td>
<td>17 (28.3)</td>
<td>19 (24.4)</td>
<td>0.74</td>
</tr>
<tr>
<td>Males, n (%)</td>
<td>132 (72.1)</td>
<td>145 (77.5)</td>
<td>210 (80.8)</td>
<td>190 (77.9)</td>
<td>40 (66.7)</td>
<td>64 (82.1)</td>
<td>0.05</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>37 (20.2)</td>
<td>35 (18.7)</td>
<td>51 (19.6)</td>
<td>43 (17.6)</td>
<td>20 (33.3)</td>
<td>15 (19.2)</td>
<td>0.21</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>113 (61.8)</td>
<td>127 (67.9)</td>
<td>145 (55.8)</td>
<td>144 (59.0)</td>
<td>44 (73.3)</td>
<td>49 (62.8)</td>
<td>0.02</td>
</tr>
<tr>
<td>Hyperlipidemia, n (%)</td>
<td>119 (65.0)</td>
<td>107 (57.2)</td>
<td>152 (58.5)</td>
<td>142 (58.2)</td>
<td>34 (56.7)</td>
<td>43 (55.1)</td>
<td>0.51</td>
</tr>
<tr>
<td>Current smoking, n (%)</td>
<td>67 (36.6)</td>
<td>65 (34.8)</td>
<td>97 (37.3)</td>
<td>88 (36.1)</td>
<td>20 (33.3)</td>
<td>28 (35.9)</td>
<td>0.90</td>
</tr>
<tr>
<td>Previous MI, n (%)</td>
<td>57 (31.2)</td>
<td>62 (33.2)</td>
<td>71 (27.3)</td>
<td>65 (26.6)</td>
<td>17 (28.3)</td>
<td>25 (32.1)</td>
<td>0.24</td>
</tr>
<tr>
<td>Stable angina pectoris, n (%)</td>
<td>105 (57.4)</td>
<td>94 (50.3)</td>
<td>111 (42.7)</td>
<td>111 (45.5)</td>
<td>30 (50.0)</td>
<td>41 (52.6)</td>
<td>0.01</td>
</tr>
<tr>
<td>Acute coronary syndromes, n (%)</td>
<td>78 (42.6)</td>
<td>93 (49.7)</td>
<td>149 (57.3)</td>
<td>133 (55.4)</td>
<td>30 (50.0)</td>
<td>37 (47.4)</td>
<td>0.002</td>
</tr>
<tr>
<td>Unstable angina, n (%)</td>
<td>16 (8.7)</td>
<td>12 (6.4)</td>
<td>10 (3.9)</td>
<td>13 (5.3)</td>
<td>2 (3.3)</td>
<td>5 (6.4)</td>
<td>0.64</td>
</tr>
<tr>
<td>Non-ST-segment elevation MI, n (%)</td>
<td>34 (18.6)</td>
<td>45 (24.1)</td>
<td>61 (23.5)</td>
<td>59 (24.2)</td>
<td>17 (28.3)</td>
<td>19 (24.4)</td>
<td>0.74</td>
</tr>
<tr>
<td>ST-segment elevation MI, n (%)</td>
<td>28 (15.3)</td>
<td>36 (19.3)</td>
<td>78 (30.0)</td>
<td>61 (25.0)</td>
<td>11 (18.3)</td>
<td>13 (16.7)</td>
<td>0.01</td>
</tr>
<tr>
<td>Multivessel disease, n (%)</td>
<td>120 (65.6)</td>
<td>111 (59.4)</td>
<td>130 (50.0)</td>
<td>125 (51.2)</td>
<td>50 (83.3)</td>
<td>66 (84.6)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*The p values relate to differences between the 3 groups of patients: 1) patients who underwent stent implantation in small vessels only; 2) patients with treatment of large vessels only; and 3) patients who underwent stent implantation in both small and large vessels.

MI = myocardial infarction; PES = paclitaxel-eluting stent; SES = sirolimus-eluting stent.
available in diameters of 2.25 to 3.50 mm and in lengths of 8 to 32 mm. All interventions were performed according to current practice guidelines for PCI. No mixture of DES was allowed within a given patient. After the procedure, all patients were advised to maintain aspirin lifelong, and clopidogrel therapy was prescribed for 12 months.

