# PREVENTION OF RESTENOSIS IN CORONARY ARTERIES: *IONIC RADIATION, NON-IONIC RADIATION AND DRUG ELUTING STENTS*

# PREVENTIE VAN RESTENOSE IN CORONAIRE BLOEDVATEN: *IONISERENDE STRALING, NIET IONISERENDE STRALING EN STENTS VOORZIEN VAN MEDICIJNEN.*

**Thesis**

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## PREVENTION OF RESTENOSIS IN CORONARY ARTERIES: IONIC RADIATION, NON-IONIC RADIATION AND DRUG ELUTING STENTS

Chapter 7 *Regar E*, Colombo A, Műgge A, Glogar HD, De Scheerder I, Disco C, Kleine J, Serruys PW:
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**PART 3: DRUG ELUTING STENTS**

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Circulation. 2002;106:1949-56.

*Chapter 1*

# INTRODUCTION AND OVERVIEW OF THESIS

# INTRODUCTION AND OVERVIEW OF THESIS

Over the last decade, coronary stents have revolutionized the field of interventional cardiology. Stent implantation has become the new standard angioplasty procedure[1-3]. This popularity has grown because of 2 main reasons: first, the unique capability to master a major complication of balloon angioplasty - (sub) acute vessel closure - and second, a superior long-term outcome in comparison to balloon angioplasty[4-8]. The high reliability of the acute angioplasty result allowed for a continuos expansion of the indication for catheter-based intervention (including ostial lesions[9], bifurcation lesions[10, 11], left main lesions[12, 13], multiple lesions[14]).

**In-stent restenosis**

However, in-stent restenosis remains the major limitation of coronary stenting. The absolute number of in-stent restenotic lesions is increasing in parallel with the steadily increasing number of stenting procedures and with the complexity of culprit lesions. The treatment of in-stent restenosis is technically challenging and costly. In subsets of lesions (such as small vessel size and diffuse disease) an anticipated high risk for restenosis may even prevent the use of stents.

Restenosis represents a local vascular manifestation of the general biologic response to injury[15]. Injury consists of denuding the intima and stretching the media. Current concepts describe three mechanisms of the restenotic process: early elastic recoil, late vessel remodeling and neointimal growth[16, 17]. We could demonstrate (chapter 2) that coronary stents provide mechanical scaffolding that virtually eliminates recoil and remodeling[18]. However, neointimal growth continues to be a major problem.

**New strategies for the prevention of in-stent restenosis**

Over the last 2 decades, efforts for the prevention of restenosis were focused on optimizing stent characteristics and implantation technique[19, 20]. The growing understanding of vascular biology and the observation that exaggerated neointimal formation shows similarities to tumor growth triggered the development of new treatment strategies.

**Intracoronary ionic radiation (brachytherapy)**

Radiotherapy has been proven successful in the treatment of hypertrophic scars, keloids, heterotopic bone formation, ophthalmic pterygia[21-23] and solid malignancies[24].

Absorbed radiation can cause damage in a tissue either directly by ionization or indirectly by interacting with other molecules to produce free radicals, which will subsequently damage the critical target (DNA)[25]. These biological effects are independent of the radiation type (gamma, beta or X-rays). In injured vascular tissue, radiation doses of 12-20 Gy appear to be efficacious in inhibiting neointimal formation[26-28]. The local mechanisms of action however, are complex[29] and dose dependent whereby low-dose radiation (4-8 Gy) even promotes

cellular growth[30, 31].
Human coronary arteries were treated for the first time by Condado et al. in 1995. Two years later, the randomized SCRIPPS trial demonstrated first in a small number of patients the effectiveness of 192-Ir gamma therapy for the treatment of in-stent restenosis[32]. The results were confirmed by the larger (252 patients) randomized multi-center GAMMA-1 trial[33].

In part 1 of this thesis, we investigated the mechanisms of action and efficacy of intracoronary brachytherapy. Specifically, we addressed the questions

- How to assess outcome and treatment effects using coronary angiography and intravascular ultrasound?
- What is the feasibility and outcome after intracoronary (beta- or gamma) radiation therapy in patients at high risk for repeat occurrence?
- What are the reasons for treatment failure?

**Intracoronary non-ionic radiation (sonotherapy)**
Therapeutic delivery of ultrasound energy has proven to be a powerful and safe therapy in various medical disciplines. The rationale for therapeutic intracoronary application of ultrasound energy is based on experimental observations that have shown various effects, which could be beneficial for the prevention of restenosis. Ultrasound energy enhances fibrinolysis [34, 35] and thus might affect early thrombus formation as peri-interventional local thrombi release growth factors, which stimulate neointimal hyperplasia [36, 37]. Ultrasound can reduce mammalian cell viability[38] and inhibits smooth muscle cell migration, adhesion [39, 40] and proliferation[41]. In a swine peripheral stent model[42] it was shown that at seven days after stent implantation cellular proliferation was significantly reduced in the sonotherapy group compared with the sham group.

In part 2 of this thesis, we investigated in a pilot study the application of intracoronary sonotherapy. We addressed the questions

- Is intracoronary sonotherapy feasible and safe in patients with simple lesions?
- Is intracoronary feasible in patients with complex lesions?
- What are the treatment effects on the coronary artery?

**Intracoronary local pharmacotherapy using drug-eluting stents**
Drug eluting stents target the pharmacological modulation of the local vascular biology. A proposed explanation for the repeated failure of clinical drug studies has been that agents given systemically cannot reach sufficient levels in injured arteries to significantly impact the restenotic process. Local administration of drugs offers advantages. The active drug is applied to the vessel at the precise site and at the time of vessel injury. Local drug delivery might be able to achieve higher tissue concentrations of the drug. No additional materials or procedures are required. Systemic release is minimal and may reduce the risk of remote or systemic toxicity.

The first significant reduction of in-stent restenosis was demonstrated for the rapamycin (sirolimus™) eluting stent. The multicenter, prospective, double blind clinical RAVEL trial (RAndomized study with the sirolimus coated BX VElocity™ balloon-expandable stent in the treatment of patients with de novo native coronary artery Lesions) randomized 238 patients to receive a single sirolimus-eluting or a bare metal BX velocity stent. At six months follow-up, the restenosis rate of the treated group was zero, the loss in minimal lumen diameter was zero, there was no target lesion reintervention and the event-free survival was 96.5%[43].

In part 3 of this thesis, we investigated the efficacy of sirolimus-eluting stents in subsets of patients with complex lesions. Specifically, we addressed the questions

- Are sirolimus-eluting stents effective in the treatment of small vessels?
- Are sirolimus-eluting stents effective in the treatment of complex in-stent restenotic lesions?
- Is sirolimus-eluting stent implantation safe in unselected patients, including unstable angina, acute myocardial infarction and complex lesions?

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*Chapter 2*

## THE PROBLEM: IN-STENT RESTENOSIS

Mudra H, *Regar E*, Klauss V, Werner F, Henneke KH, Sbarouni E, Theisen K:
**SERIAL FOLLOW-UP AFTER OPTIMIZED ULTRASOUND GUIDED DEPLOYMENT OF PALMAZ-SCHATZ STENTS.**
Circulation 1997; 95:363-370.

# Serial Follow-up After Optimized Ultrasound-Guided Deployment of Palmaz-Schatz Stents

## In-Stent Neointimal Proliferation Without Significant Reference Segment Response

Harald Mudra, MD; Evelyn Regar, MD; Volker Klauss, MD; Frank Werner, MD; Karl-Heinz Henneke, MD; Efthia Sbarouni, MD; Karl Theisen, MD

***Background*** The effects of ultrasound-guided high-pressure stenting on late stent and reference segment dimensions are unknown. In this study, we report about angiographic and ultrasound measurements to assess the amount and distribution of neointimal ingrowth within the stent and the changes of plaque burden and dimensions within the reference segments.

***Methods and Results*** Sixty-eight consecutive patients with 72 lesions received single or multiple Palmaz-Schatz coronary stents with a standardized protocol for stent optimization under ultrasound guidance. The residual angiographic diameter stenosis was 3±12% (reference diameter, 3.16±0.61 mm). At follow-up 4.8±2.5 months later, angiography revealed a diameter stenosis of 27±21% with a restenosis rate of 15.3% (confidence interval: 7.8% to 25.6%). Lumen renarrowing within the stent was exclusively due to neointimal ingrowth; no stent compression was observed. The neointima covered 20±20% of the stent area and was more pronounced in the midportion of the stent. Volumetric assessment performed in 26 patients resulted in 13±14% or 65±28% of the stent volume occupied by neointimal ingrowth in patients without or with restenosis, respectively. Vessel remodeling had an impact on lumen dimensions only at reference sites but not within the stent. Plaque burden of 46±11% and 48±11% at the proximal and distal reference sites, respectively, did not show a relevant progression during the follow-up.

***Conclusions*** Serial ultrasound analyses did not show any evidence of stent compression or relevant vessel remodeling. Restenosis was solely due to neointimal ingrowth. Despite a considerable plaque burden within the reference segments, there was no relevant progression of the disease adjacent to the stent.
**(*Circulation*. 1997;95:363-370.)**

***Key Words*** • ultrasonics • stents • angioplasty • angiography • restenosis

Tissue ingrowth and possibly stent compression are discussed as predominant mechanisms for stent restenoses in the long-term follow-up.[1] Little is known, however, about the effects of high-pressure stenting on the extent and spatial distribution of neointimal ingrowth within and adjacent to the stent as well as on late stent dimensions. Intravascular ultrasound (IVUS) is a relatively new clinical tool to assess the delicate interaction between the stent and the vessel wall that cannot be seen in coronary angiography, and it allows precise guidance for stent optimization.[2,3] Moreover, IVUS, unlike coronary angiography, can also depict the vessel wall and therefore currently is the only tool to assess the amount and composition of plaque burden[4-7] as well as changes in vessel geometry over time.[8-10]

The purpose of the present study was to compare immediate and long-term angiographic and ultrasound results after ultrasound-guided optimal stent deployment in a consecutive series of patients. We wanted to determine the mechanism of restenosis, assess the amount and distribution of neointimal ingrowth, and measure the reference segment response after IVUS-guided high-pressure stenting with respect to cross-sectional area changes of total vessel, lumen, and plaque adjacent to the stent.

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## Methods

### Patients

We prospectively studied 80 patients aged 37 to 88 years (mean age, 61 years) after successful IVUS-guided placement of Palmaz-Schatz coronary stents (Johnson and Johnson Interventional Systems) in 84 lesions between February 1994 and April 1995. All patients had given written informed consent for the implantation procedure and the follow-up investigation. The 80 patients represented a consecutive series of IVUS-guided Palmaz-Schatz stenting procedures, while 85 other patients with successful stent implantation during the same time at our institution were not eligible for the present study either because they had received a different stent type, no IVUS study was performed, or they had not yet completed the follow-up. Twelve patients were excluded from analysis because of technical shortcomings or the use of different ultrasound equipment during the follow-up investigation. Therefore, 68 patients with a total of 72 stented lesions were enrolled in the present study.

### Indications, Stents, Implantation Technique, and Adjunctive Therapy

The indications for stent deployment were acute vessel closure in 5 lesions (7%), dissection and/or suboptimal result in 18 (25%), or elective in 49 (68%, with 29 restenoses). A total of 88 Palmaz-Schatz stents (mean, 1.2±0.5 stents/lesion) were used:

45 15-mm standard stents with a central articulation, 2 new 18-mm and 25 new 14-mm stents with a double-spiral articulation, 10 half (7-mm) standard stents, and 6 new 8-mm stents. Fifty-eight lesions were covered by a single stent and 14 by 2 to 3 serial overlapping stents. The stented lesion was located within one of the main native coronary arteries in 53 cases or in a venous graft in 19 (Table 1). All target vessels allowed at least a 3.0-mm balloon diameter for stent placement. After predilation, the stents were manually crimped on the same balloon catheter and expanded until an angiographically optimal result had been achieved (ie, visual diameter stenosis <10%). IVUS was then performed to assess the diameters of both the reference segments and the stent. Redilations with higher pressure up to 22 atm and/or a larger balloon diameter were performed if necessary (Table 2) to reach an optimal stent expansion as described elsewhere.[3] For vessels with a lumen area of >9 $mm^2$, criteria for optimal stent expansion were similar to those used in the MUSIC study[11] (see "Appendix"). Short (9-mm) balloons were used in 34 (47%) of the lesions. In 21 patients, the first IVUS analysis was performed before stent placement to assess lesion composition and dimensions. All patients were receiving long-term treatment with low-dose aspirin (100 mg/d) and antianginal therapy. Before stent delivery, unfractionated heparin (10 000 to 20 000 IU) was given intravenously to maintain an activated clotting time >300 seconds. Forty-four patients met the IVUS criteria of optimal stent expansion and continued taking low-dose aspirin intake as their only antithrombotic therapy. The remaining 24 patients received a combination of low-dose aspirin and either ticlopidine (500 mg/d) or coumadin for 4 to 8 weeks.

## Follow-up Protocol

All patients in the present study were seen in the outpatient department of our institution 4 to 6 weeks after stent placement and were scheduled for repeat coronary angiography at 6 months after stent placement or earlier if symptoms or exercise tolerance tests suggested restenosis. The control angiogram was performed in all 68 patients at a mean of 4.8±2.5 months after the initial procedure.

## Angiography and Analysis

Initial and follow-up angiograms were performed in multiple biplane projections with the use of 8F guiding catheters after intracoronary injections of 0.25 mg nitroglycerin. All projections of the initial angiography were repeated at follow-up. From technically suitable angiograms, the optimal views of the stented lesion were digitized (MediaGrabber, RasterOps Corp) with an image resolution of 640×480 pixels. Qualitative analysis of baseline angiograms was performed with respect to lesion type and type of dissection after predilation according to AHA/ACC classifications.[12] Computerized quantitative analysis was performed according to previously described and validated edge-detection algorithms, with the guiding catheter taken as reference.[13] Quantitative measurements included the proximal and distal diameters of the reference, giving the mean reference diameter, the minimal lumen diameter, and the length of the lesion. Immediately after optimization of the stent and at follow-up, the minimal stent lumen diameter and the reference lumen diameters were measured and diameter stenosis was calculated with the use of the view that showed the most severe lumen narrowing. Furthermore, acute lumen gain (final minimal diameter after stent optimization minus minimal lesion diameter), late lumen loss (final minimal stent lumen diameter minus follow-up minimal lumen diameter), net lumen gain (acute lumen gain minus late lumen loss), and loss index (late lumen loss/acute lumen gain) were calculated.

## IVUS Procedure and Analysis

Every IVUS investigation within a single patient was performed with the use of the same IVUS system at baseline and at follow-up. Twelve patients with 14 lesions were studied with the use of an electronic system with a 3.5F catheter operating on a frequency of 20 MHz (Endosonics Corp). In 56 patients with 58 lesions, a mechanical system (Vingmed Corp) with a 30-MHz probe mounted on a 2.9F common sheath catheter (Cardiovascular Imaging Systems Inc) was used. After the patient was given an intracoronary injection of 0.25 mg nitroglycerin, the IVUS catheter was introduced into the coronary artery distal to the stented segment. Under continuous video registration (S-VHS, Panasonic 7330-E, Matsushita Electric Inc), a slow manual pullback was performed by the same operator (H.M.) from a distinct landmark through the entire stented lesion back to the guiding catheter. All 56 IVUS studies with the mechanical system at follow-up as well as 26 baseline studies were performed with the use of a motorized pullback system (Cardiovascular Imaging Systems Inc) at a speed of 0.5 mm/s. After every procedure, the imaging catheter was tested for correct distance calibration by imaging cylindrical phantoms with an internal diameter of 2.0 to 5.0 mm.

IVUS images of optimal quality that showed a central and coaxial position of the probe from the proximal and distal references 1 to 3 mm apart from the stent ends by use of reproducible landmarks such as calcium spots or side branches and taken from three to five distinct locations within the stent (Fig 1) were digitized off-line (MediaGrabber, RasterOps Corp).

**TABLE 1. Patient Characteristics, Lesion Morphology, and Indication for Stenting**

| | |
|---|---|
| Age, y | 61±15 |
| Men, n (%) | 58 (85) |
| Prior myocardial infarction, n (%) | 31 (45) |
| Ejection fraction, % | 58±11 |
| Angina class (CCS), n (%) | |
| I | 13 (19) |
| II | 12 (18) |
| III | 18 (26) |
| IV | 25 (37) |
| Number of diseased vessels, n (%) | |
| 1 | 14 (20) |
| 2 | 21 (31) |
| 3 | 33 (49) |
| Treated vessel, n (%) | |
| LAD | 23 (32) |
| LCx | 15 (21) |
| RCA | 15 (21) |
| CABG | 19 (26) |
| Lesion type,* n (%) | |
| A | 9 (13) |
| B | 42 (58) |
| C | 21 (29) |
| Lesion length, mm | 10.6±6.2 |
| Indication for stenting, n (%) | |
| Elective | 49 (68) |
| Emergency | 5 (7) |
| Suboptimal result | 18 (25) |
| Restenosis, n (%) | 29 (40) |
| Dissection before stenting,* n (%) | |
| None | 45 (63) |
| A | 4 (5) |
| B | 6 (8) |
| C | 12 (17) |
| D to F | 5 (7) |
| Stents per lesion, n (%) | |
| Single stent | 58 (81) |
| Two stents | 12 (16) |
| Three stents | 2 (3) |

CCS indicates Canadian Cardiovascular Society; LAD, left anterior descending artery; LCx, left circumflex artery; RCA, right coronary artery; and CABG, coronary artery bypass graft. Values are mean±SD except for percentages.

*According to American Heart Association/ACC criteria.[12]

**TABLE 2. Angiographic Measurements**

| | Before Intervention | Acute Stent Result | Follow-up |
|---|---|---|---|
| Mean reference diameter, mm | 3.04±0.72 | 3.16±0.61* | 3.09±0.60 |
| Minimal lumen diameter, mm | 0.82±0.44 | 3.04±0.86† | 2.25±0.80‡ |
| Stenosis, % | 73±12 | 3±12† | 27±21‡ |
| Acute lumen gain/late loss, mm | . . . | 2.22±0.53 | 0.78±0.72 |
| Net gain, mm | . . . | . . . | 1.44±0.74 |
| Loss index | . . . | . . . | 0.34±0.30 |
| Nominal balloon/artery ratio | . . . | 1.17±0.23 | . . . |
| Measured balloon/artery ratio | . . . | 1.10±0.15 | . . . |
| Maximal inflation pressure, atm | . . . | 13.7±3.7 | . . . |

Values are mean±SD.
*$P$<.05 vs before intervention.
†$P$<.0001 vs before intervention.
‡$P$<.0001 vs acute stent result.

### *Qualitative Analysis*

Plaques were characterized according to their acoustic properties. Type A plaques showed attenuation of the ultrasound signal within at least 45° of the vessel circumference, whereas type B plaques did not show these characteristics.

### *Quantitative Measurements*

The reproducibility of IVUS measurements within coronary stents has been previously published for use of the electronic system.[3] For the mechanical system predominantly used in the present study, reproducibility between repetitive IVUS pullbacks was additionally tested for vessel area, stent area, and lumen area determination at 40 randomly chosen corresponding sites. The absolute and relative differences (mean±SD) between two consecutive measurements for vessel area, stent area, and lumen area were 1.4±1.2, 0.7±0.6, and 1.2±1.2 mm$^2$ and 6.9±7.0%, 5.7±5.7%, and 10.2±9.7%, with correlation coefficient values of .94, .95, and .91, respectively.

The minimal lumen area, minimal stent area, and vessel area (within the medial to adventitial border) were traced in each frame and calculated by use of a commercially available software program for IVUS measurements (TapeMeasure, Indec Systems Inc). Residual plaque burden was calculated as vessel area minus lumen area. Neointimal ingrowth was defined as echogenic material within the stent at follow-up and assessed with respect to maximal thickness and absolute as well as relative area (stent area minus lumen area and stent area minus lumen area×100/stent area, respectively) at the tightest stent site and all other sites interrogated at baseline. From corresponding baseline and follow-up frames, the following parameters were determined for the stented and the reference segments: lumen loss (minimal stent or lumen area at baseline minus minimal lumen area at follow-up), stent compression (stent area at baseline minus stent area at follow-up×100/stent area at baseline), chronic vessel recoil (vessel area at baseline minus vessel area at follow-up×100/vessel area at baseline), and plaque area change [(vessel area minus lumen area at follow-up) minus (vessel area minus lumen area at baseline)]. In patients who showed a minimal lumen diameter at follow-up less than the diameter and ring-down artifact of the echo probe, the calculations of neointimal hyperplasia were based on the angiographically determined lumen diameter, assuming a circular residual lumen shape. In the 26 lesions investigated twice with a motorized pullback, an end-diastolic image was digitized every 2 seconds from the distal to the proximal reference segments throughout the stent, representing 1 mm of lesion length. In each of these sequential images, lumen and stent areas were traced and volumetric measurements of stent volume and neointimal ingrowth (stent volume minus lumen volume) were assessed by application of Simpson's rule.

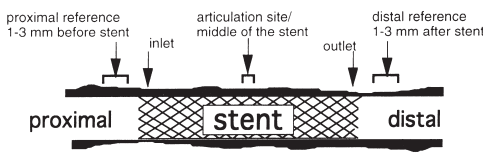


FIG 1. Schematic showing sites within the stent and the proximal and distal references assessed by intravascular ultrasound.

### Definition and Analysis of Restenosis

A stent was considered restenotic if the angiographic lumen diameter reduction at follow-up was >50% of the mean reference diameter or if the ultrasound analysis showed a minimal lumen area within the stent <25% of the mean reference segment lumen area assessed 3 to 5 mm away from the stent margins. A diffuse restenosis was defined as a lumen narrowing according to these angiographic or ultrasound criteria encompassing >50% of the stent length, while shorter restenoses were defined as focal.

### Statistical Analysis

Values are reported as mean±SD. Statistical analyses were performed with a commercially available software program (StatView 4.02, Abacus Concepts Inc). Correlations between repetitive ultrasound or angiographic measurements were tested by linear regression analysis for two variables. Intra-individual comparisons were made by use of the paired $t$ test. For unpaired variables, a Mann-Whitney $U$ test was performed. A difference was considered significant with a two-sided probability value <.05.

## Results

There were no procedural complications except two side-branch occlusions during stent optimization followed by a mild enzyme elevation with no changes in the ECG. No stent thrombosis was observed.

### Angiographic Analysis

The majority of the lesions were types B and C (Table 1), and the mean lesion length was 10.6±6.2 mm. No dissections were present at the time of the final angiogram. The quantitative angiographic and procedural data are given in Table 2. At follow-up, a lumen diameter stenosis ≥50% was seen in 11 of the stented lesions, resulting in a restenosis rate of 15.3% (CI, 7.8% to 25.6%).

### IVUS Analysis

#### *Qualitative Assessment at Baseline*

Lesion morphology was assessed in 21 lesions (29%) before stent deployment; in the remaining cases, this was achieved during the first IVUS analysis after stent place-

**TABLE 3. Intravascular Ultrasound Area Measurements at Baseline (After Stent Optimization) and at Follow-up**

| | Baseline (n=72) | Follow-up (n=72) | P |
|---|---|---|---|
| Reference segments | | | |
| Vessel area, mm$^2$ | | | |
| Proximal | 21.7±5.8 | 21.9±6.2 | NS |
| Distal | 20.0±7.4 | 20.6±6.8 | NS |
| Mean | 21.3±6.2 | 21.3±6.1 | NS |
| Lumen area, mm$^2$ | | | |
| Proximal | 11.4±3.7 | 10.6±3.8 | .002 |
| Distal | 9.8±3.9 | 9.5±3.7 | NS |
| Mean | 10.5±3.5 | 10.1±3.8 | NS |
| Plaque area, % | | | |
| Proximal | 46±11 | 50±11 | .015 |
| Distal | 48±11 | 50±10 | NS |
| Stented segment | | | |
| Vessel area, mm$^2$ | | | |
| Proximal | 24.1±6.2 | 24.2±6.2 | NS |
| Medial | 23.1±6.1 | 23.0±5.4 | NS |
| Distal | 22.8±7.5 | 23.5±7.0 | NS |
| At tightest stent site | 23.0±7.5 | 23.2±6.9 | NS |
| Mean | 23.4±5.9 | 23.5±5.9 | NS |
| Lumen area, mm$^2$ | | | |
| Proximal | 10.1±2.9 | 8.4±3.7 | <.0001 |
| Medial | 9.7±3.2 | 7.5±3.6 | <.0001 |
| Distal | 9.7±3.2 | 8.1±3.8 | <.0001 |
| Minimal | 8.4±2.9 | 7.1±3.6 | <.0001 |
| Mean | 9.5±3.0 | 7.8±3.5 | <.0001 |
| Lumen area stenosis, % | | | |
| Average stenosis | 7±15 | 15±22 | <.001 |
| Maximal stenosis | 15±14 | 30±26 | <.001 |
| Plaque, % | | | |
| Average plaque area | 54±8 | 54±8 | NS |
| Tightest site plaque area | 58±10 | 56±9 | NS |

Values are mean±SD.

ment. The plaque type at the tightest lesion site could be assessed in 66 (92%) of the 72 lesions. In 22 (33%) of these lesions, a type A plaque was found; in 44 lesions (67%), a type B plaque was found.

The vessel area could be assessed in 113 (84%) of the 134 reference segments and in 93 (40%) of 232 analyzed sites within the stent, while in the remaining sites, distal shadowing due to stent filaments and/or calcium precluded a sufficient tracing of the inner adventitial contour.

At the final IVUS analysis, all stents were properly attached to the vessel wall over their entire length. There was no evidence of plaque prolapse within or adjacent to the stent.

### *Quantitative Analysis at Baseline*

The lumen area at the proximal and distal reference sites was 11.4±3.7 and 9.8±3.9 mm$^2$, respectively. Within the stent, the lumen area at the tightest site was 8.4±2.9 mm$^2$. The average lumen area of all analyzed stent sites was 9.5±3.0 mm$^2$. This resulted in a residual maximal and averaged area stenosis of 15±14% and 7±15%, respectively. The vessel area of the proximal and distal reference sites was 21.7±5.8 and 20.0±7.4 mm$^2$, respectively. The corresponding mean plaque areas occupied 46±11% and 48±11% of the vessel area, respectively. The mean vessel area within the stent was 23.4±5.9 mm$^2$ and 23.0±7.5 mm$^2$ at the tightest in-stent site. The area encompassed by the residual plaque covered 54±8% of the vessel area on average (Table 3). At the tightest stent site, the plaque burden was significantly higher than at all other stent sites (58±10% versus 53±8%; $P$=.0087). Type B lesions showed a smaller residual mean plaque area within the stent than type A plaques ($P$=.0242) but no difference of the residual area stenosis (Table 4).

### *Qualitative Assessment at Follow-up*

At follow-up, echogenic material within the stent representing neointimal ingrowth could be clearly identified to various degrees within every stented lesion. In four lesions with severe diffuse in-stent restenosis, the diameter of the imaging catheter was larger than the residual lumen diameter, thus precluding a precise ultrasound measurement of the neointimal mass. The neointimal material showed a great variability with regard to its spatial distribution within the circumference of the stent and its thickness within each stent cross section.

### *Quantitative Analysis at Follow-up*

The lumen area of the distal reference segments remained unchanged at follow-up, whereas the proximal reference showed a slight decrease (Table 4). The intraindividual changes of reference lumen area did not correlate with the corresponding plaque burden at baseline, but type B plaques demonstrated a larger lumen loss than type A plaques ($P$=.0430) (Table 4). The average and minimal lumen areas within the stent had significantly decreased to 7.8±3.5 and 7.1±3.6 mm$^2$, respectively (Table 3). This corresponded to a maximal and average late lumen area loss of 1.8±2.3 and 1.6±2.0 mm$^2$, respectively, with a trend, albeit nonsignificant, toward a larger lumen loss in type B lesions (Table 4). Nine lesions showed a restenosis according to IVUS criteria, with a diffuse pattern in six stents and a focal pattern in three stents (two mid and one proximal). The stent area at all analyzed sites was not significantly different from the baseline value. The measured differences between baseline and follow-up demonstrated a normal distribution around zero (Fig 2A). The vessel size

**TABLE 4. Intravascular Ultrasound Measurements Within the Reference Segments and the Stented Segments in Type A and Type B Lesions at Baseline (After Stent Optimization) and at Follow-up**

| | Plaque Type | | |
|---|---|---|---|
| | Type A (n=22) | Type B (n=44) | P |
| Baseline | | | |
| Stented segment | | | |
| Area stenosis after stent implantation, % | 8±11 | 6±17 | NS |
| Residual plaque burden, % | 58±10 | 53±9 | .024 |
| Reference segment | | | |
| Residual plaque burden, % | 48±8 | 47±8 | NS |
| Follow-up | | | |
| Stented segment | | | |
| Late lumen loss, mm$^2$ | 1.4±1.7 | 2.0±2.7 | NS |
| Neointimal area (% stent area) | 17±20 | 24±24 | NS |
| Changes in plaque area (% vessel area) | 12±20 | 17±21 | NS |
| Reference segment | | | |
| Late lumen loss, mm$^2$ | −0.6±1.8 | 0.3±2.0 | .043 |
| Changes in plaque area (% vessel area) | 5±13 | 4±9 | NS |

Values are mean±SD and represent the average of all analyzed sites of a segment.

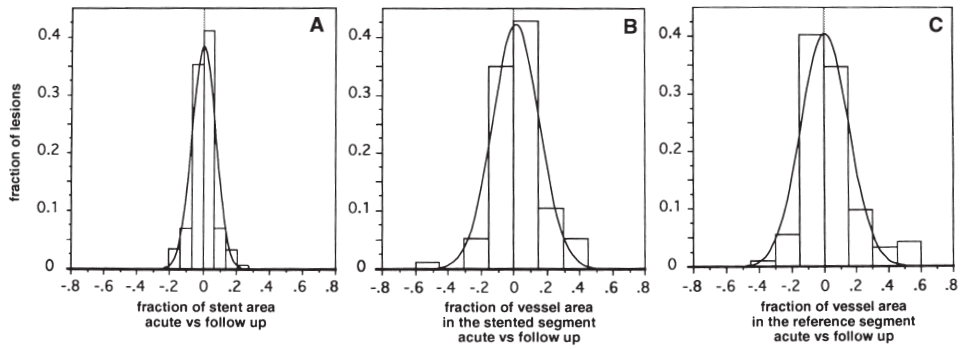


FIG 2. A, Relative change in stent area between baseline and follow-up showing a normal distribution around zero. B and C, Relative changes in vessel area between baseline and follow-up in the stent sites and reference sites, respectively. At both sites, a nearly normal distribution around zero can be seen.

of the reference and stent sites remained within the twofold interstudy variability of ±15% in most stented segments. In 7% of the reference sites and in 6% of the stent sites, the vessel size showed a decrease >15%. A >15% increase was present in 17% of the reference sites and in 15% of the stent sites (Fig 2B and 2C). A change in vessel size correlated with a parallel lumen area change only at the reference sites ($r$=.64, $P$<.0001) but not within the stent. The neointimal ingrowth had a maximal thickness of 0.6±0.7 mm and covered an area of 2.5±2.4 mm$^2$, reaching up to 1.6 mm or 11.3 mm$^2$ in patients with significant restenosis. The neointimal ingrowth covered 20±20% of the stent area on average and 26±25% at the tightest stent site (Table 5). The late lumen area loss and neointimal area were strongly correlated ($y$=0.56+0.88$x$; $r$=.94). The neointimal ingrowth was most pronounced in the midsection of the stent, as were the absolute and relative changes in plaque area (Table 5). Regions of stent overlap in multiple stents did not show a more pronounced neointimal ingrowth. Compared with the spiral-bridged Palmaz-Schatz stent, articulated 15-mm stents did not show a significantly smaller minimal lumen area at follow-up despite a smaller acute minimal stent area. Accordingly, late lumen loss and neointimal area were larger in the midsection of the nonarticulated stent despite comparable balloon size and inflation pressure used during stent optimization (Table 6). Restenotic stents did not show a smaller stent area than stents without restenosis (Table 7). The absolute and relative changes in plaque area did not significantly correlate with the lesion type or with the residual plaque area at baseline.

### *Volumetric IVUS Results*

In the 26 lesions that were assessed with motorized pullback both at baseline and at follow-up, stent volume did not decrease. In-stent lumen volume, however, decreased from 138±32 to 124±40 mm$^3$ in patients without restenosis and to 43±31 mm$^3$ in patients with restenosis due to neointimal ingrowth, resulting in a 65±28% reduction of lumen volume due to neointimal ingrowth (Table 8). The middle third of the stented segment showed a trend toward a more pronounced neointima formation than the proximal and distal thirds of the stent.

## Discussion

This follow-up study in 68 consecutive patients undergoing IVUS-guided stenting demonstrates the mechanisms and extent of lumen renarrowing within Palmaz-Schatz stents and the late response of the adjacent reference segments. Our results show that restenosis of Palmaz-Schatz stents is exclusively due to neointimal ingrowth, which is most pronounced in the middle portion of the stent, and not to stent compression. The adjacent reference segments not covered by the stent did not show a clinically relevant change in lumen dimensions or a change in total vessel area in the majority of the lesions despite application of high balloon pressures.

### Angiographic Results

IVUS guidance of stent optimization resulted in an angiographic residual lumen diameter stenosis of 3±12% and is comparable to the latest studies published by Colombo et al[14] and Hall et al,[15] which show a mean residual

**TABLE 5. Intravascular Ultrasound Measurements of Late Lumen Loss, Neointimal Ingrowth, and Change in Plaque Area at Different In-Stent Locations**

| | Stent Sites | | | | |
|---|---|---|---|---|---|
| | Proximal (n=70) | Medial (n=64) | Distal (n=71) | Tightest (n=72) | All* (n=72) |
| Late lumen loss, mm$^2$ | 1.7±2.5 | 2.1±2.5 | 1.6±2.4 | 1.8±2.3 | 1.8±2.0 |
| Neointimal area, mm$^2$ | 1.7±2.2 | 2.3±2.6 | 1.9±2.4 | 2.5±2.4 | 2.0±1.9 |
| Neointimal area, % | 17±20 | 24±27 | 20±20 | 26±25 | 20±20 |
| Maximal neointimal thickness, mm | 0.3±0.4 | 0.5±0.4 | 0.3±0.3 | 0.6±0.7 | 0.4±0.4 |
| Absolute change in plaque area, mm$^2$ | 2.2±4.1 | 2.7±3.6 | 1.7±4.2 | NA† | 2.4±3.1 |
| Relative change in plaque area, % | 10±18 | 15±19 | 10±20 | NA† | 14±20 |

Values are mean±SD.
*Average of all stent sites for each lesion.
†Not available because of different location of the tightest in-stent site at baseline and at follow-up.

**TABLE 6. Intravascular Ultrasound Measurements in Articulated and Nonarticulated Single Stents in the Midsection of the Stents**

| | Articulated (15-mm) Stent (n=34) | Nonarticulated (14-mm) Stent (n=19) | *P* |
|---|---|---|---|
| Acute stent result | | | |
| Lumen area, $mm^2$ | 7.5±2.4 | 10.7±2.6 | .0001 |
| Follow-up | | | |
| Lumen area, $mm^2$ | 6.5±2.6 | 7.4±3.3 | NS |
| Late lumen loss, $mm^2$ | 1.2±2.2 | 2.8±2.3 | .035 |
| Neointimal area, $mm^2$ | 1.3±2.2 | 3.0±2.2 | .013 |
| Neointimal area, % | 18±28 | 32±25 | NS |

Values are mean±SD.

diameter stenosis of 0±14% and 1±10% achieved with comparable definition of IVUS criteria for optimal stent deployment. Although the present study includes only a relatively small number of consecutive patients, the restenosis rate of 15.3% appears remarkably low, particularly when considering the fact that 40% of all patients presented with restenosis as the primary stent indication. These data compare favorably with the results of the STRESS and BENESTENT studies[16,17] and are comparable to the 19% restenosis rate in another series after IVUS-guided stenting.[18] This might be the result of achieving a maximal acute lumen gain through IVUS-guided stenting. This concept was previously introduced by Kuntz and colleagues[19,20] for angioplasty in general and is currently the only clinically available approach to enhance late lumen dimensions, because effective methods to reduce tissue proliferation within the stent are still under investigation. Despite the given correlation between acute gain and late loss,[20] the mean late lumen loss in this series with enhanced initial gain is only slightly higher than in the STRESS and BENESTENT studies, resulting in a higher net gain and a lower loss index.

### Ultrasound Assessment Within the Stent

The stent expansion achieved by the use of IVUS guidance led to a mean area stenosis of 7%, reaching up to 15% at the tightest stent site. The acutely achieved stent expansion remained unchanged during follow-up at each stent site, indicating a lack of any significant stent compression as shown in previous angiographic and ultrasound studies.[1,21,22] A change in vessel area within the stent occurred in ≈20% of the analyzed sites, with no correlation to the corresponding lumen area. This shows that vessel remodeling in the stented segment does not affect the lumen. Neointimal ingrowth represented the only relevant mechanism of in-stent restenosis in this series of patients. This result is in accordance with the results of animal studies showing an exaggerated intimal hyperplasia after stenting in the pig model[23,24] and with previous clinical observations.[1,21,22,25] Despite a large variability in the spatial distribution and amount of neointimal formation, there was a strong correlation between late lumen loss and neointimal area. The volumetric assessment showed a 20% reduction in stent lumen volume by neointimal ingrowth. This result in a nonselected consecutive series of patients compares favorably with the results of the Washington Center group, which showed a 20% reduction in patients without restenosis and 48% in patients with restenosis, and may be due to the larger relative stent expansion achieved in our series (93% versus 77%).[22] Regardless of the stent type (articulated or nonarticulated), the site with the largest lumen loss due to neointimal formation was located in the midportion of the stent. This finding has been reported before for articulated Palmaz-Schatz stents.[26] The articulation site, with its lack of mechanical support and more severe injury to the intima, was thought to be the main cause of excess neointima formation.[26] Our results, however, suggest that other, more lesion-specific factors, such as enhanced cellular proliferation at the center of the target lesion, are responsible for this overly proportional neointimal ingrowth. The observed trend toward a lower intimal proliferation in type A lesions also suggests a relation between plaque characteristics and the degree of cellular proliferation response after stenting.

### Ultrasound Assessment of the Reference Segments

The response of the adjacent reference segments not covered by the stent is of major interest because high-pressure dilation in this region may lead not only to acute dissections but also to severe barotrauma, triggering a cellular hyperplastic reaction.[23,24,27] A major advantage of ultrasound guidance during stent optimization consists in the detailed knowledge it provides of the true vessel dimensions and plaque burden adjacent to the stent, which allows a precise sizing of the balloon used for high-pressure inflations.[2,3] This appears to be the reason that dissections outside the stent could be avoided in this series. Moreover, the minimal late lumen loss found in this series only within the proximal reference segments, which paralleled a slight increase of plaque area, may be interpreted as the result of

**TABLE 7. Intravascular Ultrasound Measurements at Follow-up in Lesions With and Without Restenosis According to Angiographic and/or Ultrasound Criteria**

| | No Restenosis (n=61) | Restenosis (n=11) | *P* |
|---|---|---|---|
| Stent CSA, $mm^2$ | 9.6±3.2 | 9.1±1.6 | NS |
| Lumen area at follow-up, $mm^2$ | 8.5±3.3 | 3.9±2.5 | <.001 |
| Neointimal area, $mm^2$ | 1.5±1.4 | 5.4±2.9 | <.0001 |
| Neointimal area, % | 15±14 | 57±27 | <.0001 |

Values are mean±SD.

**TABLE 8. Intravascular Ultrasound Measurements of Stent Volume, Lumen Volume, and Neointimal Volume in 26 Patients Investigated With a Motorized Pullback System at Baseline and at Follow-up**

| | Total | Proximal | Medial | Distal |
|---|---|---|---|---|
| Stent volume after implantation, $mm^3$ | 138±32 | 47.0±11 | 46±12 | 45±14 |
| No restenosis (n=22) | 138±31 | . . . | . . . | . . . |
| Restenosis (n=4) | 140±40 | . . . | . . . | . . . |
| Stent volume at follow-up, $mm^3$ | 140±45 | 48±12 | 47±13 | 45±14 |
| No restenosis (n=22) | 142±36 | . . . | . . . | . . . |
| Restenosis (n=4) | 139±34 | . . . | . . . | . . . |
| Lumen volume at follow-up, $mm^3$ | 112±47 | 39±15 | 36±16 | 37±17 |
| No restenosis (n=22) | 124±40 | . . . | . . . | . . . |
| Restenosis (n=4) | 43±31 | . . . | . . . | . . . |
| Neointimal volume, $mm^3$ | 28±37 | 9±12 | 11±15 | 8±11 |
| No restenosis (n=22) | 18±19 | . . . | . . . | . . . |
| Restenosis (n=4) | 96±64 | . . . | . . . | . . . |
| Relative neointimal volume, % | 20±23 | 18±24 | 23±26 | 18±23 |
| No restenosis (n=22) | 13±14 | . . . | . . . | . . . |
| Restenosis (n=4) | 65±28 | . . . | . . . | . . . |

Values are mean±SD.

a less traumatic high-pressure dilation strategy. These observations have interesting clinical implications, because it is still not known to which vessel region the stent covering should ideally be extended to minimize the risk of restenosis. Despite an average plaque burden of 47% within the reference segments, without angiographic evidence of lumen narrowing reflecting the Glagov effect,[28] there was no evidence for a significant progression of the disease during the follow-up period.

### Limitations of the Study

The relatively small number of patients eligible for analysis in this study may render it difficult to generalize the results and to apply them to other patient populations with possibly different lesion characteristics, eg, smaller target vessels. However, this study represents a consecutive series of patients treated with a standardized protocol of IVUS guidance according to the criteria used in the MUSIC study.[11] Only a limited number of cross sections within the stented segment, ie, the proximal, medial, and distal stents, could be analyzed serially because not all patients were investigated with a motorized pullback system at baseline and at follow-up. Because the volumetric assessment performed on those patients analyzed twice by means of a motorized pullback shows similar results compared with the general study population, it seems unlikely that the analysis of more in-stent sites would have led to different results. The mode of lesion classification used in this study also represents a limitation because it was performed in most patients after stent placement, which may have altered the echo reflectiveness of the compressed plaque material. For this reason, a crude classification of plaques was used that was based solely on the presence or absence of shadowing of the ultrasound beam. An a priori analysis of every lesion before stent placement would allow a better understanding of specific lesion differences during stent placement.

### Conclusions

The results of this study of a consecutive series of patients undergoing IVUS-guided stenting clearly show that in-stent restenosis is exclusively due to neointimal ingrowth and not to stent compression. Furthermore, different stent designs (articulated or nonarticulated Palmaz-Schatz stents) did not cause different lumen dimensions at follow-up. Despite the application of high-pressure balloon inflations generally involving the reference segments with a plaque burden at baseline of nearly 50% of the vessel area, there was no relevant change of reference lumen dimensions at follow-up. This result may be of clinical relevance for the definition of optimal stent length.

## Appendix

An optimal stent expansion was defined as follows:

1. Complete apposition of the stent against the vessel wall.
2. Minimal in-stent lumen area ≥90% of the averaged reference lumen area or ≥100% of the smaller reference lumen area. In stents with a minimal lumen area ≥9.0 $mm^2$, this parameter had to be ≥80% of the averaged reference lumen area or ≥90% of the smaller reference lumen area.
3. Lumen area at the proximal stent entrance ≥90% of the proximal reference lumen area.

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## PART 1: IONIC RADIATION THERAPY

*Chapter 3*

*Regar E*, van der Giessen WJ, Vos J, de Feyter P, Smits P, Serruys PW:
**CORONARY BRACHYTHERAPY.**
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# Coronary brachytherapy

**Evelyn Regar, Willem van der Giessen, Jeroen Vos,
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# Introduction

Restenosis remains the major limitation of percutaneous, catheter-based interventional therapy. The endovascular application of radioactivity may offer a preventive treatment strategy. Since the first clinical trial, conducted in 1990 in patients with in-stent restenosis of femoropopliteal arteries using gamma (Ir-192) radiotherapy[1], a substantial number of controlled clinical trials have been completed. Coronary gamma radiation was first applied in Venezuela[2] and randomized clinical trials were first conducted in the U.S. In Europe, most experience has been gained with beta-radiation, the gamma radiation has been used in a few centers and few patients[3]. Important reasons are the strict regulatory requirements regarding shielding, storage and transportation of these sources.

