Polymer-Free Biolimus A9–Coated Stent Demonstrates More Sustained Intimal Inhibition, Improved Healing, and Reduced Inflammation Compared With a Polymer-Coated Sirolimus-Eluting Cypher Stent in a Porcine Model

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Background—Drug-eluting stents effectively reduce restenosis but may increase late thrombosis and delayed restenosis. Persistent polymer, the drug, or a combination of both could be responsible. Local delivery of Biolimus A9, a rapamycin derivative, from a polymer-free BioFreedom stent (Biosensors International) may prevent these complications.

Methods and Results—We compared high-dose (HD) (225 μg/14 mm Biolimus A9) and low-dose (LD) (112 μg/14 mm Biolimus A9) BioFreedom stents with a polymer-coated sirolimus-eluting Cypher stent (SES) and a bare-metal stent (BMS) at 28 days and 180 days in an overstretch coronary mini-swine model with histomorphometric and histological analysis. At 28 days, there was a reduction in neointimal proliferation by HD, LD, and SES compared with BMS (neointimal thickness: HD, 0.080 ± 0.032; LD, 0.085 ± 0.038; SES, 0.064 ± 0.037; BMS, 0.19 ± 0.111 mm; P < 0.001; BMS > HD/LD/SES). At 180 days, both BioFreedom stents were associated with reduced neointimal proliferation, whereas SES exhibited increased neointima (neointimal thickness: HD, 0.12 ± 0.034; LD, 0.10 ± 0.040; SES, 0.20 ± 0.111; BMS, 0.17 ± 0.099 mm; P < 0.001; SES > HD/LD; BMS > LD). At 180 days, BioFreedom stents showed decreased fibrin and inflammation, including granuloma and giant cells, compared with SES.

Conclusions—The polymer-free Biolimus A9–coated stent demonstrates equivalent early and superior late reduction of intimal proliferation compared with SES in a porcine model. After implantation of BioFreedom stent, delayed arterial healing was minimal, and there was no increased inflammation at 180 days compared with SES implantation. The use of polymer-free stents may have a potential long-term benefit over traditional polymeric-coated drug-eluting stents.

Key Words: restenosis ♦ inflammation ♦ polymer-free drug-coated stents ♦ Biolimus A9 ♦ sirolimus

Although first-generation drug-eluting stents (DES) have substantially reduced rates of restenosis compared with bare-metal stents (BMSs),1,2 the long-term safety of DES remains controversial.3,4 The presumed mechanism of late stent thrombosis is delayed arterial healing and local hypersensitivity reactions potentially related to the drug, the polymer, or both.5,6 Late restenosis is another risk reported after DES implantation.7,8 Therefore, an ideal next-generation stent should provide the safety profile of BMS and antirestenotic effectiveness of current DES without their potential risks. To reach this goal, eliminating the polymer in the coating is a strategy that needs to be tested; therefore, we developed a newly designed polymer-free Biolimus A9 (BA9)–coated stent.

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The purpose of this study is to test the hypotheses that in a coronary overstretch mini-swine model, the BioFreedom stent is as effective as the most-proven DES and as safe as the polished BMS. Histomorphometric and histological analyses were made at 28 days and 180 days to assess the efficacy and safety of the local delivery of BA9 through a polymer-free stent. Efficacy end points (degree of neointimal inhibition) were neointimal thickness and percent area stenosis, and safety end points (vascular healing and inflammation) were fibrin deposition and inflammation score. Blood concentrations, tissue concentrations, and amounts of BA9 remaining on stents also were evaluated to assess the pharmacokinetics of BA9 elution from the BioFreedom stent. After the suc-
cessful results from LEADERS (Limus Eluted From A Durable Versus ERodable Stent Coating) trial,9 the same BA9 dosage was applied to the BioFreedom stent (high dose [HD], 225 μg/14 mm). An additional group with half the BA9 dosage (low dose [LD], 112 μg/14 mm) also was examined.

To test these hypotheses, commercially available durable polymer-coated sirolimus-eluting stents (Cypher) and polished BMS (BioFlex II; Biosensors International) were chosen as controls, respectively. Cypher stent has been the most proven DES since it first became available, and the antirestenotic benefits, both short and long term, are well-known. Polished BMS, not surface-textured BMS, was chosen for the same reason.

