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## Lack of Neointimal Proliferation After Implantation of Sirolimus-Coated Stents in Human Coronary Arteries A Quantitative Coronary Angiography and Three-Dimensional Intravascular Ultrasound Study

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**Background**—Restenosis remains an important limitation of interventional cardiology. Therefore, we aimed to determine the safety and efficacy of sirolimus (a cell-cycle inhibitor)-coated BX Velocity stents.

**Methods and Results**—Thirty patients with angina pectoris were electively treated with 2 different formulations of sirolimus-coated stents (slow release [SR], n=15, and fast release [FR], n=15). All stents were successfully delivered, and patients were discharged without clinical complications. Independent core laboratories analyzed angiographic and 3D volumetric intravascular ultrasound data (immediately after procedure and at 4-month follow-up). Eight-month clinical follow-up was obtained for all patients. There was minimal neointimal hyperplasia in both groups ( $11.0 \pm 3.0\%$  in the SR group and  $10.4 \pm 3.0\%$  in the FR group,  $P=NS$ ) by ultrasound and quantitative coronary angiography (in-stent late loss,  $0.09 \pm 0.3$  mm [SR] and  $-0.02 \pm 0.3$  mm [FR]; in-lesion late loss,  $0.16 \pm 0.3$  mm [SR] and  $-0.1 \pm 0.3$  mm [FR]). No in-stent or edge restenosis (diameter stenosis  $\geq 50\%$ ) was observed. No major clinical events (stent thrombosis, repeat revascularization, myocardial infarction, or death) had occurred by 8 months.

**Conclusions**—The implantation of sirolimus-coated BX Velocity stents is feasible and safe and elicits minimal neointimal proliferation. Additional placebo-controlled trials are required to confirm these promising results. (*Circulation*. 2001; 103:192-195.)

**Key Words:** stents ■ restenosis ■ angioplasty

Restenosis remains a vexing problem of percutaneous intervention. The most promising approach to prevent restenosis has been the application of intracoronary radiation<sup>1</sup>; however, some relevant side effects (edge restenosis and late thrombosis) have been reported.<sup>2,3</sup> Numerous pharmacological approaches to reduce restenosis have failed, possibly due to insufficient local drug concentrations.<sup>4</sup> Delivering medication directly to the site of vascular injury via polymeric-coated stents is a rational approach to achieve adequate local drug delivery.<sup>5,6</sup>

Sirolimus (Rapamune), a natural macrocyclic lactone, is a potent immunosuppressive agent that was developed by Wyeth-Ayerst Laboratories and approved by the Food and Drug Administration for the prophylaxis of renal transplant rejection in 1999.<sup>7</sup> Sirolimus binds to an intracellular receptor protein and elevates p27 levels, which leads to the inhibition

of cyclin/cyclin-dependent kinase complexes and, ultimately, induces cell-cycle arrest in the late G1 phase. It inhibits the proliferation of both rat and human smooth muscle cells in vitro<sup>8,9</sup> and reduces intimal thickening in models of vascular injury.<sup>10-12</sup> However, the effects of the local administration of sirolimus in a coated stent in humans have not been reported.

The aims of this pilot study were to assess (1) the feasibility and safety of implanting 2 different formulations of the sirolimus-coated BX Velocity stent in atherosclerotic human coronary arteries and (2) the impact of the stents on neointimal proliferation.

### Methods

From December 1999 to February 2000, a single sirolimus-coated BX Velocity stent was successfully implanted in each of 30 consecutive patients with coronary artery disease. The stent is a

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laser-cut, 316L stainless steel, balloon-expandable stent that contains a fixed amount of sirolimus per unit of metal surface area (140  $\mu\text{g}$  of sirolimus per  $\text{cm}^2$ ).

Sirolimus was blended in a mixture of nonerodable polymers that have been used clinically in bone cements, ocular devices, and a drug-releasing intrauterine device.<sup>13,14</sup> Fifteen patients received a fast release (FR) formulation (<15-day drug release), and 15 received a slow release (SR) formulation ( $\geq 28$ -day drug release).

### Procedure

All stents were 18 mm long and 3.0 to 3.5 mm in diameter. After predilatation of the target lesion, stents were deployed with high-pressure (>14 atm) postdilatation guided by intravascular ultrasound (IVUS). All patients received aspirin (325 mg/d, indefinitely), which was started at least 12 hours before the procedure, and clopidogrel (300 mg immediately after stent implantation and 75 mg/d for 60 days). The protocol was approved by the Medical Ethics Committee of the Institute Dante Pazzanese of Cardiology, and informed consent was obtained from every patient.

