Vascular Responses to Drug-Eluting Stents in the Prevention of Restenosis after Percutaneous Coronary Intervention

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Vascular Responses to Drug-Eluting Stents in the Prevention of Restenosis after Percutaneous Coronary Intervention

Vasculaire reactie op drug-eluting stents ter voorkoming van restenose na percutane coronaire interventie

Thesis

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Introduction and Overview of the Thesis

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The long-term efficacy of percutaneous coronary intervention has been hampered by restenosis since its inception in 1977. Late lumen loss following balloon angioplasty is mainly attributed to negative vascular remodeling. The advent of coronary stents had reduced incidence of restenosis compared with balloon angioplasty by providing a permanent scaffold thereby preventing vessel recoil and shrinkage, and thus demonstrating a superior angiographic outcome. However, the Achilles' heel still lingers - so-called in-stent restenosis. In-stent restenosis occurs between 10-40% after the procedure. Between 30% to 80% of the patients develop recurrent in-stent restenosis regardless of the treatment strategies. This represents a major problem as the treatment of in-stent restenosis is technically challenging and costly, and the absolute number of in-stent restenotic lesions is increasing in parallel with the steadily increasing number of stenting procedures. Over the last 2 decades, underlying efforts have been put into optimizing stent characteristics and implantation technique. The procedural success rate is now satisfactory as the improvement in stent design provided more flexibility and greater radial force. However, in the long term, in-stent restenosis has not been eliminated. In addition to the efforts for stent design, there have been an enormous amount of researches into systemic pharmacological approaches to block the restenotic

cascade. So far, most of the clinical trials have failed to corroborate the beneficial effect on restenosis. The lack of efficacy in systemic drug administration was generally considered to be due to insufficient concentration of drug at the injury site. Therefore, the idea of using stents to provide a vehicle for prolonged and sufficient drug delivery has emerged. Stents represent an ideal platform for local drug delivery because after deployment they are in apposition to the vessel wall and are therefore in direct contact with the constituents of restenosis. In addition, they may serve as reservoirs of drugs for a designed period, with the goal of achieving controlled release of the anti-restenotic drug. Most stents use a coating to facilitate drug carriage and elution and it is imperative that this coating is truly biologically inert. The ideal drug released from a stent should be one that inhibits the multiple components of the complex restenosis process. Based on the mechanism of action of the agents and their target in the restenotic process, there may be 4 therapeutic options: anti-inflammatory, anti-proliferative, anti-migratory, and pro-endothelial healing. There are many potential candidate drugs. Some of the drugs target at unique mechanism while others have multiple targets in the restenotic process. After the landmark RAVEL trial demonstrated zero restenosis in the sirolimus-eluting stent arm, a steadily growing number of studies is addressing the efficacy of a variety of drug-coating combinations. At present, the randomized clinical trials with

sirolimus-eluting stent and polymer controlled paclitaxel-eluting stent have been demonstrated to remarkably reduce restenosis compared with bare metal stents, thereby these drug-eluting stents are commercially available in Europe and USA. In the bare metal stent era, the exact incidence of in-stent restenosis varies according to patient specific factors such as genetic predisposition, diabetes mellitus, and to lesion specific factors such as vessel size, lesion length, plaque burden, total occlusion, bifurcation, and to procedure specific factors such as extent of vessel damage, residual dissections, number of stents, stent size and stent area. However, chronic arterial responses to drug-eluting stents have not been fully characterized. Therefore, the purpose of this thesis was to investigate vascular responses to drug-eluting stents using refined qualitative and quantitative angiographic and intravascular ultrasound analyses.

Part 1. Sirolimus-Eluting Stents

Sirolimus-eluting stent has emerged as a potential solution for the prevention of restenosis since it was demonstrated that the treatment with sirolimus-eluting stents of native *de novo* coronary lesions was associated with no in-stent restenosis at 6 months in the RAVEL trial. Sirolimus is a potent immunosuppressive agent inducing cell-cycle arrest in the late G1 phase, which inhibits the proliferation of smooth muscle cells and reduces intimal thickening. Intravascular brachytherapy also has anti-proliferative

effects, but has been associated with some side effects such as edge restenosis, persisting dissection, late incomplete stent apposition, black holes, and late stent thrombosis. Therefore, there were some concerns that sirolimus might potentially behave the same way as brachytherapy, thus providing untoward effects on the vessel wall. In Chapter 1, we specifically looked for any evidence of the harmful effects of sirolimus eluted from the stent by investigating qualitative and quantitative intravascular ultrasound in a subset of patients enrolled in the RAVEL trial. In Chapter 2, we reported one case who showed some tissue disappearance between stent sturts following implantation of sirolimus-eluting stents. The 3-D image was nicely depicted using the ANGUS technique (combination of biplane angiography and ECG gated intravascular ultrasound). In Chapter 3, we investigated the long term intravascular ultrasound findings of the patients who had sirolimus-eluting stents incompletely apposed to the vessel wall. In Chapter 4, the fate of side branches after sirolimus-eluting stent implantation was analyzed, since the absence of reopening of occluded side branches following intracoronary brachytherapy has been previously described and considered to be related to a delayed healing process. The long term safety and efficacy of the eluting stent were evaluated in Chapter 5 and 6. In Chapter 7 to 10, we investigated the outcome of the eluting stent for the patients with in-stent restenosis,

bifurcation lesions, chronic total occlusions and left main coronary artery disease, cases at high risk for restenosis with conventional bare metal stenting.

Part 2. Paclitaxel-Eluting Stents

Paclitaxel interferes with microtubule function, which leads to the inhibition of cell division and migration, thereby interrupting the restenotic cascade. Elution of paclitaxel from stent has been reported to inhibit neointimal hyperplasia in animal models. Accordingly, as well as sirolimus, polymer-baseed paclitaxel-eluting stents have been demonstrated to dramatically reduce restenosis compared to bare metal stents in large randomized clinical trials such as the TAXUS II and IV. Part 2 of the thesis investigated chronic vascular responses to this eluting-stent within the stent (Chapter 11) and at proximal and distal edges (Chapter 12). We also studied the incidence of incomplete stent apposition after implantation of paclitaxel-eluting stent in comparison with that of bare metal stent (Chapter 13). The patients with the phenomenon were also prospectively followed. In Chapter 14, the efficacy of the eluting-stent for the patients with in-stent restenosis was evaluated.

Part 3. Other Drug-Eluting Stents

Part 3 of the thesis described drug-eluting stents other than sirolimus and paclitaxel. In Chapter 15, we performed pre-clinical (in-vitro and animal) studies for statin-eluting

stent project. Another candidate drug was actinomycin-D, the antiproliferative drug, which was highly effective in reducing neointimal proliferation in preclincal studies. We assessed the results of the ACTION trial, the first large clinical trial of actinomycin-D eluting stent in Chpater 16. Finally, in Chapter 17, we summarized other candidate drug-eluting stents and also described future perspectives.

Part 1. Sirolimus-Eluting Stent

Chapter 1

Intravascular ultrasound findings in the multicenter, randomized, double-blind RAVEL (RAndomized study with the sirolimus-eluting VElocity balloon-expandable stent in the treatment of patients with de novo native coronary artery Lesions) trial.

Serruys PW, Degertekin M, Tanabe K, Abizaid A, Sousa JE, Colombo A, Guagliumi G, Wijns W, Lindeboom WK, Ligthart J, de Feyter PJ, Morice MC. Circulation 2002 Aug 13; 106(7):798-803

Intravascular Ultrasound Findings in the Multicenter, Randomized, Double-Blind RAVEL (RAndomized study with the sirolimus-eluting VElocity balloon-expandable stent in the treatment of patients with de novo native coronary artery Lesions) Trial

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Background—The goal of this intravascular ultrasound investigation was to provide a more detailed morphological analysis of the local biological effects of the implantation of a sirolimus-eluting stent compared with an uncoated stent.

Methods and Results—In the RAVEL trial, 238 patients with single de novo lesions were randomized to receive either an 18-mm sirolimus-eluting stent (Bx VELOCITY stent, Cordis) or an uncoated stent (Bx VELOCITY stent). In a subset of 95 patients (sirolimus-eluting stent=48, uncoated stent=47), motorized intravascular ultrasound pullback (0.5 mm/s) was performed at a 6-month follow-up. Stent volumes, total vessel volumes, and plaque-behind-stent volumes were comparable. However, the difference in neointimal hyperplasia (2 ± 5 versus 37 ± 28 mm^3) and percent of volume obstruction ($1\pm3\%$ versus $29\pm20\%$) at 6 months between the 2 groups was highly significant ($P<0.001$), emphasizing the nearly complete abolition of the proliferative process inside the drug-eluting stent. Analysis of the proximal and distal edge volumes showed no significant difference between the 2 groups in external elastic membrane or lumen and plaque volume at the proximal and distal edges. There was also no evidence of intrastent thrombosis or persisting dissection at the stent edges. Although there was a higher incidence of incomplete stent apposition in the sirolimus group compared with the uncoated stent group ($P<0.05$), it was not associated with any adverse clinical events at 1 year.

Conclusions—Sirolimus-eluting stents are effective in preventing neointimal hyperplasia without creating edge effect and without affecting the plaque burden behind the struts. (***Circulation.*** **2002;106:798-803.)**

Key Words: stents ■ restenosis ■ ultrasonics ■ drugs

The main limitation of the percutaneous techniques of revascularization remains the phenomenon of restenosis, which is an exaggerated healing response to the vessel wall injury that occurs as a result of mechanical dilatation. The 3 processes involved in restenosis are immediate elastic recoil, late constrictive remodeling, and neointimal hyperplasia. The scaffolding properties of a stent can control the first 2 processes but lead to an increase in neointimal hyperplasia.

Pilot studies testing the safety, feasibility, and efficacy of the sirolimus-eluting stent have demonstrated a near complete abolition of neointimal hyperplasia.[1,2] These pilot studies have been conducted on patients with Benestent type lesions in large vessels, and the stents were implanted under intravascular ultrasound (IVUS) guidance.

The RAVEL trial is a multicenter randomized study involving patients with more complex lesions in smaller vessels in whom IVUS guidance was not used during stent implantation.[3] In a subset of the enrolled patients, quantitative 3-dimensional IVUS assessment was performed at follow-up. The goal of this investigation was to provide a more detailed morphological analysis of the local biological effects of the implantation of a sirolimus-eluting stent.

Sirolimus has potent antiproliferative and antimigratory effects.[4] Intravascular brachytherapy also has antiproliferative and antimigratory effects but has been associated with certain side effects, including edge restenosis,[5,6] persisting dissection,[7,8] increased plaque burden outside the struts of the stent with expansion of the external elastic membrane,[8,9] late malapposition,[10] late thrombotic occlusion,[11] and "black holes."[12,13]

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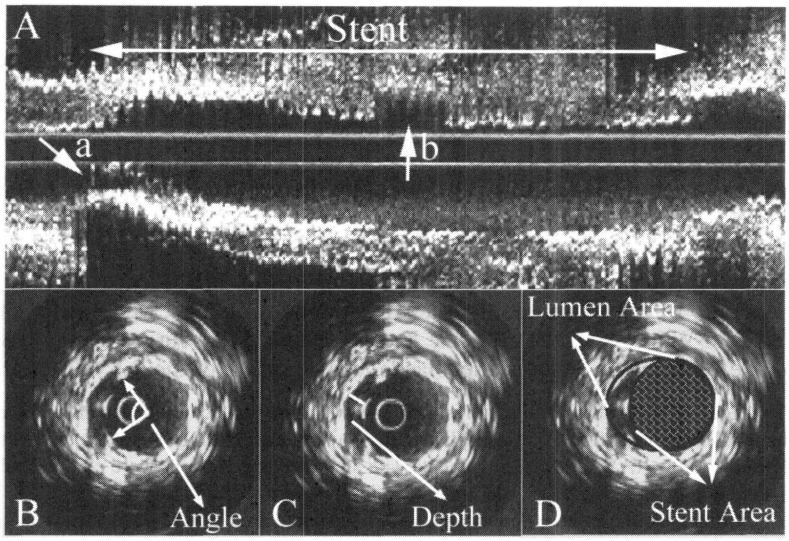

Figure 1. Methodology used to evaluate incomplete apposition at follow-up by IVUS. The figures illustrate the variety of measurements performed to quantify the incomplete apposition observed: location of incomplete apposition (arrows a and b) on a longitudinal view (A), circumferential extent in angular degree (B) maximal depth, distance between the vessel wall and the most incompletely apposed strut (C), and the area of incomplete apposition (lumen area−stent area=incomplete apposition area) in a single IVUS cross section (D).

On the basis of the previous experience with brachytherapy, we specifically looked for any evidence of these harmful effects in the patients enrolled in the RAVEL trial.

Methods

Patient Selection

The RAVEL trial enrolled 238 patients at 19 European and South American medical centers, and a subset of 95 patients enrolled at 6 centers underwent an IVUS investigation of their stents at 6 months. The study was reviewed and approved by each participating institution's Ethics Review Committee. All randomized patients signed a specific written informed consent mentioning the follow-up IVUS investigation. Patients were eligible if they had a diagnosis of stable or unstable angina pectoris or documented silent ischemia and if they had a single de novo target lesion of a native coronary artery in a vessel between 2.5 and 3.5 mm in diameter that could be covered by an 18-mm stent. Patients were not eligible for enrollment if they had an evolving myocardial infarction; an unprotected left main coronary artery stenosis ≥50%; an ostial target lesion; a calcified lesion that could not be successfully predilated; an angiographically visible thrombus within the target lesion; a left ventricular ejection fraction below 30%; or intolerance to aspirin, clopidogrel, or ticlopidine.

Study Procedures

After successful predilatation, patients were randomized 1:1 in a double-blind fashion to undergo the implantation of either an uncoated metal Bx VELOCITY Balloon-Expandable Stent or a sirolimus-eluting Bx VELOCITY Balloon-Expandable Stent (Cordis Corp, Johnson & Johnson). The sirolimus-eluting stents were indistinguishable from the uncoated metal stents to the naked eye. Postdilatation was performed as necessary to achieve a residual stenosis below 20% with a TIMI grade III flow. In case of dissection or of incomplete coverage of the lesion, additional study stents from the same randomization assignment were used as necessary.

Heparin was administered in intravenous boluses to maintain an activated clotting time >250 seconds for the duration of the procedure and was discontinued within 12 hours. Aspirin, at least 100 mg, was administered 12 hours before the procedure and continued indefinitely. A loading dose of 300 mg of clopidogrel was administered, preferably 48 hours before the procedure, followed by 75 mg once daily for 8 weeks. Alternatively, ticlopidine 250 mg twice daily was begun 1 day before the procedure and continued for 8 weeks.

Patient Follow-Up

At 30 days, 6 months, and 12 months, patients underwent evaluation of anginal status according to the Canadian Cardiovascular Society Classification of angina[14] and the Braunwald Classification for unstable angina,[15] as well as monitoring of major adverse cardiac events or additional revascularization of the index target lesion. A 12-lead ECG was performed at each visit; follow-up angiography and an IVUS investigation was performed at 180±30 days.

Quantitative Coronary Angiography

Coronary angiograms were obtained in multiple views after patients had received an intracoronary injection of nitrates. Quantitative analyses of all pre-, peri-, and postprocedural angiographic data were performed by an independent core laboratory (Cardialysis, Rotterdam, the Netherlands) and analyzed quantitatively by edge-detection techniques.[16] These data have been reported previously.

Quantitative Intravascular Ultrasound

At a 6-month follow-up, stented vessel segments were examined with mechanical IVUS (CardioVascular Imaging System, CVIS) 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 3D reconstruction of the stented segment from up to 200 cross-sectional images. Lumen, stent boundaries, and external elastic membrane were detected using a minimum cost algorithm.[17,18] Total vessel volume (TVV), stent volume (SV), and lumen volume (LV) were calculated as $V=\Sigma^{n}_{i=1} A_i \cdot H$, where V is volume, A is total vessel, stent, or lumen area (as desired) in a given cross-sectional image, H is thickness of the coronary artery slice, and n is the number of slices. Lumen volume did not include the incomplete apposition spaces, and in absence of neointimal hyperplasia, lumen volume was delineated by the boundaries of the struts. Total plaque volume (TPV), plaque volume behind the stent (PBS), and neointimal hyperplasia (NIH) were calculated as TVV−LV, TVV−SV, and SV−LV, respectively. Percentage of

TABLE 1. Comparison of Baseline Demographic and Angiographic Data of the Population Undergoing IVUS Investigation at Follow-Up With the Entire Cohort of Randomized Patients

	Sirolimus-Coated Stent (n=48)	Uncoated Stent (n=47)	All Randomized (n=238)
Age, y	62.2±10.7	58.4±9.7	60.7±10.4
Men	72.9	85.1	75.6
Diabetes mellitus	14.6	14.9	18.5
Hypercholesterolemia	45.8	52.2	51.5
Hypertension	45.8	53.3	49.2
Previous MI	41.7	27.7	35.7
Previous CABG	2.1	2.1	1.7
Previous PTCA	18.8	8.5	18.1
Current smoker	31.3	40.4	29.8
Unstable angina	58.6	57.4	50.2
Stable angina	32.6	31.9	38.7
Silent ischemia	8.7	10.6	11.1
RVD before procedure, mm	2.59±0.61	2.66±0.55	2.62±0.53
DS after procedure, %	65±10	62±9	64±10
MLD before procedure, %	0.90±0.29	1.01±0.38	0.95±0.33
RCA/LAD/CX, %	22.9/54.2/22.9	23.9/52.2/23.9	26.8/49.8/23.4

Values are given as mean±SD or percentage.

The difference between demographics and angiographic preprocedure measurements was tested by Fisher's exact and unpaired *t* tests (P=NS). MI indicates myocardial infarction; CABG, coronary artery bypass graft; PTCA, percutaneous transluminal coronary angioplasty; RVD, reference vessel diameter; DS, diameter stenosis; and MLD, minimal luminal diameter.

obstruction volume was calculated as neointimal volume/stent volume × 100 at the 6-month follow-up. For the segments proximal and distal to the stent, the vessel volume was measured at each cross section as the area lying within the external elastic lamina.

Feasibility, reproducibility and inter- and intra-observer variability of this system have been validated in vitro and in vivo.[17,18] The quantitative ultrasound analyses were performed by an independent core laboratory (Cardialysis BV, Rotterdam, the Netherlands).

Qualitative IVUS parameters assessed in the study included persisting edge tears and incomplete stent apposition. Edge tears were defined as disruption of plaque immediately adjacent to the stent ends, where the flap could be clearly differentiated from the underlying plaque. Incomplete stent apposition was defined as 1 or more struts clearly separated from vessel wall with evidence of blood speckles behind the strut,[19,20] and because it was based on the consensus of 3 independent analysts, the determination was blind for the type of stent used. The measures of agreement by Kappa analysis between 3 observers were 0.87, 0.85 and 0.80, respectively (P=NS).

The number of loci exhibiting areas of incomplete stent apposition per stent was determined by cross-sectional IVUS images. The total length of these single or multiple areas of incomplete apposition were calculated from the number of frames involved. The maximal number of struts separated from the vessel wall on 1 single cross section, as well as the maximal depth (distance between the most incompletely apposed strut and the vessel wall) and the maximal circumferential extent of incomplete apposition (expressed in angular degrees) are reported. Finally, the volume of the incompletely apposed segments was quantified in mm^3 and related to the stent volume-in percent (Figure 1).

End Points

The primary end point of the study is angiographic in-stent late loss at a 6-month follow-up as determined by quantitative coronary angiography. The secondary clinical end point of the study was a composite of major adverse cardiac events, including cardiac and noncardiac death, Q-wave and non–Q-wave myocardial infarctions, coronary artery bypass grafts, or target lesion or vessel revascularizations at 30 days, 6 months, and 12 months after the index procedure.[3]

Statistical Analysis

All analyses were performed on an intention-to-treat basis. Treatment group differences were tested by ANOVA or Wilcoxon rank sums scores for continuous variables. Discrete variables were described by counts and percentages and tested with Fisher's exact test.

The differences in event-free survival were compared by log-rank tests. A 2-sided P value <0.05 was considered statistically significant. To identify potential causative factors responsible for incomplete apposition, a multivariate analysis was performed including all the conventional pre, peri-, and postprocedural factors recorded in the frame of this trial.

Results

The baseline demographic and angiographic data of this subset of patients were similar to those observed in the entire cohort of the patients randomized in the RAVEL trial, and the IVUS population was not the result of a biased selection of patients (Table 1).

Follow-up IVUS was obtained in 80% (95 of 118) of the eligible patients. The analysis of the 2 groups within the IVUS population shows that the stent volumes were comparable. At follow-up, there was no difference in the TVV or PBS volume, suggesting that the eluted drug did not affect the plaque burden located outside the stent structure (Table 2).

The differences in neointimal hyperplasia and percent of volume obstruction between the 2 groups were highly significant, emphasizing the near complete abolition of the proliferative process inside the stent (Figure 2).

The analysis of the proximal and distal edge volumes showed no significant difference in EEM, lumen, and plaque volume at the proximal and distal edges (Table 2).

TABLE 2. IVUS Measurements at 6-Month Follow-Up

Lesion Parameters Measured	Sirolimus-Eluting Stent (n=48)			Uncoated Stent (n=47)		
	Proximal	Stent	Distal	Proximal	Stent	Distal
Total vessel volume	64±27	280±69	51±24	59±24*	280±75*	49±21*
Plaque and NIH	31±15	152±47	21±12	30±13*	183±53†	24±14*
Plaque behind stent	NA	150±44	NA	NA	146±43*	NA
Stent volume	NA	131±35	NA	NA	132±36*	NA
Neointimal volume	NA	2±5	NA	NA	37±28‡	NA
Lumen volume	33±16	129±34	30±14	30±15*	95±41‡	25±11*
% Stent volume obstruction	NA	1±3	NA	NA	29±20‡	NA

*Not significant; †$P<0.05$; ‡$P<0.001$.
NA indicates not applicable.

Qualitative assessment by IVUS did not reveal any evidence of intrastent thrombosis or persisting dissection at the stent edges, but showed a 21% incidence of incomplete apposition in the sirolimus group compared with a 4% incidence in the uncoated stent group. Table 3 provides a quantitative evaluation of the extent of incomplete apposition by the number of individual segments that were incompletely apposed, as well as their total length, maximal depth, circumferential extent, and volume of incomplete apposition. There was no significant difference between the 2 groups other than the frequency of the occurrence of this finding (21% versus 4%).

Correlation Between Quantitative Coronary Angiography and Incomplete Apposition Detected by IVUS

The binary restenosis rate and the late angiographic loss in the sirolimus group followed up with IVUS were 0% and 0.06±0.30 mm, respectively, whereas the restenosis rate and the late loss in the uncoated stent group were 23.4% and 0.91±0.58 mm.

The quantitative coronary angiography analysis of the 48 patients who received a sirolimus-eluting stent showed that the mean diameter of the stent segment remained unchanged 2.87±0.46 versus 2.87±0.49, whereas the mean diameter of the 47 patients treated with an uncoated stent decreased significantly from 2.90±0.42 to 2.17±0.48 ($P<0.001$). The mean diameter of the stents in the 10 patients who received a sirolimus-eluting stent and had incomplete apposition at follow-up was on average 3.16±0.57 mm and was significantly larger than the mean diameter of the stents of the 38 patients who had their stents well apposed at follow-up (2.79±0.43 mm, $P<0.05$). Incomplete apposition was more likely to occur in larger vessels. Stent diameter, however, was not used in the multivariate analysis of incomplete apposition.

Clinical Events at 1-Year Follow-Up

In the subset of patients (n=95) investigated with IVUS, the event-free survival rates at 1 year (98% in the sirolimus group versus 72% in the uncoated stent group, $P<0.001$) are very similar to the rates observed for the entire cohort of randomized patients (94% in the sirolimus group versus 72% in the uncoated stent group, $P<0.0001$). The 10 patients with incomplete stent apposition in the sirolimus group were asymptomatic and event-free at 1 year, whereas 1 of the 2 patients with incomplete apposition in the placebo group underwent percutaneous target lesion revascularization.

Discussion

The present results confirm the volumetric ultrasound analysis performed in the First In Man (FIM) trial at 4, 6, and 12 months.[1,2] The percent of stent volume obstruction and the volume of neointimal hyperplasia in the sirolimus group are comparable to those observed in the FIM trial and are markedly different from those measured in the control group of the RAVEL trial. The cumulative frequency curve of the NIH shows that almost 75% of the stented segments do not exhibit NIH, and the term naked struts has been coined to describe the IVUS appearance of the sirolimus-eluting stent struts. It should be emphasized that the axial resolution of IVUS is in the range of 150 to 200 μm and does not permit any assessment of the reendothelialization. The volume of PBS and the total vessel volume at follow-up were similar in both groups, suggesting that no significant plaque shrinking or positive/negative remodeling occurred as a result of sirolimus elution. This contrasts with what has been seen with intravascular brachytherapy, where both positive remodeling of the vessel and plaque progression have been reported after a 6 to 8-month follow-up.[8,9]

The quantitative and qualitative assessments in this trial have demonstrated the absence of an edge effect in drug-eluting stents when compared with the placebo, the absence of persisting intimal tears at the stent edges, and the absence of parietal thrombi or "black holes" inside the stent.

Because of the initial report that there were more cases of late incomplete apposition detected by IVUS in the sirolimus group, this observation has created a great deal of interest. It therefore seemed important to evaluate this phenomenon carefully to determine whether there were any clinical sequelae to put it in the proper perspective. Because IVUS assessment of the completeness of apposition immediately after deployment was not performed, it is not possible to determine whether these few cases of incomplete apposition observed at follow-up are the result of late acquired malapposition or the consequence of an acute incomplete deployment. Therefore, we have used the broader term "incomplete apposition." The completeness of apposition may be highly dependent on the presence or absence of intravascular guidance at the time of deployment; in the FIM trial, performed with IVUS guidance, only 2 cases of late

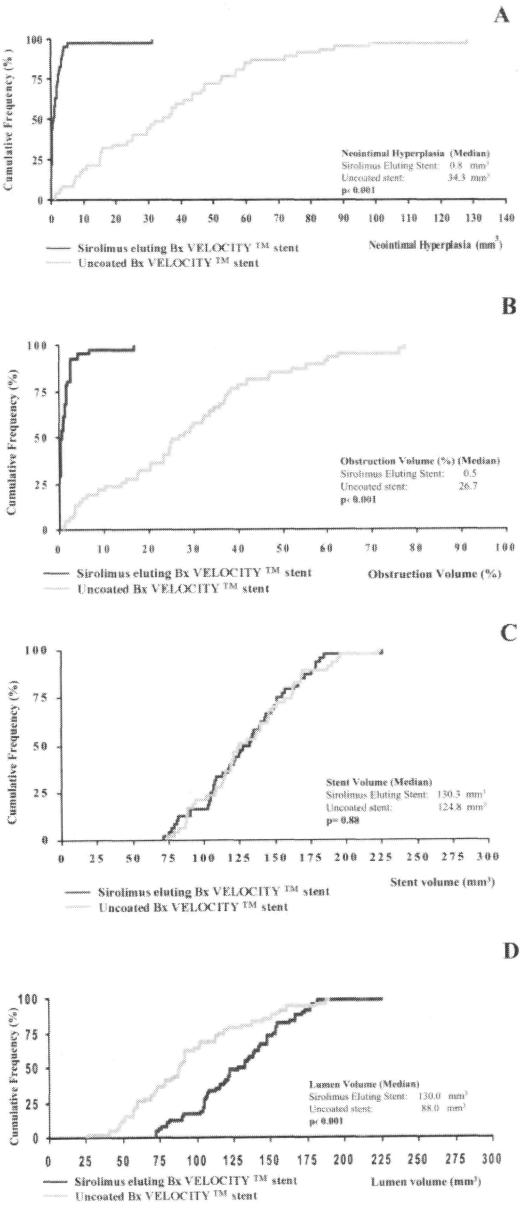

Figure 2. Cumulative distribution curve of in-stent neointimal hyperplasia volume at follow-up (A), percent obstruction volume of the stent at follow-up (B), stent volume at follow-up (C), and in-stent lumen volume at follow-up (D) for the 48 patients treated with sirolimus-eluting stent (black lines) and the 47 placebo patients treated with an uncoated Bx VELOCITY stent (gray line). Although stent volume after the procedure is similar, the neointimal and percent of obstruction volume curves are significantly shifted to the left for the sirolimus group.

acquired malapposition at follow-up were recorded out of 45 patients enrolled in this pilot study. A 17% incidence of acute incomplete apposition has been reported in a recent series of 62 patients in which bare metal stent deployment, judged optimal by angiography, was systematically evaluated by IVUS. In the IVUS-guided trials Stent Treatment Region assessed by Ultrasound Tomography (STRUT) and Angiography-directed Versus IVUS-Directed coronary stent placement trial (AVID), the incidences of malapposition are 22% and 13%, respectively.[20,21] Although the observed frequency of 21% in the sirolimus group is not very different from those reported with bare stents, it does not explain the difference seen between the 2 randomized groups in RAVEL.

Several purely speculative hypotheses may be raised to explain this general phenomenon. The first is that the antiproliferative action of the drug may preclude the growth of tissue in the void between struts and the vessel wall initially created by an incomplete deployment. The observation that larger vessels were more likely to exhibit this phenomenon seems to support this hypothesis. Second, the antimetabolite effect of the drug may induce phenomena such as necrosis or apoptosis, which may generate a new empty space between the struts and the vessel wall, which were originally in close contact. Third, the antimigratory and antiproliferative mechanism of action may prevent myoblasts from colonizing and proliferating in an organized thrombus (for example, in an unstable patient), which will dissolve at follow-up, creating a new empty space. A multivariate analysis considering conventional pre-, peri-, and postprocedural factors recorded in this trial did not identify any causative factors other than a large minimum luminal diameter after the procedure, elution of sirolimus, and absence of diabetes as predictors of incomplete apposition. The more proliferative nature of the healing process in the diabetic patients, although adequately inhibited by sirolimus (late loss 0.08 mm in diabetics), may be sufficient to fill in the gap between the sirolimus-eluting stents and the vessel wall when stents are initially incompletely deployed. This may explain why this finding was not present in any of the diabetics in this study.

Similar observations will undoubtedly be made with stents that elute drugs other than sirolimus. Serial IVUS observations from the first human experience with the QP_2-eluting polymer stent system have indicated that mild incomplete stent apposition and persistent edge tears were observed in 5% and 10%, respectively, of the 20 cases studied in this registry,[19] despite the fact that the dose of taxane analogue used in this registry seems to possess less potent antimigratory and antiproliferative properties than sirolimus (mean neointimal area of 1.16 ± 1.35 mm^2 versus of 0.09 ± 0.26 mm^2 in the present study). The angiographic late loss results reported for TAXUS I (a Feasibility Study Evaluating Safety of the NIRx Paclitaxel-Coated Conformer Coronary Stent for the Treatment of De Novo Coronary Lesions) (0.35 ± 0.47 mm), the ASian Paclitaxel-Eluting stent Clinical Trial (ASPECT) study highest dose (0.29 ± 0.72 mm) and European EvaLUation of PacliTaxel-Eluting Stents (ELUTES) highest dose (0.10 ± 0.68 mm), when the range of standard deviation is factored in, suggest the occurrence of negative late loss (or late gain) compatible with late malapposition in some patients, while at the same time suggesting in other patients substantially more neointimal hyperplasia than observed in the present study. The clinical significance of these observations in these trials remains to be determined.

It is of paramount importance to emphasize that in the sirolimus group, the incomplete apposition detected in some patients at 6 months did not translate into any subacute or late (1 year) clinical events. Furthermore, late (18-, 24-, and 36-month)

TABLE 3. Characteristics and Quantification of Incomplete Apposition of Stent

	Sirolimus-Eluting Stent	Uncoated Stent	*P*
Frequency per patient (%)	10/48 (21)	2/47 (4)	0.001
Frequency of incomplete stent apposition as a function of nominal stent size (patients can have more than 1 stent)			
2.5 mm	1/10 (10)	0/3 (0)	NS
3.0 mm	4/27 (15)	3/36 (8)	NS
3.5 mm	5/13 (38)	0/9 (0)	NS
Number of sites per stent exhibiting incomplete apposition	1.9 (1–3)	2 (2–2)	NS
Localization of incomplete apposition sites			
Proximal edge of the stent, %	5/19 (27)	1/4 (25)	NS
Middle part of the stent, %	12/19 (63)	3/4 (75)	NS
Distal edge of the stent, %	2/19 (10)	0/4 (0)	NS
Maximal number of struts separated from vessel wall on one single cross-section	3.6 (2–5)	4.0 (3–5)	NS
Total length on one single or multiple longitudinal views, mm	6.7 (3.5–13.5)	6.9 (5.3–8.4)	NS
Maximal depth, mm	0.75 (0.3–1.2)	0.62 (0.6–0.7)	NS
Maximal circumferential extent, arc°	154° (63–270)	131° (104–158)	NS
Volume per stent, mm^3	20 (3–66)	27 (16–39)	NS
Volume per stent volume, %	14 (2–42)	14 (7–20)	NS

Values are mean (%) or mean (range).
NS indicates not significant.

IVUS investigation of cases of malapposition after brachytherapy has shown that this phenomenon may disappear at follow-up (unpublished data, personal communication of J. Ligthart, MSc, January, 2002). Therefore, the significance of this phenomenon may be trivial and clinically irrelevant, but longer-term follow-up will be necessary to answer this question definitively.

Acknowledgments

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Chapter 2

True 3D-Reconstructed Images Showing Lumen Enlargement After Sirolimus-Eluting Stent Implantation.

Tanabe K, Gijsen FJH, Degertekin M, Ligthart JMR, Oortman RM, Serruys PW, Slager CJ. Circulation 2002;106:e179-80

True Three-Dimensional Reconstructed Images Showing Lumen Enlargement After Sirolimus-Eluting Stent Implantation

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A 69-year-old woman with stable angina pectoris was enrolled in the randomized, double-blind RAndomized study with the sirolimus-eluting VElocity balloon-expandable stent in the treatment of patients with de novo native coronary artery Lesions (RAVEL) trial. Coronary angiography revealed a proximal stenosis in the left circumflex coronary artery (Figure 1A). A 3.0×18 mm sirolimus-eluting Bx VELOCITY stent (Cordis Corp, Johnson & Johnson) was implanted with a satisfactory result (Figure 1B). Intravascular ultrasound (IVUS) images were then obtained with ECG-gated pullback, showing stent struts well apposed to the vessel wall (Figure 1D). At 6-month follow-up, angiography showed no restenosis (Figure 1C), whereas IVUS images revealed good stent apposition with minimal neointimal hyperplasia and some tissue disappearance between stent struts (Figure 1E and 1F). To further evaluate these observations, we combined biplane angiography and IVUS (ANGUS) for a true 3-dimensional reconstruction of the stented region. Figure 2 shows the intimal thickness color-coded on the stent surface. The blue area seen on the proximal stent surface after the procedure (Figure 2A and 2B) relates to a side branch. The images at follow-up (Figure 2C and 2D) identify additional blue areas, indicating disappearance of tissue between stent struts and lumen enlargement. Localized neointimal hyperplasia (red area) was also observed. In addition, there are small changes in 3D stent shape. In the RAVEL trial, the late loss averaged -0.01 ± 0.33 mm, consistent with the presence of lumen enlargement in some patients.

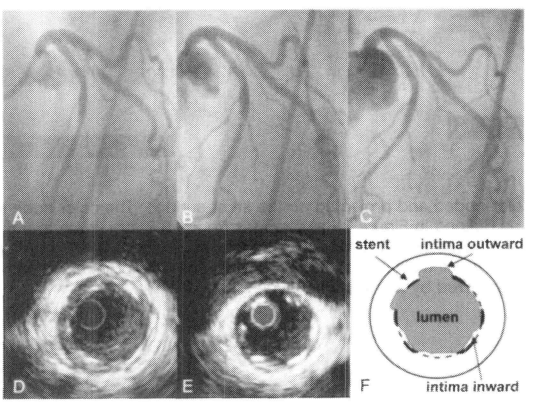

Figure 1. Coronary angiograms in left anterior oblique projection showing stenosis in the proximal segment of the left circumflex coronary artery (A), a good final result of angioplasty (B), and no restenosis at 6-month follow-up (C). The IVUS images show the stent well apposed to the vessel wall both after the procedure (D) and at follow-up (E). The schema of the IVUS image at follow-up (F) depicts minimal neointimal hyperplasia and the disappearance of tissue between stent struts.

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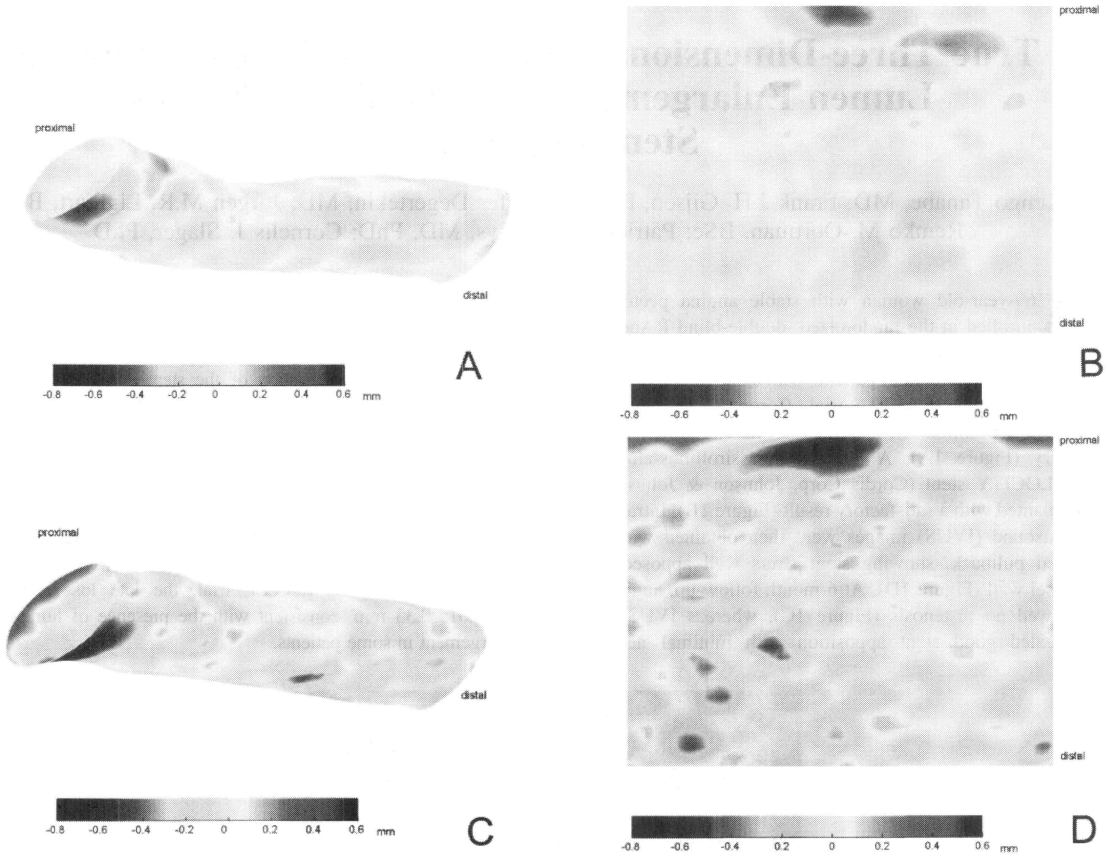

Figure 2. Local intimal thickness color-coded and projected on the stent surface. The color code indicates the relative position of lumen surface to the stent surface as defined in Figure 1F and ranges from −0.8 mm (blue) to 0.6 mm (red). A and C are the 3D-reconstructed images after the procedure and at follow-up, respectively. B and D are the unfolded images of A and C, respectively. The post-procedure image (A) shows a small thrombus (orange) opposite the side branch. At follow-up, the yellowish to orange areas demarcate the individual stent struts covered by some intimal hyperplasia.

Chapter 3

Long-term follow-up of incomplete stent apposition in patients who received sirolimus-eluting stent for de novo coronary lesions: an intravascular ultrasound analysis.

Degertekin M, Serruys PW, Tanabe K, Lee CH, Sousa JE, Colombo A, Morice MC, Ligthart JM, de Feyter PJ.
Circulation. 2003;108:2747-50

Long-Term Follow-Up of Incomplete Stent Apposition in Patients Who Received Sirolimus-Eluting Stent for De Novo Coronary Lesions

An Intravascular Ultrasound Analysis

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Background—Incomplete stent apposition (ISA) has been previously documented after sirolimus-eluting stent (SES) implantation. The aim of this study was to investigate the long-term intravascular ultrasound (IVUS) findings of ISA in patients who received SES.

Methods and Results—A total of 13 patients who received SES and showed ISA at follow-up IVUS (follow-up I) were investigated. IVUS was performed on all of these patients 12 months later (follow-up II). Quantitative ISA area measurement was also performed at follow-up I and II. No vascular remodeling was observed in the vessel segment with ISA; external elastic membrane area was 19.4±6.6 versus 19.5±6.4 mm^2 at follow-up I and II, respectively. There was also no significant change in external elastic membrane area between vessel segment with ISA and without ISA (+1.5% versus −3.0%, respectively; P=0.27) at late follow-up. The ISA area, either including (2.5±1.7 versus 3.8±6.3 mm^2; P=NS) or excluding (2.5±1.8 versus 2.4±1.7 mm^2; P=NS) a single patient with aneurysm formation, was not significantly different between follow-up I and II. One patient manifested a coronary aneurysm in the stented segment at late follow-up that was probably present at the initial follow-up but masked by thrombus. It was successfully treated with a covered stent. All patients were asymptomatic, and no patient experienced late thrombotic occlusion.

Conclusions—Vessel dimensions and area of ISA did not change over time, except for 1 coronary aneurysm that became apparent. ISA after implantation of a SES was not associated with adverse events at late follow-up. **(*Circulation*. 2003; 108:2747-2750.)**

Key Words: stents ■ vessels ■ coronary disease

The RAVEL (RAndomized study with the sirolimus-eluting Bx-VELOCITY stent) trial recently demonstrated that sirolimus-eluting stent (SES) effectively inhibits neointimal hyperplasia (NIH) without showing edge narrowing, thrombotic occlusion, or persistence of dissection.[1,2] However, incomplete stent apposition (ISA) was observed during follow-up intravascular ultrasound (IVUS) in patients who received SES.[2]

ISA has been shown to occur after brachytherapy as well as in patients who receive bare metal stents (BS).[3,4] Clinical outcomes of patients who developed ISA remain controversial. Furthermore, there are no data on serial IVUS evaluation of ISA in the long-term follow-up. Because drug-eluting stents (DES) may potentially become a routine therapy in interventional cardiology, information on the long-term effects of ISA with DES are eagerly awaited. The aim of our study was to investigate the long-term quantitative IVUS findings of ISA in patients who received SES.

Methods

Patient Population

In the RAVEL[1] and First-in-Man[5] trials, 168 patients received SES for single de novo coronary lesions and a subset of 91 patients underwent IVUS investigation at follow-up. In this report, a total of 13 patients who showed ISA at 6 or 12 months follow-up (follow-up I) were included, and quantitative IVUS was performed on all of these patients 12 months later (follow-up II).

Evaluation of ISA, Quantitative IVUS, and Coronary Angiography Analysis

IVUS was performed with automated pullback at 0.5 mm/s. All IVUS procedures were recorded on VHS videotapes. ISA was defined as 1 or more stent struts clearly separated from the vessel wall with evidence of blood speckles behind the strut without

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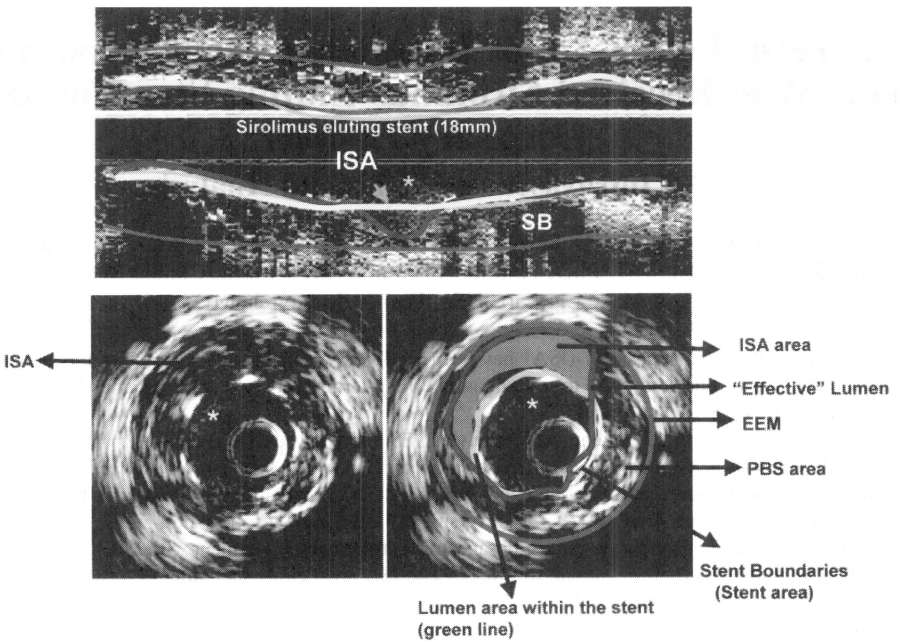

Figure 1. Longitudinal IVUS image of a patient who has a segment with ISA. Cross-sectional views correspond to the section (*) of the longitudinal view showing the red, yellow, blue, and green lines that indicate the of external elastic membrane contour, the stent contour, effective lumen area contour, and intrastent lumen area contour, respectively. PBS indicates plaque behind the stent.

overlapping side branches.[2] As previously reported, the maximum number of struts separated from the vessel wall, maximal depth, and angle of the ISA were documented.[2] The length of ISA site was measured from single or multiple longitudinal views. When the patient had >1 ISA sites separated from each other by completely well-apposed stented segment, the total length of ISA was defined as the sum of the lengths of each ISA segment.

In the segment with ISA, the lumen contours were delineated within and outside the stent strut boundaries (stent area [SA]) (Figure 1). The quantitative coronary ultrasound analysis software (Curad BV, Wijk Bij) was modified to calculate the fraction of the lumen area that lies outside of the stent, eg, ISA area.[6] ISA is thus conceptually considered part of an effective lumen. Therefore, 2 types of lumen area are reported: the intrastent lumen area (SA minus intrastent neointimal hyperplasia area) and the effective lumen area (sum of ISA area and intrastent lumen area). In addition, in the segment with ISA, external elastic membrane area (EEMA) and plaque behind stent area (EEMA minus SA minus ISA area) were measured (Figure 1).

Coronary artery aneurysm (CAA) was defined as a maximum lumen area >50% larger than the proximal reference lumen area, which is a cross section of normal appearance within 5 mm proximal to the stent.[7] Quantitative coronary angiography was performed by independent core laboratory, as previously described.[1,5]

Statistical Analysis

Quantitative data are presented as mean±1 SD and compared using paired Student's *t* test. Treatment group differences were tested by ANOVA of Wilcoxon rank-sums scores. Consecutive quantitative coronary angiography measurements were analyzed by general linear modeling with repeated measures, considering various times as factors. A value of $P<0.05$ was considered statistically significant.

Results

Of 13 patients, 8 were men (age, 58.4±11.6 years). Cardiac risk factor included hypercholesterolemia in 4 and hypertension in 5. No patient had diabetes. All patients were asymptomatic, and none experienced late thrombotic occlusion or in-stent restenosis 1 year after the diagnosis of ISA. Coronary angiography demonstrated persistent minimal late loss at late follow-up (Table 1).

Table 2 shows serial IVUS measurements of stented segments with ISA. There was no significant difference in either EEMA or plaque behind stent area between follow-up I and II. NIH remained minimal at late follow-up. There was also no significant change in EEMA between vessel segment with ISA and without ISA (+1.5% versus −3.0%, respectively; $P=0.27$) at late follow-up.

Figure 2A illustrates individual data on ISA volume at the 2 time points. At follow-up I, 22 ISA sites were found; 1 of 13 patients (4.5%) had 3 and 7 of 13 patients (31.8%) had 2 separate ISA sites. At follow-up II, the patient who had 3 ISA sites had developed an aneurysm covering the previous 2 ISA sites; apart from this patient, no new ISA sites were observed. Indeed, 4 ISA sites had resolved at follow-up II.

TABLE 1. Serial Quantitative Coronary Angiography

Parameters (n=13)	Post	Follow-Up I	Follow-Up II
Reference diameter, mm	2.98±0.48	3.00±0.46	2.93±0.49
Minimum lumen diameter, mm	2.72±0.46	2.64±0.53	2.46±0.61
Diameter stenosis, %	8.9±6.7	11.9±10.5	16.0±14.6
In-stent late lumen loss, mm	...	0.07±0.29	0.26±0.46*

Data are presented as No. relative percentages or mean±SD.
*$P=0.04$, follow-up I vs follow-up II.

