Coated Stents for the Prevention of Restenosis: Part I

Mohan N. Babapulle, MD; Mark J. Eisenberg, MD, MPH

Over the past decade, the use of endoluminal metallic stents has become common practice during percutaneous coronary intervention (PCI), especially after clinical trials showed evidence of decreased restenosis rates when compared with balloon angioplasty alone.1–3 Although stents significantly reduce restenosis when compared with balloon angioplasty, restenosis rates in patients who receive stents are still 20% to 40% at 6 months.1–6 Recently, the concept of using stents coated with agents that could potentially inhibit neointimal hyperplasia has emerged. These agents include biocompatible materials, anticoagulants, corticosteroids, and antimitotic agents. This 2-part article reviews animal studies, human observational studies, and results from randomized clinical trials investigating coated stents. Part I discusses the pathophysiology of in-stent restenosis, as well as animal studies investigating coated stents. Part II discusses human studies investigating coated stents.

Pathophysiology of In-Stent Restenosis

In-stent restenosis is primarily due to neointimal hyperplasia.7–13 Vessel injury by an angioplasty balloon or stent struts leads to the activation of platelets and mural thrombus formation.13–16 The presence of vascular injury, mural thrombus, and a metallic foreign body activates circulating neutrophils and tissue macrophages.12,13,17,18 These cellular elements release cytokines and growth factors that activate smooth muscle cells.19–23 Upregulation and expression of genes such as c-myc that regulate cell division ensues, leading to cell proliferation.24,25 Production of matrix metalloproteinases is also upregulated, leading to remodeling of the extracellular matrix, and initiating smooth muscle cell migration.26–28 The end result of this cascade of events is the uncontrolled proliferation of smooth muscle cells around the vessel intima and the deposition of extracellular matrix material, which often lead to significant luminal narrowing 3 to 6 months after PCI (Figure 1).

Coated Stents

The systemic administration of a variety of agents has not had a significant impact on post-PCI restenosis rates.29–34 Although there is some evidence that controlling mural thrombus formation may decrease neointimal hyperplasia,35–37 antiplatelet agents have not reliably resulted in reductions in restenosis rates in clinical trials.29,30 Similarly, the systemic administration of corticosteroids aimed at controlling the inflammatory process has not shown decreased restenosis rates.31 The lack of effect of systemically administered agents may be due to inadequate drug concentrations at the site of stent insertion. The limited success of these agents in decreasing rates of in-stent restenosis, coupled with side effects, prompted the development of coated stents.

Stent coatings can be divided into 2 categories, biocompatible materials and drug-eluting coatings (Table 1). Biocompatible materials currently under investigation are thought to be less thrombogenic and inflammatory, and are thereby potentially able to reduce neointimal hyperplasia. These materials include inert coatings such as carbon, gold, and silicon carbide. Phosphorylcholine, a neutrally charged phospholipid polymer found on animal plasma membranes, has also generated much interest with regard to its biocompatibility.

The drug-eluting coatings contain agents that inhibit thrombus formation (eg, heparin), inflammation (eg, dexamethasone), and cellular proliferation (eg, sirolimus and paclitaxel). These agents are often blended with synthetic polymers that act as drug reservoirs and elute the active agent over a period of several weeks or months.38–41 Unfortunately, many of these synthetic polymers induce an exaggerated inflammatory response and neointimal hyperplasia in animal models.42–44 The biocompatibility of specific polymer-coated stents has been reviewed elsewhere.45,46 Drug-eluting stents offer theoretical advantages over systemic pharmacotherapy, such as higher drug concentrations at the site of stent deployment and minimal systemic side effects.

