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, Patrick W. Serruys, David P. Foley, Kengo Tanabe, Evelyn Regar, Jeroen Vos, Peter C. Smits, Wim J. van der Giessen, Marcel van den Brand, Pim de Feyter and Jeffrey J. Popma

Circulation 2002;106;1610-1613; originally published online Sep 16, 2002;
DOI: 10.1161/01.CIR.0000034447.02535.D5
Circulation is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX 72514
 Print ISSN: 0009-7322. Online ISSN: 1524-4539

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/cm^2 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.

(*Circulation*. 2002;106:1610-1613.)

Key Words: stents ■ restenosis ■ ultrasonics ■ drugs

Coronary stents provide a mechanical scaffolding that virtually eliminates recoil and remodeling, but they do not reduce neointimal growth. Sirolimus-eluting stents may provide a definitive solution for in-stent restenosis in the short term.[1,2,3] Histological follow-up in the porcine model, however has indicated that late neointimal hyperplasia can recur at 90 and 180 days (Andrew J. Carter, DO, unpublished data, 2001). Thus, there are sufficient concerns about delayed healing with consequent risks of late restenosis[4] and thrombosis,[5] late malapposition,[6] edge effect,[7] and, on the other hand, delayed restenosis,[8] to warrant additional late follow-up catheterization. The objective of this study was to determine angiographic, intravascular ultrasound (IVUS), and clinical outcome up to 2 years after implantation of sirolimus-eluting stents in de novo coronary lesions.

Methods

Patients and Stent Implantation

The patient population consisted of 15 patients who were included at our center between February and May of 2000 in the First in Man clinical trial on sirolimus-eluting stents (FIM). The methodology has been published previously.[3]

In brief, patients with short (<15 mm) de novo coronary lesions received a single 18-mm sirolimus-eluting Bx-Velocity stent (Cordis). All lesions were predilated before stent implantation. The sirolimus coating was a slow-release formulation (≈28-day drug release with 140 μg of sirolimus per cm^2 stent surface area). All patients received aspirin (325 mg/d, indefinitely) and clopidogrel (300 mg loading dose immediately and 75 mg/d for 8 weeks).

Angiographic and IVUS Analysis

Serial coronary angiography was performed at baseline, 6 months, and late follow-up (mean 20.3±2.4; range 18 to 24 months). Two

Received May 6, 2002; revision received July 30, 2002; accepted August 5, 2002.

From Thoraxcenter, Erasmus University Medical Center, Rotterdam, the Netherlands (M.D., P.W.S., D.P.F., K.T., E.R., J.V., P.C.S., W.J.v.d.G., M.v.d.B., P.d.F.); and Brigham and Women's Hospital, Boston, Mass (J.J.P.).

Dr Popma received research grant support from Angiographic Core Laboratory.

Correspondence to Prof PW Serruys, MD, PhD, Thoraxcenter, Bd-408, University Hospital Dijkzigt, Dr. Molewaterplein-40, 3015 GD Rotterdam, The Netherlands. E-mail Serruys@card.azr.nl

***Circulation* is available at http://www.circulationaha.org** **DOI: 10.1161/01.CIR.0000034447.02535.D5**

TABLE 1. Baseline Characteristics

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

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. 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.

TABLE 2. Major Adverse Cardiac Events

	6 Months	6 to 24 Months	Up to 24 Months
Death	1†	0	1
MI*	1	0	1
TLR*	1	0	1
TVR	0	2	2
CABG	0	0	0

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.

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 mm^2 after the procedure and 3.0 mm^2 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

TABLE 3. Quantitative Coronary Angiography Analysis

	Before Procedure	After Procedure		6-Month Follow-Up		20-Month Follow-Up	
		In Lesion	In Stent	In Lesion	In Stent	In Lesion	In Stent
RD, mm	2.97±0.51	3.01±0.43		3.02±0.38		2.85±0.40	
MLD, mm	0.81±0.24	2.58±0.43	2.90±0.33	2.32±0.37	2.69±0.30	2.50±0.51	2.74±0.41
Stenosis, %	72±8	14±10	1.5±7	23±7	11±8	12±15	3±13
Late loss, mm				0.25±0.31	0.25±0.28	0.08±0.46*	0.20±0.24*
Late loss index				0.13±0.20	0.12±0.11	0.02±0.30*	0.10±0.13*

Values are mean±SD. n=10.