Design of BioFreedom Stent
The BioFreedom stent uses a stainless steel BioFlex II stent platform with a textured abluminal surface, onto which BA9 in solvent is applied (Figure 1). The BioFreedom stent was developed with 3 features. First, it releases the antiproliferative agent directly from a mechanically modified textured surface without polymer ingredient in the coating, thereby eliminating polymer-associated tissue responses. BA9 is the sole coating component that delivers antirestenotic efficacy. Once BA9 is completely taken up by the vessel wall, the implants turn into BMS that deliver long-term safety. Second, BA9, a novel sirolimus derivative that is an inhibitor of cell growth through inhibition of the mammalian target of rapamycin, is a highly lipophilic drug, roughly 10 times more so than sirolimus or everolimus (data on file at Biosensors International). Thus, BA9 easily crosses the cell membrane to achieve therapeutic effects in its target tissue and, compared with sirolimus-eluting Cypher stent (SES), leads to relatively low systemic exposure.10 Third, the drug coating is asymmetrical on the abluminal surface of the stent, allowing the drug release to be directed almost entirely into the vessel wall for treatment of injured smooth muscle cells. Therefore, the textured surface is made only on the outside of stent. Conversely, there is little drug release on the luminal surfaces of the stent where we expect endothelial cells to grow and healing to occur.

Methods
Porcine Studies
Animal experiments were conducted at Cedars-Sinai Medical Center Research Institute (Los Angeles, Calif) after the approval from the Institutional Animal Care and Use Committee, and in compliance with the US Food and Drug Administration Good Laboratory Practice Regulations (21 CFR Part 58). Stents were implanted in 34 Yucatan mini-swine pigs, weighing 55 to 90 kg, that were followed for either 28±2 days (14 animals for histological study and 4 for pharmacokinetics) or 180±4 days (14 for histological study and 2 for pharmacokinetics). Oral aspirin (325 mg) and clopidogrel (75 mg) were administered starting 3 days before the procedure and contin-
ued daily for the first 3 months and thereafter on alternate days until the end of the study. Animals were sedated and anesthetized with intravenous ketamine (20 mg/kg), thiopental (500 mg), and atropine (3 to 4 mg). Mechanical ventilation was established and anesthesia maintained with isoflurane (2% to 5%) throughout the procedure. Arterial access was achieved by a carotid cut-down, and coronary angiography then was performed using 6 Fr guiding catheters after intracoronary administration of nitroglycerin (100 μg). Each animal was intravenously heparinized with 150 U/kg body weight to achieve an activated clotting time >250 sec at the time of catheter insertion and stenting. Stents were deployed in all 3 major branches of the coronary arteries: right coronary artery, left anterior descending coronary artery, and left circumflex artery. There were 2 test groups—HD (225 μg/14 nm BA9) and LD (112 μg/14 mm BA9) BioFreedom stents (HD and LD)—and 2 reference groups—SES (positive control) and BMS (negative control) without the surface modification. For histological study, SESs were implanted in all animals and equally distributed among the 3 major branches. The other 3 stents were equally distributed throughout the remaining branches as long as the vessel anatomy accommodated stents. All stents were 2.5, 3.0, or 3.5 mm in diameter, and the artery segment was selected based on vessel diameter and ability to accommodate the length of the stent without excessive taper. Stent length was 14 mm for HD, LD, and BMS and 13 mm for SES. Balloon inflation pressure was varied according to the balloon compliance curve to achieve a balloon-to-artery ratio of 1.1:1.1 Appropriate sizing was performed by online quantitative coronary angiography. At their designated follow-up time point, the animals were returned to the catheterization laboratory for a follow-up angiogram just before euthanasia. Quantitative coronary angiography or intravascular ultrasound was not performed at follow-up due to their quality of measurement as compared with pathological analysis.

