Persistent Inhibition of Neointimal Hyperplasia After Sirolimus-Eluting Stent Implantation

Long-Term (Up to 2 Years) Clinical, Angiographic, and Intravascular Ultrasound Follow-Up

Muzaffer Degertekin, MD; Patrick W. Serruys, MD, PhD; David P. Foley, MB, MRCPI, PhD; Kengo Tanabe, MD; Evelyn Regar, MD; Jeroen Vos, MD, PhD; Peter C. Smits, MD, PhD; Wim J. van der Giessen, MD, PhD; Marcel van den Brand, MD, PhD; Pim de Feyter, MD, PhD; Jeffrey J. Popma, MD

Background—Early results of sirolimus-eluting stent implantation showed a nearly complete abolition of neointimal hyperplasia. The question remains, however, whether the early promising results will still be evident at long-term follow-up. The objective of our study was to evaluate the efficiency of sirolimus-eluting stent implantation for up to 2 years of follow-up.

Methods and Results—Fifteen patients with de novo coronary artery disease were treated with 18-mm sirolimus-eluting Bx-Velocity stents (Cordis) loaded with 140 μg sirolimus/cm² metal surface area in a slow release formulation. Quantitative angiography (QCA) and intravascular ultrasound (IVUS) were performed according to standard protocol. Sirolimus-eluting stent implantation was successful in all 15 patients. During the in-hospital course, 1 patient died of cerebral hemorrhage after periprocedural administration of abciximab, and 1 patient underwent repeat stenting after 2 hours because of edge dissection that led to acute occlusion. Through 6 months and up to 2 years of follow-up, no additional events occurred. QCA analysis revealed no significant change in stent minimal lumen diameter or percent diameter stenosis, and 3-dimensional IVUS showed no significant deterioration in lumen volume. In 2 patients, additional stenting was performed because of significant lesion progression remote from the sirolimus-eluting stent.

Conclusion—Sirolimus-eluting stents showed persistent inhibition of neointimal hyperplasia for up to 2 years of follow-up.

Key Words: stents ■ restenosis ■ ultrasonics ■ drugs
TABLE 1. Baseline Characteristics

<table>
<thead>
<tr>
<th>Male</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>60.2±14.3 (35–80)</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>9</td>
</tr>
<tr>
<td>Treated vessel</td>
<td></td>
</tr>
<tr>
<td>LAD</td>
<td>6</td>
</tr>
<tr>
<td>CX</td>
<td>5</td>
</tr>
<tr>
<td>RCA</td>
<td>4</td>
</tr>
<tr>
<td>No. of diseased vessels</td>
<td>2</td>
</tr>
<tr>
<td>1</td>
<td>13</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Catheterization follow-up period, mo</td>
<td>20.3±2.4 (18–24)</td>
</tr>
<tr>
<td>Clinical follow-up period, mo</td>
<td>23.3±1.0 (22–25)</td>
</tr>
</tbody>
</table>

Values are n or mean±SD (range). n=15.

LAD indicates left anterior descending artery; CX, circumflex artery; and RCA, right coronary artery.

Coronary segments were subjected to quantitative angiography (QCA), one in stent and one in lesion. The in-stent segment encompassed only the 18-mm 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 stenosis was defined as >50% diameter stenosis. QCA analysis was done by an independent core laboratory (Brigham and Women’s Hospital, Boston, Mass).

Stented vessel segments were examined with mechanical IVUS, using automated pullback at 0.5 mm per second. A coronary segment beginning 5 mm distal to and extending 5 mm proximal to the stented segment was also examined. A computer-based contour detection program was used for automated 3-dimensional reconstruction of the stented segment from up to 200 cross-sectional images.9

Clinical Follow-Up
We assessed the clinical outcome during the hospital stay, at 6 months, and up to 2 years later. Major adverse cardiac events were defined as death, acute myocardial infarction, and repeat revascularization of the target lesion and/or vessel by coronary artery bypass graft or percutaneous coronary intervention.

Statistical Analysis
Quantitative data are presented as mean±SD. Multiple comparisons between postprocedural 6- and 20-month follow-up measurements were performed by ANOVA. Paired comparisons were performed by Student’s t test.

Results
Six-month outcomes of the original 15 patients have been described earlier.2 Baseline characteristics are shown in Table 1. Table 2 shows the major adverse cardiac events that occurred during the follow-up period.

TABLE 2. Major Adverse Cardiac Events

<table>
<thead>
<tr>
<th></th>
<th>6 Months</th>
<th>6 to 24 Months</th>
<th>Up to 24 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>1†</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>MI*</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>TLR*</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>TVR</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>CABG</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

n=15.

MI indicates myocardial infarction; TLR, target-lesion revascularization; TVR, target-vessel revascularization; and CABG, coronary artery bypass graft.

*The same patient (periprocedural MI).
†Due to cerebral hemorrhage in hospital.

1. In brief, between 6 months and up to 2 years after stent implantation, no additional clinical events occurred. Complete sets of postprocedural, 6-month, and late follow-up cardiac catheterizations were obtained in 10 of 14 surviving patients. Four asymptomatic patients refused to undergo a second diagnostic investigation for scientific purposes only.