TABLE 2. Serial Quantitative Intravascular Ultrasound Analysis of Vessel Segment Showing Incomplete Stent Apposition (n=12)*

	Follow-Up I	Follow-Up II	*P*
Length of the ISA segment, mm	5.1±3.5	4.8±2.6	0.36
External elastic membrane area, mm^2	19.4±6.6	19.5±6.4	0.86
Maximal depth of the ISA segment, mm	0.8±0.3	0.9±0.4	0.63
Maximal circumferential extent of the ISA, arc	138±66	144±66	0.83
Maximal No. of struts separated from vessel wall on 1 single cross section	3.3±0.8	3.25±1.4	0.79
Mean ISA area, mm^2	2.5±1.8	2.4±1.7	0.60
Plaque behind stent area, mm^2	9.02±4.2	9.2±3.9	0.95
Stent area (strut boundaries), mm^2	7.95±2.40	8.15±2.31	0.57
Intrastent (NIHA), mm^2	0.02±0.01	0.05±0.04	0.047
Intrastent lumen area (stent area minus NIHA), mm^2	7.92±2.39	8.09±2.33	0.42
Effective lumen area, mm^2 (Lumen area within the stent plus ISA area)	10.4±3.6	10.3±3.4	0.88

Values are mean±SD. NIHA indicates neointimal hyperplasia area.

*Patient who showed coronary aneurysm is not included because of lack of external elastic membrane measurement.

The ISA area, either including (2.5±1.7 versus 3.8±6.3 mm^2; *P*=NS) or excluding (2.5±1.versus 2.4±1.7 mm^2; *P*=NS) a single patient with aneurysm formation, was not significantly different between follow-up I and II. In this patient with aneurysm, the border of external elastic membrane could not be delineated on 6-month IVUS. However, serial IVUS examinations suggesting dissolution of thrombotic material in a preexisting aneurysm (Figure 2B). This aneurysmal sac with a depth of 5.9 mm was successfully treated by implanting a covered stent.

Discussion

The main findings of our analysis are as follows: (1) ISA after implantation of a SES is not associated with adverse clinical events 1 year after the diagnosis; (2) the vessel segment surrounding the incompletely apposed stent does not show positive vascular remodeling over time; (3) ISA area does not significantly change at late follow-up; and (4) inhibition of in-stent NIH persists during long-term follow-up.

ISA after implantation of SES has been a major concern since it was first described.[2] The present study demonstrated that clinical course of ISA observed after SES implantation was benign; none of the patients with ISA experienced stent thrombosis or myocardial infarction. The absence of events, even in the presence of ISA, is also consistent with the observation that endothelialization after implantation of SES and BS is similar and that SES is less thrombogenic than BS.[8]

The underlying mechanism for ISA remains largely unknown. Several hypotheses have been postulated, including plaque regression, regional positive vascular remodeling, late dissolution of thrombotic material trapped behind the stent, cell necrosis, apoptosis, and allergic reaction to sirolimus.[4,9–11]

Any dilatation of the vessel lumen raises concern about progressive dilatation over time, aneurysm formation, and ultimately the potential of rupture, as is seen with aortic aneurysms. We observed 1 case of CAA in the SES-stented segment 1 year after the diagnosis of ISA. Although there was no IVUS image from the index procedure, the angiograms after the index procedure and at 6-month follow-up were similar (Figure 2). Therefore, we suspected that there was a

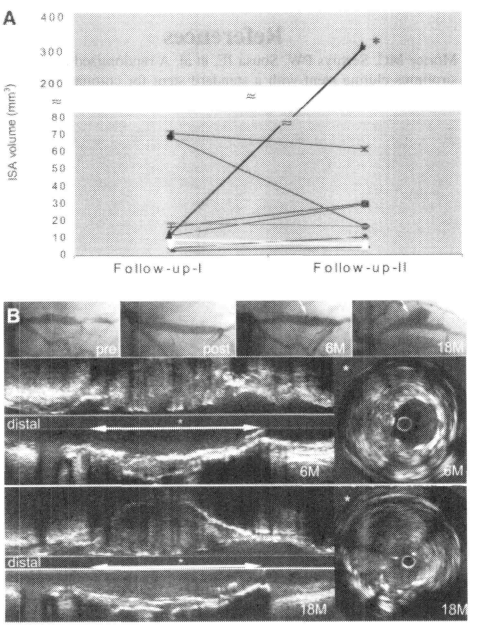

Figure 2. A, Volume changes of incomplete stent apposition (per patient) between 2 time intervals. *Patient who showed coronary aneurysm. B, Serial coronary angiography shows small pouching (arrow) at 6-month follow-up (6M). At 18-month follow-up (18M), coronary aneurysm exists at the same locality of pouching. In the IVUS (bottom), at 6M, homogeneous, low-echogenic solid mass suggests thrombus behind the stent struts. At 18M IVUS, this mass is dissolved with blood flow at the same (*) area, consistent with aneurysm formation, suggesting dissolution of thrombotic material.

preexisting CAA filled with thrombus at the time of the index procedure and that this thrombotic material had been resolved at 18 months. Based on the fact that elution of sirolimus from the stent struts continues for only 6 weeks, with a half-life of sirolimus in the tissue of 60 hours (R. Falotico, personal communication, 2002), sirolimus itself is unlikely to induce structural vessel wall changes in the longer term. Nevertheless, it remains difficult to rule out formation of CAA after SES implantation. It is worth noting that CAA is well known after BS implantation, balloon angioplasty, and coronary atherectomy.[12,13]

Excluding the aneurysm case, the vessel segment related to the incompletely apposed stent did not significantly alter in size (+1.5% change in EEMA) at late follow-up, and mean ISA area also did not significantly change. Moreover, negligible amount of NIH at late follow-up showed that the efficacy of SES in inhibiting neointimal tissue migration and proliferation was not affected by the presence of ISA. Therefore, because ISA per se was not associated with any additional adverse events, we suggest that there is no need for late mechanical correction of these cases of ISA.

Conclusions

ISA after implantation of a SES was not associated with adverse events 1 year after the diagnosis. ISA area and vessel dimensions in the segments including ISA did not change over time.

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Chapter 4

Fate of Side Branches After Coronary Arterial Sirolimus-Eluting Stent Implantation.

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Fate of Side Branches After Coronary Arterial Sirolimus-Eluting Stent Implantation

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The sirolimus-eluting stent (SES) is emerging as a potential solution for the prevention of restenosis. Although the outcome of side branches after stenting with an uncoated metal stent (UMS) has been reported, the fate of side branches after SES implantation is unknown. Furthermore, the absence of spontaneous recanalization of occluded side branches following intracoronary brachytherapy has been previously described and has been related to a delayed healing process. We assessed the procedural and 6-month follow-up angiograms of 238 patients enrolled in the RAVEL study, a double-blind controlled trial of the SES versus the UMS. Any side branch seen on the preprocedure angiogram and subsequently covered by the stent was evaluated. The side branch Thrombolysis In Myocardial Infarction (TIMI) flow grade was assessed at baseline and at follow-up by 2 observers. One hundred twenty-eight patients with ≥1 side branches were identified (63 patients in the SES group with 118 side branches, 65 patients in the UMS group with 124 side branches). Side branch occlusion occurred after stenting in 12 branches (10%) in the SES group and in 9 branches (7%) in the UMS group (p = NS). Of these occluded branches, spontaneous recanalization was observed in 11 branches (92%) in the SES group and in 6 branches (67%) in the UMS group at follow-up angiography (p = NS). Thus, the fate of side branches after SES implantation is favorable and at least as good as after UMS implantation. ©2002 by Excerpta Medica, Inc.

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The sirolimus-eluting stent (SES) is emerging as a potential solution for the prevention of restenosis.[1,2] It has been recently demonstrated that treatment of native de novo coronary lesions with the SES was associated with no in-stent restenosis at 6 months in the RAndomised, double-blind study with the Sirolimus-eluting Bx VElocity balloon expandable stent in the treatment of patients with de novo native Coronary artery Lesions (RAVEL) trial.[3] However, the fate of side branches after SES implantation is unknown. Side branch occlusion, a well-recognized complication of percutaneous coronary stenting, was reported to develop in up to 19% of cases.[4–11] However, the incidence of spontaneous recanalization at follow-up of occluded side branches is controversial. The reported rate varies from 35% to 100%.[4,7,8,10,12] Furthermore, Cottin et al[13] demonstrated the absence of spontaneous recanalization of occluded side branches in patients with in-stent restenosis followed by intracoronary radiation therapy. Debruyne et al[14] also reported that the rate of spontaneous recanalization following stent implantation with brachytherapy was lower than that observed without brachytherapy. In addition, they described a higher rate of delayed side branch occlusion in the brachytherapy group. Sirolimus is a potent immunosuppressive agent that induces cell-cycle arrest in the late G1 phase, which inhibits the proliferation of smooth muscle cells and reduces intimal thickening.[15–17] Thus, the hypothesis tested in this study is that sirolimus might potentially behave the same way as brachytherapy, and have the potential to cause a delayed healing process. We consequently also hypothesized that the rate of spontaneous recanalization of side branches occluded after SES implantation would be lower than that after uncoated metal stent (UMS) implantation.

METHODS

Patient group: From August 2000 to January 2001, 238 patients were enrolled in the RAVEL trial.[3] They had a single de novo lesion of a native coronary artery that could be covered by a single 18-mm stent. Patients were excluded if they had a target lesion involving a side branch >2.5 mm in diameter that would require side branch stenting. Enrolled patients were randomized 1:1 in a double-blind manner to receive either an uncoated metal Bx VELOCITY stent or a sirolimus-eluting Bx VELOCITY stent (Cordis Corp., Johnson & Johnson, Warren, New Jersey). The angiographic follow-up at 6 months after stent deployment included 211 patients, 128 of whom had ≥1 side branches covered by a stent and were part of this

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analysis. All randomized patients signed a written informed consent statement before enrollment.

Study protocol: Lesions were treated by means of conventional interventional techniques. Direct stenting was not allowed. Postdilation was performed as required to achieve a residual stenosis of <20%. Patients received ≥100 mg aspirin daily, indefinitely in addition to either clopidogrel (75 mg once daily) or ticlopidine (250 mg twice daily) for 8 weeks.

Angiographic analysis: Quantitative coronary angiography of the target lesion was performed by an independent core laboratory (Cardialysis BV, Rotterdam, The Netherlands).[18] The reference vessel diameter, minimal lumen diameter, and percent diameter stenosis were measured at baseline and at 6-month follow-up angiography. Late loss was calculated as the difference between the minimal lumen diameter after the procedure and that at follow-up.

Any side branch that was seen on the angiogram before the procedure and subsequently covered by the stent was analyzed by 2 observers who were blinded to allocation. The Thrombolysis In Myocardial Infarction (TIMI) grade flow in the side branch was assessed before and after the procedure. Side branch occlusion was defined as TIMI flow grade 0. The TIMI flow in the side branch was also evaluated on the follow-up angiogram. Spontaneous recanalization was defined as an increase in flow from TIMI grade 0 to ≥1. The side branch was considered to exhibit delayed occlusion if its TIMI flow grade was ≥1 after the procedure, but decreased to 0 at follow-up. Side branches were classified into 4 types by visual assessment: type A (arising within the lesion, with ostial narrowing); type B (arising within the lesion, without ostial narrowing); type C (arising from outside the lesion, with ostial narrowing); and type D (arising from outside the lesion, without ostial narrowing) (Figure 1) Side branches were also classified visually according to their take-off angle from the parent vessel (≤45° or >45°).

Intravascular ultrasound (IVUS) analysis: Fifty-eight patients with 114 side branches in the stented segment underwent IVUS imaging at 6-month follow-up. All images were obtained using an automated pull-back system at 0.5 mm/s. A complete IVUS run was recorded on videotape for off-line 3-dimensional reconstruction. A computer-based contour detection program was used. Stent and lumen boundaries were detected using a minimum cost algorithm. Total stent and lumen volumes were calculated using Simpson's rule. Neointimal hyperplasia volume was calculated as stent volume minus lumen volume.[19] This analysis was performed by the same independent core laboratory.

Statistical analysis: Continuous variables were expressed as mean ± SD and were compared using the 2-tailed Student's *t* test or variance using the Bonferroni adjustment. The chi-square test was used for categorical variables. Logistic regression analysis was performed on all clinical and procedural characteristics to identify the determinants of side branch occlusion. Because there were multiple side branches per lesion, the p values reported for side branch characteristics predictive of occlusion ignore this intracluster correlation effect. A p value <0.05 was considered statistically significant. All analyses were performed using the SPSS for Windows (version 10.0, SPSS Inc., Chicago, Illinois) statistical software package.

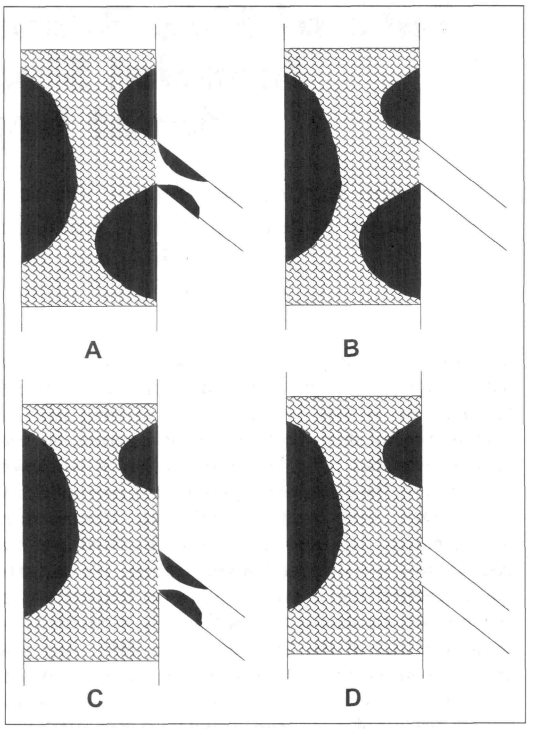

FIGURE 1. Side branch type classification: type A (arising within the lesion, with ostial narrowing); type B (arising within the lesion, without ostial narrowing); type C (arising from outside the lesion, with ostial narrowing); and type D (arising from outside the lesion, without ostial narrowing).

RESULTS

Patient characteristics: Sixty-three patients, who had 63 target lesions and 118 involved side branches, were randomized to receive a SES; 65 patients, who had 65 target lesions and 124 involved side branches, were assigned to the UMS group. With the exception of a higher percentage of men in the UMS group (85% vs 68%, p = 0.03), there were no significant differences between the 2 groups in terms of baseline clinical characteristics such as age, coronary risk factors, prior myocardial infarction, prior coronary angioplasty, and prior coronary bypass surgery.

Angiographic and IVUS characteristics of target lesions: Nearly all treated lesions were American College of Cardiology/American Heart Association type B1 or B2 (91% in the SES group vs 98% in the UMS group, p = 0.14). The reference lumen diameter after the procedure in the SES group (2.63 ± 0.53 mm) was similar to that in the UMS group (2.68 ± 0.58 mm, p = 0.62). The minimal lumen diameters after the procedure in the SES group and in the UMS group were

TABLE 1 Baseline Angiographic and Procedural Characteristics of Side Branches

	SES Group (n = 118)	UMS Group (n = 124)	p Value
TIMI flow before procedure			0.67
0	0 (0%)	0 (0%)	
1	3 (3%)	2 (2%)	
2	6 (5%)	4 (3%)	
3	109 (92%)	118 (95%)	
Side branch classification			0.29
A	45 (38%)	36 (29%)	
B	38 (32%)	52 (42%)	
C	2 (2%)	4 (3%)	
D	33 (28%)	32 (26%)	
Take-off angle >45°	80 (67%)	76 (61%)	0.29
Stent size (mm)	3.1 ± 0.3	3.1 ± 0.3	0.36
Maximal balloon size (mm)	3.2 ± 0.4	3.3 ± 0.4	0.42
Maximal inflation pressure (atm)	14.9 ± 3.1	14.9 ± 2.5	0.97
No. of inflations	3.1 ± 1.5	2.9 ± 1.1	0.19
Duration of inflations (s)	102.6 ± 54.2	84.8 ± 48.5	<0.01*

Data are presented as the mean ± SD or the number (%) of side branches.
*Statistically significant.

TABLE 2 Fate of Side Branches

	SES Group (n = 118)	UMS Group (n = 124)	p Value
Occlusion postprocedure	12 (10%)	9 (7%)	0.42
TIMI flow postprocedure			
Improved	2/9 (22%)	1/6 (17%)	0.79
Deteriorated	25/118 (21%)	16/124 (13%)	0.09
Recanalization at follow-up	11/12 (92%)	6/9 (67%)	0.15
Flow at follow-up			
Improved	24/30 (80%)	13/19 (68%)	0.36
Deteriorated	2/106 (2%)	4/115 (4%)	0.47
Delayed occlusion	2/106 (2%)	0/115 (0%)	0.14

Data are presented as the number (%) of side branches.
TIMI flow after the procedure is compared with that before procedure. The denominator in the "improved" category represents the number of side branches with TIMI flow before the procedure of <3, because TIMI 3 flow cannot improve further. TIMI flow at follow-up is compared with that after the procedure. The denominator in the "improved" category represents the number of side branches with TIMI flow after the procedure of <3. Similarly, the denominator in the "deteriorated" category represents the number of side branches with TIMI flow after the procedure of >0. In the category of "recanalization at follow-up," the denominator represents the number of side branches originally occluded after procedure.

also similar (2.48 ± 0.41 and 2.42 ± 0.46 mm, respectively, p = 0.46). In contrast, the minimal lumen diameter at 6-month follow-up was significantly greater in the SES group (2.40 ± 0.48 mm) than that in the UMS group (1.63 ± 0.59 mm, p <0.001). Thirty patients in the SES group and 28 patients in the UMS group underwent IVUS examination at follow-up. The quantitative IVUS analysis demonstrated that neointimal hyperplasia volume was significantly less in the SES group than in the UMS group (1 ± 1 and 37 ± 26 mm^3, respectively, p <0.001).

Baseline characteristics of side branches: Table 1 lists the baseline characteristics of the side branches. Although the duration of balloon inflation was longer in the SES group, the other characteristics were not different.

Fate of side branches: The fate of the side branches is described in Table 2. Immediately after intervention, occlusion was seen in 12 branches (11 patients) in the SES group versus 9 branches (9 patients) in the UMS group. Myocardial infarction (defined as an increase in creatine kinase enzyme to more than twice the upper limit of normal, accompanied by increased creatine kinase-MB) was documented in 2 patients (1 non–Q-wave myocardial infarciton in the SES group and 1 Q-wave myocardial infarction in the UMS group). Both patients were discharged without anginal complaints. There were no significant differences between the 2 groups in either flow improvement or flow deterioration after the procedure. At 6-month follow-up angiography, 11 of 12 occluded side branches in the SES group showed spontaneous recanalization. Contrary to our hypothesis, this recanalization rate (92%) was not lower than that in the UMS group (67%). Furthermore, the percentage of patients with improvement in TIMI grade flow at follow-up in the SES group was comparable to that in the UMS group. The percentage of side branches in which the flow deteriorated at follow-up was also similar in both groups, including 2 side branches in the SES group that showed delayed occlusion. However, 1 of these had TIMI 2 flow and the other had TIMI 1 flow immediately after the procedure. Table 3 lists the quantitative coronary angiography and IVUS variables in the parent vessels and relates them to the change in side branch flow at follow-up. The side branches were classified into 3 groups based on the flow change during the follow-up period (deteriorated, unchanged, and improved). These data reveal no difference in quantitative analysis among the 3 subgroups.

Predictive factor: By multivariate analysis, the presence of type A side branch morphology was the only independent predictor of side branch occlusion (odds ratio 9.7, 95% confidential interval 3.1 to 30.4). None of the factors examined detected predicted spontaneous recanalization of occluded side branches, even by univariate analysis.

DISCUSSION

The major findings of the present study are as follows: (1) the frequency of side branch occlusion after SES implantation and UMS implantation was similar; (2) SES implantation did not adversely affect the spontaneous recanalization rate of occluded side branches or flow improvement at follow-up; (3) there was no significant difference between the SES group and the UMS group in the rate of delayed side branch occlusion or the rate of flow deterioration at follow-

TABLE 3 Quantitative Coronary Angiography and IVUS Variables in the Parent Vessels in Relation to the Change in Side Branch Flow at Follow-up

	TIMI flow at Follow-up			
	Deteriorated	Unchanged	Improved	p Value
Quantitative coronary angiography at follow-up	(n = 6)	(n = 199)	(n = 37)	
Minimal lumen diameter (mm)	1.90 ± 1.12	2.01 ± 0.63	2.05 ± 0.56	0.84
Late loss (mm)	0.62 ± 1.07	0.45 ± 0.54	0.32 ± 0.46	0.31
IVUS data at follow-up	(n = 5)	(n = 96)	(n = 13)	
Stent volume (mm^3)	140 ± 32	131 ± 35	144 ± 24	0.36
Lumen volume (mm^3)	107 ± 56	114 ± 39	127 ± 35	0.50
Neointimal volume (mm^3)	33 ± 37	17 ± 24	18 ± 28	0.38

Data are presented as the mean ± SD.
TIMI flow at follow-up is compared with that after the procedure.

up; (4) the change in side branch flow during the follow-up period was not directly associated with late loss or neointimal hyperplasia volume in the parent vessel; and (5) the presence of type A side branch morphology was the most powerful predictor of side branch occlusion, and there were no factors that predicted side branch recanalization.

The putative mechanisms of side branch occlusion may include the presence of spasm, dissection, thrombus formation, embolization of plaque debris, ostial compromise by displaced stent struts, and the "snow plow" effect, where the plaque is shifted into the ostium of the side branch from the parent vessel. Because intracoronary nitroglycerin was given to our patients before angiography, spasm is an unlikely explanation. Although SES might have a slightly larger surface area than UMS due to the 5- to 10-μm thick coating, there was no difference in the incidence of side branch occlusion or flow deterioration after the procedure between the 2 treatment groups.

Previous studies have not shown consistent findings with respect to the rate of spontaneous recanalization of occluded branches.[4,7,8,10,12] These inconsistencies may be due to differences in stent design. However, most investigators reported that >60% of side branches that were occluded immediately after stenting had recanalized spontaneously at follow-up. In the present study, both the recanalization rate and the rate of flow improvement were >60% in both groups. Conversely, delayed side branch occlusion was seen in 2 branches (2%) in the SES group and in 0 branches in the UMS group, both of which are consistent with the reported rate of 4% with bare metal stents.[8,10]

This is the first study to evaluate the correlation between the neointimal hyperplasia volume and the change in side branch flow during the follow-up period (Table 3). Neointimal hyperplasia does not seem to play an important role in determining the side branch flow at follow-up because no formal statistical correlation could be demonstrated between these 2 phenomena. Therefore, we speculate that healing of dissection or disappearance of thrombus and emboli may play a role in recanalization of occluded side branches. It is clear that the SES does not adversely affect this process. Conversely, brachytherapy has been associated with a lower rate of spontaneous recanalization in previous studies, probably due to a delayed healing process.[13,14] Furthermore, because brachytherapy delays re-endothelialization, it may predispose to a continued risk of thrombosis of the ostia of side branches. This may explain the higher rate of delayed side branch occlusion following brachytherapy. The fact that no differences were seen in delayed occlusion or flow deterioration during the follow-up period between the SES group and the UMS group is consistent with the observation in animal studies that the SES does not delay re-endothelialization.[20] However, the conclusion that drug-eluting stents do not impair re-endothelialization cannot be generalized to other drug-eluting stents and should be restricted to the particular form of SES with slow release of the specific dose used in this trial. In this regard, it is worth noting that in the First In Man (FIM) and RAVEL trials, not a single case of acute, subacute, or late thrombosis or silent occlusion of the stented vessel occurred despite postprocedural administration of clopidogrel for only 2 months.[1–3]

Study limitations: The main limitation of this study is that it involves a relatively small number of patients and that side branches >2.5 mm were not assessed due to the exclusion criteria of the RAVEL trial. However, in the clinical setting, it is generally necessary to maintain patency of a side branch that is > 2.5 mm in diameter by appropriate techniques. The value of the SES for the treatment of true bifurcation lesions should be prospectively assessed in the future.

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Chapter 5

No Delayed Restenosis at 18 months After Implantation of Sirolimus-Eluting Stent.

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No Delayed Restenosis at 18 Months After Implantation of Sirolimus-Eluting Stent

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Sirolimus-eluting stent is emerging as a potential solution for the prevention of restenosis. Recently, a sustained suppression of neointimal proliferation 12 months after implantation of this stent was reported. This is the first report of angiographic and IVUS images 18 months after the implantation of a sirolimus-eluting stent. ***Cathet Cardiovasc Intervent 2002;57:65–68.*** © 2002 Wiley-Liss, Inc.

Key words: stents; restenosis; drugs

INTRODUCTION

Restenosis remains a significant limitation of percutaneous coronary angioplasty. Although intracoronary radiation therapy has been expected to prevent restenosis, recent studies have revealed some side effects such as edge restenosis, late thrombosis, and late stent malapposition [1–3]. Recently, the technique of local drug delivery with a drug-eluting stent has been developed and considered a potential alternative to provide a solution. Sousa et al. [4] reported a sustained suppression of neointimal proliferation 12 months after implantation of sirolimus-eluting stent. However, there is no report showing angiographic and intravascular ultrasound (IVUS) results more than 12 months after the deployment of a drug-eluting stent. We report the first case with 18-month follow-up angiographic and IVUS images after the implantation of sirolimus-eluting stent.

CASE REPORT

A 37-year-old man with Canadian Cardiovascular Society class IV angina pectoris was referred to our hospital and coronary angiography revealed a stenosis in the proximal segment of the left anterior descending coronary artery (Fig. 1A). The patient was enrolled in the study to evaluate safety and efficacy of sirolimus-eluting stent for treatment of a de novo coronary artery lesion and he gave written informed consent. In February 2000, a 3.5 × 18 mm sirolimus-eluting BX Velocity™ (Cordis Corp., Johnson & Johnson) balloon-expandable stent was deployed, followed by dilatation with a 4.0 × 13 mm balloon at 8 atm. The angiogram showed a successful result (Fig. 1B). IVUS using an Endosonics Visions Five was performed with manual pullback before and immediately after this procedure and showed the stent to be well deployed and apposed (Fig. 2). The patient received aspirin (100 mg/day) and clopidogrel (75 mg/day for 2 months).

At 6 and 18 months after this procedure, he returned to the catheterization laboratory for angiographic and IVUS follow-up examinations required by the protocol without complaints. The angiogram showed no signs of restenosis at either 6 or 18 months (Fig. 1C and D). Quantitative coronary angiography (QCA) was performed offline at each time (CAAS II system, Pie Medical BV). Minimal lumen diameter (MLD) postangioplasty remained basically unchanged at 18-month follow-up (Table I). IVUS images were then obtained using a 2.9 Fr, 30 MHz mechanical ultrasound catheter (Clear View, CVIS, Boston Scientific) with ECG-gated pullback at 0.2 mm/step, which showed that the stent remained well apposed to the vessel wall without any evidence of late neointimal hyperplasia (Fig. 3). ECG-gated image acquisition and digitization were performed using a workstation designed for three-dimensional reconstruction of echocardiographic images (EchoScan, TomTec). Volumetric quantification was performed by means of a Microsoft Windows-based contour detection program developed at the Thoraxcenter [5,6]. Total vessel volume, stent volume, and lumen

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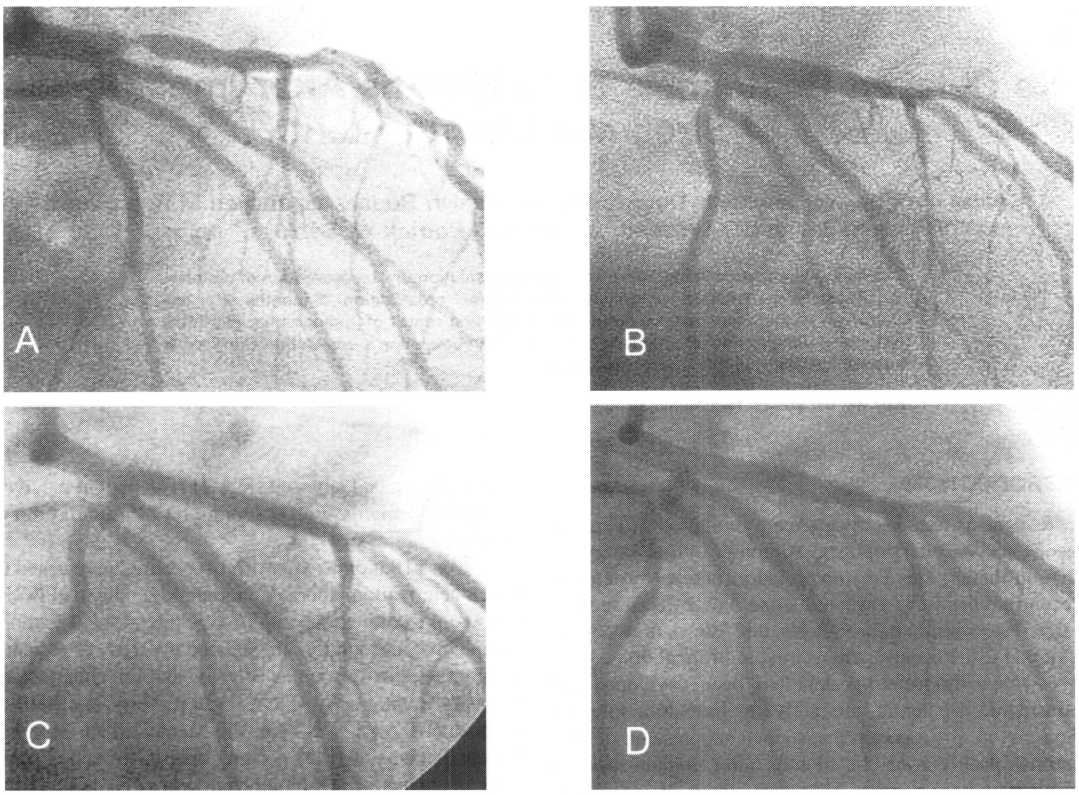

Fig. 1. Left coronary angiograms in right anterior oblique projection showing a stenosis in the proximal segment of the left anterior descending coronary artery (A), a good final angioplasty result (B), and no restenosis at either 6-month (C) or 18-month follow-up (D).

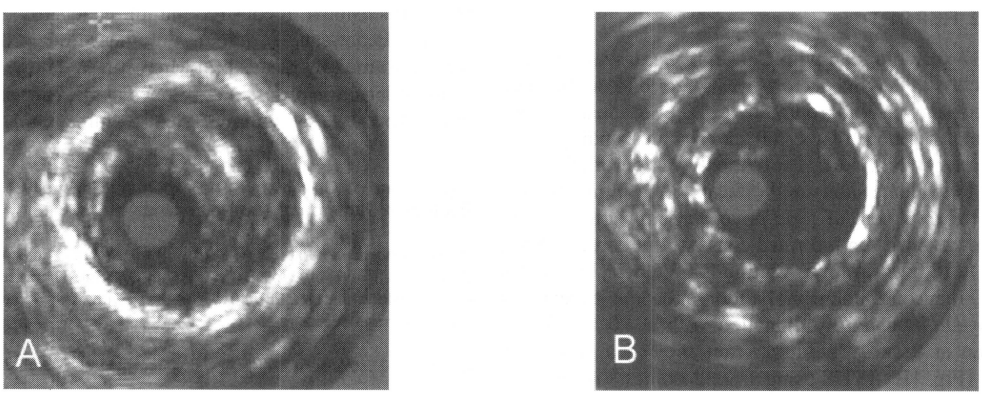

Fig. 2. Cross-sectional IVUS image before procedure (A) shows eccentric and mixed plaque. The image after procedure (B) shows the stent well dilated and apposed.

TABLE I. QCA and IVUS Analysis

	Preprocedure	Postprocedure	6 months	18 months
QCA parameters				
MLD (mm)	0.76	2.95	2.90	2.86
% diameter stenosis	78	15	17	16
IVUS parameters				
Lumen volume (mm^3)			133.9	127.4
Stent volume (mm^3)			135.6	135.0
Vessel volume (mm^3)			310.2	319.4
Neointimal hyperplasia volume (mm^3)			1.8	7.6

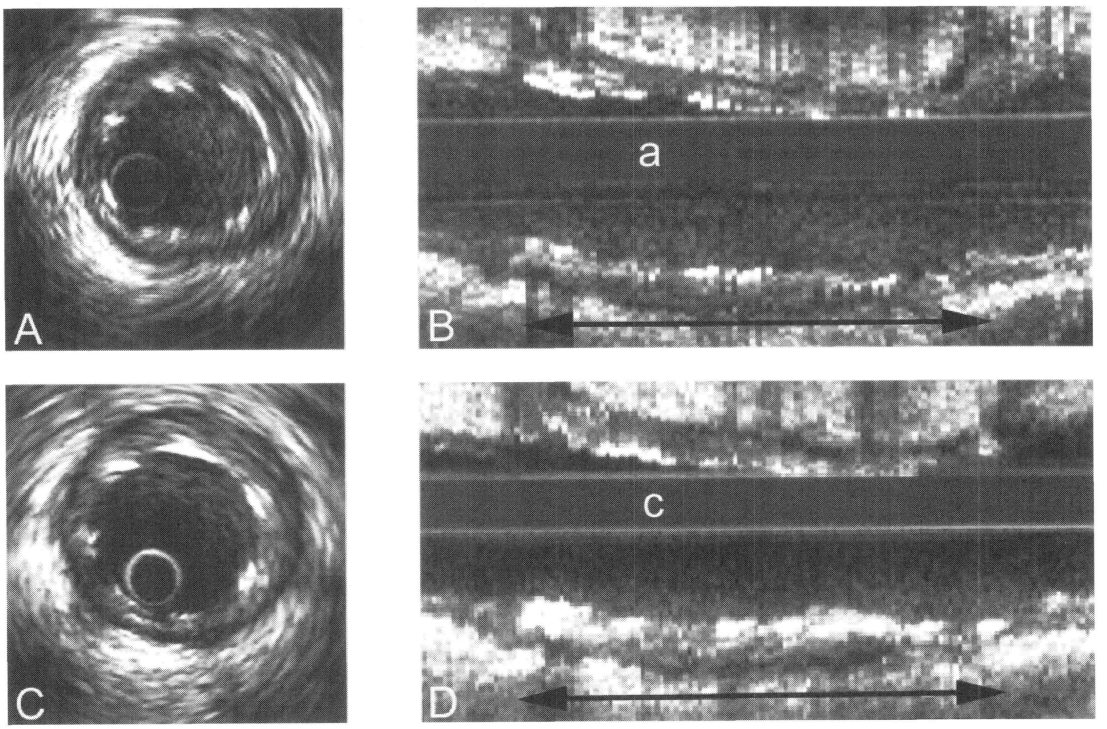

Fig. 3. IVUS images at 6-month (A and B) and 18-month follow-up (C and D) show stent struts well apposed and lack of intimal hyperplasia. Arrows in the longitudinal views (B and D) represent the position of the stent. Cross-sectional views (A and C) are corresponding to the "a" and "c" section of the longitudinal views.

volume at 18-month follow-up were similar to those measured at 6 months (Table I). Thus, a sustained absence of neointimal hyperplasia could be demonstrated up to 18 months.

DISCUSSION

This is the first report of angiographic and IVUS images 18 months after the implantation of a sirolimus-eluting stent. Sirolimus is a potent immunosuppressive agent inducing cell cycle arrest in the late G1 phase, which inhibits the proliferation of smooth muscle cells and reduces intimal thickening [7–9]. The implantation of sirolimus-eluting stent in de novo lesions was shown to be safe and effective in preventing neointimal hyperplasia at 12-month follow-up [4]. In the present case, the efficacy remained unaltered at 18 months without evidence of delayed restenosis, as was seen with radioactive stents [10]. However, to be confirmed, more cases and careful observations are necessary.

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Chapter 6

Persistent inhibition of neointimal hyperplasia after sirolimus-eluting s tent implantation: long-term (up to 2 years) clinical, angiographic, and intravascular ultrasound follow-up.

Degertekin M, Serruys PW, Foley DP, Tanabe K, Regar E, Vos J, Smits PC, van der Giessen WJ, van den Brand M, de Feyter P, Popma JJ. Circulation. 2002;106:1610-

Persistent Inhibition of Neointimal Hyperplasia After Sirolimus-Eluting Stent Implantation

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

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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

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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.

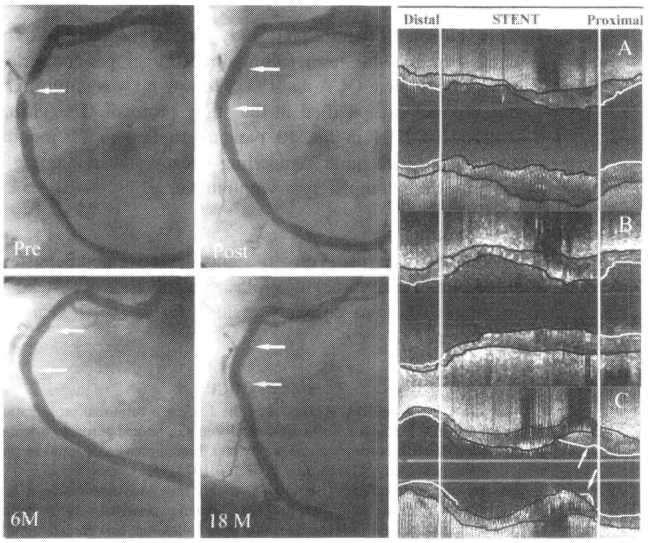

Figure 1. A 38-year-old male with unstable angina and mid-right coronary artery lesion (arrow) treated with sirolimus-eluting Bx-velocity stent. No lumen deterioration was observed at 6- and 18-month follow-up (6M and 18M). Longitudinal IVUS reconstructions demonstrate absence of NIH at 6-month follow-up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

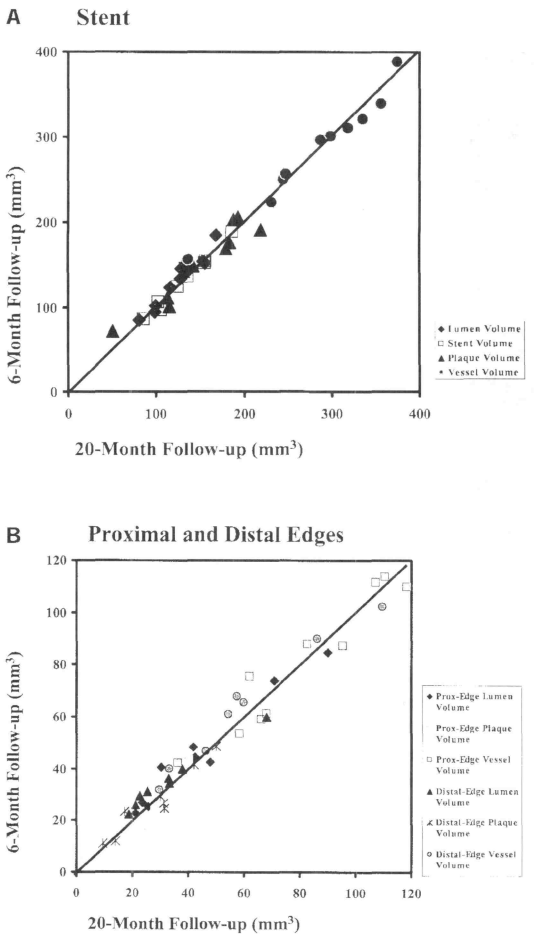

Figure 2. Changes in vessel, plaque, and lumen volume at the sirolimus-eluting stent (A) and peri-stent margins (5-mm proximal and 5-mm distal edges of the stent) (B). Individual data are presented in relation to the line of identity. *P*=NS for 6-month versus 20-month follow-up

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.

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Chapter 7

Sirolimus-eluting stent for treatment of complex in-stent restenosis. The first clinical experience.

Degertekin M, Regar E, Tanabe K, Smits PC, van der Giessen WJ, Carlier SG, de Feyter P, Vos J, Foley DP, Ligthart JM, Popma JJ, Serruys PW. J Am Coll Cardiol. 2003;41:184-9.

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CLINICAL STUDIES **Interventional Cardiology**

Sirolimus-Eluting Stent for Treatment of Complex In-Stent Restenosis

The First Clinical Experience

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OBJECTIVES In this study, we assess the value of sirolimus eluting stent (SES) implantation in patients with complex in-stent restenosis (ISR).

BACKGROUND The treatment of ISR remains a therapeutic challenge, since many pharmacological and mechanical approaches have shown disappointing results. The SESs have been reported to be effective in de-novo coronary lesions.

METHODS Sixteen patients with severe, recurrent ISR in a native coronary artery (average lesion length 18.4 mm) and objective evidence of ischemia were included. They received one or more 18 mm Bx VELOCITY SESs (Cordis Waterloo, Belgium). Quantitative angiographic and three-dimensional intravascular ultrasound (IVUS) follow-up was performed at four months, and clinical follow-up at nine months.

RESULTS The SES implantation (n = 26) was successful in all 16 patients. Four patients had recurrent restenosis following brachytherapy, and three patients had totally occluded vessels preprocedure. At four months follow-up, one patient had died and three patients had angiographic evidence of restenosis (one in-stent and two in-lesion). In-stent late lumen loss averaged 0.21 mm and the volume obstruction of the stent by IVUS was 1.1%. At nine months clinical follow-up, three patients had experienced four major adverse cardiac events (two deaths and one acute myocardial infarction necessitating repeat target vessel angioplasty).

CONCLUSIONS The SES implantation in patients with severe ISR lesions effectively prevents neointima formation and recurrent restenosis at four months angiographic follow-up. (J Am Coll Cardiol 2003;41:184–9) © 2003 by the American College of Cardiology Foundation

Coronary stent implantation is the main therapeutic approach to coronary stenosis in interventional cardiology. Consequently the most common form of restenosis today is in-stent restenosis (ISR). The treatment of ISR remains a therapeutic challenge, as all pharmacological and mechanical treatment modalities have shown disappointing results. The recurrence of ISR was reported to be in the range of 20% to 40% (1,2).

Intracoronary radiation is the only therapy for ISR proven to be effective in randomized clinical trials (3,4). However, restenosis is not eliminated. The wide spread use of brachytherapy is limited by logistic requirements and potential side effects (5,6).

Attention is now focusing on the concept of local pharmacologic intervention by drug-eluting stents. Sirolimus has been shown to be effective in de-novo lesions with a remarkable restenosis rate of 0% in some studies (7,8). These findings provoked considerable enthusiasm (9), but also profound skepticism (10). The major criticism focused on the lack of data in *complex lesions* and on the lack of *long-term* data.

The aim of our study was to evaluate the effectiveness of sirolimus eluting stents (SESs) in preventing neointimal formation in patients with severe ISR.

METHODS

Patient population. Patients with recurrent ISR in a native coronary artery and objective evidence of ischemia were included. The vessel size had to be >2.5 mm and <3.5 mm. Between March and June 2001, 16 consecutive patients were included. All patients signed a written informed consent. The Medical Ethics Committee at our institution had approved the study protocol.

ISR definition. In-stent restenosis was defined as >50% diameter stenosis (DS) by quantitative coronary angiography (QCA) within a previously (at least four months) stented vessel segment. In-stent restenosis was classified as focal (<10 mm long), diffuse (>10 mm long), proliferative (>10 mm long and extending outside the stent edges), or totally occluded (11).

Procedure. All ISR lesions were predilated. Then, a SES Bx VELOCITY (Cordis Waterloo, Belgium) was im-

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Abbreviations and Acronyms

DS = diameter stenosis
ISR = in-stent restenosis
IVUS = intravascular ultrasound
NIH = neointimal hyperplasia
QCA = quantitative coronary angiography
SES = sirolimus eluting stent
TIMI = Thrombolysis In Myocardial Infarction

planted using conventional techniques. The stent was loaded with 140 μg sirolimus/cm^2 metal surface area in a slow release formulation (>28 days drug release). All stents were 18 mm long and 2.5 to 3.5 mm in diameter. Postdilatation was performed as required.

All patients received aspirin (325 mg/day, indefinitely) and clopidogrel (300 mg loading dose immediately after stent implantation followed by 75 mg/day for two to four months at the discretion of the operator).

QCA and intravascular ultrasound (IVUS) analysis. Serial coronary angiography was performed at baseline (before and after intervention) and at four months follow-up. In-stent and in-lesion (stent plus 5 mm proximal and 5 mm distal to the stent) restenosis was defined as >50% DS at follow-up.

The QCA analysis was performed by an independent core laboratory (Brigham and Women's Hospital, Boston, Massachusetts).

Serial IVUS was performed using motorized pullback at a constant speed of 0.5 mm/s postprocedure and at four months follow-up. The quantitative ultrasound analyses were performed by an independent core laboratory (Cardialysis BV, Rotterdam, The Netherlands).

Statistical analysis. Continuous variables are expressed as mean ± standard deviation. Because of the small sample size no statistical comparison was performed. Only the IVUS data were expressed as mean and 95% confidence interval.

Table 1. Baseline Clinical Characteristics

Variable	n (%)
Patients	16
Male gender	12 (75)
Age, yrs	56.9 ± 13.9
Unstable angina pectoris	5 (31)
Multivessel disease	11 (68.7)
Diabetes mellitus	4 (25)
Hypertension	9 (56.2)
Hyperlipidemia	8 (43.7)
Previous MI	9 (56.2)
Previous brachytherapy	4 (25)
Previous CABG	1 (6.2)
Previous heart transplantation	1 (6.2)

Values are n (%) or mean ± SD.
CABG = coronary artery bypass graft surgery; MI = myocardial infarction.

RESULTS

Baseline characteristics. Sixteen patients were included in the study. The patients' demographics are summarized in Table 1. Five patients presented with unstable angina and four patients had diabetes mellitus. Four patients with recurrent ISR after intracoronary beta-brachytherapy and one heart transplant recipient with proliferative ISR were included.

Procedural data. Lesion and procedural characteristics are shown in Table 2. The average length of the restenotic segment was 18.4 ± 13.1 mm: three lesions were focal, five diffuse, five proliferative, and three showed total occlusion of the stent.

A total of 26 SESs were implanted. Nine patients received a single stent, and six patients received two stents to cover long lesions. In one patient with a totally occluded vessel, five SESs were implanted. All patients were discharged without complication one day after the procedure.

Angiographic outcome and three-dimensional IVUS analysis. The QCA data are presented in Table 3 and the IVUS data are shown in Table 4. Satisfactory angiographic results were achieved in 15 out of 16 patients. Representative sequences of angiograms and IVUS from a single patient are shown in Figure 1.

In one patient who received two SESs in an occluded obtuse marginal branch of the circumflex artery, adequate stent expansion could not be achieved despite the use of high pressure (24 atm), noncompliant balloon inflation. The final QCA revealed a residual stenosis of 34%. At follow-up, this patient showed restenosis with silent target vessel occlusion.

Two other patients showed 59% and 62% in-lesion DS, respectively, at follow-up without evidence of cardiac ischemia. The first patient had received two SESs. Both IVUS and angiographic analysis revealed a gap of ~2.2 mm between the two SESs. Neointimal hyperplasia (NIH) occurred precisely at the bare segment between the two

Table 2. Lesion and Procedural Characteristics

Treated vessels	
Left anterior descending	6 (37.5)
Left circumflex	4 (25)
Right coronary artery	6 (37.5)
In-stent restenosis type	
Focal	3 (18.7)
Diffuse intra-stent	5 (31.2)
Proliferative	5 (31.2)
Total occlusion	3 (18.7)
Lesion length, mm	18.4 ± 13.1
Lesion length >10mm	13 (81.2)
Number of previous PCI per lesion	1.68 ± 0.87
Previous implanted stent length (mm)	20.1 ± 6.1
Number of SES per lesion	1.62 ± 1.02
Implanted SES (mm)	28.5 ± 18.0
Implanted SES diameter (mm)	3.01 ± 0.38
Max. inflation pressure (atm)	16.1 ± 3.58

Data are presented as numbers, (relative percentages), or mean ± SD.
PCI = percutanenus coronary intervention; SES = sirolimus eluting stent.