### Study end points and definitions
Adverse events were assessed in the hospital, at 1, 6, and 9 months, and at 1 and 2 years. An independent clinical events committee unaware of the patients’ treatment assignments adjudicated all end points. Patients were asked to return for angiographic follow-up study at 8 months.

### Table 2 Baseline Characteristics of Lesions

<table>
<thead>
<tr>
<th>Lesions, n</th>
<th>Small Vessels Only</th>
<th>Large Vessels Only</th>
<th>Small and Large Vessels</th>
<th>p Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>SES</td>
<td>PES</td>
<td>SES</td>
<td>PES</td>
<td></td>
</tr>
<tr>
<td>Target lesion coronary artery, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left main</td>
<td>2 (0.8)</td>
<td>2 (0.8)</td>
<td>7 (2.2)</td>
<td>7 (2.3)</td>
</tr>
<tr>
<td>Left anterior descending</td>
<td>137 (53.0)</td>
<td>130 (52.9)</td>
<td>125 (43.9)</td>
<td>120 (40.1)</td>
</tr>
<tr>
<td>Left circumflex</td>
<td>77 (30.9)</td>
<td>68 (26.4)</td>
<td>37 (11.8)</td>
<td>41 (13.7)</td>
</tr>
<tr>
<td>Right</td>
<td>32 (12.9)</td>
<td>45 (18.3)</td>
<td>135 (43.0)</td>
<td>125 (41.8)</td>
</tr>
<tr>
<td>Bypass graft</td>
<td>1 (0.4)</td>
<td>4 (1.6)</td>
<td>10 (3.2)</td>
<td>6 (2.0)</td>
</tr>
<tr>
<td>ACC/AHA lesion class, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.11</td>
</tr>
<tr>
<td>A</td>
<td>57 (22.9)</td>
<td>47 (19.1)</td>
<td>53 (16.9)</td>
<td>64 (21.4)</td>
</tr>
<tr>
<td>B1</td>
<td>98 (39.4)</td>
<td>90 (36.6)</td>
<td>139 (44.3)</td>
<td>147 (49.2)</td>
</tr>
<tr>
<td>B2</td>
<td>65 (26.1)</td>
<td>65 (26.4)</td>
<td>77 (24.5)</td>
<td>62 (20.7)</td>
</tr>
<tr>
<td>C</td>
<td>29 (11.7)</td>
<td>44 (17.9)</td>
<td>45 (14.3)</td>
<td>26 (8.7)</td>
</tr>
<tr>
<td>Angiographic measurements</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lesion length (mm ± SD)</td>
<td>11.67 ± 6.40</td>
<td>11.97 ± 7.18</td>
<td>11.93 ± 7.06</td>
<td>12.61 ± 7.14</td>
</tr>
<tr>
<td>Reference vessel diameter (mm ± SD)</td>
<td>2.46 ± 0.20</td>
<td>2.46 ± 0.23</td>
<td>3.13 ± 0.26</td>
<td>3.16 ± 0.29</td>
</tr>
<tr>
<td>Minimal lumen diameter (mm ± SD)</td>
<td>0.46 ± 0.35</td>
<td>0.43 ± 0.33</td>
<td>0.55 ± 0.51</td>
<td>0.60 ± 0.48</td>
</tr>
<tr>
<td>Stenosis (% lumen diameter ± SD)</td>
<td>81.51 ± 13.76</td>
<td>82.54 ± 13.53</td>
<td>82.55 ± 15.95</td>
<td>81.29 ± 14.80</td>
</tr>
</tbody>
</table>

*The p values relate to differences between the 3 groups of patients: 1) patients who underwent stent implantation in small vessels only; 2) patients with treatment of large vessels only; and 3) patients who underwent stent implantation in both, small and large vessels.