Over the last year, a number of points have become evident in coronary application of radiation. First, radioactive stents do not show overall beneficial therapeutic effect. Second, beta-brachytherapy seems to be as effective as gamma-brachytherapy in the mid-term follow-up (1 year). Third, vascular brachytherapy is effective for the treatment of in-stent restenosis, but its effectiveness in lesions with new stent implantation is ambiguous. For the coming years, the questions regarding the duration of anti-thrombotic treatment, the long-term outcome and the benefit in de-novo lesions in patients at very high risk for restenosis have to be answered. This chapter summarizes the clinical experience and gives an overview of the current practice.

## Definition

Brachytherapy is derived from the Greek "βραχυς" (brachy) meaning short and "θεραπεια" (therapy) meaning treatment to describe the application of radioactivity by a sealed source at a very short distance to the target tissue, e.g. by intracavitary or interstitial source placement. Recently, the term *vascular brachytherapy* has been introduced to describe endovascular radiation therapy.

## Rationale

Radiotherapy has been proven successful in the treatment of hypertrophic scars, keloids, heterotopic bone formation, ophthalmic pterygia and solid malignancies[7]. In non-malignant diseases, radiation inhibits efficiently fibroblastic activity, without influencing the normal healing process, and without causing significant morbidity during long term follow-up of up to 20 years.

*Brachytherapy* has the physical benefit that very high doses of radiation can be delivered directly or almost directly to the target.

# Basic radiation physics

## Radioactivity

Radioactivity is the spontaneous process in which an unstable nucleus, which has either too many or too few neutrons, turns to a stable state (ground state) whereby superfluous energy is released.

The release of energy is called radiation, which can be in the form of electromagnetic waves, like gamma radiation, or of particle rays, like alpha, beta and neutron rays. This process is often called the "*disintegration*" of an atom.

The activity (A) can be expressed by the quotient of the number of disintegrations (dN) within a time interval (dt). The mathematical expression for the activity is:

$A = -dN/dt$ with the unit bequerel (Bq) according to the international system (SI) for units. This unit replaces the formerly used unit curie (Ci) whereby 1 Ci = 37 $10^{10}$ Bq.

## Decay

For most atoms the activity is proportional to the number of nuclei ($A=\lambda N$). The proportionality constant is called the decay constant. This leads to the decay law, $A_t=A_0\exp(-\lambda t)$, and $\lambda=\ln 2/T_{1/2}$ whereby $T_{1/2}$ is called the "physical half-life time", being the time that the original activity of a nuclide has been reduced with a factor two. The physical half-life time is characteristic for nuclids (distinct nuclear species) and isotopes (various forms of an element).

## Biological half-life

Biological half-life is used for the time needed by the body to eliminate one-half of an administered amount of any substance by regular process of elimination. This time is approximately the same for both, stable and unstable isotopes of the same element.

## Effective half-life

In case radioactive material is ingested in the human body, both, physical and biological half-live, have to be considered. Combination of both half-lives gives the effective half-life, which can be expressed by $1/T_{1/2eff} = 1/T_{1/2phy} + 1/T_{1/2biol}$.

Half-lives can be replaced by the physical and biological decay constants: $\lambda_{eff} = \lambda_{phy} + \lambda_{biol}$.

## Absorption - radiation dose

The released energy during transformation of an unstable atom into a stable atom is absorbed in tissue. The quantity of absorbed energy in a tissue is called the "dose" with the SI unit Gray (Gy=J/kg). The dose is strongly dependent of the type of radiation (activity and decay) and the time span, also called "dwell time".

## Radiation dose rate

Dose rate is the dose of radiation per time (delivered or received). The dose rate delivered by a source depends on the activity of the source and the radionuclide that it contains. Currently, all vascular brachytherapy sources deliver energy at high dose rate.

## Dose

Biological effects of the absorbed radiation are dependent on the type of radiation and the type of tissue, which is irradiated. The unit of the dose is joules per kilogram ($Jkg^{-1}$) and is called Sievert (Sv).

## Radiation weighting factor ($W_R$)

A correction factor that indicates the harmfulness of the type of radiation involved.

## Tissue weighting factor ($W_T$)

The tissue-weighting factor indicates the sensitivity of an organ/tissue to radiation.

## Equivalent dose ($H_T$).

The equivalent dose is a quantity used for radiation protection purposes. It takes into account the *probability of effects*. It is defined as the product of the averaged absorbed dose in a specified organ or tissue ($D_T$) and the radiation-weighting factor ($W_R$).

$H_T = W_R D_T$.

## Effective dose ($H_E$).

The sum of the products of the equivalent dose to the organ or tissue (HT) and the tissue weighting factor (WT) applicable to each of the body organs or tissue that are irradiated.

$H_E = \Sigma W_R W_T D_T$.

## Isodose

Descriptive of a locus at every point of which the absorbed dose is the same.

## Currently used isotopes

The most important physical properties of currently used isotopes in vascular brachytherapy are listed below.

| Isotope | Emission | Max. Energy | Av. Energy | Half-life |
|---|---|---|---|---|
| $^{192}Ir$ | gamma | 612 keV | 375 keV | 74 days |
| $^{90}Sr/^{90}Y$ | beta | 2270 keV | 970 keV | 28 years |
| $^{32}P$ | beta | 1710 keV | 690 keV | 14 days |
| $^{90}Y$ | beta | 2270 keV | 970 keV | 64 h |
| $^{188}Re$ | beta | 2130 keV | 780 keV | 69 days |

These isotopes show important physical differences. Basically, gamma radiation consists of photons, beta radiation of electrons.

## Gamma radiation

Gamma rays are photons originating from the nucleus of a radionuclide, which take the form of electromagnetic radiation. A heavy unstable nucleus will emit an alpha (heavyweight charged particle, which can travel only very short distances within tissues) or beta particle followed by gamma radiation. Gamma rays may have either 1 or 2 discrete energy values or a broad spectrum of many energy values. They penetrate deeply within tissues.

## X-ray radiation

X-rays are comparable to gamma radiation. Their physical characteristics are similar, however, their origin is different. While the photons of gamma radiation originate from the nucleus, the photons of x-rays originate from the electron orbit. X-rays used in catheterization laboratories have an energy level of maximal 125 kVp.

## Beta radiation

Beta particles are lightweight high-energy electrons, with either positive or negative charge. When beta particles, which can travel only finite distances within tissues, are slowed down by nuclei interactions, they give rise to high penetration X-rays, called Bremsstrahlung.

## Major differences between gamma and beta radiation

The interaction of photons with other material is much lower than the interactions with electrons. That means, the energy transfer to other material is less intensive for gamma than for beta radiation. In the setting of brachytherapy, this has two major consequences.

a. Dwell time: to obtain a defined dose in a tissue at a certain distance from a source, gamma sources require much higher activities or much longer dwell times in comparison to beta sources.
b. Radiation exposure: the exposure to the staff inside and - because of deep tissue penetration- outside the catheterization laboratory is much higher during treatment with gamma radiation than beta radiation. In consequence, staff should leave the catheterization laboratory during radiation treatment and additional shielding facilities have to be implemented.

The clinically and practically most relevant advantages and disadvantages are as follows:

## Gamma radiation

**PRO'S:**

- Effective in randomized, double blind, placebo-controlled trials
- Deep tissue penetration (ideal for large vessel diameters)
- No attenuation of Ir -192 gamma radiation by stent struts (ideal for in-stent restenosis)[8,9].

**CON'S:**

- Extensive shielding required (25mm lead)
- High radiation exposure for patient and staff
- Staff has to leave catheterization laboratory
- Long dwell times (8-20 min)

## Beta radiation

**PRO'S:**

- Simple shielding by means of thick plastics
- Short dwell times (3-10 min)
- Radiation exposure to the patient only local
- Radiation exposure to staff is negligible
- Staff can remain in the catheterization laboratory

**CON'S:**

- Lack of data concerning its efficacy except in-stent restenosis
- Probable not able to treat vessels with diameters >4 mm (with existing devices)
- Inhomogeneity of the dose (evtl. centering device required)
- Partially shielded by stents and calcified plaques
- Dose distribution calculations of beta emitters are more complicated

# Mechanisms of action

## Cell biological effects

Absorbed radiation can cause damage in a tissue either directly by ionization or indirectly by interacting with other molecules to produce free radicals, which will subsequently damage the critical target. Approximately 80% of the radiation damage is caused by these free radicals. The most critical target is DNA[10], in consequence, early and late toxic effects in normal tissue are mainly caused by cell death.

These biological effects are independent of the radiation type (gamma, beta or X-rays) whereas total radiation dose and dose rate are of major importance, since damage caused by radiation can be repaired between fractionated doses or during low dose rate exposure[11]. Furthermore, there seems also to be an inverse dose rate effect in human cells most probably by blocking cells in the mitosis (G2) phase of the cell cycle at low dose rate (approx. 6 mGy/min), which is known to be more radiosensitive, thereby causing more cell death.

Experiments with human cells addressed long-term effects of radiation. Human aortic cells show a significant decrease in their clonogenic potential after radiation. Modulation of the subsequent repopulation of the surviving cells under the assumption that the repopulation kinetics were similar to those in non-irradiated cells, revealed a delay by factors of approximately 6 to 8. This would shift the time to restenosis from a median of 6 months in non-radiated cells to median values from 36 months (for 13 Gy) to 43 month (for 15 Gy)[12].

## Experimental data

In injured vascular tissue, radiation doses of 12-20 Gy appear to be efficacious in inhibiting neointimal formation[13-15]. The local mechanisms of action and time course are complex, dose dependent and poorly understood. Possible high dose radiation effects include an anti-angiogenic effect[16] and decrease of smooth muscle cells[17] on the adventitia, selective inactivation of smooth muscle cells[18] and myofibroblasts[19], or complete elimination of their proliferative capacity at doses >20 Gy. Application of lower dose could mean, that restenosis would only be delayed for the period of time necessary for the population of smooth muscle cells to regenerate. Furthermore, low dose radiation even promotes cellular growth. Low dose radiation (±2 Gy) has been shown to potentiate cellular metabolic activities[20] and hormesis (immunologic response) in various tissues (splenocytes[21], thymocytes[22], macrophages[23] and hematopoietic cells[24]). Furthermore, in experimental studies of endovascular brachytherapy it was shown that relatively low-doses (±10 Gy) caused a paradoxical increase in tissue response[25,26].

Long-term experiments in normal porcine coronary arteries after balloon injury and beta radiation showed that neointima formation is not inhibited at 6-month follow-up[27,28]. Unresorbed thrombus was an important contributor of augmented neointima formation. The adventitia showed thickening with substantial collagen accumulation[27]. Fatal subacute and late thrombosis was seen at 5 days, 7 days, 3 months and 4 months after the index procedure. The animals had received the combination of aspirin and ticlopidin for 30 days after the index procedure and continued aspirin therapy until sacrifice[28].

# Summary of clinical trials

Over the last years, radiation has been applied in various ways to human coronary arteries, using different sources and mode of applications. This includes catheter-based line sources, radioactive stents, radioactive wire[29], liquid filled balloons[30]. The latter have been used in few patients only, whereas there is considerable clinical experience with catheter-based line sources and radioactive stents. A comprehensive overview has been recently published[31].

## Catheter-based line sources

Clinical trials (Figure 1) have been completed for both, gamma (Table 1) and beta radiation (Table 2), and for different lesion types.

Table 1. Results of placebo-controlled gamma radiation trials at 6-month follow-up.

| Study | No pts | Gy | Lesion length mm | Source | Restenosis Rate | MACE |
|---|---|---|---|---|---|---|
| SCRIPPS | 53 | 8-30†† | <30 | Ir-192 | 17 | 15 |
| | | | | Placebo | 54 | 48 |
| WRIST | 130 | 15* | <47 | Ir-192 | 22 | 35 |
| | | | | Placebo | 60 | 68 |
| Long WRIST | 120 | 15* | 36-80 | Ir-192 | 46 | N/A |
| | | | | Placebo | 78 | N/A |
| GAMMA-1 | 252 | 8-30†† | <45 | Ir-192 | 33 | 28 |
| | | | | Placebo | 55 | 44 |
| GAMMA-2 | 125 | 14* | < 45 | Ir-192 | 34 | 30 |

MACE = major cardiac events, N/A = not available, No pts = number of patients.
* Dose at 2 mm from the source, †† to E.E.M.

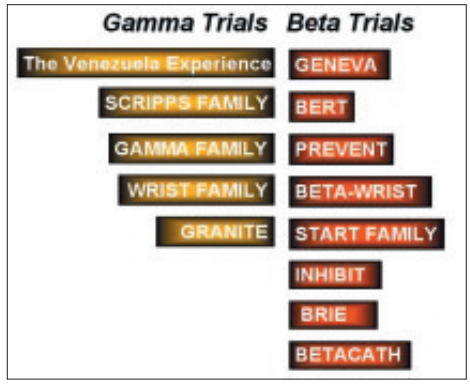
**Table 2. Results of beta radiation trials at 6-month follow-up.**

| Study | No pts | Gy | Lesion length mm | Source length mm | Source | Restenosis Rate | MACE |
|---|---|---|---|---|---|---|---|
| Geneva | 15 | 18† | <20 | 29 | Y-90 | 40 | 33 |
| BERT | 20 | 12, 14, 16* | ≤15 | 30 | Sr/Y-90 | 15 | 15 |
| BERT 1.5 | 35 | 12, 14, 16* | <20 | 30 | Sr/Y-90 | 11 | 9 |
| BetaWRIST | 50 | 20.6** | ≤ 47 | 29 | Y-90 | 34 | 34 |
| | | | | | Placebo+ | 71 | 76 |
| BRIE | 149 | 14, 18* | <20 | 30 | Sr/Y-90 | 34 | 34 |
| Dose Finding Study | 181 | 9,12,15,18** | <15 | 29 | Y-90 9Gy | 9 | 16 |
| | | | | | Y-90 18Gy | 26 | 13 |
| PREVENT | 96 | 16, 20, 24++ | <22 | 27 | P-32 | 22 | 26 |
| | | | | | Placebo | 50 | 32 |
| START | 396 | 18, 20* | <20 | 30 | Sr/Y-90 | 29 | 18 |
| | | | | | Placebo | 45 | 25.9 |
| Compassionate use Rotterdam | 18 | 16, 20* | <30 | 30 | Sr/Y-90 | 53 | 47 |

MACE = major cardiac events, No pts = number of patients. * Dose at 2 mm from the source,

† Dose at the inner arterial surface, ** Dose at 1mm from balloon, ++ dose at 1mm into vessel wall. + 50 placebo pts from WRIST.

**Figure 1.**




Overview over clinical brachytherapy trials with catheter-based line sources.

### SINGLE CENTER EXPERIENCES AND REGISTRIES

Human coronary arteries were treated for the first time by Condado *et al.* in 1995: De novo lesions where treated by balloon angioplasty followed by gamma-radiation (Ir-192). No restenosis was observed after 6 months 2. Also in 1997, Verin reported the feasibility of beta sources after balloon angioplasty[32].

The BERT trial used beta-radiation (90Sr/Y) in 23 patients after successful balloon angioplasty. Follow-up quantitative coronary angiography at 6 month showed a late loss of 0.05 mm and a restenosis rate of 15%[33,34].

BETA WRIST registry examined the beta-emitter 90-yttrium for the prevention of recurrent in-stent restenosis in 50 consecutive patients, which underwent percutaneous transluminal coronary angioplasty, laser angioplasty, rotational atherectomy, and/or stent implantation followed by radiation with a 90-yttrium centered source. At 6 months, the binary angiographic restenosis rate was 22%, and the target vessel revascularization rate was 34%[35].

The RENO registry is a large post marketing surveillance registry. At 47 centers in Europe and Israel 1032 patients were prospectively included for treatment with standard angioplasty (balloon, stent, laser, rotational and/or directional atherectomy) followed by beta-radiation therapy (90-Sr/Y source, Beta-Cath, Novoste). At 6-month follow-up, the MACE rate was 18.7% (with 1.9% death, 2.6% AMI (Q or non-Q), 16.3% target vessel revascularization) and the composite endpoint of late thrombosis 5.4%[36].

The GRANITE registry is the only multicenter gamma radiation trial conducted in Europe. A low-dose iridium-192 source was

used 96 in patients undergoing percutaneous revascularization for in-stent restenosis. At six month, event-free survival was 70%, the angiographic restenosis rate 32%[3]. Three-year follow-up is pending.

## RANDOMIZED CLINICAL TRIALS

Randomized, double blind, placebo-controlled trials have been completed for both, gamma and beta radiation, and for different lesion types (Figure 2).

*Gamma radiation trials:* The SCRIPPS trial demonstrated first the effectiveness of 192-Ir gamma therapy for the treatment of in-stent restenosis in 55 randomized patients[37]. The results were confirmed by the multi-center GAMMA-1 trial. 252 patients with in-stent restenosis were included to receive 192-Ir radiation or not[38].

The WRIST trial included 130 patients with in-stent restenosis to receive 192-Ir radiation or not[39].

*Beta radiation trials:* The PREVENT trial used a centered beta-emitting (32) P source wire. 105 patients with de novo (70%) or restenotic (30%) lesions who were treated by stenting (61%) or balloon angioplasty (39%) received 0 (control), 16, 20, or 24 Gy. Angiography at 6 months showed a target site late loss index of 11±36% in radiotherapy patients versus 55±30% in controls (P<0.0001). Restenosis rates were significantly lower in radiotherapy patients (22% versus 50%; P:=0.018) as were target lesion revascularizations (6% vs. 24%; P:<0.05)[40].

The START trial is a multicenter (50 sites in North America and Europe), randomized, placebo-controlled, trial, evaluating the safety and effectiveness of the Beta-Cath System using Sr-90 in 476 patients with recurrent ISR following successful coronary intervention. The restenosis rate within the vessel segment was reduced by 36% (control, 45.2% vs. irradiated, 28.8%), MACE was reduced by 31%; target vessel revascularization was reduced by 34%.

The multicenter BRIDGE trial randomizes patients with de novo lesions to receive or not receive beta-radiation therapy (32-P, centered device) following successful stent implantation. Antithrombotic treatment is prolonged to 11-month aspirin and clopidogrel. Enrollment is finished.

## CLINICAL OBSERVATIONS

### Positive vessel remodeling

Balloon angioplasty followed by irradiation predominantly shows an increase in minimal lumen diameter at the treated segment at follow-up[2]. This is in contrast to standard balloon angioplasty, where late lumen loss caused by neointimal growth and vessel shrinkage is the usual response[41,42]. Irradiation inhibits neointimal growth[43], may prevent shrinkage after balloon angioplasty[44] and even promote positive remodeling at the treated segments[45]. Promotion of positive vessel remodeling is dose dependent[46].

### Candy wrapper effect

In contrast, edge segments show an increase in plaque volume without adaptive remodeling[47,43,48] causing the "edge effect" or "candy wrapper effect", first described by Albiero *et al.*[49] (Figure 3).

### Geographic miss

In concordance with known cell biological effects and animal data, low dose radiation at the extremities of the source and angioplasty induced vessel injury, referred as "geographic miss" seems to play a key role in edge restenosis and

**Figure 2. Outcome of randomized brachytherapy trials at 6-month follow-up**

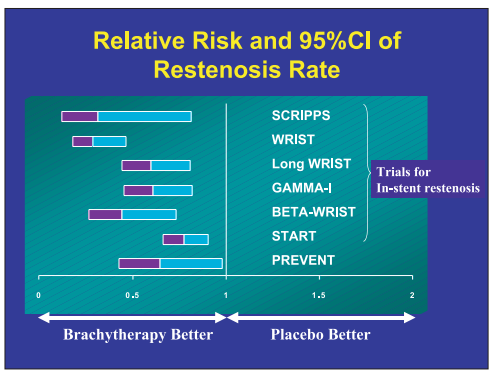



**Fig 2a.** Angiographic restenosis

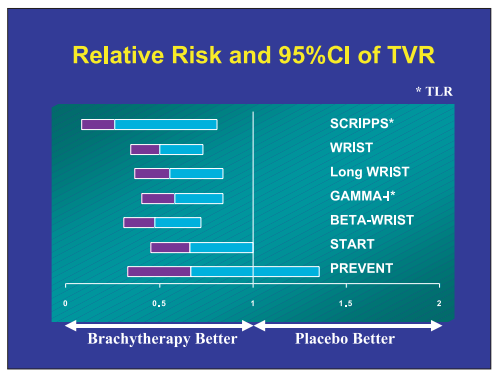
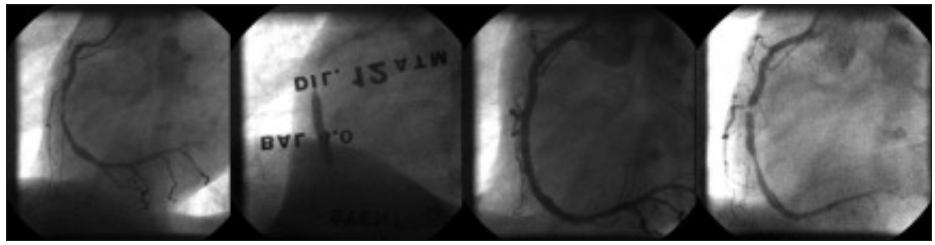



**Fig 2b.** Target vessel revascularization (TVR)

**Figure 3.**



Candy wrapper: Angiogram of a right coronary artery with a significant lesion in the left circumflex artery (I) before intervention, (II) after implantation of a radioactive stent (ACS radioactive stent, Guidant, see thin arrows) and (III) at 6 months follow-up: Significant lumen narrowing at the proximal and at the distal extremity of the stent (thick arrows), referred as "edge effect" or "candy wrapper".

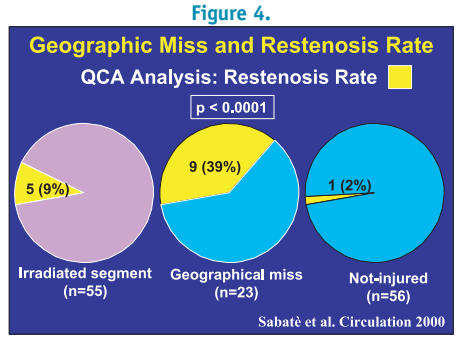
treatment failure for (beta) brachytherapy[50-52] (Figure 4; Figure 5). This is conformed by experimental studies which could demonstrate that the edge effect is associated with the combination of periprocedural vessel injury and radioactive dose fall-off at the extremities of the source[53].

## LONG-TERM OUTCOME

Progressively, long-term follow-up data of patients, which had received intracoronary brachytherapy, are becoming available. Major concerns are possible late catch-up with increased lumen loss at the treatment site, delayed restenosis and delayed major adverse clinical events.

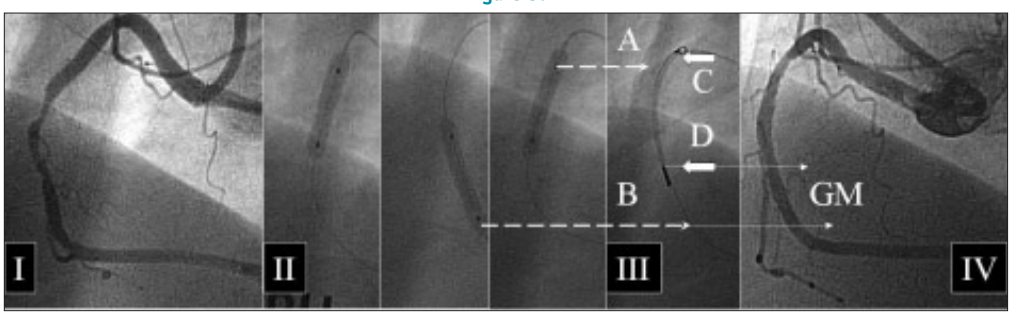
The three-year follow-up of the SCRIPPS trial demonstrated an decrease in mean minimal luminal diameter between 6 months and 3 years from 2.49±0.81mm to 2.12±0.73 mm in (192) Ir patients, whereas the minimal lumen diameter was unchanged in placebo patients. This angiographic finding,

**Figure 4.**




Association of restenosis 6 months after coronary beta-radiation therapy and geographic miss. The restenosis rate in the geographic miss segments is significantly higher than in the irradiated segment and the non-injured reference segments (39% vs. 9% and 1%).

**Figure 5.**



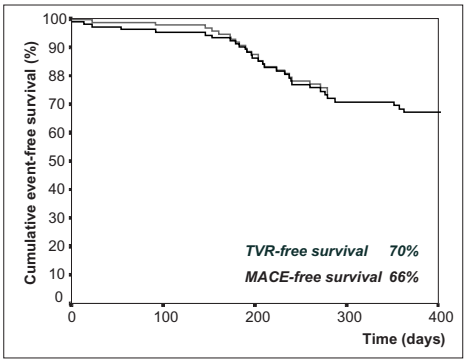

Clinical example of geographic miss during treatment of a in-stent restenosis in a right coronary artery (I). The position of the angioplasty balloons is documented at maximum inflation (II). Positioning of the source with radioopaque markers at the proximal (C) and at the distal (D) end (90Sr/90Y, BetaCath system, Novoste) (III). Line A indicates the most proximal balloon position, line B indicates the most distal balloon position within the coronary. The source is chosen to short to cover the injured area (between line a and line B), causing distal geographic miss (GM, IV).

however, was not associated with clinical events. The target-lesion revascularization was significantly lower in the (192) Ir group (15. 4% versus 48.3%) as was the restenosis rate (33% versus 64%)[54].

A two-year follow-up is available of the (192) Ir WRIST and BETA-WRIST patients. Irradiated patients had significantly lower rates of target vessel revascularizations than the placebo WRIST patients at 2 years. Beta (odds ratio 0.22, 95% confidence interval 0.09 to 0.58) and gamma (odds ratio 0.30, 95% confidence interval 0.12 to 0.74) radiation were independent predictors of event-free survival at 2 years. However, between 6 months to 2 years, significant rates of target vessel revascularization (14%) were noted in both radiation groups, yet no revascularization was required in placebo WRIST patients ($p < 0.05$)[55].

Analysis of the one-year outcome of the Thoraxcenter RENO patients revealed a major-adverse event-free survival of 66% at one year. MACE consisted in target vessel revascularization and delayed myocardial infarction (Figure 6). In this small patient population (n=100), late thrombosis with consecutive myocardial infarction occurred not exclusively in patients with freshly implanted stents and not only after discontinuing clopidogrel medication[56].

**Figure 6.**




Thoraxcenter RENO patients: Event free survival at 12 months follow-up (Kaplan -Meier). TVR indicates target vessel revascularization and includes repeat PTCA and CABG. MACE indicates major adverse cardiac events. Events are given ranked as follows: death, Q-wave myocardial infarction, CABG, repeat PTCA.

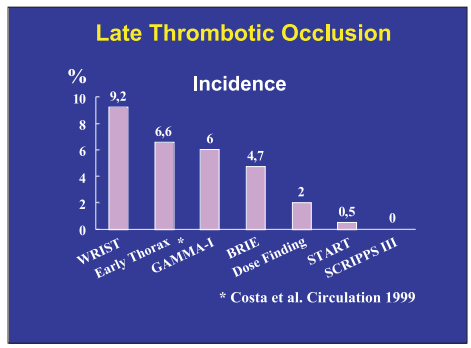
## LATE THROMBOTIC OCCLUSION: ASSOCIATION WITH ANTITHROMBOTIC REGIMEN AND NEW IMPLANTED STENTS

Early in the clinical phase, a new phenomenon became apparent, that of late thrombotic occlusion[57]. Possibly causes are increased thrombogenicity and prolonged wound healing reported in experimental series[14,58,59].

Initial clinical trials prescribed a combined antithrombotic treatment (aspirin and clopidogrel or ticlopidin) of 2[37] or 4[39] weeks after the index procedure. In the beta WRIST and in the 192Ir WRIST a late total occlusion rate of 12% and 8% is reported. Most patients presented with a clinical event within the first 6 months after the index procedure[55]. A pooled analysis from the data from the SCRPPS, WRIST and GAMMA-1 trials revealed that *new stents* and *lesion length* were predictors for late thrombosis with an event[60].

In consequence, prolonged combined antithrombotic treatment was recommended. The START trial recommended 90 days of antiplatelet treatment. However, one patient in the radiation group experienced subacute stent thrombosis at 244 days. In the WRIST PLUS trial clopidogrel and aspirin were prescribed for 6 months. The late thrombosis rate was 2.5%, at 6-month follow-up[61] (Figure 7).

**Figure 7.**




Incidence of late thrombotic vessel occlusion after catheter-based brachytherapy.

In accordance with the pooled analysis of gamma trials, the multivariate analysis of the large RENO patient population revealed the implantation of new stent as predictor for late thrombotic events after beta radiation. Additional predictors were age, initial chronic total occlusion target, and geographic miss[36].

The evolving clinical important question is the duration of platelet inhibition and whether or when to stop clopidogrel prescription. We recommend combined antithrombotic medication for 12 months after intracoronary radiation treatment.

## Radioactive stents

The results of *radioactive stents* were disappointing and could not be favorably influenced by modification in design and activity[48,60,61,62,63,66,67]. The outcome at 6 months showed a high rate of clinical events and restenosis (up to 50%), preferably at the edges of the stent[53], called the "candy wrapper".

# Actual application modalities and devices

Vascular brachytherapy is actually routinely performed by catheter-based systems, while radiation balloons are used in few clinical studies. In the U.S two brachytherapy systems have FDA approval for the treatment of in-stent restenosis, the Novoste Beta-Cath and the Cordis Checkmate system (gamma radiation, 192 Ir)[60].

In Europe, actually no gamma radiation system is commercially available; the 2 following beta-radiation systems have CE mark approval.

**The Beta-Cath System (Novoste):**

| | |
|---|---|
| *Radiation type:* | Beta ($^{90}Sr/^{90}Y$) |
| *Delivery catheter:* | 3.5F Multilumen, non-centering catheter (two closed lumen for radiation source train and fluid return lumen; one open lumen for guide wire) compatible with 7F guiding catheter and 0.014 inch guide wire. X-ray markers at each end. |
| *Dummy ribbon:* | Passive source trains with X-ray markers at each end. |
| *Source:* | $^{90}Sr/^{90}Y$ jacketed seed train. Treatment length is 40mm (16 seeds) and 60mm (24seeds). Non-radioactive, X-ray markers at each end. |
| *Source delivery unit:* | Hand held afterloader for hydraulic advancing and withdrawing of the source ribbon (sterile water). |

**The Galileo System (Guidant)**

| | |
|---|---|
| *Radiation type:* | Beta ($^{32}P$) |
| *Delivery catheter:* | Multilumen, centering balloon-catheter compatible with 7F guiding catheters and 0.014 inch guide wire. Balloon length 32mm and 52mm, balloon diameter 2.5mm, 3.0mm and 3.5mm. X-ray markers at the extremities of the balloon. |
| *Dummy ribbon:* | Passive source trains with x-ray markers. |
| *Source:* | $^{32}P$ wire (0.018inch). Source length is 20mm, sealed at the wire tip. Non-radioactive X-ray markers are placed to bracket 80% therapeutic dose range of the wire proximally and distally to the source[68]. |
| *Source delivery unit:* | High dose rate afterloader with computer controlled advancing and withdrawing of the source wire. Delivery system calculates the treatment time automatically and performes automated pullback of the source (stepping procedure). |

# Radiation protection and safety considerations

Radioactive material cannot be turned off. Therefore, secure control of the radioactive inventory and surveillance of staff and patients is of special concern.

## Regulatory considerations

For transportation, storage and handling of nuclear sources, European countries require various licenses according to individual nuclear laws.

In general, the institute or hospital needs a license for using radioactive material. Within the institute or hospital a local permission has to be obtained which is mostly linked to specific room conditions and expertise of the personnel. Mandatory key personnel includes a radiation oncologist, a medical physicist, a radiation safety officer and a cardiologist. Clinical responsibility lies with the radiation oncologist, though he may delegate practical aspects to others.

## Practical safety considerations

In Europe, standards for the protection of patients, health workers and the public against exposure to radiation have been specified in two directives (96/29/EURATOM: 97/3/EURATOM)[69,70] and are now being incorporated into national laws. Radiation protection is determined by two principles: exposure must be justified by showing that it confers more benefit than detriment and exposure should be as low as reasonable achievable (ALARA principle).

### MONITORING

Individual personnel dosimeter badges allowing for effective dose equivalent reading are mandatory in controlled areas like catheterization laboratories. Radioactivity can be further assessed by two basic instruments, the portable Geiger-Müller (GM) counter and the ionization chamber survey meter.

### SOURCE

Every source must be inspected on receipt, which involves visual inspection in the shielding, calibration to verify the exact level of activity and, in line-sources, checking the number and activity of sources.

### STORAGE

Sources must be stored securely and held under lock and key. Storing facilities must be provided with sufficient shielding, taking into account that $^{90}Sr/^{90}Y$ sources from the Beta-cath system produce Bremstrahlung. Pretreatment checks and callibrations of the source are mostly performed in the storing facilities. $^{32}P$ has a half-life of 14 days only. In consequence, $^{32}P$ sources have to be exchanged every four weeks. $^{90}Sr/^{90}Y$ sources require a yearly check especially for the mechanical condition of the source. The time necessary to transfer the source in a special delivery device to the laboratory must be taken into account by treatment protocols.

### CATHETERIZATION LABORATORY DESIGN AND EQUIPMENT

Actual shielding requirements are catheterization laboratory specific depending on size and configuration of the procedure room and the adjacent rooms. The radiation levels of the X-rays require approximately 4mm lead shielding in the walls. Beta radiation requires no additional specific shielding of the catheterization laboratory or adjacent rooms.

Gamma radiation requires special shielding (minimum thickness 25mm lead) of the procedure room and the control room to block the gamma rays (e.g. mobile shields of approx. 200kg positioned close to the patient). Outside the laboratory, the level of exposure must be estimated and regularly monitored in adjacent rooms.

### PATIENT SAFETY

**Principal risks related to intracoronary radiation include**

- damage to the artery wall with consecutive perforation and/or aneurysm formation. This risk seems to be dose related (>30Gy) and low[2,33,34,71,72].
- accelerated coronary artery disease as known side-effect of high dose radiation (>35 Gy) for the treatment of neoplasms[73-75]. Intermediate doses (30-40 Gy) have shown a low risk of cardiac disease during long term follow-up[76].
- radiation-induced carcinogenesis. This risk appears to be low at least in beta radiation as the dose beyond the immediate target lesion is low and the exposed tissues (e.g., arteries, veins, cardiac muscle, and pericardium) have a low spontaneous carcinogenicity rate.

**Technical risk related to intracoronary radiation**

The main technical risks related to intracoronary radiation is the failure to smoothly deploy and retrieve the source. Therefore, proper source passage into the target coronary artery should be routinely tested by deploying and retrieving a dummy source. A dummy source allows also for control of the treatment position within the coronary artery and repositioning of the delivery catheter if necessary.

### STAFF SAFETY

Every source is brought into the catheterization laboratory in a shielding device (pig). The shielding device can be a source of radiation. The operator's hand dose can be reduced by not touching the shielding device. During delivery into the coronary artery and retrieval, the source is unshielded for a few seconds. Again, the operator's dose is reduced by not touching the treatment catheter and keeping distance. Direct finger contact with a high dose rate source is hazardous. During treatment with gamma radiation, all personnel with exception of the radiation oncologist must leave the catheterization laboratory in order to limit their exposure to radiation.

## Procedure performance

Intravascular radiation treatment requires a substantial commitment and collaboration between the interventional cardiologist and the radiation oncologist. Prior to every brachytherapy procedure, the radiation oncologist and the medical physicist have to be informed. The radiation oncologist must be able to review the patient's anamnesis and physical condition for proper treatment planning, the medical physicist guarantees secure source transportation.

## Patient selection

### INDICATIONS

Based on the outcome of the randomized clinical trials FDA approval is limited to the treatment of in-stent restenosis in the U.S. The findings of several clinical trials point to a possibly elevated risk for thrombotic events in patients receiving radiation therapy in newly implanted stents.

Potential indications in all circumstances with elevated risk for restenosis after conventional catheter based intervention such as long lesions, sapheneous vein grafts, small coronary arteries, diabetic patients and renal insufficiency patients still need to be established.

### CONTRAINDICATIONS

Contraindications are previous radiotherapy of the chest, previous intracoronary brachytherapy, pregnancy, genetic radiation sensitivity disorders (e.g. ataxia-telangiectasia).

## Patient preparation - medication

*Pre-procedural* treatment requires no particular medication for brachytherapy other than antiplatelet regimen for routine angioplasty procedures: Aspirin (75mg-300mg) and ticlopidine or clopidogrel must be started at least 24h before the procedure, whereby we prescribe a loading dose of 750mg, followed by 250mg twice a day for ticlopidine and a loading dose of 300mg, followed by 75mg daily for clopidogrel. Beta-blockers, calcium antagonist and oral nitrates should be administered as usually prescribed.

*At the begin of the procedure,* we routinely administer neuroleptics and analgesics. Repeat bolus is given during the procedure, if needed. Furthermore, we administer 325mg aspirin intravenously and 10 000 IU heparin immediately after arterial sheath placement. Activated clotting time (ACT) is checked every 30 minutes after the first bolus injection in order to maintain ACT > 300 sec. Additional heparin is given if necessary.

*During the procedure,* GP IIbIIIa receptor blockers are given deliberately in patients with unstable angina, periprocedural intracoronary thrombus formation or dissection.

## Equipment set-up and special arrangements of the operating room

*For the angioplasty procedure,* a standard angioplasty set and eventually additional ablative devices (e.g. atherectomy catheter) is needed.

*For brachytherapy,* the catheterization laboratory must have appropriate *shielding* as described in section 5.2. The radiation oncologist prepares the brachytherapy device (e.g check for mechanical integrity, flushing of the system, dummy source, etc). We recommend for this purpose an *extra sterile table* and *light*. A *bail-out box* must be in the procedure room, typically consisting of an assortment of long-handled instruments for grasping a source and of a shielded container (lead for gamma radiation, plastic for beta-radiation source) to safely place the source. *Radiation detectors* to survey the environment during the procedure and contamination monitors for source leakage are needed. At least two timers must be available to allow for correct dwell time and to minimize treatment errors.

## Access method

We prefer the standard femoral approach for optimal guide support using a 7F sheath and guiding catheter.

## Angiography

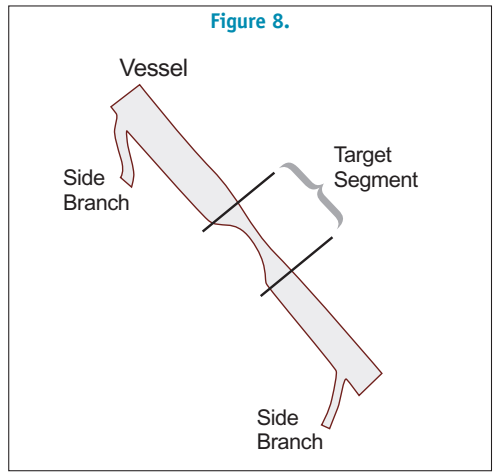
### TERMINOLOGY

Brachytherapy as new treatment with complex mechanisms of action urges detailed angiographic assessment and necessitates the introduction of a new terminology.

**• Target segment (Figure 8)**

The target segment is defined by the proximal and distal margin of the obstructed segment.

**Figure 8.**




**• Injured segment (Figure 9)**

The macroscopic injured segment is defined as the segment encompassed by the most proximal and most distal position of the angioplasty device (e.g. rotablator burr) or marker of the angioplasty balloon and all visible vessel injury as assessed by flouroscopy.

**• Irradiated segment (Figure 10)**

The irradiated segment is defined as the segment encompassed by the inner edge of the radiopaque markers of the source train.

It is of note, that the *effective irradiated segment* receiving *full* prescribed therapeutic radiation dose (>90% isodose rate) is slightly shorter as a result of the dose fall-off caused by the limited size of the source train. The exact delineation of the effective irradiated segment is complicated, as is requires the knowledge of the individual dose-profiles for each isotope and source design (Figure 11).

The Galileo-system takes the dose fall-off into account. The radioopaque markers of the dummy wire do not indicate the proximal and distal end of the source, but the length of the full-dose segment.

Figure 9.

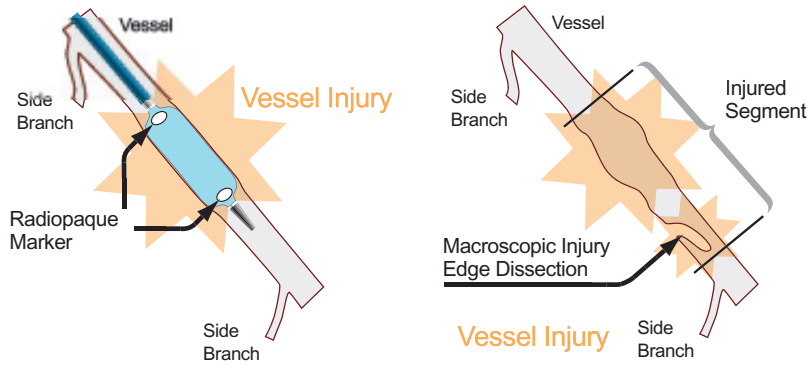



Figure 10.

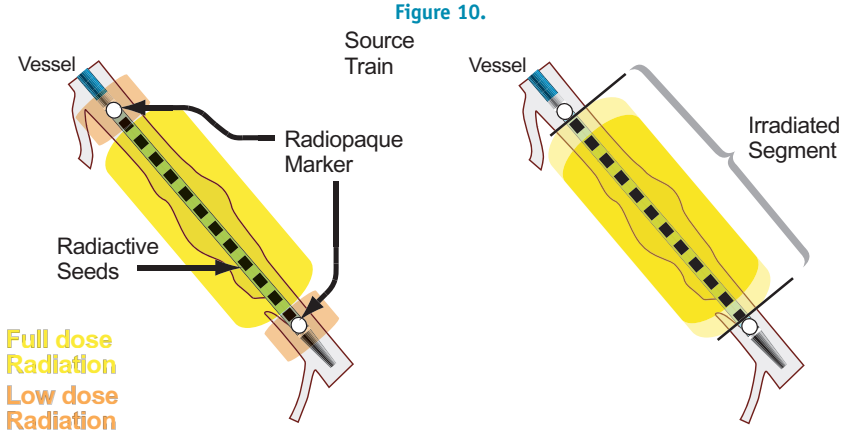
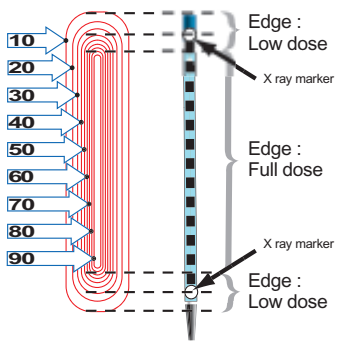



Figure 11.




• **Edge segments (Figure 12)**
Edge segments are the vessel segments at the extremities of the radiation source, which do not receive full therapeutic radiation dose. The length of the edge segments is dependent on the isodose profile of the individual source.

• **Vessel segment (Figure 13)**
The vessel segment is the coronary segment bordered by angiographically visible side-branches which encompass the original lesion, all angioplasty devices and the radiation source.

• **Geographic miss segment (Figure 14)**
In coronary brachytherapy, it is defined as a mismatch between injured and irradiated segment: Geographical miss is present when the entire length of the injured segment is not completely covered by the irradiated segment.

Figure 12.

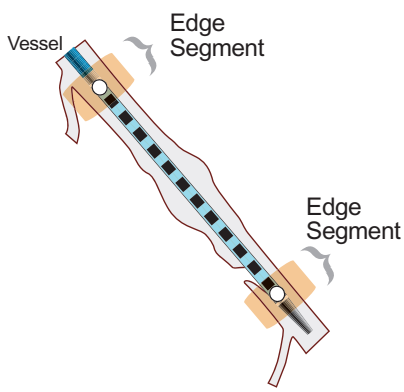
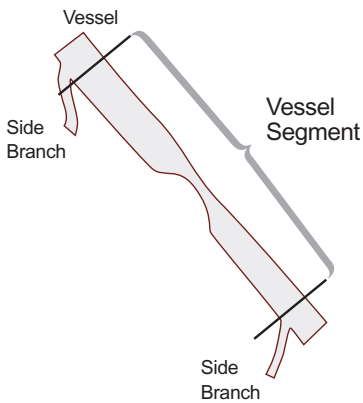


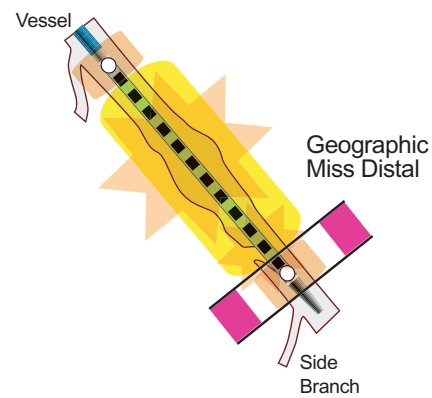

Figure 13.