Table 3. Quantitative Coronary Analysis by Core Laboratory

Parameters	15 Patients*
Pre-procedure	
RD, mm	2.68 ± 0.33
MLD, mm	0.59 ± 0.50
DS, %	77.2 ± 18.9
Lesion length, mm	18.4 ± 13.1
Post-procedure	
RD, mm	2.74 ± 0.38
In-lesion MLD, mm	2.23 ± 0.41
In-stent MLD, mm	2.58 ± 0.37
In-lesion DS, %	18.4 ± 10.0
In-stent DS, %	5.44 ± 11.3
Follow-up	
RD, mm	2.73 ± 0.40
In-lesion MLD, mm	1.97 ± 0.82
In-stent MLD, mm	2.36 ± 0.80
In-lesion DS, %	26.9 ± 27.0
In-stent DS, %	11.6 ± 27.3
Restenosis	
In-lesion (%)	2 (13.3)
In-stent (%)	1 (6.7)
Change in MLD	
In-lesion late loss	0.26 ± 0.67
In-stent late loss	0.21 ± 0.62
In-lesion late loss index	0.14 ± 0.38
In-stent late loss index	0.09 ± 0.30

Data are presented as number relative percentages or mean value ± SD. *One patient, who died 3.5 months after the procedure, was not included in this analysis.

DS = diameter stenosis; MLD = minimal luminal diameter; RD = reference diameter.

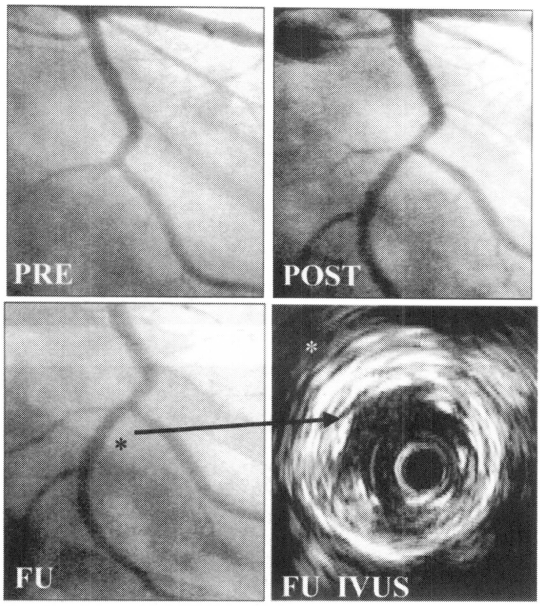

Figure 1. A chronically occluded left circumflex due to in-stent restenosis (PRE) was treated with a sirolimus eluting stent (POST). Follow-up (FU) angiography showed no restenosis; intravascular ultrasound (IVUS) revealed no neointimal hyperplasia with the clear appearance of double stent struts. * indicates the position of the IVUS catheter.

stents (Fig. 2). A repeat intervention was not performed because the patient was asymptomatic, intracoronary pressure measurement showed a fractional flow reserve of 0.80, and the stenosis was assessed as 50% DS by online QCA. The second case was the heart transplanted recipient who had a 62% DS proximal to the stent. The vessel, which had Thrombolysis In Myocardial Infarction (TIMI) grade 1 flow prior to implantation of the SESs, had been extensively ballooned during the procedure and the injured area was not completely covered by SES. As the patient had no evidence of ischemia by radionuclide scintigraphy, repeat revascularization was not performed. All other patients showed only minimal late lumen loss.

In one patient who had previously undergone brachytherapy and showed recurrent ISR associated with a "black hole" (12) (echolucent tissue, rich in proteoglycans and poor in mature collagen and elastin) prior to SES implantation, IVUS showed reappearance of the "black hole" four months after SES implantation without significant stenosis. The eccentric, nonobstructive, echolucent luminal tissue was situated in the proximal portion of the stent.

Nine months clinical outcome. The major adverse cardiac events are summarized in Table 5. One patient with severe three-vessel disease died suddenly 3.5 months after successful implantation of two overlapping SESs in the right coronary artery. Unfortunately, no clinical or autopsy information is available.

The second patient, who had received five SESs, showed no late lumen loss at five months follow-up, but developed an inferior myocardial infarction seven months after the index procedure. This event occurred after the follow-up angiogram three weeks after discontinuing clopidogrel. Angiography revealed a proximal total occlusion of the artery. The patient was treated with thrombus aspiration. Intravascular ultrasound after thrombectomy showed a well-expanded stent without NIH.

Table 4. Volumetric Intravascular Ultrasound Measurements by Core Laboratory

	Post-Procedure		4-Month Follow-Up	
N = 11	Mean	(−95% CI/+95% CI)	Mean	(−95% CI/+95% CI)
Stent length (mm)	20.5 ± 5.9	(16.5/24.4)	20.3 ± 6.3	(16.1/24.5)
Stent volume (mm^3)	159.7 ± 57.3	(121.2/198.2)	158.6 ± 69.3	(112.1/205.2)
Lumen volume (mm^3)	159.7 ± 57.3	(121.2/198.2)	157.1 ± 69.9	(110.1/204.1)
NIH (mm^3)	NA		1.5 ± 3.3	(−0.71/3.73)
Volume obstruction (%)	NA		1.1 ± 2.6	(−0.61/2.85)

CI = confidence interval; NIH = neointimal hyperplasia.

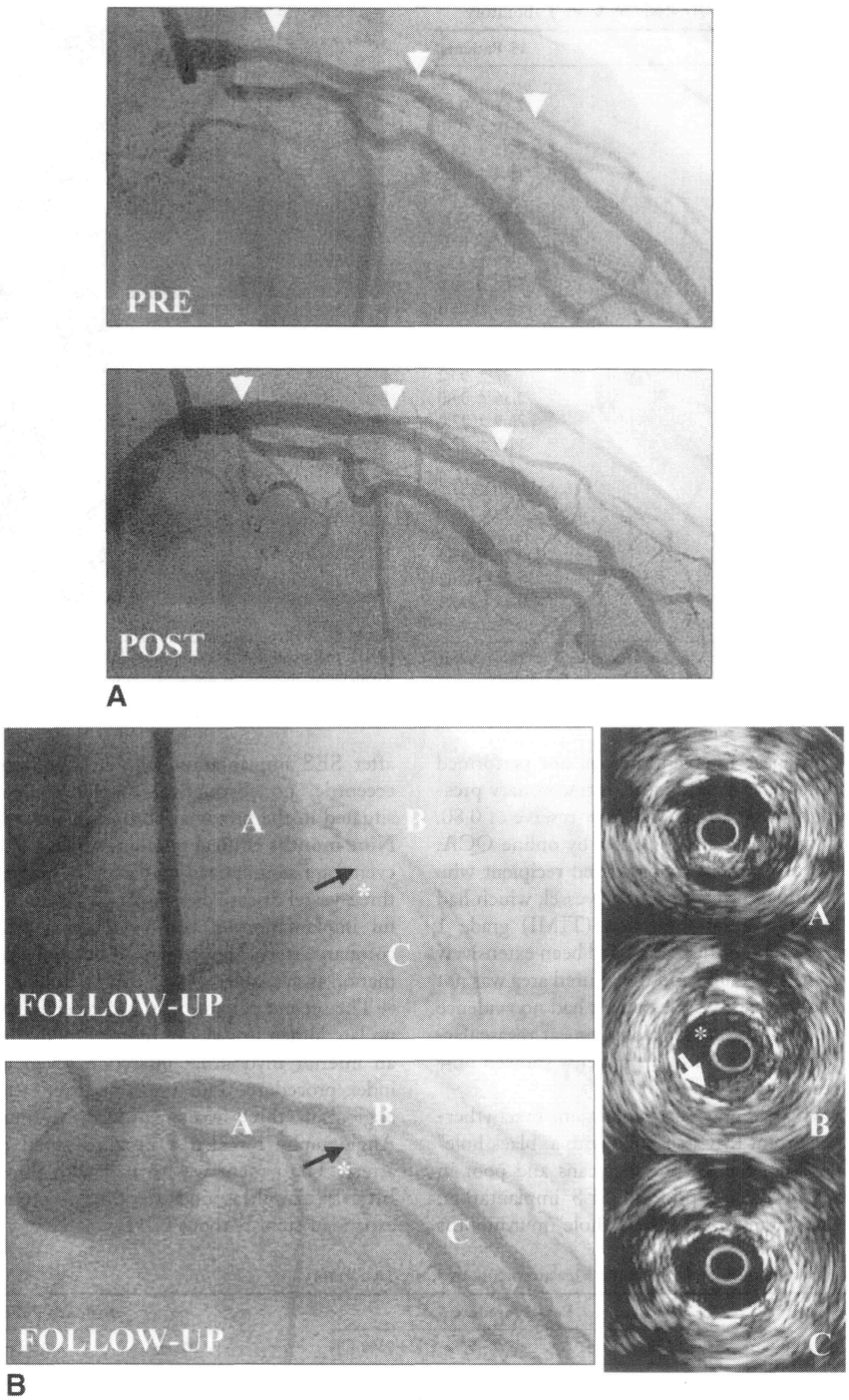

Figure 2. (A) Angiograms: the long proliferative in-stent restonsis (ISR) (PRE) was treated with two sirolimus eluting stents (SESs) (POST). The follow-up angiogram showed focal-repeat ISR (62% DS) in the gap **(arrow)**, which was not covered by the SES. No neointimal hyperplasia (NIH) was evident in the two SESs **(A and C)**. **(B)** Intravascular ultrasound (IVUS): follow-up IVUS showed no NIH in the proximal **(A)** and distal **(C)** SES with images of two layers of stent struts. Neointimal hyperplasia was noted in the gap region **(B)** where only one layer of (bare) stent struts can be seen. * indicates the position of the IVUS catheter at the gap segment.

Table 5. Individual 9-Month Outcome in 16 Patients Treated With Sirolimus Eluting Stent for ISR

Case	ISR Pattern	Number of Previous PCI	Brachytherapy Failure	Length of SES (mm)	30-Day Events	4-Month Events	4-Month Restenosis	9-Month Events*
1	Diffuse	4	Yes	18	No	Death	—	Death
2	Total occlusion	1	No	18	No	No	No	No
3	Focal	3	No	36	No	No	No	Death
4	Total occlusion	1	No	90	No	No	No	Q-MI
5	Focal	2	No	18	No	No	No	No
6	Focal	2	Yes	18	No	No	No	No
7	Proliferative	1	No	36	No	No	No	No
8	Proliferative	1	No	18	No	No	No	No
9	Diffuse	1	No	18	No	No	No	No
10	Proliferative	1	No	18	No	No	No	No
11	Diffuse	1	No	18	No	No	No	No
12	Diffuse	2	Yes	18	No	No	No	No
13	Diffuse	2	No	36	No	No	In-lesion†	No
14	Proliferative	1	No	36	No	No	No	No
15	Total occlusion	2	Yes	36	No	No	In-stent†	No
16	Proliferative	2	No	36	No	No	In-lesion†	No

*Events are death, myocardial infarction (MI), target vessel revascularization (percutaneous transluminal coronary angioplasty/coronary artery bypass graft surgery). †No repeat percutaneous coronary intervention (PCI) was performed. Treatment strategies for restenotic vessels are explained in the Results section.
ISR = in-stent restenosis; SES = sirolimus eluting stent.

The third patient, who had failed brachytherapy, had no evidence of NIH at a four months follow-up IVUS, but died due to congestive heart failure 9.5 months after the index procedure. This 79-year-old man with left main coronary artery disease and congestive heart failure had undergone bypass surgery twice and had percutaneous coronary intervention four times before the index procedure.

DISCUSSION

In this study, we describe the application of SESs in a subset of patients presenting with extremely *complex lesions* and one of the most challenging therapeutic problems today, which is ISR. Notwithstanding the challenging population treated, we found strikingly similar results in terms of suppression of neointimal proliferation to that reported previously in lower-risk patient populations (13). The acute procedural and in-hospital outcome was uneventful. At a four months angiographic follow-up, only one patient with prior total occlusion showed repeat ISR due to silent total reocclusion of the vessel. In the remaining patients, late lumen loss averaged 0.08 mm and volume obstruction within the stent was 1.1%. This is extremely low compared to other treatment strategies, including brachytherapy. By contrast, contemporary studies report a restenosis rate of 45% for bare stent–in-stent implantation with a late lumen loss of 1.36 mm (2). A registry of patients undergoing rotational atherectomy followed by beta-radiation revealed a restenosis rate of 10% with a late lumen loss of 0.37 mm (14).

Important clinical findings. Despite our relatively small patient population, we witnessed some remarkable phenomena. First, we observed NIH in a gap between two SESs and at a site of injury that was not completely covered by the SES. This case illustrates the therapeutic power of SESs, since the patient serves as his own control (Fig. 2).

Second, we monitored the treatment of a patient with severe transplant vasculopathy. The patient presented with a small, diffusely diseased vessel and impaired flow (TIMI grade 1) and received two sequential, overlapping 2.5 mm diameter SESs at the site of ISR. The vessel segment proximal to the stents was treated by balloon dilation. At follow-up there was only minimal NIH within the SESs, and angiographic restenosis occurred at the proximal adjacent vessel segment, outside the stents.

Third, we examined the treatment of patients after failed brachytherapy. We treated four patients who had failed brachytherapy, two of whom developed clinical events. The third patient revealed a reappearance of the "black hole" at follow-up IVUS; nonetheless, no significant stenosis was seen at follow-up angiography. Brachytherapy failure patients were responsible for one-third of all adverse events and represent a particular challenge. These patients can have prolonged endothelial dysfunction that can increase the risk of thrombosis; there are no current data available on the combined effect of radiation and cytostatic drug therapy in coronary arteries.

Late vessel occlusion occurred in two additional patients who had not been treated with brachytherapy. One patient with five drug-eluting stents experienced acute vessel closure and developed myocardial infarction after follow-up angiography and IVUS three weeks after discontinuing clopidogrel. Intravascular ultrasound performed at the time of the acute myocardial infarction showed no evidence of NIH within the stents and thrombus formation as the cause for the occlusion. The second patient who had received two SESs died suddenly and we have to consider this as an acute cardiac and possibly thrombotic event. Therefore, it seems wise to propose that patients receiving more than one SES for the treatment of ISR, particularly in the setting of failed brachytherapy, total vessel occlusion, or poorly deployed stents, should receive clopidogrel for an extended period.

Study limitations. This is a small observational study and only lesions with vessel diameter between 2.5 to 3.5 mm were enrolled. Therefore, the results need to be confirmed by randomized and multicenter trials. Additionally, the study comprises four months angiographic and IVUS follow-up. However, the recently reported long-term data, which demonstrated that the four months results are preserved at one year in de-novo lesions, support the notion that our four months data may be predictive of the long-term findings (13).

Conclusions. Sirolimus eluting stent implantation is an effective treatment for patients with complex ISR, even when they are at an intrinsically high risk for complications. As the use of drug-eluting stents increases, their complexity and the range of indications will expand towards higher risk patient populations. In this setting, stenting the whole area injured by the balloon, overlapping SESs properly, and good stent deployment with low residual stenosis, as well as an appropriate anti-platelet regimen will be the keys to successful treatment. When more than one eluting stent is used to treat long in-stent restenotic lesions, IVUS guidance may be advisable to optimize complete coverage of previously implanted bare metal stents and to ensure that the edges of implanted stents are overlapped.

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Chapter 8

Restenosis rates following bifurcation stenting with sirolimus-eluting stents for de novo narrowings.

Tanabe K, Hoye A, Lemos PA, Aoki J, Arampatzis CA, Saia F, Lee CH, Degertekin M, Hofma SH, Sianos G, McFadden E, Smits PC, van der Giessen WJ, de Feyter P, van Domburg RT, Serruys PW. Am J Cardiol. 2004;94:115-8.

Restenosis Rates Following Bifurcation Stenting With Sirolimus-Eluting Stents for De Novo Narrowings

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The percutaneous treatment of coronary bifurcation stenoses is hampered by an increased rate of subsequent restenosis. The present study reports on the outcomes of a consecutive series of 58 patients with 65 de novo bifurcation stenoses treated with sirolimus-eluting stent implantation in both the main vessel and side branch. At 6 months, the incidence of major adverse cardiac events was 10.3% (1 death and 5 target lesion revascularizations) with no episodes of acute myocardial infarction or stent thrombosis. © **2004 by Excerpta Medica, Inc.**

(Am J Cardiol 2004;91:115–118)

Percutaneous coronary intervention of bifurcation lesions is associated with lower procedural success rates[1] and an increased subsequent rate of major adverse cardiac events (MACEs) and restenosis. Various techniques and strategies have been applied in an attempt to improve outcomes, including kissing balloon dilatation and the use of stent implantation in both branches.[2] The use of adjunctive atherectomy was found to be disadvantageous in the Coronary Angioplasty Versus Excisional Atherectomy Trial (CAVEAT-I) trial.[3] Although there was an improved initial angiographic result with less residual stenosis, this was at the expense of a higher rate of side branch occlusion and acute myocardial infarction. In the long-term, results of angioplasty in bifurcations have been hampered by problems of restenosis, particularly after stent implantation within the side branch.[4,5] Recently, sirolimus-eluting stents (SESs) have demonstrated dramatically reduced restenosis rates in patients with relatively simple lesions.[6,7] We sought to investigate the safety and efficacy of SESs in a consecutive series of unselected patients with de novo bifurcation lesions enrolled in the Rapamycin-Eluting Stent Evaluation At Rotterdam Cardiology Hospital (RESEARCH) registry.[8]

• • •

Since April 2002, SES implantation (Cypher, Johnson & Johnson–Cordis, Miami, Florida) has been used as the default strategy for all patients treated in our institution, as part of the RESEARCH registry.[8] Briefly, this single-center registry aims to evaluate the efficacy of SES implantation in the "real world" of interventional cardiology. All consecutive patients were enrolled, irrespective of clinical presentation and lesion characteristics, and the incidence of MACEs was prospectively evaluated during follow-up. At 6 months, a total of 563 consecutive patients were treated solely with SESs. Of these, 58 patients (10.3%) with de novo bifurcation lesions were treated with SES implantation in both the main and side branches; these patients comprise the present study population. The patients' informed written consent was obtained in accordance with the rules of the institutional ethics committee, which approved the study.

All procedures were performed with standard interventional techniques, except with the use of the SES as the device of choice. The strategy of bifurcation stenting employed and the use of kissing balloon dilatation after procedure was at the operators' discretion. One of 4 methods of stenting was used: T-stenting, culotte stenting, kissing stents, or the "crush" technique. T-stenting and culotte stenting have been previously described.[5,9] Kissing stents involved simultaneous implantation of the stents within both branches, with the proximal edges alongside each other, thereby bringing forward the point of divergence. The crush technique involves positioning both stents, with the proximal part of the side branch stent lying well within the main vessel, while ensuring that the edge of the stent in the main vessel is more proximal than the side branch stent. The side branch stent is deployed first, and the balloon and wire are carefully withdrawn. The main vessel stent is then deployed, thereby crushing the proximal part of the side branch stent.[10] SESs were available in diameters from 2.25 to 3.00 mm and lengths from 8 to 33 mm. During the procedure, intravenous heparin was given to maintain an activated clotting time of ≥250 seconds. All patients were prescribed lifelong aspirin and clopidogrel for 6 months. The use of glycoprotein IIb/IIIa inhibitors was at the discretion of the operator.

Clinical and angiographic follow-up was performed at 6 months. MACEs were predefined as death, myocardial infarction, or target lesion revascu-

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TABLE 1 Baseline Clinical Characteristics (n = 58)

Age (yrs)	63 ± 10
Men	42 (72%)
Hypertension	26 (45%)
Hypercholesterolemia	35 (60%)
Diabetes mellitus	16 (28%)
Current smoker	16 (28%)
Previous myocardial infarction	22 (38%)
Previous coronary angioplasty	5 (9%)
Previous coronary artery bypass surgery	3 (5%)
No. of coronary arteries significantly narrowed	
1	15 (26%)
2	28 (48%)
3	15 (26%)
Presentation with an acute coronary syndrome	18 (31%)

Values are presented as the numbers (relative percentages) or mean value ± SD.

TABLE 2 Lesion and Procedural Characteristics (number of lesions = 65)

Coronary artery treated with bifurcation stenting	
Left anterior descending/diagonal	39 (60%)
Left circumflex/obtuse marginal	16 (25%)
Right coronary/posterior descending	4 (6%)
Left main stem—left anterior descending/circumflex	6 (9%)
Stenting technique	
T-stenting	41 (63%)
Culotte stenting	5 (8%)
Kissing stenting	2 (3%)
Crush stenting	17 (26%)
Kissing balloon dilatation after stenting	20 (31%)
Glycoprotein IIb/IIIa inhibitor use	20 (31%)

Values are presented as the numbers (relative percentages).

larization. The diagnosis of myocardial infarction required an elevation of creatine kinase levels to twice the upper limit of normal, together with an increase in the creatine kinase-MB fraction. Target lesion revascularization was defined as either surgical or percutaneous reintervention driven by significant (>50%) luminal diameter narrowing either within the stent or the 5-mm borders proximal and distal to the stent, and was undertaken in the presence of either anginal symptoms or objective evidence of ischemia.

Coronary angiograms were obtained in multiple views after intracoronary injection of nitrates. For the main branches, 3 coronary segments were subjected to quantitative angiography: in-stent, proximal edge, and distal edge segment. The in-stent analysis encompassed the length of all stents used during the procedure. The proximal and distal edge segment included up to 5 mm from the proximal and distal edge of the total segment treated with the study stents, respectively. For the side branches, 2 segments were analyzed: in-stent and distal edge 5-mm segment. Quantitative coronary angiographic (QCA) analysis was performed using the Cardiovascular Angiography Analysis System II (CAAS II; Pie Medical, Maastricht, The Netherlands). The reference vessel diameter, minimal lumen diameter, and percent diameter stenosis were measured before and after the procedure and at follow-up. The late loss was calculated as the difference between the minimal lumen diameter after the procedure and that at follow-up. Binary restenosis was defined as the presence of >50% diameter stenosis within the target lesion.

Fifty-eight patients with 65 bifurcation lesions were included in this study. Baseline patient characteristics are listed in Table 1. The lesion characteristics and stenting technique utilized are presented in Table 2. At 6 months, the survival-free of MACEs was 89.7%. One patient died after bifurcation stent implantation of the left main stem for an acute myocardial infarction. This patient was admitted in cardiogenic shock, and despite the use of abciximab and intra-aortic balloon pump support, died shortly after the procedure due to left ventricular failure. There were no episodes of acute or subacute stent thrombosis, and no patient had a myocardial infarction. Target lesion revascularization was undertaken in 5 patients (8.6%) as outlined in the following.

TABLE 3 Quantitative Coronary Angiography

	Proximal Segment	In-stent Segment	Distal Segment
Main branch (n = 44)			
Reference diameter (mm)	N/A	2.64	N/A
Minimal lumen diameter (mm)			
Preprocedure	N/A	0.64	N/A
Postprocedure	2.39	2.19	1.86
6-mo follow-up	2.26	2.07	1.85
Diameter stenosis at 6 mo (%)	28.3	22.9	25.4
Late lumen loss (mm)	0.12	0.12	0.01
Restenosis rate (%)	2.3	6.8	0
Side branch (n = 44)			
Reference diameter (mm)		1.99	N/A
Minimal lumen diameter (mm)			
Preprocedure		0.61	N/A
Postprocedure		1.80	1.57
6-mo follow-up		1.49	1.47
Diameter stenosis at 6 mo (%)		31.0	21.9
Late lumen loss (mm)		0.31	0.09
Restenosis rate (%)		13.6	0

Values are presented as mean values or relative percentages.

Of 65 lesions, 6-month angiographic follow-up was performed in 44 lesions. The binary restenosis rate was 22.7% (10 of 44 lesions). QCA data are presented in Table 3. Angiographic restenosis occurred in 4 lesions within the main branch (1 in the proximal segment; 3 in the in-stent segment), yielding a restenosis rate of 9.1%. Angiographic restenosis occurred in 6 of the side branches, all within the in-stent segment. Of these 6 restenoses, 5 occurred at the ostium of side branch after the use of T-stenting (Figure 1). All 4 patients with a restenosis within the main vessel and 1 patient with a restenosis at the ostium of a side branch underwent percutaneous target lesion revascularization with new drug-eluting stent implantation. Directional coronary atherectomy was additionally used in 1 patient. The remaining 5 patients, all with ostial side branch restenoses, were asymptomatic and treated with medical therapy alone.

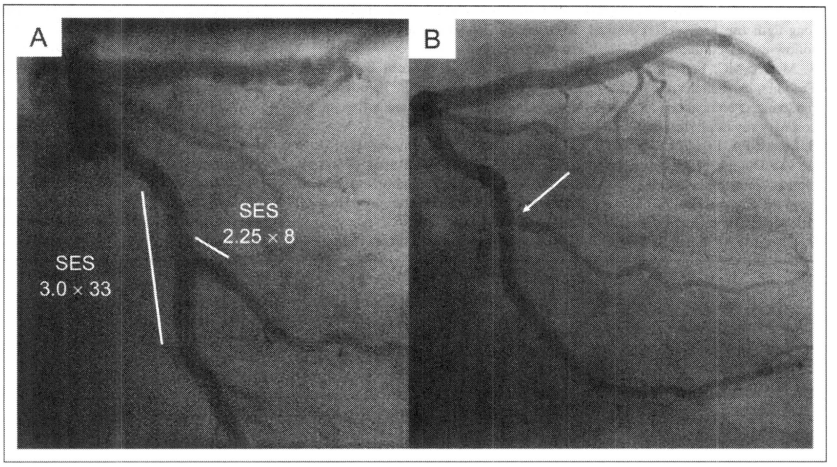

FIGURE 1. A 3.0 × 33 mm SES was implanted in the circumflex artery, and a 2.25 × 8 mm SES was implanted in the side branch (obtuse marginal) with T-stenting technique *(A)*. At 6-month angiographic follow-up, restenosis occurred at the ostium of the side branch *(arrowhead) (B)*.

• • •

The major findings of this study of bifurcation stenting include the following. (1) SES implantation in both the main and side branches is feasible and associated with a low procedural complication rate and no episodes of stent thrombosis. (2) The target lesion revascularization rate of 8.6% is seemingly diminished compared with historical controls. (3) Angiographic restenosis rates of the main and side branches are 9.1% and 13.6%, respectively, with an overall restenosis rate of 22.7%. (4) Five of the 6 restenoses occurring in the side branch were located at the ostium after using the T-stenting technique.

Drug-eluting stent deployment in both vessels to treat bifurcation lesions may raise theoretical concerns that it could result in a propensity to stent thrombosis. When we treat bifurcation lesions with SESs using the culotte, kissing, or crush stenting techniques, there are some overlapping stent struts, where the higher concentration of sirolimus may induce endothelial function impairment and thus be associated with an increased rate of stent thrombosis. Although these stenting techniques were applied in 37% of the lesions treated, no stent thrombosis was reported during follow-up, implying that sirolimus has a wide safety margin.

Several strategies have been advocated to treat bifurcation lesions with percutaneous coronary intervention, such as deployment of stents in both vessels, stenting in 1 branch with balloon angioplasty in the other, and mechanical debulking. The published reports regarding the subsequent need for target lesion revascularization utilizing bare stents range from 17% to 53%[5,11,12]; thus, the rate of 8.6% in our study is very favorable. In addition, the rate observed in the present study may underestimate the true beneficial treatment effect of SES as explained in the following.

Five of the 6 restenoses in the side branch occurred at the ostium after T-stenting. When we apply T-stenting, stent positioning must be extremely accurate to ensure complete coverage of the side branch ostium. This is particularly difficult and/or impossible to achieve when the angle between the 2 branches is much $<90°$. Restenosis at this site may therefore be mainly a reflection of incomplete coverage. The restenosis rate in the side branch following T-stenting was 16.7% (5 of 30 lesions), whereas that following the other stent techniques was 7.1% (1 of 14 lesions). The present study is limited because the choice of strategy was nonrandomized, and there is no comparison with alternative strategies, such as the use of stent implantation in the main vessel alone, with balloon-only angioplasty of the side branch. In addition, the sample size was relatively small, and any difference between the different techniques was not statistically significant. However, our results suggest that it seems wise to ensure the complete coverage of the ostium with SESs using stenting techniques other than T-stenting. The crush technique is technically easier and quicker to do than a culotte, but further data with longer follow-up from a larger population are needed to fully determine the efficacy of these techniques.

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Chapter 9

Significant reduction in restenosis after the use of sirolimus-eluting stents in the treatment of chronic total occlusions.

Hoye A, Tanabe K, Lemos PA, Aoki J, Saia F, Arampatzis C, Degertekin M, Hofma SH, Sianos G, McFadden E, van der Giessen WJ, Smits PC, de Feyter PJ, van Domburg RT, Serruys PW. J Am Coll Cardiol. 2004;43:1954-8.

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Significant Reduction in Restenosis After the Use of Sirolimus-Eluting Stents in the Treatment of Chronic Total Occlusions

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OBJECTIVES The aim of this study was to assess sirolimus-eluting stent (SES) implantation for the treatment of chronic total coronary occlusions (CTO).

BACKGROUND Long-term results after percutaneous coronary intervention (PCI) in the treatment of CTOs is hindered by a significant rate of restenosis and reocclusion. In the treatment of relatively simple nonocclusive lesions, SESs have shown dramatically reduced restenosis rates compared with bare metal stents (BMS), but whether these results are more widely applicable is unknown.

METHODS From April 2002, all patients at our institution were treated with SES as the device of choice during PCI. During the first six months, 563 patients were treated solely with SES, with treatment of a de novo CTO in 56 (9.9%). This CTO cohort was compared with a similar group of patients (n = 28) treated in the preceding six-month period with BMS.

RESULTS At one year, the cumulative survival-free of major adverse cardiac events was 96.4% in the SES group versus 82.8% in the BMS group, $p < 0.05$. At six-month follow-up, 33 (59%) patients in the SES group underwent angiography with a binary restenosis rate (>50% diameter stenosis) of 9.1% and in-stent late loss of 0.13 ± 0.46 mm. One patient (3.0%) at follow-up was found to have reoccluded the target vessel.

CONCLUSIONS The use of SESs in the treatment of chronic total coronary occlusions is associated with a reduction in the rate of major adverse cardiac events and restenosis compared with BMS. (J Am Coll Cardiol 2004;43:1954–8) © 2004 by the American College of Cardiology Foundation

Chronic total occlusions (CTO) are common, and found in approximately one-third of patients with significant coronary disease who undergo angiography (1,2). Percutaneous intervention (PCI) of CTOs accounts for 10% to 15% of all angioplasties; however, after successful recanalization, there is an increased rate of subsequent restenosis and reocclusion compared with nonocclusive stenoses (3,4). Although several randomized trials demonstrated the efficacy of stent implantation over balloon-only angioplasty, even with stents there remains a significant rate of both restenosis (32% to 55%) and reocclusion (8% to 12%) (5–9).

In the treatment of relatively simple lesions, sirolimus-eluting stents (SES) markedly reduce the restenosis rate, with continued benefit documented up to two years follow-up (10,11). Whether these results can be extrapolated to more complex lesions such as CTOs has yet to be determined. We sought to evaluate the effectiveness of the SES in a consecutive series of patients with at least one de novo CTO compared with a similar series treated with bare metal stents (BMS).

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METHODS

Patient population. Commencing in April 2002, all PCI at our institution was done solely with SESs, irrespective of clinical presentation or lesion morphology; these patients comprise the Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital registry (RESEARCH) registry (further details of the methodology are described elsewhere) (12,13). Those deemed at an increased risk of restenosis (including the CTO population) were considered for six-month angiographic follow-up. Sirolimus-eluting stents were available in lengths between 8 mm and 33 mm, and diameters 2.25 mm to 3.0 mm. In the first six months, 563 patients were treated, including 56 (9.9%) with successful revascularization of at least one CTO. These patients make up the present study cohort; all received six months dual antiplatelet therapy with clopidogrel in addition to aspirin. As predetermined by the RESEARCH protocol, this study cohort of patients were compared with all those treated for a CTO in the preceding six months with BMS, identified from the departments' dedicated database. Both groups were treated by the same operators utilizing standard techniques, the only difference being the type of stent. The protocol was approved by the local ethics committee and is in accordance with the principles of Good Clinical Practice

Abbreviations and Acronyms

BMS	= bare metal stent
CTO	= chronic total occlusion
MACE	= major adverse cardiac events
PCI	= percutaneous coronary intervention
RESEARCH	= Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital registry
SES	= sirolimus-eluting stent
TVR	= target vessel revascularization

for Trials of Medicinal Products in the European Community and the Declaration of Helsinki. All patients signed a written informed consent

CTO definition. Chronic occlusion was defined as an occlusion on angiography with no antegrade filling of the distal vessel other than via collaterals. All patients included had a native vessel occlusion estimated to be at least one month's duration (9) based on either a history of sudden chest pain, a previous acute myocardial infarction in the same target vessel territory, or the time between the diagnosis made on coronary angiography and PCI.

Length of occlusion. The length of occlusion was measured by quantitative coronary angiography either utilizing antegrade filling via collaterals, or assessment of the retrograde collateral filling. This was achieved by catheterizing both the left and right coronary arteries, and making a simultaneous injection to delineate the distance between the site of occlusion and the most proximal part of the vessel filled retrogradely.

Follow-up. Patients were followed up prospectively and evaluated for survival-free of major adverse cardiac events (MACE) using questionnaires and telephone enquiries; MACE was predefined as: 1) death; 2) nonfatal myocardial infarction; or 3) repeat target vessel revascularization (TVR). The diagnosis of acute myocardial infarction required an elevation of creatine kinase to twice the upper limit of normal, together with a rise in creatine kinase-MB fraction. Target vessel revascularization was defined as either surgical or percutaneous reintervention driven by significant (>50%) luminal narrowing within the treated vessel, and was undertaken in the presence of either anginal symptoms or objective evidence of ischemia.

Angiographic analysis. Quantitative analysis in those SES patients with follow-up angiography was undertaken in three coronary segments: in-stent (encompassing the entire length of stented segment), and the 5-mm proximal and distal edge segments either side of the in-stent segment. The target lesion comprised the in-stent plus the proximal and distal edge segments. Binary restenosis was defined as >50% diameter stenosis within the target lesion. Late lumen loss was calculated from the difference in minimal lumen diameter between postprocedure and follow-up.

Statistical analysis. Discrete variables are presented as percentages and compared with Fisher exact test. Continuous variables are expressed as mean ± SD and compared with Student *t* test. Survival-free of adverse events was calculated according to the Kaplan-Meier method. The log-rank test was used to compare MACE-free survival between the two groups. All tests were two-tailed, and a p value of <0.05 was considered statistically significant.

RESULTS

The baseline patient and lesion characteristics of the two groups are presented in Tables 1 and 2. One patient in the BMS group underwent successful recanalization and stent implantation in two CTOs, thereby making a total of 29 lesions in this group. Mean length of occlusion could be determined in 45 (80.4%) of the SES group and 17 (58.6%) of the BMS group. There was no significant difference between the groups with respect to the postprocedural quantitative angiography; however, the mean diameter of stent utilized was greater in the BMS cohort.

There were no in-hospital MACE. Clinical follow-up data was obtained in 100% of both groups. There were no deaths in either group; one non–Q-wave acute myocardial infarction occurred related to subacute stent thrombosis 11 days after SES implantation. This was successfully recanalized percutaneously; intravascular ultrasound suggested underexpansion of the SES (2.5 × 33 mm), and the patient was treated with abciximab and balloon dilation of the previously implanted stent. At one year, the cumulative survival-free of MACE was 96.4% in the SES group compared with 82.8% in the BMS group, $p < 0.05$ (Fig. 1). One patient in each group had a reocclusion (1.8% SES group vs. 3.6% BMS group, p = NS).

At six months, 33 (58.9%) patients in the SES group underwent follow-up angiography (none in the BMS group) (Table 3). The binary restenosis rate was 9.1%: one occlusion, one stenosis at the ostium of a side branch after

Table 1. Baseline Patient Demographics

	Bare Stents n = 28	SES n = 56	p Value
Mean age (yrs)	59.8 ± 11.1	60.2 ± 10.0	0.9
Male gender (%)	85.7	71.4	0.2
Current smoker (%)	35.7	26.8	0.5
Diabetes mellitus (%)	7.1	14.3	0.4
Hypertension (%)	39.3	39.3	1.0
Hypercholesterolemia (%)	57.1	55.4	1.0
Previous myocardial infarction (%)	46.4	55.4	0.6
Previous PCI (%)	21.4	12.5	0.3
Previous CABG (%)	0	0	–
Glycoprotein IIb/IIIa inhibitor usage (%)	25.0	21.4	1.0
Presence of multivessel disease (%)	60.7	46.3	0.3
PCI in at least one additional (nonoccluded) major epicardial vessel during the index procedure (%)	28.6	42.6	0.2

CABG = coronary artery bypass grafting; PCI = percutaneous coronary intervention; SES = sirolimus-eluting stents.

Table 2. Baseline Procedural Characteristics

	Bare Stents n = 29	SES n = 56	p Value
Target vessel			0.06
LAD (%)	27.6	51.8	
LCX (%)	27.6	25.0	
RCA (%)	44.8	23.2	
Mean length of occlusion (mm, range)	12.7 (2.4–31.8)	11.3 (4.0–32.1)	0.5
Bifurcation stenting (%)	17.9	14.3	1.0
Mean number of stents in the target vessel	1.8	2.0	1.0
Mean nominal diameter of stent in the main vessel (mm)	3.03 ± 0.56	2.75 ± 0.26	< 0.001
Mean length of stent in the main vessel (mm)	23.31 ± 9.34	23.89 ± 9.21	0.7
Mean total length of overlapping stents in the main vessel (mm, range)	41.8 (18–112)	45.2 (8–117)	0.7
Postprocedure vessel reference diameter (mm)	2.37 ± 0.50	2.35 ± 0.46	0.9
QCA data			
Minimal lumen diameter (mm)	2.18 ± 0.49	2.06 ± 0.48	0.3
Diameter stenosis (%)	10.4	11.6	0.6

LAD = left anterior descending artery; LCX = circumflex artery; QCA = quantitative coronary angiography; RCA = right coronary artery; SES = sirolimus-eluting stents.

T-stenting, and the third at the distal outflow of the SES (this is the same patient with the subacute thrombosis, and restenosis occurred at the site of balloon dilation during the second procedure). The patient with occlusion had undergone bifurcation T-stenting after successful recanalization of a heavily calcified left anterior descending artery. At follow-up, the artery had reoccluded, and there was new akinesis of the left ventricular anterior wall. This patient with occlusion was managed with medical therapy; the other two patients with restenosis underwent percutaneous revascularization.

DISCUSSION

Previous studies have demonstrated the importance of revascularization of CTOs, with improvement in anginal symptoms, exercise capacity, and left ventricular function (14–16). In addition, successful recanalization reduces the subsequent need for bypass surgery and, importantly, long-term evaluation has shown a 10-year survival advantage of 73.5% after successful PCI compared with 65.1% in those with unsuccessful PCI (4,17).

To our knowledge, this is the first report regarding the efficacy of SES in CTOs, a subset of patients previously excluded from other protocols and, importantly, at increased risk of developing restenosis after conventional stent implantation (3). Of the patients who underwent follow-up angiography, both the in-stent and proximal 5-mm segments analyzed showed an encouraging late loss of 0.13 ± 0.46 mm and 0.10 ± 0.80 mm, respectively. The distal 5 mm actually showed an overall benefit, with enlargement of the vessel (late loss, −0.06 ± 0.54 mm).

In addition to the angiographic data, the clinical follow-up is very encouraging. Importantly, there were no significant differences in baseline demographics between the SES and BMS groups, and all procedures were carried out in the same center by the same operators. There was an episode of subacute thrombosis in the SES group, but there appears to be an underlying mechanical cause with underexpansion of the stent documented on intravascular ultrasound. The restenosis rate for BMS is known to be inversely

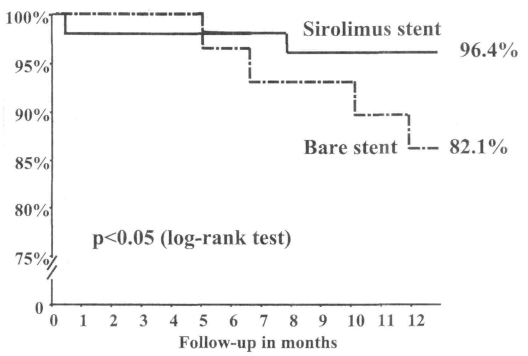

Figure 1. Kaplan-Meier curves for survival-free of death, acute myocardial infarction, or target vessel revascularization.

Table 3. Postprocedural and Six-Month Follow-Up Quantitive Angiographic Data for the Sirolimus-Eluting Stent (Patient Number n = 33)

	Proximal 5 mm	In-Stent	Distal 5 mm
Postprocedure			
Mean diameter (mm)	2.82 ± 0.66	2.58 ± 0.55	2.10 ± 0.64
Minimal lumen diameter (mm)	2.43 ± 0.51	2.04 ± 0.45	1.75 ± 0.53
% Diameter stenosis	14.1	12.9	21.8
Six-month follow-up			
Mean diameter (mm)	3.02 ± 0.53	2.46 ± 0.81	2.12 ± 0.83
Minimal lumen diameter (mm)	2.33 ± 0.90	1.91 ± 0.68	1.81 ± 0.75
% Diameter stenosis	20.1	21.9	18.2
Late lumen loss (mm)	0.10 ± 0.80	0.13 ± 0.46	−0.06 ± 0.54

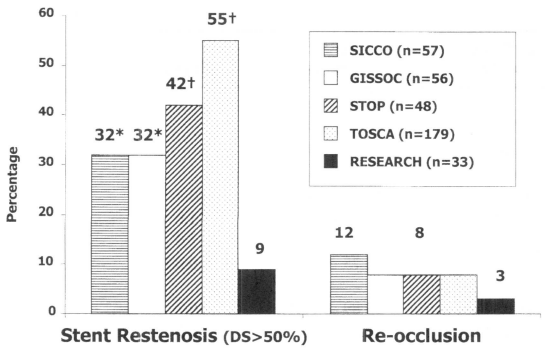

Figure 2. The percentage binary restenosis rate (>50% diameter stenosis) and reocclusion rate of Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital registry (RESEARCH) compared with published data from the patients treated with stent implantation in the randomized trials Stenting in Chronic Coronary Occlusion (SICCO) (5), Gruppo Italiano di Studio sullo Stent nelle Occlusioni Coronariche (GISSOC) (6), Stents in Total Occlusion for Restenosis Prevention (STOP) (7), and the Total Occlusion Study of Canada (TOSCA) (8). DS = diameter stenosis. *$p < 0.05$ compared with the results of RESEARCH; †$p < 0.01$ compared with the results of RESEARCH.

related to the postprocedural minimal lumen diameter and the number of stents utilized (18). In the current study, although the mean diameter of stent used was significantly greater in the BMS cohort (related to a maximum available SES diameter of 3.0 mm) with free utilization of postdilation, the postprocedural minimal lumen diameter was not significantly different between the two groups. The majority of events related to TVR, with, at one year, a significantly higher rate of survival free of MACE of 96.4% in the SES group versus 82.8% in the BMS group.

Four major randomized trials have demonstrated the efficacy of stent implantation over balloon-only angioplasty in the treatment of CTOs, reducing the six-month restenosis rate from 68% to 74%, to 32% to 55% (5–8). Compared with this historical data, our study suggests that the SES confers a marked further advantage with a significantly lower binary restenosis rate of 9.1% ($p < 0.05$) (Fig. 2). In addition, we had only one patient (3.0%) with vessel reocclusion, compared with rates of between 8% to 12% in the same published trials utilizing BMS. A recent study of the clinical results of 376 patients discharged from hospital without an adverse event after successful intervention of a CTO showed, at one-year follow-up, a MACE rate of 12.2% (19); our results are, therefore, quite remarkable, with a MACE-free survival rate of 96.4%.

Study limitations. This study evaluated only a small cohort of patients, and angiographic follow-up was not obtained in all, so additional patients with silent reocclusion cannot be excluded. However, those who did not undergo repeat angiography were all symptomatically well at follow-up. In addition, despite the discrepancy in follow-up angiography rates between the two groups, which might have biased the results towards more revascularization in the SES group, the MACE rate remained statistically significant with a beneficial effect in favor of the SES. The study was not randomized, and used a retrospective comparitive population; however, the same operators and interventional techniques were utilized.

Conclusions. The use of SESs in the treatment of complex patients with CTOs is associated with a reduction in the rate of MACE and restenosis compared with BMS.

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Chapter 10

Effectiveness of sirolimus-eluting stent for treatment of left main coronary artery disease.

Arampatzis CA, Lemos PA, Tanabe K, Hoye A, Degertekin M, Saia F, Lee CH, Ruiter A, McFadden E, Sianos G, Smits PC, van der Giessen WJ, de Feijter P, van Domburg R, Serruys PW. Am J Cardiol. 2003;92:327-9.

Effectiveness of Sirolimus-Eluting Stent for Treatment of Left Main Coronary Artery Disease

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The present study reports on the clinical outcome of 31 consecutive patients with left main coronary artery disease treated with a sirolimus-eluting stent. The implantation of this stent was associated with abolition of post-discharge fatal events and percutaneous reintervention.

(Am J Cardiol 2003;92:327–329)

Several trials have reported on the safety and feasibility of stent implantation to treat left main (LM) coronary disease, with favorable procedural and long-term results.[1–4] However, restenosis remains the major complication limiting late outcome after percutaneous intervention. In patients treated with LM stenting, the occurrence of restenosis has been particularly associated with hazardous clinical manifestations.[5] In this viewpoint, although percutaneous intervention has increasingly been reported as a possible therapeutic alternative, surgical revascularization remains the most appropriate therapy.[6] The sirolimus-eluting stent (SES) (Cypher, Johnson & Johnson–Cordis, Miami, Florida) has recently proved its efficacy to reduce restenosis[7] in selected populations. Importantly, by maintaining all mechanical properties, the late benefit observed with the SES was accomplished without compromising the excellent procedural and acute results already obtained with conventional metallic stents. Currently, the impact of SES implantation on patients with LM disease is unknown. We evaluated the efficacy of the SES on the short- and long-term clinical outcomes in 31 patients treated for LM disease.

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Since April 16, 2002, SES implantation has been adopted as the default strategy for all patients treated in our institution as part of the Rapamycin Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) registry. Briefly, the RESEARCH is a single-center registry whose aim is to evaluate the efficacy of SES implantation in the "real world" of interventional cardiology. All consecutive patients were enrolled irrespective of clinical presentation and lesion characteristics, and the incidence of major adverse cardiac events was evaluated during follow-up. At 6 months after enrollment, a total of 563 consecutive patients were treated solely with SES. Of these, 31 patients (5.5%) were treated for LM artery disease and formed the present study population. In our institution, patients with LM disease are routinely treated with surgical revascularization. Therefore, patients enrolled in this study were divided into 3 groups: (1) 5 patients treated within the acute phase of myocardial infarction, (2) 17 elective patients who were refused surgical treatment due to high preoperative risk (n = 9) or to patient's preference for percutaneous treatment (n = 8), and (3) 9 patients with bailout stenting for LM dissection that occurred during angioplasty (4 had dissection induced by the guiding catheter, 1 due to wire exit, and 3 due to proximal left anterior descending stenting) or during conventional diagnostic procedures (1 patient). The protected LM segment was defined by the presence of a patent coronary artery bypass graft (n = 11). LM dilatation was performed with implantation of a 3.0-mm SES in all patients (largest diameter available at the time of this study). Use of glycoprotein IIb/IIIa agents was left to the operator's discretion. All patients were receiving long-term doses of aspirin (>75 mg/day) and received a loading dose of 300 mg of clopidogrel, followed by a 75-mg daily single dose for 6 months. Patients' informed written consent was obtained in accordance with the rules of the institutional ethics committee that approved the study.