### Table 3 Procedural Results

<table>
<thead>
<tr>
<th>Lesions, n</th>
<th>Small Vessels Only</th>
<th>Large Vessels Only</th>
<th>Small and Large Vessels</th>
<th>p Value for Interaction*</th>
</tr>
</thead>
<tbody>
<tr>
<td>SES</td>
<td>PES</td>
<td>SES</td>
<td>PES</td>
<td></td>
</tr>
<tr>
<td>Procedures</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lesions treated per patient (n ± SD)</td>
<td>1.4 ± 0.6</td>
<td>1.3 ± 0.6</td>
<td>1.2 ± 0.5</td>
<td>1.2 ± 0.5</td>
</tr>
<tr>
<td>Stents per lesion (n ± SD)</td>
<td>1.1 ± 0.4</td>
<td>1.2 ± 0.5</td>
<td>1.1 ± 0.4</td>
<td>1.1 ± 0.4</td>
</tr>
<tr>
<td>Minimal stent diameter (mm ± SD)</td>
<td>2.6 ± 0.2</td>
<td>2.6 ± 0.2</td>
<td>3.1 ± 0.3</td>
<td>3.1 ± 0.3</td>
</tr>
<tr>
<td>Stent length per lesion (mm ± SD)</td>
<td>18.0 ± 8.5</td>
<td>20.3 ± 11.9</td>
<td>19.4 ± 11.6</td>
<td>18.5 ± 10.4</td>
</tr>
<tr>
<td>Maximal pressure (atm ± SD)</td>
<td>13.9 ± 3.1</td>
<td>13.5 ± 2.8</td>
<td>14.9 ± 3.3</td>
<td>14.6 ± 3.0</td>
</tr>
<tr>
<td>Angiographic results</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Final minimal lumen diameter (mm ± SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In-stent</td>
<td>2.36 ± 0.21</td>
<td>2.41 ± 0.22</td>
<td>2.91 ± 0.30</td>
<td>2.93 ± 0.34</td>
</tr>
<tr>
<td>In-segment</td>
<td>2.26 ± 0.27</td>
<td>2.31 ± 0.27</td>
<td>2.82 ± 0.34</td>
<td>2.93 ± 0.32</td>
</tr>
<tr>
<td>Final stenosis (% of lumen diameter ± SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In-stent</td>
<td>6.64 ± 4.48</td>
<td>5.81 ± 4.19</td>
<td>7.69 ± 4.81</td>
<td>7.21 ± 6.44</td>
</tr>
<tr>
<td>In-segment</td>
<td>8.87 ± 7.06</td>
<td>7.82 ± 6.63</td>
<td>8.54 ± 7.02</td>
<td>8.13 ± 5.75</td>
</tr>
<tr>
<td>Acute gain (mm ± SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In-stent</td>
<td>1.89 ± 0.36</td>
<td>1.98 ± 0.38</td>
<td>2.35 ± 0.54</td>
<td>2.34 ± 0.54</td>
</tr>
<tr>
<td>In-segment</td>
<td>1.79 ± 0.40</td>
<td>1.88 ± 0.42</td>
<td>2.34 ± 0.49</td>
<td>2.34 ± 0.57</td>
</tr>
</tbody>
</table>

Values are mean ± standard deviation. *The p values for interaction relate to differences between the 3 groups of patients in terms of differences in procedural results between SES and PES. Abbreviations as in Table 1.
Table 4  Clinical Events Through 2 Years