Animal Studies

The most widely used animal model of in-stent restenosis is the porcine coronary artery overstretch injury model. Porcine coronary arteries have a structure and physiology similar to human coronary arteries, and maximal neointimal hyperplasia is induced in pigs by 4 weeks after overstretch injury by an angioplasty balloon or coronary stent.47,48 The amount of neointimal hyperplasia induced in this animal model is closely linked to the degree of injury sustained by the vessel wall. Therefore, most studies investigating the effect of an experimental agent at inhibi-
iting post-PCI restenosis in the porcine model have attempted to cause a similar degree of vessel injury between the experimental and control groups to avoid possible confounding. Another commonly studied animal model of

Figure 1. Segment of a human right coronary artery with restenosis 5 months after stenting. A, Gross aspect of a cross section shows almost total occlusion caused by excessive neointimal proliferation. B and C, Exuberant neointimal formation around the stent. The sites of stent struts are indicated by arrowheads. D and E, Extensive accumulation of smooth muscle cells around the stent struts (arrowheads), with scattered macrophages and numerous microvessels in the deeper layers of the neointima. AS indicates preexisting atherosclerotic plaque; PTCA, percutaneous transluminal coronary angioplasty. Magnification ×18 (B), ×62 (C), and ×132 (D and E). Reprinted with permission from Komatsu et al.13

<table>
<thead>
<tr>
<th>Coating</th>
<th>Mechanism of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biocompatible coatings</td>
<td></td>
</tr>
<tr>
<td>Carbon</td>
<td>Chemically inert and potentially noninflammatory</td>
</tr>
<tr>
<td>Gold</td>
<td>Chemically inert and potentially noninflammatory</td>
</tr>
<tr>
<td>Silicon carbide</td>
<td>Inert semiconductor potentially less thrombogenic and inflammatory</td>
</tr>
<tr>
<td>Phosphorylcholine</td>
<td>Organic polymer potentially less thrombogenic and inflammatory</td>
</tr>
<tr>
<td>Drug coatings</td>
<td></td>
</tr>
<tr>
<td><strong>Anticoagulants</strong></td>
<td></td>
</tr>
<tr>
<td>Heparin</td>
<td>Antithrombotic and possible direct inhibition of smooth muscle cell proliferation</td>
</tr>
<tr>
<td>Hirudin</td>
<td>Antithrombotic and potentially antiproliferative</td>
</tr>
<tr>
<td>Iloprost</td>
<td>Prostacyclin analogue that is antithrombotic and potentially antiproliferative</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td></td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>Corticosteroid with potent anti-inflammatory properties</td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td>Corticosteroid with potent anti-inflammatory properties</td>
</tr>
<tr>
<td>Antimitotic agents</td>
<td></td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>Interferes with microtubule function and thereby inhibits a variety of intracellular processes including mitosis and cell migration</td>
</tr>
<tr>
<td>Sirolimus</td>
<td>Inhibits production of proteins essential for cell division; has potent immunosuppressive and antimitotic properties</td>
</tr>
<tr>
<td>Angiopeptin</td>
<td>Somatostatin analogue that inhibits many cytokines and growth factors, and potentially has antiproliferative effects</td>
</tr>
<tr>
<td>Tyrosine kinase inhibitors</td>
<td>Interfere with intracellular cell signaling that regulate cell proliferation and differentiation</td>
</tr>
</tbody>
</table>
in-stent restenosis is the rabbit iliac artery model. In this model, rabbits are fed a hypercholesterolemic diet for several weeks before endothelial injury by an angioplasty balloon, inducing pathological changes similar to those observed in human coronary arteries after stent implantation. Experimental animal models of restenosis have been reviewed in detail elsewhere.50,51

Stents Coated With Biocompatible Materials

De Scheerder and colleagues52 published the only animal study on the biocompatibility of a carbon-coated stent. The coating was a diamond-like carbon coating (Dyllyn, Bekart) and a Dyllyn coating covered by a hydrocarbon film. These investigators reported a trend toward decreased restenosis and neointimal hyperplasia at 6 weeks with the 2 types of coated stents implanted in porcine coronary arteries, although the differences were too small to reach statistical significance. Several groups have examined whether stents coated with anticoagulants or corticosteroids inhibit neointimal hyperplasia.53 Metal stents coated with phospholipid found on animal cell membranes. This biopolymer is thought to be an extremely biocompatible material based on in vitro and in vivo studies in animals.54 Metal stents coated with phospholipid are well tolerated in porcine coronary arteries, but do not seem to inhibit neointimal hyperplasia. This biopolymer is also capable of acting as a drug reservoir for programmed elution of a second agent.