In-hospital outcome information was retrieved by means of an electronic clinical database for patients maintained in our hospital after the procedure and by review of the hospital records for those discharged to secondary hospitals. After discharge, recordings of all repeat interventions (surgical and percutaneous) and repeat hospitalizations were prospectively collected in

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TABLE 1 Baseline Clinical and Procedural Characteristics (n = 31)

	Acute Myocardial Infarction (n = 5)	Bailout Stenting (n = 9)	Elective (n = 17)
Age (yrs)	64 ± 9	65 ± 16	65 ± 9
Men	3 (60%)	4 (45%)	10 (59%)
Hypercholesterolemia (patients treated with hypolipidemic agents or those with serum total cholesterol > 200 mg/dl)	3 (60%)	5 (56%)	12 (70%)
Treated diabetes mellitus	1 (20%)	3 (33%)	7 (41%)
Treated systemic hypertension	0 (0%)	3 (33%)	13 (76%)
Prior myocardial infarction	0 (0%)	3 (33%)	7 (41%)
Prior angioplasty	0 (0%)	2 (22%)	6 (35%)
Prior coronary bypass	0 (0%)	1 (11%)	10 (59%)
Clinical presentation			
Stable angina pectoris		6 (67%)	17 (100%)
Unstable angina pectoris		3 (33%)	0 (0%)
Lesion location			
Ostial	2 (40%)	6 (67%)	5 (29%)
Body	2 (40%)	0 (0%)	1 (6%)
Bifurcation	1 (20%)	3 (33%)	11 (65%)
Stents/patient	3 ± 2.3	4.5 ± 1.9	2.8 ± 1.6
Direct stenting	3 (60%)	9 (100%)	5 (29%)
Use of glycoprotein IIb/IIIa agents	4 (80%)	5 (56%)	5 (29%)
Cardiogenic shock	4 (80%)	0 (0%)	0 (0%)
Hemodynamic assist			
Intra-aortic balloon pump	4 (80%)	1 (11%)	0 (0%)
Left ventricular assistance devise	0 (0%)	0 (0%)	3 (18%)
Quantitative coronary angiography			
Minimal luminal diameter (mm), before	1.31 ± 0.32	1.66 ± 0.65	1.12 ± 0.45
Minimal luminal diameter (mm), after	2.95 ± 0.03	2.67 ± 0.48	2.71 ± 0.60
Reference vessel diameter (mm), after	2.94 ± 0.34	3.18 ± 0.51	3.22 ± 0.60

Values are expressed as mean ± SD or number (%).

a dedicated database. Follow-up information was obtained by regular outpatient evaluation, by phone contact, or by mail.

Clinical outcomes were evaluated by the incidence of major adverse cardiac events, defined as death, myocardial infarction, or any target vessel revascularization, either surgical or percutaneous. Deaths were classified as either cardiac or noncardiac. Deaths that could not be classified were considered to be cardiac related. Procedural success was characterized by Thrombolysis In Myocardial Infarction grade flow 3 and residual in-lesion stenosis ≤30%. Clinical success was defined by the summation of procedural success in the absence of major in-hospital events.

Discrete variables are presented as counts and percentages. Continuous variables are expressed as mean ± SD.

Baseline clinical and procedural characteristics of the study group are listed in Table 1. Overall, unprotected LM disease was present in 20 patients (65%). Four patients with acute myocardial infarction were admitted with cardiogenic shock (80%). Intra-aortic balloon pump or left ventricular assistance devices were used in patients with either hemodynamic compromise (n = 5) or in elective patients deemed to have a very high procedural risk (n = 3).[8] Postdilatation after SES deployment (with 3.5- to 4.5-mm balloons) was performed in 24 patients (77%). The distal LM bifurcation was treated in 15 patients (48%); in these patients, both the parent and side branch vessels received a SES. Segments other than the LM segment were treated in 19 patients (61%).

Table 2 lists the clinical outcomes for patients with acute myocardial infarction, bailout stenting, and elective angioplasty. The incidence of in-hospital major cardiac events was 60%, 11%, and 18% in the 3 groups, respectively. The in-hospital mortality rate in patients with acute myocardial infarction was 60%, in the bailout group 0%, and in elective patients, the rate was 6%. All 3 deaths in the acute myocardial infarction group occurred in patients admitted in cardiogenic shock (2 presented with a totally occluded LM segment). In-hospital repeat revascularization occurred in only 1 patient. This patient had been successfully treated for LM dissection, but developed cardiac tamponade after the procedure and underwent surgical pericardial drainage, during which time he received a venous graft to the first obtuse marginal branch.

Postdischarge complete clinical follow-up is reported in Table 3 and was available for all living patients, except for 1 patient (who could not be contacted). Mean follow-up was 5.1 months (range 3.3 to 6.9). There were no postdischarge deaths, myocardial infarctions, or percutaneous revascularizations. One patient underwent elective minimally invasive coronary bypass (total target vessel revascularization rate of 4%). Initially, this patient had an SES implantation for iatrogenic dissection of the LM segment. This patient's nontreated vessel (chronic, totally occluded left anterior descending artery) underwent elective revascularization 1 month later.

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Recently, several studies have demonstrated that stenting of the LM artery may be a safe and effective alternative to the surgical approach in carefully selected patients.[1,3,4] Although the in-hospital success rates are extremely acceptable, the death rate increases gradually for nearly 6 months after the index procedure, and thereafter reoccurrence of major cardiac events is mainly attributed to progression of atherosclerosis.[5] Solving restenosis apparently is the key to improving the long-term outcome in these patients. The SES has thus far displayed reduced restenosis rates and a reduced need for reintervention.[9,10]

The extremely high in-house mortality rate in the myocardial infarction group mirrors the fatal risk of patients having LM disease in this clinical scenario. Our findings agree with previous studies reporting in-hospital mortality rates of acute myocardial infarc-

TABLE 2 In-hospital Events (n = 31)

	Acute Myocardial Infarction (n = 5)	Bailout Stenting (n = 9)	Elective (n = 17)
Deaths	3 (60%)	0 (0%)	1 (6%)
Myocardial infarction	0 (0%)	0 (0%)	2 (12%)*
Percutaneous revascularization	0 (0%)	0 (0%)	0 (0%)
Coronary bypass	0 (0%)	1 (11%)	0 (0%)
Cumulative rate of major cardiac events	3 (60%)	0 (11%)	3 (18%)

*Both patients with non–Q-wave infarction (patient 1 with peaked creatine kinase-MB [185 IU], patient 2 with 36 IU).

TABLE 3 Post-discharge Events (mean follow-up 5.1 ± 1.8 months, n = 27)

	Acute Myocardial Infarction (n = 2)	Bailout Stenting (n = 9)	Elective (n = 16)
Deaths	0 (0%)	0 (0%)	0 (0%)
Myocardial infarction	0 (0%)	0 (0%)	0 (0%)
Percutaneous revascularization	0 (0%)	0 (0%)	0 (0%)
Coronary bypass	0 (0%)	1 (11%)	0 (0%)
Cumulative rate of major cardiac events	0 (0%)	1 (11%)	0 (0%)

tion due to LM lesions of 55% to 80%.[11,12] The major finding of this report is the absence of fatal events in all patients discharged from the hospital; this study highlights the outstanding performance of the SES. The 0% rate of percutaneous reintervention reinforces the efficacy of the SES.

In the present study, post–high-pressure dilatations with larger balloons were used to optimize stent-to-wall apposition, and overcame the 3-mm width availability of the SES. It is not known whether this (sometimes extreme) postdilatation will affect the elution properties and compromise the polymer's performance. Furthermore, by spreading the struts widely apart, the amount of drug per square millimeter of artery may be reduced and thus impair the efficacy of the SES. However, in this study, the rate of out-of-hospital clinical events was extremely low. Thus, the discrepancy between stent and postdilatation balloon size does not appear to be of clinical significance. Further investigation to confirm this is warranted.

This was a single-center observational study, and our results may have been confounded by unmeasured factors. However, the 0% follow-up mortality rate warrants clinical recognition. The importance of our findings is supported by the fact that our study population was representative of the real world of patients who undergo percutaneous coronary intervention, thus denoting the everyday practice of an interventional cardiologist.

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Part 2. Paclitaxel-Eluting Stent

Chapter 11

Chronic arterial responses to polymer-controlled paclitaxel-eluting stents: comparison with bare metal stents by serial intravascular ultrasound analyses: data from the randomized TAXUS-II trial.

Tanabe K, Serruys PW, Degertekin M, Guagliumi G, Grube E, Chan C, Munzel T, Belardi J, Ruzyllo W, Bilodeau L, Kelbaek H, Ormiston J, Dawkins K, Roy L, Strauss BH, Disco C, Koglin J, Russell ME, Colombo A. Circulation. 2004;109:196-200

Chronic Arterial Responses to Polymer-Controlled Paclitaxel-Eluting Stents

Comparison With Bare Metal Stents by Serial Intravascular Ultrasound Analyses: Data From the Randomized TAXUS-II Trial

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Background—Polymer-controlled paclitaxel-eluting stents have shown a pronounced reduction in neointimal hyperplasia compared with bare metal stents (BMS). The aim of this substudy was to evaluate local arterial responses through the use of serial quantitative intravascular ultrasound (IVUS) analyses in the TAXUS II trial.

Methods and Results—TAXUS II was a randomized, double-blind study with 536 patients in 2 consecutive cohorts comparing slow-release (SR; 131 patients) and moderate-release (MR; 135 patients) paclitaxel-eluting stents with BMS (270 patients). This IVUS substudy included patients treated with one study stent who underwent serial IVUS examination after the procedure and at 6-month follow-up (BMS, 152 patients; SR, 81; MR, 81). The analyzed stented segment (15 mm) was divided into 5 subsegments in which mean vessel area (VA), stent area (SA), lumen area (LA), intrastent neointimal hyperplasia area (NIHA), and peristent area (VA−SA) were measured. NIHA was significantly reduced in SR (0.7 ± 0.9 mm^2, $P<0.001$) and MR (0.6 ± 0.8 mm^2, $P<0.001$) compared with BMS (1.9 ± 1.5 mm^2), with no differences between the two paclitaxel-eluting release formulations. Longitudinal distribution of neointimal hyperplasia throughout the paclitaxel-eluting stent was uniform. Neointimal growth was independent of peristent area at postprocedure examination in all groups. There were progressive increases in peristent area from BMS to SR to MR (0.5 ± 1.7, 1.0 ± 1.8, and 1.4 ± 2.0 mm^2, respectively; $P<0.001$). The increase in peristent area was directly correlated with increases in VA.

Conclusions—Both SR and MR paclitaxel-eluting stents prevent neointimal formation to the same degree compared with BMS. However, the difference in peristent remodeling suggests a release-dependent effect between SR and MR. **(*Circulation*. 2004;109:196-200.)**

Key Words: stents ■ restenosis ■ drugs ■ angioplasty

Stent-based local drug delivery with a number of different types of pharmacological agents has been demonstrated to reduce neointimal hyperplasia within the stent.[1–3] However, late chronic arterial responses to drug-eluting stents have not yet been fully characterized. Even the arterial responses to bare metal stents remain controversial as to whether peristent remodeling occurs after stent implantation.[4–8] Furthermore, in studies detecting peristent remodeling, its relation to the amount of neointimal hyperplasia is controversial.[5,6]

Paclitaxel interferes with microtubule function, which leads to the inhibition of cell division and migration, thereby

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Dr Guagliumi has a consultant agreement with Boston Scientific Corp, the manufacturer of the stents that are the subject of this article; Drs Koglin and Russell are full-time employees of the company. Additionally, the TAXUS II Study was sponsored by Boston Scientific, and the hospital received a study grant from the company.

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interrupting the restenotic cascade.[9] Early clinical feasibility trials suggested paclitaxel-eluting stents as a safe and potentially efficacious way to treat de novo lesions and in-stent restenosis.[10,11] These promising preliminary results were confirmed by the randomized, double-blind, TAXUS II trial, which showed significant improvement in clinical, quantitative angiography and intravascular ultrasound (IVUS) parameters of restenosis.[2] The aim of this study was to evaluate the arterial responses to paclitaxel-eluting stents through the use of serial quantitative IVUS analyses in the TAXUS II trial.

Methods

Patient Selection

Between June 2001 and January 2002, the TAXUS II trial at 38 sites enrolled 536 patients who were randomly assigned (1:1) into 2 consecutive and independent cohorts. Patients in the first cohort received either the TAXUS-NIRx slow-release formulation (SR) paclitaxel-eluting stent or the control bare metal stent (BMS). Those in the second cohort were randomly assigned to either the TAXUS-NIRx moderate-release formulation (MR) paclitaxel-eluting stent or the BMS. Patients were eligible if they had a single de novo target lesion of a native coronary artery with an estimated stenosis between 50% and 99%, lesion length <12 mm, and vessel diameter between 3.0 and 3.5 mm. The current IVUS substudy included patients who received one study stent and underwent serial IVUS examination after the procedure and at 6-month follow-up. The study protocol was approved by the ethics review committees for all participating centers. All patients gave written informed consent before enrollment.

Study Device and Procedure

The stent used in this study was the NIR Conformer stent (Boston Scientific Corporation and Medinol Ltd). All stents were 15 mm long and 3.0 or 3.5 mm in diameter. The paclitaxel-eluting stent (TAXUS NIRx) was identical to the BMS except that it was coated with a total load of 1.0 $\mu g/mm^2$ of paclitaxel incorporated into a proprietary polymer (Translute) that provides controlled biphasic release. For both stents, the initial burst release over the first 48 hours after implantation is followed by a low-level release phase for approximately 10 days. The difference between both stents is an 8-fold-higher release rate in the initial burst of the TAXUS-MR stent when compared with the TAXUS-SR stent.

The balloon predilation procedure was performed followed by study stent implantation, with the use of standard techniques. A postdilation procedure was performed if necessary. There were no objective angiographic or IVUS criteria for ensuring optimal stenting. During the procedure, intravenous heparin was given to maintain an activated clotting time ≥250 seconds. All patients received a 300-mg clopidogrel loading dosage followed by 75 mg daily (or 250 mg ticlopidine twice daily) for 6 months and 75 mg aspirin daily indefinitely.

Quantitative Angiographic and IVUS Analysis

Quantitative coronary angiographic (QCA) and IVUS analyses were performed by an independent core laboratory that continues to be blinded to treatment allocation (Cardialysis). IVUS was performed with an automated pullback at 0.5 mm/s to examine the stented vessel segments. The lumen, stent, and external elastic membrane (EEM) contours were detected with the use of CURAD QCU analysis software (Curad BV), applying 3-D reconstruction, as described elsewhere.[12] If the EEM could not be detected (because of extensive calcification with acoustic shadowing), that patient was excluded from this substudy. For the analysis of the longitudinal distribution, the stented segment was arbitrarily divided into 5 subsegments, each 3 mm long, as previously described.[13–15] In the stented segment and in each subsegment, mean total vessel area (VA), mean stent area (SA), and mean lumen area (LA) were measured. Mean neointimal hyperplasia area (NIHA) and peristent area (PSA) were derived by SA−LA and VA−SA, respectively. Percentage of NIHA and PSA were calculated as NIHA/SA×100 and PSA/VA×100, respectively.

TABLE 1. Baseline Clinical and Procedural Characteristics

	BMS	Taxus SR	Taxus MR
No. of patients	152	81	81
Age	59.2±9.8	60.5±10.2	59.1±10.2
Male, %	78.9	71.6	74.1
Current smoker, %	26.3	25.9	25.9
Diabetes mellitus, %	13.8	11.1	14.8
Hypertension, %	60.5	61.7	58.0
Hypercholesterolemia, %	73.0	80.2	72.8
Unstable angina, %	32.2	32.1	31.3
Prior MI, %	44.7	42.0	35.8
Target vessel, %			
LAD	48.7	37.0	42.0
LCx	11.8	19.8	24.7*
RCA	39.5	43.2	33.3
Balloon artery ratio	1.1±0.2	1.1±0.2	1.1±0.2
Maximal inflation pressure, atm	12.1±2.6	12.4±2.8	12.0±3.0
Stent size, mm	3.23±0.25	3.30±0.25	3.22±0.25
Reference vessel diameter, mm	2.71±0.38	2.81±0.43	2.72±0.43

Values are presented as relative percentages or mean±SD. LAD indicates left anterior descending artery; RCA, right coronary artery; and LCx, left circumflex artery.

*$P<0.05$ vs BMS group.

Statistical Analysis

Pooling of the BMS groups of the two cohorts were combined because the baseline and 6-month follow-up data showed no significant differences. Therefore, 3 groups are reported in this study: the combined BMS, the TAXUS-SR, and the TAXUS-MR groups. Discrete variables are displayed as percentages and tested with Fisher's exact test. Continuous variables are expressed as mean±SD. In general, analyses were performed on a per-patient basis; if indicated, analyses were performed on a per-segment basis. Delta values (Δ) for each measurement were calculated as follow-up minus postprocedure values. When comparing 3 groups, overall probability values were derived from 1-way ANOVA. Comparisons between postprocedure and 6-month follow-up were performed with a 2-tailed paired t test. Comparisons between 2 groups were performed with Fisher's least significant difference test. Linear regression was performed on a per-segment basis to assess the correlation between IVUS indexes. A value of $P<0.05$ was considered statistically significant.

Results

Baseline Characteristics

Of the 536 randomly assigned patients, 314 with serial and analyzable IVUS entered this substudy (BMS, 152; SR, 81; MR, 81). There were 5 subsegments analyzed per patient yielding a total of 1570 subsegments. The patients' baseline clinical and procedural characteristics are shown in Table 1. In this subgroup, the left circumflex coronary artery was more frequent as a target vessel in the TAXUS-MR group compared with the BMS ($P=0.015$). The other baseline characteristics were comparable among the 3 groups.

TABLE 2. Quantitative IVUS Data

	BMS	Taxus SR	Taxus MR
No. of patients	152	81	81
Postprocedure			
Mean VA, mm^2	16.3±3.4	16.9±3.6	16.2±3.7
Mean SA, mm^2	8.2±1.6	8.6±1.8	8.4±1.9
Mean LA, mm^2	8.2±1.6	8.6±1.8	8.4±1.9
Mean PSA, mm^2	8.1±2.5	8.3±2.3	7.8±2.4
% PSA, %	48.9±7.7	48.5±6.3	47.5±6.8
6-mo follow-up			
Mean VA, mm^2	16.9±3.4	18.0±4.0	17.7±4.2
Mean SA, mm^2	8.3±1.6	8.7±1.9	8.5±2.0
Mean LA, mm^2	6.5±2.0	8.1±1.9*	7.8±2.1*
Mean PSA, mm^2	8.6±2.4	9.3±2.8	9.3±2.7
% PSA, %	50.0±6.7	50.8±6.9	51.6±6.3
Mean NIHA, mm^2	1.9±1.5	0.7±0.9*	0.6±0.8*
% NIHA, %	22.8±17.4	7.4±9.6*	7.7±9.8*

Values are presented as mean±SD.
*$P<0.05$ vs BMS group.

Quantitative IVUS Data

Table 2 summarizes quantitative IVUS parameters analyzed on a per-patient basis. IVUS parameters at postprocedure examination were comparable among the 3 groups. At 6-month follow-up, both the TAXUS-SR (0.7±0.9 mm^2) and the TAXUS-MR (0.6±0.8 mm^2) groups showed a significant reduction in mean NIHA compared with the BMS (1.9±1.5 mm^2; $P<0.001$). As shown in Figure 1, there was a statistically significant increase in mean VA in all groups between postprocedure and follow-up (BMS<TAXUS-SR<TAXUS-MR, ANOVA $P<0.001$). Second, there was an increase in PSA showing the same ranking (ANOVA $P<0.001$). Finally, there were decreases in LA between baseline and follow-up for all groups. This decrease was significantly larger in the BMS (−1.7±1.7 mm^2) than in the SR (−0.6±1.1 mm^2; $P<0.001$) and MR (−0.5±1.3 mm^2; $P<0.001$). However, there were no release-dependent differences in lumen reduction between the SR and the MR groups.

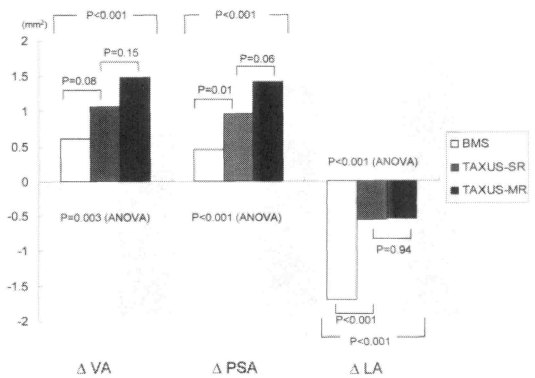

Figure 1. Changes of quantitative intravascular parameters between postprocedure examination and 6-month follow-up.

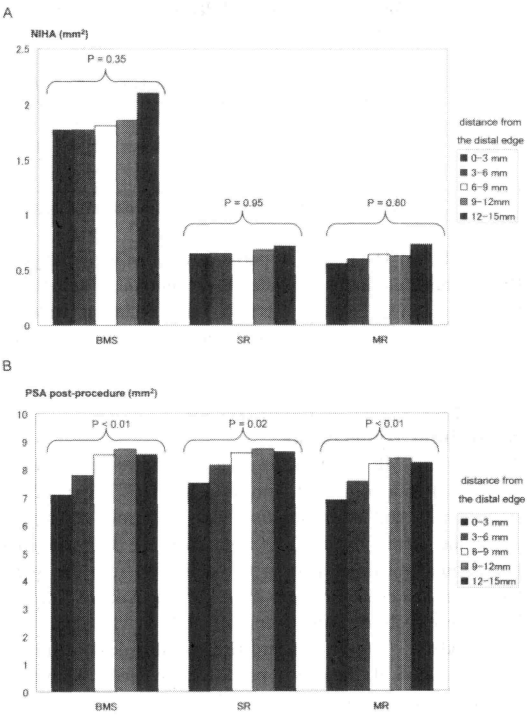

Figure 2. A, Distribution of NIHA at follow-up along the length of the stent. B, Distribution of PSA after the procedure along the length of the stent.

Distribution of Neointimal Hyperplasia

The distribution of neointimal hyperplasia among the 5 subsegments at follow-up in each group is shown in Figure 2A. There was no predilection for neointimal growth to occur within any 3-mm subsegments either in the TAXUS-SR or the TAXUS-MR group nor in the BMS (ANOVA; $P=0.95$, 0.80, and 0.35, respectively). As shown in Figure 2B, the distribution of PSA at postprocedure was not uniform. Therefore, the correlation between IVUS indexes including PSA and VA was analyzed on a per-segment basis.

Correlation Between IVUS Parameters

Table 3 summarizes regression analyses performed between IVUS parameters. In all groups, there was no significant correlation between PSA before the procedure and NIHA at follow-up, suggesting that residual plaque burden after the procedure does not affect neointimal formation. There was a significant positive correlation between ΔVA and ΔPSA in all groups ($P<0.0001$). ΔVA did not correlate with NIHA in either group.

Discussion

The major findings of this study are the following: (1) Both SR and MR paclitaxel-eluting stents inhibit neointimal growth to the same degree when compared with BMS. (2) Peristent remodeling occurs in BMS as well as the TAXUS groups. There are progressive increases in PSA from BMS to

TABLE 3. Summary of Regression Analysis

	BMS			Taxus SR			Taxus MR		
	Coefficient	P	R^2, %	Coefficient	P	R^2, %	Coefficient	P	R^2, %
PSA post vs NIHA follow-up	−0.02	0.47	0.07	0.02	0.39	0.18	−0.02	0.25	0.32
ΔVA vs ΔPSA	0.94	<0.00	68.6	1.01	<0.00	67.0	1.10	<0.00	80.6
ΔVA vs NIHA follow-up	0.04	0.38	0.1	0.02	0.82	0.01	0.04	0.79	0.01

R^2 is presented as percentage. Post indicates postprocedure.

SR to MR. (3) The degree of peristent remodeling (change in PSA) is not quantitatively related to the amount of neointimal hyperplasia. (4) Finally, there is no correlation between plaque burden after the procedure and subsequent neointimal hyperplasia.

Inhibitory Effect of Paclitaxel on Neointimal Hyperplasia

The SR and MR stents showed a significant reduction in neointimal area compared with the BMS by 73% and 79%, respectively, and this inhibition was uniformly distributed along the stent (Figure 2A), indicating the homogeneous longitudinal diffusion pattern of paclitaxel from the stent. Paclitaxel has been shown to exert dose-dependent, antiproliferative effects on smooth muscle cells in vitro and in in vivo models.[9,16] In the standard-risk, de novo lesions treated in the TAXUS II, there was no difference in the neointimal reduction between the two release formulations with differing kinetic profiles. The comparable reduction in neointimal hyperplasia suggests that the critical paclitaxel threshold to interrupt the restenotic cascade had been reached with the SR formulation in this low- risk lesion subset. These two release formations differ in that the polymer matrix regulates the amount of paclitaxel that is released in the early burst phase (first 48 hours), with an 8-fold increase in MR compared with SR.

Effect of Paclitaxel on Stented Tissue Growth (Intrastent and Peristent)

Paclitaxel may allow an increase in cells or matrix behind the stent, while preventing smooth muscle cells from proliferating and migrating into the stent. Figure 3 shows the comparison of the value of ΔPSA+NIHA among the 3 groups. This measure of stented tissue growth (intrastent and peristent) increased from SR<MR<control. This suggests that the increase in cells and/or matrix is less pronounced in the SR formulation. Ongoing studies (TAXUS V and VI) will address the issue of whether different release profiles will alter restenosis outcomes in higher risk lesions.

Peristent Remodeling After Stent Implantation

There is controversy as to whether peristent remodeling occurs after bare stent implantation. In 3 retrospective studies evaluating a total of 121 patients, Mudra et al,[4] Koyama et al,[7] and König et al[8] independently reported that remodeling did not occur. Conversely, the presence of remodeling was reported by 2 groups (Hoffmann et al[5] and Nakamura et al[6]) from an aggregate of ≈100 patients. In this TAXUS II IVUS substudy with more than 300 patients, we establish unequivocally that peristent remodeling occurs in BMS as well as TAXUS stents, and there were increases in PSA from BMS to SR to MR.

Relation Between Peristent Remodeling and Neointimal Hyperplasia

In the previous studies in which peristent remodeling was detected, the relation to the amount of neointimal hyperplasia is conflicting. Nakamura et al[6] reported an inverse correlation, whereas Hoffmann et al[5] demonstrated a positive correlation. In our large, randomized, blinded study with core laboratory analysis, the IVUS data establishes that neointimal hyperplasia is not quantitatively correlated with peristent remodeling in either BMS or TAXUS stents.

Impact of Plaque Burden at Baseline on Neointimal Hyperplasia

Initial plaque burden, referred to as peristent areas (PSAs) in this study, has been suggested to be important in restenosis because it correlated with neointimal hyperplasia in previous IVUS studies.[7,17,18] However, there are more recent reports showing contrasting results.[19,20] Plaque burden may play any number of roles in tissue responses within and out of the stent. On the one hand, it may serve as a source for cells and growth factors involved in the restenotic process; on the other, it may be a physical barrier that buffers the medial injury caused by stent struts and thus it may attenuate neointimal formation. These opposite facets may counteract each other, leading to the disparity in IVUS findings. The TAXUS II data set establishes the absence of a relation

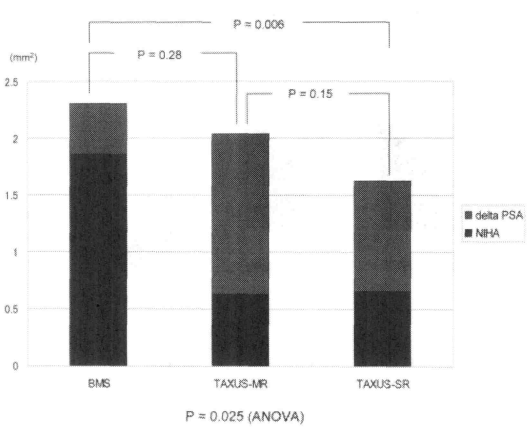

Figure 3. Comparison of the value of Δ PSA+NIHA among the 3 groups.

between plaque burden and neointimal growth in the BMS group.

It is of paramount importance to investigate whether plaque burden affects the efficacy of drug-eluting stents. The size and composition of the plaque may effect drug diffusion, penetration, and activity. We found that for both the SR and MR, there was no relation between plaque burden and neointimal hyperplasia. Since the plaque has no predictive value with respect to neointimal hyperplasia, IVUS assessment of the plaque burden will have no decision-making utility in customizing drug-eluting stents with differing potencies.

Study Limitations

First, the analyses were limited to the patients with serial IVUS, in which the EEM could be well visualized, raising the possibility of selection bias in IVUS sampling. However, this is a randomized, blinded study with a large IVUS sample size compared with previous IVUS studies, which minimizes this bias. Second, patients had relatively low risk profiles and simple lesions related to the inclusion criteria of the TAXUS II trial. Therefore, the results cannot be extrapolated to a general population of diverse patients. Third, this represents a time frame of only 6 months that may not predict subsequent findings or relations identified in this data set.

Conclusions

This study strongly supports the notion that there is no quantitative relation between plaque burden and neointimal hyperplasia after stent implantation. This would argue that the amount of postprocedural plaque burden has no predictive value for the anticipated restenosis rate in the long-term follow-up. By using the sensitivity of IVUS technology in a large cohort of patients, we show that both slow and moderate release of paclitaxel-eluting stents reduce neointimal hyperplasia to the same degree. However, by studying peristent remodeling, we demonstrate release-dependent effects on the global vessel wall response within and around the stent.

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Chapter 12

Vascular responses at proximal and distal edges of paclitaxel-eluting stents: serial intravascular ultrasound analysis from the TAXUS II trial.

Serruys PW, Degertekin M, Tanabe K, Russell ME, Guagliumi G, Webb J, Hamburger J, Rutsch W, Kaiser C, Whitbourn R, Camenzind E, Meredith I, Reeves F, Nienaber C, Benit E, Disco C, Koglin J, Colombo A. Circulation. 2004;109:627-33.

Vascular Responses at Proximal and Distal Edges of Paclitaxel-Eluting Stents

Serial Intravascular Ultrasound Analysis From the TAXUS II Trial

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Background—On the basis of brachytherapy experience, edge stenosis has been raised as a potential limitation for drug-eluting stents. We used serial intravascular ultrasound (IVUS) to prospectively analyze vessel responses in adjacent reference segments after implantation of polymer-controlled paclitaxel-eluting stents.

Methods and Results—TAXUS II was a randomized, double-blind trial with 2 consecutive patient cohorts that compared slow-release (SR) and moderate-release (MR) paclitaxel-eluting stents with control bare metal stents (BMS). By protocol, all patients had postprocedure and 6-month follow-up IVUS. Quantitative IVUS analysis was performed by an independent core laboratory, blinded to treatment allocation, in 5-mm vessel segments immediately proximal and distal to the stent. Serial IVUS was available for 106 SR, 107 MR, and 214 BMS patients. For all 3 groups, a significant decrease in proximal-edge lumen area was observed at 6 months. The decrease was comparable (by ANOVA, $P=0.194$) for patients in the SR (-0.54 ± 2.1 mm^2) and MR (-0.88 ± 1.9 mm^2) groups compared with the BMS (-1.02 ± 1.9 mm^2) group. For the distal edge, a significant decrease in lumen area was only observed with BMS (-0.91 ± 2.0 mm^2, $P<0.0001$); this decrease was significantly attenuated with SR (0.08 ± 2.0 mm^2) and MR (-0.19 ± 1.7 mm^2) stents ($P<0.0001$ by ANOVA). Negative vessel remodeling was observed at the proximal (-0.48 ± 2.2 mm^2, $P=0.011$) but not the distal edges of BMS and at neither edge of SR or MR stents.

Conclusions—The marked reduction in in-stent restenosis with SR or MR stents is not associated with increased edge stenosis at 6-month follow-up IVUS. In fact, compared with BMS, there is instead a significant reduction in late lumen loss at the distal edge with TAXUS stents. **(*Circulation*. 2004;109:627-633.)**

Key Words: angioplasty ■ drugs ■ stents ■ ultrasonics

In-stent restenosis related to neointimal hyperplasia after stent implantation remains a major clinical problem.[1,2] Over the past decade, both systemic pharmacological and novel mechanical treatment strategies to prevent in-stent neointimal hyperplasia have been unsuccessful.[3–5] Only intracoronary radiation therapy has emerged as a promising modality to attenuate the neointimal hyperplasia after stent placement.[6,7] However, initial enthusiasm in the use of radioactive stents has been limited by the occurrence of stenosis in the segments adjacent to the proximal and distal edge of the stent (so-called edge stenosis).[8,9]

Recently, stent-based local drug delivery with a number of pharmacological agents has been demonstrated to reduce in-stent neointimal hyperplasia. Randomized clinical safety and feasibility trials with sirolimus- and paclitaxel-eluting stents have shown very promising results, with prevention of in-stent restenosis in de novo coronary and in-stent restenosis lesions.[10,11] However, initial enthusiasm has been tempered by concerns regarding potential untoward effects. Among these concerns is the possibility that edge effects, analogous to those observed with radioactive stents and after intravascular brachytherapy, might limit the effectiveness of drug-

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eluting stents. In the initial trials with sirolimus-eluting stents (SES), the FIM[12] and RAVEL (RAndomized study with the sirolimus-eluting Bx VELocity balloon-expandable stent)[11] trials, no edge effect was reported. In the SIRIUS trial (a multicenter study of the SIRolImUS-eluting Bx-velocity stent in the treatment of patients with de novo coronary artery lesions), which evaluated SES in a more complex population than RAVEL, a higher rate of significant (>50% diameter stenosis) stenosis was observed at the proximal edge of the SES than at either the stented region or its distal edge (M.B. Leon, MD, unpublished data, 2002). These observations have prompted renewed concern regarding the issue of "edge" stenosis with drug-eluting stents.

In the TAXUS I trial,[10] no edge restenosis was seen with a slow-release (SR) paclitaxel formulation; however, this was a feasibility study that included only 61 patients. The TAXUS II trial compared 2 consecutive cohorts (SR and moderate-release [MR] polymer formulations of paclitaxel-eluting stents) with control bare metal stents (BMS) and mandated serial intravascular ultrasound (IVUS) examinations, which provided a unique opportunity to obtain detailed information on the outcome at vessel segments adjacent to paclitaxel-eluting stents.

Methods

Patient Selection

TAXUS II was a randomized, double-blind, controlled trial conducted in 38 centers. Patients were eligible for inclusion if (1) they had stable or unstable angina pectoris or documented silent ischemia and (2) they were scheduled for treatment of a single significant (>50% stenosis on visual assessment) de novo target lesion in a native coronary artery that could be treated with a single stent (3.0 or 3.5 mm in diameter and 15 mm long). Major exclusion criteria were total vessel occlusion (TIMI grade 0 to 1) before intervention, intervention for evolving myocardial infarction, significant (>50% diameter stenosis) unprotected left main coronary artery stenosis, ostial location of the target lesion, lesion calcification that precluded successful predilation, angiographic evidence of thrombus within the target lesion, left ventricular ejection fraction <30%, or intolerance to aspirin or clopidogrel. The current IVUS substudy included patients who received 1 study stent and underwent serial IVUS examination after the procedure and at 6-month follow-up. The study was reviewed and approved by each participating institution's Ethics Review Committee, and written informed consent was obtained from all patients.

TAXUS (Paclitaxel-Eluting) Stent System

The stent used in the present study was the NIR Conformer stent (Boston Scientific Corporation and Medinol Ltd). The control BMS was an uncoated steel stent (NIRx, Boston Scientific). The TAXUS NIRx stent was coated with proprietary polymer (Translute) designed to control paclitaxel release with an initial burst phase for ≈10 days.[13] All TAXUS stents were coated with paclitaxel (total loaded dose of 1.0 $\mu g/mm^2$). Two paclitaxel-eluting release formulations were evaluated (SR and MR), with an 8-fold higher release rate for the MR formulation in the first 48 hours. All stents were 15 mm long and 3.0 or 3.5 mm in diameter on 20-mm balloon delivery catheters.

Study Design and Procedure

To evaluate the safety and performance of the TAXUS NIRx stent, patients in 2 sequential cohorts were randomized (1:1 ratio), after successful predilation, to receive either the TAXUS or a control NIRx BMS. In cohort 1, patients were randomized to SR or BMS. In cohort 2, patients were randomized to MR or BMS.

Stents were deployed at 10 to 16 atm, and postdilation was performed as necessary to achieve a residual stenosis below 20%. Heparin was administered in intravenous boluses to maintain an activated clotting time >250 seconds for the duration of the procedure and was discontinued within 12 hours. Administration of aspirin (at least 100 mg) was begun 12 hours before the procedure and was continued indefinitely. A loading dose of clopidogrel (300 mg) was administered, preferably 48 hours before the procedure, followed by 75 mg once daily for 6 months.

Quantitative IVUS and Angiographic Analysis

Serial IVUS (after the procedure and at 6-month follow-up) procedures were performed after administration of 200 μg of intracoronary nitroglycerin, with an automated pullback at 0.5 mm/s. All IVUS procedures were recorded on VHS videotapes, and images were digitized for analysis. A computer-based contour detection was performed with QURAD QCU analysis software (Curad BV, Wijk Bij Duurstede) for 3D reconstruction, as described elsewhere.[14] In the quantitative analysis of the edge segments, the vessel segments beginning 5 mm distal to and extending 5 mm proximal to the stented segment were examined. When calcification with acoustic shadowing or side branches were located in the 5-mm segment proximal or distal to the stent, the external elastic membrane contours were not analyzable, which reduced the length of analysis to <5 mm in these segments.

To clarify the mechanism of possible edge responses to drug elution at different distances from the stent struts, we also performed IVUS analysis for each 1-mm subsegment and for the entire 5-mm edge segments. Therefore, both proximal and distal vessel segments were further divided into 1-mm subsegments and numbered from 1 (nearest the stent) to 5. For each subsegment, vessel, lumen, and plaque areas were calculated from each available cross-sectional slice (up to 50 slices/mm) obtained after digitization of the videotapes and were expressed as mean values. Area changes (Δ values) for each measurement were calculated as follow-up minus postprocedure value. To eliminate the influence of vessel size, percent change [(Δ area/postprocedure area$\times$100] was also calculated. The quantitative ultrasound and coronary angiographic analyses were performed by an independent core laboratory that remains blind to treatment allocation during follow-up (Cardialysis).

Statistical Analysis

The BMS groups of the 2 cohorts were combined because the baseline and 6-month follow-up data showed no significant differences, as described previously.[15] Therefore, 3 groups are reported in the present study: the combined BMS, the TAXUS-SR, and the TAXUS-MR groups. Discrete variables are given as percentages and were tested with Fisher's exact test. Continuous variables are expressed as mean±SD. Changes for each measurement were calculated as follow-up minus postprocedure values. When the 3 groups were compared, overall probability values were derived from 1-way ANOVA. Comparisons between postprocedure and 6-month follow-up values were performed with a 2-tailed paired t test, whereas comparisons between 2 groups were performed with Fisher's least significant difference test. A value of $P<0.05$ was considered statistically significant.

Results

Overall, 536 patients, (270 BMS, 135 MR, and 131 SR) were randomized in the TAXUS II trial. IVUS edge analysis could not be performed either in part or in all of the predefined 5-mm edge segments in some patients (n=162) for 1 or more of the following reasons: incomplete image acquisition (23%), inadequate image quality (9%), or the presence of major side branches (68%). Of the 536 patients, 427 with 1 stent and paired IVUS edge analyses (214 BMS, 106 SR, and 107 MR) entered in this substudy. Baseline clinical, demo-

TABLE 1. Baseline Clinical and Procedural Characteristics

Characteristics	Combined Control (n=214)	Taxus SR (n=106)	Taxus MR (n=107)
Age, y	59.9±9.61	61.9±10.4	59.6±10.3
Male	78.5	69.8	72.9
Current smoker	27.6	20.8	22.4
Diabetes mellitus	14.5	11.3	15.0
Hypertension	61.2	61.3	59.8
Hypercholesterolemia	73.7	81.1	77.6
Unstable angina	34.3	34.0	29.2
Prior MI	45.8	39.6	37.4
Target-lesion vessel			
LAD	46.7	39.6	42.1
LCA	14.5	19.8	22.4
RCA	38.8	40.6	35.5
RVD before intervention, mm	2.73±0.44	2.78±0.44	2.73±0.45
Maximum balloon:artery ratio	1.1±0.2	1.1±0.2	1.1±0.2
Maximum inflation pressure, atm	12.4±2.7	12.7±2.7	12.2±2.8
Quantitative angiography at follow-up			
Proximal edge late loss, mm	0.33±0.40	0.18±0.33*	0.16±0.37*
Binary restenosis	2.8 (6/214)	1.9 (2/106)	2.8 (3/107)
Distal edge late loss, mm	0.20±0.38	0.07±0.32*	0.05±0.31*
Binary restenosis	2.3 (5/214)	1.9 (2/106)	0.9 (1/107)
In-stent late loss, mm	0.74±0.44	0.30±0.30*	0.25±0.35*
Binary restenosis	15.9 (34/214)	0.9 (1/106)	0.9 (1/107)

MI indicates myocardial infarction; LAD, left anterior descending artery; LCA, left coronary artery; RCA, right coronary artery; and RVD, reference vessel diameter.

Values are % (count/sample size) or mean±SD.

*$P<0.05$ vs control group.

graphic, and angiographic characteristics were similar among BMS, SR, and MR groups (Table 1). Serial IVUS was available for the proximal edge in 161 BMS, 84 SR, and 84 MR patients and for the distal edge in 191 BMS, 97 SR, and 98 MR patients.

Mean Changes Within the Entire 5-mm Section at Proximal and Distal Edges

Mean vessel area, plaque area, and lumen area of the entire 5-mm edge segment (proximal and distal) were comparable, with no statistically significant differences between the 3 groups immediately after the procedure (baseline) or during the 6-month follow-up (Tables 2 and 3). At the proximal edge, only the control group showed significant constrictive vascular remodeling, with a decrease in mean vessel area of the entire proximal edge from baseline to follow-up ($P=0.011$), whereas neither the SR or MR groups showed any differences (SR, $P=0.689$; MR, $P=07.82$). With a comparably significant increase in mean plaque area in all 3 groups, this still translated into a significant decrease in mean lumen area in all 3 groups (Figure 1).

At the distal edge, the mean plaque and vessel area remained comparable among all 3 groups. However, the lumen area of the entire distal edge differed significantly between control (7.6±2.8 mm^2) and SR (8.4±2.9 mm^2; $P=0.0185$) groups. From baseline to follow-up, the vessel area of the distal edge decreased in the control group, whereas it increased in the SR and MR groups. With a comparable increase in mean plaque area in all 3 groups, this translated into a significant decrease in mean lumen area in the control group compared with a stable lumen area in both the SR and MR groups (Figure 1).

Analyses of the vascular response at the proximal or distal edges of the stent in the 3 groups (BMS, MR, and SR) were also performed for patients who underwent postdilation of the stent and for those who exhibited an early or late malapposition of the stent. No level of statistical significance could be detected between groups with and without postdilation, with or without malapposition. Changes in EEM volume and area, lumen volume and area, and plaque volume and area at the proximal and distal edges of the stent were not statistically different between the MR and SR groups.

Subsegmental Analysis of Longitudinal Changes at 5-mm Edge Segment of Proximal and Distal Edges

In a per-segment analysis that analyzed 5 consecutive 1-mm segments adjacent to the stent, vascular remodeling proximal to the SR and MR stents differed within the first 1-mm subsegment. Although vessel area, plaque area, and lumen area did not differ between the different segments and different groups at baseline, positive vascular remodeling, reflected by an increase in vessel area, was more pronounced

TABLE 2. Serial IVUS Results of Proximal Edge

Proximal Edge	Control (BMS) (n=161)	Taxus-SR (n=82)	Taxus-MR (n=85)	*P* Overall
Vessel area, mm^2				
Postprocedure	16.9±4.3	16.8±4.8	16.6±4.0	0.82
6-Month follow-up	16.4±4.2	16.9±4.5	16.5±4.0	0.70
P	<0.01	0.689	0.782	
Plaque area, mm^2				
Postprocedure	7.7±2.9	7.6±2.9	7.5±2.7	0.81
6-Month follow-up	8.2±2.9	8.2±2.9	8.3±2.9	0.97
P	<0.0005	<0.0005	<0.0005	
Lumen area, mm^2				
Postprocedure	9.2±3.0	9.2±2.9	9.1±2.6	0.93
6-Month follow-up	8.3±2.9	8.7±3.0	8.2±2.4	0.47
P	<0.0001	<0.02	<0.0001	

Numbers are mean±SD.
P=NS for MR vs SR. Overall *P* values are from 1-way ANOVA for continuous variables.

within this first subsegment in the SR and MR groups than in the control group ($P=0.0052$; Figure 2). Together with a comparable increase in plaque area in all 3 groups, this resulted in significantly less lumen area loss in the SR and MR groups (-0.55 ± 2.1 and -0.78 ± 2.0 mm^2) than in the control group (-1.42 ± 2.2 mm^2, $P=0.0055$). Beyond the first proximal segment, the change in lumen area, plaque area, and vessel area did not differ significantly between the SR, MR, and control groups (Figure 2).

At the distal edge, the beneficial effect of SR and MR stents on change in lumen area was evident on all 5 1-mm subsegments distal to the stent. The comparable decrease in plaque area in the first 2 subsegments in all 3 groups was balanced in the SR and MR groups by positive vascular remodeling, reflected by an increase in vessel size. This resulted in stable lumen area in all subsegments in both SR and MR patients, whereas the control group exhibited a significant decrease along all 5 subsegments of the distal edge ($P<0.001$ versus SR and MR).

Difference Between Proximal and Distal Edges

There were no significant differences between proximal and distal edges with respect to percentage changes in either vessel or plaque area among groups. However, although there were no significant differences in percent lumen area change between proximal and distal edges with the BMS (-9.6% versus -8.9%, respectively, $P=0.91$), for TAXUS stents, a significant decrease in lumen area at the proximal compared with the distal edges was seen in both the MR (-7.6% versus 0.04%, respectively, $P=0.01$) and SR (-4.4% versus 3.1%, respectively, $P=0.03$) groups.

Discussion

In the present study, we evaluated the behavior of vessel segments adjacent to polymer-controlled SR and MR paclitaxel-eluting stents (TAXUS) by serial IVUS. The major finding of the study was that the use of TAXUS stents was not associated with a significant increase in edge stenosis compared with BMS. Indeed, the luminal area at the distal edge of

TABLE 3. Serial IVUS Results of Distal Edge

Distal Edge	Control (BMS) (n=187)	Taxus-SR (n=94)	Taxus-MR (n=96)	*P* Overall
Vessel area, mm^2				
Postprocedure	14.7±4.5	14.4±4.3	14.1±4.3	0.54
6-Month follow-up	14.5±4.3	14.8±4.5	14.4±4.1	0.74
P	0.115	0.064	0.103	
Plaque area, mm^2				
Postprocedure	6.3±3.1	6.1±2.8	5.8±2.7	0.45
6-Month follow-up	6.9±3.0	6.4±2.7	6.3±2.7	0.14
P	<0.0001	0.073	<0.02	
Lumen area, mm^2				
Postprocedure	8.4±2.9	8.4±2.7	8.3±3.0	0.88
6-Month follow-up	7.6±2.8	8.4±2.9	8.0±2.8	0.05
P	<0.0001	0.767	0.190	

Numbers are mean±SD.
P=NS for MR vs SR. Overall *P* values are from 1-way ANOVA for continuous variables.

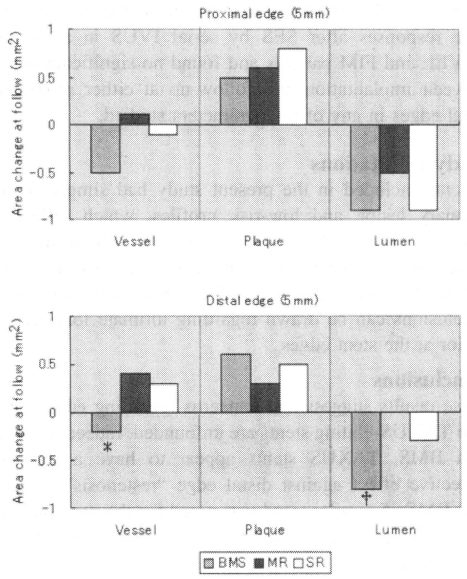

Figure 1. Averaged area changes (follow-up minus postprocedure) for entire 5-mm edge segment in lumen, plaque, and vessel at proximal and distal edge segments. *$P<0.05$, †$P<0.0005$ by 1-way ANOVA.

TAXUS stents was significantly greater than that of BMS at follow-up owing to the occurrence of positive vascular remodeling.

Edge Effects and Restenosis

The inevitable arterial injury due to balloon deployment of a stent coupled with the presence of a metallic foreign body causes inflammatory and proliferative responses.[16] Animal studies have shown that this results in neointimal hyperplasia not only within the stent but also at the edges, in the adjacent reference segments.[17] In the present study, the correlations between intrastent neointimal area and change in proximal/distal plaque area were investigated separately for all 3 groups. The statistical analysis showed that the intrastent neointimal area was correlated with the distal plaque area in each group and correlated with the proximal plaque area in the MR and control groups but failed to be significant in the SR group. These relationships would suggest that the vascular responses at the proximal and distal edges reflect a global responsiveness of the vessel to the degree of neointimal inhibition induced by the drug with both eluting formulations.