### Pharmacokinetics and Cardiac Tissue Concentrations of BioFreedom Stents

BA9 pharmacokinetics in EDTA blood was followed in animals that received at least 1 BioFreedom stent in the 28-day histological study group (n=14). Additionally, to study BA9 pharmacokinetics, cardiac tissue distribution, and BA9 remaining on the stent at the end of the study period, 3 HD and 3 LD stents were implanted in all 3 branches of 4 animals (2 with 3 HD stents, 2 with 3 LD stents) in the 28-day group and 2 animals in the 180-day group (1 with 3 HD stents and 1 with 3 LD stents). The procedure of stent implantation was the same as for the histological study. Venous EDTA blood samples were obtained for measurement of the systemic concentration of BA9 at baseline; 2 to 5, 15, 30, 60, 120 min; 2 days; 7 days; and at necropsy at 28 days or 180 days, depending on the study group. Cardiac tissue concentrations of the drug were measured in coronary artery tissues surrounding the stents and in the myocardium. BA9 was quantified in blood and tissues using a validated modification of a liquid chromatography/tandem mass spectrometry-based assay that was originally developed for sirolimus and several of its derivatives. For further details, see Ostojic et al.10

### Histological Analysis

An experienced pathologist (R.V.) who was blinded to the groups performed all histomorphometric and histological analyses. Before processing, intact hearts with stented vessels were imaged by capturing high-contrast film-based radiographs to locate and assess device placement. Stented coronary artery segments were processed for plastic embedding, staining, and histomorphometric analysis of 3 sections (proximal, mid, and distal) using published methods. Neointimal thickness was measured as the distance from the inner surface of each stent strut to the luminal border. Percent-area stenosis was calculated as \(1 - \frac{\text{stenosis area}}{\text{internal elastic lamina area}}\) \(\times 100\). A vessel injury score was calculated according to the Schwartz method and averaged over the number of struts in each section. The presence of fibrin deposition, granuloma reactions, and giant cells around the stent struts were expressed as a percentage of the total number of struts in each section (eg, the presence of fibrin around 2 of 8 struts in a section would equate to 25%).

The inflammation score was graded as follows: 0 indicated <10 inflammatory cells per strut; 1, >10 inflammatory cells per strut in >25% of total struts; 2, >10 inflammatory cells in 25% to 50% of struts; 3, >10 inflammatory cells in >50% struts; and 4, >2 strut-associated granulomatous inflammatory reactions. Vessel mor-

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**Table 1. Stent Distribution**

<table>
<thead>
<tr>
<th>Animal No.</th>
<th>RCA</th>
<th>LAD</th>
<th>LCX</th>
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<tbody>
<tr>
<td>1</td>
<td>SES</td>
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<td>HD</td>
</tr>
<tr>
<td>2</td>
<td>LD</td>
<td>SES</td>
<td>BMS</td>
</tr>
<tr>
<td>3</td>
<td>BMS</td>
<td>HD</td>
<td>SES</td>
</tr>
<tr>
<td>4</td>
<td>SES</td>
<td>HD</td>
<td>LD</td>
</tr>
<tr>
<td>5</td>
<td>BMS</td>
<td>SES*</td>
<td>LD</td>
</tr>
<tr>
<td>6</td>
<td>HD</td>
<td>BMS</td>
<td>SES</td>
</tr>
<tr>
<td>7</td>
<td>SES</td>
<td>LD</td>
<td>None</td>
</tr>
<tr>
<td>8</td>
<td>LD</td>
<td>SES</td>
<td>BMS</td>
</tr>
<tr>
<td>9</td>
<td>HD</td>
<td>BMS</td>
<td>SES*</td>
</tr>
<tr>
<td>10</td>
<td>SES*</td>
<td>HD</td>
<td>LD</td>
</tr>
<tr>
<td>11</td>
<td>LD</td>
<td>BMS</td>
<td>SES</td>
</tr>
<tr>
<td>12</td>
<td>HD</td>
<td>SES</td>
<td>BMS</td>
</tr>
<tr>
<td>13†</td>
<td>BMS</td>
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</tr>
<tr>
<td>18‡</td>
<td>LD</td>
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</table>

**Notes:**
- Animal no. 1–18, 33, and 34 had blood samples drawn. LAD indicates left anterior descending; LCX, left coronary circumflex; RCA, right coronary artery.
- *Stents were implanted but did not appear on radiograph at follow-up and no sections were taken. See text for details.
- †Early death animals were excluded from pathological analysis. Blood samples were taken before death and included in PK analysis.
- ‡Hearts were analyzed for residual BA9 concentrations and not studied for pathology.
- §Stent was underdeployed, and attempt at postdilatation failed. No sections were taken.
Phometry was completed with a digital software program (IP Laboratory software).