## GENERAL REQUIREMENTS

Angiography should be done in biplane views. At the start of the procedure, two projections are selected with more than 30 degrees difference in rotation and avoiding foreshortening and side branch overlapping. *The entire procedure should be filmed in identical projections.* The meticulous documentation of all angioplasty devices and the radiation source in place with contrast medium, using the same projections, is essential **(Figure 15)**. Inadequate angiographic documentation, hampering the identification of the irradiated and the injured segment is seen in up to 50% of the cases enrolled in brachytherapy trials.

Figure 14.




## PRIMARY ANGIOGRAPHY

Primary angiography identifies the culprit lesion, the "target segment" and the "vessel segment". Basic considerations are

- vessel size (dose prescription?)
- lesion accessibility for the source (dimensions, stiffness?)
- lesion position (ostial lesions virtually have geographic miss as source positioning with a proximal safety margin is not possible)
- strategy of angioplasty prior to radiation
- lesion length (source long enough to cover complete injured segment?)
- side branches (in bifurcation lesions, only 1 side branch can receive radiation)

Primary angiography also serves for decision on the "best projection" to document the complete procedure.

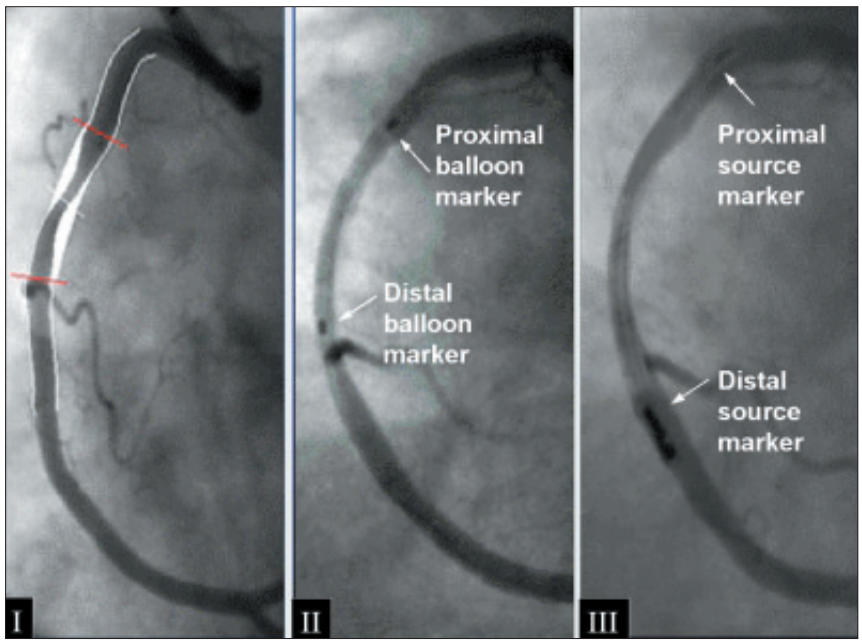
## Angioplasty

Prior angioplasty might consist in debulking (directional or rotational atherectomy, laser), stent implantation or "simple" balloon inflation and is performed in conventional technique. *Any instrumentation has to be filmed at the site of treatment surrounded by contrast medium in identical projections!* It is important, that angioplasty is not stopped before reaching a satisfactory result. Every instrumentation after radiation therapy carries inevitably the risk of geographic miss.

## Dose prescription and source selection

The treated coronary artery is usually 2-5 cm of length, with a diameter of 3-5 mm and a vessel wall thickness of 0.5-3 mm. The radiation dose given to the vessel wall should probably

**Figure 15.**




Clinical example of correct source length and source position. Angiogram of a in-stent restenosis in a right coronary artery. The white lines indicate the lesion as given by quantitative coronary analysis (I) Treatment by balloon angioplasty. The position of the balloon as given by the radioopaque markers at the extremities of the balloon is documented by injection of radioopaque contrast medium (II). The injured area is completely covered by the source ($^{90}Sr/^{90}Y$, BetaCath system, Novoste) (III).

target the media as well as the adventitia delivered at 0.5-5 mm from the source. Dose prescription and source selection are performed in close collaboration with the radiation oncologist. Dose is prescribed in relation to the long axis of the source (e.g. at 2mm).

Given the radioactivity and dose rate of the selected source, dwell time is calculated in dependency of the vessel size. The length of the source should be selected in that way, that

- the vessel segment, which has been "touched" by any angioplasty device and
- the vessel segment which shows macroscopic injury is *completely* covered
- there is sufficient safety margin at the proximal and distal end of the source to guarantee full dose radiation of the treated segment.

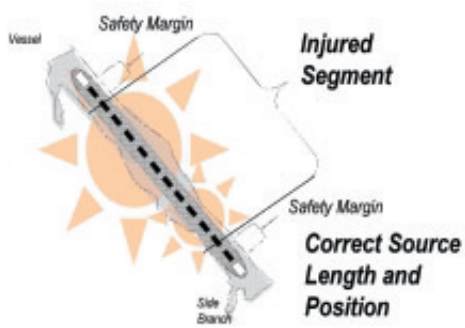
With the Beta-Cath system, we select the length of a *source train* with a "safety margin" of 1 seed to be outside the injured segment at each end (Figure 16, Figure 17).

With the Galileo system, the distal marker of the centering balloon should be positioned in such a way, that the distal injured segment is covered. Then the distal marker of dummy wire is positioned at the distal marker of the centering balloon. The segment between the inner edges of the dummy wire markers represents the full-dose radiation segment. After withdrawing the dummy wire, the active wire travels automatically 4 mm more distally than the distal marker of the dummy wire. In consequence, the dose is 100% at the distal end of the centering balloon. After completing the first radiation, the line source is proximally withdrawn by automated stepping procedure. The dose fall-off at the proximal end of the source at the first step is compensated by the dose fall-off at the distal end of the source at the second step. This compensation avoids gap in the dose distribution during the stepping procedure (Figure 18, Figure 19).

## Radiation treatment

The radiation oncologist prepares the brachytherapy device. Meanwhile it might be helpful for the operator to review the

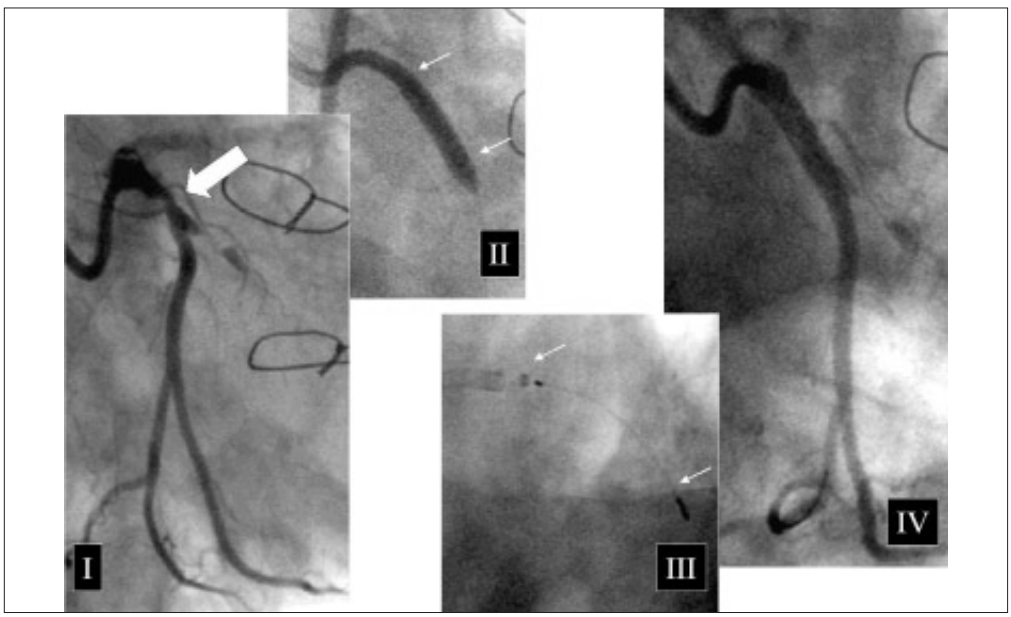
**Figure 16.**




Schematic indicating the choice of a correct source length and source position. The source is able to cover the injured area as indicated by the balloon markers and the area with macroscopic vessel injury by full-dose radiation. Proximal and distal there is a safety margin of 1 seed.

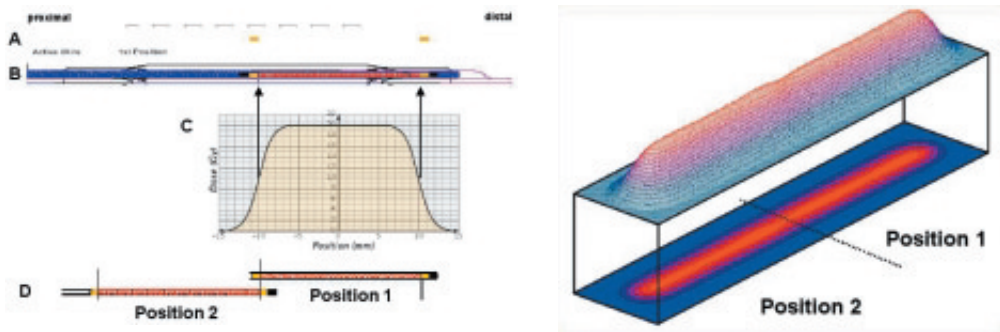
angiograms. This allows for a precise image of the "injured segment" relative to landmarks such as side-branches. The guiding catheter should be correctly positioned at the coronary ostium: if it is to deep it will obstruct flow and may creep further into the coronary artery during the procedure, if it is to far away, it may slip during the procedure and move the source ribbon. Then the catheter accommodating the dummy source is carefully advanced into the vessel. Most radiation delivery catheters are fragile without inserted ribbon, it may easily kink during insertion. If stented lesions are treated, it has to be avoided, particularly in tortuous vessels, that the catheter becomes caught on the stent struts. An angiogram with the dummy source in place should be done. If angiography confirms correct positioning with complete coverage of the injured segment and safety margins, the radiation oncologist removes the dummy source, connects the afterloader device to the catheter and delivers the source. The radioactive source must be filmed in place with contrast medium repeating the projections used for angioplasty. Care

**Figure 17.**




Treatment of a lesion in the left circumflex artery (I, arrow) with $^{90}Sr/^{90}Y$ beta radiation (BetaCath system, Novoste). The angioplasty procedure consisted in direct stent implantation, the injured segment is assessed by means of the radioopaque balloon markers (II, arrows). The $^{90}Sr/^{90}Y$ beta source with non-radioactive, X-ray markers at each end (arrows) is positioned to cover the injured segment completely with safety margins proximal and distal to the injured segment (III). The final result is given in angiogram IV.

Figure 18.




**a.** Schematic of the Galileo system source and stepping procedure. A) schematic of the spiral centering balloon with the lumen for the source B) 32-P source train. The radioopaque markers indicate the full-dose segment, receiving >80% isodose. C) Dose distribution curve of the 32-P source D) Stepping procedure: The source is automatically withdrawn in such a way, that the overlap between distal position 1 and the more proximal position 2 allows full dose radiation treatment of the complete segment.
**b.** Isodose distribution curve for the 32-P source during stepping procedure.

should be taken to not over tighten the O-ring and Y-connector while attempting to obtain good quality contrast injections, as this may crimp the delivery catheter and obstruct movement. At the end of the dwell time, the radiation oncologist removes the source. The contrast medium should be withdrawn into the delivery syringe prior to injection down the coronary artery after withdrawal of the source to avoid thrombotic embolization. While removing the delivery catheter, care should be taken not to push the guide to far distally into the vessel. A final angiogram should confirm good angioplasty result and the absence of dissections and/or thrombus.

## How to avoid geographic miss

- Source length > lesion length!
- Select a projection without foreshortening and side branch overlap
- Film any instrumentation with contrast medium to allow for anatomical orientation
- Film any instrumentation in the same projection and respiratory position
- Film the dummy and active wire in the same projection and respiratory position
- Use proximal (or distal) side branches within the vessel segment as index anatomical landmarks to assess the distances to the markers of the angioplasty balloon and the radiopaque source markers
- Consider proximal and distal safety margins
- Do not perform brachytherapy before a satisfactory angioplasty result
- Avoid instrumentation (e.g. additional stents) after brachytherapy
- Listen to your radiation oncologist!

# Complications

## Procedural complications

Procedural complications include all complications typically linked to the angioplasty/debulking procedure. Most complications related to brachytherapy by removable sources are caused by the relatively high profile and stiffness of the delivery catheter:

- myocardial ischemia with angina and/or ECG changes, which, might necessitate fractionation of the dose (approx. 4% of the patients) and
- dissection after manipulation of the delivery catheter (approx. 10% of lesions).

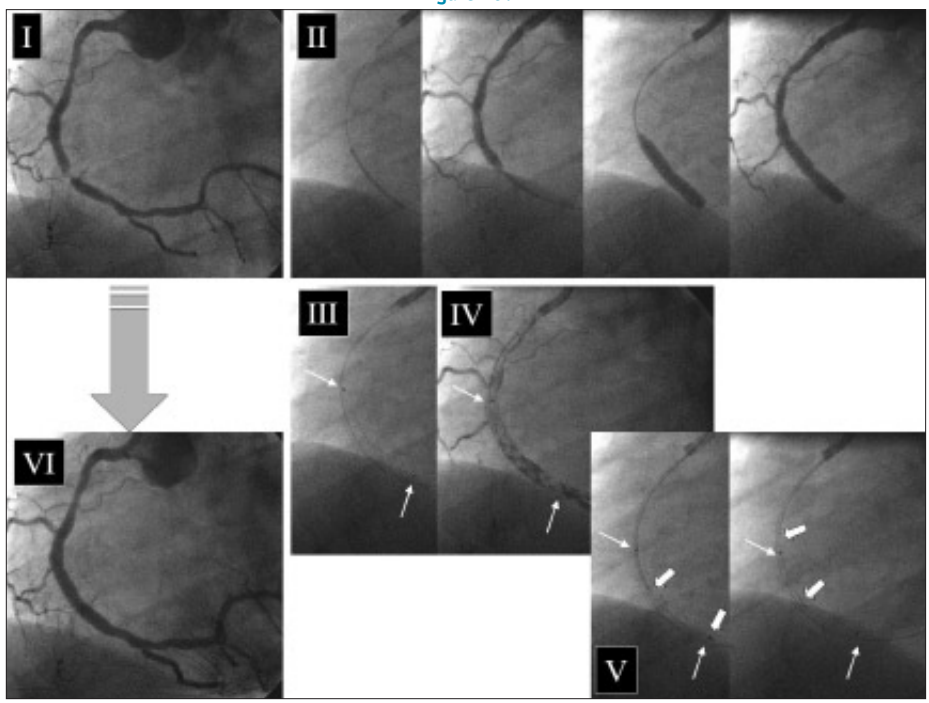
Furthermore, radiation increases local thrombogenicity[77], which promotes intracoronary thrombus formation during active treatment (approx. 4% of lesions). In these cases, GP IIb/IIIa inhibitors should be given deliberately.

## Procedural emergencies

**Catheter based line sources:**

Prolonged retrieval represents one of the most serious technical events which can produce unwanted dose to the patient and staff. In that case, the entire treatment catheter should be withdrawn and placed into the bail-out box. If that is not successful, an attempt should be made to move the

**Figure 19.**




Treatment of a lesion in the right coronary artery (I) with $^{32}P$ beta-radiation (Galileo System, Guidant) The angioplasty procedure consisted in direct stent implantation. The stent delivery system has been filmed for anatomical orientation deflated, deflated with contrast injection, at maximum inflation and at maximum inflation with contrast injection (II). The position of the spiral balloon is assessed by means of the X-rays markers at the extremities of the balloon (III, thin white arrows) and by contrast injection (IV). The source wire has x-ray markers at the proximal and distal end (V, thick arrows). Radiation is delivered during an automated stepping procedure with initial source positioning distally (V, left) followed by automated pullback (V, right) The final result is given in angiogram VI.

source into a larger diameter artery whilst calling for emergency surgery.

**Balloon based fluid or gaseous sources:**

Radioactive fluid filled balloons might leak or burst and spill their content's into the patient's blood stream. The radioactive material need to be physiologically cleared from the patient before an unacceptable dose is delivered to any tissue. Gaseous 133Xe is rapidly exhaled and presents minimum radiation hazard to the patient.

In all cases of emergency, the physicist's responsibility is to remain focused on safely retrieving the sources and minimizing unnecessary exposure of patients and staff. To allow for rapid and well directed action, contingency plans must be made in advance, discussed and rehearsed for a variety of likely and unlikely occurrences.

## Postprocedural care

The arterial sheath is withdrawn immediately after the procedure and the access site sealed with a closure device (Perclose or Angioseal). In case of a difficult arterial puncture with substantial fibrosis, the sheath is removed 6 hours after the procedure and the artery manually compressed. All patients must receive effective antiplatelet therapy for at *least 12 months*. In our institution, we prescribe aspirin indefinitely in combination with ticlopidine (250mg twice a day) or clopidogrel (75mg daily) for 12 months. This is essential to avoid late thrombotic occlusion, which has been observed with an incidence of 0-9.2% in the early phase of catheter-based brachytherapy (Figure 7)[57,78] most probably due to delay in endothelialization which might increase the chance of subacute thrombosis.

## Limitations

Low radiation doses (4-8 Gy) may stimulate neointimal proliferation. This could be due to the fact that growth factors are synthesized de novo and secreted by surviving cells. These growth factors might promote the proliferation of smooth muscle cells.

Delayed depletion of some cells (adventitial cells, fibroblast) could lead to subsequent re-population, whereby smooth muscle cells from the media could be progressively replaced by fibroblasts and extracellular matrix, leading to fibrosis, as has been previously described in animal experiments. Persistent dissections after beta-radiation have been observed at 6-month angiographical follow-up. Geographical miss, where the injured area is not completely covered by the irradiated area, is a major cause for edge restenosis. The incidences of geographical miss ranged from 18-34%. Delayed restenosis was seen in the Condado, SCRIPPS and WRIST trial.

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## PART 1: IONIC RADIATION THERAPY

*Chapter 4*

*Regar E*, Kozuma K, Sianos G, Carlier SG, Serruys PW:
**QUANTITATIVE CORONARY ANGIOGRAPHY METHODOLOGY ON VASCULAR BRACHYTHERAPY.**
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# Quantitative Coronary Angiography Methodology in Vascular Brachytherapy I

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## Introduction

The application of intracoronary radioactivity represents a relatively new therapeutic tool for the cardiologist. Radioactivity is administered by various techniques, eg, intracoronary afterloading,[1–5] radioactive stents,[6–10] or radioactive balloons[11–13] using gamma- or beta-emitting sources. The particular physics, application modalities, and mechanisms of action of this new treatment modality force us to adapt the procedural practice and the methodological approach of angiographic outcome assessment.[14,15]

Recently, a number of phenomenons associated with intracoronary brachytherapy, such as positive remodeling,[16] relocation of the minimal lumen diameter (MLD),[17] geographic miss,[18] and edge effect[19] have been described. These entities have been recognized in the past; however, their incidence and their impact on clinical outcome has reached new and so far unknown dimensions. While, after standard balloon angioplasty, neointimal hyperplasia and vessel shrinkage at the site of injury is the usual response,[20,21] in balloon angioplasty followed by irradiation, an increase in the MLD at the treated segment is predominantly seen[16] as a result of positive remodeling and neointimal inhibition.[22] This systematic change in vessel response after brachytherapy prompts us to adapt new angiographic approaches, taking into account the relocation of MLD at follow-up from its pre-interventional location. Similarly, the growing knowledge of the deleterious effects of geographic miss and the awareness of possible edge effects underline the need for standardized and detailed angiographic assessment.

This chapter will review standard quantitative coronary analysis and describe the current approach for vascular brachytherapy.

## Classical Quantitatitve Coronary Angiography Analysis

Quantitative coronary angiography (QCA) is the well-established gold standard for the assessment of coronary angiograms.[23] In classical QCA analysis, the

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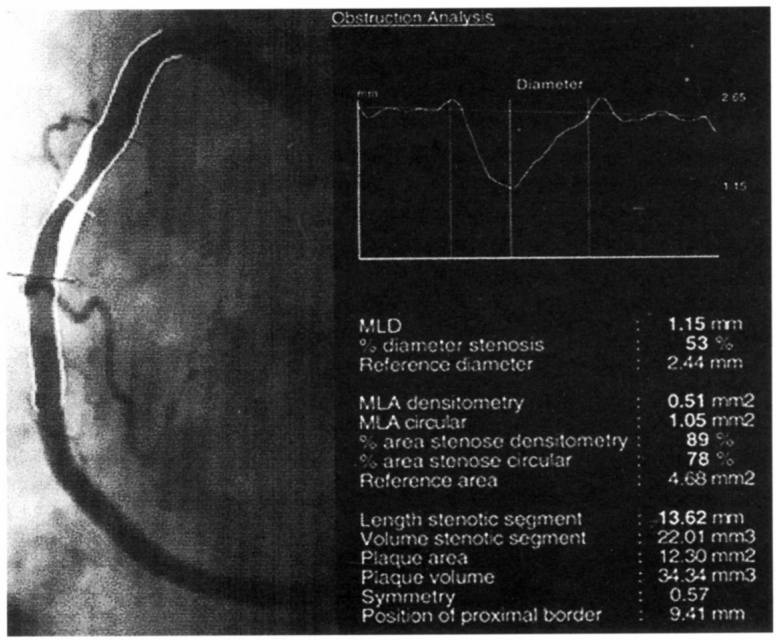


**Figure 1.** Classical quantitative coronary angiography (QCA) analysis. The analyst defines the vessel segment of interest bordered by major proximal and distal side branches. Minimal lumen diameter (MLD) and interpolated reference diameter (RD) at the site of MLD is calculated.

analyst defines the vessel segment of interest. Sophisticated edge detection algorithms define automatically the obstructed target segment. Within the target segment, MLD, interpolated reference diameter (RD), and diameter stenosis (DS) are calculated (Fig. 1).[24–28] Pre-interventional, post-interventional, and follow-up measurements are compared to analyze treatment efficacy in such terms as residual DS, acute lumen gain, late lumen loss, or dichotomous restenosis rate.[29–37]

## Limitations of Classical Quantitative Coronary Angiography Analysis

Classical QCA analysis is comprehensive from a clinical perspective, as it detects reliably whether or not relevant lumen changes occurred in a previously treated vessel segment. From a scientific perspective, however, this method is of limited value: it fails to describe precisely the anatomic location of lumen changes, as it does not provide information on the topography of the MLD within the target vessel segment at the time of repetitive measurement. Recent studies after balloon angioplasty have demonstrated that changes in RD and in the anatomic position of the MLD occur during follow-up, invalidating direct comparison of quantitative parameters over time.[38] This "relocation" makes the direct comparison of MLD questionable.[39] The dynamic lumen changes have various causes such as plaque progression, unmasking of new lesions, or remodeling, and might be triggered intentionally by intervention or nonintentionally by periprocedural vessel injury. To overcome these problems, our group, over the last 15 years, has applied a strategy

of analyzing a treated "vessel segment," rather than a focal spot representing the site of pre-interventional MLD. The treated "vessel segment" encompasses the culprit lesion and is defined in length by the most proximal and distal side branch. These side branches serve as reproducible landmarks for the follow-up analysis.[40] Similarly, the TOSCA group introduced the concept of "target lesion work length," defined as the length of contiguous target segment exposed to balloon inflation.[41] Thus, not only is the segment of the original angiographic lesion analyzed, but also the vessel segment over the entire treated length.

## New Concepts of Angiographic Assessment on Brachytherapy

### Principle of Dose-Based Segmental Assessment

Intracoronary radiation has complex and dose-dependent effects on arterial tissue.[42–50] It is usually used as an adjunctive therapeutic tool to other debulking and/or angioplasty devices. Thus, angiographic assessment must include radiation dose, proximal and distal vascular injury, and possible interactions of both (determinants of the edge effect), rather than the isolated target lesion. Based on these considerations, quantitative assessment of irradiated vessels should include different vessel segments, which are defined below (Fig. 2).

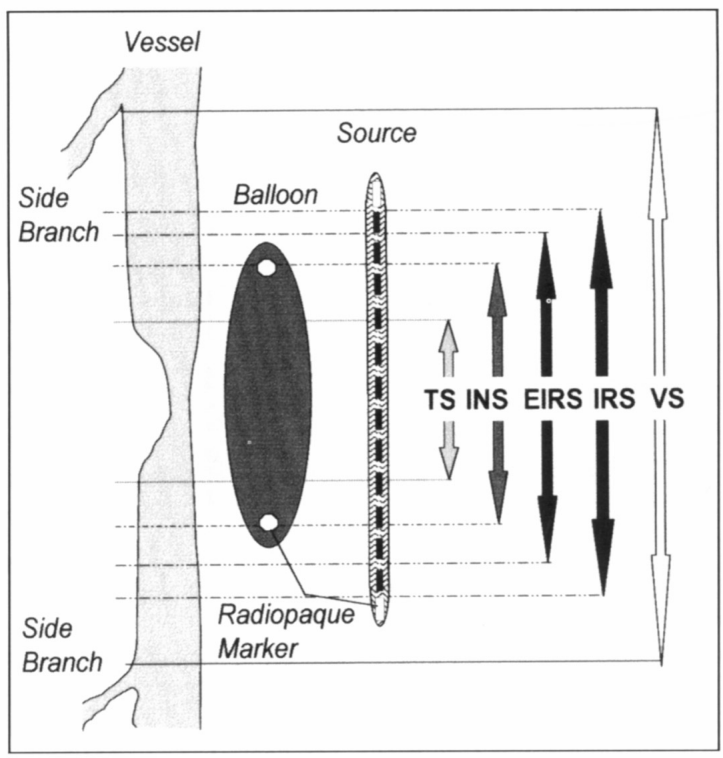


**Figure 2.** Schematic of dose-based segment definition within an irradiated coronary artery. TS = target segment; INS = injured segment; EIRS = effective irradiated segment; IRS = irradiated segment; VS = vessel segment.

### *Target Segment*

The target segment is defined by the proximal and distal margin of the obstructed segment.

### *Injured Segment*

The macroscopic injured segment is defined as the segment encompassed by the most proximal and most distal position of the angioplasty device (eg, rotablator burr) or marker of the angioplasty balloon as assessed by fluoroscopy.

### *Effective Irradiated Segment*

The effective irradiated segment is the vessel segment receiving the full prescribed therapeutic radiation dose (>90% isodose rate). In catheter-based line sources, the length of this full radiation dose segment is slightly shorter than the distance between the radiopaque markers as a result of the dose fall-off caused by the limited size of the source train (Fig. 3). The dose-fall characteristics vary in different isotopes.

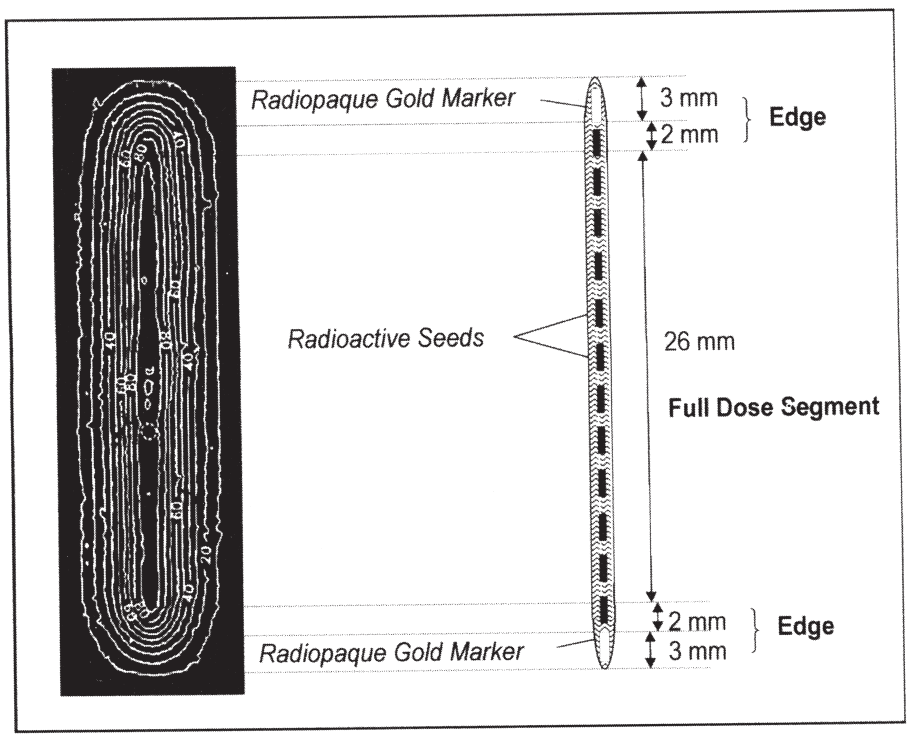


**Figure 3.** Isodose rate contour map and radiation source train. **Left:** Isodose rate contour map measured at a depth of 1.89 mm (contour intervals: 10 mGy/s) as described by the National Institute of Standards and Technology. The depth (1.89 mm) illustrates an isodose model to resemble the radius of a coronary artery. Longitudinal dose fall-off may be extrapolated from this graphic. **Right:** Radiation source train (Beta-Cath, Novoste Corp.). The central part receives an approximately full radiation dose.

Similarly, the effective irradiated segment is slightly shorter than the stent length in radioactive stents, because of the dose fall-off at the extremities of the stent, involving the most proximal and the most distal stent struts. The length of the fall-off zone varies as it is dependent on isotope and stent design. Furthermore, the dose profile is not homogeneous, but peaks behind every individual strut. This effect varies depending on the distance and the angle of observation.

### *Irradiated Segment*

In practice, the exact delineation of the effective irradiated segment is complicated, as it requires the knowledge of the individual dose profiles for each isotope and source design. Correction for the dose fall-off at the extremities of the irradiated segment is a matter of a few millimeters. Exact length measurement, however, is often hampered by the anatomy of the artery and foreshortening.

For these practical reasons, quantitative analysis is performed on an *irradiated segment,* which is defined as the segment encompassed by the inner edge of the radiopaque markers of the source train or the length of the radioactive stent.

### *Edge Segments*

Edge segments are the vessel segments at the extremities of the radiation source (catheter-based source, radioactive stent, or balloon), which do not receive the full therapeutic radiation dose. The lengths of the edge segments are dependent on the isodose profile of the individual source.

### *Geographic Miss Segment*

In coronary brachytherapy, this is defined as a mismatch between injured and irradiated segment: geographic miss is present when the entire length of the injured segment is not completely covered by the irradiated segment.

### *Vessel Segment*

The vessel segment is the coronary segment bordered by angiographically visible side branches which encompass the original lesion, all angioplasty devices, and the radiation source.

### *Image Acquisition and Procedural Implications*

In order to allow for such detailed analysis, image acquisition and angiographic documentation need to be performed in an accurate and standardized fashion. Angiography should be done in biplane views at a frame rate of 25 frames per second. The electrocardiogram (ECG) tracing must be visible on screen. Before each angiogram, nitrates should be administered by intracoronary infusion. Each angiogram should be performed at mid-inspiration. The empty (guiding) catheter[51]

should be documented for calibration, preferably near the center of the screen. At the start of the procedure, two projections should be selected with more than 30 degrees celsius difference in rotation and avoiding foreshortening and side branch overlapping. The entire procedure should be filmed in identical projections. Any instrumentation (eg, balloons or stents) should be filmed at the site of treatment surrounded by contrast medium in identical projections. The radioactive source should be filmed in place with contrast medium repeating the same projections. Follow-up angiography must performed using the same imaging projections, same contrast medium at 37°C, and documentation of the unfilled catheter. Again, intracoronary nitrates should be administered before each angiogram.

The meticulous documentation of all angioplasty devices and the radiation source using the same projections is essential. Inadequate angiographic documentation of the procedure, hampering proper angiographic assessment of geographic miss, is seen in up to 50% of the cases enrolled in brachytherapy trials.

## Angiographic Analysis of Brachytherapy

### Qualitative Assessment

The introduction the concept of "geographic miss," originating from radiation oncology,[52] into the scenario of intracoronary brachytherapy stressed the importance of assessment of the injured segment in relation to the radiation source.

To assess whether geographic miss is present or not, multiple angiographic loops and ECG-matched still frames should be displayed simultaneously, side by side, on the screen (eg, Rubo Medical Imaging, Uithoorn, The Netherlands). This approach allows definition of the location of the various subsegments (irradiated segment, injured segment, edges) in relation to side branches, and the correct matching of the angiograms. By identifying the relationship between the irradiated segment and its edges relative to the injured segment, the occurrence of geographic miss can be determined (Fig. 4). Using this method, the agreement rate of two independent cardiologists is as high as 90%.

The procedure should be considered as not interpretable in the following cases: (a) lack of correct filming with the radiation source and the balloons deflated with contrast injection, so as to allow the location of the irradiated segment, injured segment, and the edges in relation to anatomic landmarks; (b) more than 10 degrees difference in the angiographic projections, not allowing for correct matching; (c) interventions reported in the technician's worksheet, but not filmed.

### Quantitative Coronary Analysis

Dedicated analysis software (CAAS II System; Pie Medical, Maastricht, The Netherlands) allows for simultaneous assessment of the different segments. By displaying an angiographic sequence showing the lesion pre-intervention, positions of angioplasty devices, and radiation source simultaneously on a screen, the analyst indicates the different analysis segments according to the location of the angioplasty devices and radiation source relative to the original lesion (Fig. 5). The proximal (or distal) side branch within the vessel segment can be used as an index anatomic landmark to assess additionally the distances (measured on the

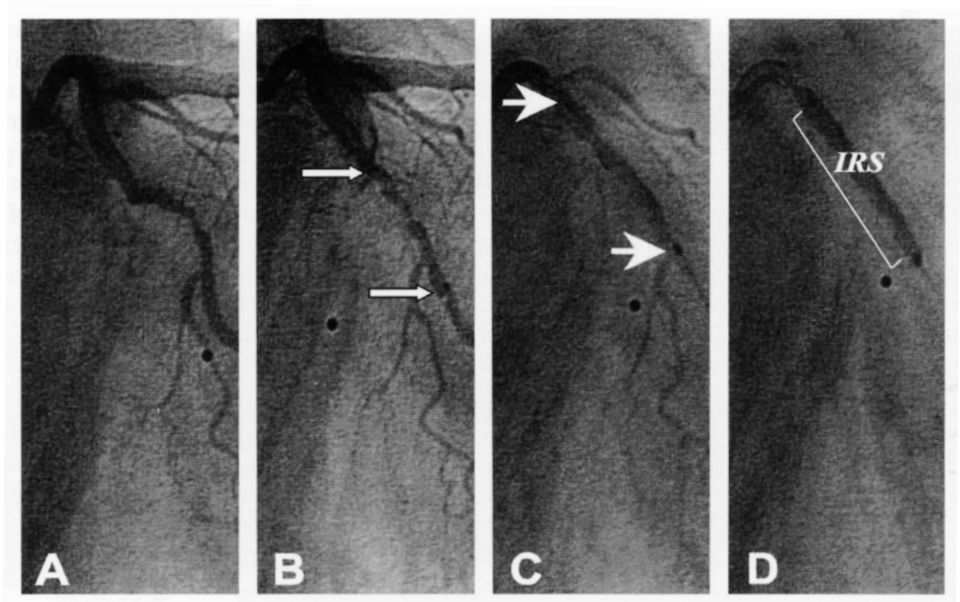


**Figure 4.** Qualitative assessment of geographic miss. Pre-intervention lesion **(A),** balloon **(B)** and radiation source **(C)** (Radiance RDX radiation balloon, Radiance Corp.) have been filmed in the same imaging plane, allowing for accurate assessment of the injured and the irradiated segments. The injured segment is distally not completely covered by the irradiation source, resulting in distal geographic miss.

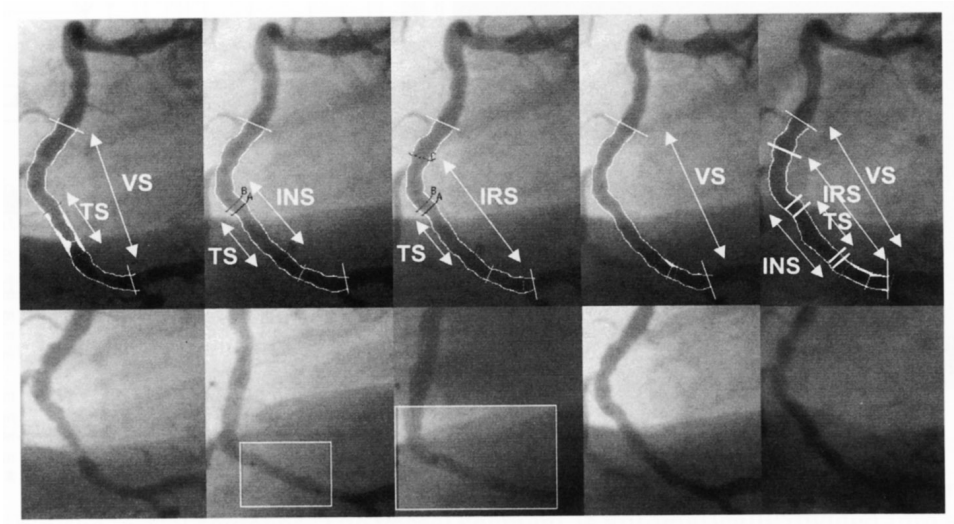


**Figure 5.** Dose-based definition of vessel segments within an irradiated coronary artery. **Lower panels:** The pre-intervention lesion, any instrumentation (balloon and source train), the post-interventional result, and follow-up have been filmed in identical projections and are displayed simultaneously on a screen. **Upper panels:** The vessel segment (VS) is defined by the analyst; the target segment (TS) is automatically defined by the quantitative coronary angiography system; the injured segment (IS) is defined as the segment encompassed by the most proximal and most distal radiopaque marker of the angioplasty balloon; the irradiated segment (IRS) has been defined between the radiopaque markers of the source.

center line) to: (1) the inner part of the proximal radiopaque marker of the radiation source; (2) the proximal marker of the angioplasty balloon; (3) the proximal margin of the obstruction segment; (4) the distal margin of the obstruction segment; (5) the distal marker of the angioplasty balloon; and, (6) the inner part of the distal radiopaque marker. All regions of interest are superimposed on the pre- and post-procedural angiograms. Thus, the occurrence of geographic miss can be directly assessed and quantified (Fig. 6). The accuracy of such quantification of geographic miss in the direction of the longitudinal vessel axis, however, is strongly dependent on an imaging projection without foreshortening. In all analysis segments, the MLD is determined by edge detection and the RD is automatically calculated. The percent DS is calculated from the MLD and the RD (Fig. 7).

### *Analysis of Restenosis: Regional Restenosis*

As in classical QCA analysis, dichotomous restenosis is defined as greater than 50% DS. As long-term radiation effects on the coronary vessel wall have shown to be dependent on dose and injury, possibly resulting in the "candy wrapper" or "edge effect," it is important to describe late outcome with respect to the dose-based subsegments.

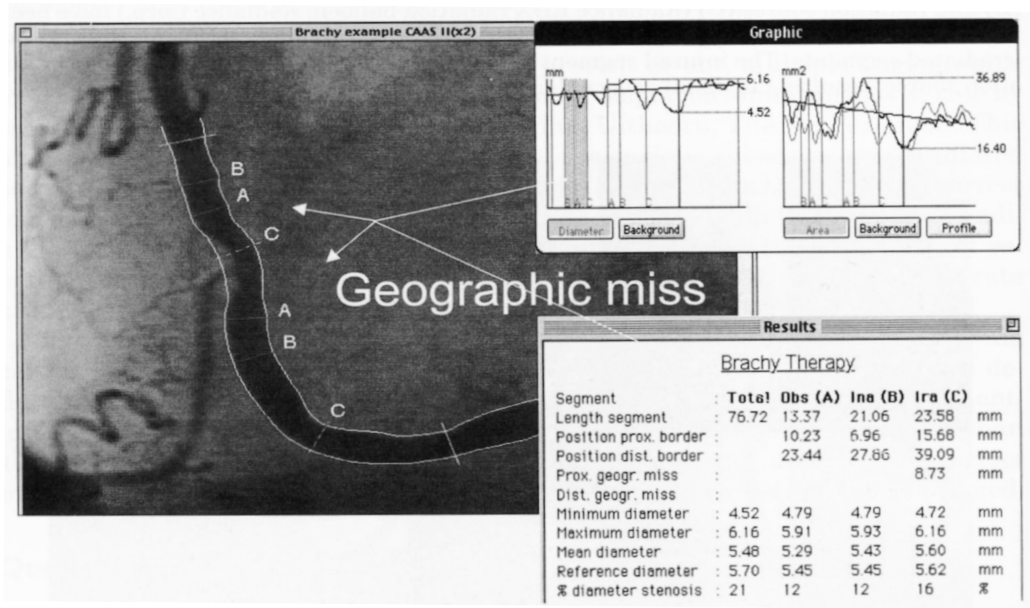


**Figure 6.** Quantitative assessment of geographic miss. Using the quantitative analysis software, the target segment **(A),** injured segment **(B),** and irradiated segment **(C)** have been defined. Ideally, the borders of the irradiated segment are most proximally and most distally situated, encompassing both, the target segment and the injured segment. Automated comparison of the position of the proximal and distal borders of each individual segment detects any deviation from this ideal pattern, indicating geographic miss. In the example, the proximal border of the irradiated segment is located more distal than the proximal border of the injured segment, indicating proximal geographic miss. The length of the geographic miss segment is 8.73 mm.

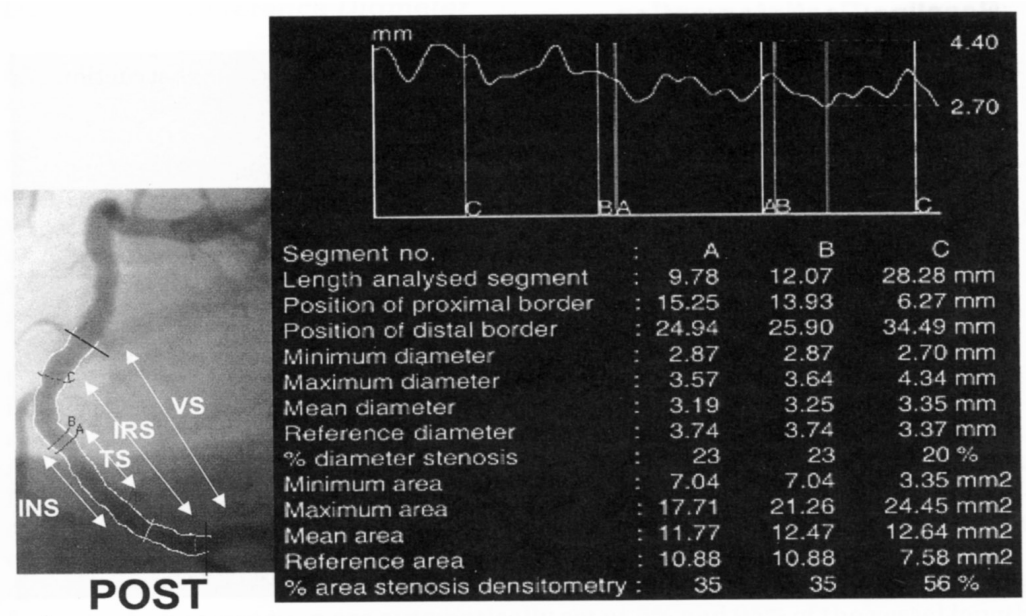


**Figure 7.** Quantitative coronary analysis of dose-based segments. Within the vessel segment (VS) quantitative parameters such as segment length, minimal lumen diameter, or reference diameter, are calculated for each segment individually. **(A)** represents the analysis for the target segment (TS); **(B)** represents the analysis for the injured segment (INS); **(C)** represents the analysis for the irradiated segment (IRS).