RD indicates reference diameter; MLD, minimal lumen diameter.

*P=NS (6-month vs 20-month follow-up). P=NS between groups (after procedure, 6-month, and 20-month follow-up). Comparison by ANOVA.

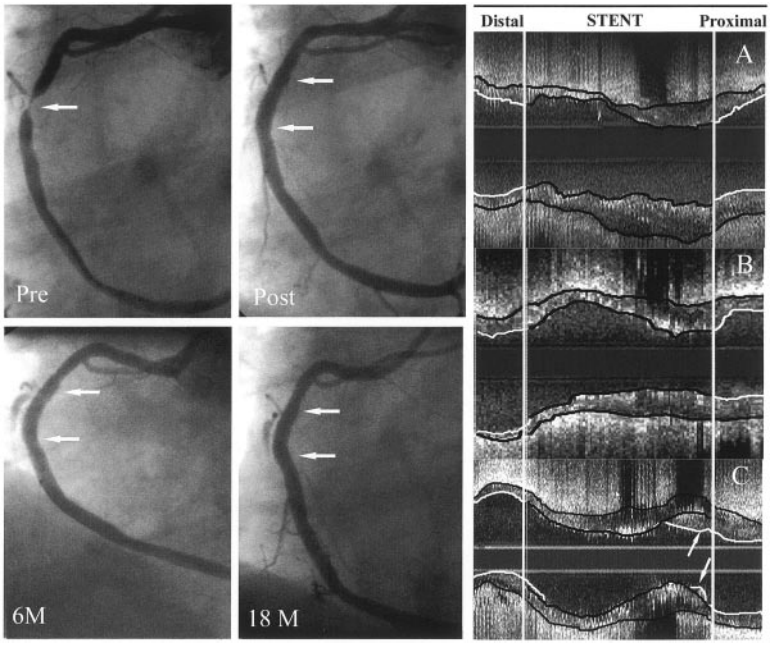

Figure 1. A 38-year-old male with unstable angina and mid-right coronary artery lesion (arrow) treated with sirolimus-eluting Bx-velocity stent. No lumen deterioration was observed at 6- and 18-month follow-up (6M and 18M). Longitudinal IVUS reconstructions demonstrate absence of NIH at 6-month follow-up (B), with minimal NIH (C, arrows) at 18 months compared with after the procedure (A).

(2.69±0.30 mm and 11±8%, respectively; P=NS). 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 mm^3 and 5.9±5.3 mm^3, 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]

TABLE 4. Volumetric IVUS Measurements

	Rotterdam (n=10)		Sao Paulo (n=14)*	
Follow-up period, mo	6	20	4	12
Stent volume	133±31	132±29	138±21	127±30
Lumen volume	132±31	126±28	137±22	124±30
NIH volume	1.4±1.6	5.9±5.3†	0.3±0.9	2.5±3.4
% Volume obstruction	1.1±1.2	4.4±3.1†	0.3±0.8	2.2±3.4

*Data from Sao Paulo[3] (slow-release formulation stent group).
†P<0.05, 6-month vs 20-month follow-up.

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 al[3] (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-month[12,13] 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.