The concerns regarding edge effects with a drug-eluting stent reflect potential similarities between the effects of radioactive stents and those of drug-eluting stents, such as local inhibition of neointimal growth and delayed endothelial healing.[18] In patients treated with radioactive stents, edge stenosis has proved to be an important clinical problem, occurring in 30% of patients.[8,19] TAXUS II confirmed that no edge effect greater than that found with a BMS occurs with either MR or SR paclitaxel-eluting stents. As reported previously, the term "edge effect" is used to connote an effect greater than would be seen with BMS.[8,19] In fact, there was a slight but nonsignificant decrease in edge stenosis compared with BMS. Edge stenosis (diameter stenosis >50%) rates for BMS were 3.4% (proximal) and 3.1% (distal), whereas for the SR and MR groups, the rates were 1.6% and 2.3% at the proximal and distal edges, respectively.

In sirolimus-eluting stent trials, no edge stenosis was reported in the FIM and RAVEL trials. However, in the SIRIUS trial, which included patients with more complex lesions than either the RAVEL[11] or TAXUS II trials, edge stenoses, which were more frequently observed at the proximal than at the distal edges and in smaller (<3 mm) vessels, occurred in 5.8% of patients, although the in-stent restenosis rate (3.2%) was similar to that in TAXUS II.

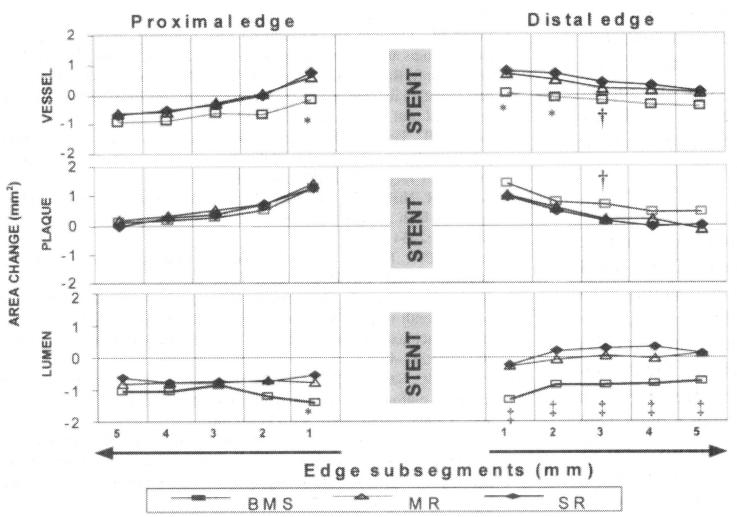

Figure 2. Every 1-mm mean area change (follow-up minus postprocedure) in lumen, plaque, and vessel at proximal and distal edge subsegments. *$P<0.05$, ‡$P<0.01$ by 1-way ANOVA; †$P=0.0052$, BMS vs SR.

Remodeling in Segments Adjacent to the Stent: Insights From IVUS

Previous serial IVUS studies reported that significant lumen loss occurs at the proximal segment after BMS implantation. However, there is controversy as to the mechanism(s) involved. Hoffmann et al[2] and Weissman et al[20] reported that this luminal loss was predominantly related to negative remodeling, whereas Mudra et al[1] suggested that it was related to an increase in plaque burden. In the present study, both BMS and TAXUS stents showed a significant decrease in lumen area in the proximal reference segment at follow-up. Whereas this was due to both negative remodeling and plaque increase in BMS, it was related to plaque increase without significant vessel remodeling in TAXUS stents. Subsegment analysis for BMS demonstrated that in the 2 mm proximal to the stent, lumen loss was exclusively due to plaque increase, whereas more proximally, it reflected both plaque increase and negative remodeling. With TAXUS stents, lumen loss was significantly less than for BMS. This was due to the fact that plaque increase was compensated by positive remodeling. However, there was no statistical argument to suggest the superiority of one eluting formulation over the other.

Previous studies regarding distal edge behavior in BMS have produced conflicting results. Mudra et al[1] reported no significant lumen loss or negative remodeling in the 3 mm distal to BMS edges, whereas Weissman et al[20] reported discordant results showing significant lumen loss throughout the distal reference segment. In the present study, BMS demonstrated significant lumen loss in the distal reference segment without negative remodeling. In detailed subsegment analyses, we demonstrated that lumen loss in the 2 mm distal to the stent edge was related to plaque increase, in accordance with the results of Weisman et al.[20]

In contrast to BMS, TAXUS stents were associated with a beneficial effect on the distal reference segment, where no significant lumen narrowing was observed at follow-up. The subsegment analysis showed that this reflects the fact that positive vascular remodeling compensated for the increase in plaque burden in the reference segment immediately (<2 mm) adjacent to the stent. Possible reasons for the beneficial effects of the drug at the distal edge and for the difference between the behavior of proximal and distal edge segments include higher downstream concentrations of the drug or the relatively smaller distal vessel size.

Previous Drug-Eluting Stent Trials

The IVUS findings in TAXUS II are consistent both with the quantitative angiographic results reported in TAXUS I and II (Table 1) and with the results of the sirolimus-eluting stent trials, all of which showed a decrease in lumen loss, compared with BMS, at the distal edge of the stent. Only 2 studies (Honda et al,[21] and the ASian Paclitaxel-Eluting Stent Clinical Trial [ASPECT][22]) reported serial IVUS edge analysis in small numbers of patients. In the ASPECT study,[22] there were no significant changes at either edge, whereas in the study by Honda et al,[21] there was significant lumen loss at the distal edge. This observation in the latter study is contrary to the findings of the present study. We have recently evaluated edge responses after SES by serial IVUS in a subset of RAVEL and FIM patients and found no significant changes between implantation and follow-up at either proximal or distal edges in any of the parameters studied.

Study Limitations

Patients included in the present study had simple de novo coronary lesion and low-risk profiles, which reflects the inclusion criteria of the TAXUS II trial. The study results cannot be extrapolated to more complex coronary lesions. Furthermore, the follow-up period is relatively short, and no conclusions can be drawn regarding ultimate long-term behavior at the stent edges.

Conclusions

These results suggest that concerns regarding edge stenosis with TAXUS-eluting stents are unfounded. Indeed, compared with BMS, TAXUS stents appear to have a significant protective effect against distal edge "restenosis" compared with BMS. A similar trend was noted for the proximal edge. These effects were observed with both SR and MR formulations.

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Chapter 13

Incomplete Stent Apposition Following Implantation of Paclitaxel-Eluting Stents or Bare Metal Stents: Insights from the Randomized TAXUS II trial.

Tanabe K, Serruys PW, Degertekin M, Grube E, Guagliumi G, Urbaszek W, Bonnier J, Lablanche JM, Siminiak T, Nordrehaug J, Figulla H, Drzewiecki J, Banning A, Hauptmann K, Dudek D, Bruining N, Hamers R, Hoye A, Ligthart JMR, Disco C, Koglin J, Russell ME, Colombo A.
Circulation (in press).

Incomplete Stent Apposition following Implantation of Paclitaxel-Eluting Stents or Bare Metal Stents: Insights from the Randomized TAXUS-II Trial

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Abstract

Background: Clinical impact of late incomplete stent apposition (ISA) for drug-eluting stents is unknown. We sought to prospectively investigate the incidence and extent of ISA post-procedure and at 6-month follow-up of paclitaxel-eluting stents in comparison with bare metal stents (BMS) and survey the clinical significance of ISA over a period of 12 months.

Methods and Results: TAXUS II was a randomized, double-blind study with 536 patients in 2 consecutive cohorts comparing slow release (SR; 131 patients) and moderate release (MR; 135 patients) paclitaxel-eluting stents to BMS (270 patients). This intravascular ultrasound (IVUS) substudy included patients who underwent serial IVUS examination post-procedure and at 6-month (BMS 240 patients, SR 113, MR 116). The qualitative and quantitative analyses of ISA were performed by an independent, blinded core laboratory. More than half of ISA observed post-procedure resolved at 6-month in all groups. There was no difference in the incidence of late acquired ISA among the 3 groups (BMS 5.4%, SR 8.0%, MR 9.5%, p=0.306) with a similar ISA volume (BMS 11.4mm^3, SR 21.7 mm^3, MR 8.5 mm^3, p=0.18). Late acquired ISA was the result of an increase of vessel area without change in plaque behind the stent. Predictive factors of late acquired ISA were lesion length, unstable angina and absence of diabetes. No stent thrombosis occurred in the patients diagnosed with ISA over a period of 12 months.

Conclusion: The incidence and extent of late acquired ISA are comparable in paclitaxel-eluting stents and BMS. ISA is a pure IVUS finding without clinical repercussion.

Condensed Abstract

This IVUS substudy of the TAXUS II trial included 240 patients in the bare metal stent group, 113 in the paclitaxel-eluting slow release group, and 116 in the moderate release group. More than half of post-procedural incomplete stent apposition (ISA) resolved at 6-month in all groups. There was no difference in the incidence or extent of late acquired ISA among the 3 groups. Late acquired ISA was due to an increase of vessel area without change in plaque behind the stent. No stent thrombosis occurred in the patients with ISA, indicating that clinical significance of ISA is benign.

Although intravascular brachytherapy has been proven to be effective in preventing recurrent in-stent restenosis[1], potential issues such as late thrombosis[2], black holes[3], and late acquired incomplete stent apposition (ISA)[4] became evident with its wide clinical application. There was one retrospective intravascular ultrasound (IVUS) registry suggesting that ISA at the time of procedure might be associated with subsequent stent thrombosis[5]. Therefore, late acquired ISA was postulated to contribute to late stent thrombosis following brachytherapy by providing a nidus for thrombus formation[6]. However, there has been no prospective analysis to elucidate the clinical significance of late acquired ISA.

Recently, sirolimus- and paclitaxel- eluting stents have been demonstrated to dramatically reduce restenosis rates[7,8]. Despite these promising results, there remain concerns that these drug-eluting stents may have the same potential risks as brachytherapy with some similarities between the 2 technologies in anti-proliferative effects on vascular smooth muscle cells and endothelial cells. The aims of this prospective IVUS analysis of the TAXUS-II study were: 1) to investigate the incidence of ISA following implantation of paclitaxel-eluting stents and compare it with bare metal stents, 2) to evaluate the extent of ISA quantitatively, and 3) to survey the clinical significance of ISA once the diagnosis has been made.

Methods

Patient selection

Between June 2001 and January 2002, the TAXUS II trial enrolled 536 patients who were randomized into 2 consecutive and independent cohorts[8]. Patients in the first cohort received either the TAXUS-NIRx slow release (SR) paclitaxel-eluting stent or the bare metal stent (BMS). Those in the second cohort were randomized to either the TAXUS-NIRx moderate

release (MR) paclitaxel eluting stent or the BMS. Patients were eligible if they had a single de novo lesion of a native coronary artery with an estimated stenosis between 50 and 99 %, lesion length < 12mm, and vessel diameter between 3.0 and 3.5mm. The current IVUS substudy included patients who underwent serial IVUS examination post-procedure and at 6-month follow-up. The study protocol was approved by the ethics committees for all participating centers. All patients gave written informed consent prior to enrollment.

Study device and procedure

The study stent was the NIR™ Conformer stent (Boston Scientific Corporation, Natick, MA and Medinol Ltd., Jerusalem). All stents were 15 mm long and 3.0 or 3.5 mm in diameter. The paclitaxel-eluting stent (TAXUS NIRx) was identical to the BMS except it was coated with a total load of 1.0 $\mu g/mm^2$ of paclitaxel incorporated into a proprietary polymer (Translute™) that provides controlled biphasic release. For both stents, the initial burst release over the first 48 hours after implantation is followed by a low-level release phase for approximately 10 days. The difference between both stents is an 8-fold higher release rate in the initial burst of the TAXUS-MR stent when compared to the TAXUS-SR stent.

Balloon pre-dilatation was performed followed by study stent implantation. Post-dilatation was performed if necessary. Use of additional stents was permitted if patency of the stented vessel was compromised. Second stents were of the same type as originally assigned. Third stents could be of any type considered appropriate by the investigator, except for study stents. However, this IVUS study excluded the patients who received stents other than the allocated stents. There was no objective angiographic or IVUS criteria for ensuring optimal stenting. All patients received clopidogrel 300 mg loading dosage followed by 75 mg daily (or ticlopidine 250 mg twice daily) for 6 months and aspirin 75 mg daily indefinitely.

Clinical follow-up

Clinical status was assessed at hospital discharge and 1,6, and 12 months after procedure. The 6-month follow-up was an office visit together with angiographic and IVUS follow-up. The 12-months follow-up was an office visit or a phone call. The 12-month clinical follow-up was completed in 99% in the first cohort and 98% in the second cohort.

IVUS imaging and visual evaluation of ISA

Serial IVUS procedures were performed using an automated pullback at 0.5 mm/s. All IVUS procedures were recorded on VHS videotapes. ISA was defined as one or more struts clearly separated from the vessel wall with evidence of blood speckling behind the stent struts without overlapping side branches[5,9]. The determination of ISA was based on the consensus of 2 independent analysts blind for the type of stent. ISA was classified into the following 3 groups on the basis of serial assessment; 1) Resolved: ISA present at post-procedure but no longer present at follow-up. 2) Persistent: ISA present both at post-procedure and follow-up. 3) Late acquired: ISA not present at baseline but present at follow-up.

Quantitative IVUS analysis

Quantitative IVUS analysis was performed by an independent core laboratory that continues to be blinded to treatment allocation (Cardialysis, Rotterdam, The Netherlands). In the stented segment, the lumen, stent, and external elastic membrane (EEM) contours were detected using the CURAD QCU analysis software (Curad BV, Wijk Bij Duurstede, The Netherlands) applying 3-D reconstruction, as described elsewhere[10]. In the segment with ISA, the lumen contour was delineated outside the stent contour (Figure 1). The QCU software detected and calculated the fraction of the lumen area that lies outside of the stent, e.g. ISA

area. ISA is thus conceptually considered as a part of a "functional" lumen. In the segment with ISA, mean vessel area (VA), mean stent area (SA), mean lumen area (LA), mean neointimal hyperplasia area (NIHA), mean ISA area (ISAA), maximal ISA area, and ISA volume (ISAV) were measured. Plaque behind stent area (PBSA) was derived by 'VA-SA-ISAA' (Figure 1-2).

Statistical analysis

Pooling of the control BMS groups of the two cohorts were combined because the baseline and 6-month follow-up data showed no significant differences between the 2 individual BMS groups. Therefore, 3 groups are reported in this study: the combined BMS, the TAXUS-SR, and the TAXUS-MR groups. Discrete variables are displayed as percentages and tested with Fisher's exact test. Continuous variables are expressed as mean ± standard deviation. Delta values (Δ) for each measurement were calculated as 'follow-up – post-procedure'. When comparing 3 groups, overall p values were derived from one-way ANOVA. Comparisons between post-procedure and 6-month follow-up were performed with a 2-tailed paired t test. A value of $p<0.05$ was considered statistically significant. To identify potential causative factors responsible for late acquired ISA, multivariable modeling analyses were performed including all the conventional pre-, peri- and post- procedural factors recorded in the frame of this trial. All covariates were modeled univariately on each outcome, as well as multivariately using a stepwise procedure in an appropriate regression model (logistic regression for binary outcomes, linear regression for continuous outcomes). The significance level thresholds for entry and exit of independent variables were set at 0.1.

Results

Baseline characteristics

Of the 536 randomized patients, 469 with serial and visually analyzable IVUS entered this substudy (BMS 240, SR 113, MR 116). The patients' baseline clinical and procedural characteristics are shown in Table 1. Except for the older age in the SR group (p=0.044 by ANOVA), all baseline characteristics were comparable among the 3 groups.

Incidence and predictors of incomplete stent apposition

The incidence of ISA is shown in Table 2 according to the classification of ISA. Post-procedural ISA was less frequent in the MR group (2.6%) than the other groups (BMS; 7.9%, SR; 11.5%, p = 0.028 by ANOVA). Of 19 ISA observed post-procedure in the BMS group, 11 (58%) were resolved at 6-month. In the SR group, 8 of 13 (62%) were resolved. All post-procedural ISA were resolved in the MR group. The incidence of late acquired ISA was similar among the 3 groups, ranging from 5.4% to 9.5%. A multivariate analysis identified lesion length, unstable angina, and absence of diabetes as predictive factors of late acquired ISA. The treatment allocation was not retained in the multivariate analysis with a p-value of 0.16 in the univariate analysis.

Clinical outcome of incomplete stent apposition

Table 3 summarizes the clinical outcome of patients who exhibited ISA in comparison with those without ISA. Up to 12 months after deployment of the stents, both in the BMS and TAXUS groups, there were no differences in adverse clinical event rates between the patients who showed ISA post-procedure and those who did not (Table 3-1). Similarly, ISA detected at 6-month follow-up was not associated with an excess of adverse event rates at 12-month clinical follow-up either in the BMS or TAXUS group (Table 3-2). No stent thrombosis was reported in patients diagnosed with ISA.

Quantification of incomplete stent apposition

Of 33 patients with late acquired ISA, the quantification was not possible in 4 patients. Although ISA was recognized visually on the videotapes in these patients, it was impossible to differentiate the lumen outside the stent from the plaque behind the stent on the digitized still images. Thus, 29 patients with 32 late acquired ISA segments were quantitatively assessed. For similar reasons, the quantification was possible in 18 patients (20 segments) of 22 patients with resolved ISA. Quantification was done in all 13 patients (15 segments) with persistent ISA. The extent of late acquired ISA measured by length, volume, mean area and maximal area is summarized in Table 4. All quantitative ISA parameters were similar among the 3 groups. Figure 2 shows the change of IVUS variables (VA, PBSA, LA) in the segments with late acquired and resolved ISA, including all groups. In the segments with late acquired ISA, VA at follow-up significantly increased, while PBSA did not change. As a result, there was a significant increase in LA with occurrence of ISA at follow-up. In the segments with resolved ISA, there was no difference in VA between post-procedure and at 6-month, while PBSA significantly increased. As a result, LA significantly decreased together with disappearance of ISA at follow-up. NIHA at follow-up in the segments with late acquired and resolved ISA was 0.36 mm^2 and 1.35 mm^2, respectively ($p = 0.0003$).

Discussion

The major findings of this study are the following: 1) More than 50% of post-procedural ISA resolve at follow-up. 2) An increase of plaque behind the stent without change in vessel area results in resolved ISA at follow-up. 3) The incidence of late acquired ISA following implantation of paclitaxel-eluting stents is similar to that of BMS. The extent (length, volume, and area) is similar between paclitaxel-eluting stents and BMS. 4) An increase of vessel area

without change in plaque behind the stent is the "mechanistic" IVUS change observed in the patients with late acquired ISA. 5) The predictive factors of late acquired ISA are lesion length, unstable angina, and absence of diabetes. 6) The presence of ISA is not associated with adverse clinical events.

Post-procedural ISA

In the previous IVUS guided trials such as the STRUT (Stent Treatment Region assessed by Ultrasound Tomography), the CRUISE (Can Routine Ultrasound Influence Stent Expansion), and the AVID (Angiography-directed Versus IVUS-Directed coronary stent placement), the incidence of post-procedural ISA as a result of incomplete deployment was reported to range from 4% to 22%[5]. Although there was a significant difference in the incidence of post-procedural ISA among the 3 groups in our study, the incidence of 2.6 ~ 11.5% was similar to the previous observations.

In the previous reports, late outcome of post-procedural ISA was not documented. In our study, of 19 post-procedural ISA in the BMS group, 11 (58%) disappeared at 6-month follow-up. Similarly, 8 of 13 (62%) in the SR group and 3 of 3 (100%) in the MR group were resolved at follow-up. The quantitative assessment of resolved ISA demonstrated that the disappearance of post-procedural ISA was attributable to an increase of tissue behind the stent without change in vessel area. It is apparent that paclitaxel elution from the stent did not adversely affect this spontaneous resolution of post-procedural ISA. However, it seems wise to avoid incomplete stent deployment in order to ensure efficient drug release from the stent struts to the vessel wall.

Late acquired ISA

ISA was more frequently observed at 6-month follow-up in the sirolimus-eluting stent group than the control group in the RAVEL trial[9]. However, the true incidence of late acquired ISA could not be determined, since no IVUS examination was performed post-procedure. In addition, in a retrospective analysis, it has been recently reported that late acquired ISA occurs in 4.4% after BMS implantation[11]. For the first time, we prospectively investigated the incidence of late acquired ISA following implantation of polymer-controlled paclitaxel-eluting stents in comparison with BMS. The rate of late acquired ISA in the SR and MR groups (8.0% and 9.5%) was similar to that in the BMS group (5.4%). Furthermore, the quantitative assessment revealed no differences in the extent of ISA. In the ASPECT trial which compared non-polymeric paclitaxel-eluting stents with BMS, late acquired ISA was observed only in one case in the high dose group (3.6%, 1/28)[12]. The incidence in the ASPECT trial was smaller than this study, however, it is difficult to compare the results due to an imbalance in the number of serial IVUS examinations between the two studies (81 in the ASPECT and 469 in the TAXUS II).

Several potential underlying mechanisms of late acquired ISA may be postulated: peri-stent remodeling, regression of plaque behind the stent, dissolution of thrombotic material behind the stent, cell necrosis, and cell apoptosis. The serial quantitative assessment in this study showed that an increase in vessel area (peri-stent remodeling) in the absence of increase in plaque behind the stent resulted in late acquired ISA. Our finding with 33 late acquired ISAs confirms the recent report which demonstrated that regional positive remodeling was the main cause of late acquired ISA in 11 stents[13]. Peri-stent remodeling has been shown to occur after bare metal stent implantation[14,15]. This suggests that the key mechanism to late

acquired ISA is an imbalance between peri-stent remodeling and tissue growth behind the stent. The multivariate analysis in this study identified absence of diabetes and unstable angina as predictive factors of late acquired ISA. It is likely that the more proliferative nature of healing process in diabetic patients tends to prevent the occurrence of ISA. In contrast, in patients with unstable angina, it is suspected that the culprit lesions often contain thrombotic materials which may dissolve at follow-up and create a new empty space behind the stent.

Clinical significance of ISA

Uren et al. retrospectively investigated the post-procedural IVUS findings of 53 patients who developed stent thrombosis[5]. The incidence of ISA was higher in their patient population compared to the previous reports. For the first time, we prospectively followed the 35 patients (19 in the BMS group and 16 in the TAUXS group) with ISA post-procedure. Despite the termination of clopidogrel at 6-month, no stent thrombosis was reported up to 12 months. In addition, during the time frame of 12 months, no stent thrombosis occurred in the 46 patients (21 in the BMS, 25 in the TAXUS) in whom IVUS identified ISA at 6-month follow-up. Therefore, the clinical significance of ISA is considered to be benign and inconsequential, but larger cohorts are necessary to confirm this information. Degertekin et al has recently reported a benign feature of ISA after sirolimus-eluting stent implantation[16], but the conclusion can not be generalized to other drug-eluting stents and should be restricted to the specific dose and elution profile of polymer-controlled paclitaxel-eluting stents and sirolimus-eluting stents.

Study Limitations

First, the analyses were limited to the patients with serial IVUS, raising the possibility of selection bias. However, of the 536 patients enrolled in the TAXUS-II trial, as many as 469 (87.5%) entered this substudy. Second, this represents a time frame of 12 months and longer-term follow-up will be necessary to confirm our findings.

Conclusion

The polymer controlled paclitaxel-eluting stents do not increase the incidence of late acquired ISA compared to BMS. In addition, paclitaxel elution from the stent maintains the process of spontaneous resolution of post-procedural ISA. By prospectively following the patients with ISA, we demonstrate that ISA is a pure IVUS finding without clinical repercussion.

Acknowledgments

We thank all of the investigators, their staff and the study staff.

Figure legends

Figure 1

In Figure 1-1, Panel A and B show the cross-sectional and longitudinal IVUS images of a patient who has a segment with incomplete stent apposition (ISA) at the middle of a stent. The cross-sectional view (A) corresponds to the "a" section of the longitudinal view (B). Panel C and D show the images after contour detection is performed in A and B. The green, blue, and red lines indicate the external elastic membrane (EEM) contour, the stent contour and the lumen contour, respectively. ISA is recognized as the area where the lumen contour is delineated outside the stent. Figure 1-2 shows a schematic diagram of contours and definitions. NIHA indicates neointimal hyperplasia area; ISAA, incomplete stent apposition area; VA, vessel area; LA, lumen area; SA, stent area; PBSA, plaque behind stent area.

Figure 2

Change of IVUS variables in the segments with late acquired ISA (A) and resolved ISA (B).

*$p < 0.01$

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Table 1. Baseline Clinical and Procedural Characteristics

	BMS	Taxus SR	Taxus MR
Number of patients	240	113	116
Age	59.5 ± 9.7	62.0 ± 10.2	59.0 ± 10.4
Male (%)	78.3	68.1	74.1
Current Smoker (%)	28.3	21.1	24.1
Diabetes Mellitus (%)	14.6	12.4	15.5
Hypertension (%)	60.8	62.8	59.5
Hypercholesterolemia (%)	72.4	82.3	76.7
Unstable Angina (%)	35.6	32.7	28.7
Prior MI (%)	44.2	38.1	40.5
Target vessel (%)			
LAD	47.9	40.7	44.0
LCx	15.4	20.4	21.6
RCA	36.7	38.9	34.5
Balloon artery ratio	1.1 ±0.2	1.1 ± 0.2	1.1 ±0.2
Maximal inflation pressure (atm)	12.3 ± 2.8	12.6 ± 2.7	12.1 ± 2.8
Stent Size (mm)	3.26 ± 0.25	3.27 ± 0.25	3.24 ± 0.25

Values are presented as relative percentages or mean value ± SD.

LAD indicates left anterior descending artery; RCA, right coronary artery; LCx, left circumflex artery; MI, myocardial infarction

Table 2. Incidence of Incomplete Stent Appostion

	BMS (n = 240)	Taxus SR (n = 113)	Taxus MR (n = 116)	P value
ISA post-procedure	19 (7.9%)	13 (11.5%)	3 (2.6%)	0.028
Resolved ISA	11 (4.6%)	8 (7.1%)	3 (2.6%)	0.285
Persistent ISA	8 (3.3%)	5 (4.4%)	0 (0%)	0.056
Late Acquired ISA	13 (5.4%)	9 (8.0%)	11 (9.5%)	0.306

Values are presented as numbers and relative percentage.
ISA indicates incomplete stent apposition.

Table 3. Adverse Clinical Events and Presence of Incomplete Stent Apposition

Table 3-1. Post-Procedural Incomplete Stent Apposition

	BMS (N = 240)			TAXUS SR + MR (N = 229)		
	No-ISA post-procedure	ISA post-procedure	P	No-ISA post-procedure	ISA post-procedure	P
Number of patients	221	19		213	16	
Up to 6 months						
Death	0 (0.0%)	0 (0.0%)	NA	0 (0.0%)	0 (0.0%)	NA
Q-MI	1 (0.5%)	0 (0.0%)	1.000	0 (0.0%)	0 (0.0%)	NA
nonQMI	8 (3.6%)	0 (0.0%)	1.000	1 (0.5%)	1 (6.3%)	0.135
TLR	27 (12.2%)	1 (5.3%)	0.707	7 (3.3%)	0 (0.0%)	1.000
Stent thrombosis	0 (0.0%)	0 (0.0%)	NA	0 (0.0%)	0 (0.0%)	NA
Up to 12 months						
Death	1 (0.5%)	0 (0.0%)	1.000	0 (0.0%)	0 (0.0%)	NA
Q-MI	1 (0.5%)	0 (0.0%)	1.000	3 (1.4%)	0 (0.0%)	1.000
nonQMI	8 (3.6%)	0 (0.0%)	1.000	1 (0.5%)	1 (6.3%)	0.135
TLR	28 (12.7%)	1 (5.3%)	0.484	7 (3.3%)	0 (0.0%)	1.000
Stent thrombosis	0 (0.0%)	0 (0.0%)	NA	2 (0.9%)	0 (0.0%)	1.000

Table 3-2. Incomplete Stent Apposition Observed at 6-month

	BMS (N = 240)			TAXUS SR + MR (N = 229)		
	No-ISA at 6-month	ISA at 6-month	P	No-ISA at 6-month	ISA at 6-month	P
Number of patients	219	21		204	25	
Up to 6 months						
Death	0 (0.0%)	0 (0.0%)	NA	0 (0.0%)	0 (0.0%)	NA
Q-MI	1 (0.5%)	0 (0.0%)	1.000	0 (0.0%)	0 (0.0%)	NA
nonQMI	8 (3.7%)	0 (0.0%)	1.000	1 (0.5%)	1 (4.0%)	0.207
TLR	28 (12.8%)	0 (0.0%)	0.145	7 (3.4%)	0 (0.0%)	1.000
Stent thrombosis	0 (0.0%)	0 (0.0%)	NA	0 (0.0%)	0 (0.0%)	NA
Up to 12 months						
Death	1 (0.5%)	0 (0.0%)	1.000	0 (0.0%)	0 (0.0%)	NA
Q-MI	1 (0.5%)	0 (0.0%)	1.000	3 (1.5%)	0 (0.0%)	1.000
nonQMI	8 (3.7%)	0 (0.0%)	1.000	1 (0.5%)	1 (4.0%)	0.207
TLR	29 (13.2%)	0 (0.0%)	0.086	7 (3.4%)	0 (0.0%)	1.000
Stent thrombosis	0 (0.0%)	0 (0.0%)	NA	2 (1.0%)	0 (0.0%)	1.000

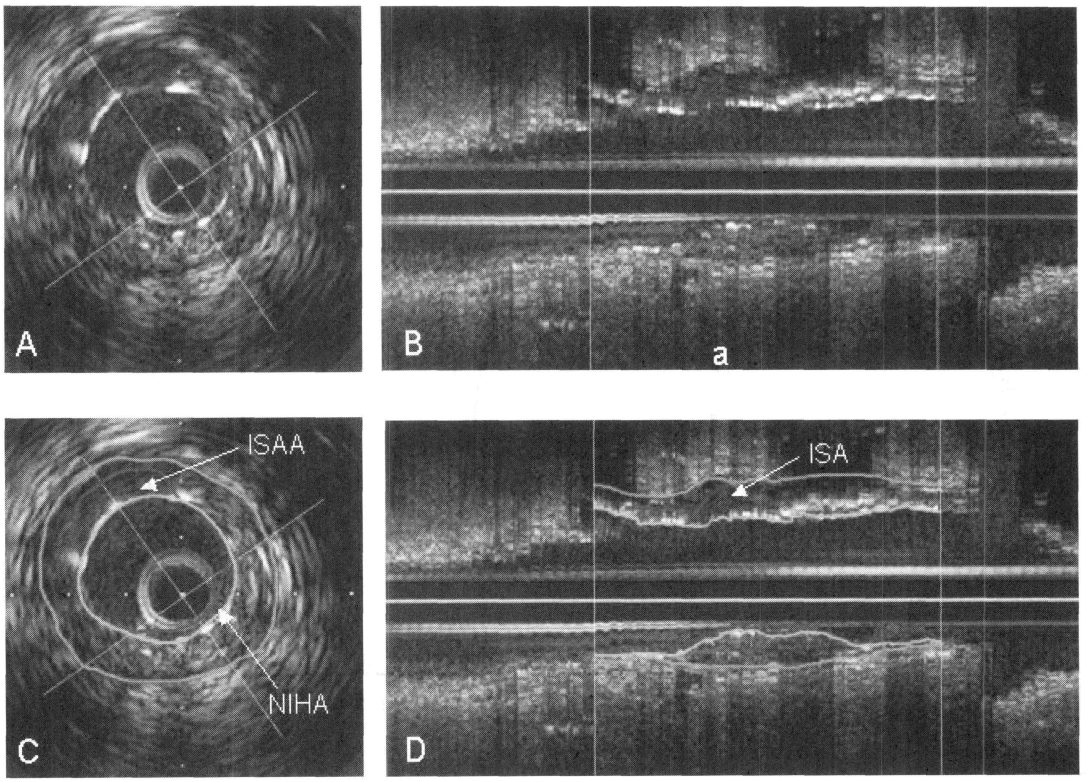
Values are presented as numbers (relative percentages).

"ISA post-procedure" includes both persistent and resolved ISA (Table 3-1). "ISA at 6-month" includes both persistent and late acquired ISA (Table 3-2). ISA indicates incomplete stent apposition; NA, not applicable; MI, myocardial infarcation; TLR, target lesion revascularization.

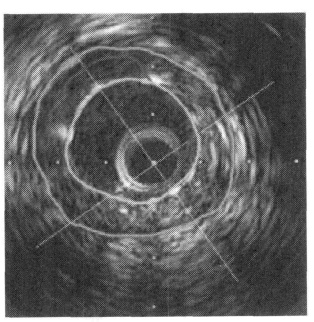
Table 4. Quantification of Late Acquired Incomplete Stent Apposition

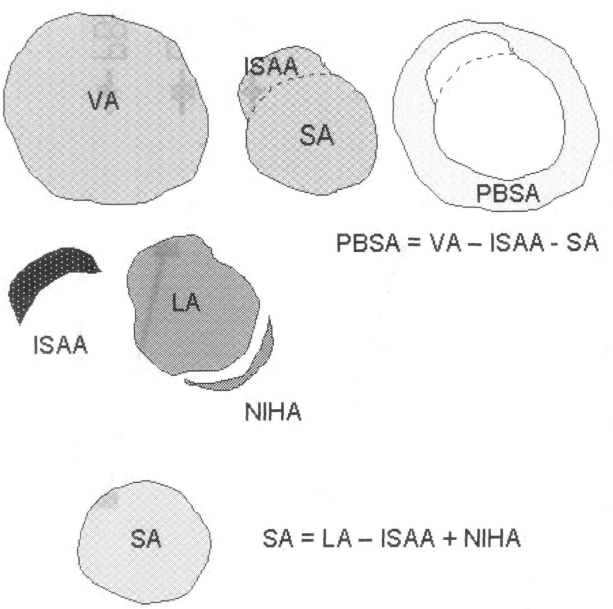
	BMS	SR	MR	P value
Number of patients	12	7	10	
Number of ISA segments	13	8	11	
ISA length (mm)	3.6 ± 2.2	5.7 ± 3.9	2.8 ± 2.4	0.089
ISA volume (mm^3)	11.4 ± 12.7	21.7 ± 20.6	8.5 ± 13.9	0.181
Mean ISA area (mm^2)	3.0 ± 2.1	3.6 ± 1.2	2.1 ± 1.4	0.179
Maximal ISA area (mm^2)	4.0 ± 2.6	5.1 ± 1.8	3.4 ± 2.6	0.342

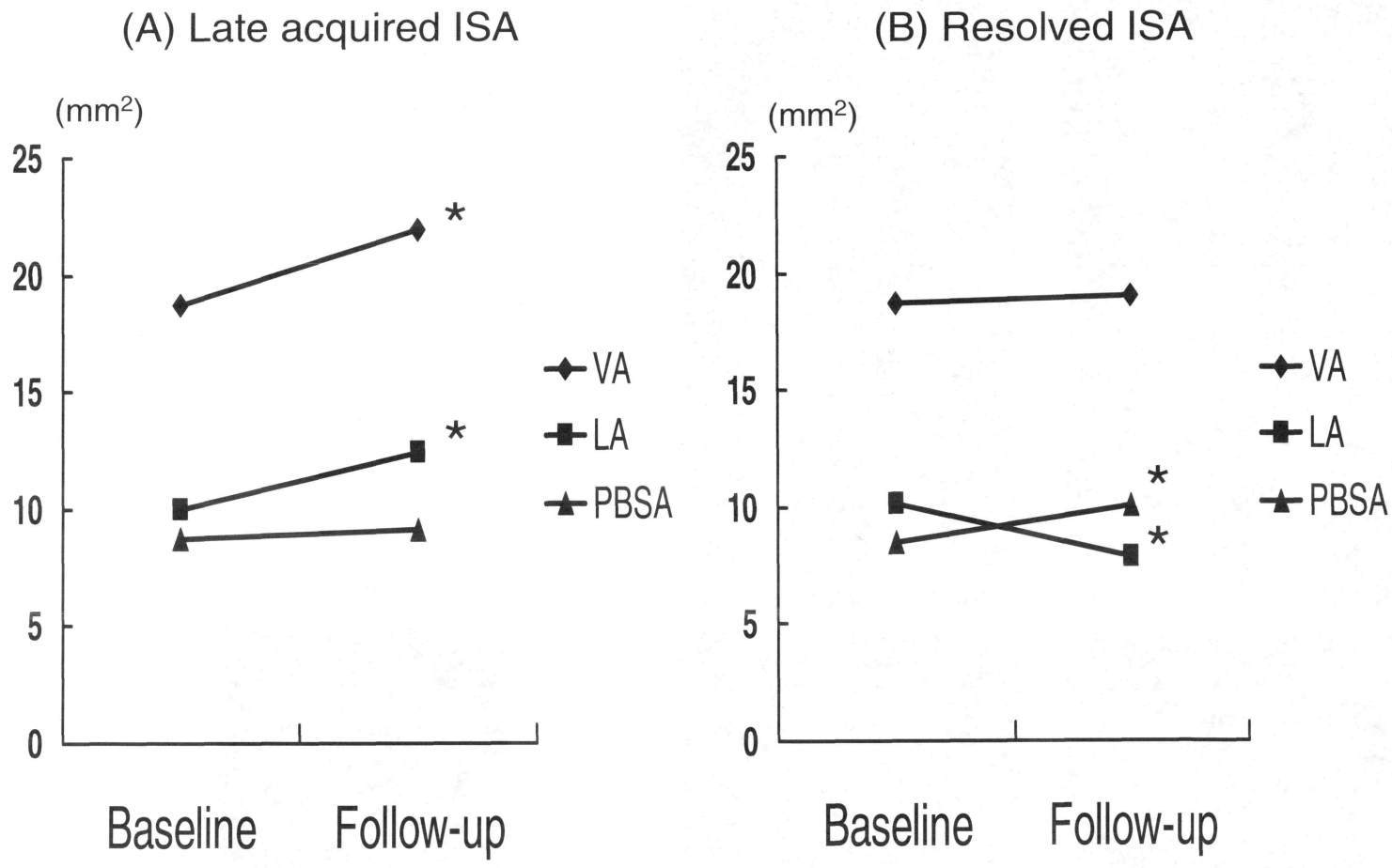
1-1


A
B
a
ISAA
NIHA
C
ISA
D

1-2




VA
ISAA
SA
PBSA
PBSA = VA – ISAA - SA
LA
ISAA
NIHA
SA
SA = LA – ISAA + NIHA


(A) Late acquired ISA
(mm2)
25
20
15
10
5
0
*
*
VA
LA
PBSA
Baseline
Follow-up
(B) Resolved ISA
(mm2)
25
20
15
10
5
0
*
*
VA
LA
PBSA
Baseline
Follow-up

Chapter 14

TAXUS III Trial: In-stent Restenosis Treated with Stent Based Delivery of Paclitaxel Incorporated in a Slow Release Polymer Formulation.

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TAXUS III Trial

In-Stent Restenosis Treated With Stent-Based Delivery of Paclitaxel Incorporated in a Slow-Release Polymer Formulation

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Background—The first clinical study of paclitaxel-eluting stent for de novo lesions showed promising results. We performed the TAXUS III trial to evaluate the feasibility and safety of paclitaxel-eluting stent for the treatment of in-stent restenosis (ISR).

Methods and Results—The TAXUS III trial was a single-arm, 2-center study that enrolled 28 patients with ISR meeting the criteria of lesion length ≤30 mm, 50% to 99% diameter stenosis, and vessel diameter 3.0 to 3.5 mm. They were treated with one or more TAXUS NIRx paclitaxel-eluting stents. Twenty-five patients completed the angiographic follow-up at 6 months, and 17 of these underwent intravascular ultrasound (IVUS) examination. No subacute stent thrombosis occurred up to 12 months, but there was one late chronic total occlusion, and additional 3 patients showed angiographic restenosis. The mean late loss was 0.54 mm, with neointimal hyperplasia volume of 20.3 mm^3. The major adverse cardiac event rate was 29% (8 patients; 1 non–Q-wave myocardial infarction, 1 coronary artery bypass grafting, and 6 target lesion revascularization [TLR]). Of the patients with TLR, 1 had restenosis in a bare stent implanted for edge dissection and 2 had restenosis in a gap between 2 paclitaxel-eluting stents. Two patients without angiographic restenosis underwent TLR as a result of the IVUS assessment at follow-up (1 incomplete apposition and 1 insufficient expansion of the stent).

Conclusions—Paclitaxel-eluting stent implantation is considered safe and potentially efficacious in the treatment of ISR. IVUS guidance to ensure good stent deployment with complete coverage of target lesion may reduce reintervention. (***Circulation.*** **2003;107:559-564.)**

Key Words: stents ■ restenosis ■ drugs

The development of coronary stents has revolutionized the field of interventional cardiology by reducing the incidence of restenosis after balloon angioplasty.[1,2] With the widespread clinical use of coronary stents, in-stent restenosis (ISR) has become the most challenging problem.[3] Previous pharmacological and mechanical approaches have shown disappointing results in eliminating this iatrogenic disease. Presently, intravascular brachytherapy is the only treatment for ISR proven to be effective in clinical randomized trials.[4–6] Brachytherapy requires special handling and is hampered by potential issues such as edge restenosis,[7,8] late thrombosis,[9] geographical miss,[10] late stent malapposition,[11] persisting dissection,[12,13] and positive vascular remodeling after treatment.[14,15]

Stent-based local drug delivery is expected to cause a revolutionary change in the field of percutaneous intervention, with recent clinical trials of paclitaxel or sirolimus-eluting stents demonstrating promising results in the treatment of de novo lesions.[16–19] Paclitaxel is a microtubule inhibitor presently used to treat several kinds of cancer, most commonly breast and ovarian. Microtubular dynamics regulate many of the inflammatory and profibrotic steps implicated in the restenotic cascade. This agent has been reported to reduce vascular cell proliferation and migration in vitro and in vivo.[20–23] In accordance with these experimental results, paclitaxel-eluting stents for de novo lesions showed no restenosis in the TAXUS I feasibility trial.[16] However, it has not been established whether this is applicable to a more complex patient group, such as patients with ISR. The TAXUS III trial is a single-arm, 2-center study aiming to evaluate the feasibility and safety of this eluting stent for the treatment of ISR.

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Methods

Patient Selection

Patients were eligible if they had ISR of a native coronary artery with objective evidence of ischemia. Angiographic inclusion criteria were lesion length ≤30 mm, 50% to 99% diameter stenosis, and vessel diameter between 3.0 and 3.5 mm. Patients were excluded if they had an acute myocardial infarction, left ventricular ejection fraction <30%, stroke within the last 6 months, a renal dysfunction (serum creatinine >1.7 μg/100 mL), or a contraindication to aspirin, clopidogrel, or ticlopidine. Between May 2001 and August 2001, patients were enrolled in two centers (Thoraxcenter, Rotterdam, the Netherlands, and Heart Center Siegburg, Siegburg, Germany). All patients gave written informed consent. The study was reviewed and approved by both institutions' ethics review committees.

Procedure

The stent used in the study was the TAXUS NIRx paclitaxel-eluting stent (Boston Scientific Corporation), with a total load of 1.0 μg/mm^2 of paclitaxel incorporated into a slow-release copolymer carrier system that gives biphasic release. The initial release is over the first 48 hours followed by slow release over the next 10 days. All stents were 15 mm long and 3.0 or 3.5 mm in diameter. Balloon predilatation was performed followed by NIRx paclitaxel-eluting stent implantation using conventional techniques. Postdilatation was performed if necessary. Periprocedural intravenous heparin was given to maintain an activated clotting time ≥250 seconds, and all patients received aspirin (at least 75 mg) and clopidogrel (300 mg loading dose followed by 75 mg once daily for 6 months).

Follow-Up

Clinical information was collected 6 and 12 months after procedure. Angiographic and intravascular ultrasound (IVUS) follow-ups were performed at the 6-month visit. Major adverse cardiac events (MACEs) were defined as death, myocardial infarction (MI), target-vessel repeat percutaneous coronary intervention, or coronary artery bypass grafting (CABG). MI was defined as Q-wave MI (development of new pathological Q waves in 2 or more leads with CK-MB levels elevated above normal) or non–Q-wave MI (elevation of CK levels to >2 times upper normal limit with CK-MB levels elevated above normal).

Angiographic Analysis

Coronary angiograms were obtained in multiple views after intracoronary nitrate. ISR was classified according to a modified Mehran classification.[3] Three coronary segments underwent quantitative angiography: in-stent, proximal edge, and distal edge segment. The in-stent analysis encompassed the entire length of all stents used during the procedure. The proximal and distal edge segments included up to 5 mm on either side of the in-stent segment. Quantitative coronary angiographic analysis was performed by an independent core laboratory (Cardialysis, Rotterdam, the Netherlands).[24] The reference vessel diameter, minimal lumen diameter (MLD), and percent diameter stenosis were measured before procedure, after procedure, and at follow-up. Late loss was calculated as the difference between the MLD after procedure and that at follow-up. The target lesion was defined as the in-stent segment plus the proximal and distal edge segments. Angiographic restenosis was defined as >50% diameter stenosis within the target lesion.

IVUS Analysis

IVUS images were acquired after procedure and at 6-month follow-up using automated pull-back at 0.5 mm/s following intracoronary nitrate.[25] The total coronary analysis segment beginning 5 mm distal to and extending 5 mm proximal to the study stent was examined. A computer-based contour detection program was used for automated 3D reconstruction of the segments from up to 200 cross-sectional images. Lumen, stent boundaries, and external elastic membrane were detected using a minimum cost algorithm, and volumetric quantification was performed.[26,27] Percent volume obstruction was calculated as neointimal volume/stent volume×100. The quantitative ultrasound analysis was performed by the same independent core laboratory.

TABLE 1. Baseline Clinical Characteristics

Patients	28
Age, y	63.2±10.5
Male sex	19 (67.9)
Diabetes mellitus	4* (14.3)
Hypertension	18 (64.3)
Hypercholesterolemia	20 (71.4)
Family history	5 (17.9)
Current smoker	2 (7.1)
Unstable angina pectoris	2 (7.1)
Multivessel disease	7 (25)
Previous MI	16 (57.1)
Previous CABG	5 (17.9)

Values are presented as numbers (relative percentages) or mean±SD.
*In 1 patient, the information on diabetes mellitus was unknown.

Statistical Analysis

Continuous variables are expressed as mean±SD. Comparisons between postprocedure and 6-month follow-up measurements were performed with a 2-tailed paired *t* test. $P<0.05$ was considered statistically significant.

Results

Baseline Clinical and Lesion Characteristics

Twenty-eight patients with 28 target lesions were included. The patients' baseline clinical and lesion characteristics are summarized in Tables 1 and 2, respectively. The incidence of diabetes, previous MI, and previous CABG are in keeping with the higher risk population of ISR.[3] Diffuse ISR pattern

TABLE 2. Lesion Characteristics

No. of target lesions	28
Treated vessel	
Left anterior descending	10 (35.7)
Left circumflex	6 (21.4)
Right coronary artery	11 (39.3)
Left main	1 (3.6)
Type of ISR, Mehran classification	
IA, gap	0 (0)
IB, margin	3 (10.7)
IC, focal body	6 (21.4)
ID, multifocal	1 (3.6)
II, diffuse intrastent	13 (46.4)
III, proliferative	4 (14.3)
IV, total occlusion	1 (3.6)
Lesion length, mm	13.61±6.36
No. of implanted paclitaxel-eluting stents	
1 Stent per lesion	15 (53.6)
2 Stents per lesion	13 (46.4)

Values are presented as numbers (relative percentages) or mean±SD.

TABLE 3. Cumulative Clinical Outcome

	30 Days	6 Months	12 Months
Death	0	0	0
Q-wave MI	0	0	0
Non–Q-wave MI	1 (3.6)	1 (3.6)	1 (3.6)
CABG	0	1 (3.6)	1 (3.6)
Target vessel revascularization	0	6 (21.4)	6 (21.4)

Values are presented as numbers (relative percentages).

was present in 64% of target lesions. Thirteen lesions (46%) were treated with 2 paclitaxel-eluting stents.

Clinical Outcome

Table 3 summarizes MACE up to 12 months after procedure. No subacute stent thrombosis occurred, and no deaths were reported. There was 100% technical success in deploying the study stents; however, 1 patient had postprocedural non–Q-wave MI, yielding a 30-day MACE rate of 4%.

During the 6-month follow-up, an additional 7 patients had a MACE, for a 6-month rate of 29%. One patient underwent CABG attributable to progression of left main and ostial left circumflex lesions, which were at a distance from the target lesion. The remaining 6 patients underwent percutaneous target lesion revascularization (TLR). For 3 of these patients, the indication for TLR was angiographic restenosis. In the remaining 3 patients, 1 without angiographic restenosis had TLR because of anginal symptoms in the presence of a small MLD (1.33 mm). IVUS findings at follow-up triggered 2 additional interventions in the absence of angiographic restenosis. One showed incomplete stent apposition, the other showed insufficient stent expansion, and neither showed neointimal hyperplasia (percent volume obstruction, 0%). It was unknown whether the incomplete apposition was already present at baseline, because no IVUS assessment was performed after procedure. Between 6 and 12 months, no additional MACE was reported.