### Quantitative Measurements

Quantitative coronary angiography (QCA) and IVUS imaging were performed immediately after the procedure and at 4-month follow-up in all patients after a bolus infusion of intracoronary nitrates. IVUS images were acquired using motorized pull-back at a constant speed of 0.5 mm/s. Quantitative angiographic and volumetric IVUS analyses were performed by independent core laboratories (Brigham and Women's Hospital, Boston, Mass, and Cardialysis BV, Rotterdam, The Netherlands, respectively).<sup>15-17</sup> Three segments were selected for volumetric IVUS analysis: the stented segment (18 mm long) and 2 edge segments that were axially 5 mm proximal and distal to the stent margins.

### Statistical Analysis

Continuous variables are expressed as mean $\pm$ SD. Comparisons between postintervention and follow-up measurements were performed with a 2-tailed paired *t* test. Comparisons between groups were performed using an unpaired Student's *t* test.  $P < 0.05$  was considered statistically significant.

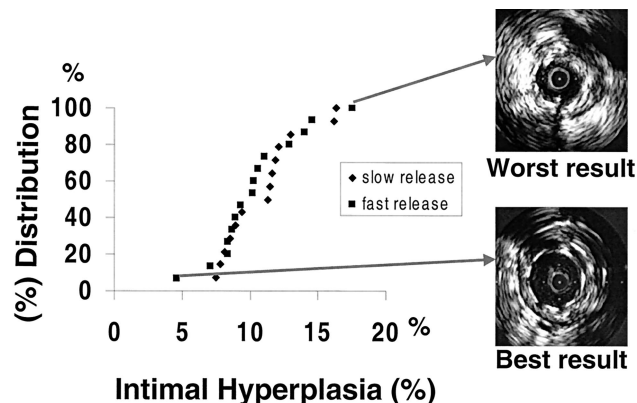
### Results

Twenty-six patients had stable angina and 4 patients had unstable angina. Their mean age was  $57.9 \pm 10$  years (SR) and  $55.1 \pm 7$  years (FR); 63% of the patients in each group were male. The incidence of prior myocardial infarction was 33.3% (SR) and 53.3% (FR), and 14% (FR) and 26% (SR) of the patients were diabetics. All stents were implanted successfully, and all patients were discharged without complications 24 hours after treatment. Creatine kinase and creatine kinase-MB levels, sampled at 6 and 18 hours after the procedure, were within the normal range in all patients.

Angiographic and volumetric IVUS data are presented in Tables 1 and 2. No patient approached  $\geq 50\%$  vessel narrowing by QCA or IVUS, and only 3 patients had  $>15\%$  intimal hyperplasia (IH) by IVUS (Figure 1). In both the edge segments and in the stented segment, lumen loss detected by IVUS was minimal (Figure 2). All patients completed 4 months of angiographic and 8 months of clinical follow-up. There were no repeat revascularizations, stent thromboses, or major clinical events (cerebrovascular accident, myocardial infarction, or death).

### Discussion

This is the first human experience with the implantation of sirolimus-coated BX Velocity stents. The absence of adverse



**Figure 1.** Left, Cumulative distribution curves of percent IH in SR and FR groups. Upper right panel shows follow-up IVUS cross-section with largest amount of IH (17.5%), and lower right panel displays IVUS cross-section with lowest amount of IH (4.6%). In both vessels, a FR stent was implanted (arrows).

events for up to 8 months of follow-up suggests that the implantation of this stent, which is coated with a potent cell-cycle inhibitor, is feasible and safe.

The amount of IH after the implantation of noncoated stents ranges from 19% to 48% of stent volume<sup>3,18,19</sup> by IVUS, and late loss averages 0.8 to 0.9 mm by QCA.<sup>19</sup> Even in nonrestenotic stents that are  $\leq 15$  mm long, an average IH

