Coated Stents for the Prevention of Restenosis: Part II

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This is the second part of a 2-part article that reviews the literature on coated stents and their effects on in-stent restenosis after percutaneous coronary intervention (PCI). Part I of this review discussed the pathophysiology of in-stent restenosis, specific stent coatings, and animal studies investigating coated stents. Part II discusses nonrandomized studies and clinical trials in humans. Studies in humans have examined stents coated with biocompatible materials and drug-eluting stents. Complications and controversies associated with this new technology are also addressed.

Human Studies

The risk of developing in-stent restenosis is related to a variety of factors, both clinical and procedural.1–7 On the basis of these risk factors, patients enrolled in both nonrandomized studies and clinical trials have been classified as having a high, intermediate, or low risk of restenosis. Therefore, the binary restenosis rates (>50% diameter stenosis angiographically) and major adverse cardiac event (MACE) rates in human studies vary greatly depending on the overall risk profile of patients enrolled in these studies.

Non-Randomized Studies

Stents Coated with Biocompatible Materials

The biocompatibility of stents coated with several materials, including carbon, gold, silicon carbide, and phosphorylcholine, has been investigated in humans. The Carbostent (Sorin Biomedica Cardio) is a metal stent coated with a carbon film that is thought to be less thrombogenic than uncoated steel stents.8 Antoniucci et al9 investigated the long-term biocompatibility of the Carbostent in a group of 112 patients with an intermediate risk of developing restenosis. Six-month follow-up revealed low MACE and restenosis rates of 12% and 11%, respectively. A second study in another group of 112 patients at high risk for restenosis resulted in a MACE rate of 20% and a binary restenosis rate of 25% by 6 months.10 These results suggest that the Carbostent is well tolerated in vivo and possibly inhibits neointimal hyperplasia, especially in high-risk patients (Table I).

Gold has been touted as a biocompatible material and has been thought to be ideal for coating coronary stents because of its radio-opaque properties.1 Two studies evaluating the biocompatibility of gold-coated stents suggested equivalency with uncoated steel stents.11,12 However, two other studies concluded that these stents may increase neointimal hyperplasia compared with uncoated stents, although patients at a higher risk for restenosis were enrolled.13,14 Follow-up angiography at 6 months demonstrated a relatively high lumen late loss (postintervention minimum luminal diameter minus the minimum luminal diameter at follow-up) and diameter stenosis in both studies (Table I). Overall, there have been conflicting results in observational studies examining gold-coated stents, and the restenosis rates seem to be no better than those obtained with uncoated steel stents.

Silicon carbide is an inert semiconductor that can be coated onto prosthetic surfaces and has been shown to be relatively biocompatible and hemocompatible in in vitro studies.15,16 Stents coated with silicon carbide also appear to be less thrombogenic than bare metal stents when implanted in human coronary arteries.17 In an observational study of 165 patients, Heublein et al18 reported a MACE rate of 32%, with a propensity for more events in higher risk patients. Follow-up angiography was done only on 27% of patients who developed symptoms after stent implantation, and revealed a restenosis rate of 36% by 5 months. Silicon carbide-coated stents were used in the stent arm of a clinical trial comparing balloon angioplasty alone with balloon angioplasty plus stenting in the setting of an acute myocardial infarction.19 Long-term follow-up results of the stent arm of this study suggest that silicon carbide-coated stents did not significantly decrease restenosis rates. Two other observational studies have been published with similar clinical event rates.20,21 A major limitation of most of these studies is the lack of routine follow-up angiography. Overall, silicon carbide-coated stents do not appear to have a significant effect on restenosis (Table I).

Five nonrandomized studies have evaluated the properties of stents coated with phosphorylcholine, a naturally occurring phospholipid polymer. In a study of 224 patients, Zheng et al22 reported a MACE rate of 9% on the basis of clinical follow-up of 132 patients at 6 months. Repeat angiography was performed in only 28 patients, 8 of whom had angiographically documented in-stent restenosis. In a similar study of 218 consecutive patients who received a phosphorylcholine-coated stent, Galli et al23 reported a 6-month MACE rate of 13%, confirming that

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this type of stent is very well tolerated in humans. The same group\textsuperscript{24} showed that phosphorylcholine coated stents had low rates of subacute stent thrombosis (0%) and restenosis (12%), even when used in the setting of primary PCI for acute myocardial infarction.