<table>
<thead>
<tr>
<th>Clinical Events Through 2 Years</th>
<th>Small and Large Vessels Only</th>
<th>Large Vessels Only</th>
<th>Small Vessels Only</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>183</td>
<td>260</td>
<td>370</td>
</tr>
<tr>
<td>Death</td>
<td>10 (5.4)</td>
<td>14 (5.7)</td>
<td>14 (3.8)</td>
</tr>
<tr>
<td>Cardiac death</td>
<td>7 (3.7)</td>
<td>8 (3.1)</td>
<td>12 (3.2)</td>
</tr>
<tr>
<td>MI</td>
<td>1 (0.5)</td>
<td>1 (0.4)</td>
<td>2 (0.5)</td>
</tr>
<tr>
<td>TLR</td>
<td>14 (7.7)</td>
<td>17 (6.6)</td>
<td>21 (5.7)</td>
</tr>
<tr>
<td>Percutaneous</td>
<td>5 (2.7)</td>
<td>10 (3.8)</td>
<td>18 (4.9)</td>
</tr>
<tr>
<td>Surgical</td>
<td>5 (2.7)</td>
<td>8 (3.1)</td>
<td>10 (2.7)</td>
</tr>
<tr>
<td>TVR</td>
<td>14 (7.7)</td>
<td>17 (6.6)</td>
<td>21 (5.7)</td>
</tr>
<tr>
<td>Percutaneous</td>
<td>5 (2.7)</td>
<td>10 (3.8)</td>
<td>18 (4.9)</td>
</tr>
<tr>
<td>Stent thrombosis</td>
<td>4 (2.2)</td>
<td>5 (1.9)</td>
<td>9 (2.4)</td>
</tr>
<tr>
<td>Stent thrombosis</td>
<td>4 (2.2)</td>
<td>5 (1.9)</td>
<td>9 (2.4)</td>
</tr>
<tr>
<td>TVF</td>
<td>19 (10.4)</td>
<td>24 (9.2)</td>
<td>30 (8.1)</td>
</tr>
<tr>
<td>TVR</td>
<td>14 (7.7)</td>
<td>17 (6.6)</td>
<td>21 (5.7)</td>
</tr>
<tr>
<td>Percutaneous</td>
<td>5 (2.7)</td>
<td>10 (3.8)</td>
<td>18 (4.9)</td>
</tr>
<tr>
<td>Stent thrombosis</td>
<td>4 (2.2)</td>
<td>5 (1.9)</td>
<td>9 (2.4)</td>
</tr>
<tr>
<td>TVF</td>
<td>19 (10.4)</td>
<td>24 (9.2)</td>
<td>30 (8.1)</td>
</tr>
</tbody>
</table>

**Values in (n:%).** The p values relate to differences between patients treated with SES as opposed to PES for each clinical end point, for interactions, and for interaction between the 3 groups of patients: 1) patients who underwent stent implantation only in lesions with a RVD ≤2.75 mm; 2) patients who underwent stent implantation only in lesions with a RVD >2.75 mm; and 3) patients who underwent stent implantation in both small and large vessels. Statistical analysis. A stratified analysis of clinical and angiographic outcomes, which was specified after completion of patient recruitment, was performed according to vessel size. We used quantitative coronary angiography to determine the RVD. Patients, who underwent stent implantation only in lesions with an RVD ≤2.75 mm were categorized as having undergone treatment of small vessels. Conversely, patients who underwent stent implantation only in lesions with an RVD >2.75 mm were categorized as having undergone treatment of large vessels. Patients with stent implantations in both small and large vessels were classified as “mixed.” All randomized patients were included in the analysis of primary and secondary clinical outcomes in the groups to which they were originally allocated to.
interaction between treatment effect and type of vessel disease, we used likelihood ratio tests. Stratified analyses require about 4 times as many events to detect treatment by patient interactions of a magnitude of the overall treatment effect (17). The trial was designed to detect a relative risk of 0.5 of MACE in the primary analysis of all patients at 9 months, when 86 events had occurred, with a power of 90% (14). A post hoc power analysis based on 142 MACE that had occurred at up to 2 years indicated that the trial would have a power of 44% to detect an interaction between treatment and vessel size of a similar magnitude.

The differences in treatment effects between small- and large-vessel disease were driven by percutaneous TLR. For this end point we performed an additional series of sensitivity analyses: in addition to the term for the treatment by vessel size interaction, we included terms for interactions between treatment and age, gender, diabetes, hypertension, and acute coronary syndrome and determined whether the treatment by vessel size interaction was affected by the inclusion of these additional interaction terms. Analyses were performed in Stata Version 9.2 (Stata, College Station, Texas); p values are 2-sided.

Results

Baseline clinical, angiographic, and procedural data. A total of 1,012 patients were randomly assigned to treatment with SES (503 patients with 694 lesions) and PES (509 patients with 715 lesions); 370 patients (37%) with 495 lesions had only small-vessel (RVD ≤2.75 mm), 504 patients (50%) with 613 lesions had only large-vessel (RVD >2.75 mm), and 138 patients (14%) with 301 lesions had small- and large-vessel (mixed) disease.