Angiographic and IVUS Outcome

Of 28 patients, 25 (89%) underwent 6-month follow-up angiography. Binary angiographic restenosis was documented in 4 patients (16%). One of these patients had target vessel total occlusion. Two paclitaxel-eluting stents had been implanted to treat ISR of a covered stent, which had been used to treat ISR of a gold-coated stent. Additional intervention was not undertaken, because the patient had no anginal symptoms.

Of the remaining 3 patients, 1 had restenosis in a bare metal stent implanted because of a dissection at the distal edge of the paclitaxel-eluting stent. Two patients had restenosis in a gap between 2 paclitaxel-eluting stents, as evident on IVUS (Figure 1). Minimal neointimal hyperplasia is seen in the segments with double contours of stent struts; however, where there is a single layer of stent struts, ie, a gap between the paclitaxel-eluting stents, occlusive neointimal tissue is evident. Hence, of the 4 with binary restenosis, 3 occurred within a region with no local delivery of paclitaxel.

The quantitative coronary angiographic data are summarized in Table 4. The mean reference vessel diameter was

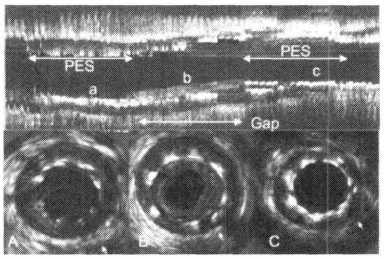

Figure 1. The IVUS images at follow-up of a patient who showed restenosis in a gap between the 2 paclitaxel-eluting stents (PES). Minimal neointimal hyperplasia was observed within the PES (A and C), whereas neointimal hyperplasia was noted in a gap (B). The cross-sectional views (A, B, and C) correspond to the a, b, and c sections of the longitudinal views.

2.75 mm. Figure 2 shows the cumulative distribution curve of MLD in the in-stent segment. The MLD at follow-up (1.84 mm) was significantly lower than that after procedure (2.40 mm). Diameter stenosis at follow-up was 30.8%, with an average in-stent late loss of 0.54 mm. Late loss of the proximal and distal edges were 0.20 and 0.11 mm, respectively, without angiographic restenosis.

Seventeen patients underwent IVUS examination at follow-up. The neointimal hyperplasia volume amounted to 20.3 ± 23.1 mm^3 with the stent volume of 172.1 ± 85.4 mm^3. In addition, serial analysis (n=14 pairs) of the total vessel volume after procedure (411.2 ± 332.9 mm^3) versus follow-up (435.8 ± 217.5 mm^3) showed no statistically significant change, suggesting that paclitaxel-eluting stent does not cause positive or negative vessel remodeling. No late acquired incomplete stent apposition was detected by serial IVUS investigation.

Subgroup Analysis

We performed subgroup analysis to estimate the treatment effect within stented segments directly exposed to local paclitaxel delivery by excluding the 3 patients who showed restenosis in a bare stent or a gap between 2 paclitaxel-eluting stents, as tabulated in Table 4. In this subgroup, the late loss and restenosis rate was 0.47 mm and 4.5%, respectively.

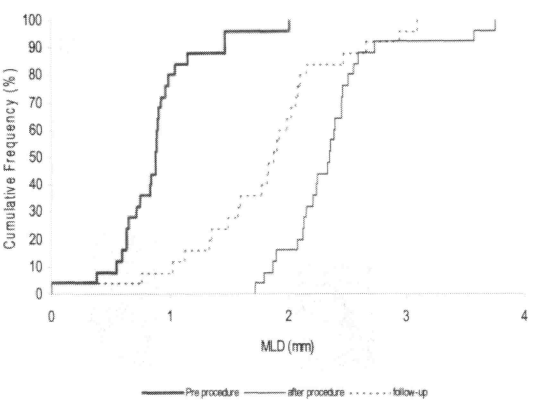

Figure 2. The cumulative distribution curve of the MLD.

TABLE 4. QCA Data

	n	Proximal Edge, All Patients	In Stent, All Patients	Distal Edge, All Patients	n	In Stent, Subgroup*
Reference diameter						
Before procedure, mm	28	NA	2.75±1.20	NA	25	2.84±1.25
After procedure, mm	28	3.08±0.40	2.91±0.43	2.81±0.43	25	2.91±0.45
6-Month follow-up, mm	25	2.86±0.43†	2.67±0.42†	2.54±0.43†	22	2.64±0.45†
Minimal lumen diameter						
Before procedure, mm	28	NA	0.87±0.38	NA	25	0.90±0.39
After procedure, mm	28	2.67±0.54	2.40±0.44	2.27±0.47	25	2.41±0.46
6-Month follow-up, mm	25	2.45±0.54†	1.84±0.63†	2.17±0.49	22	1.93±0.61†
Percent diameter stenosis						
Before procedure, mm	28	NA	67.3±11.3	NA	25	67.1±11.8
After procedure, mm	28	13.9±9.4	17.4±7.6	19.3±11.0	25	16.9±7.6
6-Month follow-up, mm	25	14.3±10.5	30.8±20.5†	14.8±9.5	22	26.9±18.6†
Late loss, mm	25	0.20±0.40	0.54±0.51	0.11±0.33	22	0.47±0.48

*The subgroup is the group that excludes the patients who showed angiographic restenosis in a bare metal stent or a gap between the paclitaxel-eluting stents.

†$P<0.05$ vs after procedure.

Figure 3 shows the results of subgroup analysis between patients with single stent (n=13) and those with 2 stents (n=12). Post-hoc statistical analysis showed a significantly smaller MLD and larger diameter stenosis at follow-up for the 2-stent group ($P<0.01$). Post-hoc statistical analysis of IVUS data at follow-up reveal that percent volume obstruction in the single-stent group (n=10; length, 15.4±2.8 mm) was 12.4±15.7% for a stent volume of 111.9±27.9 mm^3, whereas percent volume obstruction in the 2-stent group (n=7, length 29.4±3.0 mm) was 10.1±8.2% for a stent volume of 258.1±60.3 mm^3. In this latter group, the analysis included only 1 of the 4 patients who had angiographic restenosis.

Discussion

In the present study, we report the first clinical experience with the TAXUS NIRx paclitaxel-eluting stent for the treatment of ISR. The major findings of the TAXUS III trial are as follows. First, this polymer-based paclitaxel-eluting stent is feasible and safe for the treatment of ISR with no subacute stent thrombosis. Second, late loss (0.54 mm) is seemingly diminished compared with historical controls. Third, angiographic restenosis rate is 16%; however, when present, it tends to occur in a gap between 2 paclitaxel-eluting stents. Fourth, the TLR rate of 21.4% (6 of 28 patients) is promising given that 3 were not performed according to predefined angiographic criteria.

Safety Consideration

At up to 12 months of clinical follow-up, there has been no late subacute stent thrombosis in our patient population, although clopidogrel was discontinued at 6 months. There was 1 patient with silent total occlusion who had preexisting in-stent restenosis in gold-coated and covered stent sandwich subsequently treated with the study stents. However, the mechanism of this occlusion is difficult to decipher, because the effect of paclitaxel on the adjacent covered stent sandwich is unknown and the covered stent precluded the IVUS assessment with respect to the detection of either a gap or an overlap. The promising safety data in our study contrasts with

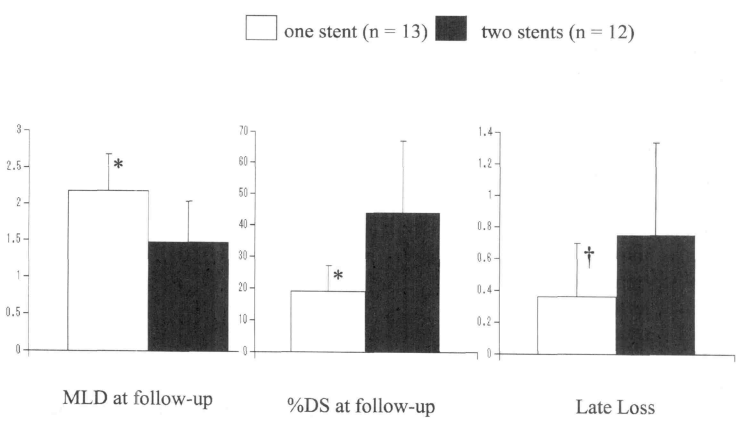

Figure 3. Post-hoc analysis between single stent and 2 stents of angiographic parameters (MLD at follow-up, percent diameter stenosis (DS) at follow-up, and late loss). It has to be emphasized that the 2 stent group include 1 total occlusion, 2 gaps between the stents, and 1 bare-stent restenosis. *$P<0.01$ vs 2 stents by unpaired t test; †$P=0.054$ versus 2 stents.

the high incidence of late subacute stent thrombosis in the randomized Score trial, evaluating de novo lesions with the QuaDS stent that used 4 or 5 polymer sleeves to deliver high concentrations (800 μg/sleeve) of paclitaxel derivative.[28] The enrollment of the Score trial was prematurely stopped because of a major imbalance in MACE between the study and control groups associated with stent thrombosis. Previous animal studies showed that paclitaxel may delay the healing process in a dose-dependent manner,[29] and stent thrombosis is likely the result of incomplete healing and reendothelialization. Additional preclinical and clinical data will give insight as to whether the dose of paclitaxel (1.0 μg/mm^2 [loaded drug/stent surface area]) used in this trial will maintain the promising safety margin.

Efficacy of the TAXUS NIRx Paclitaxel-Eluting Stent for Treatment of In-Stent Restenosis

Previous reports using bare metal stent for treatment of ISR showed a late loss of 0.9 to 1.4 mm.[30–32] The overall late loss (0.54 mm) in our study was more favorable, even though it underestimates the treatment effect. If the 2 patients with restenosis attributable to a gap between 2 paclitaxel-eluting stents and the patient with restenosis in a bare stent are excluded, the adjusted late loss is 0.47 mm. In addition, the late loss in the single-stent group was 0.36 mm (Figure 3). These values are close to the loss of 0.35 mm (placebo group, 0.70 mm) observed in the TAXUS I trial on de novo coronary lesions treated with the same slow-release formulation. Furthermore, the neointimal volume from the TAXUS III patients with 1 NIRx stent was 15.6 mm^3, comparable to 14.8 mm^3 in the TAXUS I patients treated with one NIRx stent. These two values are both lower than the value of 21.6 mm^3 seen in the TAXUS I uncoated bare stent group. Taken together, these data suggest that paclitaxel on the NIRx seems to attenuate neointimal formation for ISR as well as de novo lesions.

Restenosis at the Gap

In 2 patients, IVUS identified a gap between 2 eluting stents that led to restenosis. Our hypothesis is that barotrauma from balloon inflation in an area of preexisting in-stent neointima may have triggered the local exuberant hyperplasia in the gap where the concentration of paclitaxel is insufficient to prevent neointimal hyperplasia. Accordingly, we speculate that paclitaxel does not diffuse substantially from the edge of the stent to have biological effect in the gap. Therefore, when treating ISR with the paclitaxel-eluting stents, covering the entire length of the previously implanted stents and providing a margin at either side may reduce TLR associated with restenosis near the drug-treated segments. With this in mind, IVUS guidance may be useful, and the advent of longer-eluting stents will be advantageous.

TLR Without Angiographic Restenosis

The TLR rate of this trial has been artificially inflated by reinterventions because of ultrasound or angiographic findings not always clinically driven or justified by predefined angiographic criteria. In this trial, 3 of 6 TLRs had diameter stenosis <50%. Two of these patients underwent TLR as a result of IVUS findings at follow-up. In one, there was an incomplete apposition at follow-up without postprocedural assessment. In the other patient, the stent was considered at follow-up to be insufficiently expanded, although the mean lumen area of the stent was 4.41 mm^2 without neointimal hyperplasia. The third patient had anginal symptoms despite a diameter stenosis of 32.5% and underwent TLR in an attempt to increase the MLD (1.33 mm) and reference diameter (1.96 mm). In this trial, the incidence of TLR may underestimate the clinical benefit related to the inhibition of neointimal hyperplasia resulting from the drug elution.

Study Limitations

The limitations of this study are its small sample size and single-arm open-label design without randomization. The angiographic follow-up rate was acceptable, although a higher IVUS follow-up rate may have provided more information on neointimal hyperplasia. Ongoing clinical follow-up will provide insight on long-term outcomes in this challenging population.

Conclusion

Paclitaxel-eluting stent implantation is considered safe and potentially efficacious in the treatment of ISR. The IVUS guidance to ensure good stent deployment with complete coverage of target lesion may reduce reintervention.

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Part 3. Other Drug-Eluting Stents

Chapter 15

Preclinical Results with a Statin Releasing Stent

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Introduction

Although stents have improved the short and long term results of percutaneous coronary interventions (PCI) [1,2], in-stent restenosis still remains a significant limitation. Recently, local drug delivery from eluting stents has been tested in clinical trials. The promising results with sirolimus-eluting stent and paclitaxel-eluting stent indicate that drug-eluting stents may be considered as a potential solution to this vexing problem of in-stent restenosis[3-6].

Statins are the most commonly prescribed drugs for the treatment of hypercholesterolemia. Clinical trials have demonstrated that statins can reduce the relative risk of major cardiac events and are highly beneficial in patients with high baseline risks[7-10]. Furthermore, early initiation of fluvastatin in patients with average cholesterol levels following their first PCI has been shown to reduce the risk of major adverse cardiac events[11]. However, previous major clinical studies failed to corroborate the beneficial effect on restenosis after coronary balloon angioplasty and stenting[12-15]. These disappointing results had not been expected prior to the studies because preclinical experiments seemed promising. First, statins have been shown to exert anti-proliferative effects on smooth muscle cells in vitro by arresting the cell cycle between G1/S phase transition [16-19]. Corsini et al. also investigated the effect of whole

blood sera from statin-treated patients on smooth muscle cell proliferation [20]. The sera from patients treated with fluvastatin showed a significant inhibition of cell growth, while those treated with pravastatin showed no effect. Second, Indolfi et al. reported that the systemic administration of simvastatin reduced the neointimal formation in the stented common carotid artery of rats [21]. Consequently statins other than pravastatin were considered to be effective in preventing restenosis by interrupting the restenotic cascade. The discrepancy between the experimental data and clinical findings may be due to the fact that systemic administration for a local problem such as restenosis does not the most logical approach. Therefore Terumo Corporation has undertaken the project of statin-eluting stent. Some preliminary in vitro and in vivo experiments were performed as described below.

Methods

In vitro. The effects of 5 statins (pravastatin, simvastatin, atorvastatin, fluvastatin and cerivastatin) and rapamycin on in vitro proliferation of smooth muscle cells and endothelial cells were assessed. Stock solutions of these drugs were diluted in culture medium in order to achieve test concentrations between 0.001 and 100 μM. The human coronary artery smooth muscle cells (CASMC7441) and the human coronary artery

endothelial cells (HCAEC7039) were used in this study. After incubation in 5% foetal calf serum (FCS) in order to synchronize the cell cycles, these cells were seeded onto 96-well dishes at a density of 3000 cells/well.

Wst-1 test. Wst-1 test was performed as previously described [22,23]. In brief, after the cells had been cultured in 5% FCS for 24 hours, test compounds at six concentrations were added. After 3 days, Wst-1 assay was performed to determine their cellular mitochondrial dehydrogenase activity as a measure for proliferation of these cells.

LDH assay. After the cells had been cultured in 0.5% FCS for 72 hours, test compounds at each concentration were added. After another 24 hours, a lactate dehydrogenase (LDH) assay was carried out to study the cytotoxicity of these test compounds. LDH release is considered as a potential marker of cell injury and death [17,24].

In vivo. 15 Wister rats at 11 weeks of age were included in this study to assess the effect of simvastatin and rapamycin on in vivo smooth muscle cell proliferation. The rats were anesthetized with intra peritoneal pentobarbital and their left carotid arteries were denuded. For angioplasty, a 1.5mm × 20mm balloon catheter (2Fr. Fogarty) was introduced into the external carotid artery by direct arteriotomy and then advanced into the common carotid artery. The vessel was damaged by passing the inflated balloon through the lumen twice. After angioplasty, the rats were randomized in the simvastatin

group (SIM, n = 6), the rapamycin group (RAP, n = 6) or the control group (CON, n = 3). The osmotic pump (ALZET, USA) was placed outside the injured common carotid artery. Then the skin was sutured and the rats were allowed to recover. The osmotic delivery system was filled with 1% ethanol containing 10μM simvastatin in the SIM group or 10μM rapamycin in the RAP group. In the CON group, the system was filled with only 1% ethanol. In all groups, the infusion was performed at 0.5 μl/hour and continued for 14 days [25]. As a result, 0.70 μg simvastatin in the SIM group and 1.54 μg rapamycin in the RAP group were administered in total. At 14 days, 3 rats in the SIM group, 3 rats in the RAP group and 3 rats in the CON group were anesthetized. The carotid arteries were fixed by perfusion with 30% formalin and removed. The sections of the carotid arteries were stained with hematoxylin-eosin to demarcate cell types and also stained with a polyclonal antibody against von Willebrand factor to confirm the re-endothelialization [26]. The sections of the carotid arteries of the remaining 3 rats in the SIM group and the RAP group were made after additional 14 days (28 days after balloon injury). It has been demonstrated that in this model the amount of neointimal hyperplasia is maximal, reaching a plateau 14 days after balloon injury [27]. Therefore, in the CON group, the neointimal thickness was evaluated only 14 days after injury. The present animal experiment was in accordance with the Terumo Corporation Animal Care

and use Committee.

Results

Effect of statins and rapamycin on the cell proliferation. The WST-1 test revealed that cerivastatin emerged as the strongest growth inhibitor of human coronary smooth muscle cells (Figure 1A) and endothelial cells (Figure 1B) among the test compounds. However no effect on the proliferation of both cells was observed with pravastatin. The other statins started to reduce cell proliferation at concentration higher or equal to 1μM. On the other hand, the WST-1 test of rapamycin already showed less than 75% of the control value at concentration as low as 0.001 μM. Therefore, the WST-1 test of rapamycin was performed at concentration including less than 0.001 μM. Three observations were made in this additional experiment. Simvastatin was also evaluated. Interestingly, the inhibitory effect of rapamycin on smooth muscle cells (Figure 2A) appeared at 10^{-5}μM reaching a plateau of approximately 50% of the control value. Then, this effect augmented at concentration higher than 10μM. This trend was similarly observed in endothelial cells (Figure 2B), however the effect on the proliferation appeared at concentration as low as 10^{-7}μM. In summary, the anti-proliferative potencies of statins in both cell types were in the following order of magnitude:

pravastatin << atorvastatin < fluvastatin = simvastatin << cerivastatin.

Cytotoxicity of statins and rapamycin. The LDH assay results showed that LDH release from human coronary artery smooth muscle cells (Figure 3A) as well as endothelial cells (Figure 3B) was dose dependent after treatment with the test compounds with the exception of pravastatin. It is noteworthy that at concentration lower or equal to 10μM, the LDH assay of each drug was less than 20% of the value of totally lysed cells with Triton-X100. Therefore, these drugs are likely to be cytostatic rather than cytotoxic. The order of statins' cytotoxic potencies in both cell types was similar to that seen in the WST-1 test.

Effect of simvastatin and rapamycin on neointimal formation after balloon injury in vivo. A significant reduction of neointima was observed in the SIM group ($p = 0.03$) and the RAP group ($p = 0.02$) at 14 days after the balloon injury compared with the CON group (Figure 4,5). In the SIM group, the neointimal thickness observed at 28 days after the procedure was similar to that at 14 days ($p = 0.53$). In contrast, the neointimal thickness at 28 days increased compared with that at 14 days in the RAP group. However, this trend ($p = 0.07$) failed to be statistically significant.

Figure 6 shows the representative sections stained with a polyclonal antibody against von Willebrand factor. At 14 days regenerated endothelium is almost complete in the

SIM group (Figure 6A), while the RAP group shows incomplete re-endothelialization (Figure 6B). The endothelialization scores at 14 days were examined. The score in the SIM group was greater than that in the RAP group and the CON group (Figure 7).

Discussion

The present experiments in vitro showed that cerivastatin was the most powerful statin to inhibit the proliferation of human coronary artery smooth muscle cells. However, this agent has recently been recalled from clinical use, due to the high incidence of rhabdomyolysis especially when it was given with gemfibrozil [28]. Therefore, according to the order of the anti-proliferative potencies observed in the WST-1 test, the Terumo Corporation considers that simvastatin appears one of the most likely candidate drugs for being incorporated in a drug-eluting stent. Consequently, an animal study was performed with an osmotic pump by which simvastatin was delivered in the vicinity of injured common carotid arteries. Rapamycin was chosen as a reference since it has been already demonstrated that this agent suppresses neointimal proliferation by local delivery via stents in human clinical trials [4,5,29]. This experiment showed that simvastatin as well as rapamycin reduced neointimal formation at 14 days after balloon

injury. Furthermore, this suppression by simvastatin was sustained at 28 days.

What is an ideal drug to prevent restenosis?

Firstly, it is imperative that the anti-proliferative effect of a drug on smooth muscle cells is potent enough to prevent restenosis. On the other hand, if a drug delayed re-endothelialization on a stent implanted in a clinical setting, stent thrombosis might occur. Theoretically, it is desirable that a drug inhibits only the proliferation of smooth muscle cells but does not inhibit the proliferation of endothelial cells. The comparison of the anti-proliferative effect of a compound on smooth muscle cells and endothelial cells may suggest the existence of an ideal therapeutic window. Figure 8 shows the anti-proliferative effects of simvastatin and rapamycin on smooth muscle cells together with those on endothelial cells. No therapeutic window for these drugs could be found when comparing the two inhibition curves. However, figure 8 shows that endothelial cells have been reduced to less than 40% of control by rapamycin before an effect on smooth muscle cells occurs. The indication as a more pronounced effect of rapamycin on endothelial cells was also observed in the in vivo study (Figure 6,7). In contrast, the local simvastatin delivery with the osmotic pump reduced neointimal formation, while effective re-endothelialization was observed in the injured carotid arteries of rats in this model. Furthermore, the beneficial effects of statins on endothelial function have been

previously reported [30-32]. These observations suggest that simvastatin might be the better candidate for drug elution.

Other than proliferation of smooth muscle cells, restenosis after stenting implies complex pathophysiological processes including migration of smooth muscle cells, thrombosis and inflammation. Therefore, secondly, an ideal drug should have a beneficial impact on these processes. The anti-migratory effect of statins on smooth muscle cells has been previously reported [17,18]. Moreover, statin therapy has been shown to inhibit platelet aggregation and the release of platelet derived mediators [33,34] as well as to reduce inflammatory responses of the vascular wall [35,36]. These properties of statins also might contribute to prevent restenosis and stent thrombosis.

Thirdly, a hydrophobic drug seems to be ideal because it passes easily through cell membranes and because its intramural diffusion and distribution are superior when compared to a hydrophilic drug [37]. With the exception of pravastatin, statins are hydrophobic. Thus, simvastatin is considered to be a good candidate also from this viewpoint.

Possibility as a treatment for vulnerable plaque

The majority of acute myocardial infarction arises from atherosclerotic lesions that are minimal to moderate in severity as quantified by angiography. It is of paramount

importance to diagnose and treat vulnerable plaques preventively. If a drug-eluting stent would eliminate restenosis without any side effects, it would be justified to treat such a vulnerable plaque with a drug-eluting stent. In this prospect, statin-releasing stents are also ideal because experimental animal models demonstrate that statin therapy can stabilize atherosclerotic plaques [36,38].

Platform.

The Terumo Corporation considers the Tsunami™ stent (Figure 9) as the platform for local simvastatin delivery. This stent has a 6 cells-jointed structure, which provides flexibility and conformability. The alternative arrangement of diamond-shaped cells assures the vessel coverage on bends. These characteristics are advantageous in delivering the stent in complex lesions. The first pilot trial demonstrated the safety and feasibility of the Tsunami™ stent [39].

Future prospect.

It is important that a drug acts in the target lesion at the optimal concentration and appropriate time. To be confirmed, it will be necessary to investigate the local concentrations and gradients of simvastatin when released from a stent. Now, animal evaluations of polymer based simvastatin-eluting Tsunami™ stent are ongoing. We will see in the near future whether this eluting stent works as we expect.

Limitations.

The osmotic pump model used in the present experiment provided local drug delivery from the outside of the adventitia. This is the major limitation of this study because this model is quite different from a clinical setting of a drug-eluting stent. However, this

model enables us to deliver a drug at a constant concentration during a definite time. The small number of observations made in this study is also a limitation.

Conclusion

The preliminary experiments show that, with the exception of pravastatin, statins are potent against the proliferation of smooth muscle cells in vitro. Furthermore simvastatin showed sustained reduction of neointimal hyperplasia in a balloon-injury model, while it had a favorable effect on re-endothelialization. Simvastatin is considered to be a good candidate for local delivery via a drug-eluting stent.

FIGURE LEGENDS

Figure 1.

Wst-1 test of smooth muscle cells (A) and endothelial cells (B) after 3 days' treatment with the test compounds. Each value is expressed as the average percentage of the control value (A: 1.212 O.D. (450nm) units/well, B: 0.420 O.D. (450nm) units/well). Each data point is the average of 6 observations. *$p < 0.05$ versus the value at 0.001 μM.

Figure 2.

Wst-1 test of smooth muscle cells (A) and endothelial cells (B) after 3 days' treatment with rapamycin and simvastatin. Each value is expressed as the average percentage of the control value. Each data point is the average of 3 observations. *$p < 0.05$ versus the value at 10^{-7} μM (A) and 10^{-10} μM (B).

Figure 3.

LDH assay of smooth muscle cells (A) and endothelial cells (B) after 24 hours' treatment with the test compounds. Each value is expressed as the average percentage compared with the value of totally lysed cells with Triton-X100. Each data point is the average of 6 observations. *$p < 0.05$ versus the value at 0.001 μM.

Figure 4.

The neointimal thickness of common carotid arteries from the rats 14 days after the balloon injury **(solid bars)** and the rats 28 days after the balloon injury **(open bars)**. SIM = the simvastatin group; RAP = the rapamycin group; CON = the control group

*$p < 0.05$ versus CON group

Figure 5.

Representative histologic sections stained with hematoxylin-eosin of the common carotid arteries from (A) a rat treated with simvastatin 14 days after balloon injury; (B) a rat treated with rapamycin 14 days after balloon injury; (C) a rat treated with simvastatin 28 days after balloon injury; (D) a rat treated with rapamycin 28 days after balloon injury.

Figure 6.

Representative histologic sections stained with a polyclonal antibody against won Willebrand factor of the common carotid arteries from (A) a rat treated with simvastatin 14 days after balloon injury; (B) a rat treated with rapamycin 14 days after balloon injury. The arrows show arrows indicate the p the cells positive of the stain.

Figure 7.

Endothelialization scores at 14 days

Figure 8.

Wst-1 test of simvastatin and rapamycin. This graph shows the anti-proliferative effect on human coronary smooth muscle cells (SMC) together with human coronary endothelial cells (EC).

Figure 9.

Tsunami™ stent.

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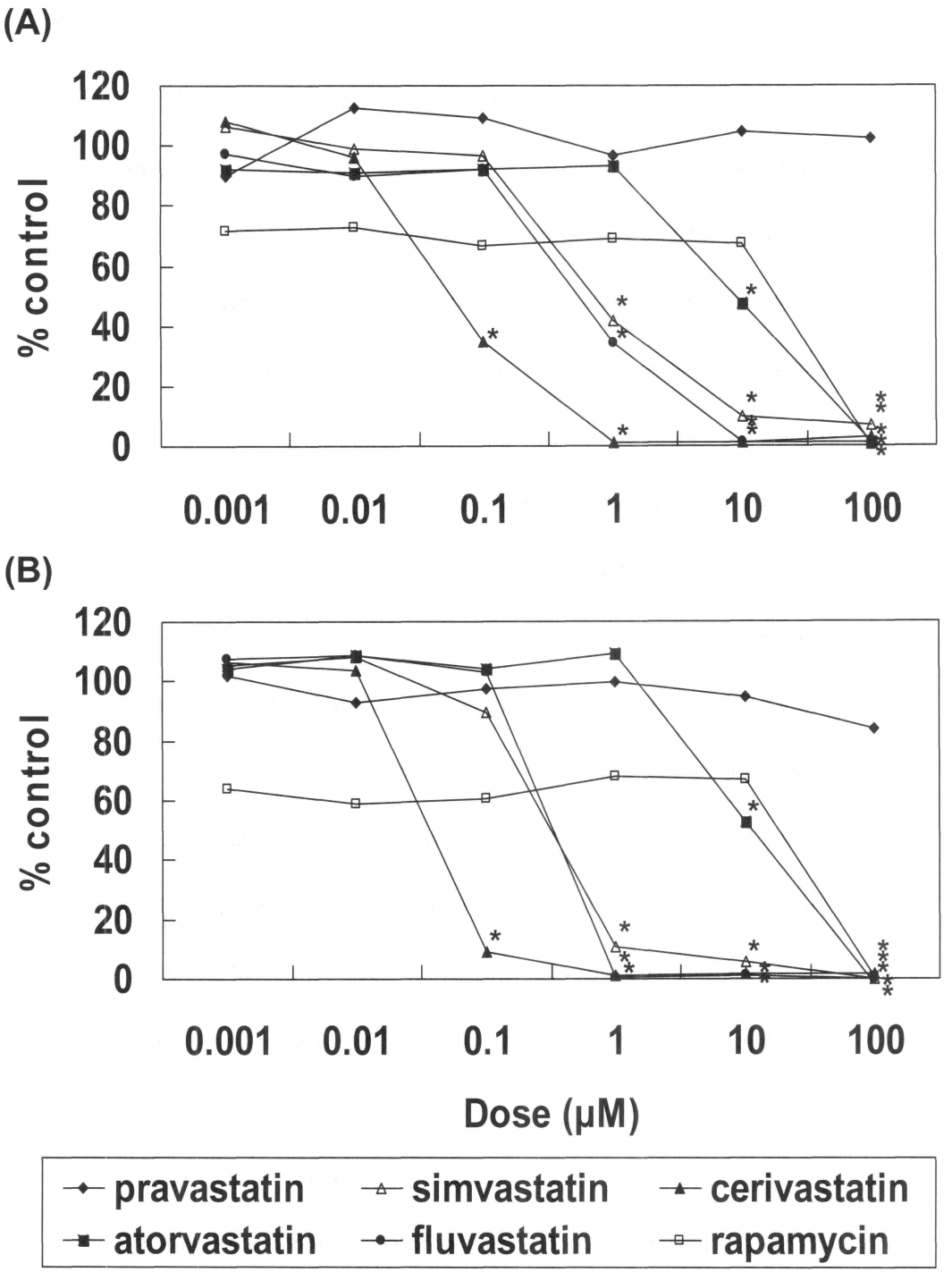
Figure 1


(A)
120
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40
20
0
% control
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0.1
1
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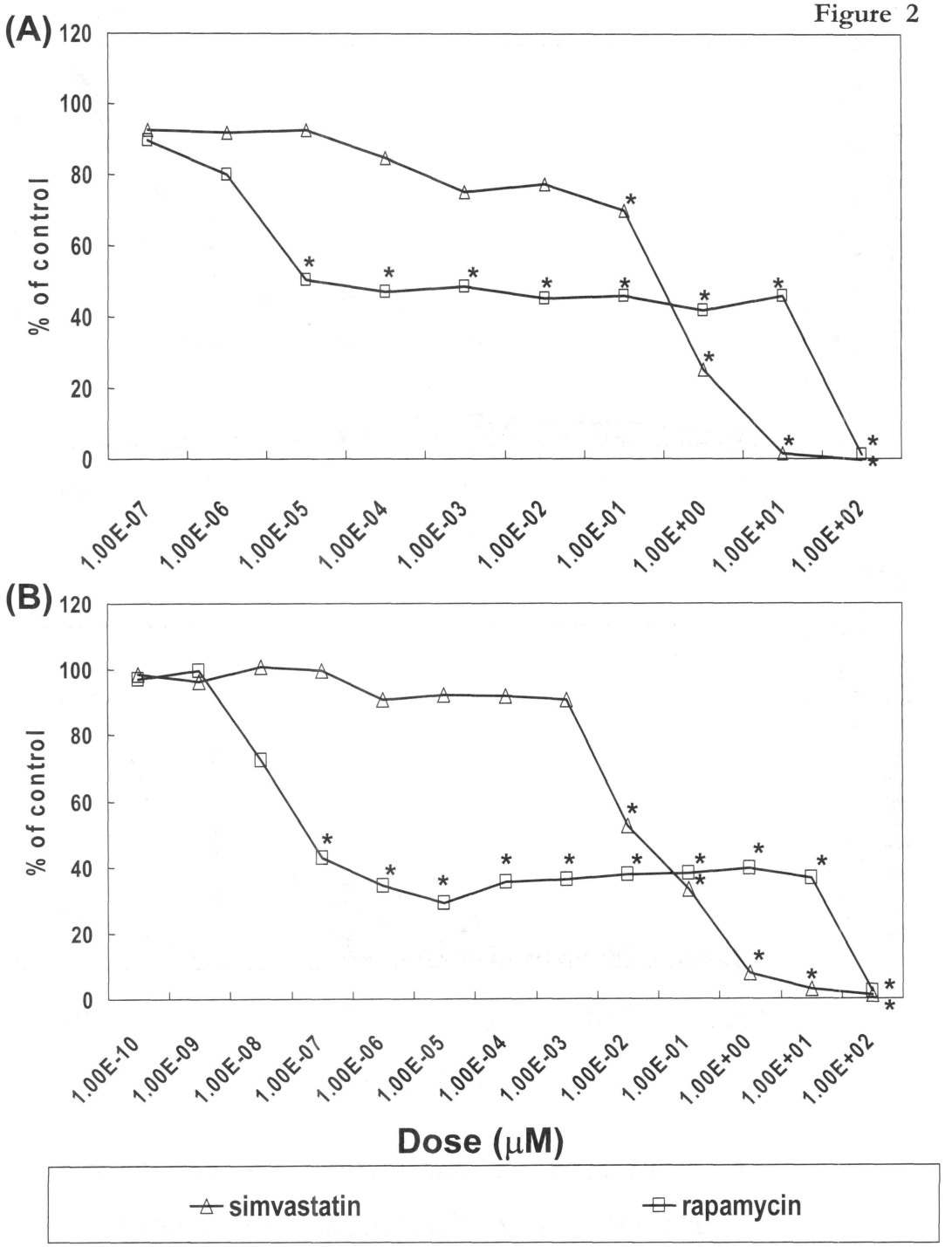
100
(B)
120
100
80
60
40
20
0
% control
0.001
0.01
0.1
1
10
100
Dose (μM)
pravastatin
simvastatin
cerivastatin
atorvastatin
fluvastatin
rapamycin

Figure 2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% of control
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1.00E-04
1.00E-03
1.00E-02
1.00E-01
1.00E+00
1.00E+01
1.00E+02
(B)
120
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% of control
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1.00E-07
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1.00E-05
1.00E-04
1.00E-03
1.00E-02
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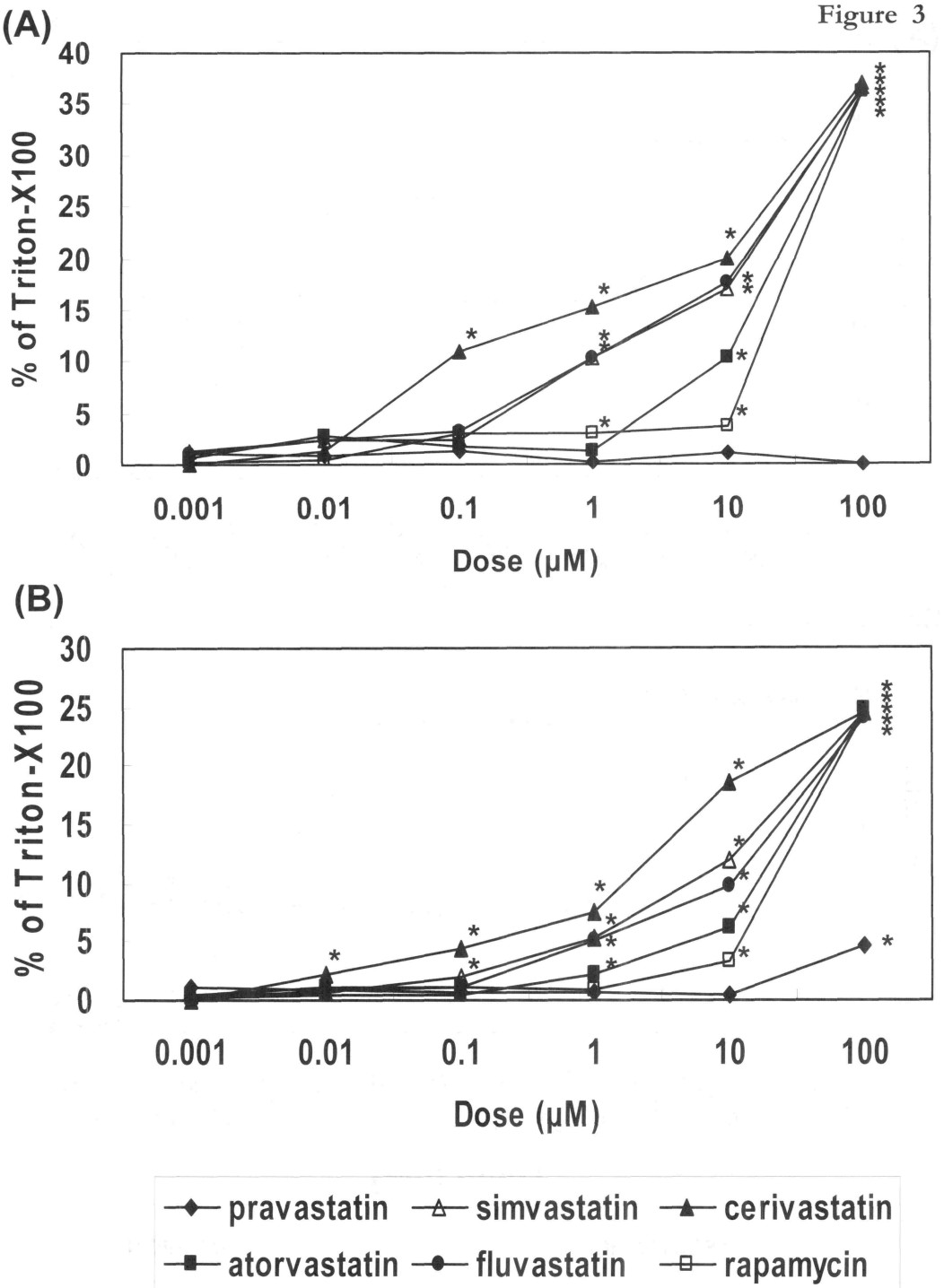
1.00E+00
1.00E+01
1.00E+02
Dose (μM)
simvastatin
rapamycin

Figure 3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% of Triton-X100
40
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30
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20
15
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0.1
1
10
100
Dose (μM)
(B)
% of Triton-X100
30
25
20
15
10
5
0
0.001
0.01
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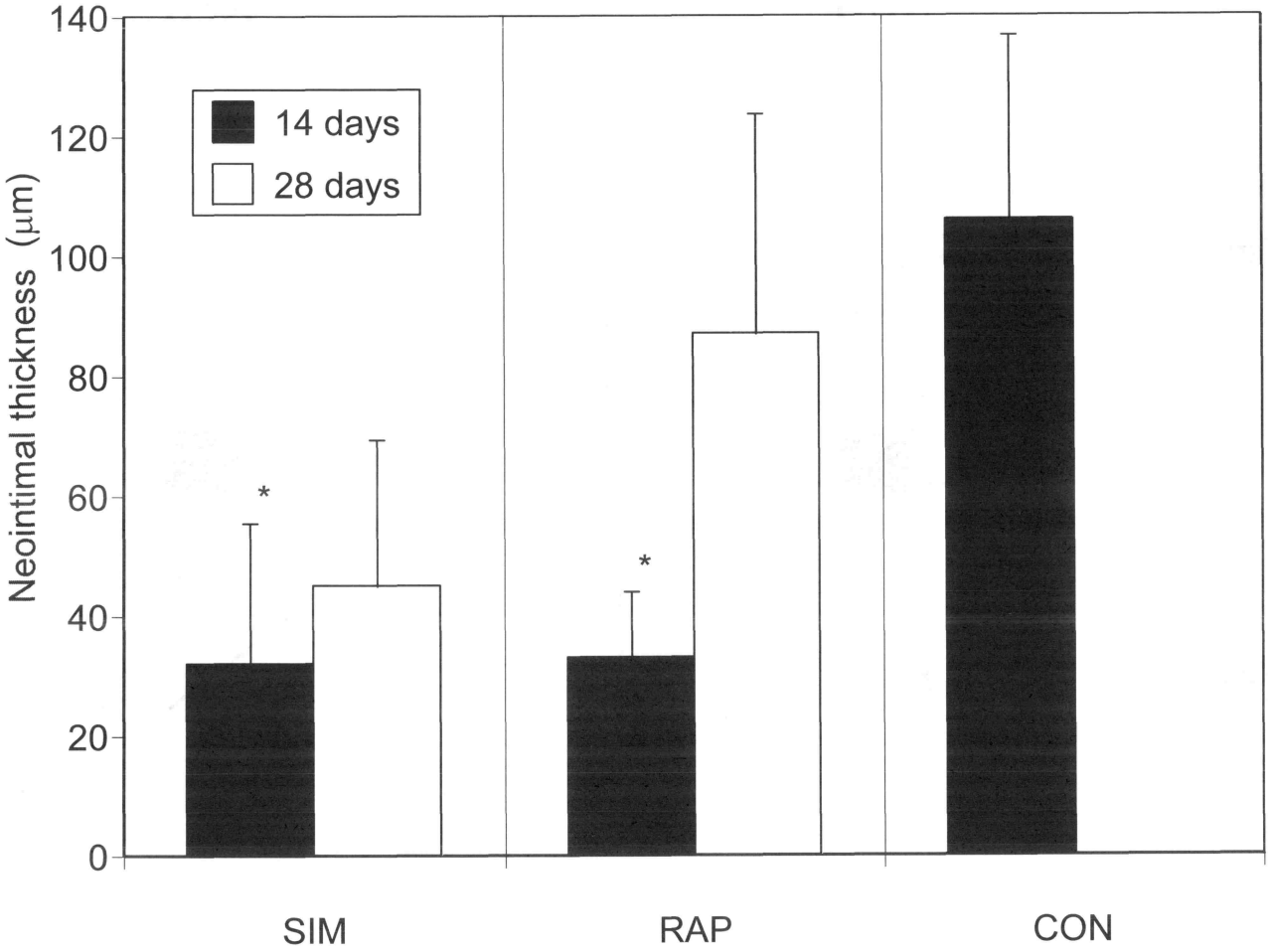
Dose (μM)
pravastatin
simvastatin
cerivastatin
atorvastatin
fluvastatin
rapamycin

Figure 4


140
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Neointimal thickness (μm)
14 days
28 days
*
*
SIM
RAP
CON

Figure 5

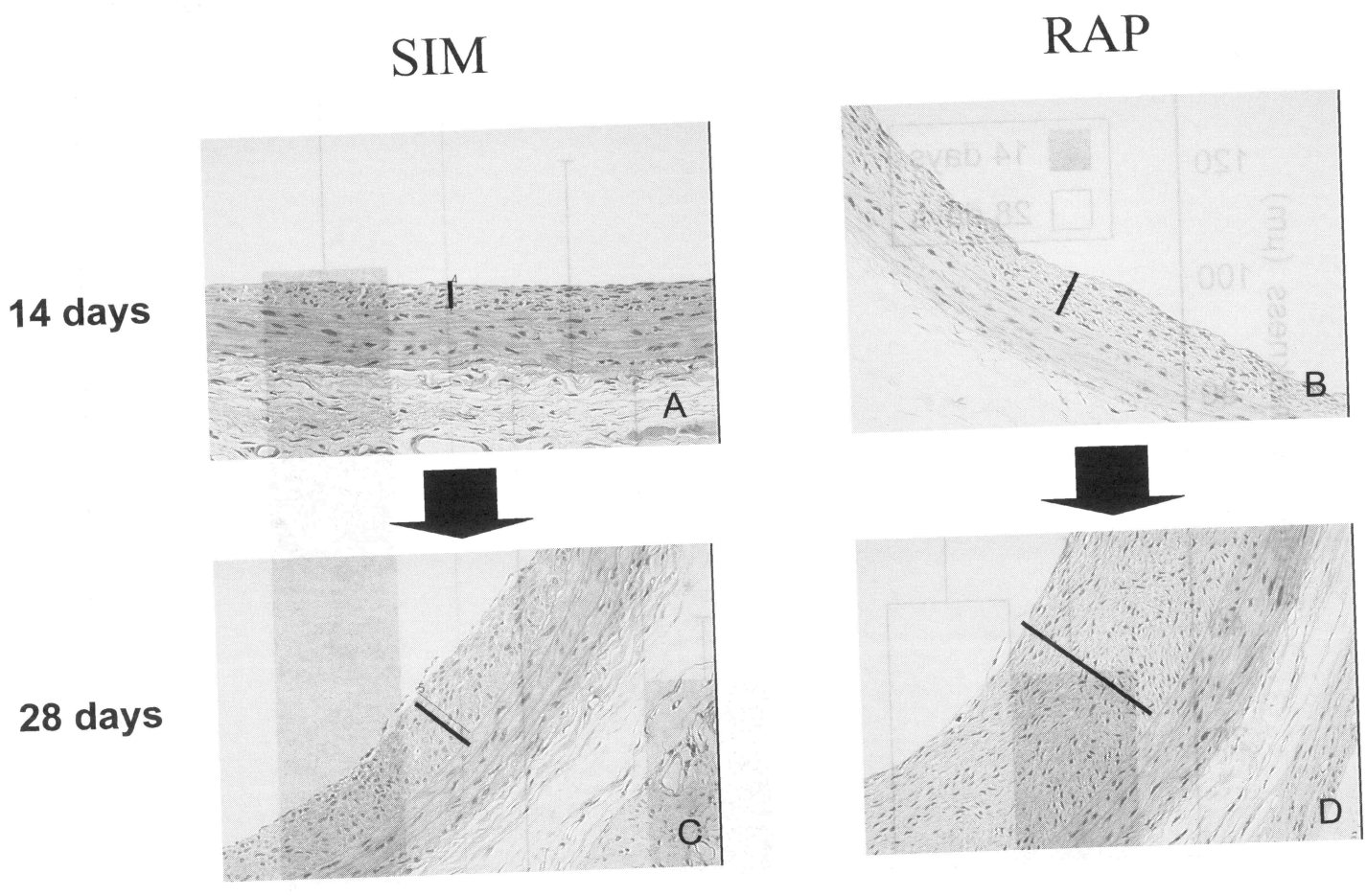


Figure 6

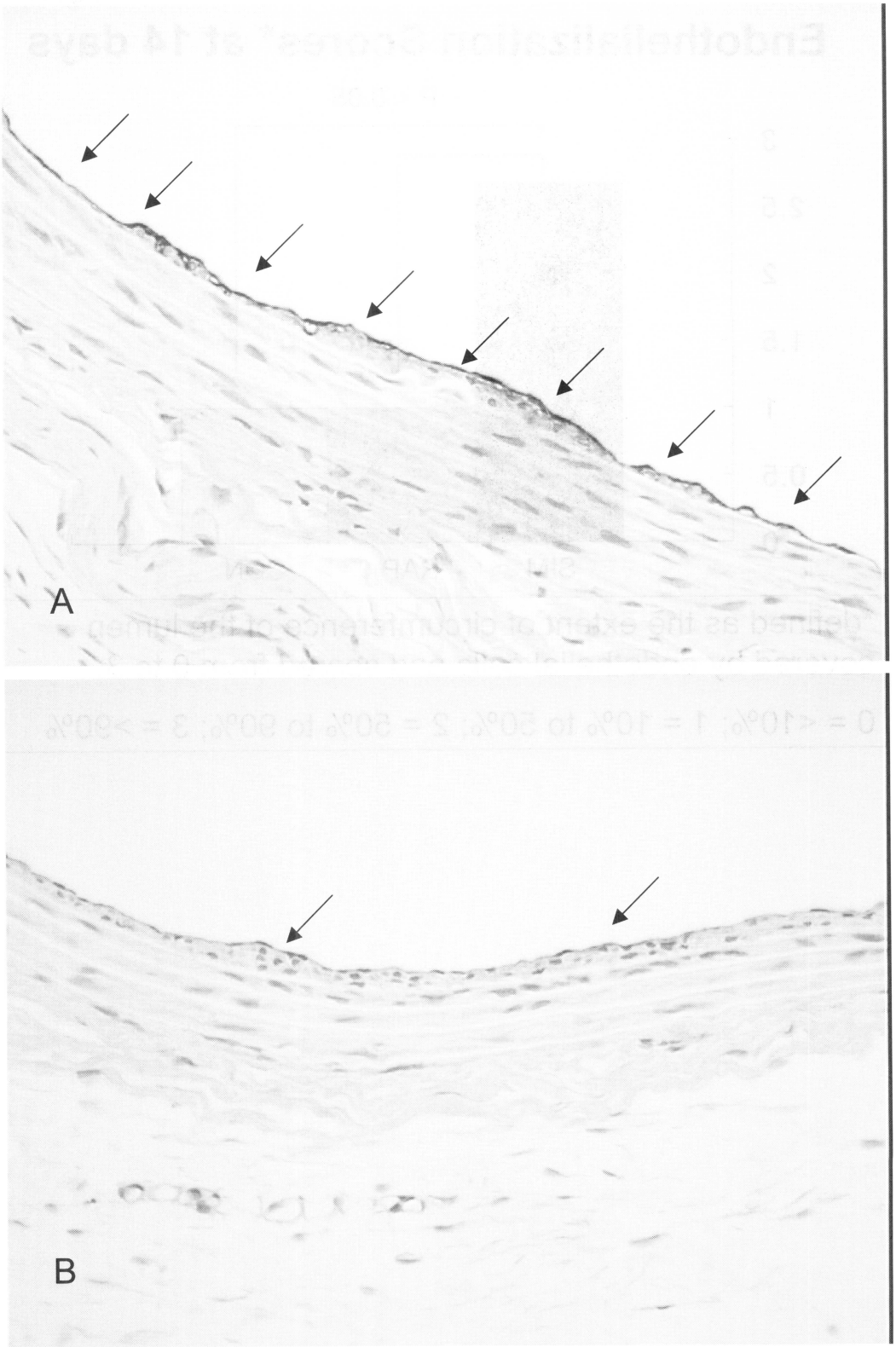
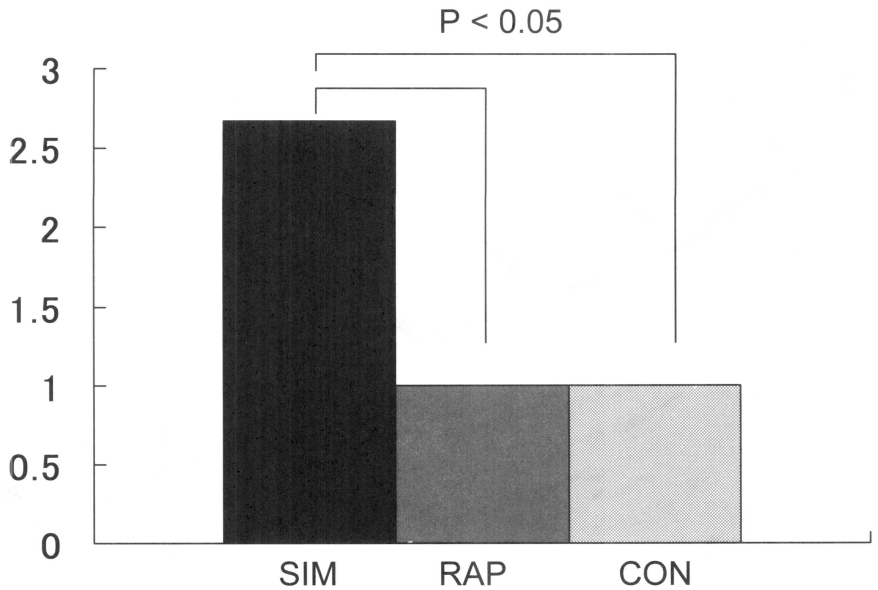