Phosphorylcholine-coated stents have also been examined in the setting of PCI of small coronary vessels. In a retrospective series of 90 patients undergoing stenting of vessels 2.0 to 2.8 mm in diameter, Beaudry et al\textsuperscript{25} reported a MACE rate of 20%. Similar results have been obtained after deploying these stents in vessels <2.0 mm in diameter.\textsuperscript{26} Unfortunately, the lack of routine follow-up angiography is the major limitation of these 5 studies, and although well tolerated, it is unclear if phosphorylcholine-coated stents inhibit neointimal hyperplasia to a significant degree (Table 2).

**Stents Coated with Heparin**

Observational studies in animals have suggested that heparin-coated stents may decrease rates of subacute thrombosis and inhibit neointimal hyperplasia (see Part I of this review). Small series such as that by Atalar et al\textsuperscript{27} have demonstrated the safety of heparin-coated stents in humans. The Heparin-Coated Wiktor Stents in Human Coronary Arteries (MENTOR) study was a prospective study of 132 patients undergoing implantation of heparin-coated stents in coronary lesions at low risk of restenosis.\textsuperscript{28} The MACE rate was 15% at 6 months and the binary restenosis rate was 22% (Table 2). These results are comparable to those in previous studies using uncoated stents, such as in the stent arm of the first Belgium Netherlands Stent trial.\textsuperscript{29}

Results suggesting equivalency between uncoated and heparin-coated stents in low risk lesions prompted other investigators to test the efficacy of heparin-coated stents in more complex lesions. Van Langenhove et al\textsuperscript{30} reported a MACE rate of only 10% and a binary restenosis rate of 22% at 6 months when heparin-coated stents were implanted in saphenous vein grafts.\textsuperscript{30} Shin et al\textsuperscript{31} assessed the efficacy of heparin-coated stents in 102 patients with an acute myocardial infarction undergoing primary PCI. Standard oral anti-platelet agents were given, but patients were not treated with intravenous heparin or glycoprotein IIb/IIIa inhibitors after stent deployment. Clinical and angiographic follow-up at 2 weeks did not reveal any findings of subacute stent thrombosis, and follow-up at 6 months revealed a MACE rate of 14% and an angiographic restenosis rate of 17%. The results of these 2 studies compare favorably with those of prior studies using uncoated stents in comparable patient populations.\textsuperscript{32,33}

Several prospective studies comparing balloon angioplasty alone with balloon angioplasty plus stent implantation in treating coronary stenoses have used heparin-coated stents.\textsuperscript{34–36} The primary objective of these trials was not to compare heparin-coated stents with uncoated steel stents, but rather to examine the effect of coronary stenting on restenosis rates after PCI. In 3 clinical trials, patients were randomized to either balloon angioplasty alone or balloon angioplasty with the implantation of heparin-coated stents. In those patients who had heparin-coated stents implanted, the 6-month MACE rates ranged from 13% to 16%, and the binary restenosis rates ranged from 16% to 55% (Table 2). Heparin-coated stents have also been evaluated in small coronary arteries (2.1 to 3.0 mm in diameter) and have shown promising results, with a MACE rate of only 10% and a binary restenosis rate of 10% at 6 months.\textsuperscript{37} The low clinical event rates were maintained at 1-year follow-up.\textsuperscript{38} These results also compare well with the results of other studies investigating uncoated stents in small-caliber coronary vessels.\textsuperscript{39,40}

The characteristics of the treated lesions and the study protocols differ among the studies investigating heparin-coated stents, making comparisons with earlier studies difficult. Generally speaking, the results of these studies suggest that heparin-coated stents are well tolerated. Although the rate of subacute thrombosis for these stents seems to be lower than for uncoated steel stents, these stents do not seem to have a significant long-term impact on either MACE or restenosis rates when compared with uncoated stents (Table 2).

TABLE 1. Human Observational Studies Investigating Stents Coated With Biocompatible Materials