The pre-, post-intervention, and follow-up angiograms with the dose-based subsegments are superimposed and compared in two orthogonal projections. Thus, the location of the segment with restenosis can be assessed in relation to the dose-based segments. Regional restenosis is classified as restenosis in the irradiated segment, edge restenosis (proximal and/or distal), and restenosis outside the injured segment. The criterion for binary restenosis might be fulfilled in more than one subsegment in the same vessel segment.

### *Subsegmental QCA Analysis: Relocation*

Using current analysis software, subsegmental analysis can be performed within the vessel segment. The vessel segment is automatically divided into subsegments of equidistant length (on average, 5 mm). In each subsegment MLD, RD, and percentage DS is automatically calculated.

***Relocation*** For relocation analysis, the subsegment containing the MLD at baseline is taken as the index segment. Relocation is defined whenever the MLD in subsequent analysis is located in a subsegment other than the index segment. Sequential analysis may refer to pre-interventional to post-interventional MLD, or post-interventional (Fig. 8) to follow-up MLD (Fig. 9).

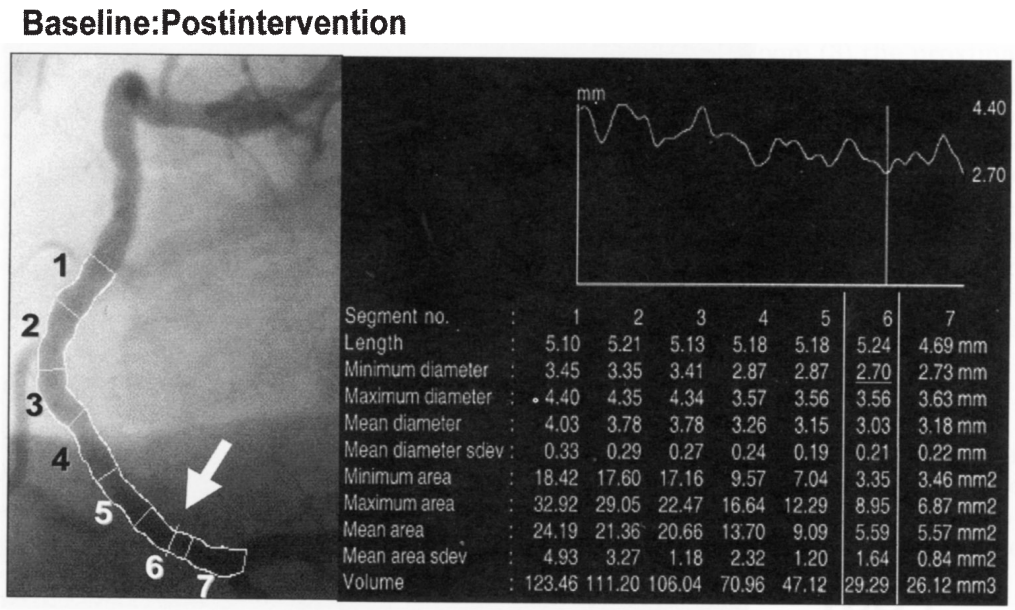


**Figure 8.** Subsegmental analyis. The vessel segment is automatically divided into subsegments of equidistant length (on average 5 mm). In each subsegment minimal lumen diameter (MLD), reference diameter (RD), and percentage diameter stenosis is automatically calculated.

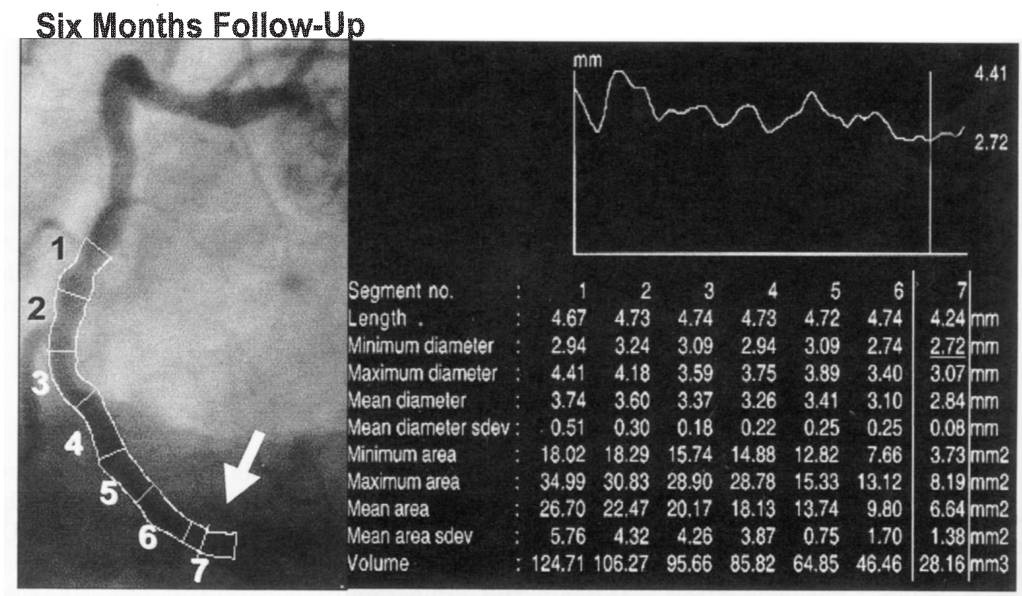


**Figure 9.** Subsegmental analysis–relocation of minimal lumen diameter (MLD). This figure shows the same coronary artery as Figure 8 at 6-month follow-up. At post intervention (Fig. 8), the MLD is located in subsegment no. 6. At subsequent follow-up analysis (Fig. 9), the MLD is located in subsegment no. 7.

### *Definition of Reference Diameter*

***Methods of Reference Diameter Calculation*** In the early years of quantitative angiographic assessment, the RD was "user-defined." The analyst set proximal and distal calipers at "normal" reference sites (Fig. 10). This method, however, was strongly user-dependent and showed high variability in measurements. To circumvent this limitation, the concept of the "interpolated reference diameter" was introduced in 1982. The interpolated RD is calculated at the site of the MLD and represents the diameter of the artery when the obstruction would not be present. This method is completely automated and user-independent, once the margins of the vessel segments are given (Fig. 11).

These concepts of RD definition are based on the assumption that a non-treated reference segment preserves its stable dimensions over time. Following intracoronary radiation, however, therapy-associated changes in vessel dimensions have been consistently observed due to edge effect, relocation of the MLD, and positive remodeling. Under these circumstances, the interpolated RD became less reliable. To overcome these problems, "computer-constructed reference diameter analysis" has been developed. The method is not influenced by development of a new (edge) stenosis close to the original treatment site as the RD is calculated apart from the treatment side. In the first step, proximal and distal boundaries for diameter construction are automatically set at 5% and 95% of the vessel length under study. This reference position is averaged over a width of 3 mm to suppress the influence of noise on the local diameter. In the second step, the computer-constructed RD is then reconstructed at the position of the MLD, based on a line fitted through the proximal and distal boundaries by linear interpolation. Thus, this approach gives more reliable reference dimensions over serial measurements;

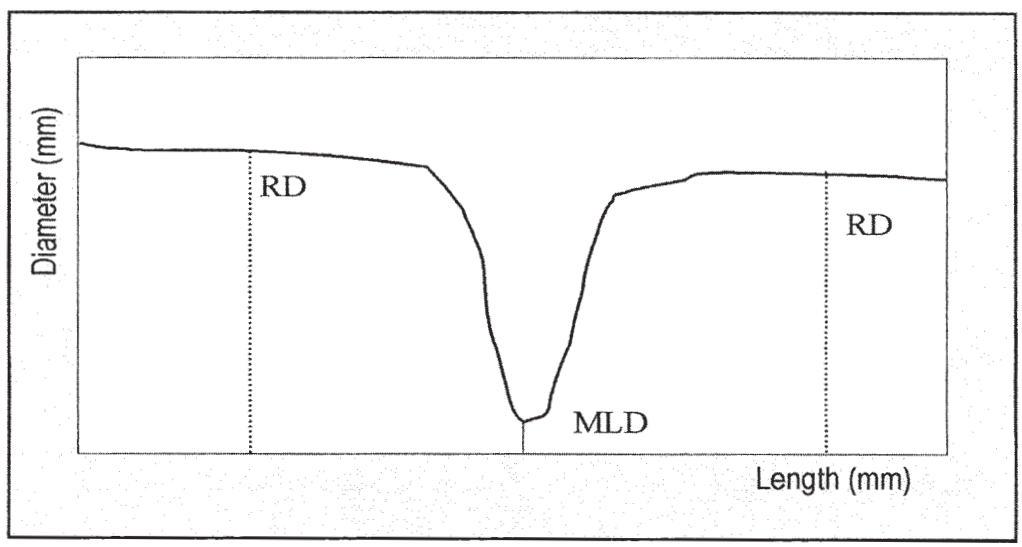


**Figure 10.** User-defined reference diameter. Diameter profile of a stenotic coronary artery segment. The analyst set proximal and distal markers at "normal" reference sites. MLD = minimal lumen diameter; RD = reference diameter.

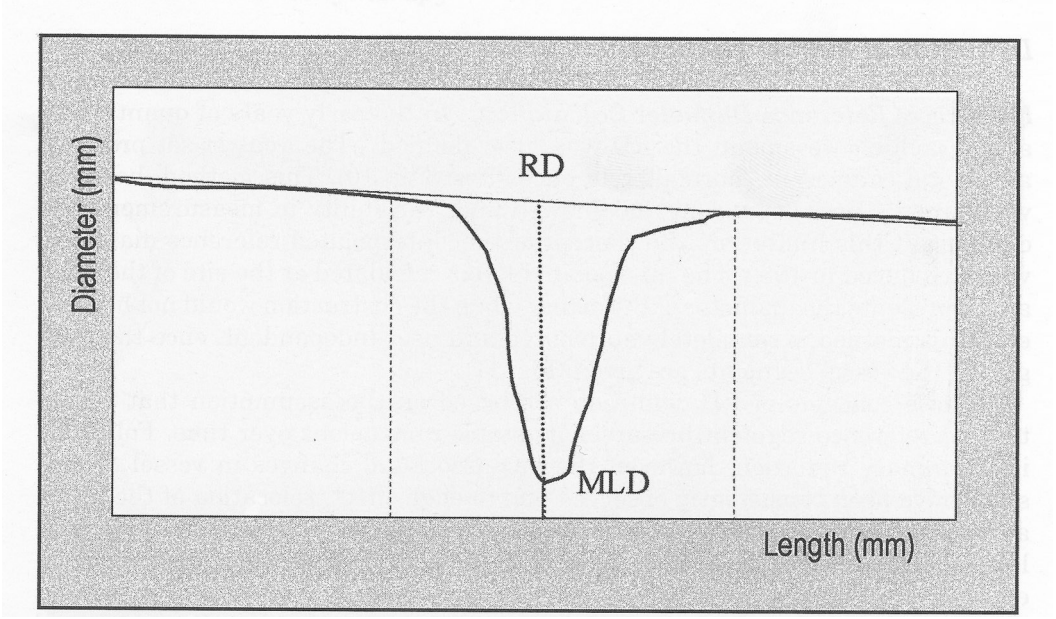


**Figure 11.** Interpolated reference diameter (RD). Diameter profile of a stenotic coronary artery segment. The "interpolated reference diameter" is automatically calculated at the site of the minimal lumen diameter (MLD) and represents the diameter of the artery when the obstruction is not present.

however, it does not cure the principal problem of relocation of the MLD. In consequence, the RD might be calculated at different positions within a vessel segment at baseline and follow-up measurement (Fig. 12).

***Selection of Reference Diameter*** Analysis of dose-based segments and subsegmental analysis gives an MLD and an RD for each individual segment. This might be helpful in the analysis of specific mechanistic questions. For the analysis of treatment efficacy and side effects, however, all measurements should de referred to one single "reference diameter." The RD calculated for the vessel segment is considered to best represent the "true" vessel dimensions, and thus, should be used for standardized reporting.

## Clinical Implications

Intracoronary radiation has shown an effective inhibition of neointimal proliferation. The local mechanisms of action are poorly understood. Recent intravascular ultrasound studies demonstrated that mechanic vessel injury in combination with radioactivity can cause both beneficial and deleterious effects. Irradiation may prevent shrinkage after balloon angioplasty[53] and even promote positive remodeling at the irradiated site.[54] In contrast, edge segments show an increase in plaque volume without adaptive remodeling.[10,22,55] These findings have indicated a need to differentiate between the reporting of angiographic outcomes.

Dose-based segmental analysis allows for an accurate description of local lumen changes in different portions of the irradiated vessel. This is a prerequisite to study both the therapeutic and the side effects. Based on this methodology, angiographic analysis could demonstrate, that geographic miss plays a key role in

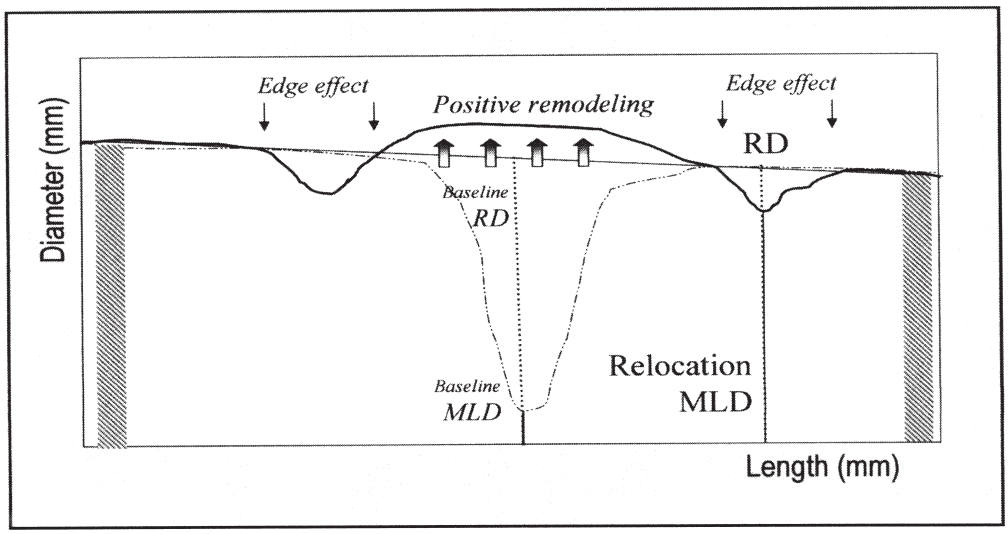


**Figure 12.** Computer constructed reference diameter (RD). Diameter profile of a stenotic coronary artery segment. At the proximal and the distal end of the vessel segment, boundaries (shaded area) for diameter calculation are automatically set. The "computer constructed reference diameter" is reconstructed at the position of the minimal lumen diameter (MLD), based on a line fitted through the proximal and distal boundaries by linear interpolation. In this example there is relocation of the MLD due to the edge effect. Thus, the RD is calculated at different positions within a vessel segment at baseline (gray lines) and follow-up (black line).

restenosis after (beta) brachytherapy,[18,56] emphasizing the need for complete coverage of the injured segment.

It could also been shown that late lumen loss differs considerably according to the selected segment. In consequence, the dichotomous restenosis rate varied from 3.1% in the "target segment" to 13.8% when analysis was extended to the "vessel segment" (Table 1).[17] Consistently, others found variation within a similar range (14.2% to 28.8%).[57] This has important impact on the reporting, interpretation, and comparison of study results.

Detailed analysis of computer-defined subsegments is of great help to gain insights in pathophysiological effects, and might be highly recommended for in vitro and/or "mechanistic" studies. Such detailed angiographic analysis could demonstrate that within the target segment, positive remodeling is a major effect of irradiation therapy, whereas relocation of the MLD within the injured segment has a substantially higher incidence after brachytherapy compared to conventional angioplasty.[17] Possible mechanisms of relocation include: tapering of the vessel; development of new coronary lesions in any of the dose-based subsegments; "unmasking " of pre-existing plaque (stenosis) outside the irradiated segment, which becomes angiographically apparent over follow-up time; progression of disease inside (treatment failure, edge effect?) or outside the irradiated area; and geographical miss. Further studies are needed to understand the complex interactions and mechanisms of action of radiation, dose, and normal and atherosclerotic arterial tissue. Analysis of the "target segment" may demonstrate the effect of brachytherapy in optimal conditions (maximum injury fully covered by radiation),

**Table 1**

Quantitative Coronary Angioplasty Data for Dose-Based Coronary Vessel Segments*

| | TS | INS | IRS | VS |
|---|---|---|---|---|
| MLD pre-intervention (mm) | 1.06±0.2 | 1.06±0.2 | 1.06±0.2 | 1.06±0.2 |
| MLD post-intervention (mm) | 2.17±0.5 | 1.99±0.4 | 2.00±0.4 | 1.91±0.4 |
| MLD follow-up (mm) | 2.36±0.5 | 1.97±0.5 | 1.97±0.5 | 1.84±0.5 |
| DS follow-up (%) | 20.3±11 | 33.2±11 | 33.4±11 | 37.9±10 |
| Acute gain (mm) | 1.12±0.4 | 0.93±0.4 | 0.94±0.4 | 0.85±0.4 |
| Late loss (mm) | −0.18±0.4 | 0.01±0.4 | 0.03±0.4 | 0.07±0.3 |
| Restenosis rate (%) | 2 (3.1) | 5 (7.7) | 6 (9.2) | 9 (13.8) |
| Segment length (mm) | 5.0±0.3 | 18.7±4.2 | 22.9±3.5 | 36.9±8.4 |

*From Reference 17.

MLD = minimal lumen diameter; DS = diameter stenosis; TS = target segment; INS = injured segment; IRS = irradiated segment; VS = vessel segment.

while analysis of the injured segment and the edge segments may be helpful to identify potential causes of failure (ie, geographic miss, non injury-related edge effect, etc.).

In clinical trials, however, treatment effectiveness is the major endpoint. Angiographic outcome measurements should therefore be referred to the clinically relevant "vessel segment." This represents the targeted region used in most of the historical trials, under the assumption that the patients symptoms and need for re-intervention are driven by flow-limiting lesions within the treated vessel, irrespective of the precise anatomic position. A restrictive definition of the "target segment" with follow-up analysis of the site of the initial MLD pre-treatment would be misleading and would make any comparison to previous nonradiation studies inaccurate.

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## PART 1: IONIC RADIATION THERAPY

*Chapter 5*

Kozuma K*, Regar E,* Bruining N, Boersma E, Foley DP, van der Giessen WJ, de Feyter PJ, Levendag PC, Serruys PW:
**SENSITIVITY AND SPECIFICITY OF QCA IN DETECTING CORONARY ARTERIAL REMODELING AFTER CORONARY BRACHYTHERAPY: A COMPARISON TO SERIAL VOLUMETRIC 3-D IVUS ANALYSIS.**
Submitted for publication.

# Sensitivity and specificity of QCA in detecting coronary arterial remodeling after intracoronary brachytherapy: A comparison to serial volumetric 3-D IVUS analysis.

## Can we detect positive remodeling by luminography?

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## ABSTRACT

**Background.** After treatment with intracoronary brachytherapy, enlargement of lumen (negative late loss) at follow-up has been demonstrated. The aim of the study is to analyze the sensitivity and specificity of QCA parameters to detect a positive vessel remodeling after intracoronary beta radiation as compared to IVUS.

**Methods.** Twenty-seven patients (27 vessels) treated with balloon angioplasty followed by catheter-based intracoronary ß-radiation with a $^{90}Sr/^{90}Y$ source were assessed by both QCA and 3D IVUS with ECG-gated pullback. Irradiated segments were analyzed over the total treatment length and in subsegments of 5mm length each.

**Results.** Change in MLD was not a predictor for the positive remodeling in both, total irradiated segmental and 5-mm subsegmental analysis with a 54.3% ROC curve area (95%CI: 30% - 79%), a sensitivity of 39% and a specificity of 44% (p=NS), and 55.9% ROC curve area (46% - 66%), a sensitivity of 55% and a specificity of 54% (p=NS), respectively. Changes in mean and maximal lumen diameter were not significant parameters to detect positive vessel remodeling as well. When only central subsegments were analyzed, change in MLD was a significant predictor: 63.3% ROC curve area (52-75%), sensitivity 55%, specificity 64% (p=0.029).

**Conclusions.** Lumen enlargement detected by QCA does not reliably indicate a positive vessel remodeling after intracoronary radiation. IVUS analysis may be necessary to investigate the mechanism of restenosis after balloon angioplasty followed by catheter-based radiation.


**Keywords:** brachytherapy, quantitative coronary angiography, intravascular ultrasound, vessel enlargement, balloon angioplasty


## BRIEF ABSTRACT

The aim of the study is to analyze the sensitivity and specificity of QCA parameters to detect a positive vessel remodeling after intracoronary ß-radiation. Irradiated segments (the total segments and subsegments of 5mm length) of 27 patients treated with balloon angioplasty followed by catheter-based radiation with a $^{90}Sr/^{90}Y$ source were assessed by both QCA and ECG-gated 3D IVUS. Change in MLD was not a predictor for the positive remodeling in both total irradiated segmental and 5-mm subsegmental analysis with a 54.3% ROC curve area, a sensitivity of 39% and a specificity of 44% (p=NS), and 55.9% ROC curve area, a sensitivity of 55% and a specificity of 54% (p=NS), respectively. When only central subsegments were analyzed, change in MLD was a significant predictor: 63.3% ROC curve area, sensitivity 55%, specificity 64% (p=0.029). Lumen enlargement detected by QCA does not reliably indicate a positive vessel remodeling.

## INTRODUCTION

For more than a decade, quantitative coronary angiography (QCA) has been the gold standard for the assessment of coronary stenosis because of its accuracy and objectivity as compared to visual and hand-held caliper measurements. [1-3] After the introduction of intracoronary brachytherapy, the QCA methodology for the assessment of irradiated coronary had to be adjusted to this new mode of therapy because of the existence of new regions of interest: the target segment, injured segment, radiated segment and vessel segment[4]. In a recent report, enlargement of lumen (negative late loss) has been demonstrated in a subset of vessels receiving 18 Gy catheter-based beta-radiation after balloon angioplasty alone[5]. Previously we have reported vessel enlargement accommodating plaque increase in the volumetric 3-D intravascular ultrasound investigation[6]. In that report, the lumen remained unchanged at follow-up as an average. In other words, half of the irradiated segments responded to the radiation with a lumen enlargement. Therefore, intracoronary radiation has a potential to increase the lumen diameter[5,7].

The aim of the study is to analyze the sensitivity and specificity of QCA parameters to detect a positive vessel remodeling after intracoronary ß-radiation as compared to IVUS.

## METHODS

### Patients

The study population consists of consecutive 27 patients who underwent balloon angioplasty followed by catheter-based intracoronary ß-radiation with $^{90}Sr/^{90}Y$ source in a single vessel and IVUS imaging with ECG-gated pullback. Patients presented with angina pectoris and/or positive stress test. Patients with myocardial infarction within 72 hours prior to treatment or left ventricular ejection fraction < 30% were not included in this study. Angiographic inclusion criteria consisted in a reference vessel diameter > 2.5 mm and < 4.0 mm and a lesion length < 20 mm.
The Medical Ethics Committee of the University Hospital Rotterdam Dijkzigt approved the protocol of intracoronary radiation. All patients gave written informed consent.

### Radiation System

The source train of the Beta-Cath™ System consists of a series of 12 independent cylindrical seeds, which contain pure ß-emitting $^{90}Sr/^{90}Y$, and is bordered by 2 gold markers (30mm total length of radioactive seeds). The profile of the catheter is 5 French and the source train is not centered. The radiation sources remain at the treatment site for approximately 2-4 minutes to deliver a predetermined dose at 2mm from the centerline of the axis of the source train. Prescribed radiation doses were 12Gy (8 vessels), 14Gy (5 vessels), 16 Gy (9 vessels), and 18Gy (5 vessels).

### Procedure

All patients received aspirin (250 mg/day) and heparin IV (10.000 IU) during the procedure and additional heparin was given to maintain the activated clotting time >300sec. Balloon angioplasty (BA) was performed according to standard clinical practice. After successful BA, intracoronary β radiation was performed as previously described, [8] and repeat angiography and IVUS pullback were carried out. Intracoronary isosorbide dinitrates (200 μg) were administered immediately prior

to each of the IVUS pullbacks. At follow-up (6-8 month), further IVUS analysis of the treated vessel was performed.

**QCA analysis**

QCA analysis was performed off-line by an independent analyst. All angiograms were evaluated after intracoronary administration of nitrates. The analysis was performed with the CAAS II analysis system (Pie Medical BV, Maastricht, The Netherlands). Calibration of the system was based on dimensions of the catheters unfilled with contrast medium. This method of analysis has been previously validated[2,3]. Within a region of interest, the MLD (minimal lumen diameter) is determined by edge detection and averaged from the two orthogonal projections. Reference diameter is automatically calculated by the interpolated method. The analyst is able to perform additionally a subsegmental analysis, using the software of the CAAS system. The region of interest is automatically divided into subsegments of equidistant length (5.0±0.3 mm).
Additionally, the system computed the mean lumen diameter, maximal lumen diameter and MLD in every subsegment. Late loss was defined as MLD post-treatment minus MLD at follow-up.

**IVUS image acquisition and quantitative analysis**

The coronary segment subject to 3-dimensional reconstruction was examined with a mechanical IVUS system (CVIS, Boston Scientific Corporation, Maple Grove, MN) incorporating a 30 MHz single-element transducer rotating at 1800 rpm. ECG-gated image acquisition and digitization was performed by a workstation designed for the 3-D reconstruction of echocardiographic images (EchoScan, Tomtec, Munich, Germany). Description of this system has been reported in detail elsewhere[9-11]. In brief, the steering logic of the workstation considered the heart rate variability and only acquired images from cycles meeting a predetermined range and coinciding with the peak of the R wave.
A Microsoft Windows™-based contour detection program, developed at the Thoraxcenter, was used for off-line volumetric quantification[12]. Briefly, this program constructed longitudinal sections from the data set and identified the contours corresponding to the lumen and media boundaries. Volumetric data were calculated by the formula: $V= \sum^{n}_{i=1} A_i * H$, where V = volume, A = area of EEM (external elastic membrane), lumen or plaque in a given cross-sectional ultrasound image, H = thickness of the coronary artery slice, that was reported by this digitized cross-section, and n = the number of digitized cross-sectional images encompassing the volume to be measured. Checking and editing of the contours of the planar images were performed by two independent experienced analysts. Intra-observer variability assessed by analyzing IVUS volumetric studies at least 3 months apart has been reported: -0.4 ± 1.1% in lumen volume, -0.4 ± 0.6% in total vessel (EEM) volume and -0.3 ± 1.0% in vessel wall (plaque + media) volumes using motorized ECG-gated pullback[11]. The application of this system has been reported in clinical studies[6,13-15].

**Definitions**

Total vessel volume (TVV), lumen volume (LV) and plaque volume (PV) were calculated from the contours of each cross-section by the software as stated above. In order to assess the volumetric changes of the vessel structures after 6-8 months, the delta value for each measurement was calculated (delta (Δ) = follow-up – post-procedure). To eliminate the influence of the vessel size, percent change (delta volume / post-procedure volume) was also calculated.
Remodeling of the vessel wall was defined when total vessel (EEM) volume increased or decreased, compared to post-procedure measurements by at least two standard deviations (± 1.2%) of the intra-

observer variability. By using this technique, the potential intrinsic error of the method may be avoided[16-18].

**Selection of the region of interest**

The region of interest was the irradiated segment (IRS). It was selected for QCA after reviewing all cinefilms performed during the index procedure. Any angiographic sequence showing the lesion of pre-intervention, post-intervention, follow-up, and the position of radiation source may be displayed simultaneously on the screen using the Rubo DICOM Viewer (Rubo Medical Imaging, Uithoorn, The Netherlands). The ECG tracing is also displayed in any angiographic sequence. By selecting frames in the same part of the cardiac cycle, we were able to define the location of the radiation source relative to the original lesion (30-mm in length). Side branches were used as index anatomical landmarks. Distances from this proximal or distal side branches to the inner part of the proximal and distal gold markers were computed by the CAAS software. The segment encompassed by the inner part of the 2 radio-opaque markers defined the IRS (Figure 1). All regions of interest were superimposed on the post-procedural and follow-up angiograms.

The methodology to define the segment of interest angiographically using this technique has been described previously[19].

By applying the same methodology using the Rubo DICOM Viewer and CAAS system, we were able to define the location of the radiation source train with anatomical landmarks on IVUS (Figure 1). IRS was selected based on the anatomical landmarks and the distances from them calculated by the 3D-reconstruction system post-procedure. At follow-up, correct matching of the region of interest was assured by both the use of the same IVUS motorized pull-back system and the comparison of the longitudinal view to that of post-procedure. This methodology for IVUS has been described in detail previously[6,20,21].

**Statistical analysis**

Quantitative data are presented as mean ± standard deviation. The comparisons between the volumetric data were performed using a two-tailed Student's t-test. Categorical data were compared by means of Fisher's exact test. Linear regression analysis was used to investigate the relationship between QCA and IVUS parameters. Sensitivity and specificity were calculated to show the true positive and true negative probability of positive remodeling (+2.4% increase in TVV). Receiver operator characteristic (ROC) curves were constructed to investigate the diagnostic power of the variable. A value of $p<0.05$ was considered statistically significant.

## RESULTS

**Irradiated segment analysis (30 mm in length; n=27)**

QCA and IVUS data per patient are presented in Table 1. When change in MLD by QCA was used for the detection of positive remodeling, a ROC curve area of 54.3% (95%CI: 29.7% to 78.9%), a sensitivity of 38.9% and a specificity of 44.4% were observed (p=NS). Interpolated reference diameter and maximal diameter of the target vessel did not show significant results as well.

**Subsegmental analysis (n=138)**

Subsegmental QCA and IVUS data are shown in Table 2. Twenty-four subsegments were excluded from the final analysis because of diffuse calcification (n=14) or side branches that involved >90° of circumferential arc in >30% of the cross sections (n=10). There were significant increases only in IVUS derived parameters: TVV, PV and any of wall thickness (mean, max and min). Only poor correlation was observed between QCA parameters and change in TVV (Figure 2). According to the ROC curve analysis, change in MLD derived from QCA was not a good indicator of positive remodeling with a sensitivity of 55% and a specificity of 54% (Table 3). Changes in mean and maximal diameter were not significant parameters to detect positive vessel remodeling as well.

Since the radiation source has an acute dose fall off, both extreme subsegments received lower dose than the central part of the irradiated segments[18]. When only central subsegments were analyzed, ROC curve area and sensitivity and specificity were better than total subsegments (Table 3).

LV quantified by 3-D IVUS correlates with change in TVV ($r=0.562$, $p<0.001$). Change in mean vessel wall thickness showed a significant but only weak correlation with change in TVV ($r=0.265$, $p=0.002$). To investigate the lumen determinant, Pearson correlation analysis was performed (Figure 3 and 4). Change in lumen volume was partially correlated to the changes in both TVV and PV. Change in TVV is also associated with delta PV. Zone A, B and C in Figure 4 represent lumen enlargement. The majority of subsegments showing lumen increase places in zone A, which demonstrate positive vessel remodeling accommodating tissue growth.

**Segments where MLD was initially located (n=27)**

It has been reported that relocation of MLD is more frequent in brachytherapy than in conventional balloon angioplasty[4]. In the current study, relocation of MLD from pre-procedure to post-procedure has occurred in 74% of vessels. Between post-procedure and follow-up, the rate of relocation was 82%. Since MLD is used as a target of the treatment, only the segments where MLD was initially located were examined. Changes in mean diameter, maximal diameter and MLD of those segments were not an indicator of positive vessel remodeling as well as the total subsegmental analysis (Table 3).

## DISCUSSION

The aim of this study is to investigate the usefulness of QCA in understanding the mechanism of prevention of restenosis by intracoronary brachytherapy. This study demonstrates that parameters derived from QCA are not sufficient to establish the presence of positive vessel remodeling after balloon angioplasty in the setting of catheter-based β-radiation ($^{90}Sr/^{90}Y$ source). However, mean diameter and MLD were significant indicators for a positive vessel remodeling when only the fully irradiated segments were considered.

**Mechanisms of prevention of restenosis**

In animal experimental models, it has been emphasized that intracoronary radiation inhibits neointimal proliferation[22-24]. However, experimental data have also suggested that radiation have an effect on vessel remodeling by modifying cell responses in the adventitia. [25,26] Whether intracoronary radiation mainly affects positive remodeling or inhibition of tissue proliferation remains to be

investigated. It is also a point of debate in human IVUS investigations. Positive vessel remodeling accommodating neointimal ingrowths after 6 months has been demonstrated using 3-D IVUS quantification[6], whereas total vessel area and plaque area remained unchanged in another study[27]. In the present study, total vessel volume and wall thickness derived from IVUS was partially correlated to the lumen change (Figure 3). Therefore, the contribution of vessel remodeling and tissue proliferation to the lumen preservation may have different patterns depending on individual and local elements (local vessel dimensions, delivered dose, plaque morphology and degree of injury). In addition, the central parts of irradiated segments showed higher sensitivity and specificity with significant ROC curve area in changes in MLD and mean diameter. This finding may demonstrate that higher dose radiation has an effect to reduce the variability of the response, which leads to the vessel enlargement. Dosimetric analysis would be required to address this issue.

**Value of OCA**

QCA has been a standard research tool for more than a decade, providing accurate and reproducible measurements. Most of clinical trials on restenosis after coronary intervention have used angiographic measurements (minimal lumen diameter and % diameter stenosis) for their end points. However, we recently reported that QCA methodology for the assessment of irradiated coronary arteries had to be adjusted to this new mode of therapy because of the existence of various regions of interest (target segment, injured segment, radiated segment and vessel segment) [4]. In addition, lumen enlargement with negative late lumen loss has been rarely reported before the introduction of coronary brachytherapy. The dose-finding study using a $^{90}Y$ source has shown lumen enlargement after catheter-based beta-radiation following balloon angioplasty for the first time[5].

**Possible mechanisms of lumen enlargement**

There are some important aspects in understanding the mechanism of lumen enlargement detected by QCA. First, radiation can potentially induce positive vessel remodeling (i.e. TVV increase) and medial thinning or thickening (i.e. changes in PV). These various changes in vessel wall and morphology may be one of the reasons for the complexity of vessel response after balloon angioplasty followed by intracoronary radiation (Figure 4). Second point may be the delivered dose of this β-emitting source ($^{90}Sr/^{90}Y$ source). Indeed, dose inhomogeneity within the irradiated segments was observed in a previous study. [28] In that report, plaque volume at follow-up (comparable to wall thickness at follow-up) was associated with actual dose, which widely ranged over the entire irradiated segments. In the present study, central fully irradiated segments showed better sensitivity and specificity. These findings suggest that actual delivered dose may be a major determinant of vessel remodeling. It is of note that the actual dose delivered to the adventitia cannot be assessed by QCA. Third, highly frequent relocation of MLD in the present study may also support the variability of the response. This result suggests that the comparison between post-procedure and follow-up is assessed in different positions in most of the cases. Finally, another factor influencing the poor prediction of positive vessel remodeling may be an inaccuracy of edge-detection method of QCA. Especially immediately after the procedure, poor correlation between QCA and IVUS results has been reported because of complex lumen morphology after balloon angioplasty[29]. Therefore, lumen increase detected by QCA may not be fully explained by positive vessel remodeling.

**Limitations**

Small inaccuracies cannot be completely ruled out because of axial movement of the radiation source during the cardiac cycle. However, 3-dimensional reconstructed volumetric IVUS analysis with ECG-gated pullback used in the present study is the most precise method currently available in terms of selection of region of interest by eliminating the artifacts from the cardiac movement. By using this technique, we have demonstrated the behavior of the irradiated vessels comparing the vessel geometry at follow-up with post-procedure[6,30]. To investigate the mechanism of action of radiotherapy, this comprehensive technique representing the entire segment of interest may be more relevant instead of assessing single cross-sectional image or angiographic results, since relocation of MLD frequently occurs after balloon angioplasty followed by intracoronary beta-radiation[4]. However, it is nevertheless important to note that the common angiographic end points (i.e. restenosis rate) would be enough to assess the effectiveness of intracoronary brachytherapy in clinical protocols, considering that discrete lesions at follow-up can be well detected by QCA[29].

## CONCLUSIONS

Lumen enlargement detected by QCA does not always mean a positive vessel remodeling after intracoronary radiation. IVUS analysis may be necessary to investigate the mechanism of restenosis after balloon angioplasty followed by catheter-based radiation.

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## FIGURE LEGENDS

**Figure 1**
Selection of region of interest
At the time of procedure, radiation source surrounded by contrast was filmed (central upper panel). From the position of the source related to anatomical landmarks and the distance from them, irradiated segments were selected on IVUS (left side panel). At follow-up, same segments were identified on angiogram and IVUS by using the anatomical landmarks (central lower panel and right side panel).

**Figure 2**
Correlation between QCA parameters and change in TVV (subsegmental analysis)
DTVV = change in total vessel volume, dmean = change in mean diameter of the sub-segment, Dmaxd= change in maximum diameter of the subsegment, dmld = change in minimum lumen diameter of the sub-segment

**Figure 3**
Correlation between change in LV and TVV (left side panel) and LV and PV (right side panel)

**Figure 4**
Correlation between change in TVV and PV

**Figure 4**
Correlation between change in TVV and PV

**Table 1. QCA and IVUS data per patient (n=27)**

| | post | 6M | p-value |
|---|---|---|---|
| ***QCA parameters*** | | | |
| Reference diameter (mm) | 2.93±0.71 | 2.95±0.62 | 0.81 |
| Max lumen diameter (mm) | 3.75±0.84 | 3.65±0.60 | 0.62 |
| Min lumen diameter (mm) | 2.06±0.68 | 1.88±0.63 | 0.08 |
| %diameter stenosis (%) | 31.5±7.9 | 35.0±18.1 | 0.27 |
| ***IVUS parameters*** | | | |
| LV ($mm^3$) | 247.5±108.4 | 249.1±121.5 | 0.88 |
| TVV ($mm^3$) | 445.3±145.6 | 481.6±165.0 | 0.004 |
| PV ($mm^3$) | 197.7±56.6 | 232.5±66.9 | 0.001 |

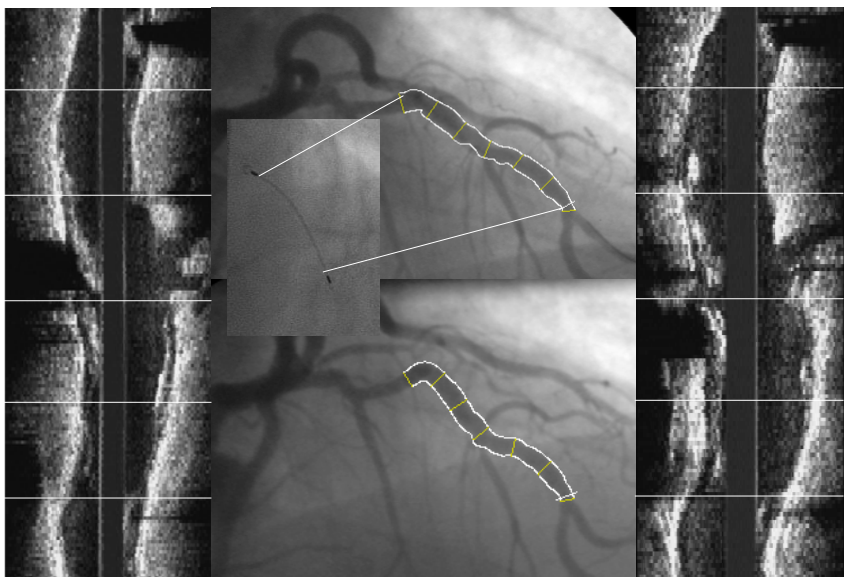
**Table 2. Subsegmental analysis (n=138)**

| | post | 6M | p-value |
|---|---|---|---|
| ***QCA parameters*** | | | |
| Mean lumen diameter (mm) | 2.83±0.71 | 2.81±0.61 | 0.55 |
| Max lumen diameter (mm) | 3.23±0.78 | 3.18±0.65 | 0.34 |
| Min lumen diameter (mm) | 2.46±0.69 | 2.43±0.63 | 0.40 |
| ***IVUS parameters*** | | | |
| LV ($mm^3$) | 43.4±22.4 | 43.2±21.8 | 0.88 |
| TVV ($mm^3$) | 78.9±28.9 | 85.1±31.0 | 0.001 |
| PV ($mm^3$) | 35.5±15.7 | 41.8±16.3 | 0.001 |
| Mean lumen diameter (mm) | 3.25±0.77 | 3.26±0.71 | 0.86 |
| Max lumen diameter (mm) | 3.60±0.83 | 3.65±0.77 | 0.34 |
| Min lumen diameter (mm) | 2.91±0.73 | 2.89±0.68 | 0.70 |
| Mean wall thickness (mm) | 1.19±0.43 | 1.37±0.41 | 0.001 |
| Max wall thickness (mm) | 1.52±0.50 | 1.70±0.47 | 0.001 |
| Min wall thickness (mm) | 0.86±0.37 | 1.06±0.37 | 0.001 |

**Table 3. Predictive Values of Positive vessel remodeling (subsegmental analysis)**

| | ROC area | p-value | 95%CI | Sensitivity | Specificity |
|---|---|---|---|---|---|
| ***All subsegments (n=138)*** | | | | | |
| Delta mean diameter (mm) | 57.1 | 0.152 | 48-67 | 58% | 54% |
| Delta max diameter (mm) | 56.3 | 0.202 | 47-66 | 60% | 54% |
| Delta MLD (mm) | 55.9 | 0.231 | 46-66 | 55% | 54% |
| ***Central part (n=94)*** | | | | | |
| Delta mean diameter (mm) | 62.0 | 0.048 | 50-74 | 55% | 64% |
| Delta max diameter (mm) | 58.1 | 0.184 | 46-70 | 56% | 64% |
| Delta MLD (mm) | 63.3 | 0.029 | 52-75 | 55% | 64% |
| ***Segments where MLD originally located (n=27)*** | | | | | |
| Delta mean diameter (mm) | 63.6 | 0.266 | 40-87 | 36% | 80% |
| Delta max diameter (mm) | 55.7 | 0.639 | 47-66 | 29% | 80% |
| Delta MLD (mm) | 70.0 | 0.101 | 48-92 | 57% | 70% |

**Figure 1**



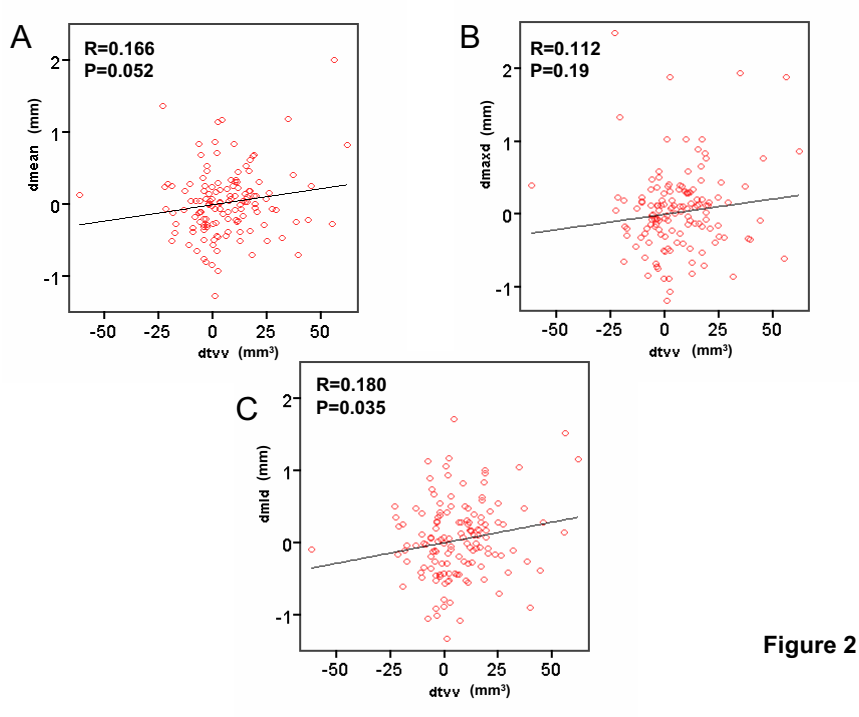



**Figure 2**

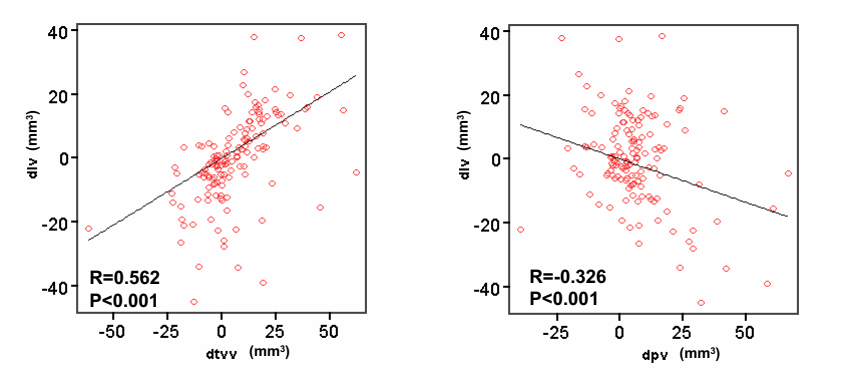
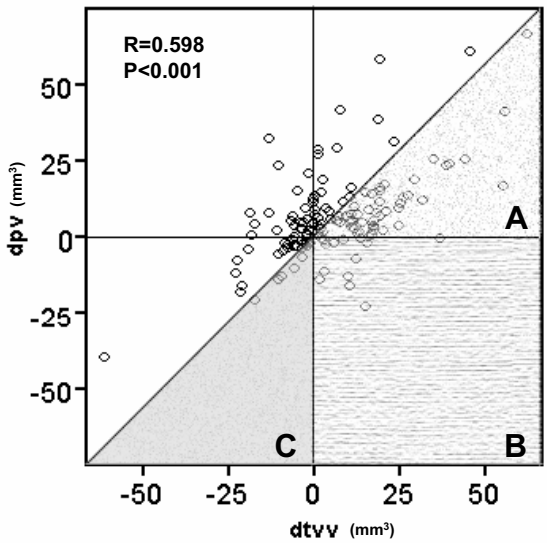



**Figure 3**




**Lumen enlargement due to**

**A: TVV increase > PV increase**

**B: TVV increase + PV decrease**

**C: TVV decrease < PV decrease**

**Figure 4**

## PART 1: IONIC RADIATION THERAPY

*Chapter 6*

*Regar E*, Kozuma K, Sianos G, Coen VLMA, van der Giessen WJ, Foley DP, de Feyter P, Rensing B, Smits P, Vos J, Knook AHM, Wardeh A, Levendag PC, Serruys PW:

**ROUTINE INTRACORONARY BETA-IRRADIATION: ACUTE AND ONE YEAR OUTCOME IN PATIENTS AT HIGH RISK FOR RECURRENCE OF STENOSIS.**

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# Routine Intracoronary Beta-Irradiation: Acute and One Year Outcome in Patients at High Risk for Recurrence of Stenosis

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**Running head:** Safety of routine coronary irradiation

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## Abstract:

**Aims:** Intracoronary radiation is a promising therapy potentially reducing restenosis following catheter-based interventions. Currently, only limited data on this treatment are available. The feasibility and outcome in daily routine practice however is unknown.