**TABLE 1. Offline Quantitative Coronary Analysis by Core Laboratory**

Parameters	SR Group (n=15)	FR Group (n=15)
Before procedure		
RD, mm	2.98 $\pm$ 0.4	2.94 $\pm$ 0.3
MLD, mm	1.16 $\pm$ 0.3	0.93 $\pm$ 0.4
DS, %	62 $\pm$ 7	68 $\pm$ 14
Lesion length, mm	12.9 $\pm$ 1.97	13.1 $\pm$ 2.2
Lesion type B1,* %	27	47
Lesion type B2,* %	73	33
After procedure		
RD, mm	3.1 $\pm$ 0.4	2.96 $\pm$ 0.3
In-lesion MLD, mm	2.74 $\pm$ 0.4	2.68 $\pm$ 0.3
In-stent MLD, mm	2.94 $\pm$ 0.44	2.84 $\pm$ 0.3
In-lesion DS, %	11.44 $\pm$ 5.5	9.7 $\pm$ 5.8
In-stent DS, %	5.09 $\pm$ 6.72	4.2 $\pm$ 7.4
Follow-up		
RD, mm	2.99 $\pm$ 0.4	3.07 $\pm$ 0.3
In-lesion MLD, mm	2.6 $\pm$ 0.5	2.7 $\pm$ 0.4
In-stent MLD, mm	2.9 $\pm$ 0.5	2.93 $\pm$ 0.3
In-lesion DS, %	14.5 $\pm$ 9.1	12.7 $\pm$ 8.2
In-stent DS, %	5.04 $\pm$ 6.7	4.55 $\pm$ 5.7
In-lesion late loss, mm	0.16 $\pm$ 0.3	-0.02 $\pm$ 0.3
In-stent late loss, mm	0.09 $\pm$ 0.3	-0.1 $\pm$ 0.3

Values are mean $\pm$ SD. RD indicates reference diameter; MLD, minimum lumen diameter; and DS, diameter stenosis.

\*According to AHA/ACC classification

**TABLE 2. Postprocedure and Follow-Up 3D IVUS Measurements by Core Laboratory**

	Lumen Volume, mm <sup>3</sup>			Stent Volume, mm <sup>3</sup>			Neointimal Hyperplasia	
	Post	FUP	P	Post	FUP	P	Volume, mm <sup>3</sup>	Percent
Total	141.6±35	127.8±36	<0.01	141.6±35	142.8±39	NS	15.0±5	10.7±3.0
SR group	152.2±40	137.6±40	<0.01	152.2±40	154.4±44	NS	16.8±6	11.0±3.0
FR group	131.3±31	118.7±30	<0.01	131.3±31	132.0±31	NS	13.3±4	10.4±3.0
P	NS	NS		NS	NS		0.07	NS

Data are mean±SD, unless otherwise indicated. Post indicates postprocedure; FUP, follow-up.  
\*SR vs. FR.

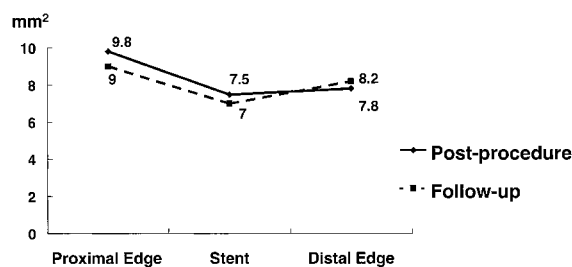
of 19.7% has been observed by IVUS.<sup>18</sup> Although differences in population and stent design limit scientific comparison with other reports, it is worth noting that the amount of IH detected in the present study (10.7%; essentially zero late loss by QCA) is much lower than previously reported. This is likely due to the cytostatic effect of sirolimus.<sup>10–12,20</sup>

Using the same IVUS methodology, the amount of in-stent IH with radioactive stent implantation varied from 7.4% (6 to 12  $\mu$ Ci radioactive stent) to 16.7% (0.75 to 1.5  $\mu$ Ci).<sup>17</sup> However, neither edge restenosis nor stent thrombosis, both of which have been reported after radiation,<sup>2,3</sup> were observed after the implantation of sirolimus-coated stents (Figure 2).

As a result of their permanent scaffolding action, stents have become an attractive platform for delivering medications locally.<sup>5,21</sup> Although some polymers have been associated with a marked inflammatory reaction,<sup>22</sup> these findings were not observed with the polymers used in the present investigation or in other clinical situations.<sup>13,14</sup> In the present study, similar favorable results were observed with both the FR and SR formulations of the sirolimus-coated stent. Whether one sirolimus coating matrix is superior to the other (SR versus FR) requires further investigation.

### Limitations

The study comprises a registry of only 30 patients with 4 months of QCA and 3D IVUS data and 8 months of clinical data. However, considering the absence of late loss by QCA and the virtual absence of IH observed in the present study by 3D IVUS and the well-documented degree of late loss with uncoated stents, these early results are promising. Twelve-month angiographic and IVUS follow-up will be performed in all patients to assess whether this effect is sustained.



**Figure 2.** Postprocedure and follow-up mean lumen areas within stent and at 5-mm edge segments (n=30), as assessed by 3D IVUS.

### Conclusion

Sirolimus-coated BX Velocity stents seem to be safe and effective in preventing neointimal formation at 4 months after stent implantation in de novo lesions. These seminal findings warrant further confirmation by large, placebo-controlled, multicenter trials.

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