<table>
<thead>
<tr>
<th>Study</th>
<th>Coating</th>
<th>N</th>
<th>Restenosis Risk</th>
<th>Follow-Up, months</th>
<th>MACE, %</th>
<th>Mean Late Loss, mm</th>
<th>Mean Diameter Stenosis, %</th>
<th>Binary Restenosis, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antoniucci et al\textsuperscript{9}</td>
<td>Carbon</td>
<td>112</td>
<td>Intermediate</td>
<td>6</td>
<td>12</td>
<td>0.75±0.73</td>
<td>22±23</td>
<td>11</td>
</tr>
<tr>
<td>Antoniucci et al\textsuperscript{10}</td>
<td>Carbon</td>
<td>112</td>
<td>High</td>
<td>6</td>
<td>20</td>
<td>0.81±0.88</td>
<td>27±29</td>
<td>25</td>
</tr>
<tr>
<td>Harding et al\textsuperscript{11}</td>
<td>Gold</td>
<td>181</td>
<td>Intermediate</td>
<td>11</td>
<td>23</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Cremonesi et al\textsuperscript{12}</td>
<td>Gold</td>
<td>165</td>
<td>Intermediate</td>
<td>6</td>
<td>12</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Danzi et al\textsuperscript{13}</td>
<td>Gold</td>
<td>116</td>
<td>High</td>
<td>6</td>
<td>40</td>
<td>1.20±1.00</td>
<td>42±24</td>
<td>32</td>
</tr>
<tr>
<td>Hoffmann et al\textsuperscript{14}</td>
<td>Gold (InFlow)</td>
<td>73</td>
<td>Low</td>
<td>6</td>
<td>NR</td>
<td>1.17±0.66</td>
<td>47±19</td>
<td>NR</td>
</tr>
<tr>
<td>Hoffmann et al\textsuperscript{14}</td>
<td>Gold (NIR)</td>
<td>12</td>
<td>Low</td>
<td>6</td>
<td>NR</td>
<td>1.14±0.79</td>
<td>36±38</td>
<td>NR</td>
</tr>
<tr>
<td>Heublein et al\textsuperscript{15}</td>
<td>SiC</td>
<td>165</td>
<td>Intermediate</td>
<td>5</td>
<td>32*</td>
<td>NR</td>
<td>NR</td>
<td>36†</td>
</tr>
<tr>
<td>Scheller et al\textsuperscript{16}</td>
<td>SiC</td>
<td>44</td>
<td>High</td>
<td>35</td>
<td>23</td>
<td>0.9±0.9</td>
<td>NR</td>
<td>24</td>
</tr>
<tr>
<td>Carrie et al\textsuperscript{17}</td>
<td>SiC</td>
<td>241</td>
<td>Intermediate</td>
<td>12</td>
<td>16</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Kalnins et al\textsuperscript{18}</td>
<td>SiC</td>
<td>100</td>
<td>Low</td>
<td>6</td>
<td>14</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

NR indicates not reported; SiC, silicon carbide. InFlow (Invatec InFlow Dynamics) and NIR (Medinol) are 2 types of steel stents.

*The MACE does not include acute and subacute (<14 days) events.
†Only symptomatic patients underwent follow-up angiography.
‡The sample size listed is only those in the stent arm of the trial.
TABLE 2. Human Observational Studies Investigating Stents Coated With Phosphorylcholine and Heparin

<table>
<thead>
<tr>
<th>Study</th>
<th>Coating</th>
<th>N</th>
<th>Restenosis Risk</th>
<th>Follow-Up, months</th>
<th>MACE, %</th>
<th>Mean Late Loss, mm</th>
<th>Mean Diameter Stenosis, %</th>
<th>Binary Restenosis, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zheng et al</td>
<td>PC</td>
<td>132</td>
<td>High</td>
<td>6</td>
<td>9</td>
<td>NR</td>
<td>NR</td>
<td>6*</td>
</tr>
<tr>
<td>Galli et al</td>
<td>PC</td>
<td>218</td>
<td>High</td>
<td>6</td>
<td>13</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Galli et al</td>
<td>PC</td>
<td>70</td>
<td>High</td>
<td>7</td>
<td>13</td>
<td>0.35 ± 0.20</td>
<td>30 ± 18</td>
<td>12</td>
</tr>
<tr>
<td>Beaudry et al</td>
<td>PC</td>
<td>90</td>
<td>High</td>
<td>6</td>
<td>20</td>
<td>NR</td>
<td>NR</td>
<td>17*</td>
</tr>
<tr>
<td>Grenadier et al</td>
<td>PC</td>
<td>97</td>
<td>High</td>
<td>6</td>
<td>10</td>
<td>NR</td>
<td>NR</td>
<td>8*</td>
</tr>
<tr>
<td>Vrolix et al</td>
<td>Heparin</td>
<td>132</td>
<td>Low</td>
<td>6</td>
<td>15</td>
<td>0.78 ± 0.69</td>
<td>40 ± 18</td>
<td>22</td>
</tr>
<tr>
<td>Van Langenhove et al</td>
<td>Heparin</td>
<td>50</td>
<td>High</td>
<td>6</td>
<td>10</td>
<td>0.82 ± 1.07</td>
<td>34 ± 25</td>
<td>22</td>
</tr>
<tr>
<td>Shin et al</td>
<td>Heparin</td>
<td>102</td>
<td>High</td>
<td>6</td>
<td>14</td>
<td>0.45 ± 0.25</td>
<td>39 ± 24</td>
<td>17</td>
</tr>
<tr>
<td>Serruy et al</td>
<td>Heparin</td>
<td>413†</td>
<td>Low</td>
<td>6</td>
<td>13</td>
<td>0.80 ± 0.54</td>
<td>35 ± 17</td>
<td>16</td>
</tr>
<tr>
<td>Buller et al</td>
<td>Heparin</td>
<td>202†</td>
<td>High</td>
<td>6</td>
<td>16</td>
<td>0.97 ± 0.75</td>
<td>53 ± 21</td>
<td>55</td>
</tr>
<tr>
<td>Grines et al</td>
<td>Heparin</td>
<td>452†</td>
<td>High</td>
<td>7</td>
<td>13</td>
<td>0.76</td>
<td>36 ± 22</td>
<td>20</td>
</tr>
<tr>
<td>Moer et al</td>
<td>Heparin</td>
<td>74</td>
<td>High</td>
<td>6</td>
<td>10</td>
<td>0.54 ± 0.48</td>
<td>30 ± 18</td>
<td>10</td>
</tr>
</tbody>
</table>