**Methods and results:** In 100 consecutive patients, intracoronary β-radiation was performed with a 90Strontium system (Novoste Beta-Cath™) following angioplasty. Predominantly complex (73% type B2 and C) and long lesions (length 24.3±15.3mm) were included (37% de-novo, 19% restenotic and 44% in-stent restenotic lesions). Radiation success was 100%. Mean prescribed dose was 19.8±2.5Gy. A pullback procedure was performed in 19% lesions. Geographic miss occurred in 8% lesions. Periprocedural thrombus formation occurred in 4 lesions, dissection in 9 lesions. During hospital stay, no death, acute myocardial infarction, or repeat revascularization was observed. Major adverse cardiac events (MACE) occurred predominantly between 6 and 12 months after the index procedure with MACE-free survival of 66% at 12 month (1 death, 10 Q-wave myocardial infarction, 23 target vessel revascularization; ranked for worst event).

**Conclusion:** Routine catheter-based intracoronary β-radiation therapy after angioplasty is safe and feasible with a high acute procedural success. The clinical one-year follow-up showed delayed major adverse cardiac events occurring between 6 and 12 month after the index procedure


**Key words:** brachytherapy, angioplasty, safety, radioisotopes

## Unstructured abstract:

We describe the feasibility and outcome of intracoronary beta-radiation in daily routine practice. Radiation therapy was successfully performed in 100 consecutive patients with predominantly complex and long de-novo or in-stent restenotic lesions. Periprocedural complications included thrombus formation (4 lesions) and dissection (9 lesions). During hospital stay, no death, acute myocardial infarction, or repeat revascularization was observed. The clinical one-year follow-up showed delayed occurrence of major adverse cardiac events between 6 and 12 month after the index procedure with a MACE-free survival of 66%.

## Introduction:

Although balloon angioplasty and stent placement has become the predominant modes of coronary revascularization, restenosis remains the major limitation for catheter-based therapies. Restenosis rates in short type A and B lesions are reported to be 30%-40% for conventional balloon angioplasty and 15-30% for stents [1,2]. Coronary radiation is a promising therapy potentially reducing restenosis. Current concepts for coronary irradiation include external radiation [3], radioactive balloons [4], radioactive stents [5-7] and afterloading. Currently, only limited data on this treatment are available [8-10]. The safety and feasibility in daily routine application however are unknown. We report on the acute procedural and long-term clinical success using routine $^{90}$Strontium/Yttriumin radiation in a patient population at high risk for recurrence of stenosis.

## Methods:

**Patients:**

The patient population consisted of consecutive patients with angina and/or objective evidence of ischemia, who had angiographic documented coronary artery disease and were scheduled to undergo beta-brachytherapy within the multi-center RENO registry[11]. Patients were included after successful treatment with conventional angioplasty and/or debulking procedures. Patients with impaired left ventricular function (LVEF <30%), undergoing or having prior chest radiotherapy, acute myocardial infarction or angiographic evidence of fresh thrombus (filling defect proximal to or involving the stenosis) prior to radiation therapy were excluded. All included patients had given written informed consent.

**Angioplasty and radiation procedure:**

Angioplasty was performed using routine procedures with commercially available systems and 8F guiding catheters by femoral approach. The position of all balloons, stents or debulking devices was documented angiographically. After the initial catheter-based procedure, the absence of dissection, thrombus or spasm prior to placement of the Beta-Rail delivery catheter™ was assured by contrast injection after a waiting period of 5-10 minutes.

Pre-interventional medication included non-enteric aspirin (325mg) and intravenous heparin (10 000 to 15 000 IU), in order to keep the activated clotting time >300sec during procedure. Post-interventional medication consisted of chronic aspirin and antiplatelet therapy (clopidogrel 75mg daily after a loading dose of 300mg at the day of procedure) for 3-7 months.

Intracoronary beta-irradiation was performed using a $^{90}$Strontium/Yttrium source with a non-centering catheter (Novoste Beta-Cath™). Following successful angioplasty, the Beta-Rail™ delivery catheter was advanced over the guide wire into the vessel so that the radiopaque markers on the delivery catheter were equidistant from the center of the injured segment, with a margin to the edge of the

injured segment of at 7mm. After withdrawal of the guide wire, the source train was transported hydraulically to the distal end of the delivery catheter. The position of the source was documented angiographically. At the end of the calculated radiation time, the source was withdrawn and the Beta-Rail™ delivery catheter was removed over the guide wire. The dose was prescribed at 2mm from the source axis and adapted to the vessel diameter. Dosage calculation and the delivery of the radioactive seeds were carried out by a radiation oncologist. The length of the source train was 30mm, 40mm or 60mm. If the injured segment could not be covered completely with one source, a pullback procedure was performed. The source train was first positioned to cover the distal portion of the injured segment, then withdrawn to cover the proximal portion of the injured segment. Proximal positioning of the delivery catheter was performed using a dummy source train and overlay imaging technique. An ECG-gated video-loop, showing the distal source position was projected on the actual fluoroscopic image, done in the same projection, table position and expiration position of the patient. The delivery catheter was placed in such a way, that the radiopaque marker indicating the proximal end of the distal source overlapped with the distal marker of the proximal dummy source. After exact positioning, the dummy source was removed hydraulically and the active source train inserted.

**Success:**

Procedural success was defined ≤ 30% residual stenosis post procedure before removal of the guiding catheter and a successful radiation therapy procedure. Brachytherapy success was defined as complete (>90%) delivery of prescribed radiation dose, including dose interruption and resumption. Clinical success was defined as procedural success without the occurrence of major adverse cardiac events (MACE: Death, myocardial infarction, target vessel Re-PTCA or coronary artery bypass grafting (CABG)) during hospital stay.

**Angiography:**

On line quantitative coronary analysis was performed using the CAAS II system (Pie Medical, Maastricht, NL)[12]. All angiograms were evaluated after intracoronary administration of nitrates. The minimal lumen diameter (MLD) was determined by edge detection, reference diameter (RD) was automatically calculated by the interpolated method. The percent diameter stenosis (DS) was calculated from the minimal lumen diameter and the reference diameter. Lesion were classified as discrete (<10mm length) or diffuse (>10mm length).[13]

**Follow-up:**

Clinical follow-up has been performed within 12 months after the radiation procedure for the occurrence of MACE.

**Statistical analysis:**

All statistical analysis was performed with commercially available software (SPSS 9.0, SPSS Inc. Chicago, Illinois). Data are presented as mean ± standard deviation, median and [interquartile range] or proportions. Survival analysis was done using the Kaplan-Meier method.

## Results:

In 100 prospectively included patients 108 arteries were treated.

**Patient characteristics:**

Patient baseline characteristics are given in TABLE 1. The population showed typical age, gender and coronary risk factor distribution. Twenty-seven patients presented with unstable angina (of whom one had acute myocardial infarction), 29 had prior myocardial infarction and 45 showed severe coronary artery disease with significant lesions in several epicardial arteries.

**Lesion characteristics and angiographic data:**

Lesions were located in 102 native arteries (36 LAD, 28 LCx, 38 RCA) and in 6 venous bypass grafts. 40 were de-novo lesions whereas 68 lesions were restenoses, of which 47 were in-stent restenotic lesions. Lesion type was A in 4 lesions, B1 in 17, B2 in 46 and C in 33 lesions, of which 12 showed total occlusion. Lesion length was 24.3±15.3mm, with 90% lesions longer than 10mm. Reference diameter was 3.02±0.58mm and minimal lumen diameter 1.09±0.18mm resulting in a mean diameter stenosis of 77.2±13.4%. Final reference diameter was 3.13±0.56mm, the final minimal lumen diameter 2.47±0.21mm and final diameter stenosis 21.2± 7.8%.

**Angioplasty procedure:**

Angioplasty was performed in all lesions (n=108). In 4 lesions debulking was used prior to balloon angioplasty and irradiation (3 laser, 1 directional atherectomy). Angioplasty consisted of balloon inflation in 25 lesions and stent implantation in 79 lesions. Stenting was performed electively in 80%, due to insufficient angioplasty result in 9% and due to dissection after balloon dilatation in 11%. In 39 lesions direct stenting was performed. The procedural success rate was 92%.

**Brachytherapy success:**

Intracoronary beta-irradiation was possible in all 108 lesions, resulting in a brachytherapy success rate of 100%. Mean prescribed dose was 19.8±2.5Gy at 2mm from the center of the source axis. To cover the injured vessel segment, a long source of 60mm was used in 3 lesions and in 21 lesions a pullback procedure was done (TABLE 2). Complete coverage with a safety margin of at least 7mm proximal and distal to the injured segment could be achieved in 99/108 lesions, thus causing geographic miss in 8.3% of the lesions.

Irradiation had to be fractionated in 4 patients due to severe angina and ECG changes indicative of myocardial ischemia. Non flow-limiting thrombus formation successfully treated with GPIIb/IIIa inhibitors occurred in 4 lesions. Dissections were observed after manipulation of the delivery catheter in 9 lesions. Of these, 3 were Type B and C dissections, necessitating stent implantation, 6 were non flow-limiting Type A dissections not requiring further treatment.

**Clinical success:**

After the procedure and during hospital stay, no death, acute myocardial infarction, or repeat revascularization was observed. One patient, who underwent the procedure for acute myocardial infarction showed a raise in creatinin kinase up to 723 IU/l. Thus, clinical success rate was 91%. Median time to hospital discharge after the procedure was 2 (1;2) days. One patient, treated for a type C lesion in the medial RCA with direct stent implantation (slotted tube stent 3.0/20mm) followed by irradiation with a 30mm source developed pericardial tamponade after the procedure which was caused by an exit of the PTCA guide wire prior to irradiation. It could be successfully treated with pericardial drainage. The patient was discharged 4 days after the procedure. Two patients with insulin dependent diabetes mellitus and pre-existing impairment of renal function (creatinin 137mmol/l and 154mmol/l) developed acute transient renal insufficiency after the procedure resolving after forced hydration in combination with furosemide. The further hospital stay of these patients was uneventful, one left the hospital 4 days,

the other 10 days after the procedure. Four patients developed isolated mild creatinin kinase elevation (mean 374±123 IU/l) within 24h after the procedure without chest pain or ECG changes (TABLE 3).

**One year follow-up:**

During 12 months clinical follow-up, 34 patients experienced major adverse cardiac events, which are given in TABLE 4. Mean follow-up time was 359±34 days. Event-free survival is given in FIGURE 1. Target vessel repeat PTCA was clinically driven by the recurrence of angina in all patients. In the patient group undergoing CABG, one patient showed severe progression of coronary artery disease including the left main stem, but no restenosis at the target vessel. Three patients experienced myocardial infarction prior to CABG.

In the 29 patient with target vessel restenosis, restenosis was discrete (<10mm length) in 17 patients and located at the proximal (n=6), the distal (n=5) or both extremities (n=6) of the index lesion. 7 patients showed diffuse restenosis (>10mm length) and 5 patients total vessel occlusion.

During the follow-up period 9 patients experienced acute myocardial infarction (while 1 patient underwent the index procedure for acute myocardial infarction as described above). Out of these 9 patients 3 had received a new stent at the index procedure, 5 stent -in stent implantation and 1 balloon dilatation of a restenotic stent. Myocardial infarction occurred in 2 patients under clopidogrel medication at day 13 and day 54 after the index procedure. The other 7 patients experienced myocardial infarction after stopping 6 months clopidogrel medication between day 191 to day 363 after the index procedure. Maximum creatinin kinase rise was 1361[762; 2409] IU/l.

In the patient population, which developed MACE more females (37%), diabetics (27%), patients with three vessel disease (23%) and unstable angina (41%) were found than the total group. Indication for angioplasty was de-novo lesion in 46%. A total of 88% patients received a new stent at the index procedure.

## Discussion:

**Study population:**

This study describes the clinical outcome of routine intracoronary beta-irradiation in a large number of patients at high risk for recurrence of stenosis. This is indicated by the relatively high proportion of patients with multivessel disease, restenosis, Type B2 and C lesions and the lesion length. Thus, our series is likely to reflect "real world" lesions in a tertiary care center. The generalizability of study results plays an important role on the background that the number of centers licensed for intracoronary radiation therapy is growing rapidly since the first patient in Europe has been randomized in 1997 at our center.

**Feasibility in the "real world":**

Brachytherapy was applied routinely with excellent success rate. The prescribed radiation dose could be delivered to all lesions. Special care was taken to cover the complete injured vessel segment in order to avoid "geographic miss", the deleterious effect of balloon induced injury and low dose radiation at the extremities of the source train [14]. To overcome this potential limitation of intracoronary irradiation, sequential pullback or combination of source trains with different length was performed in a relatively high proportion of patients. The 60mm long source became available only at the end of the study. The use of a long source, however, might spare the relatively complex pullback procedures in the future. Every step of the procedure needed to be documented by contrast injection to avoid geographic miss. This increased the consumption of contrast agents, which was not without risk, as seen in our patients who developed transient renal insufficiency.

**Procedural complications:**

No acute or subacute major adverse cardiac events or irradiation induced major complications were seen. The procedural costs (assessed by the costs of the used material), however, raised substantially

from a mean of 3200.- Euro for conventional coronary angioplasty procedures (1/2000 - 5/2000) to 4100.- Euro. Thus, the cost-effectiveness of intracoronary brachytherapy still needs to be proven.

Our findings are in accordance with previous published data [9] on various afterloading techniques. In some of these series, however, irradiation induced adverse events were reported. Using a 192 Iridium source, Condado describes successful gamma-radiation delivery in all 21 patients following balloon angioplasty, however, one patient developed prolonged coronary spasm, an other patient suffered subacute thrombosis [15], whereas in another series of 26 patients with restenotic or in-stent restenotic lesions no in hospital adverse events were seen [8]. In a larger patient cohort (n=130) undergoing randomized gamma irradiation for in-stent restenosis, 2 patients in the placebo and 2 patients in the radiation group required fractionation of radiation due to angina and ischemia, 2 patients required vascular access site repair and 8% of patients had CKMB elevation [16]. Similarly, dose fractionation due to ischemia was required in 11/50 patients receiving beta-afterloading with a centered device for in-stent restenosis [17], indicating insufficient distal perfusion with the centering balloon during irradiation as it was also seen in 4/15 patients in the Geneva series [18]. In our study with a non-centered device, dose fractionation was necessary in 4/108 lesions only. The need for dose fractionation might be further reduced by the introduction of smaller 3.5F brachytherapy catheters.

*Thrombus:*

The most frequently seen possible irradiation associated events were thrombus formation and dissections. In our series, in 4 lesions intracoronary thrombus formation during the procedure could be visualized as a contrast-filling defect by angiography. In all 4 lesions, thrombus formation was not flow limiting. All patients received intravenously GP IIbIIIa inhibitors for 12h, their in-hospital course was uneventful, without evidence for (sub-)acute thrombosis. Weight adjusted heparin dosage and more frequent use of GP IIbIIIa inhibitors possibly could have possibly prevented thrombus formation.

*Dissection:*

In 9/108 lesions dissections were documented angiographically at the end of the irradiation procedure. In 3/9 lesions, further preventive stent implantation was performed [19]. However, the prognostic impact of non flow-limiting dissections in patients undergoing brachytherapy in poorly understood. Previous case series (16 patients each) with acute dissection following balloon angioplasty and intracoronary beta-irradiation have shown that these dissections persist in approximately 50% of the patients [20,21] at six months follow-up. Persisting dissections were not associated with a change in angina status or any acute or subacute clinical sequelae [21]. In contrast 2/6 patients presenting sudden thrombotic events after balloon angioplasty and beta irradiation showed a Type B dissection after the procedure [22]. No correlation between persistence of dissection and the prescribed dose was seen [20].

**One year outcome:**

Major-adverse event-free survival of our patients was 66% at one year. This seems worse that after conventional stent implantation in the Benestent trial, were a MACE -free survival of 77% at one year is reported [23]. However, our patient population was at high risk for recurrence of stenosis presenting with less than 5% "Benestent" type A lesions. When looking at patient populations which are more comparable to ours like patients treated with gamma-radiation for in-stent restenosis then our data are very similar to the reported event-free survival of 65%[16].

MACE consisted in target vessel revascularization and delayed myocardial infarction. This is possibly caused by increased thrombogenicity and prolonged wound healing reported in experimental [24-26] and clinical series [22]. The evolving clinical important question is the duration of platelet inhibition and whether or when to stop clopidogrel prescription. Data from the SCRIPPS trail suggest that late thrombosis and myocardial infarction become infrequent after 12 months [10]. Furthermore, the complex interaction between freshly implanted stents, radiation therapy and late thrombosis needs to be clarified. In our patients late thrombosis with consecutive myocardial infarction occurred not exclusively in patients with freshly implanted stents and not only after discontinuing clopidogrel medication, while

other data suggest an association between these parameters [27]. Here, further investigations are clearly needed.

**Limitations:**

This is a non-randomized, non-placebo controlled mono-centre experience. We evaluated only one type of beta radiation delivery catheter, thus these results can not be extrapolated to other radiation (e.g. centering) delivery systems or other (e.g. gamma) sources. These data are restricted to the 12 months outcome. Possibly radiation induced delayed restenosis needs to be further investigated. The small number of events in this study does not allow to identify patient or lesion related factors predicting adverse procedural outcome.

## Conclusion:

Routine catheter-based intracoronary β-radiation therapy after angioplasty is safe and feasible with a high acute procedural success. However, the clinical one-year follow-up showed delayed major adverse cardiac events occurring between 6 and 12 month after the index procedure.

## Acknowledgments:

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## Tables:

**Table 1:**

Patient baseline characteristics

Data are presented as mean ± standard deviation or proportions of patients (n=100)

| | |
|---|---|
| Mean age (years) | 59±10 |
| Gender (male) | 72 |
| Angina status | |
| Stable angina (CCS 1-4) | 73 |
| Unstable angina | 27 |
| Cardiovascular risk factors | |
| History of smoking | 46 |
| Diabetes mellitus | 14 |
| History of hypertension | 39 |
| History of hypercholesterolemia | 58 |
| Prior myocardial infarction, related to target vessel | 29 |
| Extent of vessel disease | |
| One vessel disease | 55 |
| Two vessel disease | 32 |
| Three vessel disease | 13 |

CCS Canadian Cardiovascular Society

**Table 2:**

Radiation procedure

Data are presented as mean ± standard deviation or proportions of lesions (n=108)

| | |
|---|---|
| Source length (mm) | |
| 30 | 36.1 |
| 40 | 61.1 |
| 60 | 2.8 |
| Pullback procedure (%) | 19.0 |
| Radiation dose (Gy) | |
| 16.1 | 6.7 |
| 18.4 | 61.0 |
| 20.7 | 2.9 |
| 23.0 | 24.8 |
| 25.3 | 4.8 |
| Dwell time (min) | 3.34±0.44 |

**Table 3:**

In hospital major adverse cardiac and clinical events

Data are given as numbers (no) of events, no patient experienced multiple events

| Event | No of events |
|---|---|
| Major adverse cardiac event (MACE) | |
| Death | 0 |
| Q-wave myocardial infarction | 1* |
| CABG | 0 |
| Repeat PTCA | 0 |
| Clinical event | |
| Pericardial tamponade | 1 |
| Renal insufficiency | 2 |
| Isolated CK elevation | 4 |

CABG coronary artery bypass graft

PTCA percutaneous transluminal coronary angioplasty

CK creatinine kinase

* One patient underwent the angioplasty procedure for acute myocardial infarction

**Table 4:**

Major adverse cardiac events at 12 months follow-up

Data are given as numbers (no) of events and ranked (ranking) as follows: death, Q-wave myocardial infarction, CABG, repeat PTCA.

| Event | No of events | Ranking |
|---|---|---|
| Death | 1 | 1 |
| Q-wave myocardial infarction | 10* | 10 |
| CABG | 6 | 3 |
| Repeat PTCA | 24 | 20 |

CABG coronary artery bypass graft

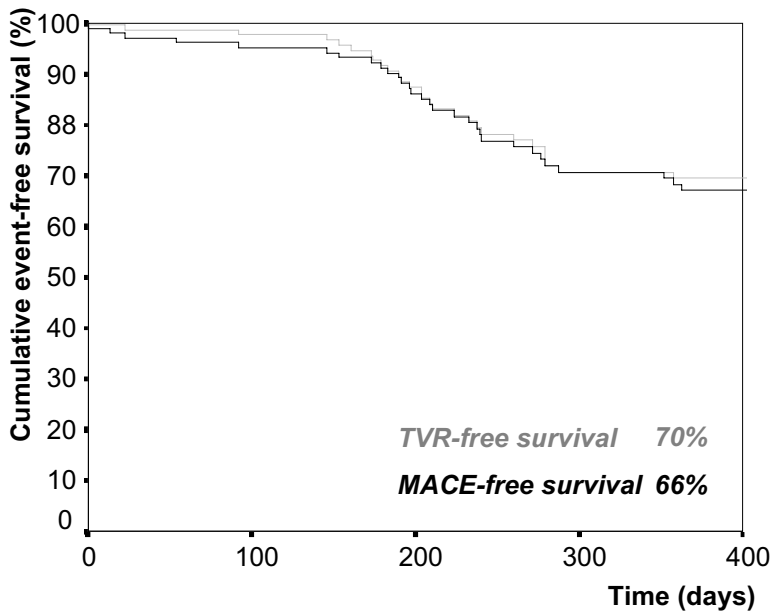
PTCA percutaneous transluminal coronary angioplasty

* One patient underwent the angioplasty procedure for acute myocardial infarction

## Figure Legend:

**Figure 1:** Event free survival at 12 months follow-up (Kaplan -Meier). TVR indicates target vessel revascularization and includes repeat PTCA and CABG. MACE indicates major adverse cardiac events. Events are given ranked as follows: death, Q-wave myocardial infarction, CABG, repeat PTCA.

**Fig 1:**



## PART 1: IONIC RADIATION THERAPY

*Chapter 7*

*Regar E*, Colombo A, Műgge A, Glogar HD, De Scheerder I, Disco C, Kleine J, Serruys PW:
**GAMMA RADIATION TO ATHEROMATOUS NEOINTIMA USING INTRACORONARY THERAPY IN EUROPE: THE GRANITE STUDY**.
Submitted for publication.

# Gamma RAdiation to in-stent Neointima using Intracoronary Therapy in Europe: the GRANITE study

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*Submitted for publication*

## ABSTRACT

Recently, several trials on vascular gamma-radiation therapy, conducted in the United States of America, have shown a significant reduction of neointimal growth and restenosis in selected patient populations. The objective of this registry was to introduce catheter-based gamma radiation in Europe.

Methods and results: 96 patients undergoing percutaneous revascularization for in-stent restenosis were included. Angioplasty was successful performed in all lesions (1 rotablator, 1 directional atherectomy, 94 balloon or cutting balloon). In 21 lesions additional new stents were implanted (mean length 18.9±10.8mm). Intracoronary gamma radiation (iridium-192) was successfully delivered in 95 lesions (99%). Antiplatetelet therapy included aspirin indefinitely and clopidogrel (for at least 12 months if new stents were implanted). At six-month angiographic follow-up, the repeat restenosis rate was 32%. Sub-segment analysis revealed a restenosis rate of 16% in the obstructed segment, 17% in the injured segment, 27% in the radiated segment. The rate of geographic miss was low (10.4%). At one-year follow-up, event-free survival was 58%. No subacute or late stent thrombosis occurred.

Conclusion: This multi-center, European registry of gamma radiation for in-stent restenosis showed an excellent procedural success rate, a remarkably low repeat restenosis rate at 6 month and a favorable long-term outcome at 1 year in a patient population at high risk for repeat occurrence.


## INTRODUCTION

Restenosis limits the long-term success of coronary stent implantation and significantly reduces 10-year event-free survival (1). In-stent restenosis is predominantly caused by "intimal hyperplasia" (2), the growth of smooth muscle cells, fibroblasts, and intercellular matrix into the lumen of the vessel in response to the injury of the angioplasty procedure (3).

Recently, several randomized trials on vascular gamma-radiation therapy, conducted in the United States of America, have shown a significant reduction of neointimal growth and restenosis (4);(5);(6). In Europe, however, the therapeutic application of gamma sources is hampered by rigorous legal regulations (7, 8).

The objective of this registry was to introduce catheter-based gamma radiation in Europe. A low-dose iridium-192 source was used in patients undergoing percutaneous revascularization for in-stent restenosis.

## METHODS

### Patients

Between December 1999 and September 2000, patients with coronary ischemia attributable to an in-stent restenosis were enrolled into this prospective, uncontrolled study at 8 centers in Europe. In-stent restenosis was defined as of ≥50% diameter stenosis (DS) at online QCA in a lesion treated ≥4 weeks previously. The target lesion had to be located in a native coronary artery ≥2.75 and ≤4.0mm in lumen diameter and ≤45mm in length. All patients gave written informed consent. The local Ethic committees of all participating centers approved the study.

### Angioplasty procedure

In-stent restenosis was treated with high-pressure balloon inflations (>12atm; balloon-to-

artery ratio 1.2). If a <30% residual diameter stenosis (DS) could not be obtained or a significant dissection occurred, new stents were implanted. After successful coronary intervention, intracoronary radiation (IRT) was performed. If the immediate post-IRT angiography results were not satisfying (DS>15%), additional PTCA ("touchup" PTCA) including stent implantation was possible.

**Concomitant medication**
All periprocedural medications were given according to the local routine. Discharge medications included aspirin indefinitely (at least 80mg/day). If new stents were implanted, clopidogrel was prescribed for at least 12 months (or ticlopidine 250 mg bid).

**Radiation and dose prescription**
The radiation system consisted of a 3.7F delivery catheter that accommodated the source and a hand-cranked delivery device (Cordis, Waterloo, Belgium). The source consisted of a ribbon of 6, 10, or 14 iridium-192 seeds (Best Industries of Springfield, Virginia), corresponding to a length of 23, 39 or 55mm. The dose prescription was 14Gy at a depth of 2mm radial distance from the source (for vessels ≤4mm lumen diameter). The dwell time (15-45 minutes) was calculated by the radiation oncology physicist based on the activity of the source and the total length of the radioactive seed train. Assumptions for dose prescription were that the closest distance from source center to arterial wall is 0.6mm given the outer catheter diameter of 1.24mm.

**Radiation procedure**
IRT was performed immediately after PTCA, or within at most 24 hours. The radiation delivery catheter was positioned into the coronary artery. Then, the radioactive Ir-192 strand was inserted by the radiation oncologist. The strand was kept in place to deliver the prescribed dose.

**Technical and clinical success**
Technical success was defined as DS<50% at the completion of the procedure and successful delivery of the IRT. Clinical success was defined technical success in the absence of MACE during the hospital stay.

**Angiographic analysis**
Angiographic lesion morphology was assessed using the Mehran classification (9). Offline quantitative analyses (QCA) by edge detection techniques were performed using the CAAS II system (Pie Medical, Maastricht, NL)(10). All angiograms were evaluated after intracoronary administration of nitrates. Reference diameter (RD), minimal luminal diameter (MLD) and degree of stenosis (as percentage of diameter, DS) were measured before dilatation (pre), at the end of the procedure (post) and at 6 months follow-up (fup). Repeat restenosis was defined as >50% diameter stenosis at fup. Late loss was defined as minimal luminal diameter post minus minimal luminal diameter fup.

**Definition of sub-segments:**
Any angiographic sequence showing the lesion pre-intervention, positions of angioplasty devices and radiation source were displayed simultaneously, side by side, on the screen (Rubo Medical Imaging, Uithoorn, The Netherlands). The analyst indicated the following subsegments (11, 12).
Obstructed segment: segment ( ±5mm) containing the initial MLD;

| | |
|---|---|
| Injured segment: | encompassed by the most proximal and most distal position of the angioplasty device or marker of the angioplasty balloon. |
| Irradiated segment: | encompassed by the inner edge of the radiopaque markers of the source train |
| Vessel segment: | bordered by angiographically visible sidebranches, which encompass the original lesion, all angioplasty devices and the radiation source. |
| Geographic miss: | topographic mismatch between injured and irradiated segment causing incomplete full-dose radiation coverage of the injured segment. |

**Follow-up:**
Angiographic follow-up has been performed within 210 days after the procedure, clinical follow-up at 360 days. We assessed the incidence of repeat restenosis (>50% DS) and of major adverse events (MACE). MACE included death, acute myocardial infarction (MI), coronary artery bypass graft (CABG), and repeat target vessel PTCA. The following safety parameters were assessed: coronary perforation, need for blood transfusion, need for surgical repair of the access site, cerebral vascular accident (CVA) or stent thrombosis.
MI was diagnosed when a least 1 of the following occurred: enzyme changes defined by more than twice the upper limit of normal creatin kinase and the presence of MB iso-enzyme twice greater than the upper limit of normal, ECG changes with the development of a new abnormal Q-wave (Minnesota Code).

**Statistics**
Data are presented as mean ±(1SD) or median [interquartile range] when appropriate. Event-free survival is assessed using the Kaplan-Meier method.

## RESULTS

**Patients**
A total of 96 patients were included. The patient's baseline characteristics are summarized in Table 1.

**Angiographic baseline characteristics and angioplasty procedure**
Angiographic characteristics at baseline are given in Table 2. Nine lesions very located at the ostium of the coronary artery, in 21 lesions a significant side-branch was involved. 18 lesions showed angiographic moderate to severe calcification.
Angioplasty was successfully performed in all lesions (1 rotablator, 1 directional atherectomy, 94 balloon or cutting balloon). In 21 lesions additional new stents (range 1-4) were implanted. The mean length of the new stents was 18.9±10.8mm. Stenting was performed because of an insufficient angioplasty result in 17 lesions and due to severe dissection (≥ type C) after balloon dilatation in 4 lesions. 5 patients received GPIIbIIIa inhibitors during the procedure.

**Irradiation procedure**
Intracoronary gamma radiation was successfully delivered in 95 lesions, one lesion could not be crossed with the radiation delivery catheter (success 99%). Mean dwell time was 21.2±4.0min, total procedural time was 66.1±44min. Mean source length was 37.9±10.2mm, (25% 23mm source, 58% 39mm source, 17% 55mm source). Irradiation had to be

fractionated in 2 patients due to severe angina, in 2 other patients for correction of the source position and in one patient because he needed nurse assistance. In one lesion, an overdose was given with a prolonged total dwell time of 38min. Dissections (6 type A, 7 type B, 1 type C) were observed after manipulation of the delivery catheter in 14 lesions that were treated with additional stent implantation in 4 lesions. The technical success rate was 98%.

**Clinical outcome**

During hospital stay no patient died or underwent CABG. One patient developed MI and underwent PTCA for a lesion remote from the target lesion, another patient experienced subacute vessel occlusion that was treated by repeat PTCA and GPIIbIIIa inhibition without development of MI. The clinical success rate was 95%.

**Long-term follow-up**

At six-month follow-up or at the time of re-intervention 51 patients were free of angina, 19 patients had mild stable angina (CCS class 1 and 2), 7 patients had angina CCS class 3 and 7 patients presented with unstable angina. Silent ischemia was detected in 7 patients.

During 360 days clinical follow-up, 40 patients experienced major adverse cardiac events, which are given in Table 3. Event-free survival is given in FIGURE 1. No patient experienced subacute or late stent thrombosis. 3 Patients showed cerebrovascular symptoms during follow up (1 transient ischemic attack, 1 PRIND, 1 stroke).

**Angiographic analysis**

QCA data are summarized in Table 4. Sub-segment analysis was possible in 81 lesions. We excluded lesions with no correct filming of the radiation source and the balloons deflated with contrast injection, more than 10 degrees difference in the angiographic projections or interventions reported in the technician's work sheet but not filmed.

Angiographic restenosis for the individual sub-segments and the overall group is given in Figure 2. Geographic miss occurred in 10 lesions (7 proximal, 2 distal and in 1 lesions proximal and distal) and was caused by balloon injury in all lesions. No geographic miss segment showed restenosis at 6 month follow-up.

## DISCUSSION

We describe the first experience with intracoronary gamma-radiation therapy in Europe. Gamma radiation could be applied safely and with excellent technical success. Our long-term outcome with an angiographic restenosis rate of 32% in patients with in-stent restenosis is favorable and reproduces the results of the American studies. However, this trial is not just a simple "remake" of previous studies.

**Lessons learned**

The Granite trial reflects the dynamic changes and summarizes the experiences in the field of intracoronary radiation over the last two years. This is documented by the excellent in-hospital and relatively good long-term outcome with an event-free survival of 58% at 1 year in a population at high risk for repeat events.

**Reduction in geographic miss**

The concept of "geographic miss", originating from radiation oncology (13), has been described for beta radiation therapy and introduced as a contributor to treatment failure (11,

12). The awareness of this potential problem urged the Granite investigators for careful source positioning, and resulted in a substantial reduction of geographic miss (10.4% versus previously reported rates of 30% (14) to 40% (12)). In fact, geographic miss was eliminated as reason for treatment failure. No patient with geographic miss developed repeat restenosis. This might be explained by the fact that repeat edge restenosis is much stronger associated with stent injury (and low dose radiation) than with balloon injury (and low dose radiation)(12).

**A new methodological approach for QCA**

Another consequence from this concept was the need for much more detailed angiographic analysis. We introduced a new methodological approach using dedicated software for automated quantification of sub-segments. This allowed for accurate quantitative analysis instead of semi-quantitative assessment for the presence of geographic miss and standardized reporting of restenosis rates. Our results clearly underline the need for such meticulous reporting, as the restenosis rate at lesion site is only half of that of the complete vessel segment.

**Implantation of new stents and antithrombotic regimen**

Another fact that became obvious during the course of the Granite trial is the elevated complication rate associated with the periprocedural implantation of new stents (6). The Granite investigators therefore markedly restricted the implantation of new stents to 20% of lesions. Furthermore, the antithrombotic regimen in these patients was gradually prolonged by study protocol amendments from 4 to 6 to 12 months of combined antiplatelet therapy with aspirin and ticlopidine. The benefit of this dynamic adaptation of study protocol is documented by a late thrombosis rate of zero. While early studies with short antiplatelet medication reported late thrombosis rates in the range of 7% (15) to 9.6%, prolonged 6-month antiplatetelet therapy reduced this event to 2.5% (16).

**Comparison to other studies**

The angiographic restenosis rate of 32% is very favorable for a patient population at high risk for repeat restenosis and matches exactly the results of the WRIST series. In vessels between 2.5 and 3.0mm diameter and a lesion length of 15-30mm, a repeat restenosis rate of 32% was found after radiation therapy whereas the control group showed a repeat restenosis rate of 71% (17). The long-tem outcome of 58% at 1 year is comparable to previous gamma radiation trials. It is somewhat lower than in the Scripps trial (85%)(4) and the WRIST trial (65%) (5) but favorable in comparison to the Gamma –1 trial where event-free survival at 9 month was 43% (6).

## CONCLUSION

This multi-center, European registry of gamma radiation for in-stent restenosis showed an excellent procedural success rate, a remarkably low repeat restenosis rate at 6 month and a favorable long-term outcome at 1 year in a patient population at high risk for repeat occurrence.

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## APPENDIX

Principal investigators and centers listed in the order of the number of included patients:

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## FIGURE LEGENDS

Fig 1 For the segment length assessment the side-branch which delineates the proximal border of the vessel segment was taken as reference to measure (on the center line) the distances to: (1) the inner part of the proximal radiopaque marker of the radiation source; (2) the proximal marker of the angioplasty balloon; (3) the proximal margin of the obstructed segment; (4) the distal margin of the obstructed segment; (5) the distal marker of the angioplasty balloon; and, (6) the inner part of the distal radiopaque marker.

Fig 2 Angiographic restenosis (>50 diameter stenosis) at 6 month follow up in the overall group and in the subsegment analysis that was possible in 81/96 patients.

Fig 3 Event-free survival at 1 year follow-up (Kaplan –Meier method). Events included death, acute Q-wave myocardial infarction, repeat target vessel revascularization (CABG, PTCA).

**TABLE 1**

**Baseline clinical characteristics**

| Characteristic | | |
|---|---|---|
| Age (yr) | 63 {56; 69} | |
| Male sex | 73 | (76) |
| Coronary risk factors | | |
| Smoking# | 18 | (19) |
| Diabetes mellitus | 17 | (18) |
| Hypertension | 61 | (64) |
| Hypercholesterolemia* | 69 | (72) |
| Family history of coronary artery disease | 39 | (41) |
| Medical history | | |
| Previous myocardial infarction | 42 | (44) |
| Previous coronary artery bypass grafting | 7 | (7) |
| Previous stroke/TIA | 5 | (5) |
| Renal insufficiency | 1 | (1) |
| Symptoms | | |
| Stable angina | 63 | (66) |
| CCS class 1 | 2 | (2) |
| CCS class 2 | 28 | (29) |
| CCS class 3 | 26 | (27) |
| CCS class 4 | 7 | (7) |
| Unstable angina | 19 | (20) |
| Silent ischemia | 5 | (5) |
| Extent of coronary artery disease | | |
| One vessel disease | 56 | (58) |
| Two vessel disease | 27 | (28) |
| Three vessel disease | 13 | (14) |
| Left ventricular ejection fraction (%) | 58±11 | |

| | |
|---|---|
| CCS | Canadian Cardiovascular Society |
| TIA | Transient ischemic attack |
| * | total cholesterol > 6.0mmol/l or > 235mg/l |
| # | current cigarette smoking |

Values are given as mean±1 SD, or median {1st quartile-3rd quartile} or no. (%) .

**TABLE 2**

**Angiographic characteristics at baseline (n=96)**

| Characteristic | n | (%) |
|---|---|---|
| Target vessel | | |
| Right coronary artery | 28 | 29 |
| Left anterior descending artery | 42 | 44 |
| Left main stem | 1 | 1 |
| Left circumflex artery | 25 | 26 |
| Coronary flow | | |
| Occluded (TIMI 0) | 1 | 1 |
| TIMI 1 | 3 | 3 |
| TIMI 2 | 18 | 20 |
| TIMI 3 | 74 | 76 |
| Details of previous implanted stent | | |
| Lesion treated prior to stent implantation | 36 | (38) |
| Length of restenotic target stent (mm) | 21.95±9.03 | |
| In-stent restenosis lesion characteristics | | |
| Mehran class I | 21 | 23 |
| Mehran class II | 29 | 32 |
| Mehran class III | 39 | 43 |
| Mehran class IV | 1 | 1 |

Values are given as mean±1 SD or no. (%)

TIMI according to TIMI study group

**TABLE 3**

Frequency of primary clinical endpoints in-hospital, at 31, 210 and 360 days follow-up in descending order of severity

| Event | All events | Ranking |
|---|---|---|
| Death | | |
| In hospital | 0 | 0 |
| At 31 days | 0 | 0 |
| At 210 days | 0 | 0 |
| At 360 days | 1 | 1 |
| Q-wave MI | | |
| In hospital | 1 | 1 |
| At 31 days | 1 | 1 |
| At 210 days | 1 | 1 |
| At 360 days | 1 | 1 |
| Non Q-wave MI | | |
| In hospital | 1 | 1 |
| At 31 days | 1 | 1 |
| At 210 days | 3 | 3 |
| At 360 days | 6 | 5 |
| CABG | | |
| In hospital | 0 | 0 |
| At 31 days | 0 | 0 |
| At 210 days | 5 | 4 |
| At 360 days | 6 | 4 |
| Repeat PTCA | | |
| In hospital | 2 | 1 |
| At 31 days | 3 | 2 |
| At 210 days | 32 | 25 |
| At 360 days | 41 | 29 |
| Any event | | |
| In hospital | 4 | 3 |
| At 31 days | 5 | 4 |
| At 210 days | 41 | 33 |
| At 360 days | 55 | 40 |

All events: Total count of events i.e., if a patient underwent repeat PTCA and later coronary bypass surgery, the total count of events will reflect both events.