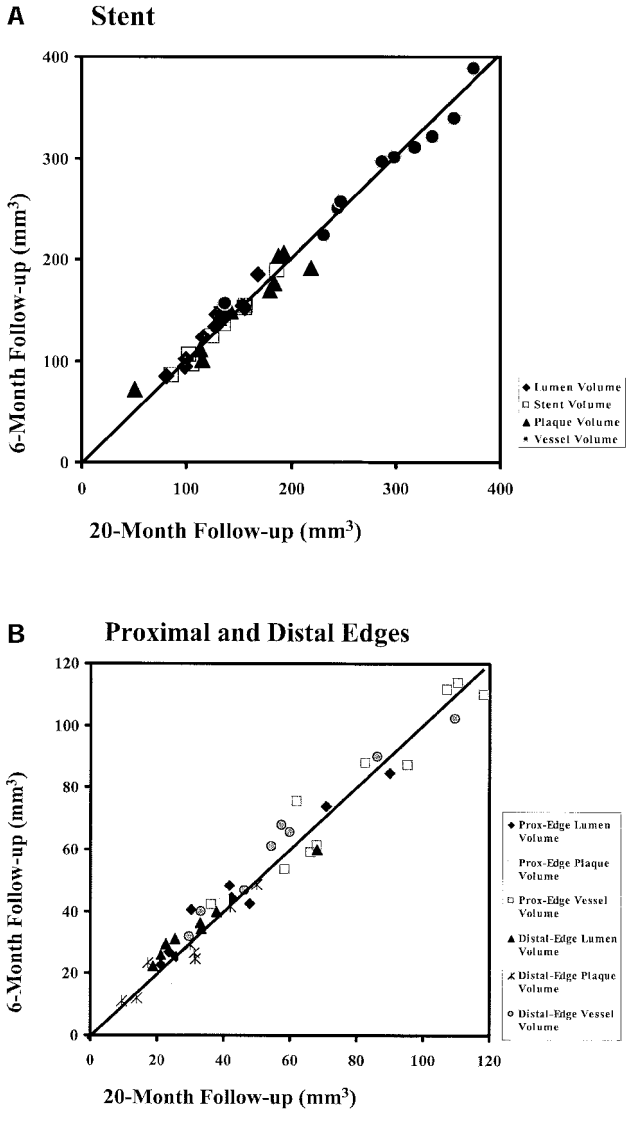

Figure 2. Changes in vessel, plaque, and lumen volume at the sirolimus-eluting stent (A) and peri-stent margins (5-mm proximal and 5-mm distal edges of the stent) (B). Individual data are presented in relation to the line of identity. *P*=NS for 6-month versus 20-month follow-up

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

1. Sousa JE, Costa MA, Abizaid A, et al. Lack of neointimal proliferation after implantation of sirolimus-coated stents in human coronary arteries: a quantitative coronary angiography and three-dimensional intravascular ultrasound study. *Circulation*. 2001;103:192–195.
2. Rensing B, Vos J, Smits P, et al. Coronary restenosis elimination with a sirolimus eluting stent: first European human experience with six month angiographic and intravascular ultrasonic follow-up. *Eur Heart J*. 2001; 22:2125–2130.
3. Sousa JE, Costa MA, Abizaid AC, et al. Sustained suppression of neointimal proliferation by sirolimus-eluting stents: one-year angiographic and intravascular ultrasound follow-up. *Circulation*. 2001;104: 2007–2011.
4. Suzuki T, Kopia G, Hayashi S, et al. Stent-based delivery of sirolimus reduces neointimal formation in a porcine coronary model. *Circulation*. 2001;104:1188–1193.
5. Costa MA, Sabate M, van der Giessen WJ, et al. Late coronary occlusion after intracoronary brachytherapy. *Circulation*. 1999;100:789–792.
6. Kozuma K, Costa MA, Sabate M, et al. Late stent malapposition occurring after intracoronary beta-irradiation detected by intravascular ultrasound. *J Invasive Cardiol*. 1999;11:651–655.
7. Albiero R, Nishida T, Adamian M, et al. Edge restenosis after implantation of high activity (32)P radioactive beta-emitting stents. *Circulation*. 2000;101:2454–2457.
8. Kay IP, Wardeh AJ, Kozuma K, et al. Radioactive stents delay but do not prevent in-stent neointimal hyperplasia. *Circulation*. 2001;103:14–17.
9. Hamers R, Bruining N, Knook M, et al. A novel approach to quantitative analysis of intravascular ultrasound images. *Comput Cardiol*. 2001;28: 589–592.
10. Serruys PW, Regar E, Carter AJ. Rapamycin eluting stent: the onset of a new era in interventional cardiology. *Heart*. 2002;87:305–307.
11. Teirstein PS. Living the dream of no restenosis. *Circulation*. 2001;104: 1996–1998.
12. Acute platelet inhibition with abciximab does not reduce in-stent restenosis (ERASER study). The ERASER Investigators. *Circulation*. 1999; 100:799–806.
13. Serruys PW, Foley DP, Pieper M, et al. The TRAPIST Study: a multicentre randomized placebo controlled clinical trial of trapidil for prevention of restenosis after coronary stenting, measured by 3-D intravascular ultrasound. *Eur Heart J*. 2001;22:1938–1947.
14. Kimura T, Yokoi H, Yoshihisa N, et al. Three-year follow-up after implantation of metallic coronary artery stents. *N Engl J Med*. 1996;334: 561–566.
15. Morice MC, Serruys PW, Sousa JE, et al. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. The RAVEL trial. *N Engl J Med*. 2002;346:1773–1780.