**Statistical Analysis**

Data are expressed as mean±SD. The 3 sections per stent were treated as independent samples. To control for within-animal correlation, variables were compared between treatment groups using generalized estimating equations with individual animals entered as subject group (SPSS version 17). In the case of highly skewed variables with exact zeros (percent fibrin), Tweedie distribution was used, setting the variance power parameter to 1.5, and in the case of ordinal dependent variables (inflammation score) a multinomial distribution was used. Where the distribution of the dependent variable could not be accurately modeled as panel data (percentage granuloma, 180-day percentage giant cells), an overall comparison by stent group was made using the Kruskal-Wallis test. Intergroup differences were assessed where appropriate using generalized estimating equations or the Mann–Whitney U test (180-day giant cells) and adjusted using the Holm-Bonferroni method. The distribution of stent size between the treatment groups was compared using Pearson $\chi^2$ analysis. An overall or adjusted $P<0.05$ was considered significant.

**Results**

Ninety-eight of 99 stents were successfully implanted in the coronary arteries of 34 swine. One stent was underdeployed, and an attempt to postdilate failed. This stent was excluded from the analysis. Thirty-three of 34 animals survived until the follow-up phase of the study. There was 1 early death in the 28-day histological study group that occurred the day after the implantation procedure due to vascular access site complication. This event was confirmed unrelated to stent deployment. Blood samples taken before the death of the animal were included in the pharmacokinetic analyses. Accordingly, 17 pigs in the 28-day group and 16 in the 180-day group survived and were included in the study analysis. Stent distribution is summarized in Table 1. Three implanted SESs in the 28-day group and 1 HD in the 180-day histological study group were not present in coronary arteries at follow-up angiography and could not be identified radiologically. They were treated as missing data. It is reasonable to assume that technical issues were involved related to the quality of fluoroscopy at implantation. All other stents remained patent at follow-up angiography and conformed well to the contour of the vessel lumen, with evenly expanded struts and no strut fractures seen on radiographs.

**Pharmacokinetics and Tissue Concentrations**

The pharmacokinetic results are summarized in Figure 2. Peak BA9 concentration in blood was seen at 120 min in both HD and LD (Figure 2A). After 28 days, 2 of 17 animals had quantifiable blood concentrations. After 180 days, all BA9 concentrations were below the lower limit of quantitation (10 pg/mL). BA9 in the myocardium samples only was quantifiable in sporadic samples at 28 days and 180 days (Figure 2B).
There were significant concentrations of BA9 in the tissues surrounding the stent (Figure 2C), suggesting a steep concentration gradient between these tissues and the rest of the myocardium. There was a clear decrease in concentrations of BA9 remaining on the stents after 28 days and 180 days (Figure 2D). Only 0.02% BA9 remained on the stents after 180 days.

**Histomorphometry and Histology**

The histomorphometric analysis is summarized in Figure 3 and Table 2. Two of the sections were not measurable due to a processing artifact. The distribution of stent size (2 mm, 2.5 mm, and 3 mm) was not different between the groups ($\chi^2$, $P=\text{ns}$). At 28 days, there was a significant reduction of neointimal proliferation with HD, LD, and SES compared with BMS. At 180 days, in contrast to the BioFreedom stent, there seemed to be an increase in neointimal proliferation in the SES group. Both doses of the BioFreedom stents showed statistically significantly lower-area stenosis compared with the SES group and still lower than the BMS group (Figure 4). The histological analysis is summarized in Figure 5. At 28 days, fibrin deposition was significantly greater for all 3 DES