Ranking: For each follow-up interval only the worst event was counted for each patient. e.g. if a patient underwent repeat PTCA at 1 months follow-up and coronary bypass surgery at 6 months follow-up, repeat PTCA is considered the worst event at 1 months, whereas at 6 months CABG is considered the worst event for this patient. Thus, the preceding repeat PTCA is not counted at 6 months.

| | |
|---|---|
| MI | myocardial infarction |
| CABG | coronary artery bypass graft |
| PTCA | percutaneous transluminal coronary angioplasty |
| mo | months |

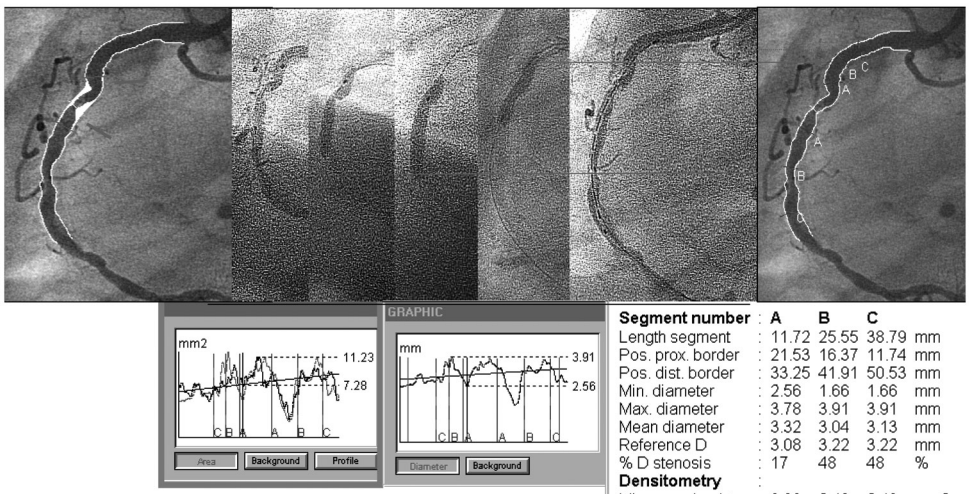
**TABLE 4**

**Quantitative angiographic parameter**

| Characteristic | ALL (n=96) | SUB-SEGMENT ANALYSIS (n=81) | | | |
|---|---|---|---|---|---|
| | | Vessel segment | Irradiated segment | Injured segment | Obstructed Segment |
| Length | 52 ± 12 | 52 ± 11 | 39 ± 10 | 29 ± 11 | 20 ± 9 |
| Reference diameter (mm) | | | | | |
| Before | 2.59 ± 0.55 | 2.61 ± 0.56 | 2.61 ± 0.56 | 2.61 ± 0.56 | 2.61±0.56 |
| After | 2.48 ± 0.53 | 2.49 ± 0.53 | 2.55 ± 0.51 | 2.64 ± 0.47 | 2.69±0.45 |
| Follow-up | 2.56 ± 0.53 | 2.56 ± 0.54 | 2.60 ± 0.50 | 2.68 ± 0.46 | 2.73±0.47 |
| Minimal lumen diameter (mm) | | | | | |
| Before | 0.88 ± 0.31 | 0.88 ± 0.31 | 0.88 ± 0.31 | 0.88 ± 0.31 | 0.88 ± 0.31 |
| After | 1.59 ± 0.41 | 1.61 ± 0.39 | 1.68 ± 0.37 | 1.83 ± 0.38 | 1.89 ± 0.40 |
| Follow-up | 1.42 ± 0.35 | 1.43 ± 0.35 | 1.50 ± 0.38 | 1.69 ± 0.41 | 1.76 ± 0.46 |
| Diameter stenosis (%) | | | | | |
| Before | 65 ± 13 | 65 ± 13 | 65 ± 13 | 65 ± 13 | 65 ± 13 |
| After | 35 ± 12 | 34 ± 12 | 33 ± 9 | 30 ± 10 | 29 ± 11 |
| Follow-up | 45 ± 19 | 42 ± 15 | 41 ± 16 | 36 ± 15 | 34 ± 18 |
| Restenosis (%) | 32 | 27 | 28 | 17 | 16 |
| (≥50% diameter stenosis at follow-up) | | | | | |
| Late loss (mm) | 0.19 ± 0.48 | 0.17 ± 0.47 | 0.18 ± 0.47 | 0.14 ± 0.48 | 0.13 ± 0.50 |

Late loss (Minimal lumen diameter after) - (Minimal lumen diameter follow-up)
Loss index Acute gain/Late loss

Values are given as mean ± 1SD or no. (%)




| Segment number | A | B | C | |
|---|---|---|---|---|
| Length segment | 11.72 | 25.55 | 38.79 | mm |
| Pos. prox. border | 21.53 | 16.37 | 11.74 | mm |
| Pos. dist. border | 33.25 | 41.91 | 50.53 | mm |
| Min. diameter | 2.56 | 1.66 | 1.66 | mm |
| Max. diameter | 3.78 | 3.91 | 3.91 | mm |
| Mean diameter | 3.32 | 3.04 | 3.13 | mm |
| Reference D | 3.08 | 3.22 | 3.22 | mm |
| % D stenosis | 17 | 48 | 48 | % |
| **Densitometry** | | | | |
| Min area absolute | 6.98 | 2.46 | 2.46 | mm2 |
| Maximum area | 11.23 | 11.23 | 11.23 | mm2 |
| Mean area | 8.62 | 7.45 | 7.65 | mm2 |
| MLA densitometry | 7.28 | 2.59 | 2.59 | mm2 |
| Reference area | 7.45 | 8.18 | 8.18 | mm2 |
| % area stenosis | 2 | 68 | 68 | % |

**Fig 1**

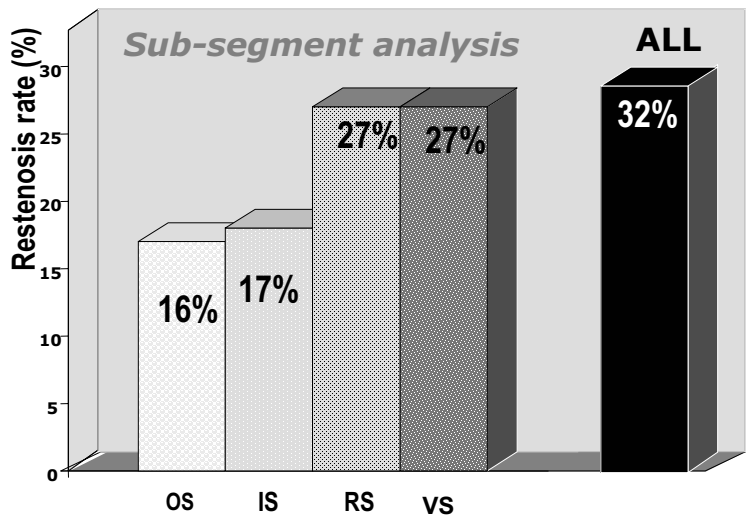



**Fig 2**

**Event-free survival at 1 year follow-up**

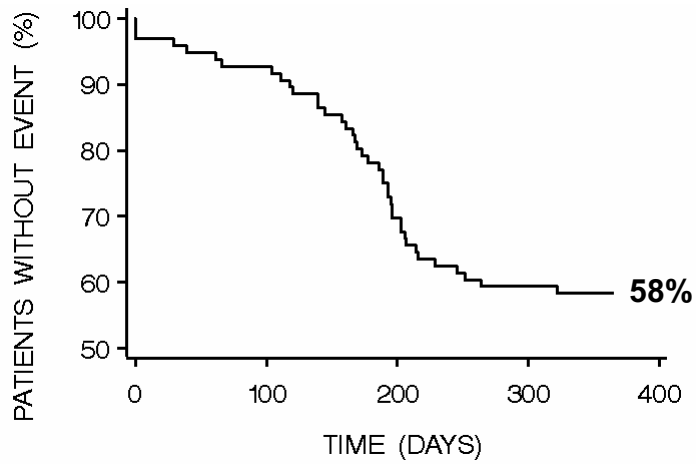



**Fig 3**

## PART 1: IONIC RADIATION THERAPY

*Chapter 8*

van der Giessen WJ, *Regar E*, Harteveld M, Coen VLMA, Bhagwandhoe R, Au A, Levendag PC, Ligthart J, Serruys PW, den Boer A, Verdouw PD, Boersma E, Hu T, van Beusekom HMM:

**THE "EDGE-EFFECT" OF P-32 RADIOACTIVE STENTS IS CAUSED BY THE COMBINATION OF CHRONIC STENT INJURY AND RADIOACTIVE DOSE FALL-OFF.**

Circulation. 2001;104:2236-40.

# "Edge Effect" of $^{32}P$ Radioactive Stents Is Caused by the Combination of Chronic Stent Injury and Radioactive Dose Falloff

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***Background***—Radioactive stents have been reported to reduce in-stent neointimal thickening. An unexpected increase in neointimal response was observed, however, at the stent-to-artery transitions, the so-called "edge effect." To investigate the factors involved in this edge effect, we studied stents with 1 radioactive half and 1 regular nonradioactive half, thereby creating a midstent radioactive dose-falloff zone next to a nonradioactive stent-artery transition at one side and a radioactive stent-artery transition at the other side.

***Methods and Results***—Half-radioactive stents (n=20) and nonradioactive control stents (n=10) were implanted in the coronary arteries of Yucatan micropigs. Animals received aspirin and clopidogrel as antithrombotics. After 4 weeks, a significant midstent stenosis was observed by angiography in the half-radioactive stents. Two animals died suddenly because of coronary occlusion at this mid zone at 8 and 10 weeks. At 12-week follow-up angiography, intravascular ultrasound and histomorphometry showed a significant neointimal thickening at the midstent dose-falloff zone of the half-radioactive stents, but not at the stent-to-artery transitions at both extremities. Such a midstent response (mean angiographic late loss 1.0 mm) was not observed in the nonradioactive stents (mean loss 0.4 to 0.6 mm; $P<0.01$).

***Conclusions***—The edge effect of high-dose radioactive stents in porcine coronary arteries is associated with the combination of stent injury and radioactive dose falloff. **(*Circulation*. 2001;104:2236-2241.)**

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

The use of stents has markedly reduced the rate of restenosis after percutaneous coronary interventions.[1,2] To reduce the restenosis rate even further, endovascular radiation therapy with line sources[3–5] or radioactive stents[6–8] was introduced. Although both methods proved very effective in reducing restenosis in the irradiated area, significant new disease was introduced at the edges of the treated lesions, particularly with radioactive stents.[9–12] There is only anecdotal evidence of the substrate of this edge effect.[13] Possible explanations for this edge phenomenon are the stimulation of tissue proliferation[14,15] or excessive extracellular matrix[16,17] by low-dose irradiation, by mechanical injury,[18–20] or by a combination of both. The latter has been described in clinical endovascular radiotherapy as geographic miss.[21] Therefore, we performed an experimental study that aimed to discriminate between these factors (radiation dose falloff, dose falloff plus injury, or injury per se) by using specially designed stents made radioactive over half of their length.

## Methods

### Animal Preparation

Experiments were performed in 10 nonatherosclerotic adult female Yucatan micropigs (20 to 30 kg). The protocol was approved by the Committee on Experimental Animals of Erasmus Medical Center Rotterdam. The day before the procedure, antiplatelet prophylaxis was started with 150 mg clopidogrel (Plavix, Sanofi) and 300 mg aspirin orally. After an overnight fast, the animals were sedated with 20 mg/kg ketamine hydrochloride. Anesthesia was induced with 11 mg/kg thiopental IV (Nesdonal, Aventis). After endotracheal intubation, the pigs were connected to a ventilator that administered a mixture of oxygen and nitrous oxide (1:2, vol/vol). Anesthesia was maintained with 0.5 to 2 vol% isoflurane (Forene, Abbott Laboratories). Intramuscular antibiotic prophylaxis was administered with 200 mg procaine-benzylpenicillin and 250 mg streptomycin. Under sterile conditions, an introduction sheath was placed in the left carotid artery, and 5000 IU heparin was administered. A guiding catheter was advanced to the ascending aorta. Activated partial thromboplastin time was measured at regular intervals and kept at >3 times normal values. After measurement of arterial blood pressure, heart rate, and blood gases, coronary angiography was

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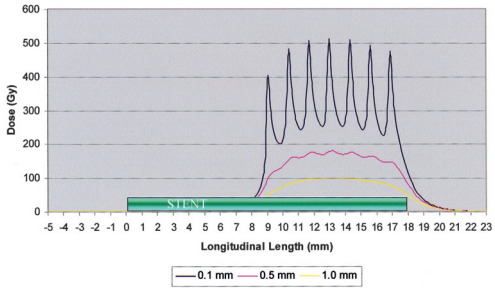


**Figure 1.** Schematic of stent radioactivity. Colored lines at radioactive stent half are cumulative isodose lines at a distance of 0.1 (black), 0.5 (pink), and 1.0 (yellow) mm from stent struts over a period of 12 weeks.

performed with iomeprol (Iomeron 370, Bracco-Byk) as contrast agent.

## Half-Radioactive Multi-Link Stent

Regular 18-mm-long Multi-Link Duet stents (Guidant) were made radioactive with $^{32}P$ ($\beta$-emitter, half-life 14 days) over half of their length in the Forschungszentrum Karlsruhe GmbH, Germany. This yielded 1 radioactive half of 0.9 $\mu$Ci/mm stent length (range 7.2 to 9.0 $\mu$Ci/9 mm) and 1 nonradioactive half (Figure 1). Stents were crimped onto dedicated balloons (3.0 mm in diameter) designed with so-called short transitional edge protection (STEP) technology to limit balloon-induced damage outside the stented segment (Figure 2). Half-radioactive stents with the radioactive part directed distally or proximally on the balloons, as well as nonradioactive control stents, were provided sterile, covered by a polymeric shielding, and encoded to allow for random implantation.

## Stent Implantation and Quantitative Coronary Angiography

A segment with a diameter of 2.7 to 3.0 mm was selected in each coronary artery by use of quantitative coronary angiography (QCA) (CAAS II, PIE Medical). Thereafter, 2 half-radioactive stents (1 hot-distal and 1 hot-proximal) and 1 control stent per animal were randomly implanted in different vessels at 8 atm balloon inflation pressure, aiming at a balloon-to-artery ratio of 1.1:1. After repeat angiography of the stented coronary arteries, the catheter and introducer sheath were removed, and the arteriotomy and the skin were closed. Animals received 300 mg aspirin and 75 mg clopidogrel daily during follow-up. After 4 and 12 weeks, QCA was repeated in the same projection.

## 3D Intracoronary Ultrasound Analysis

Intravascular ultrasound (IVUS) image acquisition was performed at 12-week follow-up with a 30-MHz mechanical system (ClearView, CVIS, Boston Scientific Corp). Motorized catheter pullback was ECG-gated (peak of the R wave) to eliminate motion artifacts (EchoScan, Tomtec). 3D volumetric lumen volume and neointimal volume were assessed with a semiautomatic contour detection program.[22] Data are given as volumes normalized to 1 mm stent length ($mm^3/mm$) to allow for direct comparison of zones of different lengths.

## Histomorphometry

The coronary arteries were pressure-fixed in situ and processed for microscopy as described.[23] After ≥7 half-lives of 14 days, the embedded stents were cut into equal longitudinal halves after alignment under fluoroscopic control. Thereafter, the specimens were placed on radiochromic film for 48 hours to allow identification of the radioactive part and the individual radioactive struts (Figure 3).

The neointima on top of the individual stent struts was measured on en-bloc toluidine blue–stained specimens with a microscopy image analysis system (Impak C, Clemex Technologies). The distance between the endothelial lining and the stent strut or internal elastic lamina was taken as the thickness of the intima.

After completion of morphometric analysis, transverse thin sections were cut for qualitative histological examination. Hematoxylin-eosin was used as routine stain, and resorcin-fuchsin was used as elastin stain.

## Definition of Subsegments

The stented vessel was divided into subsegments that were defined as follows (the stent spanned a distance from 0 to 18 mm, Figure 1): Reference zone: proximal (−5 to −3 mm) or distal (21 to 23 mm) vessel segment adjacent to the stent and not affected by radiation or balloon injury. Hot transition zone: zone between radioactive half and reference zone (17 to 21 mm). Hot zone: radioactive stent segment with full dose (10 to 16 mm). Mid zone: zone connecting nonradioactive and radioactive stent half (7 to 10 mm). Cold zone: nonradioactive segment within the stent (2 to 6 mm). Cold transition zone: between nonradioactive half and reference zone (−3 to 1 mm).

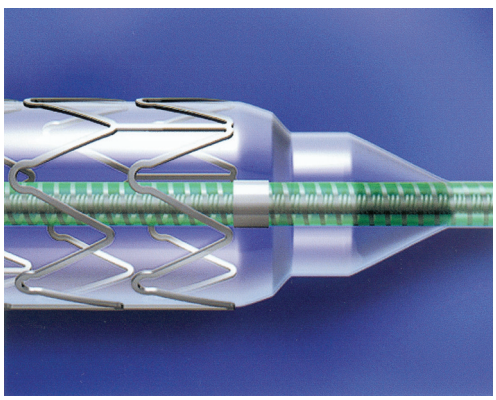

**Figure 2.** Detail of delivery balloon system (STEP technology), which was designed to prevent balloon-induced damage outside stent-covered area (magnification ×20).

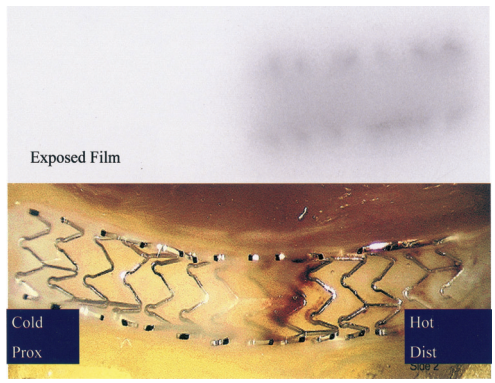


**Figure 3.** Explanted stents were embedded in plastic, cut longitudinally (bottom), and placed on radiochromic film for 48 hours. After processing of exposed film (top), radioactive half and individual radioactive struts of stents could be identified (magnification ×9).

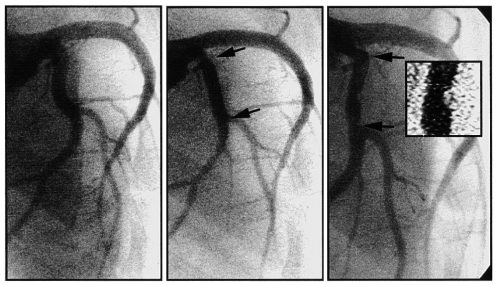

**Figure 4.** Angiograms taken (left to right) before, directly after, and 12 weeks after stent implantation (between arrows) in left circumflex coronary artery. Inset on right shows detail of mid-stent narrowing.

### Statistical Analysis

Data were expressed as mean±SD. Angiographic data were analyzed by 2-way repeated-measures ANOVA followed by post hoc Dunnett's test. Histological data were analyzed by 2-way ANOVA and Dunnett's test. For these parameters, a value of $P<0.05$ was considered statistically significant, because Dunnett's test corrects for repeated testing. IVUS data were analyzed by 2-way ANOVA and unpaired $t$ test. Because of repeated comparisons, a value of $P<0.01$ was considered statistically significant. Sigmastat and SPSS statistical software were used.

## Results

### Stent Implantation and Follow-Up

Stents were placed in 10 animals. One animal died at the end of the procedure of respiratory insufficiency. Final analysis was therefore performed in 9 animals.

At 4 weeks, angiography showed a reduction in lumen at the mid zone in all half-radioactive stents, but not in control stents (Figure 4). Two animals were killed to examine this phenomenon. Between 4 and 12 weeks, 2 animals died suddenly. Postmortem examination showed a thrombotic occlusion at the narrowed mid zone of the half-radioactive stent in the LAD. Five surviving animals remained for angiographic, IVUS, and histological examination at 12 weeks.

### Radioactivity of Stents After Explantation

Exposure of radiochromic film by the embedded stent specimen revealed the activity of the individual stent struts (Figure 3). Typically, per half-radioactive stent, 7 struts per longitudinal cross section were identified as hot, and the remaining 7 struts were identified as cold.

### QCA Measurements

QCA showed similar lumen diameters of the arteries with half-radioactive or control stents at baseline (Table). Average balloon size was 2.8±0.1 mm, and balloon-to-artery ratio was 1.1±0.1. After stenting, the vessels measured 2.8±0.1 mm, and no differences between groups were observed.

At 4 weeks, both types of half-radioactive stents showed a significantly smaller lumen diameter of 1.9 mm in the mid zone versus 2.4 mm in the cold and hot parts of the same stents ($P<0.05$). The mean diameter of the control stents was 2.3±0.3 mm, and in the midstent zone, 2.1±0.4 mm ($P$=NS).

Control stents showed no change in lumen diameter between 4- and 12-week data (2.2±0.4 mm). In the half-radioactive stents, however, a significant further decline of diameter at the mid zone could be observed. For the "proximal-hot" and the "distal-hot" stents, mid-zone diameters were 1.5±0.3 mm and 1.5±0.9 mm, respectively ($P<0.05$ versus control).

### 3D IVUS

IVUS examination at 12 weeks showed no difference in neointimal volume of the control stent (3.2±3.5 $mm^3$/mm stent), cold zones (4.5±3.9 $mm^3$/mm), and hot zones (2.0±1.3 $mm^3$/mm). At the mid zones of the half-radioactive stents, however, a significant increase in neointimal volume was observed (6.0±3.5 $mm^3$/mm; $P<0.01$).

### Histopathological Examination

#### *Macroscopy*

The half-radioactive stents, but not the control stents, explanted after 4 and 12 weeks all demonstrated narrowing at the mid zone (Figure 5). Specimens retrieved from animals that died suddenly showed thrombotic occlusion at narrowed mid zones of LAD stents.

#### *Microscopy*

Both control stents and cold zones of the half-radioactive stents showed the typical appearance of a stented normal artery: mild to moderate intimal thickening consisting of smooth muscle cells (SMCs) in extracellular matrix with

**Mean Angiographic Diameter of Arteries Receiving Stents With the Proximal Half-Radioactive, Distal Half-Radioactive, and Control Stents**

| | Proximal Half Radioactive | | | Distal Half Radioactive | | | Control | | |
|---|---|---|---|---|---|---|---|---|---|
| | Hot-Prox | Mid | Cold-Dist | Cold-Prox | Mid | Hot-Dist | Prox | Mid | Dist |
| Baseline | 2.63±0.22 | 2.50±0.22 | 2.46±0.26 | 2.71±0.31 | 2.65±0.37 | 2.85±0.31 | 2.66±0.22 | 2.60±0.15 | 2.57±0.16 |
| Post | 2.72±0.10 | 2.69±0.09 | 2.72±0.11 | 2.87±0.11 | 2.81±0.13 | 2.84±0.10 | 2.85±0.14 | 2.75±0.14 | 2.83±0.13 |
| 4 wk | 2.46±0.27 | 1.96±0.34* | 2.55±0.19 | 2.34±0.29 | 1.82±0.51* | 2.54±0.30 | 2.34±0.30 | 2.09±0.41 | 2.25±0.32 |
| 12 wk | 2.21±0.23 | 1.56±0.34*† | 2.13±0.37 | 2.21±0.55 | 1.54±0.96*† | 1.95±0.61 | 2.24±0.37 | 1.95±0.41 | 2.13±0.41 |

Prox indicates proximal; dist, distal. Per group, the data of 3 zones within the stents (hot zone, mid zone, and cold zone) are shown. Values are in millimeters (mean±SD).

*$P<0.05$ mid zone vs cold and hot zone.

†$P<0.05$ vs control.

**Figure 5.** Overview of a longitudinally cut stent stained en block with toluidine blue. Mid zone between cold and hot zones (dotted line) shows clearly localized narrowing consisting of intimal tissue.

sparse inflammatory cells and covered by continuous endothelium (Figure 6A).

The mid zone of the half-radioactive stents was characterized by tissue appearing in a specific order (Figure 6B). From cold to hot: (1) enlarged cells with nuclear atypia (as previously described in association with radiotherapy[24]); (2) a steep increase in neointima containing SMCs in disarray within abundant extracellular matrix, dispersed macrophage foam cells, and amorphous proteinaceous material (edema) infiltrated by leukocytes. Endothelialization and neointimal cellularity decreased in parallel toward the hot zone; and (3) a sharp decrease in intimal thickness with a concomitant change to immature granulation tissue after reaching the first hot stent strut.

The hot zone generally showed immature granulation tissue of variable thickness containing amorphous proteinaceous material with few endothelial cells and a diffuse inflammatory response (Figure 6C). The intima-media border zone contained areas with barely organized thrombotic material (especially overlying stent struts).

The hot transition zone showed asymmetrical intimal thickening with incomplete endothelialization and characteristic pathological features: barely organized thrombotic material overlying the stent struts and the intima-media border zone, foam cells in the intima-media border zone, proteinaceous material infiltrated by leukocytes that composed the body of the intima, arborizing SMCs within an abundant extracellular matrix that composed the body of the intima and luminal border zone, and hypertrophic cells with nuclear atypia scattered throughout the intima and media. Normal vascular architecture returned in both control and half-radioactive stents within 2 mm from the stent edges.

***Morphometry***

Comparison of the mean neointimal thickness over the struts in the cold zone (struts 2 to 5) and the hot zone (struts 10 to 13) with the mid zone struts (struts 7 and 8) showed a significantly larger amount of neointima in the mid zone ($P<0.05$; Figure 7). Also, the difference between the maximal neointimal thickness of the half-radioactive mid zones ($0.65\pm0.06$ mm) and the control stent mid zones ($0.40\pm0.08$ mm) was significant ($P<0.05$).

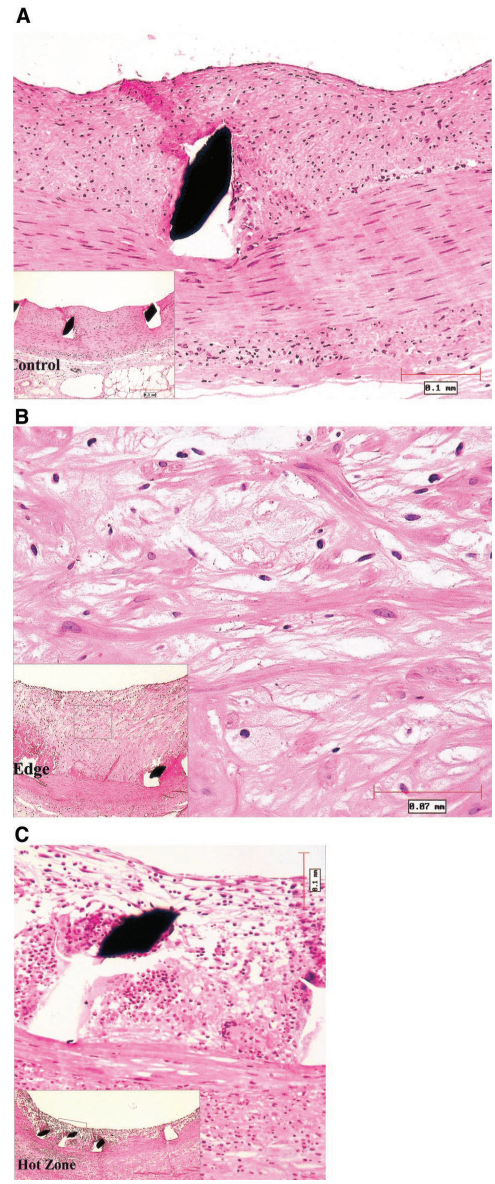


**Figure 6.** Light microscopy of 3 distinctive zones. Control (cold zone, A) shows typical appearance of a normal stented porcine artery. In contrast, mid zone (B, edge) shows extensive intimal thickening containing SMCs in disarray with abundant extracellular matrix. Hot zone (C) shows immature granulation tissue.

## Discussion

### Radioactive Stents Reduce Restenosis but Are Susceptible to Edge Renarrowing

In-stent restenosis is the main limitation of coronary stenting and is caused predominantly by neointimal hyperplasia.[18–20,25] Stud-

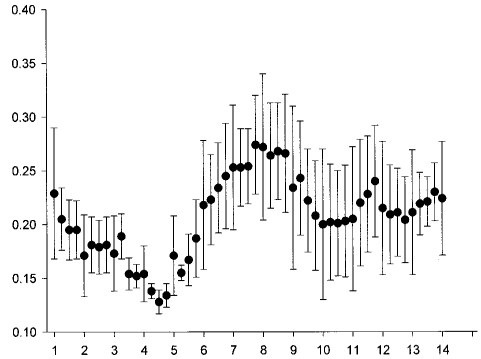


**Figure 7.** Morphometric analysis per stent strut. Data of half-radioactive stent arteries were pooled; their radioactive struts are struts 7 to 14 (horizontal axis). Data for neointimal thickness (vertical axis) are expressed in millimeters (mean±SD).

ies with radioactive $^{32}P$ stents showed that tissue response within the stent was markedly reduced but revealed a significant renarrowing at the edges of the implant.[9,11,12] IVUS studies in stented arteries treated with catheter-based brachytherapy demonstrated negative remodeling and neointimal thickening at the edges of the irradiated zone.[26] In the absence of geographic miss, however, stent edge effects were rare. In radioactive stents, however, the incidence of edge restenosis was considerably higher than after catheter-based brachytherapy, especially at doses that reduced in-stent hyperplasia. The present study was designed to gain insight into the mechanism of this edge effect. To that purpose, we studied different configurations of stents and $\beta$-radiation in a half-radioactive stent model. This stent on the STEP balloon allowed us to compare the tissue responses to stent-induced injury, full-dose radiation, radiation falloff, and their combination at 3 distinct transition zones.

### Main Findings

In the present study, a moderate reduction of lumen diameter in the control, nonradioactive stents was observed, which was evenly distributed over the length of the stent. In contrast, the half-radioactive stents showed a maximal reduction of lumen diameter at the mid zone. This increased tissue response at the midstent zone exceeded that at the stent edges and demonstrated distinct histopathological features, such as an increased amount of extracellular material and thrombus, features recently described in a human case report.[13]

### Effect of Injury and Low-Dose Radiation on Neointimal Hyperplasia

The mid-zone hyperplasia coincided with the presence of the stent and a sharply decreasing radioactive dose level. Each of these can promote cellular proliferation. The stent does so by inflicting chronic injury, causing inflammation and tissue proliferation.[27,28] Low-dose radiation (±2 Gy) has been shown to potentiate cellular metabolic activities[29] and immunological responses in various cells of mesodermal origin.[30–33] Furthermore, experimental studies of endovascular brachytherapy have shown that relatively low doses (±10 Gy) caused a paradoxical increase in tissue response,[14,15] whereas higher doses proved antiproliferative. In a model of concanavalin-induced proliferation, low-dose radiation enhanced the tissue response.[30] Combining the chronic mechanical irritation by the stent with low-dose radiation also had an additive effect on tissue proliferation in the present study. These findings suggest that low-dose radiation catalyzes the tissue response to pro-proliferative factors. To the best of our knowledge, low-dose radiation alone was never able to induce such a degree of tissue proliferation in normal tissue. The fact that significant neointima was not observed at the transition from hot stent half to artery underscores this.

Our results indicate that edge effects of radioactive stents may be avoided by limiting arterial trauma at the edges of the stent combined with measures to effectively irradiate the first 2 to 3 mm outside the stent extremities. The former could be done by using dedicated delivery systems or by manufacturing thinner and more flexible stent edges. The latter might be achieved by use of more penetrating radiation qualities, such as $\gamma$-radiation.

### Conclusions

This study demonstrates that the combination of radioactive dose falloff and the presence of stent material in the artery wall may be responsible for the edge restenosis that limits the efficacy of radioactive stents in the clinical setting. Further studies on the relationship between radiation dose and tissue response may enhance our understanding of the balance between tissue radiosensitivity, arterial injury, and effective radiation dose.

## Acknowledgments

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## PART 2: NON-IONIC RADIATION THERAPY

*Chapter 9*

*Regar E,* Thury A, van der Giessen WJ, Sianos G, Vos J, Smits PC, Carlier SG, de Feyter P, Foley DP, Serruys PW:
**SONOTHERAPY, ANTI-RESTENOTIC THERAPEUTIC ULTRASOUND IN CORONARY ARTERIES - THE FIRST CLINICAL EXPERIENCE IN EUROPE.**
Cathetet Cardiovasc Intervent. Accepted for publication.

# SONOTHERAPY, ANTI-RESTENOTIC THERAPEUTIC ULTRASOUND IN CORONARY ARTERIES - THE FIRST CLINICAL EXPERIENCE.

Regar E, Thury A, van der Giessen WJ, Sianos G, Vos J, Smits PC, Carlier SG,
de Feyter P, Foley DP, Serruys PW

*Cathetet Cardiovasc Intervent. Accepted for publication*

## SYNOPSIS

We studied the safety and feasibility of intracoronary sonotherapy (IST) and its effect on the coronary vessel at 6 months.
37 patients with stable or unstable angina were included (40 lesions). The indication was de-novo lesion (n=26), restenosis (n=2), in-stent restenosis (n=11) and a total occlusion of a venous bypass graft. After successful angioplasty, IST was performed using a 5F catheter with 3 serial ultrasound transducers operating at 1MHz. IST was successfully performed in 36 lesions (success rate 90%). IST exposure time per lesion was 718±127sec. During hospital stay, one patient died due to a bleeding complication. At 6-month follow-up, 1 patient experienced acute myocardial infarction, 8 patients underwent repeat PTCA. No patient underwent CABG. Late lumen loss was 1.05±0.70mm with a restenosis rate of 25%. IVUS analysis revealed a neointima burden of 25±11%.
IST can be applied safely and with high acute procedural success. Sonotherapy-related major adverse events were not observed. Late lumen loss and neointimal growth was similar to conventional PTCA approaches. These results justify the initiation of randomized, clinical efficacy studies.

## INTRODUCTION

Restenosis remains the major limitation of catheter-based coronary interventions. Restenosis is considered as a local biologic response to catheter-induced injury. Current concepts describe three mechanisms of the restenotic process: early elastic recoil, late vessel remodeling and neointimal growth[1,2]. Neointima is basically an accumulation of smooth muscle cells within a proteoglycan matrix that narrows the previously (by injury) enlarged lumen.
Coronary stents provide mechanical scaffolding that virtually eliminates recoil and remodeling[3]. However, stents do not reduce neointimal growth. Intracoronary radiation therapy has been employed to decrease smooth muscle cell proliferation and neointimal formation. However, restenosis rates in the treatment arm of randomized brachytherapy studies are still in the range of 15-30% for de novo lesions[4,5] and approximately 30 % for in-stent restenotic lesions[6,7].
We describe the clinical application of a new treatment concept to prevent neointimal growth, that of high intense ultrasound. In vitro studies demonstrated that ultrasound can reduce mammalian cell viability[8] and inhibit smooth muscle cell migration, adhesion[9,10] and proliferation[11]. In a swine peripheral stent model[12] it was shown at seven days after stent implantation, that cellular proliferation was significantly reduced in the IST group compared with the sham group.
The aim of our study was to study the safety and feasibility of intracoronary sonotherapy (IST) using a catheter-based approach and to analyze the effect on the coronary segment at six months.

## METHODS

### Patients

The patient population consisted of patients included between January and June 2000 in the multi-center "Sonotherapy for In-Lesion Elimination of Neointimal Tissue" (SILENT) study[13] at our institution and of patients of the single-center COMPASSIONATE USE registry. The SILENT trial is designed to assess the safety of catheter-based intravascular sonotherapy for the treatment of newly stented coronary arteries. Patients were eligible if they presented with stable angina, an objective proof of ischemia and a single de

novo or non-stent restenosis lesion in a native coronary artery. The COMPASSIONATE USE trial is a safety and feasibility protocol in complex lesions. Patients were included if they presented with stable or unstable angina and de-novo or restenotic lesions in one or multiple coronary vessels.

**Angioplasty procedure**

Angioplasty was performed using routine procedures with commercially available systems and 7F guiding catheters by femoral approach. In the SILENT cohort, coronary balloon angioplasty and stent implantation were performed according to standard clinical practice. In the COMPASSIONATE USE cohort, debulking procedures, cutting balloon and stent implantation were performed according to standard clinical practice. Balloon-expandable stents were used, only.

**Sonotherapy equipment**

The intracoronary sonotherapy (IST) system (PharmaSonics Sonotherapy™ system, Sunnyvale, CA) consists of an IST catheter connected to the IST user console. The IST catheter is a 5F, over the wire catheter compatible with standard o.o14 inch guide wires and 7F guiding catheters. The IST-catheter has 3 serial ultrasound transducers (1MHz) at the distal tip. Each transducer has a length of 6mm, the gap between the transducers is 4mm (FIGURE 1).

**Sonotherapy procedure**

After successful angioplasty procedure, the IST catheter was introduced. The IST catheter was placed in such a way, that the most distal transducer covered the injured lesion site. The catheter was activated for 5 minutes by pushing the activation button at the proximal end of the IST catheter. Then, the IST catheter was carefully withdrawn to cover the gaps between the transducers (FIGURE 2) and again activated. The pullback procedure was repeated two to three times to allow for complete coverage of the treated segment, whereby anatomical landmarks (e.g. calcification spots, side branches) and the radiopaque stents were used for topographic orientation. The position of the table and image intensifier were not changed between angioplasty and IST.

**Concomitant medication**

The patients received aspirin (250 mg) and heparin i.v. (10.000 U) before the procedure. The activated clotting time was measured every 30 min and intravenous heparin was given to maintain an activated clotting time > 300 sec.

Before the introduction of the IST catheter 2mg ISDN i.c. was given to avoid coronary spasm and angina. Clopidogrel was administered at the day of procedure with a loading dose of 300mg and continued after the procedure for a period of 2 months at a dose of 75mg daily. Aspirin was given at conventional dose daily indefinitely.

**Angiographic analysis**

All angiograms were evaluated after intracoronary administration of nitrates. Quantitative coronary analysis was performed using the PHILIPS system (Philips, NL). To analyze the impact of sonotherapy on the vessel, the following sub-segments were defined (FIGURE 4):

| | |
|---|---|
| Vessel segment (VS) | segment bordered by angiographically visible sidebranches, which encompass the originally obstructed segment, all angioplasty devices and the sonotherapy transducers. |
| Lesion segment (LS) | defined by the proximal and distal margin of the original obstruction. |

| | |
|---|---|
| Treated segment (TS) | segment encompassed by the most distal and the most proximal position of the radiopaque sonotherapy transducers. |

Within the VS, the minimal lumen diameter (MLD) was defined by edge detection, the reference diameter (RD) at the site of MLD was automatically calculated by the interpolated method. The diameter stenosis (DS) was calculated from the MLD and RD.
At follow-up, the position of the MLD and the site of restenosis within the sub-segments were analyzed. Restenosis was defined as >50% diameter stenosis at follow-up and classified as discrete (<10mm length) or diffuse (> 10 mm length)[14].

**Intracoronary ultrasound (IVUS) analysis**
IVUS image acquisition and analysis has been described in detail[15]. In brief, IVUS was performed with a mechanical 30MHz single element transducer system (CVIS, Boston Scientific Corp, Maple Grove, MN) or a 20MHz phased array system (Endosonics, Rancho Cordova, CA). Motorized catheter pullback was performed after intracoronary administration of isosorbide dinitrate (2mg). For volumetric analysis, a Microsoft-NT based semi-automatic contour detection program was used. Volumetric data were calculated by means of the Simpson's rule. Neointima volume was calculated as difference between stent volume and lumen volume, neointima burden as neointima volume divided by stent volume. Patients with restenosis, in whom it was not possible to cross the lesions before predilatation where excluded from this analysis.

**Clinical follow-up**
We assessed the incidence of major adverse cardiac events (MACE) during hospital stay and at 6 months. MACE included death, acute myocardial infarction and repeat revascularization of the target vessel by coronary artery bypass graft (CABG) or RePTCA. A diagnosis of acute myocardial infarction was made when a least 2 of the following occurred: History of chest discomfort for at least 30 min duration, enzyme changes defined by more than twice the upper limit of normal creatin kinase and the presence of MB iso-enzyme twice greater than the upper limit of normal, the development of a new abnormal Q-wave (> 0.4 sec) on ECG.

**Statistical analysis**
All statistical analysis was performed with commercially available software (SPSS 10.0, SPSS Inc. Chicago, Illinois). Data are presented as mean ± standard deviation, median and interquartile range or proportions. A p-value <0.05 was considered statistically significant.

## RESULTS

**Patients baseline characteristics**
A total of 37 patients was included (n=24 SILENT trial; n=13 COMPASSIONATE USE) with treatment of 40 lesions. In 35 patients single vessel treatment was carried out, in one patient all three major epicardial arteries were treated, in another patient 2 vessels were treated. The patient's baseline characteristics are given in TABLE 1. The population showed typical age, gender and coronary risk factor distribution. A relatively high proportion of patients (54%) presented with unstable angina.

**Lesion characteristics and angioplasty procedure**
The angioplasty procedure was performed in 26 vessels with de-novo lesions, in 2 vessels with

restenosis, in 8 vessels with in-stent restenosis, in 1 vessel with in-stent restenosis after radioactive stent implantation, in 2 vessels with second in-stent restenosis after earlier treatment with beta-radiation and in a total occlusion of a venous bypass graft.
The lesions were located in the LAD (n=18), LCx (n=9) and RCA (n=12), CABG (n=1). The lesion were predominantly type C (n=13; 33%), type B2 (n=10; 25%), type B1 (n=10; 25%) and type A (n=7; 18%).
Angioplasty was successfully performed in all 40 lesions. Six lesions were treated with cutting balloon and in 31 lesions a new stent was additionally implanted. A mean of 1.28±0.6 stents/lesion were used, the mean stent length was 22.8±8.1mm. Glycoprotein IIb/IIIa antagonists were administered in 17 (46%) patients. Mean procedural time was 88±35min. One patient experienced an abrupt vessel closure after balloon dilatation in a heavily calcified lesion due to type E dissection, which was successfully treated with implantation of a stent before sonotherapy was performed. The patient developed an acute myocardial infarction with a maximum rise in creatin kinase to 536 IU (CK-MB 65 IU). The further clinical course of this patient was uneventful.

**Sonotherapy success**
Sonotherapy was successfully performed in 36/40 lesions (sonotherapy success rate 90%). Mean IST activation was 2.6±0.8 times, the mean exposure time was 718±127sec. Three patients were unable to be treated due to technical difficulties (n=1) or inability to cross the stented lesion with the IST catheter (n=2). In another patient, IST had to be interrupted due to severe angina and ischemia documented by ECG.
In 2 patients, the manipulation of IST catheter caused a coronary dissection. In one patient a non-flow limiting, retrograde type B dissection did not require further treatment. In another patient, a type D dissection proximal to a new implanted stent necessitated the additional implantation of a stent following sonotherapy.

**In-hospital events**
In-hospital major adverse cardiac events are summarized in TABLE 2. One patient died due to massive internal bleeding. Another patient developed a transient ischemic attack (TIA) at 24 hours after the procedure. During hospital stay no repeat intervention occurred.

**Six month outcome**
Clinical follow-up time was 222 [180; 282] days. The major adverse cardiac events are summarized in TABLE 3. Eight patients underwent repeat PTCA of the target vessel. Of these, PTCA was performed in 6 cases at the target lesion and in 2 cases in de-novo lesions further distally in the target vessel. No patient underwent CABG.

**Angiographic analysis**
At baseline, the pre-intervention lesion length was 14.1±6.7mm, RD 2.88±0.55mm and MLD 0.85±0.56mm with a DS of 73±15%. After the intervention, RD was 3.19±0.52mm, MLD 2.60±0.51mm and the residual DS 18±13% for the overall group (n=40 vessels).
At follow-up, quantitative angiographic data were available in 28/37 (76%) patients (TABLE 4). The length of the VS was 48±16mm, of the TS of 32±15mm and of LS 13±5mm. The position of MLD at follow-up was located within the LS in 16 (57%) vessels, in 8 (29%) vessels outside the LS, but within the TS and in 4 (14%) vessels distal to the TS.
Restenosis occurred in 7 vessels (25%). The range of diameter stenosis was 51%-86%. In these vessels, the maximal lumen obstruction was located at the LS in 5 cases and outside the LS, but within the TS in 2 cases. We observed predominantly discrete restenosis pattern (n=7), only one lesion showed diffuse

restenosis.

**IVUS analysis**

IVUS data at follow-up were available in 17 patients. IVUS showed a uniform coverage of the stents with neointimal tissue over the complete length. Volumetric analysis revealed a stent volume of 199±65mm$^3$, a vessel volume of 363±128mm$^3$, and a lumen volume of 149±56mm$^3$. The neointima volume was 50±22mm$^3$, and the neointima burden 25±11%.

## DISCUSSION

**Therapeutic delivery of ultrasound energy**

Ultrasound energy offers theoretically several advantages. First, high intense ultrasound has proven to be a powerful and safe therapy in other medical disciplines. Second, ultrasound energy appears to be safe for the normal vessel wall. Catheter based therapeutic ultrasound used for clot dissolution[16-18] and plaque ablation[19,20] has been shown not to damage the normal vessel wall. Third, experimental data have shown various ultrasound effects which could be beneficial for the prevention of restenosis: In-vitro and in-vivo experiments of demonstrated inhibitory effects on smooth muscle cells, which are one of the key factors for neointimal growth. Furthermore, ultrasound energy enhances fibrinolysis[21,22] and thus might affect early thrombus formation as peri-interventional local thrombi release growth factors, which stimulate neointimal hyperplasia[23,24]. Fourth, the handling of ultrasound energy in practice is simple, as it does not require additional protection and shielding measures or additional personnel and logistics (as needed when using ionizing radiation).

We hypothesized, that the delivery of ultrasound energy following standard angioplasty can prevent exaggerated neointimal tissue growth. The main findings of this first clinical study were (1) the catheter-based intracoronary application of high intense ultrasound is safe, (2) the sonotherapy success rate is 90% and (3) there were no sonotherapy-related major adverse cardiac events during hospital stay and follow-up.

**Feasibility and safety**

The broad inclusion criteria allowed us, to test the feasibility in a spectrum of highly complex lesions. Intracoronary sonotherapy proved applicable in newly stented lesions, in-stent restenotic and also in bifurcation lesions. During ultrasound treatment, transient signs of coronary ischemia were the most common side effects. This effect is clearly caused by the size of the device (5F) and well described for other diagnostic[25] and therapeutic tools, such as brachytherapy catheters.