Baseline clinical and angiographic variables for all 3 groups are summarized in Tables 1 and 2. There were significant differences in the prevalence of hypertension (p = 0.02) and stable angina pectoris (p = 0.01). Among patients with acute coronary syndromes, ST-segment elevation myocardial infarctions were more frequent in those with stent implantations in large vessels only (p = 0.002). The incidence of multivessel disease was highest in the mixed-vessel disease group (p < 0.001). Target lesion involvement of the left anterior descending and circumflex coronary arteries was more frequent in those with stent implantations in large vessels only (p = 0.002). The incidence of multivessel disease was highest in the mixed-vessel disease group (p < 0.001). Target lesion involvement of the left anterior descending and circumflex coronary arteries was more frequent in the small-vessel group, whereas the right coronary artery was more frequently treated in the large-vessel population (Table 2). Lesion length and degree of stenosis were similar, whereas minimal lumen diameter and RVD differed among the 3 groups.

Procedural results are presented in Table 3. The number of lesions treated per patient was higher in the mixed group (2.2 ± 0.4), compared with small (1.4 ± 0.6) and large (1.2 ± 0.5; p < 0.001) vessels only. Stents implanted into large vessels were deployed at higher mean pressure than those implanted into small vessels (p < 0.001). With p values for interaction of ≥0.16, there was little evidence for
Table 5  Angiographic Follow-Up Results at 8 Months Stratified by Vessel Size

<table>
<thead>
<tr>
<th>Lesions (n)</th>
<th>SES</th>
<th>PES</th>
<th>Difference (95% CI)</th>
<th>p</th>
<th>Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small Vessels Only</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minimal lumen diameter (mm ± SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In-stent</td>
<td>2.29 ± 0.28</td>
<td>2.15 ± 0.55</td>
<td>0.14 (0.04 to 0.26)</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>In-segment</td>
<td>2.14 ± 0.39</td>
<td>1.94 ± 0.64</td>
<td>0.20 (0.07 to 0.34)</td>
<td>0.004</td>
<td></td>
</tr>
<tr>
<td>Large Vessels Only</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Late loss (mm ± SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In-stent</td>
<td>8.40 ± 8.36</td>
<td>14.46 ± 20.53</td>
<td>-6.07 (-9.97 to -2.14)</td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td>In-segment</td>
<td>13.36 ± 13.71</td>
<td>21.96 ± 24.27</td>
<td>-8.59 (-13.6 to -3.60)</td>
<td>0.001</td>
<td></td>
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<tr>
<td>Binary restenosis (%)</td>
<td></td>
<td></td>
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<tr>
<td>In-stent</td>
<td>1.5</td>
<td>8.8</td>
<td>-7.3 (-13.3 to -1.3)</td>
<td>0.02</td>
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<tr>
<td>In-segment</td>
<td>4.5</td>
<td>16.2</td>
<td>-11.7 (-19.4 to -4.0)</td>
<td>0.003</td>
<td></td>
</tr>
</tbody>
</table>

Values are mean ± standard deviation. *The p values relate to differences between patients treated with SES as opposed to PES for each stratum. The p values for interaction relate to differences in mean or percentage between the 3 groups of patients: 1) patients who underwent stent implantation in small vessels only; 2) patients with treatment of large vessels only; and 3) patients who underwent stent implantation in both small and large vessels.

Abbreviations as in Tables 1 and 4.

differences in procedural outcome between SES and PES in all 3 groups.

Clinical outcome. Clinical events at 2-year follow-up stratified for vessel size are listed in Table 4. In patients with small-vessel disease, SES more effectively reduced MACE than PES at 2 years (10.4% vs. 21.4%, respectively, hazard ratio [HR] 0.45, 95% confidence interval [CI] 0.26 to 0.78; p = 0.004). This difference was largely driven by a 69% reduction in the risk of TLR in favor of SES (6.0% vs. 17.7%, HR 0.31, 95% CI 0.16 to 0.62; p = 0.001) (Fig. 1A). There were no significant differences between SES and PES in small-vessel disease patients with respect to death, cardiac death, or myocardial infarction at up to 2 years of follow-up.