<table>
<thead>
<tr>
<th></th>
<th>HD</th>
<th>LD</th>
<th>SES</th>
<th>BMS</th>
<th>Overall P Value</th>
<th>Paired Comparisons, $P&lt;0.05$</th>
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<td><strong>28-day follow-up, n</strong></td>
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<td>26</td>
<td>30</td>
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<tr>
<td>IEL, mm$^2$</td>
<td>7.14±1.51</td>
<td>7.04±1.39</td>
<td>7.78±1.56</td>
<td>8.15±2.31</td>
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<tr>
<td>EEL, mm$^2$</td>
<td>8.49±1.83</td>
<td>8.32±1.62</td>
<td>9.21±1.85</td>
<td>9.72±2.68</td>
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<tr>
<td>Neointimal thickness, mm</td>
<td>0.080±0.032</td>
<td>0.085±0.038</td>
<td>0.064±0.037</td>
<td>0.19±0.111</td>
<td>&lt;0.001</td>
<td>BMS &gt; HD/LD/SES</td>
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<tr>
<td>Percent area stenosis, %</td>
<td>17.7±4.0</td>
<td>17.4±5.1</td>
<td>16.4±3.9</td>
<td>26.7±12.4</td>
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<tr>
<td>Injury score</td>
<td>0.70±0.25</td>
<td>0.71±0.29</td>
<td>0.68±0.28</td>
<td>0.72±0.28</td>
<td>0.99</td>
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<td><strong>180-day follow-up, n</strong></td>
<td>23</td>
<td>27</td>
<td>39</td>
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<td>IEL, mm$^2$</td>
<td>7.92±1.87</td>
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<td>7.36±1.53</td>
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<td>EEL, mm$^2$</td>
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<td>8.48±1.73</td>
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<td>8.31±1.21</td>
<td>0.56</td>
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<tr>
<td>Neointimal thickness, mm</td>
<td>0.12±0.034</td>
<td>0.10±0.040</td>
<td>0.20±0.111</td>
<td>0.17±0.099</td>
<td>&lt;0.001</td>
<td>SES &gt; HD/LD, BMS &gt; LD</td>
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<tr>
<td>Percent area stenosis, %</td>
<td>21.1±4.4</td>
<td>20.0±5.4</td>
<td>33.8±11.1</td>
<td>28.6±9.3</td>
<td>&lt;0.001</td>
<td>SES &gt; HD/LD, BMS &gt; HD/LD</td>
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<td>Injury score</td>
<td>0.90±0.23</td>
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<td>1.07±0.46</td>
<td>0.98±0.24</td>
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Data are presented as mean±SD unless otherwise indicated. EEL indicates external elastic lamina; IEL, internal elastic lamina; n, number of sections.
groups than BMS (Figure 6). Accumulated fibrin in DES is highest with SES followed by both doses of BioFreedom stents. Both doses of BioFreedom stents showed equivalent amounts of fibrin deposition. At 180 days, fibrin deposition decreased in each of the groups. SES showed persistent occasional fibrin deposits (Figure 7), with rare instances in HD and LD and none in BMS. SES displayed significantly higher residual fibrin deposits compared with the other 3 groups. Endothelialization was nearly complete in all stent groups at 28 days and fully complete for all stents except for 1 SES, which exhibited incomplete endothelialization at 180 days. Inflammation score and giant cell counts were the highest in the SES group at both time points. Granulomas were observed in 1 of the 10 SESs at 28 days and 3 of the 13 SESs at 180 days and consisted of macrophages, occasional lymphocytes, eosinophils, and giant cells (Figure 8). HD, LD, and BMS did not contain granuloma at any time point. Most granulomas after SES implantation involved more than 2 segments in 3 sections (proximal, mid, and distal) and were multifocal or circumferential. Morphometry also was analyzed, excluding sections with granuloma. At 180 days, there was increased neointimal thickness in SES compared with

**Figure 4.** Low-magnified \((2\times)\) photomicrographs showing 28 days (top) and 180 days (bottom) after the placement of HD, LD, SES, and BMS. Both doses of BioFreedom stents showed inhibited neointima at both days in contrast to SES, which showed steady increase in the amount of neointimal thickness at 180 days. Sections shown are stained by Elastic Van Gieson.

**Figure 5.** Comparison of histological data. The bars represent means±SD; \(n\) indicates number of sections. \(*P<0.05\).
both doses of BioFreedom stents (neointimal thickness: HD, 0.12±0.034 mm [n=27]; LD, 0.10±0.040 mm [n=23]; SES, 0.18±0.078 mm [n=32]; BMS, 0.17±0.099 mm [n=24]; P≤0.001; SES > HD/LD).

**Discussion**

In this porcine overstretch coronary model study, we evaluated the newly designed polymer-free BA9-coated BioFreedom stent and compared it with SES and BMS at 28 days and 180 days. The present study showed that the BioFreedom stent and its polymer-free technology with a mechanically modified surface successfully delivered BA9, resulting in long-term efficacy in contrast to SES that resulted in late restenosis, delayed healing, and persistent inflammation in the late phase.

