Four-Year Angiographic and Intravascular Ultrasound Follow-Up of Patients Treated With Sirolimus-Eluting Stents

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Background—Despite the proven superiority of sirolimus-eluting stents (SESs) compared with bare stents in the first year after implantation, long-term outcomes of patients treated with these novel devices remain unknown. Our goal was to evaluate the clinical, angiographic, and intravascular ultrasound (IVUS) outcomes of patients treated with SESs 4 years after implantation.

Methods and Results—The study included 30 patients treated with sirolimus-eluting Bx Velocity stenting (slow release [SR; n = 15] and fast release [FR; n = 15]). Twenty-six patients underwent 4-year angiographic and IVUS follow-up and had matched assessments at all time points (index and 4-, 12-, 24-, and 48-month follow-up). One death occurred during the study period in a patient with a patent SES. There were no target-vessel revascularizations or thromboses between 2- and 4-year follow-up examinations. There was no stent thrombosis, target-lesion revascularization, death, or myocardial infarction in the SR group up to 4 years. Cumulative event-free survival rate was 87% for the total population (80% in the FR group and 93% in the SR group). In-stent late loss was slightly greater in the FR group (0.41 ± 0.49 mm) than the SR group (0.09 ± 0.23) after 4 years. One patient in the FR group had a 52% in-stent restenosis lesion. Percent neointimal hyperplasia volume, as detected by IVUS, remained minimal after 4 years (FR = 9.1% and SR = 5.7%).

Conclusions—This study confirms the longevity of the optimal outcomes observed in patients treated with sirolimus-eluting Bx Velocity stents 4 years after implantation. In-stent lumen dimensions remained essentially unchanged at 4-year follow-up, particularly in the population treated with the currently available SES (SR formulation). (Circulation. 2005;111:2326-2329.)

Key Words: angiography • restenosis • stents

Drug-eluting stent (DES) implantation is rapidly becoming the prime revascularization strategy for obstructive coronary artery disease because of reduced incidence of in-stent restenosis. Despite much enthusiasm, only a few DES devices have proven clinical effectiveness, and long-term data are lacking.

Most bioactive agents of DESs alter cell cycle division and have unpredictable long-term effects in the vessel wall. These cellular effects, which may resemble the mechanism of action of radiation therapy, have raised concerns about the safety of the DES beyond the initial years after implantation. In addition, nonbiodegradable polymer coatings, as well as residual medication in some devices, remain on the stent surface in close contact with arterial wall structures and represent a potential source for late inflammation, restenosis, or other side effects. The present study provides a unique opportunity to evaluate clinical, angiographic, and intravascular ultrasound (IVUS) outcomes of patients treated with sirolimus-eluting stents (SESs) 4 years after implantation.

Methods

The study sample and study protocol have been described previously. In brief, 30 consecutive patients were implanted with a single sirolimus-eluting Bx Velocity stent from December 1999 to February 2000. Each stent contained a standard concentration of sirolimus per unit of metal surface area (140 μg of sirolimus/cm²). Fifteen patients received a fast-release (FR, <15-day drug release) SES, and 15 received a slow-release (SR, ≥28-day drug release) SES. All stents were 18 mm long and 3.0 to 3.5 mm in diameter. Patients received aspirin (325 mg/d, indefinitely) started at least 12 hours before the procedure and a 300-mg loading dose of clopidogrel immediately after stent implantation and 75 mg/d for 60 days. All patients had 4-month and 1-, 2-, and 4-year angiographic and IVUS follow-up.
scheduled per protocol. The Medical Ethics Committee at Institute Dante Pazzanese approved the protocol, and each patient provided informed consent.

Quantitative Measurements
Quantitative coronary angiography and IVUS imaging were performed after bolus infusion of intracoronary nitrates during the index procedure and at follow-up assessments. IVUS images were acquired with a motorized pullback at a constant speed of 0.5 mm/s. Quantitative angiographic and volumetric IVUS analyses were performed by independent core laboratories. Two coronary segments were subjected to coronary angiography: (1) in-stent and (2) in-lesion segments. The in-stent analysis encompassed only the 18-mm-long segment covered by the stent. The in-lesion segment was defined as the stent plus 5 mm proximal and 5 mm distal to the edge or the nearest side branch. In-stent and in-lesion restenosis were defined as ≥50% diameter stenosis (DS) at follow-up within the stent and target lesion, respectively. Minimal lumen diameter and percent DS were measured for each segment. In-stent late lumen loss was calculated as postprocedural minimal lumen diameter minus follow-up minimal lumen diameter. Intimal hyperplasia volume was calculated as stent volume minus luminal volume. Percent intimal hyperplasia was defined as intimal hyperplasia volume divided by stent volume.