At 18 months after the procedure, 1 patient demonstrated a significant stenosis (60% diameter stenosis; fractional flow reserve 0.65) located distally to the sirolimus stent (8 mm from distal edge by quantitative IVUS) that was treated by direct stenting. Another patient presented with effort angina 22 months after the index procedure and underwent stenting because of progression of a preexisting atherosclerotic lesion 12 mm from the distal edge of the sirolimus stent (minimal lumen area by IVUS 3.5 mm² after the procedure and 3.0 mm² at 22-month follow-up). Volumetric IVUS measurements showed no neointimal hyperplasia (NIH) in the stented segment. Lumen volume of both 5-mm proximal and distal edges of the sirolimus stent revealed virtually no changes when comparing postprocedural, 6-month, and 22-month follow-up measurements.

At almost 2 years of follow-up, 1 death (noncardiac) and 1 target-lesion revascularization occurred, both of which were in the early in-hospital period (Table 2).

Quantitative Coronary Angiography and IVUS Analysis
Quantitative coronary angiography data are shown in Table 3. Twenty-month in-stent minimum lumen diameter (2.74±0.41 mm) and percent DS (3±13%) remained unchanged compared with 6-month follow-up data.
Representative sequences of angiograms from a single patient are shown in Figure 1.

IVUS analysis demonstrated persistent inhibition of NIH at long-term follow-up (Table 4). FIM study data from Sao Paulo cohort are also shown in Table 4. Between the 6- and 20-month follow-ups, a small change in NIH (1.4±1.6 mm³ and 5.9±5.3 mm³, respectively) and in percent volume obstruction of the stent (1.1±1.2% and 4.4±3.1%, respectively) was observed. Only 1 patient reached 10% NIH of stent volume as shown by IVUS, which corresponded with an actual luminal loss of 0.29 mm at the 18-month follow-up (Figure 1). In addition, no significant change in lumen or vessel volume was observed in either proximal or distal edges of the stent (Figure 2). No late stent malapposition was detected.

**Discussion**

First clinical applications of sirolimus-eluting stents in de novo lesions were shown to be safe and feasible in preventing NIH at 6 months and 1 year, with a complete abolition of restenosis.1–3 Such findings have provoked considerable interest but have also raised concerns about the long-term follow-up.10,11 In the present study, NIH assessed by IVUS at both 6 and 20 months was not substantially different from the 12-month follow-up data presented by Sousa et al3 (Table 3). In addition, the percent volume obstruction of the stent detected by volumetric IVUS in our study (4.4%) at 20-month follow-up is importantly less than those observed at 6-month follow-up in other trials (36% and 25%) using uncoated stents.12,13 Similarly, in-stent late loss and late loss index (LLI; 0.20 mm and 0.10, respectively) at a 20-month follow-up is markedly lower than with bare metal stents, in which late loss averages were 1.04 to 0.61 mm (LLI 0.59 to 0.39) at a 6-month12,13 and 0.46 mm (LLI 0.30) at a 36-month follow-up.14 Therefore, our findings provide considerable reassurance with regard to persistent inhibition of late restenosis or rebound hyperplasia, such as was previously observed with radioactive stents.8

In fact, minimal hyperplasia in humans up to 2 years after the procedure constitutes the first evidence that behavior in humans is at variance with the porcine model, where 90-day data actually demonstrate the recurrence of considerable NIH (Andrew J. Carter, unpublished data). For the first time in interventional cardiology, a new antirestenosis therapy performs better in humans than in the animal models.

Concern about potential late complications, such as late occlusion, thrombosis, late malapposition, aneurysm, and edge restenosis as reported in patients treated with brachytherapy,13 has not been observed in our patient population during up to 2 years of follow-up.

It has to be emphasized that short-term (8-week) antiplatelet therapy as used here and in the RAndomized study with the sirolimus-eluting Bx-VElocity balloon-expandable stent (RAVEL)15 provides adequate protection against subacute and late thrombotic occlusion. Nonetheless, generalization of these findings to treatment of long and complex lesions, total chronic occlusion, left main stem, etc, needs to be specifically evaluated in clinical trials.

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**TABLE 4. Volumetric IVUS Measurements**

<table>
<thead>
<tr>
<th>Follow-up period, mo</th>
<th>Rotterdam (n=10)</th>
<th>Sao Paulo (n=14)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>6</td>
<td>20</td>
</tr>
<tr>
<td>Stent volume</td>
<td>133±31</td>
<td>132±29</td>
</tr>
<tr>
<td>Lumen volume</td>
<td>132±31</td>
<td>128±28</td>
</tr>
<tr>
<td>NIH volume</td>
<td>1.4±1.6</td>
<td>5.9±5.3†</td>
</tr>
<tr>
<td>% Volume obstruction</td>
<td>1.1±1.2</td>
<td>4.4±3.1†</td>
</tr>
</tbody>
</table>

*Data from Sao Paulo (slow-release formulation stent group).
† P<0.05, 6-month vs 20-month follow-up.
The need for late target-vessel revascularization in 2 patients in lesions remote from the sirolimus stent again emphasizes the indolent nature of atherosclerosis in some patients. Although this study confirms that sirolimus-eluting stents constitute a major advance in restenosis prevention, the problem of atherosclerosis itself remains a considerable challenge.

**Limitations**

This is a small observational study and the results need to be confirmed by long-term follow-up in larger patient series. Lack of complete QCA and IVUS follow-up was unfortunate but was not prespecified in the study protocol. The virtual absence of NIH in the 10 patients studied at 20 months renders the data quite compelling because the remaining 4 patients were completely asymptomatic.

**Conclusion**

Sirolimus-eluting Bx-Velocity stents demonstrated persistent inhibition of neointimal hyperplasia and absence of restenosis in single de novo coronary lesions for up to 2 years of follow-up.

**References**

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