PC indicates phosphorylcholine; NR, not reported.
*Only symptomatic patients underwent follow-up angiography.
†The sample size listed is only those in the stent arm of the trial.

Stents Coated With Corticosteroids and Antimitotic Agents

In contrast with animal studies, there have been no published nonrandomized studies in humans examining stents coated with corticosteroids, and only a few studies have been published examining stents coated with antimitotic agents (Table 3).

The First In Man (FIM) study was the first published nonrandomized study in humans to investigate stents coated with antimitotic agents. It was conducted jointly in Brazil and Europe to assess the efficacy of sirolimus-coated stents in inhibiting neointimal hyperplasia. In the Brazilian cohort, 30 patients with low-risk lesions were randomized to receive either a fast-release sirolimus-coated stent (drug elution <15 days) or a slow-release sirolimus-coated stent (drug elution >28 days). The patients had quantitative coronary angiography (QCA) and intravascular ultrasound (IVUS) done at 4 months, with clinical follow-up at 8 months. No patient had binary restenosis shown by IVUS, and all patients had <20% diameter stenosis by IVUS. No MACE had occurred by 8 months. There was also no difference in clinical or angiographic end points between the fast-release and slow-release formulations. The 1-year follow-up results of this cohort have also been published, showing essentially unchanged QCA variables. Only 1 MACE occurred by the 15-month clinical follow-up (Table 3).

Rensing et al published the European experience with the sirolimus-coated stent in 15 patients undergoing PCI as part of the FIM study. All stents contained the slow-release formulation of sirolimus. There were QCA and IVUS follow-up at 6 months and clinical follow-up at 9 months. The angiographic restenosis rate was 0%, with IVUS demonstrating a mean in-stent late loss of 0.0 mm (range –0.37 to 0.25 mm). There was 1 death due to an intracranial hemorrhage. The combined Brazilian and European results of the FIM study show no binary restenosis and no MACE up to 12 months, suggesting that both fast-release and slow-release sirolimus-coated stents have a potent inhibitory effect on neointimal hyperplasia in humans.

QP2, a taxane analogue structurally similar to paclitaxel, is another agent whose efficacy at inhibiting neointimal hyperplasia has been investigated in humans. In a study of 14 patients, Honda et al reported a binary restenosis rate of 0%. Only a minimal amount of neointimal proliferation was visible by IVUS by the 8-month follow-up period. The authors reported a significant increase in plaque area immediately proximal and distal to the stents, however, leading to revascularization procedures in 2 patients. These observations have caused concern about the possibility of edge restenosis with stents coated with antimitotic agents similar to that seen with radioactive stents. A cohort of 32 patients in Argentina who had QP2-coated stents inserted were reported to be clinically asymptomatic up to 2 years after stent implantation. QCA and IVUS demonstrated a 0% binary restenosis rate in a subgroup of 13 patients who underwent repeat cardiac catheterization (Table 3). Interestingly, 5 patients in this study had the QP2-coated stent deployed within a previously implanted stent with in-stent restenosis. Edge restenosis was not reported in the subgroup that underwent IVUS.