Statistical Analysis
Continuous variables are expressed as mean±SD. Comparisons between the same measurements at different time points were performed with a 2-tailed paired $t$ test. Comparisons between groups were performed with an unpaired Student $t$ test. A probability value $<0.05$ was considered statistically significant. SYSTAT 11 software (Systat Software Inc) was used.

Results
Baseline characteristics were similar between both the FR and SR groups, as reported previously.

Clinical Data
The overall incidence of major adverse cardiovascular events was 13% for the total population, 20% in the FR group, and 7% in the SR group. Survival rate was 97% (29/30) at 4-year follow-up. One patient in the FR group who had been treated in the right coronary artery died at 49-month follow-up. This patient underwent aortic and mitral valve replacement without complications 3 years after SES implantation and had severe left ventricular dysfunction. He had a cardiac arrest out of the hospital in January 2004; he was resuscitated but had severe cerebral damage. Postarrest angiography and IVUS, which coincided with the 4-year follow-up assessment, revealed no neointimal hyperplasia. The patient developed brain death and subsequently died. Necropsy, as reported previously, revealed a well-healed stented segment with >95% of the stent surface endothelialized as demonstrated by scanning electron microscopy. Approximately 75% of the stent struts were covered by a thin, type I collagen-rich neointima that contained smooth muscle cells.

There were 3 target-vessel revascularizations, which included 2 target-lesion revascularizations and 1 non–target-lesion revascularization, as reported previously. There were no target-vessel revascularizations or thromboses between 2-and 4-year follow-up. There were no stent thromboses, target-lesion revascularizations, deaths, or myocardial infarctions in the SR group up to 4 years. There was no aneurysm formation on angiography.

Angiographic and IVUS Data
Angiographic and IVUS imaging were performed in 26 patients at 4-year follow-up. Four patients did not undergo 4-year follow-up assessment: 3 had target-vessel revascularization before scheduled follow-up angiography, and 1 asymptomatic patient refused repeated angiography.

Only 1 patient (FR group) developed restenosis at 4 years. This patient had stenosis progression from 10% DS at 2 years to 52% DS at 4-year follow-up. Cumulative distributions of minimal lumen diameter at postprocedural, 2-year, and 4-year follow-up are shown in Figure 1. Net late loss was >0.5 mm in 7 patients. Of these, 6 patients were in the FR group, whereas only 1 patient with 0.51-mm late lumen loss was treated with the SR formulation. No other patient treated with an SR SES had ≥0.34 mm of late loss at 4-year follow-up (Figure 2).

Figure 1. In-stent minimal lumen diameter (MLD) over 4 years. Angiography was performed at postprocedural, 2-year, and 4-year follow-up.

Figure 2. Angiography shows lesion in proximal portion of left descending coronary artery (white arrow), which was treated with implantation of sirolimus-coated BX-Velocity stent (top right). Lumen dimensions remained unchanged at 4-, 12-, 24-, and 48-month follow-up. Pre indicates before procedure; Post, after procedure.
In the FR group, late loss progression averaged \( \approx 0.1 \text{ mm/y} \), totaling 0.4 mm at 4 years after implantation. In the SR group, a triphasic pattern of late loss was observed. Lumen loss was observed between postprocedural and 1-year follow-up and between 2- and 4-year follow-up, but lumen gain was noted between the 1- and 2-year follow-up examinations. As a result, the mean net late loss after 4 years was only 0.09 mm. Between 2 to 4 years, lumen loss was similar between the FR and SR groups. The temporal progression of late loss is shown in Table 1.

IVUS volumetric data are reported in Table 2. There were no changes in vessel volume or media plus plaque volume behind the stent between postprocedural and 4-year follow-up.