Stents Coated With Anticoagulants

Initial animal studies examined stents coated with anticoagulants such as heparin and hirudin. These studies assessed the effects of these drugs on subacute thrombus formation and whether these effects lead to reductions in neointimal hyperplasia.56–59 The studies reported possible beneficial effects on subacute thrombus formation, but variable reductions in neointimal hyperplasia were reported when histomorphometric analyses were done at 4 to 12 weeks after stent implantation. A study by Matsumoto et al60 using stents coated with multiple layers of releasable heparin showed less neointimal hyperplasia within the heparin-coated stents compared with uncoated controls (Table 2). This finding raises the possibility of a dose-dependent inhibition of neointimal hyperplasia by heparin, although these results have not yet been duplicated.

Stents Coated With Corticosteroids and Antimitotic Agents

Several groups have examined whether stents coated with corticosteroids inhibit neointimal hyperplasia in animals. Although dexamethasone-coated stents reduced the inflammatory reaction induced by a synthetic polymer, the effect on neointimal hyperplasia was minimal in 2 studies in pigs.61,62 In contrast, De Scheerder and colleagues63 reported that methylprednisolone-coated stents had an inhibitory effect on polymer-induced inflammation and restenosis at 6 weeks compared with controls. Overall, the results of animal studies investigating corticosteroid-coated stents and their effect on neointimal hyperplasia have been unimpressive (Table 2).

The equivocal results with corticosteroid-coated stents in inhibiting neointimal proliferation led several investigators to evaluate the efficacy of stent-based delivery of other antimitotic agents. Paclitaxel inhibits microtubule depolymerization, and thereby has potent effects on cell division and migration.64 Encouraging results have been reported in several animal studies investigating paclitaxel-coated stents. These studies have demonstrated reductions of neointimal hyperplasia of up to 60% when compared with controls in the rabbit iliac artery and porcine coronary artery models.65–68 The inhibitory effect appears to be dose-dependent (Figures 2 and 3) and was sustained up to 6 months in one study (Table 2).

**TABLE 2. Animal Studies Investigating Stents Coated With Biocompatible Materials, Anticoagulants, and Corticosteroids**

<table>
<thead>
<tr>
<th>Study</th>
<th>Model</th>
<th>Coating</th>
<th>N*</th>
<th>Follow-Up, Weeks</th>
<th>Mean Minimum Lumen Diameter, mm†</th>
<th>Mean Neointimal Thickness or Area‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>De Scheerder et al52</td>
<td>Pig</td>
<td>DNL</td>
<td>13</td>
<td>6</td>
<td>2.65±0.27</td>
<td>2.52±0.29 NS</td>
</tr>
<tr>
<td>Whelan et al54</td>
<td>Pig</td>
<td>PC</td>
<td>16</td>
<td>12</td>
<td>3.20±0.50</td>
<td>2.90±0.40 NS</td>
</tr>
<tr>
<td>De Scheerder et al 63</td>
<td>Pig</td>
<td>Heparin</td>
<td>20</td>
<td>6</td>
<td>2.50±0.27</td>
<td>2.62±0.55 NS</td>
</tr>
<tr>
<td>Hardhammar et al55‡</td>
<td>Pig</td>
<td>Heparin</td>
<td>20</td>
<td>12</td>
<td>3.20±0.40</td>
<td>2.80±0.20 &lt;0.01</td>
</tr>
<tr>
<td>Ahn et al56</td>
<td>Pig</td>
<td>Heparin</td>
<td>30</td>
<td>4</td>
<td>3.10±0.54</td>
<td>2.90±0.42 NS</td>
</tr>
<tr>
<td>Alt et al57§</td>
<td>Pig</td>
<td>HIR/PGI2</td>
<td>18</td>
<td>4</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Matsumoto et al60</td>
<td>Pig</td>
<td>Heparin</td>
<td>10</td>
<td>4</td>
<td>2.32±0.14</td>
<td>1.81±0.17 &lt;0.01</td>
</tr>
<tr>
<td>Lincoff et al61</td>
<td>Pig</td>
<td>DEX</td>
<td>30</td>
<td>4</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Muller et al62</td>
<td>Pig</td>
<td>DEX</td>
<td>20</td>
<td>5</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>De Scheerder et al63</td>
<td>Pig</td>
<td>MP</td>
<td>20</td>
<td>6</td>
<td>2.73±0.34</td>
<td>1.36±0.72 &lt;0.005</td>
</tr>
</tbody>
</table>