The efficacy of QP2-coated stents at reducing restenosis when inserted in lesions with preexisting in-stent restenosis has also been investigated in 1 study. The baseline patient and lesion characteristics predicted a high risk of restenosis. The 6-month clinical and QCA results suggested efficacy at reducing in-stent restenosis (MACE rate of 40% and binary restenosis rate of 13%). By the 12 month follow-up period, however, 87% of the patients had experienced a MACE and 62% of the implanted stents were restenotic (Table 3). These results suggest that QP2-coated stents may delay but do not decrease restenosis in lesions with preexisting neointimal hyperplasia.

In summary, observational studies in humans suggest that stents coated with inert materials do not have a significant impact on restenosis. It is unclear if phosphorylcholine-coated stents decrease restenosis rates, but they appear to be well tolerated and have the added advantage of potentially...
acting as a reservoir of an antiproliferative agent for drug elution. Heparin-coated stents reduce subacute thrombosis but do not have a significant inhibitory effect on neointimal hyperplasia. Several small observational studies examining stents coated with antimitotic agents in humans suggest that they have a potent inhibitory effect on neointimal hyperplasia. Sirolimus-coated stents have demonstrated a significant inhibitory effect on restenosis, although it is unclear if this antiproliferative effect will be sustained over the long term. The results of 3 studies investigating stents coated with QP2, a taxane analogue, are less conclusive. QP2-coated stents appear to have an antiproliferative effect, but do not significantly alter restenosis rates in high-risk lesions. Excessive proliferation of atherosclerotic plaques immediately proximal and distal to the site of stent insertion has also been reported with QP2 coated stents.

**Clinical Trials**

There are only a few published randomized clinical trials evaluating the efficacy of coated stents, although several have released results in abstract form, and several more are currently in progress.

**TABLE 3. Human Observational Studies Investigating Stents Eluting Antimitotic Agents**

<table>
<thead>
<tr>
<th>Study</th>
<th>Coating</th>
<th>N</th>
<th>Restenosis</th>
<th>Follow-Up, months</th>
<th>MACE, %</th>
<th>Mean Late Loss, mm</th>
<th>Mean Diameter Stenosis, %</th>
<th>Binary Restenosis, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sousa et al⁴¹⁺</td>
<td>Sirolimus (fast release)</td>
<td>15</td>
<td>Low</td>
<td>4</td>
<td>0</td>
<td>-0.10±0.3</td>
<td>4.6±5.7</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Sirolimus (slow release)</td>
<td>15</td>
<td>Low</td>
<td>4</td>
<td>0</td>
<td>0.09±0.3</td>
<td>5.0±6.7</td>
<td>0</td>
</tr>
<tr>
<td>Sousa et al⁴²⁺</td>
<td>Sirolimus (fast release)</td>
<td>15</td>
<td>Low</td>
<td>12</td>
<td>0</td>
<td>0.09</td>
<td>8.9±6.1</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Sirolimus (slow release)</td>
<td>15</td>
<td>Low</td>
<td>12</td>
<td>0</td>
<td>0.07</td>
<td>6.7±7.0</td>
<td>0</td>
</tr>
<tr>
<td>Rensing et al⁴³</td>
<td>Sirolimus (slow release)</td>
<td>15</td>
<td>Low</td>
<td>6</td>
<td>0</td>
<td>0.00</td>
<td>13.7</td>
<td>0</td>
</tr>
<tr>
<td>Honda et al⁴⁴</td>
<td>QP2</td>
<td>14</td>
<td>Low</td>
<td>8</td>
<td>10</td>
<td>0.10</td>
<td>13.3±15.1</td>
<td>0</td>
</tr>
<tr>
<td>de la Fuente et al⁴⁵</td>
<td>QP2</td>
<td>32</td>
<td>Intermediate</td>
<td>11</td>
<td>0</td>
<td>0.42±0.36</td>
<td>6.3±9.3</td>
<td>0</td>
</tr>
<tr>
<td>Liistro et al⁴⁶</td>
<td>QP2</td>
<td>15</td>
<td>High</td>
<td>12</td>
<td>87</td>
<td>1.36±0.94</td>
<td>NR</td>
<td>62</td>
</tr>
</tbody>
</table>

NR indicates not reported
*These are the 4- and 12-month follow-up results of the same cohort of 30 patients