Figure 7

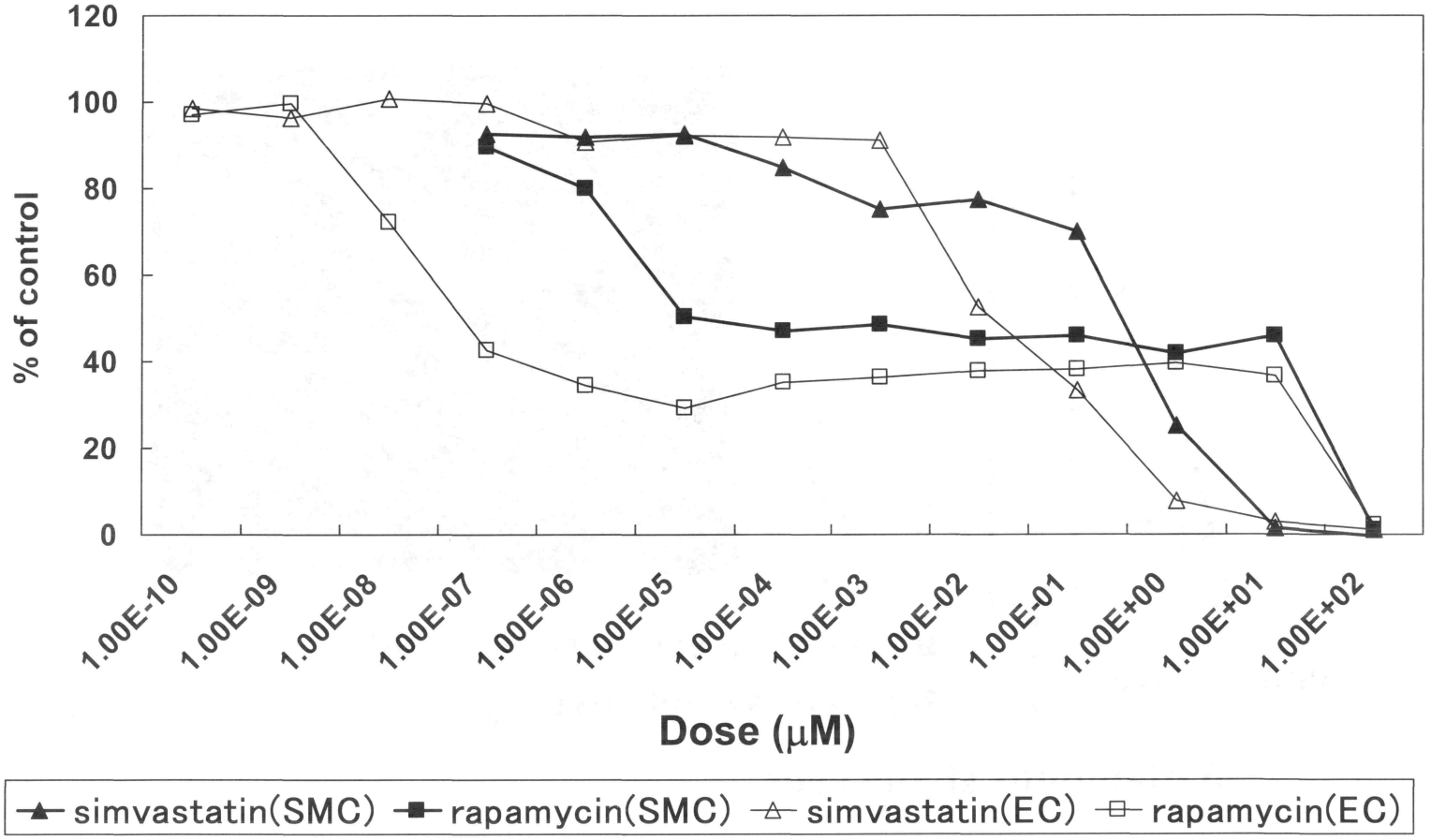
Endothelialization Scores* at 14 days



*defined as the extent of circumference of the lumen covered by endothelial cells and scored from 0 to 3:

0 = <10%; 1 = 10% to 50%; 2 = 50% to 90%; 3 = >90%

Figure 8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40
20
0
% of control
1.00E-10
1.00E-09
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1.00E-07
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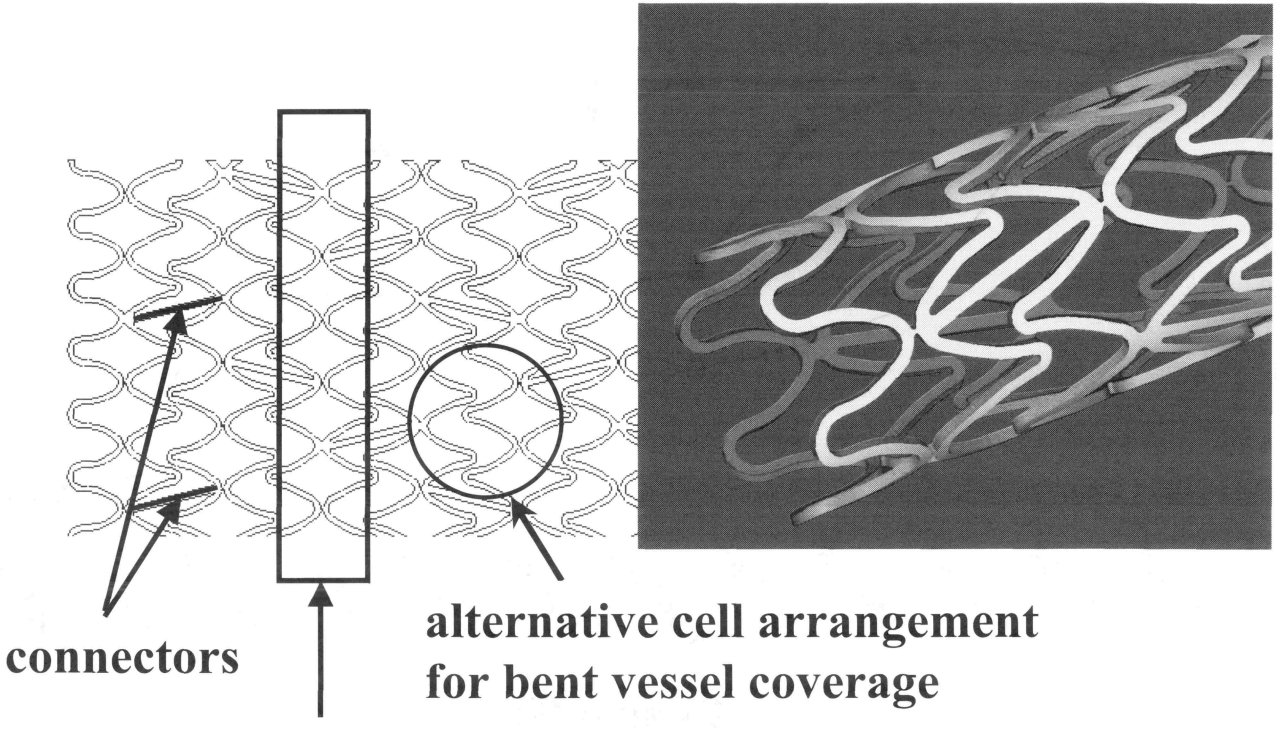
1.00E-05
1.00E-04
1.00E-03
1.00E-02
1.00E-01
1.00E+00
1.00E+01
1.00E+02
Dose (μM)
simvastatin(SMC)
rapamycin(SMC)
simvastatin(EC)
rapamycin(EC)


connectors
alternative cell arrangement
for bent vessel coverage
6 diamonds shape cells

Chapter 16

Actinomycin Eluting Stent for Coronary Revascularization: A Randomized Feasibility and Safety Study (The ACTION Trial)

Serruys PW, Ormiston JA, Degertekin M, Tanabe K, Sousa JE, Grube E, den Heijer P, de Feyter P, Buszman P, Schömig A, Marco J, Polonski L, Thuesen L, Zeiher AM, Bett JHN, Suttorp MJ, Glogar HD, Pitney M, Wilkins GT, Whitbourn R, Veldhof S, Miquel K, Johnson R, Virmani R.

Actinomycin Eluting Stent for Coronary Revascularization: A Randomized Feasibility and Safety Study (The ACTION Trial)

Patrick W. Serruys, John A. Ormiston, Muzaffer Degertekin, Kengo Tanabe, J. Eduardo Sousa, Eberhard Grube, Peter den Heijer, Pim de Feyter, Pawel Buszman, Albert Schömig, Jean Marco, Lech Polonski, Leif Thuesen, Andreas M. Zeiher, J.H. Nicholas Bett, Maarten J. Suttorp, Helmut D. Glogar, Mark Pitney, Gerard T. Wilkins, Robert Whitbourn, Susan Veldhof, Karine Miquel, Rachel Johnson, Renu Virmani

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ABSTRACT

Background- Drug-eluting stents (DES) releasing sirolimus or paclitaxel almost abolish restenosis. The antiproliferative drug, Actinomycin-D, highly effective in reducing neointimal proliferation in preclincal studies was selected for clinical evaluation.

Methods and Results- The multi-center, single blind, 3-armed Action Trial, randomized 360 patients to receive a DES (2.5 or 10 mcg/cm^2 of Actinomycin-D per stent), or a metallic stent (MS). The primary endpoints at 30 days were Major Adverse Cardiac Events (MACE), and at 6 months diameter stenosis by angiography and tissue effects and neointimal volume by Intravascular Ultrasound (IVUS). When early monitoring revealed an increased rate of repeat revascularization the protocol was amended to allow for additional follow-up for DES patients. Angiographic control of MS patients was no longer mandatory. The biased selection of the DES patients undergoing IVUS follow-up invalidated the interpretation of IVUS findings.

The late lumen loss in-stent and at the proximal and distal edges was higher in both DES groups when compared with MS and resulted in higher six months and one year MACE (34.8 % and 43.1% vs 13.5%) driven exclusively by target vessel revascularisation (TVR) without excess death or MI.

Conclusions: the results of the Action trial indicate that all antiproliferative drugs will not uniformaly show a drug class effect in the prevention of restenosis.

CONDENSED ABSTRACT

Actinomycin-D, an antiproliferative agent effective in preclinical studies in reducing neo-intimal hyperplasia, was evaluated clinically in the ACTION trial. This single blind, 3 arm trial randomized 360 patients to receive a stent coated with either 2.5 or 10 mcg of drug per cm^2 of stent, or to receive a metallic stent. Restenosis was higher in both drug-eluting arms compared with the metallic stent arm resulting in more repeat revascularization but not death or myocardial infarction by 12 months.

Keywords: Drug eluting stent, Actinomycin-D, Randomised trial

Introduction

Restenosis after Percutaneous Coronary Intervention (PCI) remains a major limitation of efficacy[1]. The concept of further reducing restenosis by coating a stent with an appropriate medication that elutes has great appeal. The stent can abolish recoil and negative remodeling while a drug can be delivered in sufficient concentration directly to the injured site potentially limiting the intimal hyperplastic component of restenosis[2].

Delivery platforms incorporating sirolimus[3,4] and paclitaxe[5,6] almost completely abolish restenosis in simple lesions but efficacy has yet to be demonstrated in more complex lesions.

Actinomycin-D affects the "S"phase of the cell cycle by forming a stable complex with double-stranded DNA inhibiting RNA synthesis and is a powerful inhibitor of cell proliferation. To create the Actinomycin-D stent, Actinomycin was coated onto the stainless steel Multilink Tetra stent in a polymer.

Following preclinical studies, the ACTION Trial (Actinomycin eluting stent Improves Outcomes by reducing Neointimal hyperplasia), the first clinical evaluation of the Multi-Link Actinomycin-D coronary stent system aimed to test the safety and efficacy of 2 doses of Actinomycin-D compared with the MULTI-LINK TETRA MS.

Methods

Study design

This was a prospective, randomized, parallel, 3-arm, single-blind trial with two doses of Actinomycin-D (2.5 and 10 mcg/cm^2) coated on the Actinomycin eluting stent compared with the uncoated MULTI-LINK TETRA stent as the control. The protocol was approved by the ethics committees of each of the 28 participating institutions (appendix) and all patients gave written informed consent.

Endpoints

The primary safety endpoints were MACE at 30 days, and local tissue effects at 6 months (incomplete stent apposition, persisting dissection, edge stenosis and thrombus formation). MACE was defined as a composite of death, Q-wave myocardial infarction (QMI), non-Q-wave myocardial infarction (NQMI), more than 3 times the upper limit of normal CK levels and revascularization by surgery (CABG) or repeat PCI attributed to the target site (the stented segment including 5 mm proximal and distal to the stent). When target vessel (vessel containing the target site) revascularization was included in MACE, the composite end-point was re-named target vessel failure (TVF).

The primary performance endpoints were, at 6 months, the reduction of in-stent volumetric burden assessed by IVUS and reduction of target site angiographic diameter stenosis.

The secondary performance endpoints were TVF at 6 and 12 months and angiographic binary restenosis at 6 months.

Power calculation and sample size

To detect a difference of 6.6% in diameter stenosis and of 11.5mm^3 in intimal hyperplasia with a significance level of 0.05 and 90% power, 110 patients would be needed in each of the 3 arms. A sample size of 120 patients was chosen.

Patient selection

Patients were eligible for the study if they were able to comply with the study protocol, were over 18 years of age, and had angina pectoris or silent ischemia. Additional eligibility criteria were the presence of a single de novo ≥ 50-< 100% diameter stenosis, in a native coronary artery that was ≥ 3.0 mm and ≤ 4.0 mm in diameter by visual estimate, that could be covered by an 18mm stent. Blood flow was required to be TIMI grade 1 or higher. Patients were ineligible if they had an evolving MI, had an unprotected left main coronary stenosis equal to or greater than 50 percent, an untreated lesion of 40% diameter stenosis proximal or distal to the target site, an aorto-ostial lesion, a calcified lesion without successful predilatation, or had intolerance of aspirin, clopidogrel or ticlopidine.

Randomization was done by a telephone allocation service.

Study device

The 3 components of the investigational device were the Multilink Tetra stent, a polymeric coating and an anti-proliferative drug, Actinomycin-D [7,8].

The flat phenoxazone and large polypeptide rings of Actinomycin-D form a stable complex with double-stranded DNA (via deoxyguanosine residues), thus inhibiting DNA-primed RNA synthesis. The 2.5 and 10 micrograms (mcg) per cm^2 of metal stent

surface area of Actinomycin-D used in the polymer-coated stent is equivalent to <1% to <2% of the recommended daily total chemotherapy dose of 500 μg given intravenously for 5 days to adults. The eluting profile of Actinomycin-D is targeted to release 80% of drug in 28 days.

Stenting procedure

Stents were 18 mm in length and 3.0, 3.5 or 4.0 mm in diameter.To avoid vessel damage outside the stent predilatation and postdilatation balloons shorter than the stent were recommended. For major dissections or abrupt occlusions in the DES arms, a single bailout stent from the same randomization arm was allowed. Clopidogrel 75 mg daily was to be administered for 6 months and aspirin 100-325 mg daily for at least 1 year after the procedure.

Quantitative Coronary Angiographic Evaluation

In quantitative angiographic analyses, binary restenosis and late loss were determined in-stent and within the target site [4]. The "vessel segment" was defined as that portion of artery bounded by side-branches proximal and distal to the target site. Coronary aneurysms were defined on angiography as localised coronary artery dilatation ≥ 1.5 x reference diameter. [9]

Quantitative Intravascular Ultrasound

Target site IVUS evalutation was performed as previously described. [10,11,12]

Statistical analysis

All analyses were based on the intent to treat principle. For continuous variables, differences between the treatment groups were evaluated by analysis of variance or Wilcoxon's rank-sum test. For discrete variables, differences were expressed as counts and percentages and were analysed with Fisher's exact test.

Event free survival times were analyzed using the Kaplan-Meier method. Differences between each of the doses and the MS were compared with the use of the Wilcoxon and log-rank test.

All tests are 2-sided and unadjusted for multiple comparisons.

Study organization

The Data and Safety Monitoring Board (DSMB), and the Clinical Events Committee were separate groups independent from the study, that monitored safety and adjudicated clinical endpoints respectively. The angiographic and ultrasound core laboratory (Cardialysis BV, Rotterdam, the Netherlands) was blinded to the treatment and clinical outcomes and assessed each imaging modality independently. The trial sponsor was Advanced Cardiovascular Systems, Inc., a subsidiary of Guidant Corporation, Santa Clara, CA.

Results

Patient baseline characteristics

Between August 2001 and November 2002, 360 patients were randomly assigned to receive a DES with a dose of 2.5 mcg/cm^2 (120 patients) or 10 mcg/cm^2 (121 patients), or a MS (119 patients). Three patients (1 in the MS arm and 2 in the 10 mcg DES arm) were deregistered as they did not receive either a DES or control stent. Baseline clinical and angiographic characteristics (Table 1) did not differ between treatment groups except that there were fewer diabetic patients in the MS group. The significant difference in minimal lumen diameter (MLD) post procedure between the MS and DES groups could not be accounted for by procedural differences.

Patient enrolment, procedural characteristics, and clinical outcomes in-hospital and at 1 month

There was adherence to the randomization in all but one patient. Post dilatation was performed in 37% of the patients with an average pressure of 14.8 atmospheres. The procedural success was 99%. Platelet glycoprotein IIb/IIIa inhibitors were administered to 16% of patients.

A second DES for a suboptimal result was implanted in 15 patients who were analysed on an intention to treat basis.

The in-hospital MACE were confined to the 4 patients (1.1%) with non-Q MI. MACE rates at 30 days ranged between 0.8 and 2.5%, without differences between groups.

However, early monitoring of a subset of 39 DES patients angiography revealed an increased rate of TSR suggesting that the investigational device was not performing as intended. After the sponsor informed the principal investigator and the DSMB, the

following recommendations were made: 1. Accelerated angiographic follow-up for DES patients. 2. A second angiographic and clinical follow-up 6 months later. 3. Possible re-intervention for moderate restenosis (>30% DS). 4. Extension of clopidogrel administration for at least a further 6 months for DES patients. 5. Angiographic and IVUS follow-up was no longer mandatory for MS patients as primary performance endpoints could not be reached. Consequently, only 65 of 118 MS patients underwent imaging and 101 clinical follow-up at 6 months.

Angiographic outcomes

The late loss and restenosis at 6-months in-stent and in-lesion were higher in both DES groups compared with MS (Table 2). Aneurysm formation was infrequent with 2 (3.1%) in MS and 5 (2.2%) in DES patients.

Clinical outcomes at 12 months

At 12 months, MACE and TVF were higher in the DES than in the MS patients due mainly to increased TSR (Table 3). Of the 2 deaths, the one with a MS was sudden at 44 days and the one with low-dose DES was due to MI at 306 days. After 30 days, there were 2 additonal non-QMIs in the low dose and 1 in the high dose DES arms. To 1 year, there were 14 DES patients who had a second reintervention and in 2 a third reintervention.

IVUS outcomes

There was late-acquired incomplete stent apposition (ISA) in 6 patients in the low dose and 7 in the high dose group but there was late persisting dissection in only 1 patient who was from the high dose group.

At variance with the angiographic findings, there were apparently no differences between groups in volumetric obstruction measured by IVUS. This discrepancy may result from a biased selection of the DES patients undergoing IVUS during follow-up (Table 4), as demonstrated by the higher binary "vessel segment" restenosis rate (32% and 47.8%) in the DES patients who did not undergo IVUS follow-up, when compared with those who did (25.8% and 23.7%). This biased selection of the DES patients undergoing IVUS during follow-up invalidated interpretation of the IVUS findings. Directional atherectomy, a standard treatment for in stent restonosis, retrieved restenotic material in 7 patients. Histopathological analysis revealed presence of proteoglycan matrix and smooth muscle cells interspersed with collagen type III. There were rare foci of CD68 positive macrophages and T lymphocytes (CD45 Ro). Cell proliferation identified by Ki 67 antigen staining was also rare. Incidentally some areas showed the presence of persisting fibrin consistent with delayed healing.) (See Figure 2)

Discussion

Summary

The results of this trial showed that while in-hospital and 1 month outcomes were similar in each group, by 6 months there was increased restenosis, late lumen loss, and target site revascularization in the DES arm. Despite this increased rate of restenosis, mortality and rate of myocardial infarction were very low in ACTION, contrasting with the medium or long-term follow-up of the SCORE study (unpublished data, personal communication from M. Russel MD) showing high incidence of late death and myocardial infarction. In addition, the relatively benign nature of the restenotic pathological material retrieved by DCA contrasts with that from patients

treated with QuaPDs stents, where in some specimens there were large aggregates of macrophages and T-lymphocytes suggesting a persisting active inflammation process with a high proliferation index (Ki-67 immunostaining) [13].

Preclinical Studies

The safety of the polymer, was demonstrated in the porcine coronary model, where the histological response was similar to MS to 180 days.

DES with 4 doses of Actinomycin-D (2.5, 10, 40 and 70 mcg/cm2) were evaluated in preclinical studies in the porcine coronary model by angiography, histomorphometry and histopathology at 28 days. At this time, all vessels were patent and there was marked suppression of neointimal formation above the stent with all doses. Neointimal thickness above the internal elastic lamina was equivalent to that with the MS. Medial thinning and necrosis was observed in the high dose groups, as was positive remodeling. Intimal fibrin deposition and inflammation were present with all doses but most marked with the higher doses. Based on these preclinical findings, the two lower doses were considered safe for further evaluation in humans with 3 months data pending.

Long-term animal data and lessons learned from this trial

At the time of the design of this trial it was current practice for MS, which was extended to DES, to commence clinical investigation following analysis of 28-day animal data.[3] As soon as the sponsor became aware of the clinical events and the outcomes of long-term animal data, immediate action, as previously described, was taken. This trial has demonstrated that 28-day animal data do not provide sufficient information to judge safety and efficacy of DES. In the light of animal results at 3

months and the results of the Action trial, it is now reasonable to conclude that medial necrosis and inflammation at 28 days are predictors of poor outcomes at 3 months. Efficacy may not be predictable from 28 day data and 3 month data may be needed especially if the balloon-to-artery ratio for stent deployment is 1.1:1.

Methodological implications of an early detection of lack of efficacy

Traditionally it has been believed that the histological results observed in pigs at 30 days correspond to the anatomo-morphologic change documented in humans at 6-months and similarly animal observations made at 3 months should be correlated to some extent with the anatomical findings made in humans at 18 to 24 months. Since there was deterioration in the histological findings in animals between 30 and 90 days, there was a concern that there would be deterioration in patients between 6 and 18 months. Therefore, a policy of accelerated angiographic follow-up (before 6 months) with possible intervention for moderate restenosis >30% DS even in asymptomatic patients were implemented and a second angiographic investigation 6 months later was recommended. As a consequence, a bias toward MACE (re-intervention) in the DES patients cannot be excluded.

As primary performance endpoints could not be reached, angiographic and IVUS follow-up was no longer mandatory for MS patients. This lead to bias in the MS group towards higher MACE because of selection of symptomatic patients for follow-up angiography. Counterbalancing this there may be a bias towards lower MACE in the MS group, because of lower angiography driven repeat intervention in asymptomatic patients [14].

IVUS in restenotic lesions in the DES groups was not pursued with the same assiduity as seen in a trial with favourable outcome resulting in a disproportionately

low number of severe restenoses studied with IVUS. This latter phenomenon led us to declare invalid the comparison of neointimal volume and percent volume obstruction between the 3 groups. However, serial IVUS analyses, although biased towards patients without restenosis, revealed significant increase in the plaque behind the stent struts which was higher in the 10 mcg group (32±39 mm^3 $p<0.001$, $n=55$) than in the 2.5 mcg (21±29 mm3 $p<0.001$, $n=52$) and control MS (18±45 mm^3 $p=0.11$, $n=17$) group. In addition, the serial analysis of the 5mm proximal and distal edges of the stent in the 10mcg group showed a significant increase (+7±10 mm^3 and +7±13 mm^3, $p<0.001$) in plaque (vessel volume-lumen volume) resulting in a decrease (-4±12 mm^3 and -6±14 mm^3,$p<0.01$) in lumen volume in absence of change in vessel volume. Since cell culture experiments did not show signs of paradoxically increased proliferation of smooth muscle cells with Actinomycin-D concentrations down to of 10^{-12} Molar these IVUS findings may be interpreted as signs of cytotoxicity with late inflammatory and proliferative response.

Conclusion

The impressive results observed in the first drug-eluting stent trials with sirolimus and paclitaxel have led to speculation that any antiproliferative DES would have a beneficial effect on restenosis. However, the ACTION trial shows that there is no class effect and all antiproliferative drugs are not effective in the prevention of restenosis. It has become clear that promise in early pre-clinical studies (30 days) does not necessarily translate into clinical effectiveness at 6 months and that late safety animal data (90 days) is a prerequisite for clinical investigation [15].

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Table 1. Baseline clinical and angiographic characteristics of each study group

	MS (n=118)	2.5 mcg (n=120)	10 mcg (n=119)
Age, years (mean ± SD)	60 ± 10	61 ± 11	60 ± 11
Gender, male	78	78	80
Previous MI	41	38	37
Diabetes mellitus*	5	15	11
Treated dyslipidemia	53	58	54
Treated hypertension	50	49	45
Current smoker	30	23	29
Angina pectoris†			
CCS Class I	7	4	4
CCS Class II	34	34	35
CCS Class III	21	21	23
CCS Class IV	15	14	13
Target coronary artery			
LAD	37	44	42
RCA	42	40	35
LCX	21	16	23
Lesion type			
A	7	7	2
B1	23	21	29
B2	66	64	64
C	4	8	5
Reference vessel diameter,	2.83	2.84	2.91
(mm)	11.3	11.6	10.7
Lesion length, (mm)	1.00	1.01	1.04
MLD pre, (mm)	2.64	2.78	2.82
MLD post, (mm)			
	64	64	63
Diameter stenosis pre			

Plus-minus value are means ±SD; Unless indicated otherwise, all data are presented as percent of patients.

MI = myocardial infarction; LAD = left anterior descending; RCA = right coronary artery; LCX = left circumflex.; MLD = minimal luminal diameter

* Difference and 95% CI in incidence of diabetes; Control vs 2.5 mcg/mm^2 : –9.9% [-17%, -2.3%]; Control vs 10 mcg/ mm^2: –5.8% [-12%, 1.02%]. † Angina was defined according to the system of the Canadian Cardiovascular Society (CCS).

In the 2.5 and in the 10 mcg groups there were 7 and 8 lesions receiving 2 Actinomycin-D-stents respectively.

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In the 2.5 and in the 10 mcg groups there were 7 and 8 lesions receiving 2 Actinomycin-D-stents respectively.

Table 2. Serial QCA analyses

	MS (n=65)	2.5 mcg (n=114)	P	10 mcg (n=115)	P
In-Stent					
MLD Post mm	2.64±0.34	2.77±0.45	0.02	2.82±0.43	0.002
MLD FUP mm	1.88±0.58	1.76±0.70	0.25	1.90±0.68	0.87
Late loss mm	0.76±0.43	1.01±0.58	0.001	0.93±0.58	0.03
Restenosis %	11	25	0.03	17	0.38
Edges					
Prox MLD Post mm	2.60±0.53	2.73±0.58	0.12	2.79±0.56	0.02
Prox MLD FUP mm	2.32±0.60	2.22±0.67	0.35	2.26±0.76	0.58
Prox Late loss mm	0.28±0.38	0.51±0.52	0.002	0.53±0.61	<0.001
Prox Restenosis %	3	5	0.71	14	0.02
Distal MLD Post mm	2.31±0.56	2.40±0.58	0.32	2.41±0.58	0.25
Distal MLD FUP mm	2.23±0.53	2.05±0.61	0.05	1.99±0.64	0.009
Distal Late loss mm	0.08±0.31	0.35±0.50	<0.001	0.43±0.57	<0.001
Distal Restenosis %	2	4	0.65	6	0.26
Target site*					
DS %	35±15	40±18	0.08	40±19	0.05
Restenosis %	14	26	0.06	28	0.04
Vessel segment					
IRD FUP mm	2.76±0.58	2.71±0.55	0.58	2.78±0.48	0.81
DS %	37±13	41±18	0.11	41±18	0.06
Restenosis rate	14	27	0.04	28	0.04
Median time of angio-fup days	162±53	161±40	NS	160±41	NS

Continuous variables: T-Test (two sided) compared to MS control arm. Discrete varaibles: Fishers exact two sided test compared to MS control arm.* Target site diameter stenosis- primary performance endpoint; intention to treat analysis. MLD = minimal luminal diameter; Prox = proximal; DS = diameter stenosis; IRD = ... Reference Diameter

Table 3. **Most severe (hierarchical) and total count of cardiac events up to 12 months in each treatment group**

	MS n=104*	2.5mcg n=120 †	P Value	10mcg n=119†	P Value
Death, n (%)	1 (0.8)	1(0.8)	ns	0 (0.0)	ns
Myocardial infarction					
Q-wave, n (%)	0 (0.0)	0 (0.0)	ns	0 (0.0)	ns
Non Q-wave, n (%)	1 (1.0)	2 (1.7)	ns	4 (3.4)	ns
Target Site Revascularization					
CABG, n (%)	1(1.0)	0 (0.0)	ns	5 (4.2)	ns
PCI, n (%)	11 (10.6)	37(30.8)	<0.001	41 (34.5)	<0.001
Hierarchical MACE: n (%)‡	14 (13.5)	40 (33.3)	<0.01	50 (42.0)	<0.001
Event-free survival, n (%)	90 (86.5)	80 (66.7)		69 (58.0)	
Target Vessel Revascularization (CABG and PCI) n (%)	3 (2.9)	4 (3.3)	ns	1 (0.8)	ns
Target vessel failure, n, (%) §	17 (16.3)	44 (36.7)	<0.001	51 (42.9)	<0.001
Total count of events, n (%)	16	45		61	

CABG = coronary artery bypass graft; PCI; percutaneous coronary intervention; MACE = major adverse events

* Follow-up no longer mandatory for MS group, therefore for 14 patients no follow-up available.

† For 5 and 3 patients in the 2.5 and 10 mcg group respectively no follow-up case report forms have been received, however, these patients have been contacted and all are alive and had no other MACE at 12 months follow up timeframe.

‡ Includes Death, MI, Target Site Revascularization

§ Includes Death, MI, Target Site Revascularization and / or Target Vessel Revascularization

p-values are displayed for descriptive purposes only since they were not the result of formally planned statistical hypothesis testing, and have not been adjusted for multiple comparisons

Table 4. Incidence of vessel segment restenosis in patients with and without IVUS

	MS	2.5 mcg	10 mcg
Vessel segment restenosis			
Patients with IVUS n (%)	4/39 (10.3)	23/89 (25.8)	22/93 (23.7)
Patients without IVUS n (%)	5/26 (19.2)	8/25 (32.0)	11/23 (47.8)
	*p = 0.47	p = 0.61	p = 0.037

*Fischer's exact test

FIGURE LEGENDS

Figure 1

Kaplan-Meier estimates of survival free of repeated target site revascularization among patients who received Actinomycin-eluting 2.5 and 10 mcg stents and those who received standard stents.

The rate of event-free survival was significantly higher in the control stent group than in the Actinomycin stent group (P < by the Wilcoxon and log-ranks tests).

Figure 2

Atherectomy specimen of restenosis tissue. The Movat pentachrome stain shows a tissue fragment consisting mostly of SMCs proteoglycan matrix and focal fibrin accumulation (arrows). Alcian blue stain demonstrating proteoglycans.

Sirius red shows a green birefringence consistent with collagen type III. There were rare foci of CD68-positive macrophages andT-lymphocytes (CD45Ro). Cell proliferation identified by Ki-67 antigen staining was also rare.

Figure 1.

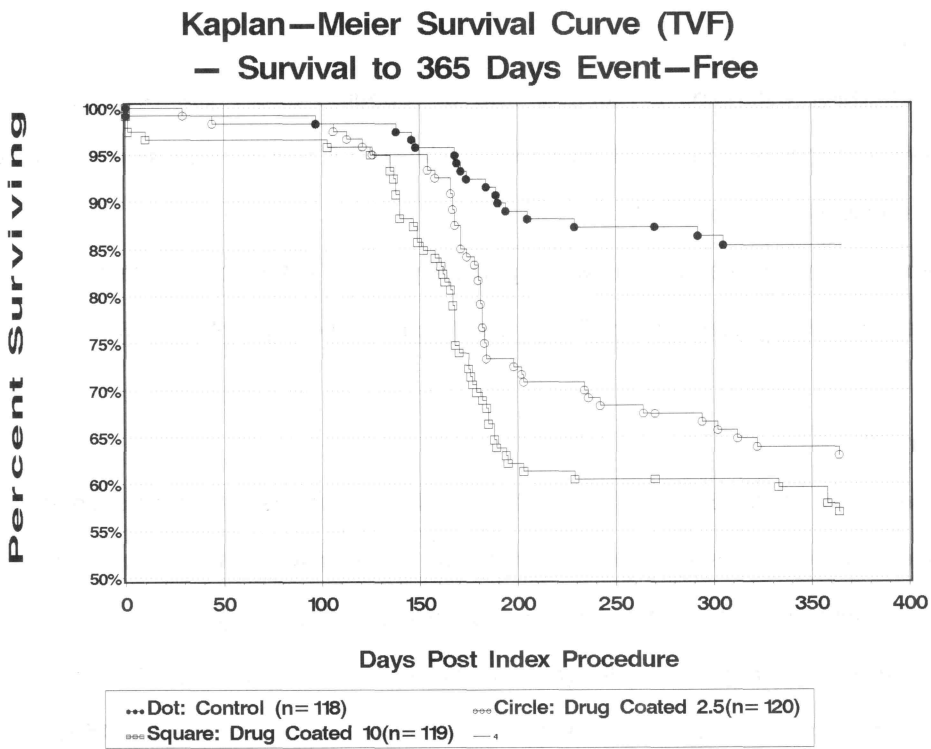
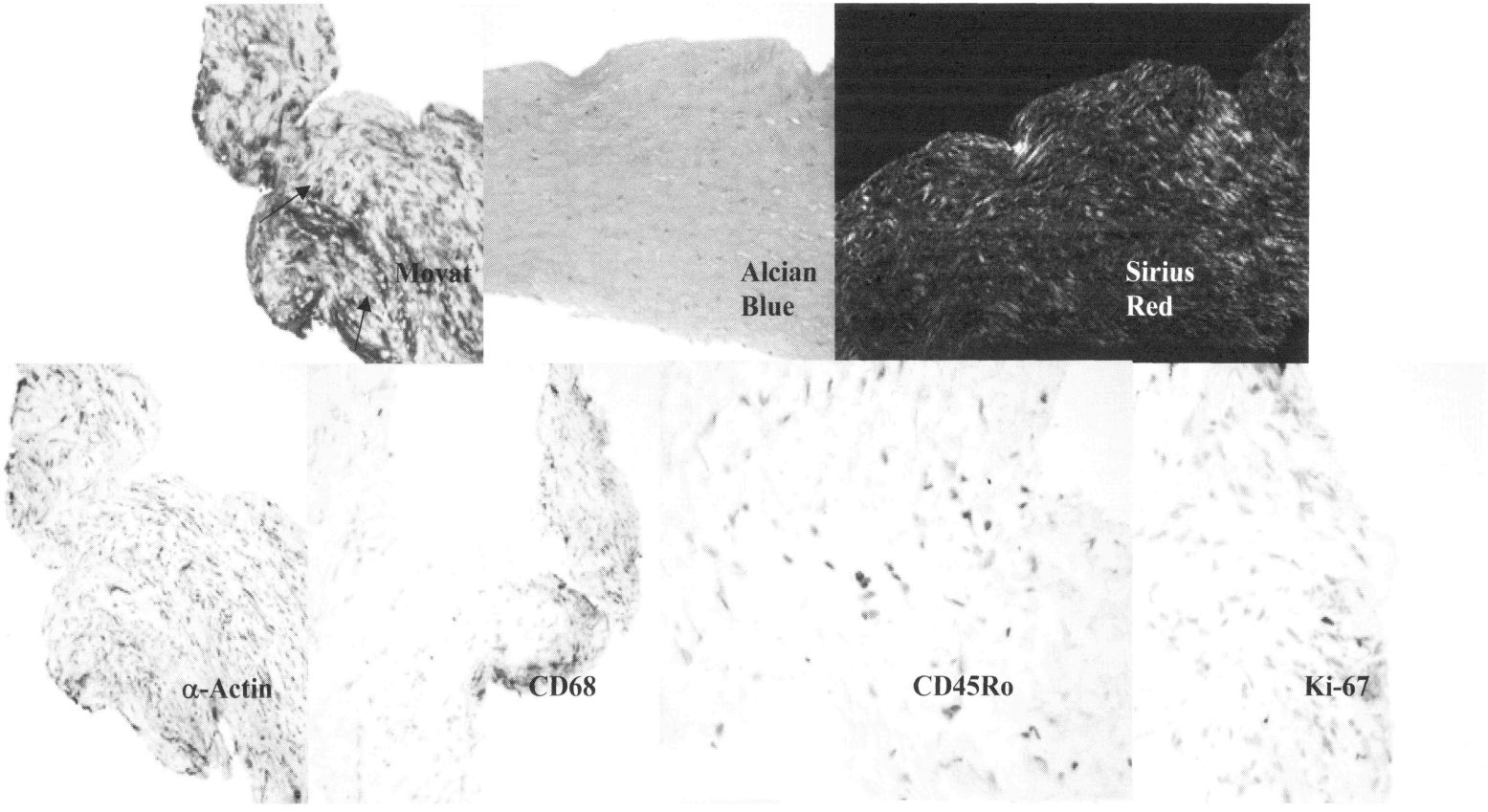

Kaplan—Meier Survival Curve (TVF)
— Survival to 365 Days Event—Free
Percent Surviving
100%
95%
90%
85%
80%
75%
70%
65%
60%
55%
50%
0
50
100
150
200
250
300
350
400
Days Post Index Procedure
Dot: Control (n= 118)
Circle: Drug Coated 2.5(n= 120)
Square: Drug Coated 10(n= 119)

Figure 2.



Chapter 17

Local drug delivery using coated stents: new developments and future perspectives. Tanabe K, Regar E, Lee CH, Hoye A, van der Giessen WJ, Serruys PW. Curr Pharm Des. 2004;10:357-67.

Local Drug Delivery Using Coated Stents: New Developments and Future Perspectives

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Abstract: Percutaneous coronary intervention has been hampered by restenosis since its inception. Many research projects including the use of various devices and systemic drug administration have shown disappointing results. The clinical data reported from trials with sirolimus- and paclitaxel- eluting stents have been very promising, such that stents with the capability of drug elution are currently attracting the medical community for the prevention of restenosis. Based on the mechanism of action of the drugs released from the stent and the target of the restenotic process, there may be 4 therapeutic objectives: anti-inflammatory, anti-proliferative, anti-migratory, and pro-endothelial healing. There are many candidate agents for drug-eluting stents, however, it now becomes clear that not all drug-eluting stents are equally effective. This article describe candidate agents which have been tested or currently under investigation, and summarize the latest information.

Key Words: drugs, stent, restenosis.

INTRODUCTION

Restenosis has been the most vexing problem of percutaneous coronary intervention since its inception in 1978 [1]. Late lumen loss following balloon angioplasty is mainly attributed to negative vascular remodeling [2]. The advent of coronary stents had reduced incidence of restenosis compared with balloon angioplasty [3, 4]. Stents provide a permanent scaffold thereby preventing vessel recoil and shrinkage, and thus demonstrating a superior angiographic outcome. However, the Achilles' heel still lingers - so-called in-stent restenosis. This represents a major problem as the treatment of in-stent restenosis is technically challenging and costly, and the absolute number of in-stent restenotic lesions is increasing in parallel with the steadily increasing number of stenting procedures. Over the last 2 decades, underlying efforts have been put into optimizing stent characteristics and implantation technique. The procedural success rate is now satisfactory as the improvement in stent design provided more flexibility and greater radial force. However, in the long term, in-stent restenosis has not been eliminated. In contrast to restenosis after balloon angioplasty, in-stent restenosis is mainly due to exuberant neointimal hyperplasia as a result of the arterial response to an injury inflicted by stent implantation. [5, 6]. At least 4 phases of the vascular response to endovascular stent implantation have been identified: thrombosis, inflammation, cell proliferation and migration, and remodeling [7]. All these steps provide a target for a diverse range of therapeutic strategies. There have been an enormous amount of researches into systemic pharmacological approaches to block the restenotic cascade in order to prevent in-stent restenosis. So far, most of the clinical trials have failed to show encouraging results [8-12]. The lack of efficacy in systemic drug administration was generally considered to be due to insufficient concentration of drug at the injury site. Therefore, local drug delivery using novel balloon catheters has been tested. Although pre-clinical studies with catheter-based drug delivery appeared promising, this approach was found to be ineffective in reducing restenosis in human beings [13-15]. There are several potential reasons for this failure. Firstly, the damage inflicted by the catheters might actually induce more pronounced intimal proliferation [16]. Thus, for local drug delivery to reduce restenosis, the agents should be potent enough to compensate for this additional neointimal hyperplasia from the infusion itself. Secondly, the intramural retention of the infused agents might be inadequate to exert a sustained effect. Thirdly, the duration of action of the medication might be too short to prevent neointimal formation. In addition, there is a risk of stent dislocation as a result of the passage with the delivery system [17].

The idea of using stents to provide a vehicle for prolonged and sufficient drug delivery emerged early in the stent era. Stents represent an ideal platform for local drug delivery because after deployment they are in apposition to the vessel wall and are therefore in direct contact with the constituents of restenosis. In addition, they may serve as reservoirs of drugs for a designed period, with the goal of achieving controlled release of the anti-restenotic drug. Most stents use a coating to facilitate drug carriage and elution and it is imperative that this coating is truly biologically inert. If not, the coated stents may elicit untoward effects such as direct local toxicity to the vessel wall, and induction of inflammation potentially leading to a subsequent increase in neointimal hyperplasia. Furthermore, the coating should be able to tolerate the mechanical stresses associated with stents

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that are implanted in coronary arteries and must also maintain their physicochemical properties after sterilization. Of course, the coating must be non-thrombogenic, otherwise it may cause (sub)acute stent thrombosis after deployment. The development of a coating that meets all of these criteria has been extremely challenging. Many substances have been proposed as potential candidate for stent coating as listed in Table **1**. Van der Giessen *et al.* investigated the biocompatibility of 5 different biodegradable polymers (polyglycolic acid/ polylactic acid [PGLA], polycaprolactone [PCL], polyhydroxybutyrate valerate [PHBV], polyorthoester [POE],

Table 1. Candidate Substances for Stent Coating

Polyethylene glycol copolymers
Polyglycolic acid / Polylactic acid
Polycaprolactone
Polyhydroxybutyrate valerate
Polyorthoester
Polyethyleneoxide / Polybuthylene terephthalate
Polyurethane
Silicone
Polyethylene terephthalate
Polyvinyl pyrolidone / cellulose esters
Polyvinyl pyrolidone / polyurethane
Polymethylidene maloleate
Polylactide/ glycoloide copolymers
Polyethylene vinyl alcohol
Polydimethyl siloxane (silicone rubber)
Phosphorylcholine
Pyrolytic carbon

and polyethyleneoxide/ polybuthylene terephthalate [PEO/ PBTP]) and 3 nonbiodegradable polymers (polyurethane [PUR], silicone [SIL], and polyethylene terephthalate [PETP]) as strips deployed 90° of the cicumferential surface of coil wire stents in porcine coronary arteries [18]. All polymers tested were demonstrated to induce a marked inflammatory reaction within the coronary artery with subsequent neointimal thickening, which was not expected on the basis of *in vitro* examination. It has taken a lot of time and effort to get biocompatible polymers and recently the engineering of micrometer-thick coatings has proven safe. Most of the polymers currently used in drug-eluting stents are proprietary.

The ideal drug released from a stent should be one that inhibits the multiple components of the complex restenosis process. Based on the mechanism of action of the agents and their target in the restenotic process, there may be 4 therapeutic options: anti-inflammatory, anti-proliferative, anti-migratory, and pro-endothelial healing. Potential candidate drugs for drug-eluting stents are given in Fig. (**1**) according to the therapeutic approach. Some of the drugs target at unique mechanism while others have multiple targets in the restenotic process. After the landmark RAVEL trial demonstrated zero restenosis in the sirolimus-eluting stent arm [19], a steadily growing number of studies is addressing the efficacy of a variety of drug-coating combinations. This article provides an overview of the developments of drug-eluting stents and their future perspectives. We focus on the agents other than sirolimus and steroids, which are described on this issue in the journal.