Although the first-generation DES have shown efficacy in reducing restenosis,1,2 there still is ongoing debate regarding a possibly higher incidence of late stent thrombosis compared with BMS.3 One proposed mechanism of late stent thrombosis is delayed arterial healing. Recently, pathological studies in patients who died from late stent thrombosis showed delayed arterial healing characterized by persistent fibrin deposition and poor endothelialization.5 DES implantation resulted in substantial impairment of arterial healing when compared with BMS. Angioscopic study showed incomplete neointimal coverage 3 to 6 months after SES implantation compared with that of BMS.19 Although antiproliferative agents, such as sirolimus or paclitaxel, reduce neointimal proliferation by impeding smooth muscle cell proliferation and migration, these drugs also impair the normal healing processes of the injured arterial wall. Drug choice and release kinetics controlled by the drug itself and its coating system, such as a polymer, play an important role in DES technology because they determine the type of vascular response and time-course of healing.

Another possible mechanism of late stent thrombosis is a hypersensitivity reaction to the polymer. Virmani et al6 reported that patients who died of late stent thrombosis 18 months after SES implantation showed a severe localized hypersensitivity reaction that was characterized by an extensive inflammatory infiltrate involving the whole vessel wall and was composed primarily of eosinophils, lymphocytes, and giant cells. The authors suggested that this reaction may be caused by polymer as considered from the drug-release kinetics of SES.

Granulomas, defined by the presence of macrophages, lymphocytes, and giant cells, are a hypersensitivity reaction induced by foreign body reactions from infectious organisms, metal particles, cleaning solutions, drugs, or polymers. The frequency of granulomas in swine studies often is unpredictable. However, in our study, granulomas were only present in the SES group, possibly implicating the polymer coating on the SESs. The presence of granulomas cause increased

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Figure 6. Representative images of stents at 28 days: HD (A), LD (B), SES (C), and BMS (D). All DES show more accumulated fibrin (boxes) compared with BMS (hematoxylin/eosin 20×).

Figure 7. SES shows persistent fibrin deposition (arrow) at 180 days (hematoxylin/eosin 20×).
This increase of neointima in late phase is another concern with first-generation DES. Previous studies assessing the effects of SES in porcine coronary models have demonstrated that long-term inhibition of neointimal hyperplasia is not sustained.20 Delayed cellular proliferation was observed despite marked early suppression. Histopathologic evaluation of patients with delayed restenosis after implantation of 7-hexanoyltaxol-eluting polymer stents showed delayed healing with persistent fibrin deposits and inflammation in late restenosis.8 The authors suggested that high concentration of the drug, extended-release kinetics, and the nonabsorbable polymer are possible causes. Polymers are known to have the potential to induce a certain degree of inflammation that correlates with neointimal proliferation.21,22 However, the significance of this “late catch-up” restenosis effect in humans remains the subject of debate.

Polymer coating on stents had been proposed to improve the biocompatibility of the stents or as a vehicle to load drugs onto stents. In the first-generation DES, Cypher and Taxus stents were successful at delivering the drugs for the prevention of restenosis with the use of nonerodable polymers. However, because polymers have been identified as a possible cause of late complications of DES, efforts are being made to improve polymers or to bond drugs on stents without polymers. Biodegradable polymers likely are to be safer than nonerodable polymers because any tendency to inflammation will be eliminated after the polymer degrades.9 Another solution is to use a mechanically modified surface to coat drugs on it without polymer. Some polymer-free stents have been tested in humans and have produced promising results.23,24 We developed a new polymer-free BioFreedom stent with features as previously mentioned.

The present study suggests that BA9 is a drug that seems well suited for coating on nonpolymer stents. One rationale for using polymers on DES is to retain the drug and maintain efficacious drug concentrations in the target coronary tissue over an extended time period. One would expect that a DES without polymer will release the drug in a relatively short amount of time, resulting in relatively high systemic and tissue peak concentrations. The pharmacokinetic and tissue concentration analyses showed that for BioFreedom stents this was not the case. Importantly, there was no high early peak of BA9 in blood. The frequent early blood sampling after stent implantation was designed to detect such an early peak concentration. On the other hand, BA9 was present in the coronary tissues until 180 days after stent implantation, albeit <1% of the original amount, on the BioFreedom stent. This finding may be partially due to a long half-life of BA9 in the target tissues. The lipophilicity of BA9 and this coating pattern may explain the relatively low blood concentrations while effective tissue concentrations were reached. One also could speculate that the better healing compared with the Cypher stent was enabled by the fact that there was no drug and polymer on the inside surfaces of the stent where endothelial cell growth and healing are expected. This hypothesis will require further confirmation.