**TABLE 4. Clinical Trials Investigating Coated Stents**

<table>
<thead>
<tr>
<th>Study</th>
<th>Coating</th>
<th>N</th>
<th>Restenosis</th>
<th>Follow-up, months</th>
<th>MACE, % Coated</th>
<th>MACE, % Uncoated</th>
<th>P Value</th>
<th>Binary Restenosis, % Coated</th>
<th>Binary Restenosis, % Uncoated</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kastrati et al⁴⁸</td>
<td>Gold</td>
<td>731</td>
<td>Intermediate</td>
<td>12*</td>
<td>37.1</td>
<td>26.1</td>
<td>0.001</td>
<td>49.7</td>
<td>38.1</td>
<td>0.003</td>
</tr>
<tr>
<td>vom Dahl et al⁴⁹</td>
<td>Gold</td>
<td>204</td>
<td>Low</td>
<td>6</td>
<td>3</td>
<td>2</td>
<td>NS</td>
<td>36</td>
<td>24</td>
<td>0.13</td>
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<tr>
<td>Park et al⁵⁰</td>
<td>Gold</td>
<td>216</td>
<td>Intermediate</td>
<td>9*</td>
<td>23.6</td>
<td>15.1</td>
<td>0.113</td>
<td>46.7</td>
<td>26.4</td>
<td>&lt;0.05</td>
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<tr>
<td>Wohrle et al⁵¹</td>
<td>Heparin</td>
<td>277</td>
<td>Intermediate</td>
<td>6</td>
<td>25.2</td>
<td>25.7</td>
<td>NS</td>
<td>33.1</td>
<td>30.3</td>
<td>NS</td>
</tr>
<tr>
<td>Morice et al⁵²</td>
<td>Sirolimus</td>
<td>238</td>
<td>Low</td>
<td>12*</td>
<td>5.8</td>
<td>28.8</td>
<td>0.001</td>
<td>0.0</td>
<td>26.6</td>
<td>0.001</td>
</tr>
<tr>
<td>Park et al⁵³</td>
<td>Paclitaxel (high dose)</td>
<td>§</td>
<td>Low</td>
<td>6</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>4</td>
<td>27</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
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<td>§</td>
<td>Low</td>
<td>6</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>12</td>
<td>27</td>
<td>NA</td>
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<tr>
<td>Gershlick et al⁵⁵†</td>
<td>Paclitaxel</td>
<td>192</td>
<td>Low</td>
<td>6</td>
<td>11</td>
<td>11</td>
<td>NS</td>
<td>3</td>
<td>21</td>
<td>0.055</td>
</tr>
<tr>
<td>Grube et al⁵⁶</td>
<td>Paclitaxel</td>
<td>61</td>
<td>Low</td>
<td>6</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>0</td>
<td>11</td>
<td>0.106</td>
</tr>
<tr>
<td>Grube et al⁵⁷</td>
<td>QP2</td>
<td>266</td>
<td>Low</td>
<td>6</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>10.1</td>
<td>36.9</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

NS indicates not significant; NA, data not available.
*Angiographic follow-up at 6 months.
†The values given here are for the highest-dose paclitaxel group (2.7 μg/mm2).
‡9.4% due to subacute and delayed stent thrombosis.
§The total number for this 3 arm trial was 177.

**Stents Coated With Biocompatible Materials**

Three randomized, controlled, nonblinded clinical trials have evaluated the efficacy of gold-coated stents at reducing restenosis rates. Kastrati et al⁴⁸ randomized 731 patients to receive either a gold-coated stent or an uncoated stent. Although there was no difference between the 2 groups with regard to acute and subacute events or survival, there was a significant difference in MACE rates at 1 year, with a worse outcome in the gold-coated stent group (26.1% uncoated versus 37.1% gold-coated, P=0.001). Results of angiographic variables such as binary restenosis, luminal late loss, and percent diameter stenosis also showed a worse outcome, suggesting that gold-coated stents actually increase the risk of restenosis when used in complex lesions (Table 4). Smaller clinical trials by vom Dahl et al⁴⁹ and Park et al⁵⁰ that enrolled a total of 420 patients have published similar results, demonstrating a worse outcome in the gold-coated stent arms of the trials. The authors of these studies concluded that gold-coated stents appear to exaggerate the proliferative response after PCI when implanted in complex lesions (Table 4).
Stents Coated With Heparin
To our knowledge, only 1 clinical trial comparing heparin-coated stents with uncoated stents for the prevention of restenosis has been published. Wohrle et al\textsuperscript{51} randomized 277 patients with predominantly complex lesions to receive either heparin-coated or uncoated stents. The heparin was eluted from the stents by a polyamine (polymer) coating previously shown to be inert. Clinical and angiographic follow-up at 6 months did not reveal a significant difference between the 2 groups in restenosis rates (heparin-coated 33.1\% versus uncoated 30.3\%) or MACE (heparin-coated 25.2\% versus uncoated 25.7\%). The results of this trial are consistent with those of nonrandomized studies and suggest that heparin-coated stents do not have a significant impact on in-stent restenosis.