Rates of MACE (10.4% vs. 13.1%, respectively, HR 0.78, 95% CI 0.46 to 1.29; p = 0.33) and TLR (6.9% vs. 8.6%, respectively, HR 0.79, 95% CI 0.42 to 1.49; p = 0.47) at 2 years were similar for SES and PES in patients with large-vessel disease (Fig. 1B). Similarly, there were no significant differences with respect to death, cardiac death, or myocardial infarction at up to 2 years of follow-up. In patients with both small- and large-vessel disease (mixed group), rates of MACE (16.7% vs. 18.0%, respectively, HR 0.91, 95% CI 0.41 to 2.05; p = 0.83) and TLR (16.7% vs. 15.4%, respectively, HR 1.08, 95% CI 0.47 to 2.50; p = 0.86) were comparable for SES and PES at 2 years (Fig. 1C). Differences between small- and large-vessel disease were driven by percutaneous TLR, and tests for interaction between treatment effect and vessel size reached formal statistical significance only for this outcome. When including additional terms for age, gender, diabetes, hypertension, and acute coronary syndrome for percutaneous TLR, we found the interaction between treatment and vessel size unaffected (data available on request).

The incidence of stent thrombosis was low and estimates of hazard ratios imprecise (Table 4). The cumulative frequency of stent thrombosis at 2 years amounted to 2.2% for SES and 2.7% for PES in small-vessel disease (HR 0.81, 95% CI 0.22 to 3.01; p = 0.75), 1.9% and 3.3%, respectively, in large-vessel disease (HR 0.58, 95% CI 0.19 to 1.78; p = 0.35), and 5.0% and 1.3%, respectively, in the mixed group (HR 3.93, 95% CI 0.41 to 37.8; p = 0.24). Angiographic results. Angiographic follow-up at 8 months was obtained in 200 of 370 patients with small-vessel disease (54%), 252 of 504 patients with large-vessel disease (50%), and 68 of 138 patients with mixed disease (49%) (Table 5). Patients undergoing angiographic follow-up were younger (p < 0.001), less likely to have diabetes (p = 0.04) or hypertension (p = 0.04), and more likely to be male (p = 0.004) and to have experienced chest pain (p = 0.01). There was a difference in in-stent (2.29 ± 0.28 mm vs. 2.15 ± 0.55 mm; p = 0.01) and in-segment (2.14 ± 0.39 mm vs. 1.94 ± 0.64 mm; p = 0.004) minimal lumen diameter in favor of SES in small-vessel disease, whereas results were similar in large- and mixed-vessel disease. The SES more effectively reduced in-stent late luminal loss in all 3 subgroups, but differences were more pronounced in the small-vessel group (0.08 ± 0.18 mm vs. 0.26 ± 0.49 mm; p < 0.001). Although the rate of in-segment binary restenosis was significantly lower with SES (4.5%) than PES (16.2%; p = 0.003) in small-vessel disease, rates were similar in large-vessel (SES 7.6%, PES 7.0%; p = 0.85) and mixed-vessel disease (SES 9.1%, PES 12.8%; p = 0.55). Tests for interaction between treatment
effect and vessel size reached formal statistical significance for in-segment minimal lumen diameter, diameter stenosis, late luminal loss, and binary stenosis.

**Discussion**

The principal findings of this subgroup analysis of the SIRTAx trial stratified by vessel size are as follows:

1. Sirolimus-eluting stents more effectively reduce rates of MACE and TLR in patients with small-vessel disease (RVD =2.75 mm).
2. The therapeutic benefit of SES over PES is maintained at 2 years’ follow-up.
3. Differences in rates of MACE and TLR tend to be less pronounced in patients with large-vessel and mixed-vessel disease at 1 and 2 years’ follow-up.
4. There are no significant differences between SES and PES with respect to death, cardiac death, myocardial infarction, or stent thrombosis in patients with small-, large-, and mixed-vessel disease at 2 years.
5. Sirolimus-eluting stents provide lower late luminal loss, translating into lower rates of binary restenosis, particularly in patients with small-vessel disease.

The results of the present study are biologically plausible, because a reduction in luminal diameter by a constant amount of neointimal hyperplasia results in a proportionally higher-grade diameter stenosis in small compared with large vessels. Moreover, SES have been invariably shown to afford lower late luminal loss in all trials with angiographic follow-up directly comparing SES and PES (13,14,18–20), and late luminal loss is an established marker to discriminate between different stent types (15). However, the impact of differences in late luminal loss on clinical outcome remains controversial, and the present study may help to identify patients who derive the greatest benefit from SES.