DLN indicates diamond-like nanocomposite coating (Dyllyn); DLC, diamond-like carbon film; PC, phosphorylcholine; HIR, hirudin; PGI2, iloprost (a prostacyclin analogue); DEX, dexamethasone; MP, methylprednisolone; NR, not reported; and NS, not significant.

*The number of animals in both the treatment and control groups combined.

†At follow-up.

‡The results given are for the high-dose heparin (20 pmol/stent) and control groups.

§Standard deviations were only displayed graphically. Therefore, the numerical values provided here are approximate.
3). Farb et al.\(^6\) however, reported a tendency toward incomplete healing and intra-intimal hemorrhage in higher-dose paclitaxel groups. The authors also reported that inhibition of neointimal proliferation was not observed at 3 months.

Sirolimus (rapamycin) is a macrolide antibiotic with potent antiproliferative effects on vascular smooth muscle cells.\(^6\),\(^7\) Suzuki et al.\(^7\) investigated the efficacy of this agent at inhibiting neointimal hyperplasia in the porcine model. Stents coated with a polymer containing sirolimus, dexamethasone, or a combination of sirolimus and dexamethasone along with uncoated controls were inserted in the major coronary arteries of 16 pigs after overstretch injury. Histological analysis and quantitative coronary angiography (QCA) at 28 days revealed highly significant reductions in inflammation, neointimal area, and percent area stenosis between sirolimus-coated stents and uncoated controls (Table 3). There was no difference in the above variables between the stents coated only with dexamethasone and the controls. Klugherz et al.\(^7\) also demonstrated inhibition of neointimal hyperplasia by sirolimus-coated stents in rabbits. This inhibition appeared to be dose-dependent (Table 3). These studies show that sirolimus causes a short-term reduction in neointimal hyperplasia in animal models, although it is not clear if this reduction is sustained over a longer period.

Some novel antiproliferative agents aimed at reducing neointimal hyperplasia have also been investigated in animal models. Angiopeptin is a synthetic somatostatin analogue with antiproliferative effects on vascular smooth muscle cells, although its exact mechanism of action is unclear.\(^7\),\(^5\) De Scheerder et al.\(^7\) studied the effects of angiopeptin loaded onto stents coated with polyorganophosphazene, a polymer known to induce an exaggerated inflammatory and proliferative response. At 6 weeks, a significant difference in the minimum luminal diameter and neointimal area between angiopeptin-treated arteries and untreated controls was noted in this model of accelerated restenosis in porcine coronary arteries. In contrast, Armstrong et al.\(^7\) did not report a reduction in neointimal growth when angiopeptin was eluted by stents coated with phosphorylcholine, a polymer thought to be more biocompatible than polyorganophosphazene. A second novel antiproliferative agent that has been investigated is ST638, a specific inhibitor of intracellular tyrosine kinase enzymes that mediate smooth muscle cell migration and proliferation.\(^7\) Three weeks after successfully deploying stents coated with ST638 in porcine coronary arteries, Yamawaki et al.\(^7\) observed that there was significantly less luminal narrowing and neointimal proliferation on histological analysis. Although the results with angiopeptin and ST638 are encouraging, they have not yet been duplicated in animals or humans.

In summary, animal studies investigating coated stents have shown variable results. Stents coated with diamond-like carbon have not shown an inhibitory effect on restenosis. Although phosphorylcholine-coated stents do not seem to inhibit neointimal hyperplasia, they are well tolerated in vivo and have drug-eluting potential. Animal studies have also demonstrated encouraging results with respect to the efficacy of stent-based drug delivery. Stents coated with heparin do not appear to have a major effect on neointimal hyperplasia. Stents coated with corticosteroids may have an effect on the inflammatory response, but do not exhibit a significant antiproliferative effect. Stents eluting antimitotic agents such as paclitaxel and sirolimus show the most promise, with significant inhibitory effects on neointimal hyperplasia.