Stents Coated With Antimitotic Agents
The RAandomized study with the Sirolimus-coated BX VE-locity balloon expandable stent in the treatment of patients with de novo native coronary artery lesions (RAVEL) was a randomized, double-blind, controlled trial that evaluated a sirolimus-coated stent in humans.\textsuperscript{52} The sirolimus was blended with a mixture of polymers to achieve programmed elution of most of the drug within 30 days. Two hundred thirty-eight patients with low-risk lesions in native coronary arteries were randomized to receive either a sirolimus-coated stent (n=120) or an uncoated steel stent (n=118). All patients were treated with either clopidogrel or ticlopidine for 8 weeks following PCI. Follow-up at 1 year revealed a remarkable difference in the primary clinical end-point of MACE between the sirolimus-coated and the uncoated stent groups (5.8\% versus 28.8\%, \(P<0.001\)). Only 1 patient in the sirolimus-coated stent group had a MACE that was attributable to the stented vessel. The difference in the MACE rates between the 2 groups was primarily due to a difference in rates of percutaneous revascularization of the target lesion. Angiographic follow-up at 6 months also revealed a significant difference in the primary angiographic end-point of luminal late loss. The binary restenosis rate was 0\% among patients who received a sirolimus-coated stent compared with a 26.6\% restenosis rate for patients who received an uncoated stent (Table 4). No edge restenosis or delayed stent thrombosis occurred in the sirolimus group. The angiographic findings were confirmed in a subset of 95 patients who underwent IVUS in both arms of the trial.\textsuperscript{55}

Four other clinical trials investigating stents eluting antimitotic agents have released preliminary results in abstract form at recent conferences, although they remain unpublished (Table 4). The ASian Paclitaxel-Eluting stent Clinical Trial (ASPECT) was a 177 patient prospective, multicenter, double-blind study comparing stents coated with 2 different concentrations of paclitaxel (high-dose, 3.1 \(\mu g/mm^2\) or low-dose, 1.3 \(\mu g/mm^2\)) versus uncoated stents.\textsuperscript{54} Paclitaxel did not have a carrier polymer in this study. At 6 months, the angiographic parameters of percent diameter stenosis (14\%\(\pm\)21\% versus 39\%\(\pm\)27\%) and binary restenosis (4\% versus 27\%) were both decreased significantly in the high-dose group compared with the uncoated stents (\(P<0.001\)). The MACE rates for this trial have not yet been published.

The EvaLUation of Paclitaxel-Eluting Stents (ELUTES) trial randomized 192 patients in Europe with low-risk lesions in native coronary arteries to receive either an uncoated stent or a paclitaxel-coated stent with no carrier polymer in 4 different concentrations: 0.2 \(\mu g/mm^2\), 0.7 \(\mu g/mm^2\), 1.4 \(\mu g/mm^2\), or 2.7 \(\mu g/mm^2\).\textsuperscript{55} All patients were treated with aspirin and clopidogrel for 3 months. There was no difference in the 6-month MACE rates between the paclitaxel-coated and uncoated stent (11\% in both groups). The binary restenosis rate, however, was 3\% in the highest-dose paclitaxel group versus 21\% in patients that received uncoated stents (\(P=0.055\)). The late loss and percent diameter stenosis were both in favor of the paclitaxel-stent group (\(P<0.01\)) (Table 4).

The TAXUS I trial was a double-blind randomized trial comparing uncoated stents (n=30) with paclitaxel-coated stents (n=31).\textsuperscript{56} Patients were treated with clopidogrel for 6 months. The angiographic results at 6 months have been reported to be in favor of the coated stent group (diameter stenosis 13\%\(\pm\)12\% versus 27\%\(\pm\)17\%, \(P<0.0005\), and binary restenosis 0\% versus 11\%, \(P=0.106\)), although the difference in binary restenosis rates was not statistically significant. Finally, the Study to COmpare REstenosis rates between QueST and QuaDDS-QP2 (SCORE) was a randomized multicenter trial that was terminated prematurely after interim analysis showed a dramatically increased predisposition for subacute and delayed stent thrombosis (9.4\%) in the QP2-stent group compared with the uncoated stent group (0\%).\textsuperscript{57} The 6-month angiographic results suggest that these stents inhibit neointimal hyperplasia, even after accounting for the excessive stent thrombosis rates in the QP2-stent group (Table 4).