The findings of this subgroup analysis of a large-scale randomized trial directly comparing SES and PES are consistent with previously published data on: 1) indirect comparisons of SES and PES in small vessels (21–23); 2) registry experience comparing SES and PES in small vessels (24); and 3) direct comparison in a dedicated randomized trial of SES and PES in small vessels (25). Stone et al. (21) reported relatively high rates of restenosis (31%) and TLR (10.4%) in 108 patients treated with the 2.25-mm diameter PES in the TAXUS (In-Stent Restenosis Treated With Stent-Based Delivery of Paclitaxel Incorporated in a Slow-Release Polymer Formulation) V trial. In contrast, Nikolsky et al. (22) observed lower rates of restenosis (17%) and TLR (4.3%) in a similar patient population of 100 patients treated with 2.25-mm diameter SES. Similar results have been observed in the SES-SMART (Sirolimus-Eluting Stent and a Standard Stent in the Prevention of Restenosis in Small Coronary Arteries) trial (23) with restenosis and TLR rates of 10% and 7%, respectively, in SES-treated vessels. In a registry comparison of SES and PES from the Thoraxcenter, Rotterdam, rates of both TLR and MACE were higher for PES than SES (TLR: 5% vs. 1.4%; p = 0.08; MACE: 17.8% vs. 5.6%; p = 0.007) (24). In the REALITY (Prospective Randomized Multi-Center Head-to-Head Comparison of the Sirolimus-Eluting Stent [Cypher] and the Paclitaxel-Eluting Stent [Taxus]) trial (13), late loss was significantly lower in SES- compared with PES-treated patients, confirming the results of the present study. However, the difference in late loss in favor of SES failed to translate into a significant difference regarding binary restenosis (SES 9.6% vs. PES 11.1%; p = 0.31). This may be explained in part by a significantly lower postprocedural

<table>
<thead>
<tr>
<th>Lesions (n)</th>
<th>SES</th>
<th>PES</th>
<th>Difference (95% CI)</th>
<th>p Value*</th>
<th>p Value for Interaction*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimal lumen diameter (mm ± SD)</td>
<td>55</td>
<td>94</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In-stent</td>
<td>2.44 ± 0.58</td>
<td>2.37 ± 0.66</td>
<td>0.08 (−0.12 to 0.27)</td>
<td>0.43</td>
<td>0.17</td>
</tr>
<tr>
<td>In-segment</td>
<td>2.26 ± 0.65</td>
<td>2.18 ± 0.71</td>
<td>0.09 (−0.14 to 0.31)</td>
<td>0.44</td>
<td>0.03</td>
</tr>
<tr>
<td>Stenosis (% of lumen diameter ± SD)</td>
<td>0.54</td>
<td>0.52</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In-stent</td>
<td>0.29 ± 0.11</td>
<td>0.28 ± 0.08</td>
<td>−0.10 (−0.28 to 0.08)</td>
<td>0.26</td>
<td>0.35</td>
</tr>
<tr>
<td>In-segment</td>
<td>0.33 ± 0.54</td>
<td>0.33 ± 0.54</td>
<td>0.09 (−0.29 to 0.11)</td>
<td>0.39</td>
<td>0.05</td>
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<td>Late loss (mm ± SD)</td>
<td>2.75</td>
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<tr>
<td>In-stent</td>
<td>17.27 ± 10.00</td>
<td>17.27 ± 10.00</td>
<td>−3.1 (−11.7 to 5.6)</td>
<td>0.49</td>
<td>0.23</td>
</tr>
<tr>
<td>In-segment</td>
<td>20.27 ± 10.00</td>
<td>20.27 ± 10.00</td>
<td>−3.7 (−15.6 to 8.2)</td>
<td>0.55</td>
<td>0.06</td>
</tr>
</tbody>
</table>

**Table 5 Continued**
in-stent minimal luminal diameter in SES compared with PES (2.08 vs. 2.16 mm; p < 0.001). Accordingly, the more potent effect of SES in reducing neointimal hyperplasia may have been offset in part by the inferior immediate postprocedural result.

Finally, a dedicated randomized trial directly compared SES and PES in a patient population of size similar to the present subgroup analysis and observed significantly lower late loss (0.13 ± 0.56 mm vs. 0.34 ± 0.57 mm; p < 0.001), in-segment restenosis (11.4% vs. 19.0%; p = 0.047), and TLR (6.6% vs. 14.7%; p = 0.008) in SES- compared with PES-treated patients, respectively (25).