Figure 2. Four-week follow-up angiograms of stented porcine coronary arteries. A, No paclitaxel (control); B, intermediate-dose paclitaxel (15 µg/stent); and C, high-dose paclitaxel (187 µg/stent). Arrows show approximate midpoint of stent. Reprinted with permission from Heldman et al.\(^6\)

Figure 3. Photomicrographs of stented porcine arteries (magnification ×40). A, No paclitaxel (control); B, low-dose paclitaxel (0.2 µg/stent); C, intermediate-dose paclitaxel (15 µg/stent); and D, high-dose paclitaxel (187 µg/stent). Black material partially filling lumen in A is barium gelatin dye contrast medium. Solid and open arrows indicate boundaries formed by internal and external elastic laminae, respectively. L indicates lumen; N, neointima; M, tunica media; and A, tunica adventitia. Reprinted with permission from Heldman et al.\(^6\)
TABLE 3. Animal Studies Investigating Stents Coated With Antimitotic Agents

<table>
<thead>
<tr>
<th>Study</th>
<th>Model</th>
<th>Coating</th>
<th>N*</th>
<th>Follow-up, weeks</th>
<th>Mean MLD, mm†</th>
<th>Mean Neointimal Thickness or Area‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drachman et al45</td>
<td>Rabbit</td>
<td>Paclitaxel</td>
<td>NR</td>
<td>8</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Heldman et al8‡§</td>
<td>Pig</td>
<td>Paclitaxel, 187 mg/stent</td>
<td>18</td>
<td>4</td>
<td>2.3±0.2</td>
<td>1.6±0.15 &lt;0.05</td>
</tr>
<tr>
<td>Hong et al8‡§</td>
<td>Pig</td>
<td>Paclitaxel</td>
<td>19</td>
<td>4</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Farb et al8‡§</td>
<td>Rabbit</td>
<td>Paclitaxel, 20.2 mg/stent</td>
<td>25</td>
<td>4</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Farb et al8‡§</td>
<td>Rabbit</td>
<td>Paclitaxel, 42.0 mg/stent</td>
<td>24</td>
<td>4</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Suzuki et al11</td>
<td>Pig</td>
<td>Sirolimus</td>
<td>16</td>
<td>4</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Suzuki et al11</td>
<td>Pig</td>
<td>Sirolimus + DEX</td>
<td>14</td>
<td>4</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Klugherz et al17</td>
<td>Rabbit</td>
<td>Sirolimus, 64 mg/stent</td>
<td>10</td>
<td>4</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Klugherz et al17</td>
<td>Rabbit</td>
<td>Sirolimus, 196 mg/stent</td>
<td>10</td>
<td>4</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>De Scheerder et al20</td>
<td>Pig</td>
<td>Angiopeptin</td>
<td>20</td>
<td>6</td>
<td>2.20±0.57</td>
<td>1.57±0.68 &lt;0.01</td>
</tr>
<tr>
<td>Armstrong et al18</td>
<td>Pig</td>
<td>Angiopeptin</td>
<td>4</td>
<td>4</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Yamawaki et al31</td>
<td>Pig</td>
<td>ST 638</td>
<td>6</td>
<td>3</td>
<td>1.98±0.13</td>
<td>1.45±0.12 &lt;0.05</td>
</tr>
</tbody>
</table>

MLD indicates minimum luminal diameter; DEX, dexamethasone; NR, not reported; and NS, not significant. ST 638 is a specific tyrosine kinase inhibitor.

*The number of animals in both the treatment and control groups combined.
†Results in this study were only displayed graphically; therefore, the numerical values given here are approximate.
‡Data only for the high-dose groups are provided here.
¶The standard deviation reported here is most likely incorrect because of a typographic error in the original reference.

Acknowledgments

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References


**KEY WORDS:** restenosis ■ stents ■ drugs
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