IMMUNOSUPPRESSIVE DRUGS

Everolimus (SDZ RAD)

Everolimus is a novel semi-synthetic macrolide with immunosuppressive, antifungal, and anti-proliferative properties, which is a sirolimus (rapamycin) analogue bearing a hydroxyl chain at position 40. Everolimus is used for the prophylaxis of organ rejection in patients receiving an allogenic renal or cardiac transplant. The mechanism of action at the cellular and molecular level is the same as sirolimus. Everolimus as well as sirolimus blocks G1 to S cell cycle progression by interacting with a specific target protein (mTOR - mammalian Target Of Rapamycin) and inhibits its activation. The inhibition of mTOR suppresses cytokine-driven (IL-2, IL-4, IL-7 and IL-15) T-cell proliferation. The inhibition of mTOR has several important effects, including the inhibition of translation of a family of mRNAs that code for proteins essential for cell cycle progression; the inhibition of IL-2 induced transcription of proliferating cell nuclear antigen (PCNA) that is essential for DNA replication; the blocking of CD28-mediated sustained upregulation of IL-2 transcription in T cells and the inhibition of the kinase activity of the cdk4/cyclinD and cdk2/cyclin E complexes, essential for cell cycle progression. This mechanism of action is distinct from other immunosuppressive drugs that act solely by inhibiting DNA synthesis, such as mycophenolate mofetil (CellCept) and azathioprine (Imuran).

In vitro, everolimus inhibits growth factor-driven cell proliferation in general, as demonstrated for cell proliferation of a lymphoid cell line and of vascular smooth muscle cells [20]. Although the immunosuppressive activity of everolimus is about 2 to 3 times lower than sirolimus *in vitro*, oral everolimus is as potent as sirolimus *in vivo* [20]. Also, oral everolimus has been demonstrated to reduce intimal thickening of rat aortas caused by immunological and ischemic injury [21]. In a non-atherosclerotic rabbit model, orally administrated everolimus significantly inhibited neointima growth at 28days after stent implantation in iliac arteries. Everolimus was given in 2 different dose regimens, high dose: 1.5mg/kg/day for 17 days followed by 1.0mg/kg/day for 11 days; or low dose: one loading dose of 1.5mg/kg/day followed by 0.75mg/kg/day for 28 days. In both groups, neointima formation was significantly reduced when compared to controls. However, in the high dose group there was evidence of medial thinning, hypo-cellularity and variable healing with focal neointimal fibrin deposition [22]. Inhibition of neointima formation has also been shown after

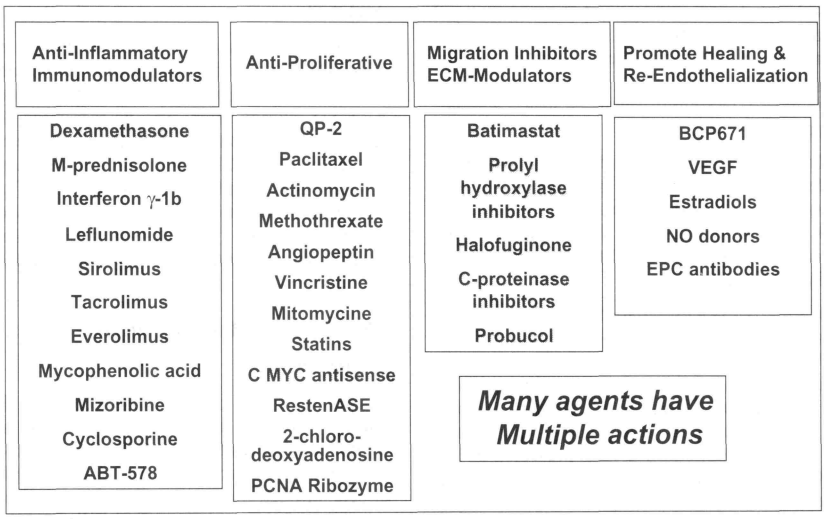

Fig. (1). Multiple approaches to restenosis.

implantation of everolimus-eluting stents in the pig coronary model, for both low-dose and high dose stents. All everolimus-eluting stents showed complete endothelial regeneration at 30 days [23]. In a similar model, area stenosis was similar between bare stents and everolimus-eluting stents at 90 days follow-up. Persisting voids around the stent struts were present in the everolimus-eluting stents, however, there was no difference in intimal inflammation, fibrin deposition or matrix formation between bare and everolimus eluting stents [24].

The FUTURE (First Use To Underscore Reduction in restenosis with Everolimus) trial completed the enrollment of 42 patients. This is a single-blind, randomized, single center study to evaluate the safety of everolimus-eluting stent in de novo coronary lesions. The interim results have been recently presented by Dr. E. Grube at the CRF drug-eluting stent symposium in Chicago, March 2003. Twenty-seven patients with everolimus-eluting stents underwent angiographic follow-up at 6-month after deployment. So far, no patient developed angiographic in-stent restenosis, but there was one patient with edge restenosis. The late lumen loss in the in-stent segment (0.10 mm) was significantly smaller than the control group (0.83 mm). Given that the loss of 0.10 mm is comparable to that of sirolimus-eluting stent in the large randomized trials (-0.01 mm in the RAVEL trial and 0.17 mm in the SIRIUS trial), promising results are anticipated. The FUTURE-II trial is a prospective, randomized, multi-center, and double blind study of which enrollment is targeted approximately 100 patients per arm. We will see in the near future whether this eluting stent works as we expect.

Tacrolimus (FK 506)

Tacrolimus is a derivative of a soil fungus (streptomyces tsukubaensis) which was first described in 1987. Like cyclosporine, it is insoluble in water, but it dissolves readily in alcohol and some oils. It has very similar immunosuppressive properties to cyclosporine, but is 10 to 100 times more potent on a per gram basis. It is currently used for the prophylaxis of organ rejection after allogeneic transplantation.

Marx *et al.* examined the antiproliferative effects of sirolimus on human and rat vascular smooth muscle cells and compared them with the effects of FK 520 (an analogue of tacrolimus) [25]. Sirolimus inhibited DNA synthesis and cell growth in smooth muscle cells at concentrations as low as 1 ng/ml, but FK520 did not inhibit the cell growth. Mohacsi *et al.* also investigated the inhibitory effects of 6 different immunosuppressive drugs (sirolimus, mycophenolic acid, cyclosporine, tacrolimus, leflunomide, and methyprednisolone) *in vitro* on the growth factor-induced proliferation of vascular smooth muscle cells and endothelial cells isolated from human and rat thoracic aortas [26]. Sirolimus was found to be the most potent among the tested agents. Tacrolimus showed a moderate inhibitory activity but, interestingly only for human cells. There has been another report recently presented by Matter *et al.* at Transcatheter Cardiovascular Therapeutics (TCT) 2002. They made a comparison between tacrolimus and sirolimus in terms of the antiproliferative effects on human smooth muscle cells and endothelial cells. The cells were isolated from human saphenous veins and Inhibitory concentration$_{50}$ (IC_{50}) values were determined as the concentration of the drug needed to obtain 50% inhibition of proliferation compared to the control value. Sirolimus exerted more antiproliferative potency than tacrolimus on both smooth muscle cells and endothelial cells. For sirolimus, the value of IC_{50} in smooth muscle cells was higher than endothelial cells. It is noteworthy that the value of IC_{50} in smooth muscle cells was lower than the endothelial cells for tacrolimus. Theoretically, it is desirable that the drug inhibits only the proliferation of smooth muscle cells but does not inhibit the proliferation of endothelial cells. If the drug delayed re-endothelialization on

a stent implanted in a clinical setting, stent thrombosis might occur. Therefore, the comparison of the anti-proliferative effect of a compound on smooth muscle cells and endothelial cells may suggest the existence of an ideal therapeutic window. In this regard, tacrolimus seems an ideal candidate for drug-eluting stent.

Accordingly, animal experiments with tacrolimus-coated stent were performed. A coronary stent graft loaded with 980 μg of tacrolimus showed a moderate reduction of neointimal formation at 4 and 8 weeks in rabbit iliac arteries (unpublished data, presented by Dr. G.W. Stone at CRF Drug-Eluting Stent Symposium, 2002).

The PRESENT I trial (PREliminary Safety Evaluation of Nanoporus Tacrolimus eluting stent) was a prospective, non-randomized study evaluating the safely of nanoporous ceramic coated stents loaded with 60 μg tacrolimus. There was no stent thrombosis. Three of 22 patients (13.6%) needed target lesion revascularization (TLR). The in-stent restenosis rate was 19% (unpublished data, presented by Dr. E. Grube at ACC 2003). Although safety was demonstrated, the results were not so impressive given that the lesion profile was relatively simple. Hence, the PRESENT II trial with higher dose (230 μg) tacrolimus-loaded nanoporous ceramic stent has been planed. In contrast to expectations, the preliminary analysis revealed as high as 28.0% of TLR rate (unpublished data, presented by Dr.E.Grube at American College of Cardiology (ACC), 2003). The EVIDENT trial (EndoVascular Investigation DEtermining the safety of New Tacrolimus eluting stent grafts) enrolled 20 patients treated with tacrolimus-eluting (352 μg) PTFE coronary stent graft for saphenous vein disease. To date, 11 patients completed 6-month follow-up and 3 patients (27.3%) underwent TLR (unpublished data, presented by Dr.E.Grube at ACC, 2003). Based on the preliminary results of these clinical trials, the efficacy of the tacrolimus-eluting stent is questionable.

Mycophenolic Acid (MPA)

Mycophenolate mofetil (MMF) was approved in the United States in 1995 and in Europe in 1996 for prophylaxis of organ rejection in patients receiving allogeneic renal, heart or liver transplants. MMF is rapidly and completely absorbed, after which the pro-drug is essentially converted to mycophenolic acid (MPA). MPA interferes with the proliferation of T- and B-lymphocytes by inhibiting key enzymes in the de novo synthesis of guanosine nucleotide, thus preventing the synthesis of DNA. MPA inhibits the growth factor induced proliferation of both vascular smooth muscle cells and endothelial cells [26]. In a 28-day porcine coronary model, the MPA-eluting stent reduces neointimal area by 40% in comparison to bare metal stents without signs of arterial toxicity or delayed repair (presented by Dr. A.J. Carter at TCT 2002). The IMPACT (Inhibition with MPA of Coronary Restenosis Trial) is the first clinical trial to compare the safety and efficacy of MPA-eluting stent with bare metal stent. The eluting stent was coated with 3.3 μg/mm^2 of MPA in the 2 different formulations: slow release (45 days) and fast release (14 days). The trial has completed the enrollment of 150 patients with de novo coronary artery lesions. Angiographic follow-up at 6-month will be completed by May 2003.

ABT-578

ABT-578 is another synthetic analogue of sirolimus ($C_{52}H_{79}N_5O_{12}$). *In vitro*, ABT-578 exerts an anti-proliferative effect on human coronary artery smooth muscle cells. The ABT-578 eluting stent was demonstrated to significantly reduce in-stent neointimal formation in pig coronary arteries (presented by Dr.R Kuntz at TCT 2002). There was no local coronary artery wall toxicity in the form of medial necrosis or stent malapposition. All stents showed evidence of stable healing responses. The multi-center randomized PREFER trial has been planned to corroborate the safety and efficacy in human beings.

ANTI-PROLIFERATIVE DRUGS

Paclitaxel

Paclitaxel was originally isolated from the bark of the Pacific Yew. It is an antineoplastic agent that is currently used to treat several types of cancer, most commonly breast and ovarian cancer. Paclitaxel exerts its pharmacological effects through formation of numerous decentralized and unorganized microtubules. This enhances the assembly of extraordinarily stable microtubules, interrupting proliferation, migration and signal transduction [27, 28]. Unlike other anti-proliferative agents of the colchicine type, which inhibit microtubuli assembly, paclitaxel shifts the microtubule equilibrium towards microtubule assembly. It is highly lipophilic, which promotes a rapid cellular uptake, and has a long-lasting effect in the cell due to the structural alteration of the cytoskeleton.

In vitro and *in vivo* studies have shown that paclitaxel may prevent or attenuate neointimal growth. Paclitaxel inhibits proliferation and migration of cultured smooth muscle cells in a dose-dependent manner [29]. In a rat balloon injury model, intraperitoneal administration of paclitaxel reduced neointimal area. However, the local, vascular administration of paclitaxel showed conflicting results. It reduced neointimal thickness in an atherosclerotic rabbit model [30-32], but did not reduce neointima formation in native pig coronary arteries following stent implantation [33]. Stent-based delivery of paclitaxel has been investigated by several groups, using different stent types and preparation (copolymer coatings for paclitaxel elution [34, 35] or direct dip-coating of paclitaxel on the stent [36, 37]) in animal models (pig [36, 37], rabbit [34, 35]). These studies consistently revealed a significant, dose-dependent inhibition of neointimal hyperplasia. Furthermore, they could show that the tissue responses in paclitaxel-treated vessels included incomplete healing, few smooth muscle cells, late persistence of macrophages and dense fibrin with little collagen as well as signs of positive remodeling of the stented segment. There is, however, discrepancy regarding the long-term outcome. Farb and colleagues used polymer coated stents containing 42.0 or 20.2 μg of paclitaxel in a rabbit model. At 90 days after stenting neointimal growth was no longer suppressed [35]. In the Drachman series a much higher dose of paclitaxel was used (polylactide-co-sigma- caprolactone copolymer containing 200 μg paclitaxel), also in a rabbit model. Intimal and medial cell proliferation was reduced three-fold at seven days after stenting as compared to control stents. Six months after stenting, long after drug release and polymer degrada-

tion were likely complete, neointimal area was two- fold lower in paclitaxel-releasing stents [34]. The relevance of these findings for the application of either drug concentration and formulation in humans is unclear, as the response to injury and endovascular prosthesis is dependent on the species under study [38, 39].

Some clinical trials with paclitaxel-eluting stents have been performed using different platforms to adhere paclitaxel on the stents. They are basically categorized into the following 3 groups: polymer sleeve, non-polymer-based delivery, polymer-based delivery. The randomized clinical trials with paclitaxel-eluting stents for de novo lesions are summarized in Table **2**. The angiographic restenosis rate and event free rate in the completed trials with paclitaxel-eluting stents are shown in Fig. (**2** and **3**), respectively.

QuaDDS QP2-Eluting Stent

QuaDDS QP-2 eluting stent (Quanam Medical Corp) is covered with 4 or 5 non-biodegradable polymer sleeves to deliver high concentrations (800 _g/sleeve) of paclitaxel-derivative (QP2: 7-hexanoyltaxol). The BARDDS (Buenos Aires Registry for Drug Dellivery Stents) was a single arm registry of 32 patients receiving the QuaDDS QP-2 eluting stents [40]. Angiographic follow-up was performed at a mean of 11 months in 13 patients. No patient developed angiographic binary restenosis in the in-stent segment. There was another single-arm study which enrolled 20 patients [41]. Intravascular Ultrasound (IVUS) analyses were performed at 8 months after procedure in 14 patients with 15 lesions. No patients showed clinically significant in-stent or edge restenosis during the follow-up period. As a consequence of promising results in the early human studies, the multi-center, randomized SCORE (Study to COmpare REstenosis rate between QueST and QuaDS-QP2) was conducted. However, the enrollment of the SCORE trial was prematurely stopped due to a major imbalance in major adverse cardiac events between the study group and the control group associated with stent thrombosis [42]. These events were considered to be due to the poor stent design and

Table 2. Randomized Clinical Trials with Paclitaxel-Eluting Stents for De Novo Lesions

	Drug	Stent	Polymer	Number of patients	Follow-up
SCORE	QP2	QuaDS	Polymer sleeve	266	6 months
ASPECT	Paclitaxel	Supra G	No	177	6 months
ELUTES	Paclitaxel	V-Flex	No	190	6 months
DELIVER	Paclitaxel	Multilink Penta	No	1043	6 months
TAXUS-I	Paclitaxel	NIR	Yes	61	6 months
TAXUS-II	Paclitaxel	NIR	Yes	536	6 months

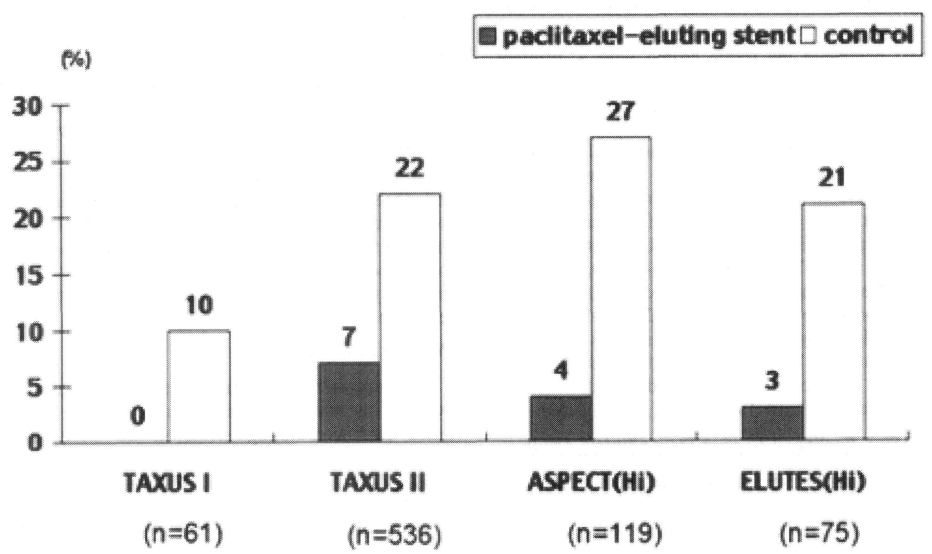

Fig. (2). Binary restenosis rate (in segment) in paclitaxel-eluting stent trials.

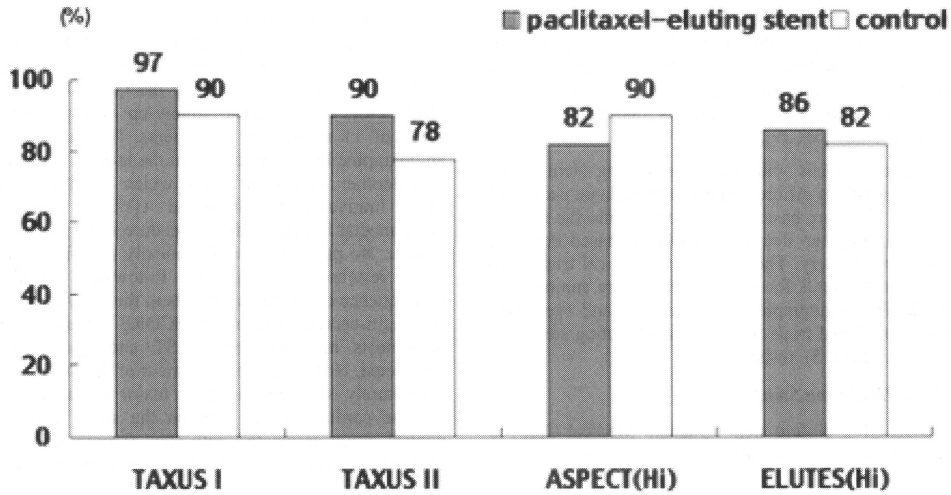

Fig. (3). Event-free rate in paclitaxel-eluting stent trials.

high concentration of the drug resulting in incomplete endothelialization on the stent. The QuaDS QP2-eluting stent was also evaluated in 15 patients with in-stent restenosis [43]. The reported beneficial effect observed at 6-month (restenosis rate = 13.3%) had subsided by 12-month where 61.5% of the patients had restenosis. The authors attributed the late restenosis to the presence of multiple bulky plastic sleeves and/or high concentration of the drug.

Non-Polymer Based Delivery

There are the following 4 clinical trials using the stents coated with paclitaxel without a polymer.

ELUTES (European evaLUation of pacliTaxel-Eluting Stent)

This trial compared the stents coated with 4 different dose formulations of paclitaxel (0.2 $\mu g/mm^2$; 0.7 $\mu g/mm^2$; 1.4 $\mu g/mm^2$ and 2.7 $\mu g/mm^2$) versus bare metal stents for the treatment of de novo native coronary artery lesions. The stents were directly impregnated with paclitaxel without a polymer. At 6-month follow-up, a clear dose relationship was seen, with percent diameter stenosis ranging from 34% for the bare stent, to 33, 26, 23, and 14% for ascending dose densities of the paclitaxel-coated stents. Late loss reflected the same pattern with 0.73 mm for controls and 0.10 mm for the highest dose stent ($p<0.005$). The binary in-stent restenosis rate for controls was 21%, with 20, 12, 14, and 3% rates for ascending doses [84]. At 12 months follow-up MACE-free rates were 86% vs 82% for the high dose and control groups, respectively. (presented by Dr. I. De Scheerder at American Heart Association (AHA), 2002).

ASPECT (ASian Paclitaxel-Eluting Stent Clinical Trial)

This study compared the stents coated with 2 different dose formulations of paclitaxel (1.3 $\mu g/mm^2$ and 3.1 $\mu g/mm^2$) versus bare metal stents for the treatment of de novo native lesions. In 37 patients, cilostazol was used in place of clopidogrel or ticlopidine for anti-platelet regimen. At 6-month follow-up, the high dose group, as compared to the control group, had significantly better angiographic results for late lumen loss (0.29mm versus 1.04mm) and binary restenosis rate (4% versus 27%). IVUS analysis demonstrated a dose-dependent reduction in the volume of neointimal hyperplasia (13, 18, and 31 mm^3 in the high dose, low dose, and control groups, respectively) [44, 45]. There was a higher rate of major cardiac events in patients receiving cilostazol than in those receiving ticlopidine or clopidogrel. It was associated with the higher incidence of subacute stent thrombosis. Among patients receiving ticlopidine or clopidogrel, event-free survival at 12-month was 92 % in the high dose group (presented by Dr. Lee at AHA 2002).

DELIVER

This study compared the stents directly impregnated with 3.1 $\mu g/mm^2$ of paclitaxel with the bare metal stents. The preliminary data have recently been reported by Dr. O'Neill at CRF drug-eluting stent symposium in Chicago in March 2003. There was no significant difference in angiographic restenosis rate between the 2 groups (16.7% in the eluting-stent group versus 22.4% in the control arm). The duration of the drug release from non-polymer based drug-eluting stents might be too short to demonstrate beneficial effects uniformly, however, further analysis is needed to identify the reason for this failure.

Polymer Based Delivery

A series of human clinical trials have been designed to evaluate the safety, feasibility, and efficacy of polymer-based paclitaxel-eluting stents in a variety of clinical settings.

TAXUS-I

This study is a prospective, double-blind, 3-center study randomizing 61 patients with de novo lesions to receive a polymer-based paclitaxel-eluting stent or a control bare

metal stent. At 12 months, the major adverse cardiac event rate was 3% in the eluting stent group and 10% in the control group. No stent thrombosis was reported. The angiographic restenosis rate and the late lumen loss in the eluting-stent group was 0% and 0.36mm, respectively.

TAXUS-II

As a consequence of the promising results in the TAXUS-I, the larger randomized, multi-center TAXUS-II trial was performed. This trial enrolled 536 patients at 38 centers in 2 consecutive cohorts comparing slow release (SR; 131 patients) and moderate release (MR; 135 patients) paclitaxel-eluting stents to bare metal stents (BMS; 270 patients). The paclitaxel-eluting stent was identical to the BMS except it was coated with a total load of 1.0 $\mu g/mm^2$ of paclitaxel incorporated into a proprietary polymer (Translute™) that provides controlled biphasic release. For both stents, the initial burst release is over the first 48 hours after implantation followed by a low-level release phase for approximately 10 days. The release rate in the initial burst of the MR stent is 8-fold higher than that of the SR stent. The final results have recently been presented by Dr. Colombo at TCT 2002. The major adverse cardiac events rate at 6-month was significantly lower in patients in the SR (8.5%) and the MR (7.8%) compared with the BMS (19.8%). The significant difference in the events rate was persistent at 1 year (10.9% in the SR, 9.9% in the MR, and 21.7% in the BMS). At 6 months after implantation, the degree of restenosis measured as percent in-stent net volume obstruction by IVUS was significantly lower for the both eluting-stents (7.9% in the SR and 7.8% in the MR) compare to the BMS (21.9%). The binary in-stent restenosis rates were 2.3% (SR), 4.7% (MR), and 19.0% (BMS), respectively. Both the eluting stents showed significantly smaller late lumen loss (0.31mm in the SR and 0.30mm in the MR) than the BMS (0.78mm). As the safety, feasibility, and beneficial effects of this eluting stent has been demonstrated in this large prospective trial, the TAXUS EXPRESS™ paclitaxel eluting-stent has received CE mark and is currently commercially available in Europe. The release formulation of this stent is the slow-release type.

TAXUS-III

This trial is a single-arm, two-center study evaluating the feasibility and safety of the slow-release paclitaxel-eluting stent for the treatment of in-stent restenosis (ISR) [46]. Twenty-eight patients with ISR were treated with one or more paclitaxel-eluting stents. No subacute stent thrombosis occurred, but one late chronic total occlusion was observed. In addition, 3 patients showed angiographic restenosis. The incidence of major adverse cardiac events was 29% (8 patients: 1 non-Q wave myocardial infarction, 1 coronary artery bypass grafting, 6 target lesion revascularization (TLR)). Of those patients with TLR, 2 patients had restenosis at a gap between 2 paclitaxel-eluting stents. Therefore, when treating ISR with drug-eluting stents, it seems important to cover the whole length of the previously implanted stents leaving an eluting stent margin outside the restenotic stent and avoiding a gap. With this in mind, IVUS guidance is recommended to confirm complete coverage or longer eluting stents will avoid this technical limitation. The reported late lumen loss of 0.54mm is encouraging, because the published reports on late loss of bare metal stent for ISR were not as favorable, ranging from 0.9 mm to 1.4mm [47-49].

TAXUS-IV, V and VI

The TAXUS-IV and V are the pivotal large randomized trials in the United States. The TAXUS-IV trial has enrolled 1326 patients with de novo coronary lesions varying from 10 to 28mm in length. The patients were treated with either a single slow-release paclitaxel-eluting stent or bare metal stent. The results at 9-month will be presented in September, 2003. The TAXUS V study will include 1108 patients with longer lesions (up to 40mm). The study stent is also slow-release type and implantation of multiple stents is allowed in the protocol. The TAXUS-VI is a European trial which will enroll 440 patients with de novo lesions. The aim of this trial is to evaluate the efficacy of moderate release paclitaxel-eluting stents for the treatment of long lesions (18-40 mm in length).

Actinomycin-D

Actinomycin-D has been marketed worldwide since the 1960s. Actinomycin-D is an antibiotic used for its antiproliferative properties in the treatment of various malignant neoplasmas (e.g. Wilms tumor, sarcomas, carcinoma of testis and uterus). In contrast to paclitaxel which acts specifically on the depolymerization of the microtubules in the anaphase, actinomycin-D affects all phases of the cell cycle by forming forms a stable complex with double-stranded DNA inhibiting RNA synthesis and is therefore a powerful inhibitor of cell proliferation. The ACTION trial (ACTinomycin eluting stent Improves Outcomes by reducing Neointimal hyperplasia) was the first clinical evaluation of the actinomycin-D eluting stent. This prospective, randomised, multi-center study enrolled 360 patients treated with two doses of actinomycin-D eluting stent (2.5 and 10 $\mu g/cm^2$) or bare metal stents. Actinomycin was coated onto the stent in a polymer made from ethylene and vinyl alcohol monomers. Early monitoring of a subset of 39 patients in the eluting stent group having clinically driven or mandated angiography revealed an increased rate of target lesion revascularization in the range of 40% suggesting that the investigational device was not performing as intended. Therefore, the study was unblined prematurely. The final results have been reported by Dr. Serruys at the European Society of Cardiology (ESC), 2002. The in-segment restenosis rates were statistically higher in the eluting-stent group (28% in the high dose and 27% in the low dose) than the control group (14%). The impressive results reported in the paclitaxel-eluting stent trials have led to speculate that any anti-proliferative drug-eluting stents would decrease in-stent restenosis, however, the results of the ACTION trial indicate that not all anti-proliferative drugs show a uniform drug class effect in the prevention of restenosis in humans.

Angiopeptin

Cellular growth is regulated in part by the interaction of the cell with proteins and polypeptides in serum. Insulin-like growth factor (IGF-1) has been identified as important component for cell proliferation [50]. The effect of IGF is potentiated by platelet-derived growth factor (PDGF) [51, 52]. In addition, fibroblast growth factor increases the binding

of IGF-1 to smooth muscle cells, promoting the growth stimulation of IGF-1. Angiopeptin is a cyclic octapeptide analogue of somatostatin. The discovery that angiopeptin reduces IGF-1 accumulation in the vascular smooth muscle cells of rabbit and human coronary arteries increased an interest in this agent as a candidate for the treatment of restenosis [53]. The systemic administration of angiopeptin was shown to inhibit the development of intimal hyperplasia in various animal models [54, 55]. However, despite these promising results in animals, the large human clinical trial of subcutaneous treatment with angiopeptin failed to demonstrate a reduction in restenosis, although a significant reduction in clinical events was observed [56]. The recent advent of stent coating has led to a re-evaluation of this agent as a candidate for drug elution. The SWAN (Stent With Angiopeptin) trial is an open label registry to test the safety, feasibility, and impact on tissue growth of angiopeptin-eluting stents in human native coronary artery de novo lesions. Thirteen patients with 14 lesions were enrolled. Thirteen stents were loaded with 22μg of angiopeptin, whereas 1 stent was loaded with 126μg. No major adverse cardiac events were reported up to 30 days after deployment [57]. Long-term follow-up data are pending.

Statins

Statins are the most commonly prescribed drugs for the treatment of hypercholesterolemia. Clinical trials have demonstrated that statins reduce the relative risk of major cardiac events and are particularly beneficial in patients with high baseline risks [58-60]. Early initiation of fluvastatin in patients with average cholesterol levels following their first PCI has been shown to reduce the risk of major adverse cardiac events [61]. However, previous major clinical studies have failed to corroborate this with a beneficial effect on restenosis after coronary balloon angioplasty and stenting [9, 62]. These disappointing results had not been expected prior to the studies because preclinical experiments seemed promising. Firstly, statins have been shown to exert anti-proliferative effects on smooth muscle cells *in vitro* by arresting the cell cycle between G1/S phase transition [63-65]. Corsini *et al*. also investigated the effect of whole blood sera from statin-treated patients on smooth muscle cell proliferation [66]. The sera from patients treated with fluvastatin showed a significant inhibition of cell growth, while those treated with pravastatin showed no effect. Secondly, Indolfi *et al*. reported that the systemic administration of simvastatin reduced the neointimal formation in the stented common carotid artery of rats [67]. Local simvastatin delivery with an osmotic pump also reduced neoinimal formation in rats with complete re-endothelialization [68]. Now, statin-eluting stents have now been developed and animal experiments are ongoing.

ANTI-MIGRATORY DRUGS

Batimastat

Matrix metalloproteinases (MMPs) have the ability to digest collagen and facilitate smooth muscle cell migration. Batimastat is a synthetic non-specific inhibitor of MMP. Inhibition of MMPs can reduce the degradation of extracellular matrix and therefore reduce smooth muscle cell migration. An in-vitro study suggested that batimastat can suppress injury-induced DNA synthesis and migration in vascular smooth muscle cell cultures [69]. Up-regulation of ERK1/ERK2 phosphorylation, which is an important cell signaling pathway in injured secondary cultures that are treated with bFGF (fibroblast growth factor), was also reduced by batimastat. These data suggest that batimastat inhibits injury-induced activation of smooth muscle cells by acting on MMPs. Intraperitoneal injection of batimastat after balloon angioplasty in atheroscrelotic Yucatan minipigs resulted in a significant reduction (50%) in late lumen area loss by inhibiting constrictive remodeling. Neointima formation was not inhibited [70]. Preclinical studies with batimastat-eluting stents showed a reduction in neointimal area compared to the control group. Thus, the BRILLIANT (Batimastat anti-Restenosis trialL utiLIzing the biodivysio locAl drug delivery pc-steNT) study was designed to test the batimastat-eluting stent to treat de novo coronary lesions in 173 patients. This was a prospective, non-randomized, multicenter registry. Although the safety was demonstrated, the late lumen loss at 6 months averaged as high as 0.88mm, yielding a 21% angiographic restenosis rate (presented by Dr.De Scheerder at TCT, 2002). Further clinical studies have not at present been planned.

PRO-ENDOTHELIALIZATION APPROACH

The promotion of healing in the vascular endothelium may be a natural approach to prevent restenosis. Endothelial denudation and dysfunction is common at the site of endovascular interventions and associated with thrombosis and restenosis [71]. Therefore, immediate restoration of endothelial function may prevent restenosis. This approach is to promote the proliferation, migration, viability and other biological function of endothelial cells. This is in an attempt to develop an enriched population of cells that will function as a durable means of indirectly inhibiting proliferative and migratory functions of the other cells which are believed to contribute to restenosis.

Estradiol

The sex hormone estrogen is known to have cardio-protective properties [72]. The beneficial effects include modulation of lipoproteins, coagulation and fibrinolysis. Estradiol may also improve vascular healing, reduce smooth muscle cell proliferation and migration, and promote local angiogenesis [73]. The 17beta-estradiol-eluting, phosphoryl-choline-coated stent has been demonstrated to show a reduction in neointimal formation by 40% compared with the control stent in a porcine model [74]. There was complete endothelial regeneration at 30 days and a similar inflammatory response to stenting on histopathology in all groups. The EASTER (Estrogen And Stents To Eliminate Restenosis) trial was the first clinical trial to evaluate the 17beta-estardiol-eluting (2.54 $\mu g/mm^2$) stent. This was a non-randomized registry of 30 patients with de novo coronary lesions. Late lumen loss in the in-stent segment was 0.57mm. The binary restenosis rate was 6.6%. No incidence of myocardial infarction was reported in the study population (presented by Dr. Abizaid at the CRF drug-eluting stent symposium in Chicago, March 2003). Further investigation in large randomized trial is necessary to confirm the efficacy.

EPC (Endothelial Progenitor Cell) Capture

Hematopoietic stem cells derived from the peripheral blood can be used in lieu of bone marrow to provide sustained hematopoietic recovery [75]. This implies that the circulating blood volume might contain a population of endothelial cell precursors. It has been postulated that incorporation of circulating endothelial progenitor cells into the neo-endothelium of the disrupted arterial segment might then abort the initiation of restenosis. Research is being undertaken to develop a unique stent that will capture circulating EPCs onto its surface after implantation. The stent was coated with antibodies to CD34 receptors on EPCs. Preliminary results showed the feasibility of capturing EPCs in-situ [76]. The efficts of this novel stent on restenosis have yet to be demonstrated.

FUTURE PERSPECTIVES

Given the promising clinical data reported from trials with sirolimus- and paclitaxel- eluting stents, drug-eluting stents for the prevention of restenosis are currently attracting great interest among scientists, cardiologists and industry. However, it has now become clear that not all drug-eluting stents are equally effective. Several clinical trials such as SCORE, ACTION and BRILLIANT have been stopped prematurely because of lack of efficacy or even an excess rate of adverse cardiac events. Although sirolimus- and paclitaxel-eluting stents have demonstrated dramatically reduced rates of restenosis compared to conventional bare metal stents, the problem has not been fully eradicated, with a small, but sizable number of patients still developing restenosis at follow-up. Therefore, there remains room for further improvement, and indeed, several projects are underway. Fixed drug release kinetics and vessel wall portioning may limit the effectiveness of drug-eluting stents. Recently, a newly designed metallic stent has been developed to enable programmable drug release pharmacokinetics. The stent contains honeycombed strut elements with inlaid stacked layers of drug and polymer [77], raising the potential possibility of being able to vary the dosage of drug / its release properties. This can then be targeted to the clinical scenario, for example selecting a relatively high dosage of drug for high-risk patients or complex lesions. Furthermore, although the first pilot study with sirolimus-eluting stents has demonstrated safety and effectiveness up to 2 years after implantation [78], the medical community is still worried about the long-term efficacy of drug-eluting stents. Once drug elution is completed, if the stent polymer is not fully biocompatible, it would induce late neointimal formation. In this regard, the development of biodegradable drug-eluting stents seems ideal. With the current drug-eluting stent technology we are winning the battle against in-stent restenosis, hopefully in the future, with the progression of this innovation, the war will finally be won.

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Summary and Conclusions

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In Chapter 1 to 10, chronic arterial responses to sirolimus-eluting stents were explored. In Chapter 1, we demonstrated that there were no adverse edge effects or persisting dissection after sirolimus-eluting stent implantation in a subset of the patients enrolled in the RAVEL trial. However, we, for the first time, found that the incidence of incomplete stent apposition was higher in sirolimus-eluting stents than bare metal stents. Intravascular ultrasound was a useful tool for detecting the unusual phenomenon that we had never recognized before the advent of this new technology. In Chapter 2, we, also for the first time, illustrated tissue disappearance between stent struts following implantation of sirolimus-eluting stents using the ANCUS technique. It was speculated that the negative late loss found in some clinical trials with drug-eluting stents, which had never been achieved in trials with conventional bare metal stents, might be attributable to this phenomenon. In Chapter 3, we demonstrated that incomplete stent apposition was not associated with adverse clinical events 1 year after the diagnosis, emphasizing the benign feature of the phenomenon. Although the absence of reopening of occluded side branches following intracoronary brachytherapy has been previously reported and considered to be related to a delayed healing process, Chapter 4 confirmed

that spontaneous recanalization was not adversely affected by sirolimus-eluting stents. The fate of side branches after sirolimus-eluting stent implantation is favorable and at least as good as after bare metal stent implantation. There was another concern that drug-eluting stents might develop late restenosis and late catch-up phenomenon. In Chapter 5 and 6, we demonstrated persistent inhibition of neointimal hyperplasia up to 2 years. Larger clinical trials with adequate and complete longer follow-up will provide definitive data regarding the durability of the anti-proliferative property of sirolimus. In Chapter 7, we studied the efficacy of sirolimus-eluting stents for the treatment of in-stent restenosis. This eluting stent effectively prevented neointimal formation and recurrent in-stent restenosis. In Chapter8, the outcomes patients undergoing bifurcation stenting were explored. We demonstrated that sirolimus-eluting stent implantation in both the main and side branches was feasible and safe with no episodes of stent thrombosis. We witnessed some cases who had restenosis at the ostium of side branch following T stenting technique. Therefore, it seems important to completely cover the ostium of side branch with drug-eluting stents, however, further studies are needed in order to find which technique is the best. Chapter 9 examined the impact of the eluting stent on chronic total occlusions. Sirolimus-eluting stents were associated with a reduction in the rate of major adverse cardiac events and restenosis compared with bare

metal stents. In Chapter 10, sirolimus-eluting stents were found to be safe and effective for the treatment of left main coronary disease. In Chapter 11 to 14, chronic arterial responses to polymer-controlled paclitaxel-eluting stents were evaluated. In Chapter 11, we investigated vascular responses within paclitaxel-eluting stents using a large number of serial intravascular ultrasound examination both at baseline and at 6-month follow-up. The major findings were as follows. Both slow and moderate release paclitaxel-eluting stents inhibited neointimal growth to the same degree when compared with BMS. Peri-stent remodeling occurred in bare metal stent as well as the eluting-stent groups. There were progressive increases in peri-stent area from bare metal stent to slow release to moderate release. By studying peri-stent remodeling we, for the first time, demonstrated release-dependent effects on the global vessel wall response. In Chapter 12, the arterial responses at edges were explored. We found that paclitaxel-eluting stents were not associated with increased edge stenosis at follow-up. In fact, compared with bare metal stents, there was a significant reduction in late lumen loss at the distal edge with paclitaxel-eluting stents. In Chapter 13, we investigated incomplete apposition following implantation of paclitaxel-eluting stents and compared with bare metal stents. There were no differences in the incidence or the volume. Furthermore, this phenomenon was not associated with adverse clinical events such as stent thrombosis.

Therefore we concluded that incomplete stent apposition was pure intravascular ultrasound finding without clinical percussion. In Chapter 15, the effectiveness of paclitaxel-eluting stents in the treatment of in-stent restenosis was evaluated. This eluting stent was found to be safe, feasible and effective for in-stent restenosis, however, we also witnessed some patients with recurrent restenosis due to a gap between 2 eluting stents. It seems important to ensure good stent deployment with complete coverage of target lesion by intravascular ultrasound guidance. In Chapter 16 to 18, drug eluting stents other than sirolimus and paclitaxel were summarized. We learned that not all anti-proliferative drugs will show a class effect in the prevention of restenosis.

In conclusion, sirolimus- and paclitaxel eluting stents have been demonstrated to be highly effective in the prevention of restenosis without adverse chronic vascular responses. Given these promising results, drug-eluting stents are currently attracting great interests among cardiologists and industries. However, there are small, but sizable number of patients who still develop restenosis following implantation of the current drug-eluting stents (first generation). Therefore, it is imperative to put efforts into optimizing drug-eluting stents and develop second generation. In addition, we must realize the fact that drug-eluting stents are able to reduce restenosis, but not to eliminate

cardiac death. In this regard, it is important to look for the way how we can detect and treat vulnerable plaque, which cause myocardial infarction.

Samenvatting en Conclusies

Samenvatting en conclusies

In hoofstuk 1 tot en met 10, werden chronische arteriële reacties op sirolimus afscheidende stents onderzocht. In hoofdstuk 1 lieten we zien dat geen stentrand restenose of blijvende dissectie na sirolimus-stent implantatie optrad in een subgroep van patienten geïncludeerd in de RAVEL-studie. Voor het eerst zagen we dat het vóórkomen van onvolledig aanliggen van de stent vaker vóórkwam bij sirolimus stents dan bij conventionele stents. Intravasculaire Ultrasound was een zeer bruikbare techniek om dit ongewone fenomeen, welk nog niet eerder waargenomen was vóór de komst van de nieuwe technologie, te herkennen. In hoofdstuk 2 toonden we, eveneens voor de eerste keer, het verdwijnen van weefsel tussen de draden van de sirolimus-stent aan, gebruikmakend van de ANGUS-techniek. Vermoed werd dat het achteraf verdwijnen van weefsel, welk nooit voorgekomen was in studies met conventionele stents hiervoor verantwoordelijk is geweest. In hoofstuk 3 toonden we aan dat het onvolledig aanliggen van de stent niet gerelateerd was aan nadelige klinische gebeurtenissen een jaar na de diagnose welk het goedaardige karakter van het fenomeen benadrukt. Hoewel het uitblijven van heropening van dichte zijtakken volgend op brachytherapie eerder aangetoond was en toegeschreven werd aan een vertraagd genezingsproces, toonde hoofstuk 4 aan dat spontane rekanalisatie niet nadelig beïnvloed werd door sirolimus stents. Het open blijven van de zijtakken na sirolimus-stent implantatie is veelbelovend en minstens zo goed als bij conventionele stents. Een andere zorg was dat drug-eluting stents late restenose door inhaalgroei zouden veroorzaken. In hoofdstuk 5 en 6 toonden we een tot 2 jaar aanhoudende remming van neointimale groei aan. Grotere klinische studies met adequate en complete langere follow-up zullen definitievere gegevens verschaffen over de duurzaamheid van de anti-proliferatieve eigenschap van de sirolimus. In hoofstuk 7 bestudeerden we de doeltreffendheid van sirolimus stents voor de behandeling van in-stent restenose. Deze stent voorkwam succesvol neointimale groei en opnieuw optredende restenose. In hoofstuk 8 werden de resultaten van patienten die bifurcatie stenting ondergingen bestudeerd. We lieten zien dat sirolimus-stent implantatie in zowel hoofstam als zijtak uitvoerbaar en veilig was zonder episodes van stent thrombose. We waren getuige van enkele gevallen restenose op het ostium van de zijtak volgend op T-stenting techniek. Daarom lijkt het belangrijk om het ostium van de zijtak volledig te bedekken met drug stents, echter, verdere studie is nodig om de beste techniek te ontdekken. Hoofstuk 9 onderzocht de invloed van de drug stent op totale occlusies. Sirolimus stents werden in verband gebracht met een verlaging van het aantal cardiale complicaties en restenose ten opzichte van conventionele stents. In hoofstuk 10 werden sirolimus stents effectief en veilig bevonden voor de behandeling van hoofdstam lesies. In hoofstuk 11 tot en met 14, werden chronisch arteriële reacties op polymeer bevattende paclitaxel stents geëvalueerd. In hoofstuk 11 bestudeerden we vasculaire reakties op de paclitaxel stent gebruik makend van een groot aantal opéénvolgende intravasculaire ultrasounds zowel op de behandeldag als na 6 maanden. De bevindingen waren als volgt. Paclitaxel stents, zowel bij langzaam als sneller vrijkomen van de stof, onderdrukken neointimale groei even effectief in vergelijking met conventionele stents. Groei rondom de stent kwam zowel bij conventionele- als eluting stents voor maar nam meer toe bij de langzaam paclitaxel-afgevende stent en het meest bij de snellere afgifte. Bij de bestudering van weefselgroei rondom de stent toonden we dus voor het eerst, afgifte afhankelijke effecten op de algemene vaatwand reaktie aan. In hoofstuk 12 werden vaatreakties aan de uiteinden van de stent bestudeerd. Bij vervolg-onderzoek zagen we dat paclitaxel stents geen aanleiding gaven tot verhoogde randstenose. In feite trad er, in vergelijking met de conventionele stent, een aanzienlijke vermindering van laat lumen verlies op. In hoofdstuk 13, bestudeerden we incompleet aanliggen van de stent volgend op paclitaxel stent implantatie in vergelijking met

conventionele stents. Er waren geen verschillen wat betreft aantal en volume. Bovendien was er geen verband met complicaties zoals stent-thrombose. Hieruit concludeerden we dat onvolledig aanliggen van de stent puur een ultrasound bevinding zonder klinische percussie was. In hoofstuk 15 werd de effectiviteit van paclitaxel stents in de behandeling van in-stent restenose geëvalueerd. Deze stent bleek veilig, haalbaar en effectief voor de behandeling van in-stent restenose. Echter, we zagen ook enkele patienten met opnieuw optredende restenose veroorzaakt door een leemte tussen de twee stents. Goede stentplaatsing met een volledige bedekking van de lesie met behulp van IVUS lijkt vereist. In hoofstuk 16 tot en met 18, werden andere drug stents samengevat (anders dan sirolimus en paclitaxel). We constateerden dat niet alle anti-proliferatieve medicijnen tot een goed resultaat leiden in het voorkómen van restenose.

Concluderend kunnen we stellen dat sirolimus-en paclitaxel stents zeer effectief blijken te zijn in het voorkómen van restenose zonder nadelige vasculaire reakties. Gezien de veelbelovende resultaten staan drug stents momenteel bijzonder in de belangstelling bij cardiologen en de industrie. Echter, enkele patienten blijken toch restenose te ontwikkelen als gevolg van de eerste generatie drug stents. Daarom is het noodzakelijk inspanningen te doen om een tweede generatie drug stents te optimaliseren. Bovendien moeten we ons er bewust van zijn dat drug stents weliswaar restenose blijken te reduceren maar niet in staat zijn cardiale dood te elimineren. Daarom is het belangrijk een manier te vinden om instabiele plaque, welk het myocard infarct veroorzaakt, op te sporen en te behandelen.

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On the 5th floor

Second day in Rotterdam, I was placed at the room on the 5th floor. The roommates were Evelyn Regar, Muzaffer Degertekin, and Dirk van Essen.

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Curriculum Vitae

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List of Publications

List of Publications

Original Reports (peer reviewed publications)

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Vascular Responses to Drug-Eluting Stents in the Prevention of Restenosis after Percutaneous Coronary Intervention

Kengo Tanabe

1. Both sirolimus- and paclitaxel eluting stents have been demonstrated to be highly effective in the prevention of restenosis. (this thesis)

2. Late incomplete stent apposition occurs following implantation of sirolimus- and paclitaxel-eluting stents. However, this is a pure intravascular ultrasound finding without clinical percussion. (this thesis)

3. Sirolimus-eluting stents are safe and effective for the treatment of complex coronary artery disease, such as in-stent restenosis, bifurcation lesions, chronic total occlusions, and left main coronary artery disease. (this thesis)

4. Peri-stent remodeling occurs in bare metal stent as well as paclitaxel-eluting stent. There are progressive increases in peri-stent area from bare metal stent to slow release to moderate release paclitaxel-eluting stent. (this thesis)

5. Not all anti-proliferative drugs show a class effect in the prevention of restenosis. (this thesis)

6. Failure of many interventional devices to prevent restenosis was a stepping stone to success of drug-eluting stent.

7. The drug-eluting stent is mightier than the surgery.

8. Japanese should not become such perfectionists as to be afraid of engaging in any conversations with foreigners.

9. To explain oneself coherently in an international discussion, Japanese society has to get more used to a debating style without too much concern for "face" or hierarchy. At the same time, we, Japanese, should keep politeness, benevolence, sincerity, and courage, so-called "Samurai" spirit.

10. Thoraxcenter was not built in a day.

11. Drug-eluting stents and statin a day keep the doctor away.