The impact of vessel size on outcome with DES has recently been evaluated by Elezi et al. (26). They observed lower late luminal loss for SES compared with PES in all 3 vessel size tertiles, which translated into a lower rate of TLR in favor of SES (8.6% vs. 16.4%; p = 0.002) only in the lowest vessel size tertile (RVD <2.41 mm). In a separate registry analysis of predictive factors of restenosis after implantation of SES and PES, Kastrati et al. (27) identified vessel size and DES type as strongest predictors of restenosis. Thus, results of a classification and regression tree revealed that rates of TLR were lower for SES than PES (7.8% vs. 15.6%) in vessels smaller than 2.6 mm and similar (7.2% vs. 7.2%) in larger vessels. The present study corroborates the findings of those studies and adds additional information, because the data were derived from a large-scale randomized trial with adequate concealment of allocation, minimizing the risk of selection bias at study entry and assuring similar patient and lesion characteristics between SES- and PES-treated patients. Moreover, regular follow-up at predefined intervals provided additional rigor of data collection and allowed extending the observation period to 2 years.

The frequency of diabetes in the present study tends to be higher in small-vessel than in large-vessel disease, but is not as pronounced as reported by Elezi et al. (26), who described a higher frequency of diabetes in patients in the lowest vessel size tertile (RVD <2.41 mm). However, the frequency of diabetes in patients was similar in the middle tertile (RVD 2.41 to 2.84 mm). Differences in RVD between diabetic and nondiabetic patients in the TAXUS IV trial (29) and the SIRIUS (Sirolimus-Eluting Stent in Coronary Lesions) trial (30) were only minimal and in accordance with our results.

**Study limitations.** This is a subgroup analysis of a randomized trial not powered to detect treatment-subgroup interactions. It was not prespecified and is therefore exploratory in nature. A post hoc power analysis indicated that the trial would have a power of only 44% to detect a clinically relevant interaction between treatment and vessel size. Not surprisingly, the majority of interaction tests did not reach formal statistical significance and we cannot exclude that some of the observed differences in treatment effects between small- and large-vessel disease may have occurred by chance alone. However, the concordance between clinical and angiographic results suggests that the observed pattern may be real. Irrespective of the results of interaction tests, it can be concluded that SES is more beneficial than PES in small-vessel disease in terms of a reduction of TLR and MACE. The advantage of SES over PES appears less pronounced in large- and mixed-vessel disease, and interaction tests indicate that this trend toward a less pronounced advantage of SES over PES in large-vessel disease may have occurred by chance alone.

The SIRTAX trial was performed in an unselected “all comers” population, and 138 patients were treated for both small- and large-vessel disease (mixed group). These latter patients were more complex, as evidenced by a higher prevalence of multivessel disease and a nearly 2-fold higher number of lesions treated per patient compared with both the small- and the large-vessel disease groups. Although overall rates of MACE were similar for SES and PES in the mixed group, most of the adverse events were related to small vessels.

The rate of angiographic follow-up (51%) was low. This may have been related to the absence of a financial incentive and the broad inclusion criteria, with elderly patients and those with comorbid conditions being more reluctant to undergo repeat angiography than younger healthier patients typically included in angiography trials. Angiographic routine follow-up is known to increase the rate of TLR, and the incomplete angiographic follow-up in the present trial may have led to attrition bias (28), potentially resulting in an overestimation of differences in TLR and MACE between SES and PES. We consider this unlikely, because the difference in MACE in favor of SES was already apparent before the scheduled angiographic follow-up at 6 months (HR for MACE at 6 months 0.56, 95% CI 0.32 to 0.96; p = 0.035).

**Conclusions**

Vessel size remains an important determinant of adverse outcome in the DES era. Sirolimus-eluting stents are more effective than PES in reducing angiographic and clinical measures of restenosis. The benefit is particularly pronounced in small vessels less able to accommodate neointimal hyperplasia, whereas the selection of a particular DES appears less relevant in larger vessels. The observed therapeutic benefit is likely to apply to newer second-generation DES using limus analogues with similar reductions of late luminal loss but the potential for an improved safety profile.

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REFERENCES