### Discussion

The present report confirms the longevity of the optimal results of the SES in a small number of patients and eases most concerns about the potential late toxicity of this device, particularly in patients treated with the SR SES, which is the same as the commercially available Cypher stent. There were no deaths, myocardial infarctions, thromboses, or target-lesion revascularizations in the SR group after 4 years. Neointimal proliferation remained minimal in both groups.

There was a steady progression of lumen loss at a low rate of 0.1 mm/y in the FR group. Lumen loss in patients treated with the SR SES was virtually absent (0.09 mm on average) 4 years after implantation. Indeed, this population experienced lumen gain between 1- and 2-year follow-up (Table 1). Similar patterns of lumen dimension variations, with an early restenosis phase at 6 months and an intermediate regression phase between 6 and 36 months, followed by a late narrowing phase beyond 4 years, were observed after implantation of Palmaz-Schatz stents.

Although the pattern of lumen loss over time may appear similar between bare stents and the SR SES, there are significant differences between the late angiographic outcomes of both devices. Unlike bare metal stents, which showed a 0.45-mm late lumen loss between 3- and \( \approx 4 \)-year follow-up angiography, changes in lumen dimensions after SR SES implantation were minimal.

Furthermore, an SD of late lumen loss in the SR group of only 0.23 mm suggests that the angiographic results were reproducible among the patient population. Other stent studies, including some DES trials,7-9 have reported broader SDs for late lumen loss, which may reflect a high variability of the restenotic process among the study populations. A recent study (P. Lemos, MD, unpublished data, 2004) suggested that the pattern of late loss after SES implantation has an atypical statistical distribution, which is skewed to the right, with most measurements showing lower values than seen with bare stents. Another hypothesis is the possibility of a biological all-or-none response of restenosis, which may explain the presence of very focal lesions adjacent to a stent segment, with no intimal hyperplasia observed in patients who develop restenosis after SES.10

As already noted at 2-year follow-up,1 patients in the SR group appeared to have superior outcomes compared with the FR population. These results may highlight the importance of drug-release kinetics for the long-term success of the DES and the need for long-term follow-up assessments in DES studies. The present study was not designed to compare the 2 formulations of SESs, and definitive conclusions should not be drawn from the present data. Whether drug release for at least 4 weeks after implantation is a requirement for prolonged antirestenosis protection remains to be determined.

### Acknowledgments

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### References


### Table 1. Temporal Evolution of In-Stent Late Loss Over 4-Year Follow-Up

<table>
<thead>
<tr>
<th>Population</th>
<th>Late Loss, mm</th>
<th>From Postprocedural to 1-Year Follow-Up</th>
<th>From 1- to 2-Year Follow-Up</th>
<th>From 2- to 4-Year Follow-Up</th>
<th>From Postprocedural to 4-Year Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients (n=26)</td>
<td>0.08±0.26</td>
<td>-0.03±0.26</td>
<td>0.20±0.31</td>
<td>0.25±0.41</td>
<td></td>
</tr>
<tr>
<td>FR group (n=13)</td>
<td>0.08±0.31</td>
<td>0.12±0.25</td>
<td>0.21±0.36</td>
<td>0.41±0.49</td>
<td></td>
</tr>
<tr>
<td>SR group (n=13)</td>
<td>0.08±0.23</td>
<td>-0.19±0.15</td>
<td>0.20±0.27</td>
<td>0.09±0.23</td>
<td></td>
</tr>
<tr>
<td>P (SR vs FR)</td>
<td>NS</td>
<td>0.002</td>
<td>NS</td>
<td>0.1</td>
<td></td>
</tr>
</tbody>
</table>

### Table 2. IVUS Volumetric Data at 4-Year Follow-Up

<table>
<thead>
<tr>
<th>3D IVUS Parameters</th>
<th>FR Group (n=13)</th>
<th>SR Group (n=13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stent volume, mm$^3$</td>
<td>140.4±38.79</td>
<td>145.9±36.57</td>
</tr>
<tr>
<td>Lumen volume, mm$^3$</td>
<td>130.1±35.47</td>
<td>137.3±36.25</td>
</tr>
<tr>
<td>Intimal hyperplasia volume, mm$^3$</td>
<td>12.5±8.93</td>
<td>8.7±5.80</td>
</tr>
<tr>
<td>Percent intimal hyperplasia volume, %</td>
<td>9.1±5.40</td>
<td>5.7±4.25</td>
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