In summary, the results of 4 clinical trials investigating gold-coated and heparin-coated stents do not show any benefit with respect to reducing MACE or restenosis. Gold-coated stents may in fact confer a worse outcome compared with uncoated stents. There are no published trials evaluating corticosteroid-coated stents. Several small clinical trials assessing the efficacy of stents coated with antimitotic agents (sirolimus and paclitaxel) at reducing restenosis have been completed. The patients enrolled in these trials have had lesions in native coronary arteries at a low-risk for developing in-stent restenosis, but have demonstrated significant reductions in MACE and binary restenosis rates over 6 to 12 months. A total of 942 patients have been enrolled in these trials, but long-term follow-up results are not yet available.

Clinical Trials in Progress
Many trials evaluating drug-eluting stents are currently in progress (Table 5). These may enroll close to 6000 patients and involve stents coated with agents aimed at inhibiting cell proliferation (sirolimus, paclitaxel, and tacrolimus), cell migration (batimastat, a matrix metalloproteinase inhibitor), and abnormal healing (estradiol). Recruitment in the ACTinomycin-eluting stent Improves Outcomes by reducing Neointimal hyperplasia (ACTION) trial\textsuperscript{59} was stopped after interim analysis of the first 90 enrolled patients showed an above average restenosis rate in patients randomized to both coated stent and uncoated stent arms of the trial. Recruitment in the European Batimastat...
Complications and Controversies

Except for gold-coated stents, stents coated with other biocompatible materials and heparin seem to be well tolerated in humans. However, it is still premature to comment on the safety profile of stents coated with potent antimitotic agents such as sirolimus and paclitaxel. These agents inhibit smooth muscle cell proliferation, and therefore have a mechanism of action similar to that of radioactive stents. Synthetic polymers are often used as carriers for these agents, and polymer biocompatibility remains a concern, as polymers often induce an exaggerated inflammatory reaction. Chronic, low-grade inflammation, poor wound healing responses with incomplete endothelialization, and intra-intimal hemorrhage have been noted in porcine coronary arteries treated with paclitaxel-coated stents.63 Accelerated atherosclerosis immediately proximal and distal to QP2-coated stents has also been reported in humans,44 although preliminary trial data suggest that this may not be a major issue.51 Delayed stent thrombosis has also been described with QP2-coated stents.57,62 Concern regarding this phenomenon has prompted many clinical trials investigating stents eluting antimitotic agents to treat enrolled patients with oral antithrombotic agents for up to 6 months after implantation of these stents. Lack of a long-term effect on restenosis as described with radioactive stents63 may also become apparent in the future. The added cost of these stents may, at least initially, limit their use to patients at high risk for in-stent restenosis and is an issue yet to be addressed. Although many other potential problems with these stents may be foreseen, the small numbers of patients enrolled and the short follow-up periods of the clinical trials evaluating drug-eluting stents remain the most important limitations.

Conclusions

In-stent restenosis is a common problem, affecting 20% to 40% of patients by 6 months after PCI, with neointimal hyperplasia being the primary cause. The systemic administration of various pharmacological agents has had little effect on the occurrence of restenosis. Stents coated with biocompatible materials, anticoagulants, and corticosteroids have been examined in both animal and human studies. These studies suggest that stents coated with these agents do not have a significant inhibitory effect on neointimal hyperplasia. Stents eluting antimitotic agents such as sirolimus and paclitaxel seem to be the most beneficial in this regard. Results of observational studies in animals and humans investigating these antimitotic agents are promising, with extremely low rates of clinical events and restenosis over the short and mid-term. The preliminary results of several clinical trials evaluating stents eluting these agents in de novo lesions at a low risk for restenosis are also encouraging. Small sample sizes and short follow-up periods remain important limitations of these trials. If these preliminary results are borne out in larger trials with extended follow-up periods, drug-eluting stents may resolve the long-standing issue of post-PCI restenosis.

Note Added in Proof

After this article went into publication, preliminary results of SIRIUS and TAXUS II were released at a recent interventional cardiology conference. The results are available at http://www.clinicaltrialresults.com.

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References


51. Wohrle J, Babapulle and Eisenberg Coated Stents


**KEY WORDS**: restenosis ■ stents ■ drugs
Coated Stents for the Prevention of Restenosis: Part II
Mohan N. Babapulle and Mark J. Eisenberg

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