Although some studies show dose-dependent intimal inhibition, toxicity induced by higher local drug concentration has a risk of inducing poor arterial healing and incomplete endothelialization.23,25 Late restenosis also is potentially induced by higher-dose drug toxicity, as shown in some studies.26,27 These results could suggest that the use of a lower dose is desirable in terms of safety as long as the degree of intimal inhibition is acceptable. Unlike the biodegradable polymer-coated BA9-eluting BioMatrix stent containing 225 μg/14 mm BA9,9 we investigated a reduced dose of 112 μg/14 mm BA9 (LD) BioFreedom stent in this study. The LD-coated stent demonstrated an equivalent efficacy and safety profile compared with HD in both early and late phases.

This study had several limitations. First, as with all other preclinical studies, is the lack of direct correlation of the findings between animal models and human clinical trials.28 We need to recognize the time difference in the course of healing between human and animal for the evaluation because the response to healing after stent implantation in a human coronary artery is 5 to 6 times longer than in the porcine model. However, the stages of healing are comparable, and the porcine model is considered the standard preclinical model for evaluation of new DES, where it can provide useful information on the pathology of arterial healing responses.11 Another difference is that coronary arteries are normal and healthy in a porcine model in contrast to human subjects. In humans, stents are deployed into coronary arteries with atherosclerotic changes, and their vessels are sometimes tortuous and calcified. It will be necessary to await
human clinical trials to confirm the results of this study. Second, the extent of endothelialization was assessed by histological assessment of sections, without the use of scanning electron microscopy. The use of scanning electron microscopy might have shed better light on the true differences in endothelialization. Third, the sample sizes were small; nonetheless, they exhibited consistent histological findings that should allow for meaningful conclusion. It should be noted that potential interindividual differences in inflammatory responses was reduced by implantation of BioFreedom and SES into different coronary vessels of the same animals. Finally, the quality of fluoroscopy was poor, resulting in the failed deployment of 4 stents; however, the other stents were appropriately deployed with equivalent injury score between the stent types.

In conclusion, compared with SES, the polymer-free BA9-coated BioFreedom stent demonstrates equivalent early intimal inhibition with more durable long-term efficacy. In addition, there was superior arterial healing, as evidenced by the rare presence of persistent fibrin, and less inflammation with BioFreedom stents than with SES. These findings may confer long-term advantages for the use of a nonpolymeric DES over a traditional polymeric DES. The first-in-human BioFreedom clinical trial has started in Europe in 2008.

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References


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**CLINICAL PERSPECTIVE**

Drug-eluting stents still have late stage disadvantages that might be attributable to the polymer. We hypothesized that polymer-free drug release may reduce late events and developed a newly designed polymer-free Biolimus A9–coated stent. The BioFreedom stent has 3 unique features. First, BioFreedom stents release the antiproliferative agent directly from a mechanically modified textured surface of the stent without the use of polymer. Second, Biolimus A9 is a highly lipophilic drug, which means it easily crosses the cell membrane to achieve therapeutic effects in its target tissue. Third, BioFreedom stents use asymmetrical coating on the outside surface of the stent. To test the hypotheses, we compared BioFreedom stents to a polymer-coated sirolimus-eluting Cypher stent and a bare-metal stent in an overstretch coronary mini-swine model. As a result, BioFreedom stents demonstrated equivalent early reduction of intimal proliferation with late efficacy compared with sirolimus-eluting Cypher stents. There appeared to be delayed healing and persistent inflammation in sirolimus-eluting Cypher stents compared with BioFreedom stents. The use of this new generation of polymer-free drug-eluting stents versus traditional polymeric drug-eluting stents may be beneficial and should be examined in a randomized clinical trial.
Polymer-Free Biolimus A9-Coated Stent Demonstrates More Sustained Intimal Inhibition, Improved Healing, and Reduced Inflammation Compared With a Polymer-Coated Sirolimus-Eluting Cypher Stent in a Porcine Model
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