During hospital stay, no IST related side effects or complications have been noticed. Similarly, follow-up did not reveal any harmful unwanted IST related effects. One patient experienced periprocedural myocardial infarction due to abrupt vessel closure. However, vessel closure occurred before the introduction of the sonotherapy catheter into the vessel and was clearly not related to IST. Furthermore, we encountered 1 death in our study, the patient died within 24h after the procedure due to internal bleeding under a intravenous GP IIbIIIa antagonist.

**Outcome**

During follow-up, no acute cardiac event occurred and no patient underwent CABG. Six patients underwent target lesion revascularization because of recurrent angina.

**Effect on coronary artery**

At follow-up, the IST treated segments showed a slight lumen loss over the complete length. The late loss was maximal at the site of the original obstruction. Consecutively, the MLD at follow-up was predominantly at the site of the original obstruction or within the IST treated segment. Furthermore, all restenoses occurred within the IST treated segment. There were no edge effects at the adjacent proximal or distal vessel segments. IVUS analysis showed complete coverage of the stents with neointimal tissue. The observed neointima burden of 25% is in the range of conventional balloon expandable stents[3].

These data show (1) that neointimal tissue growth is not completely eliminated, (2) neointimal tissue growths is pronounced at the site of the original obstruction and (3) no unwanted effects at vessel segments adjacent to IST.

**Restenosis**

The comparison of our results with other studies is of only limited value, because our patients represent a population with relatively complex lesions and at high risk for (repeat) restenosis as indicated by the number of stents per lesion[26] and the number of patients with second restenosis due to failed radiation therapy. Furthermore, the study was not designed to test efficacy.

Being aware of these limitations we would like however, to try to put our study in the context of previously published data. In contrast to sonotherapy, preliminary clinical data of drug eluting stents suggest a complete abolition of neointima growth with a restenosis rate of 0% at 6 month after rapamycin eluting stent implantation in short (<18mm) de-novo coronary lesions[27].

After conventional stent implantation a restenosis rate of 13% (95% confidence interval 10%-16%) can be expected in selected, short (<15mm), de novo lesions[28] given the vessel size of 3.12mm and the final angiographic diameter stenosis of 22% while the OPTICUS trial, conducted in a mixed patient population (de-novo and restenotic lesions) showed a restenosis rate of 23%[29]. The initial lesion length (11.6mm) and the length of the implanted stents (21mm) were comparable to our study. The late lumen loss was 1.00±0.58mm, which is similar to our late lumen loss of 1.05±0.70mm. In another study, the outcome after repeat intervention for in-stent restenotic lesions, a repeat restenosis rate of 22% is described[30] whereas in a study of unselected lesions a restenosis rate of 36% is reported[31]. Seen the angiographic and IVUS data, the late lumen loss and neointimal growths in our patients seem similar to conventional approaches.

These results, the potential benefits of a preserved but possibly modulated neointima formation and the absence of known long-term safety issues justify the initiation of randomized, clinical efficacy studies.

**Limitations**

The present study is an observational study in a relatively small number of patients. However, the included lesions represent a wide spectrum of lesion types, which allows for a feasibility assessment under "daily life" conditions. Furthermore, our study is limited by the duration of follow-up. The lack of a dose-response analysis is another limitation.

## CONCLUSION

Intracoronary sonotherapy can be safely applied in the clinical setting with high acute procedural success. In-hospital and during follow-up, no major sonotherapy-related complication was observed. Angiographic and IVUS analysis at 6 months showed a late lumen loss and neointimal growths similar to conventional approaches. These results justify the initiation of randomized, clinical efficacy studies.

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## TABLES

**Table 1: Patients baseline characteristics**

Data are presented as mean ± standard deviation or number (proportion, %) of patients (n=37)

| | |
|---|---|
| Mean age (years) | 59±10 |
| Gender (male) | 26 (70%) |
| Angina status | |
| Stable angina (CCS 1-4) | 17 (46%) |
| Unstable angina | 20 (54%) |
| Cardiovascular risk factors | |
| History of smoking | 10 (27%) |
| Diabetes mellitus | 5 (14%) |
| History of hypertension | 13 (35%) |
| History of hypercholesterolemia | 24 (65%) |
| Pos. Family history of CAD | 11 (30%) |
| Extent of vessel disease | |
| One vessel disease | 29 (78%) |
| Two vessel disease | 1 (3%) |
| Three vessel disease | 7 (19%) |
| History of CABG | 4 (11%) |
| History of myocardial infarction | 10 (27%) |
| History of stroke | 3 (8%) |

CAD Coronary artery disease
CCS Canadian cardiovascular society
CABG Coronary artery bypass graft

**Table 2: Major adverse cardiac events during hospital stay**

Data are given as numbers (no) of events and ranked (ranking) as follows: death, myocardial infarction, CABG, repeat PTCA. Only the worst event is counted for each patient., e.g. if a patient experienced myocardial infarction and later Re-PTCA, myocardial infarction is considered the worst event and is counted.

| Event | No of events* | Ranking |
|---|---|---|
| Death | 1 | 1 |
| Acute myocardial infarction | 1 | 1 |
| CABG | 0 | 0 |
| Repeat PTCA | 0 | 0 |

CABG coronary artery bypass graft
PTCA percutaneous transluminal coronary angioplasty

**Table 3: Major adverse cardiac events at 6 months follow-up**

Data are given as numbers (no) of events and ranked (ranking) as follows: death, myocardial infarction, CABG, repeat PTCA. Only the worst event is counted for each patient., e.g. if a patient experienced myocardial infarction and later Re-PTCA, myocardial infarction is considered the worst event and is counted.

| Event | No of events* | Ranking |
|---|---|---|
| Death | 1 | 1 |
| Acute myocardial infarction | 1 | 1 |
| CABG | 0 | 0 |
| Repeat PTCA | 8 | 7 |

CABG coronary artery bypass graft
PTCA percutaneous transluminal coronary angioplasty

**Table 4: Quantitative angiographic data (for patients who underwent follow-up angiography, n=28 vessels)**

Data are presented as mean ± standard deviation or proportions of lesions

| Parameter | pre | post | fup |
|---|---|---|---|
| MLD (mm) | 1.19±0.58 | 2.77±0.67 | 1.73±0.62 |
| RD (mm) | 3.12±0.65 | 3.53±0.53 | 2.99±0.43 |
| DS (%) | 63±16 | 22±14 | 42±19 |
| LL (mm) | ----- | ----- | 1.05±0.70 |
| Restenosis, n (%) | ----- | ----- | 7 (25) |

| | |
|---|---|
| pre | pre-intervention |
| post | post-intervention |
| fup | follow-up |
| RD | reference diameter |
| MLD | minimum lumen diameter |
| DS | diameter stenosis |
| LL | late lumen loss |

## FIGURE LEGENDS

**Figure 1** Intracoronary sonotherapy (IST) system. The user console (I) is connected to a 5F IST catheter (II). The IST catheter has 3 radioaque serial transducers (1 MHz) at the distal tip (arrows). The length of the transducer is 6mm, the gap between the transducer is 4mm (III) .

**Figure 2** Schematic of the ultrasound energy distribution (I, cross sectional view, II longitudinal view). During clinical application, the IST catheter is initially placed distal into the vessel (IIa) and afterwards withdrawn in such a way, that the gaps between the transducers are covered (IIb) and the vessel is treated uniformly by ultrasound energy (IIc).

**Figure 3** Definition of sub-segments for quantitative coronary analysis. At baseline, the following segments were defined: I) LS=lesion segment, computer-defined by the proximal and distal margin of the obstruction. II) TS=treated segment (TS), defined as the segment encompassed by the most distal (IIa) and the most proximal position of the radiopaque sonotherapy transducers (IIb). III) VS=vessel segment, defined as the segment bordered by angiographically visible sidebranches which encompass the originally obstructed segment, all angioplasty devices and the sonotherapy transducers. These segments were analyzed at six months follow-up (IV).

**Figure 4** Example of a "compassionate use" IST treatment. (I) The patient presented with second in-stent restenosis after failure of intracoronary beta-brachytherapy in the left anterior descending artery. Treatment consisted of directional coronary atherectomy using a 3.5mm device (IIa), postdilatation with a 3.5mm balloon at 18 atm (IIb) followed by IST (2 times 5 minutes; IIc), achieving an angiographic adequate result (III). Six months follow-up angiography showed a good long-term result without lumen narrowing (IV).

-

**Figure 1**

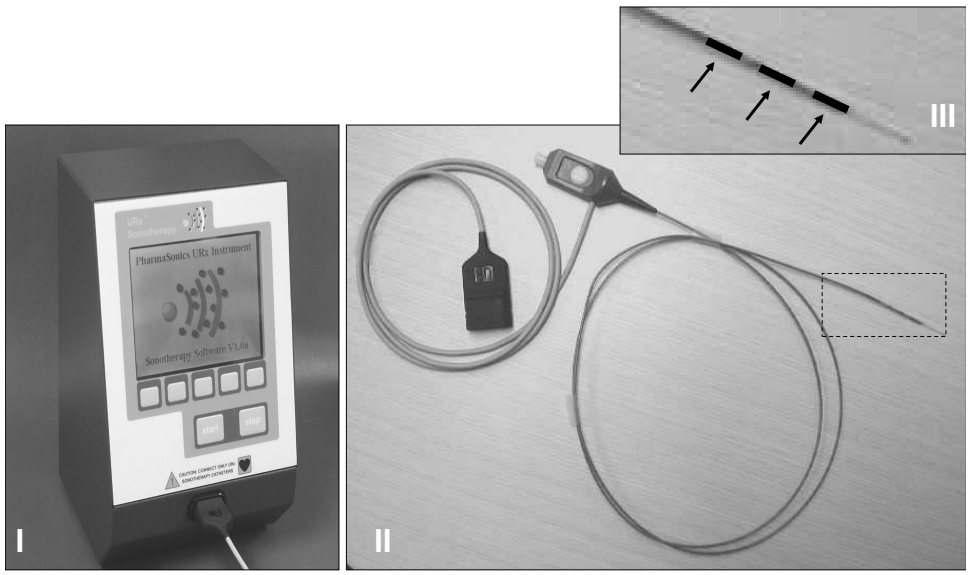



**Figure 2**

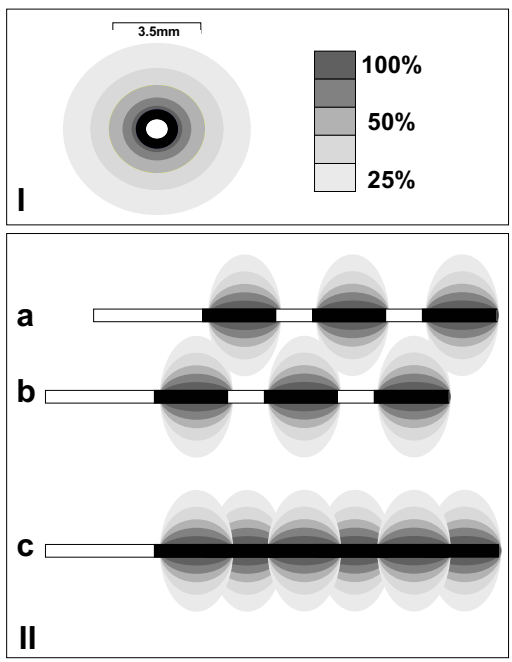


**Figure 3**

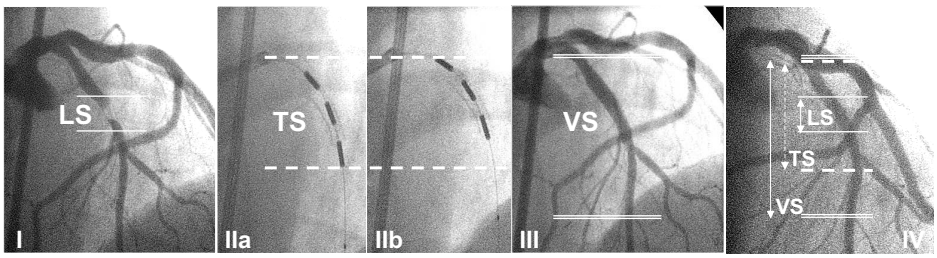
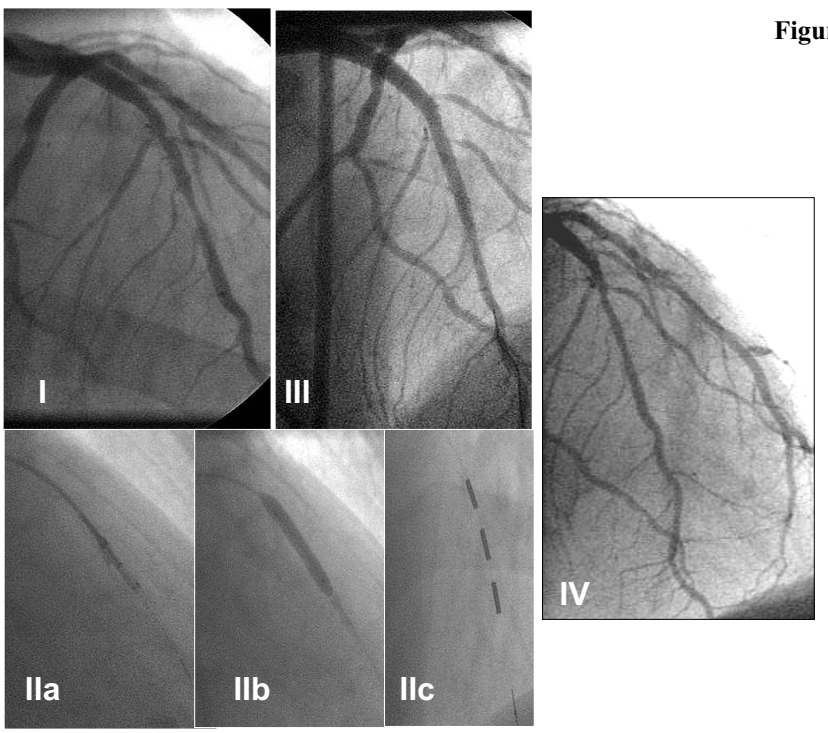



**Figure 4**



## PART 3: DRUG ELUTING STENTS

*Chapter 10*

*Regar E,* Degertekin M, Tanabe K, van der Giessen WJ, Vos J, Smits PC, de Feyter P, Serruys PW:

**DRUG ELUTING STENT.**

In Marco J, Serruys PW, Biamino G, Fajadet J, de Feyter P, Morice MC (Eds): The Paris course on revascularization.

Paris: Europa edition.2002. ISBN 2-913628-07-9.

# Drug eluting stent

**Evelyn Regar, Muzaffer Degertekin, Kengo Tanabe,
Willem van der Giessen, Jeroen Vos,
Peter Smits, Pim de Feyter, Patrick W Serruys**

# Introduction

Over the last decade, coronary stents have revolutionized the field of interventional cardiology. Stent implantation has become the new standard angioplasty procedure[1-3]. However, the long-term success of coronary stenting is hampered by in-stent restenosis. This represents a major problem as the absolute number of in-stent restenotic lesions is constantly increasing in parallel with the steadily increasing number of stenting procedures and as the treatment of in-stent restenosis is, despite progresses in radiation therapy, technically challenging and costly.

In-stent restenosis is caused by exaggerated neointimal formation. Neointimal proliferation is considered as a component of the general vascular response to injury[4,5]. Catheter-induced injury consists in denuding of the intima and stretching of the media and adventitia (Fig 1a, 1b). The wound-healing reaction starts with the inflammatory phase, characterized by platelets, growth factor and smooth muscle cell activation (Fig 1c). The granulation phase is characterized by smooth muscle cell and fibroblast migration (Fig 1d) and proliferation into the injured area (Fig 1e). The remodeling phase is characterized by maturation of the neointima, proteoglycan and collagen synthesis, which replaces early fibronectin as major component of extracellular matrix (Fig 1f)[6].

The risk of in-stent restenosis is associated with patient specific factors such as genetic predisposition or diabetes mellitus[7], lesion specific factors such as vessel caliber[8], lesion length or plaque burden[9] and procedure specific factors such as extent of vessel damage, residual dissections[10], number of stents, minimal stent diameter or minimal stent area[11].

Over the last 2 decades, efforts for the prevention of restenosis were focused on optimizing stent characteristics and implantation technique. All attempts of systemic pharmacological therapy have not been not successful so far[12,13,14].

# Rationale

A proposed explanation for the repeated failure of clinical drug studies has been that agents given systemic cannot reach sufficient levels in injured arteries. Local drug administration offers advantages. The active drug is applied to the vessel at the precise site and at the time of vessel injury. Local drug delivery

Figure 1.

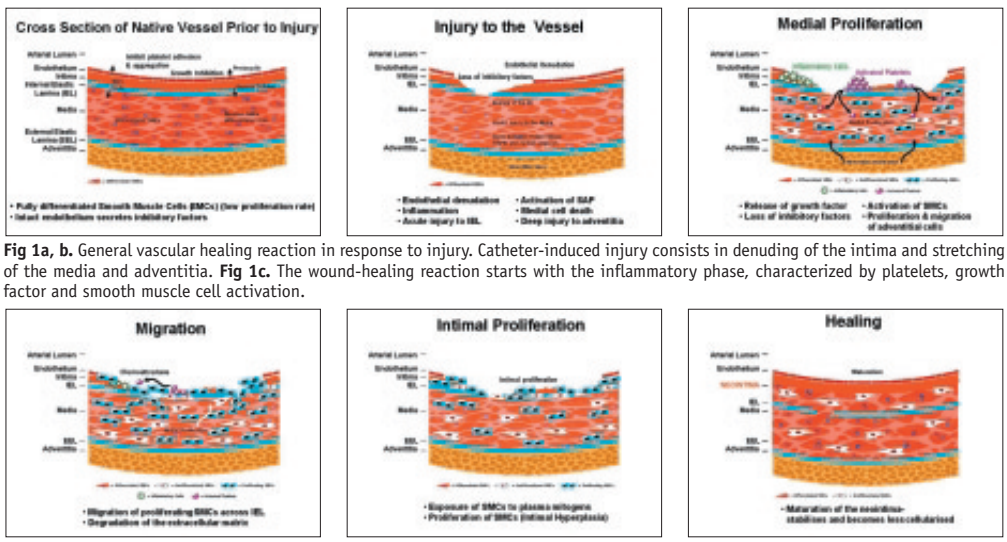



**Fig 1a, b.** General vascular healing reaction in response to injury. Catheter-induced injury consists in denuding of the intima and stretching of the media and adventitia. **Fig 1c.** The wound-healing reaction starts with the inflammatory phase, characterized by platelets, growth factor and smooth muscle cell activation.

**Fig 1d, e.** The granulation phase is characterized by smooth muscle cell and fibroblast migration and proliferation into the injured area. **Fig 1f.** The remodeling phase is characterized by maturation of the neointima, proteoglycan and collagen synthesis, which replaces early fibronectin as major component of extracellular matrix.

is able to achieve higher tissue concentration of the drug. No additional material or procedure is required. Systemic release is minimal and may reduce the risk of remote systemic toxicity.

# The principle

The idea to combine the principle of mechanical scaffolding with that of local pharmacological action emerged early in the stent era. Stent-based antirestenotic therapies were hampered by complex multifactorial cellular and extracellular matrix responses to stent-induced injury, adverse and exaggerated tissue responses to materials bound to stents and the brevity of contact between delivered agents and target vascular tissue.

Polymers have shown conflicting results in the experimental setting[15-17] with some provoking a severe tissue response[18]. A number of other coatings like inert polymer[19], heparin[20-22], or phosphorylcholine[23,24] demonstrated improved biocompatibility and/or a reduction in (sub-) acute stent thrombosis rate. In the clinical practice, however, the acute beneficial effect on stent thrombosis is of minor relevancy as already modern generation uncoated stents show a very low (sub-) acute thrombosis rate. Furthermore, the acute beneficial effect did not translate in a substantial decrease in in-stent restenosis[25]. In response to this, the interest in coatings has shifted towards considering coatings as vehicles for local drug delivery. The goal is the controlled release of an efficient drug from a stable coating.

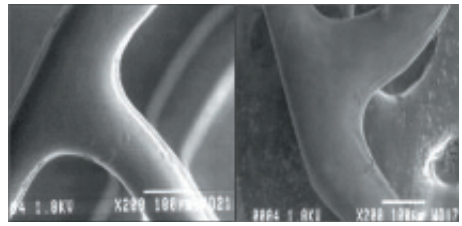
## The delivery vehicles

The delivery vehicle must fulfill pharmacological, pharmacokinetic and mechanical requirements. The release of the drug into the vessel must take place in a manner that is consistent with the drug's mode of action. Drug release must be predictable and in controllable concentration and time spent. The delivery vehicle must be suitable for sterilization, it must follow the geometric change of configuration during stent expansion and resist mechanical injury caused by the inflation of the balloon (Fig 2). Today these problems are controlled, guaranteeing intact coating during clinical application. An overview of delivery vehicles for drug eluting systems is given in Table 1.

**Table 1. Overview of drug delivery vehicles**

- Poly vinyl pyrolidone/cellulose esters
- Poly vinyl pyrolidone/poly urethane
- Poly methylidene maloleate
- Poly lactide/glycoloide copolymers
- Poly ethylene glycol copolymers
- Poly ethylene vinyl alcohol
- Poly dimethyl siloxane (silicone rubber)

**Figure 2.**



Coated stent after sterilization and balloon expansion. The coating follows the symmetric changes of the stent struts without mechanic damage.

## The drugs

The drug should be one that inhibits the multiple components of the complex restenosis process. Uncontrolled neointima tissue accumulation shows some parallels to tumor growths, thus the usage of anti-tumor strategies seems to be a logical consequence. Numerous pharmacological agents with antiproliferative properties have been tested for their potential to inhibit restenosis with mostly disappointing results[26]. Antimitotic compounds like methotrexate and colchicine have failed to inhibit smooth muscle cell proliferation and intimal thickening[27,28]. In these early studies, the drug effect was only limited to the elevation of the polymer vehicle's pro-proliferative action. In contrast, other agents such as angiopeptin[29], GP IIb/IIIa inhibitors[30,31] or steroids[32-34] have shown a promising inhibitory effect on neointimal proliferation. Potential candidates for local drug delivery are given in Table 2. There is a enormous variety of potential drugs, however, not all of them show convincing preclinical results, a prerequisite for clinical testing. The following drugs are now being tested in randomized clinical trials.

### ACTINOMYCIN D (COSMEGEN®)

Actinomycin D (Fig 3) 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). It inhibits the proliferation of cells. Actinimycin D (C62H86N12O16) forms via deoxyguanosins residues a stable complex with double-stranded DNA and inhibits DNA-primed RNA synthesis.

### RAPAMYCIN (SIROLIMUS; RAPAMUNE®)

Rapamycin (Fig 4) is a FDA approved drug for the prophylaxis of renal transplant rejection (Rapamune®) since 1999. It is a naturally occurring macrocyclic lactone which is highly effective in preventing the onset and severity of disease in

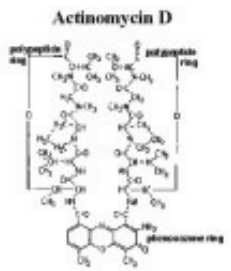
**Table 2. Overview of potential candidates for drug elution**

| | |
|---|---|
| • **Anti-neoplastic** | • **Anti-thrombins** |
| – Paclitaxel (Taxol™) | – Hirudin and Iloprost |
| – Taxol derivative (QP-2) | – Heparin |
| – Actinomycin D | – Abciximab |
| – Vincristine | • Immunosupressants |
| – Methotrexate | – Sirolimus (Rapamycin™) |
| – Angiopeptin | – Tacrolimus (FK506) |
| – Mitomycin | – Tranilast |
| – BCP 678 | – Dexamethason |
| – Antisnese c-muy | – Methylprednisolon |
| – Abbott ABT 578 | – Interferon gamma 1b |
| | – Leflunomide |
| | – Cyclosporin |

**Migration inhibitor/ ECM modulators**
- Halofuginone
- Propyl hydroxylase inhibitor
- C-proteinase inhibitor
- Metalloproteinase inhibitors
- Batimastat

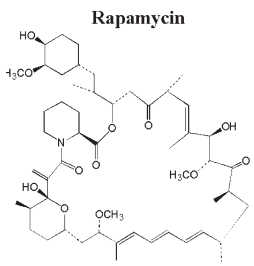
**Enhance healing/Promote endothelial function**
- VEGF
- 17-ß-estradiol
- Tkase inhibition
- BCP 671
- HMG CoA reductase inhibitors

**Figure 3.**




Chemical structure of actinomycin D.

**Figure 4.**



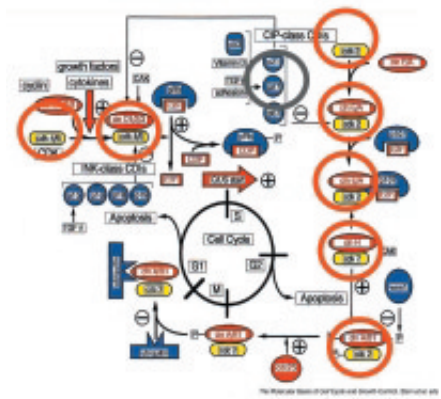

Chemical structure of rapamycin (sirolimus).

several animal models of autoimmune disease, such as insulin-dependent diabetes mellitus, systemic lupus erythematosus and arthritis.

Rapamycin 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 profliferation.

MTOR is a key regulatory kinase. Its inhibition 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. On overview over rapamycin effects within the cell cycle is given in Fig 5. The mechanism of action is distinct from other immunosuppressive drugs that act solely by inhibiting DNA synthesis, such as mycophenolate mofetil (CellCept) and azathioprine (Imuran). Rapamycin is synergistic with cyclosporin A and has much lower toxicity than other immunosupressive agents.

**Figure 5.**

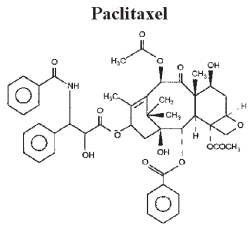



Overview of cellular mechanisms of action of rapamycin (sirolimus).

## Paclitaxel (Taxol®)

Paclitaxel (Fig 6) 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.

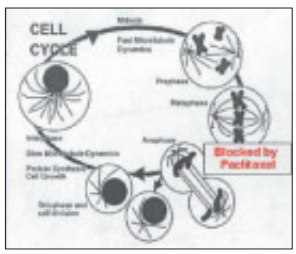
**Figure 6.**




Chemical structure of paclitaxel.

It is a diterpenoid with a characteristic taxane-skeleton of 20 carbon atoms and has a molecular weight of 853.9 Daltons. Paclitaxel exerts its pharmacological effects through formation of numerous decentralized and unorganized microtubules (Fig 7). This enhances the assembly of extraordinarily stable microtubules, interrupting proliferation, migration and signal transduction[35,36]. Unlike other anti-proliferative agents

**Figure 7.**




Cellular mechanisms of action of paclitaxel.

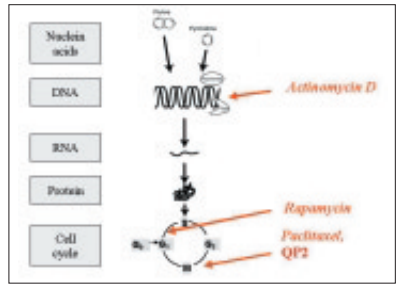
of the colchicine type, which inhibit microtubuli assembly, paclitaxel shifts the microtubule equilibrium towards microtubule assembly. It is highly lipophylic, which promotes a rapid cellular uptake, and has a long-lasting effect in the cell due to the structural alteration of the cytoskeleton.
A summary of the drug action on cellular level is given in Fig 8.

# Experimental and clinical data

## Experimental data

There are a variety of preclinical studies on different pharmacological principles and drugs available. The studies vary in the applied drug, its concentration, the stent preparation, coating, pharmacokinetic and the animal species. We restrict our summary of preclinical results to drugs, which are actually under clinical investigation.

**Figure 8.**




Overview of cellular mechanisms of action of drugs, that are now beeing clinically tested with drug eluting stents.

Despite major differences in study set-up and design, animal experiments for both, sirolimus and paclitaxel, showed
**1.** consistently a significant reduction of neointima formation for the drug eluting stent as compared to the bare stent with a clear dose response curve.
**2.** no increased inflammatory response in drug eluting stents as compared to bare stents.
**3.** less smooth muscle cell colonization and more residual fibrin deposition for the drug eluting stents as compared with the bare stents.

### RAPAMYCIN (SIROLIMUS; RAPAMUNE®)

Rapamycin prevents proliferation of T cells but also proliferation[37,38] and migration[39] of smooth muscle cells. Furthermore, rapamycin has been shown to diminish smooth muscle cell hyperproliferation in several animal models of arteriopathy[40-42]. Pre-clinical efficacy studies demonstrated a 35 to 50% reduction in in-stent neointimal hyperplasia for the rapamycin coated stents as compared with bare metal stents at 28 days in the porcine and rabbit model[43]. The stents were coated with a thin layer of a poly-n-butyl methacrylate and polyethylene-vinyl acetate copolymer containing 185 µg sirolimus. Histological assessment revealed that the neointima of the sirolimus coated stents consisted of smooth muscle cells, matrix proteoglycans, and focal regions of residual fibrin adjacent to the stent struts. Focal medial necrosis or intimal hemorrhage was not observed within any of the bare metal or drug-coated stents. The morphology of non-stented reference arterial wall sections was similar for the metal and the drug-coated stents. A semi-quantitative histological grading system demonstrated less smooth muscle cell colonization and more residual fibrin deposition for the rapamycin eluting stents as compared with the bare metal stents. The focal remnants of residual fibrin deposition that

was observed in the vessel with rapamycin coated stents may reflect a delay in arterial repair or impaired fibrin degradation secondary to the local effects of the drug. Endothelialization scores were identical for the metal (2.9±0.4) and the sirolimus eluting stents (2.9±0.4, P=0.66).

### PACLITAXEL (TAXOL®)

In vitro and in vivo studies have shown that paclitaxel. may prevent or attenuate restenosis. Paclitaxel inhibits proliferation and migration of cultured smooth muscle cells in a dose-dependent manner[44]. In a rat balloon injury model, intraperitoneal administration of paclitaxel reduced neointimal area. The local, vascular administration of paclitaxel showed conflicting results. It reduced neointimal thickness in an atherosclerotic rabbit model[45-47] but did not reduce neointima formation in native pig coronary arteries following stent implantation[48].

Stent-based paclitaxel has been investigated by several groups, using different stent types and preparation (copolymer coatings for paclitaxel elution[49,50] or direct dip-coating of paclitaxel on a stainless steel stent[51] or self-expanding stents[52]) and animal models (pig[51,52], rabbit[49,50]). 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[50]. 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 degradation were likely complete, neointimal area was two- fold lower in paclitaxel-releasing stents[49].

The relevance of these findings for the application of either drug, drug concentration, and formulation in humans is unclear, as the response to injury and endovascular prosthesis is dependent of the species under study[53,54]. This is illustrated by the fact, that an inflammatory response to bare metal and polymer-coated stents has been seen in the porcine, but not the canine model[43].

## Clinical data

### ACTINOMYCIN D

There is no published research to date documenting the use of actinomycin D for treatment of coronary artery disease and/or restenosis. A phase 1, randomized clinical trial "ACTinomycin eluting stent Improves Outcomes by reducing Neointimal Hyperplasia" (ACTION) started in June 2001 to evaluate the safety and performance of the Multi-link tetra™ -D stent system. 360 patients were randomized to receive a actinomycin D coated stent (high dose 10 µg/cm$^2$; low dose 2.5 µg/cm$^2$) or a non-coated stent for treatment of de-novo lesions in native coronary arteries with a vessel caliber of 3.0 mm - 4.0 mm. Six month angiographic follow-up is expected to be completed in June 2002, 12 month clinical follow-up up is expected to be completed in the end of 2002.

### RAPAMYCIN (SIROLIMUS)

*The Sao-Paulo registry:* Thirty patients with angina pectoris were electively treated with 2 different formulations of rapamycin-coated BX Velocity® stents (Cordis) (slow release [SR], n=15, and fast release [FR], n=15). All stents (18mm) were successfully delivered, (3.0-3.5 vessel caliber) and patients were discharged without clinical complications. At 4-months angiographic and IVUS follow-up, there was minimal neointimal hyperplasia in both groups (11.0±3.0% in the SR group and 10.4±3.0% in the FR group by ultrasound; in-stent late loss 0.09±0.3 mm [SR] and –0.02±0.3 mm [FR] by QCA). No in-stent or edge restenosis was observed. No major clinical events (stent thrombosis, repeat revascularization, myocardial infarction, and death) had occurred by 8 months[55]. At 1 year follow-up, IVUS volumetric analysis and angiography indicated minimal amounts of neointimal hyperplasia that were scarcely different from the 4 month data in both groups, with some patients showing no evidence of hyperplasia whatsoever. One late acute MI occurred in the fast-release group at 14 months. There were no other MACE and no restenosis in either group[56].

*The Rotterdam registry:* In Rotterdam, 15 patients were treated. All stent implantations were successful, one patient died on day 2 of cerebral hemorrhage and one patient suffered subacute stent occlusion due to edge dissection. At 6-months follow-up, QCA revealed essentially no change in minimal lumen diameter and percent diameter stenosis by angiographic criteria and hence no in lesion or in-stent angiographic restenosis was observed. Quantitative ultrasound showed that intimal hyperplasia volume and percent obstruction volume at follow-up were neglectable with 5.3mm$^3$ and 1.8% respectively. No edge effect was observed

in the segment proximal and distal to the stent[57]. At 9 months follow-up no further adverse events had occurred and all patients were angina free.

*The RAVEL trial (**RA**ndomized study with the sirolimus coated BX **VE**locity™ ballooon-expandable stent in the treatment of patients with de novo native coronary artery **L**esions):* The multicenter, prospective, double blind clinical trial compared bare metal and the drug coated stent. Two hundred thirty-eight patients were randomized to a single rapamycin coated (140µg/cm$^2$) versus a bare metal BX velocity stent. At six months follow-up, the restenosis rate of the treated group was zero, the loss in minimal lumen diameter was zero, there was no target lesion reintervention and the event-free survival was 96.5%[58].

*The SIRIUS study* is a multicenter, prospective, randomized double blind trial that is conducted in 55 centers in the USA. Eleven-hundred patients with focal de novo native coronary arterial lesions (2.5mm to 3.5mm diameter, 15mm to 30 mm long) were randomized to treatment with rapamycin coated or bare metal BX velocity balloon expandable stents. The primary endpoint of the SIRIUS trial is target vessel failure (death, myocardial infarction, target lesion revascularization) at 9 months. In addition, secondary endpoints are core laboratory analysis of angiographic and intravascular ultrasound data to determine treatment effects on neointimal hyperplasia and in-stent restenosis. The six months follow-up will be completed in March 2002. Clinical follow-up will extend to 3 years in order to assess for late events.

In addition to the pivotal RAVEL and SIRIUS trials, feasibility studies are ongoing to assess efficacy of rapamycin coated stents in more complex lesion subset such as in-stent restenosis.

## PACLITAXEL

*Taxus trial family:* There are several clinical trials on paclitaxel coated stents ongoing. The Taxus 1 trial is a safety study[61]. Patients with de novo lesions were randomized to receive a paclitaxel coated, slow release formulation (1.0µg/mm$^2$) NIR conformer or a bare NIR stent. At 6 month follow-up, no restenosis was seen in the paclitaxel coated stent group while the restenosis rate in the bare stent group was 11%. The late lumen loss of 0.35±0.47mm was significantly lower in the paclitaxel coated stent group as in the bare stent group (0.71±0.88mm)[59]. Taxus -II is an efficacy study. 532 Patients are being enrolled to receive a paclitaxel coated, sequential slow and moderate release formulation stent. The TAXUS-III trial is a feasibility trail. 30 Patients were enrolled to receive a paclitaxel coated, slow release formulation stent for in-stent restenosis. Primary endpoint is the rate of major adverse cardiac events at 30 days follow-up. The Taxus IV pivotal study is enrolling 1600 patients with in-stent restenotic or de-novo lesions in the U.S. to receive a paclitaxel coated, moderate release formulation EXPRESS stent. Primary endpoint will be the target vessel revascularization rate at 8 months follow-up.

The Asian ASPECT trial showed a clear dose response. 177 patients were randomized to receive a high dose (3.1µg/mm$^2$) paclitaxel coated, a low dose (1.3 µg/mm$^2$) paclitaxel coated or a bare stent. The restenosis rate at 6 months was 4%, 12% and 27%, respectively[60].

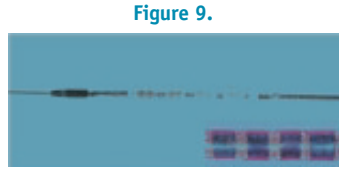
The ELUTES trial (**E**va**LU**ation of pacli**T**axel-**E**luting **S**tent) assessed the safety and efficacy of four doses of paclitaxel versus an uncoated Cook V-Flex(tm) Plus stent. 192 patients were randomised to receive dosages of 0.2 µg/mm$^2$; 0.7 µg/mm$^2$; 1.4 µg/mm$^2$ and 2.7 µg/mm$^2$ or control stent. At 6-month follow-up, quantitive coronary angiography showed a clear dose relationship, 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[61].

*Quanam stent trials:* In other clinical trials, the taxol derivate QP2 was used.

The *European QP2 pilot study* included 32 patients with de-novo or restenotic lesions who underwent QuaDS-QP2 stent implantation (Quanam Medical Corporation, Santa Clara, CA). The stainless steel, slotted tube stent was 13 or 17mm in length and coated with multiple polymer sleeves that slowly release QP2 (up to 4000 µg) (Fig 9). At 8-month follow-up, IVUS revealed only moderate neointima formation with a neointima burden of 13.6±14.9%[62].

In the South-American *QuaDS-QP-2 registry (BARDDS)*, thirty-two patients were treated with the QuaDS-QP-2 stent (containing up to 4000 µg QP2). 13 patients underwent

**Figure 9.**



The Quanam drug eluting stent. Quanam polymer sleeves loaded with a microtubular inhibitor. Polymere sleeves are tightly stretched over dedicated Quanam metal stents that are mounted on custom made rapid exchange balloon catheters.

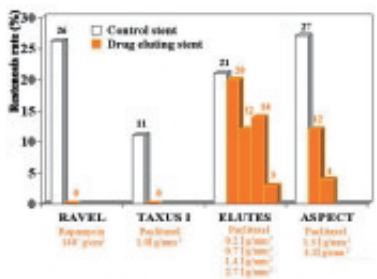
angiographic and IVUS follow-up (at 6-15 months). Although all 13 QuaDS- QP-2 stents were patent, two reinterventions have been required, both relate to either new disease or to distal, small-vessel disease beyond the stent. Twenty-five patients were asymptomatic at 2-year follow-up[63].

The multicenter, SCORE trial randomized 266 patients to receive a QuaDS-QP2 stent (4000 µg with an elution over 180d) or a bare stent. However, this trial has been stopped by the safety committee because of an excessive adverse event rate in the QuaDS-QP2 stent group of 10.2%[64], consisting in periprocedural myocardial infarction (MI 7.1%) and subacute stent thrombosis65 (SAT and death 6.3%), most probably caused by the polymer sleeves.

An overview of the angiographic restenosis rate and late lumen loss at 6 months follow-up angiography in randomized clinical trials of drug eluting stents is given in Fig 10 and Fig 11.

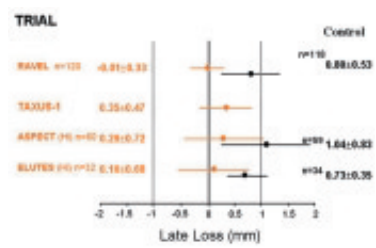
Besides these trials, a variety of other drugs are planned or just started enrolling patients in first clinical studies. Paclitaxel will be used in the upcoming PATENCY and DELIVER trials. Upcoming trials will include antisense c-myc, deaxamethosin (STRIDE), batimastat (BRILLIANT, BATMAN) and 17-ß-estradiol (EASTER, St. THOMAS) (Fig 12).

**Figure 10.**



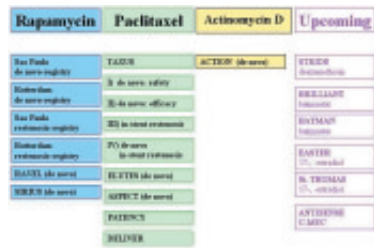

Aniographic restenosis rates (>50% diameter stenosis) at 6 month follow-up in randomized clinical trials of drug eluting stent.

**Figure 11.**




Aniographic late lumen loss at 6 month follow-up in randomized clinical trials of drug eluting stent.

**Figure 12.**




Overview of clinical trials with drug eluting coronary stents.

# Contemporary application modalities and devices

## Actinomycin D: Multi-Link Tetra™-D stent (Guidant, Santa Clara, CA, USA)

**Stent:** The stent is fabricated from medical 316L stainless steel tubing and is composed of a series of cylindrically oriented rings aligned along a common longitudinal axis. Each ring consists of 3 connecting bars and 6 expanding elements (Fig 13). The stent is pre-mounted on a delivery catheter.

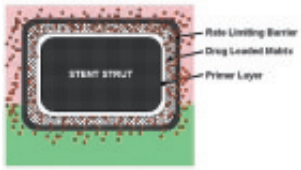
**Figure 13.**

Actinomycin D: Multi-Link Tetra™-D stent (Guidant, Santa Clara, CA, USA).

**Coating:** Actinomycin-D is the antiproliferative drug. The finished Multi-Link Tetra stent is coated with a polymer matrix (semi-crystalline ethylene-vinyl alcohol co-polymer: EVAL) which contains a maximal dose of 150 µg actinomycin-D (Fig 14-15). This is between 20 and 200 times less than the recommended total human adult dose of 500 (g /day given intravenously for 5 days.

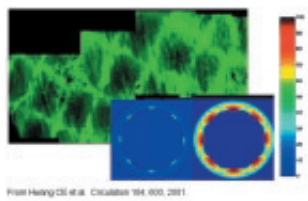
**Delivery system:** The delivery catheter has a rapid exchange design (0.014 inch guide wire). It is equipped with two radiopaque markers located underneath the balloon to mark

**Figure 14.**




Multi-Link Tetra ™-D stent: Coating formulation (Guidant, Santa Clara, CA, USA).

**Figure 15.**



Drug concentration along the stent struts (Fram Hawang *et al.*, Circulation 2001).

the ends of the stent and has a "stepped" balloon design to optimize balloon shoulder configuration.

## NIRx™-Paclitaxel eluting conformer coronary stent (Boston Scientific USA)

**Stent:** The stent is fabricated from medical 316LS stainless steel. The geometry is a continuos, uniform, multicellular design with adaptive cells capable to differential lengthening. This enables the stent to be flexible in the unexpanded configuration. Stent length is 15mm. The stent is premounted on a delivery catheter (Fig 16).

**Coating:** The antiproliferative drug is paclitaxel. Paclitaxel is incorporated into a fast-release triblock coplymer carrier system on the stent. There are two drug concentration. The "low dose" concentration is 1.0 µg/mm$^2$ (loaded drug/stent surface area; total dose 85 µg per stent) and gives sustained release over approx. 28 days. The "moderate dose" is 2.0 µg/mm$^2$ (loaded drug/stent surface area) and provides a rapid release in the first 24h, followed by a slower release over the following 28 days.

**Figure 16.**

NIRx ™-Paclitaxel eluting conformer coronary stent (Boston Scientific USA).

**Delivery system:** The delivery catheter is a monorail design (0.014 inch guide wire/6F guiding catheter). It is equipped with two radiopaque markers located underneath the balloon to mark the ends of the stent.

## Paclitaxel eluting stent (Cook Inc. USA)

**Stent:** The stent is a stainless steel, slotted tube design with high radial strength and low recoil.

The stent length is 15 mm, the diameter is 2.5, 3.0 or 3.5 mm (Fig 17).

**Figure 17.**

Paclitaxel eluting stent (Cook Inc. USA).

**Coating:** The antiproliferative drug is paclitaxel. Paclitaxel adhered to the abluminal surface with no polymer using a proprietary process. Paclitaxel is applied in two concentrations. The high dose is 3.1 µg/mm$^2$, the low dose is 1.3 µg/mm$^2$.

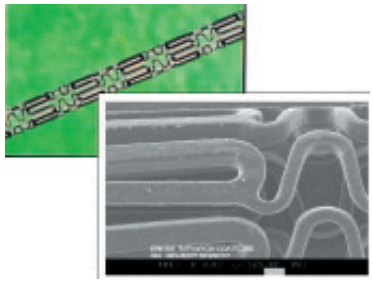
**Delivery system:** The delivery catheter is a monorail design (0.014 inch guide wire/6F guiding catheter). It is equipped with two radiopaque markers located underneath the balloon to mark the ends of the stent.

## Cypher™: The sirolimus eluting BX™ velocity stent (Cordis, Warren, USA)

**Stent:** The stent is fabricated from medical 316LS stainless steel. It is available in 2 cell configurations (6 cell configuration: expanded diameter 2.5-3.25mm) and 7 cell design (expanded diameter 3.5-3.75mm). Stent length is 18mm (Fig 18). The stent is pre-mounted on a delivery balloon.

**Coating:** The antiproliferative drug is sirolimus. The stent contains 140µg/cm$^2$ which gives a total sirolimus content of 153 µg on the 6-cell stent and 180 µg on the 7-cell stent. The slow release coating formulation consists of 30% sirolimus by weight in a 50:50 mixture of the polymer polyethylenevinylacetate (PEVA) and polybutylmethacrylate (PBMA) (Fig 19).

**Figure 18.**



Cypher™: The sirolimus eluting BX™ velocity stent (Cordis, Warren, USA).

**Figure 19.**


The sirolimus eluting BX™ velocity stent: Coating formulation, (Cordis, Warren, USA).

**Delivery system:** The delivery catheter utilizes a rapid exchange design (0.014 inch guide wire/6F guiding catheter). It is equipped with two radiopaque markers located underneath the balloon to mark the ends of the stent. The delivery balloon is 2.5mm, 3.0mm and 3.5mm in diameter.

# Procedure performance

## Patient selection

### INDICATIONS

The indications for drug eluting stent implantation are not yet established. Clinical data are up to now only available in patients with simple, short de novo lesions. An clinical example of sirolimus eluting stent implantation is given in Fig 20.

### CONTRAINDICATIONS

There are up to now, no absolute contraindications for drug eluting stent implantation defined. Caution should be taken in patients after failed brachytherapy. There is no data available on the combined effect of radiation and cytostatic therapy in coronary arteries. In oncology, however, this combination is known to produce highly complex and poorly understood interactions[66-69].

**Figure 20.**

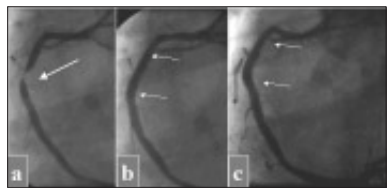



**Figure 20.** Clinical example of sirolimus eluting BX™ velocity stent implantation. **Fig 20a.** preprocedural angiogram of the right coronary artery with a short, de novo lesion (arrow) **Fig 20b.** Postprocedural angiogram after implantation of a 3.0/18mm sirolimus coated BX™ velocity stent **Fig 20c.** 6-month follow-up angiography. The angiogram shows a patent artery with no evidence for neointimal hyperplasia.

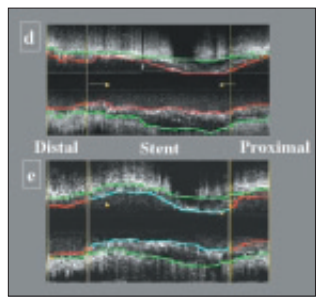



**Fig 20d.** Longitudinal IVUS view after sirolimus eluting BX velocity stent implantation. The lumen boundary (red) and the vessel boundary (green) is traced. **Fig 20e.** Longitudinal IVUS view at 6-month follow up. The yellow lines indicate the proximal and the distal end of the stent. Lumen (red) volume remained unchanged over time, no neointima formation within the stent is detected. Thus, the stent (light blue) boundary is superimposed to the lumen boundary. Vessel volume (green) remained stable over time.

## Patient preparation - medication

*Pre-procedural* treatment requires no particular medication for drug eluting stent implantation other than antiplatelet regimen for routine angioplasty procedures: Aspirin (75mg-300mg) and ticlopidine or clopidogrel must be started at least 24h before the procedure, whereby we prescribe a loading dose of 750mg, followed by 250mg twice a day for ticlopidine and a loading dose of 300mg, followed by 75mg daily for clopidogrel. Beta-blockers, calcium antagonist and oral nitrates should be administered as usually prescribed.

*In begin of the procedure*, we routinely administer neuroleptics and analgesics. Repeat bolus is given during the procedure, if needed. Furthermore, we administer 325mg aspirin intravenously and 10 000 IU heparin immediately after arterial sheath placement. Activated clotting time (ACT)

is checked every 30 minutes after the first bolus injection in order to maintain ACT > 300 sec. Additional heparin is given if necessary.

*During the procedure,* GP IIbIIIa receptor blockers are given deliberately in patients with unstable angina, periprocedural intracoronary thrombus formation or dissection.

## Angioplasty

For the angioplasty procedure, a standard angioplasty set is needed. We prefer the standard femoral approach for optimal guide support using 6F sheath and guiding catheter. Stent implantation is performed in conventional technique. It is important, that angioplasty is not stopped before reaching a satisfactory result.

*Handling of the stent*

Care should be taken while handling the drug eluting stent. The polymer coating is considered to be mechanically and chemically stable. Thus, there should be no drug release while preparing and handling the stent system during the procedure. However, we recommend not to stress the stent mechanically during unpacking and preparation to avoid cracking and flaking of the coating layer caused by distortion of the stent. In dependency of the drug and coating, losses up to 17% of the drug doses can occur during ex vivo manipulation. Furthermore, the stent should be placed rapidly into the coronary system. Losses to the blood lipids may occur during the brief (30-second) exposure to the coronary circulation before deployment. This was demonstrated in washout experiments with paclitaxel in which a 30-second exposure to pig blood at 37°C resulted in loss of <5% of the applied dose[51].

*Stent implantation technique*

The question of *direct stenting* has not been addressed yet. Possible concerns are, again, increased mechanical stress to the stent and prolonged blood exposure in lesions, were it is difficult to advance the stent into the lesion. Therefore, all clinical trial protocols recommend predilatation of the lesions.

*Multiple stents*

Another important question is the drug distribution in the vessel wall when multiple stents are used. Experimental studies with Actinomycin D eluting stents in pigs indicated 70 mg of Actinomycin D as the toxic dose. If an 40 mg coated stent is overlapped with another 40 mg coated stent, the toxic dose in that vessel is exceeded[70]. Vice versa, the drug concentration might drop to inefficient levels, when stents are placed with a "gap"in-between.

# Complications

## Procedural complications

Procedural complications include all complications typically linked to the angioplasty/debulking procedure.

## Long-term complications

Up to now, no longterm complications are known. The animal experimental data, which are showing delayed or incomplete healing point to the potential danger of delayed thrombosis. This risk seems to be rather small for the sirolimus eluting stent. The Sao Paulo and the Thoraxcenter registry as well as the multicenter RAVEL trial prescribed clopidogrel for only two month after stenting and no (sub) acute or delayed thrombotic event was seen.

Theoretically, all potential complications related to the specific drugs used may apply. The systemic concentration of these drugs, however is extremely low or not even measurable. Under these circumstances, severe systemic complications seem very unlikely.

# Postprocedural care

The arterial sheath is withdrawn immediately after the procedure and the access site sealed with a closure device (Perclose or Angioseal). In case of a difficult arterial puncture with substantial fibrosis, the sheath is removed 6 hours after the procedure and the artery manually compressed. All patients must receive effective antiplatelet therapy for at least 2 months. In our institution, we prescribe aspirin indefinitely in combination with ticlopidine (250mg twice a day) or clopidogrel (75mg daily).

# Limitations

Although the principle of stent implantation is well established and although (most of) the applied drugs and polymers were used in clinical practice since years, there is little experimental and only preliminary clinical knowledge of the acute and long-term effects of drug-eluting stents in coronary arteries. Thus, a number of concerns and open questions have to be investigated in the future.

The concerns include drug toxicity as well as acute and late vascular effects. A number of toxic effects are known for all drugs applied in cancer therapy such hematological toxicity (neutropenia), neurotoxicity (peripheral neuropathy), hypersensitivity reactions, or cardiac disturbances. However, these side effects are described in patients undergoing high-dose chemotherapy for a malignant disease with plasma levels 100

to 1000 times higher (and over longer time periods) than plasma levels that result from a local delivery. Another concern is possible delayed wound healing and re-endothelialization. This would increase thrombogenicity and the danger of (late) stent thrombosis. Further potential side effects could be late positive remodeling and aneurysma formation. Thus the most suitable antithrombitic regimen following drug-eluting and/or biodegradable stent implantation still has to be evaluated.

A series of open questions exists on the mechanism of action and consecutively the design of local drug delivery systems and drug-eluting stents. Little is known of specific pharmakokinetic issues. There is a paucity of data on the most appropriate tissue concentration and the rate and duration and of drug-release over time. The tissue concentration is dependent on close mechanical contact of the stent to the vascular tissue and on physiological transport forces into the tissue. Hydrophobic drugs, like paclitaxel have greater variability in terms of drug delivery, while hydrophilic drugs, like heparin, have less variability and achieve higher local concentrations. Local concentrations and concentration gradients however, are crucial parameters for biological effects. The relationship between vascular effects and physicochemical properties of the drug-loaded stent is poorly understood. Drug distribution within the vessel wall seems to be significantly affect by the stent expansion pattern (uniform versus non-uniform)[71].

## Conclusion and future perspectives

Drug-eluting stents represent one of the most promising fields in interventional cardiology today. However, a lot of unanswered questions still have to be resolved before determining their potential. Hopefully, after the completion of planned and ongoing trials many of these issues will be answered. Furthermore, these new technologies will have to proof effective in daily routine patients presenting with long lesions, small vessels, chronic occlusion, bifurcation, multivessel and/or left main stem disease or acute myocardial infarction.

Stent development will investigate a variety of possibilities to resolve the restenosis problem. Possibilities range from the further exploitation of different classes of drugs which are potential candidates for the inhibition of restenosis to the combination of biodegradability with drug delivery, or local gene therapy (e.g. local expression of proliferation regulatory genes; transfer of cytotoxic genes, VEGF).

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## PART 3: DRUG ELUTING STENTS

*Chapter 11*

*Regar E,* Serruys PW, Bode C, Holubarsch C, Guermonprez JL, Wijns W, Bartorelli A, Constantini C, Degertekin M, Tanabe K, Nijssen K, Disco C, Morice MC on behalf of the RAVEL study group:
**ANGIOGRAPHIC FINDINGS OF THE MULTICENTER, RANDOMIZED STUDY WITH THE SIROLIMUS-ELUTING BX VELOCITY BALLOON-EXPANDABLE STENT (RAVEL).**
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# Angiographic Findings of the Multicenter Randomized Study With the Sirolimus-Eluting Bx Velocity Balloon-Expandable Stent (RAVEL)

## Sirolimus-Eluting Stents Inhibit Restenosis Irrespective of the Vessel Size

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***Background***—Restenosis remains the major limitation of coronary catheter-based intervention. In small vessels, the amount of neointimal tissue is disproportionately greater than the vessel caliber, resulting in higher restenosis rates. In the Randomized Study With the Sirolimus-Eluting Bx Velocity Balloon-Expandable Stent (RAVEL) trial, ≈40% of the vessels were small (<2.5 mm). The present study evaluates the relationship between angiographic outcome and vessel diameter for sirolimus-eluting stents.

***Methods and Results***—Patients were randomized to receive either an 18-mm bare metal Bx VELOCITY (BS group, n=118), or a sirolimus-eluting Bx VELOCITY stent (SES group, n=120). Subgroups were stratified into terciles according to their reference diameter (RD; stratum I, RD <2.36 mm; stratum II, RD 2.36 mm to 2.84 mm; stratum III, RD >2.84 mm). At 6-month follow-up, the restenosis rate in the SES group was 0% in all strata (versus 35%, 26%, and 20%, respectively, in the BS group). In-stent late loss was 0.01±0.25 versus 0.80±0.43 mm in stratum I, 0.01±0.38 versus 0.88±0.57 mm in stratum II, and −0.06±0.35 versus 0.74±0.57 mm in stratum III (SES versus BS). In SES, the minimal lumen diameter (MLD) remained unchanged (Δ −0.72 to 0.72 mm) in 97% of the lesions and increased (=late gain, ΔMLD <−0.72 mm) in 3% of the lesions. Multivariate predictors for late loss were treatment allocation ($P$<0.001) and postprocedural MLD ($P$=0.008).

***Conclusions***—Sirolimus-eluting stents prevent neointimal proliferation and late lumen loss irrespective of the vessel diameter. The classic inverse relationship between vessel diameter and restenosis rate was seen in the bare stent group but not in the sirolimus-eluting stent group. **(*Circulation*. 2002;106:1949-1956.)**

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

Restenosis remains the major limitation of coronary catheter-based intervention.[1] In stented vessels, the major contributor to restenosis is neointimal proliferation, which is a ubiquitous, local, vascular reaction to catheter-induced vessel injury.[2] Vessel diameter is an established predictor of angiographic outcome after catheter-based intervention, with a higher restenosis rate in smaller vessels.[3] This is because of the disproportionately greater amount of neointimal tissue relative to the vessel caliber.[4] Although coronary stents provide major benefits versus simple balloon angioplasty by inhibiting acute vessel closure, early vessel recoil, and late vessel constriction, they stimulate neointimal proliferation. Therefore, restenosis rates in small vessels may be similarly high with these 2 treatment modalities.[5,6] Inhibition of neointimal proliferation by local pharmacological interventions is a promising concept. Sirolimus (rapamycin) is an immunosuppressive drug approved for the prevention of renal transplant rejection. It also has potent antiproliferative and antimigratory effects on vascular smooth muscle cells.[7] Recent clinical experience with sirolimus-eluting coronary stents has shown excellent results, with 0% restenosis at 4-month,[8] 6-month,[9] and 12-month follow-up.[10] At the time of these pilot studies, sirolimus-eluting stents were only available in a 3.0-mm or 3.5-mm diameter, limiting treatment to relatively large vessels. In the Randomized Study With the Sirolimus-Eluting Bx Velocity Balloon-Expandable Stent (RAVEL) trial, a smaller sirolimus-eluting stent with a diameter of 2.5 mm was available, and it allowed smaller

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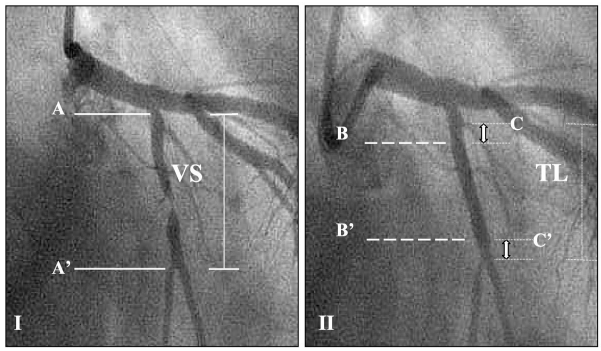


**Figure 1.** I, Vessel segment (VS) was defined as the segment bounded by side branches proximal (A) and distal (A′) to the stent segment. II, Target lesion (TL) encompassed the stent segment and edge segments. The length of the vessel covered by stent struts defined the stent segment (from B to B′). The edge segments encompassed the vessel 5 mm proximal (C) and distal (C′) to the stent.

vessels to be stented. This small sirolimus-eluting stent was used in 18% of patients.[11] The present study investigated the relationship between angiographic outcome and vessel diameter for sirolimus-eluting stents compared with bare metal stents.

## Methods

### Patients and Stent Implantation

The patient population and stent implantation technique have been described in detail elsewhere.[11] The 238 patients enrolled in the RAVEL trial had a single de novo lesion of a native coronary artery.

Patients were randomized (double-blind) for implantation of either an 18-mm uncoated bare metal Bx VELOCITY stent (BS), or a sirolimus-eluting Bx VELOCITY balloon-expandable stent (Cordis Corp, Johnson & Johnson) (SES). All drug-eluting Bx VELOCITY stents contained 140 $\mu$g sirolimus/cm$^2$ ($\pm$10%). Total sirolimus content was 153 $\mu$g ($\pm$10%) on the 6-cell stent (2.5 and 3.0 mm in diameter) and 180 $\mu$g ($\pm$10%) on the 7-cell stent (3.5 mm in diameter). This difference in content was due to the differences in the surface area of the two stents. Stent implantation was performed in the conventional manner after predilation. Postdilatation was performed as necessary to achieve a residual stenosis below 20% with TIMI grade III flow. Patients received aspirin (at least 100 mg) indefinitely with either clopidogrel (75 mg daily) or ticlopidine (250 mg, twice daily) for 8 weeks.

### Quantitative Coronary Angiographic Analysis

Coronary angiograms were obtained in multiple views after intracoronary injection of nitrates. Quantitative analyses by edge-detection techniques were performed by an independent core laboratory (Cardialysis BV) blinded to treatment allocation. Reference diameter (RD), minimal luminal diameter (MLD), and degree of stenosis (as percentage of diameter) were measured before dilatation, at the end of the procedure, and at a 6-month follow-up. Restenosis was defined as >50% diameter stenosis at follow-up. Late loss was defined as MLD after the procedure minus MLD at follow-up.

The target lesion was defined as the stent segment plus 5 mm proximal and 5 mm distal to the edge of the stent. The vessel segment was defined as the segment bounded by side branches proximal and distal to the stent segment (Figure 1).

The accuracy of the method has been reported in detail.[12] Given the accuracy of quantitative coronary angiography for MLD measurements, we used 2 standard deviations[12] as the cut-off point for the classification of late loss indicating whether MLD was unchanged (no loss, $\Delta$MLD $-0.72$ to 0.72 mm), reduced (late loss, $\Delta$MLD >0.72 mm), or larger (late gain, $\Delta$MLD $<-0.72$ mm, "negative late loss") at follow-up.[13]

### Subgroup Definition

Both groups were stratified according to their vessel diameter. Vessel diameter was defined as the baseline RD in the vessel segment analysis before intervention. The terciles for the RD were calculated and used as cut-off points for subgroup definition.

### Sample Size Estimation and Statistical Analysis Based on Late Loss

A sample size of 95 in each group had 87% power to detect a difference in means of 0.25 mm (the difference between a bare stent late loss mean, $\mu_B$, of 0.80 mm and a sirolimus stent late loss mean, $\mu_S$, of 0.55 mm), assuming that the common standard deviation is 0.55 using a 2-group $t$ test with a 0.05 1-sided significance level. The sample size was increased to 110 in each group to account for noncompliance to 6-month angiographic follow-up.

Data are presented as mean$\pm$SD or proportions. For comparison of continuous data, a 2-tailed Student's $t$ test was performed. A value of $P<0.05$ was considered significant. To identify the factors that might be related to late lumen loss, linear regression analyses were performed. Predictors were chosen by stepwise linear regression using an entry criterion of 0.20 and a stay criterion of 0.05.

## Results

The 238 patients were randomly assigned (SES, n=120; BS, n=118). There were no significant differences with regard to procedural success (96.6% versus 93.1%), stents per patient (1.0$\pm$0.3 versus 1.1$\pm$0.3), and nominal stent diameter (3.06$\pm$0.34 mm versus 3.10$\pm$29 mm; SES versus BS, respectively).

Before the procedure, RD (2.60$\pm$0.54 mm versus 2.64$\pm$0.52 mm) and MLD (0.94$\pm$0.31 mm versus 0.95$\pm$0.35 mm) were similar in both groups. After the procedure, there were also no meaningful differences (postprocedural RD, 2.62$\pm$0.44 mm versus 2.68$\pm$0.45 mm; postprocedural MLD, 2.43$\pm$0.41 mm versus 2.41$\pm$0.40 mm; SES versus BS, respectively). At follow-up, the SES group showed a larger MLD (2.42$\pm$0.49 mm versus 1.64$\pm$0.59 mm, $P<0.001$) and lower late lumen loss ($-0.01\pm0.33$ mm versus 0.80$\pm$0.53 mm, $P<0.001$). Binary restenosis was 0.0% in the SES group and 26.6% in the BS group ($P<0.001$).

Figure 2 illustrates the relation between postprocedural MLD and MLD at follow-up. In the SES group, the MLD (Figure 2A) remained basically unchanged; late loss was seen in 1 lesion and late gain was seen in 4 lesions (3%). In contrast, lumen reduction over time was seen in approximately half of the BS patients (n=55, 47%), and no late gain

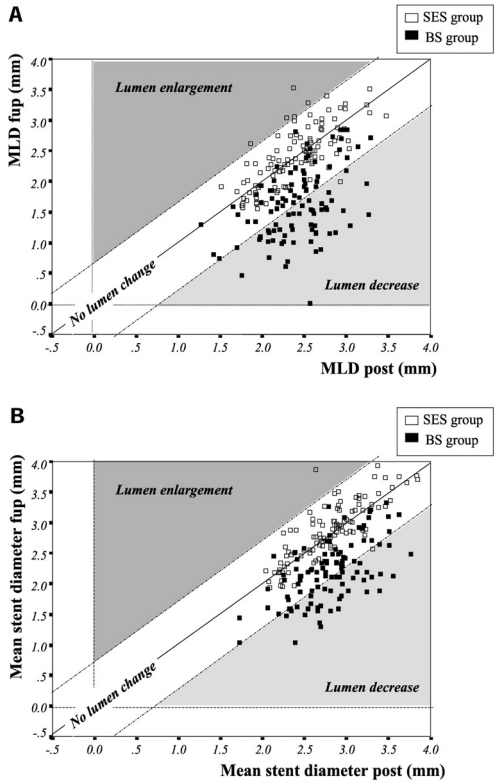


**Figure 2.** Relationship between measurements after implantation and at 6-month follow-up for the SES group and the BS group: MLD (A), mean diameter over the entire length of the stent (B). Dashed lines indicate the range of ±0.72 mm change in diameter.

was seen. A similar pattern was found for the mean diameter over the entire length of the stent (Figure 2B).

## Stratification

Subgroups were stratified according to their RD (Figure 3). There were no significant differences in baseline patient and lesion characteristics in the SES and BS subgroups. There were also no significant differences in procedural parameters (Table 1).

Analysis of the strata revealed a higher proportion of diabetic patients in small and intermediate vessels. The stent implantation procedure showed a decreasing balloon to artery ratio (stratum I versus stratum III: $P<0.001$ in both, BS and SES group) and increasing inflation pressure from stratum I to stratum III (stratum I versus stratum III: $P<0.01$ SES group; $P=0.22$ BS group).

Table 2 summarizes the key angiographic data. Vessel segment analysis showed similar preprocedural and postprocedural MLD in both treatment groups throughout corresponding strata.

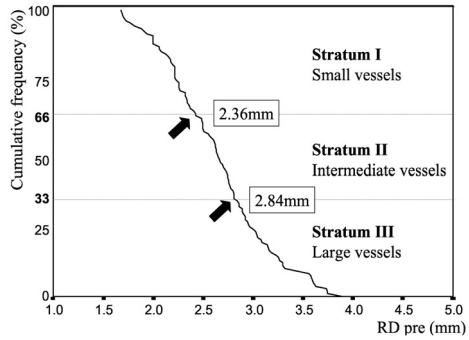


**Figure 3.** Subgroup stratification: cumulative frequency distribution curve of the preinterventional reference diameter. Arrows indicate cut-off values at the 33rd and the 66th percentile.

## Restenosis, Late Lumen Loss, and Vessel Size

At follow-up, the MLD was consistently larger in the SES groups. In all strata, the restenosis rate was 0% in the SES groups, with extremely low and consistently uniform late loss. In the BS strata, the classic inverse relationship between restenosis rate and vessel diameter was seen. Restenosis rate virtually doubled with decreasing vessel size from 20% in large vessels (stratum III) to 35% in small vessels (stratum I). The amount of late loss, however, was similar in the 3 groups (0.80 mm in stratum I, 0.88 mm in stratum II, and 0.74 mm in stratum III). Therefore, the observed increase in restenosis rate in smaller vessels in this series is driven largely by the relative amount of obstruction as a function of vessel diameter rather than being due to an absolute increase in neointimal hyperplasia in smaller vessels.

## Subsegment Analysis

### *Vessel Segment Analysis*

Vessel segment analysis revealed minimal late gain in both the MLD and RD over time in SES subgroups but not in BS groups (Table 2).

## Target Lesion Analysis (Including Stent Segment and the Proximal and Distal Edges)

The SES subgroups showed minimal late loss at the stent segment (0.01±0.25 mm, 0.01±0.38 mm, and −0.06±0.35 mm in strata I, II, and III, respectively) and proximal edges (0.04±0.34 mm, 0.08±0.42 mm, and 0.03±0.43 mm in strata I, II, and III, respectively), whereas the distal SES edges had minimal late gain (−0.05±0.29 mm, −0.14±0.31 mm, and −0.09±0.31 mm in strata I, II, and III, respectively). In contrast, the BS subgroups showed pronounced late loss in the stent segment and moderate late loss at the proximal and distal edges.

## Multivariate Analysis

Univariate predictors for late loss included treatment allocation and postprocedural MLD (Table 3). Multivariate predictors for late loss were treatment allocation ($P<0.001$) and the MLD after the procedure ($P=0.008$) (Table 4).

**TABLE 1. Baseline Characteristics for Sirolimus-Eluting and Bare Stents, Stratified by Vessel Size**

| Stratum/Parameter | SES | BS | Difference (95% CI) | *P* |
|---|---|---|---|---|
| I | | | | |
| n | 42 | 37 | ... | ... |
| Age, y | 62±12 | 62±10 | −0.4 (−5.0, 4.3) | ... |
| Male sex | 73.8 | 75.7 | −1.9 (−21.0, 17.3) | ... |
| Diabetes mellitus | 19.0 | 27.0 | −8.0 (−26.6, 10.6) | ... |
| Unstable angina | 40.4 | 48.6 | −8.1 (−30.0, 13.7) | ... |
| Lesion length, mm | 9.5±3.2 | 8.8±2.8 | 0.70 (−0.64, 2.04) | ... |
| Discrete (<10 mm) | 64.3 | 64.9 | −0.6 (−21.7, 20.6) | ... |
| Tubular (10–20 mm) | 35.7 | 35.1 | 0.6 (−20.6, 21.7) | ... |
| Lesion type (AHA/ACC) | | | | |
| A | 9.5 | 2.7 | 6.8 (−3.5, 17.1) | ... |
| B1 | 28.6 | 32.4 | −3.9 (24.2, 16.5) | ... |
| B2 | 61.9 | 64.9 | −3.0 (−24.2, 18.3) | ... |
| C | 0 | 0 | 0 | ... |
| Mean stent diameter, mm | 2.8±0.2 | 2.9±0.2 | −0.10 (−0.22, 0.01) | 0.08 |
| 3.5 | 2.3 | 5.4 | −3.0 (−11.6, 5.4) | 0.59 |
| 3.0 | 58.1 | 73.0 | −14.8 (−35.3, 5.7) | 0.24 |
| 2.5 | 39.5 | 21.6 | 17.9 (−1.8, 37.6) | 0.10 |
| Balloon-artery ratio | 1.3±0.1 | 1.3±0.2 | 0 (−0.09, 0.09) | 0.96 |
| Maximal inflation pressure, atm | 14.2±3.5 | 14.2±3.4 | −0.03 (−1.5, 1.5) | 0.97 |
| Postprocedural dissection | | | | 1.00 |
| None | 76.2 | 75.7 | 0.5 (−18.4, 19.4) | ... |
| Type A | 7.1 | 2.7 | 4.4 (−4.9, 13.8) | ... |
| Type B | 9.5 | 18.9 | −9.4 (−24.8, 6.0) | ... |
| Type C | 7.1 | 2.7 | 4.4 (−4.9, 13.8) | ... |
| Other | 0 | 0 | 0 | ... |
| II | | | | |
| n | 40 | 38 | ... | ... |
| Age, y | 61±10 | 59±11 | 1.3 (−3.5, 6.2) | ... |
| Male sex | 72.5 | 81.6 | −9.1 (−27.6, 9.5) | ... |
| Diabetes mellitus | 22.5 | 21.1 | 1.4 (−16.9, 19.8) | ... |
| Unstable angina | 51.2 | 54.0 | −2.7 (−25.2, 19.6) | ... |
| Lesion length, mm | 9.0±2.9 | 8.4±2.2 | 0.54 (−0.62, 1.70) | ... |
| Discrete (<10 mm) | 89.5 | 83.8 | 5.7 (−9.7, 21.1) | ... |
| Tubular (10–20 mm) | 10.5 | 18.9 | −8.7 (−24.5, 7.1) | |
| Lesion type (AHA/ACC) | | | | |
| A | 5.1 | 5.4 | −0.3 (−10.3, 9.8) | ... |
| B1 | 53.8 | 35.1 | 18.7 (−3.2, 40.7) | ... |
| B2 | 41.0 | 59.5 | −18.4 (−40.5, 3.7) | ... |
| C | 0 | 0 | 0 | ... |
| Mean stent diameter, mm | 3.0±0.3 | 3.1±0.2 | −0.03 (−0.16, 0.09) | 0.60 |
| 3.5 | 26.1 | 26.3 | −0.1 (−19.4, 19.1) | 1.00 |
| 3.0 | 61.9 | 68.4 | −6.5 (−27.3, 14.3) | 0.64 |
| 2.5 | 11.9 | 5.2 | −6.6 (−5.4, 18.7) | 0.44 |
| Balloon-artery ratio | 1.1±0.1 | 1.2±0.2 | −0.1 (−0.1, −0.03) | 0.008 |
| Maximal inflation pressure, atm | 14.7±3.1 | 15.5±2.6 | −0.7 (−2.0, 0.5) | 0.26 |
| Postprocedural dissection | | | | 0.62 |
| None | 71.8 | 64.9 | 6.9 (−14.0, 27.8) | ... |
| Type A | 10.3 | 21.6 | −11.4 (−27.7, 5.0) | ... |
| Type B | 7.7 | 8.1 | −0.4 (−12.6, 11.7) | ... |
| Type C | 5.1 | 2.7 | 2.4 (−6.2, 11.1) | ... |

**TABLE 1. (Continued)**

| Stratum/Parameter | SES | BS | Difference (95% CI) | *P* |
|---|---|---|---|---|
| Other | 5.1 | 0 | 5.1 (−1.8, 12.1) | ... |
| III | | | | |
| n | 38 | 42 | ... | ... |
| Age, y | 62±9 | 57±9 | 5.3 (1.2, 9.4) | ... |
| Male sex | 63.2 | 88.1 | −24.9 (43.1, −6.7) | ... |
| Diabetes mellitus | 5.3 | 16.7 | −11.4 (−24.7, 1.9) | ... |
| Unstable angina | 54.0 | 52.3 | 1.6 (−20.3, 23.7) | ... |
| Lesion length, mm | 10.1±3.8 | 11.4±3.4 | −1.27 (−2.91, 0.38) | ... |
| Discrete (<10 mm) | 85.7 | 74.4 | 11.4 (−6.6, 29.3)... | |
| Tubular (10–20 mm) | 14.3 | 25.6 | −11.4 (−29.3, 6.6) | ... |
| Lesion type (AHA/ACC) | | | | |
| A | 7.9 | 4.8 | 3.1 (−7.6, 13.9) | ... |
| B1 | 34.2 | 35.7 | −1.5 (−22.4, 19.4) | ... |
| B2 | 57.9 | 59.5 | −1.6 (−23.2, 20.0) | ... |
| C | 0 | 0 | 0 | ... |
| Mean stent diameter, mm | 3.3±0.2 | 3.2±0.2 | 0.07 (−0.04, 0.18) | 0.22 |
| 3.5 | 64.9 | 51.2 | 13.7 (−7.7, 35.1) | 0.26 |
| 3.0 | 35.1 | 48.8 | −13.7 (−35.1, 7.7) | 0.26 |
| 2.5 | 0 | 0 | 0 | ... |
| Balloon-artery ratio | 1.0±0.1 | 1.0±0.1 | 0.03 (−0.05, 0.10) | 0.51 |
| Maximal inflation pressure, atm | 16.2±3.6 | 15.1±3.2 | 1.0 (−0.4, 2.5) | 0.18 |
| Postprocedural dissection | | | | 0.76 |
| None | 86.8 | 83.3 | 3.5 (−12.1, 19.1) | ... |
| Type A | 0 | 7.1 | −7.1 (−14.9, 0.6) | ... |
| Type B | 7.9 | 9.5 | −1.6 (−14.0,, 10.7) | ... |
| Type C | 5.3 | 0 | 5.3 (−1.8, 12.4) | ... |
| Other | 0 | 0 | 0 | ... |

AHA/ACC indicates American Heart Association/American College of Cardiology classification.

## Discussion

We investigated the relationship between vessel diameter and angiographic outcome 6 months after sirolimus-eluting stent implantation in patients in the RAVEL trial. The main findings of the study are that sirolimus-eluting stents prevent restenosis irrespective of vessel diameter and do not show the classic inverse relationship of vessel diameter to restenosis rate.

Quantitative coronary angiography convincingly demonstrates the absence of neointimal proliferation and restenosis in all patients treated with the sirolimus-eluting stent within the first 6 months, unlike those treated with bare metal stents. This truly remarkable finding creates a totally new paradigm in interventional cardiology and puts paid to the well-established existing paradigm, the classic inverse relationship between vessel diameter and restenosis rate.[3]

### Prevention of Neointima Growth

Neointimal growth is a normal reaction to vascular injury. Smooth muscle cells are considered to be the main components of coronary artery neointima after stent implantation, and the severity of the reaction may be modulated by the extent of stent-induced vessel injury[14] and the inflammatory reaction around the stent struts.[15]

Vessel injury is influenced by stent surface material, geometric configuration, implantation technique, and vessel size.[16] Neointimal hyperplasia and persistent tissue proliferation are related to the degree of vessel injury (balloon/artery ratio×inflation pressure).[17]

In our patients, 2 stent configurations (6-cell and 7-cell designs) were used. Stent implantation technique varied with vessel size. In small vessels, a relatively higher balloon to artery ratio of 1.3 was achieved, whereas the balloon to artery ratio was lower (1.0) in large vessels. Conversely, the inflation pressure was lower in small vessels than in larger vessels (14 atm versus 16 atm).

In the present study, the effectiveness of the sirolimus-eluting stent was extremely strong and was affected neither by established risk factors for restenosis nor by stent configuration, balloon to artery ratio, or balloon pressure. Other than treatment allocation, the only independent predictor for late loss was the postprocedural MLD.

The very low late loss, which is consistently reported in all studies with sirolimus-eluting stents,[8–10] raised concerns about late lumen enlargement. In the present study, there was evidence of late lumen gain (negative late lumen loss) in 3% of SES patients.

**TABLE 2. Quantitative Coronary Angiography Analysis of Sirolimus-Eluting Stents and Bare Stents, Stratified by Vessel Size**

| | | | | | Target Lesion | | | |
|---|---|---|---|---|---|---|---|---|
| | Vessel Segment | | Stent Segment | | Proximal Edge | | Distal Edge | |
| Stratum/Parameter | SES | BS | SES | BS | SES | BS | SES | BS |
| I | | | | | | | | |
| RD, mm | | | | | | | | |
| Before | 2.09±0.21 | 2.07±0.21 | … | … | … | … | … | … |
| After | 2.30±0.30 | 2.26±0.33 | 2.38±0.26 | 2.40±0.31 | … | … | … | … |
| Follow-up | 2.34±0.42 | 2.11±0.33 | 2.45±0.38 | 2.12±0.32 | … | … | … | … |
| MLD, mm | | | | | | | | |
| Before | 0.82±0.19 | 0..77±0.18 | 0.82±0.19 | 0.77±0.18 | 1.84±0.38 | 1.71±0.40 | 1.53±0.31 | 1.56±0.36 |
| After | 1.66±0.30 | 1.57±0.30 | 2.05±0.25 | 2.06±0.29 | 2.01±0.37 | 1.95±0.33 | 1.82±0.31 | 1.71±0.33 |
| Follow-up | 1.69±0.38 | 1.20±0.37 | 2.04±0.32 | 1.26±0.41 | 1.96±0.42 | 1.73±0.43 | 1.85±0.35 | 1.69±0.41 |
| RR, % | 0 | 35 | … | … | … | … | … | … |
| LL, mm | −0.04±0.29 | 0.37±0.37 | 0.01±0.25 | 0.80±0.43 | 0.04±0.34 | 0.20±0.46 | −0.05±0.29 | 0.03±0.45 |
| II | | | | | | | | |
| RD, mm | | | | | | | | |
| Before | 2.58±0.14 | 2.60±0.14 | … | … | … | … | … | … |
| After | 2.60±0.27 | 2.71±0.34 | 2.74±0.21 | 2.81±0.25 | … | … | … | … |
| Follow-up | 2.77±0.47 | 2.62±0.31 | 2.84±0.42 | 2.58±0.24 | … | … | … | … |
| MLD, mm | | | | | | | | |
| Before | 0.97±0.26 | 0.94±0.21 | 0.97±0.26 | 0.94±0.21 | 2.29±0.44 | 2.19±0.50 | 2.00±0.38 | 2.08±0.40 |
| After | 1.99±0.26 | 2.06±0.32 | 2.45±0.27 | 2.41±0.25 | 2.45±0.31 | 2.48±0.33 | 2.09±0.31 | 2.22±0.36 |
| Follow-up | 2.06±0.43 | 1.58±0.50 | 2.44±0.39 | 1.59±0.53 | 2.38±0.47 | 2.13±0.45 | 2.23±0.45 | 2.13±0.32 |
| RR, % | 0 | 26 | … | … | … | … | … | … |
| LL, mm | −0.07±0.35 | 0.56±0.51 | 0.01±0.38 | 0.88±0.57 | 0.08±0.42 | 0.40±0.39 | −0.14±0.31 | 0.14±0.41 |
| III | | | | | | | | |
| RD, mm | | | | | | | | |
| Before | 3.25±0.38 | 3.22±0.30 | … | … | … | … | … | … |
| After | 2.99±0.43 | 3.01±0.33 | 3.18±0.34 | 3.19±0.29 | … | … | … | … |
| Follow-up | 3.09±0.45 | 2.91±0.50 | 3.29±0.32 | 2.97±0.49 | … | … | … | … |
| MLD, mm | | | | | | | | |
| Before | 1.04±0.41 | 1.13±0.47 | 1.04±0.41 | 1.13±0.47 | 2.75±0.59 | 2.75±0.59 | 2.47±0.46 | 2.55±0.50 |
| After | 2.31±0.36 | 2.35±0.27 | 2.81±0.28 | 2.73±0.31 | 2.98±0.38 | 2.89±0.45 | 2.51±0.50 | 2.65±0.32 |
| Follow | 2.35±0.33 | 1.89±0.46 | 2.86±0.37 | 2.01±0.56 | 2.96±0.32 | 2.64±0.62 | 2.60±0.45 | 2.47±0.43 |
| RR, % | 0 | 20 | … | … | … | … | … | … |
| LL, mm | −0.06±0.25 | 0.47±0.50 | −0.06±0.35 | 0.74±0.57 | 0.03±0.43 | 0.27±0.56 | −0.09±0.31 | 0.18±0.43 |

RR values are given as percentages; all other values are mean±SD in millimeters.
RR indicates restenosis rate; and LL, late lumen loss.

Furthermore, minimal but consistently negative late loss was seen at the distal edges of the stent. This phenomenon might be related to the downstream elution of the drug.

Although the finding of late lumen gain in a very small percentage of patients is interesting, it is worth noting that there have been no clinical events attributable to this phenomenon in the patients treated with the sirolimus-eluting stent at 1-year follow-up, or in the patients of Sousa et al[10] for up to 2 years. Mechanistic angiographic analysis of the Sao Paulo series[10] showed stable lumen dimensions with minimal late lumen loss between 4- and 12-month follow-up (in-stent MLD 2.90±05 mm at 4 months and 2.87±0.4 mm at 12 month; slow-release group) that matches well with the stable clinical result.

### The Importance of Late Loss as a Predictor of Restenosis

The classic inverse relationship between vessel diameter and restenosis rate was not seen in the sirolimus-eluting stent group. This offers new therapeutic options for small vessels, in which conventional stenting is of questionable value.[5] This is especially true for diabetic patients, who often have small arteries because of diffuse coronary artery disease.[18] In addition, they frequently have an exaggerated neointimal

**TABLE 3. Univariate Predictors of Late Loss for All Patients Treated**

| Univariate Predictor of Late Loss | Parameter | Standard Error | R2 | *P* |
|---|---|---|---|---|
| Treatment | 0.814371 | 0.059535 | 0.4653 | <0.001* |
| MLD after procedure, mm | 0.223776 | 0.100029 | 0.0227 | 0.026* |
| Age, y | −0.00724 | 0.003924 | 0.0156 | 0.066 |
| Total length of stents, mm | 0.021843 | 0.012981 | 0.0130 | 0.094 |
| Eccentric IB lesion before procedure | −0.13079 | 0.087642 | 0.0106 | 0.137 |
| Smoking, previous or current | −0.12488 | 0.088079 | 0.0093 | 0.158 |
| Diabetes mellitus | 0.144408 | 0.103526 | 0.0090 | 0.165 |
| Number of stents | 0.222425 | 0.168080 | 0.0081 | 0.187 |
| Thrombus lesion before procedure | −0.28244 | 0.230559 | 0.0072 | 0.222 |
| MLD before procedure, mm | 0.148352 | 0.121476 | 0.0069 | 0.223 |
| Diameter stenosis after procedure, % | −0.03379 | 0.003864 | 0.0045 | 0.328 |
| Lesion type B2 | 0.075694 | 0.082215 | 0.0039 | 0.358 |
| Diameter stenosis after procedure, % | −0.00591 | 0.006459 | 0.0039 | 0.361 |
| QCA lesion length before procedure, mm | 0.011469 | 0.012559 | 0.0040 | 0.362 |
| Unstable angina at screening | 0.072019 | 0.082139 | 0.0036 | 0.382 |
| Male sex | 0.080158 | 0.096519 | 0.0032 | 0.407 |
| Hypertension | 0.064092 | 0.081323 | 0.0029 | 0.432 |
| Eccentric 1A lesion before procedure | 0.064127 | 0.084667 | 0.0028 | 0.450 |
| Eccentric IIa lesion before procedure | 0.102716 | 0.138269 | 0.0026 | 0.458 |
| Previous PTCA | −0.07700 | 0.108119 | 0.0024 | 0.477 |
| Previous CABG | −0.20522 | 0.348366 | 0.0016 | 0.556 |
| Hypercholesterolemia | −0.04599 | 0.081463 | 0.0015 | 0.573 |
| Eccentric IIB lesion before procedure | 0.090999 | 0.186324 | 0.0011 | 0.626 |
| LAD treated | −0.03735 | 0.081421 | 0.0010 | 0.647 |
| Readily accessible lesion before procedure | 0.052347 | 0.132952 | 0.0007 | 0.694 |
| Previous myocardial infarction | 0.020693 | 0.084594 | 0.0003 | 0.807 |
| Calcification (moderate/heavy) before procedure | −0.01526 | 0.096575 | 0.0001 | 0.875 |
| Reference diameter before procedure, mm | 0.003010 | 0.076780 | 0.0000 | 0.969 |

Predictors were chosen by stepwise linear regression using an entry criterion of 0.20 and a stay criterion of 0.05.

QCA indicates quantitative coronary angiography; PTCA, percutaneous transluminal coronary angioplasty; CABG, coronary artery bypass grafting; and LAD, left anterior descending artery.

*Significant.

proliferative response that manifests as significantly greater late loss at the treatment site and a resultant 2-fold increase in in-stent restenosis in small vessels (44% versus 23%, $P=0.002$) as compared with nondiabetic patients with similar-sized vessels.[19] In our study, diabetes mellitus did not attenuate the effectiveness of the sirolimus-eluting stent. These findings contrast markedly with what was seen in the bare stent group. Restenosis rates almost doubled from the tertile with the largest diameter vessels to the one with the smallest vessels (20% to 35%), whereas late loss increased only modestly (0.74 mm to 0.80 mm). This dramatic increase in restenosis rate is explicable on the basis of hydraulics. A late loss of 0.80 mm in a 3.0-mm diameter vessel versus a 2.0-mm diameter vessel results in a 46% versus a 64% obstruction. Late loss is the most sensitive and operator-independent assessment of the effect of drug-eluting stents and can be used to predict what the restenosis rate will be in vessels of different diameters. Simply reporting angiographic restenosis rates, which can be influenced by case selection and operator techniques, is no longer sufficient in the era of drug-eluting stents.

**TABLE 4. Multivariate Predictors of Late Loss**

| Multivariate Predictor of Late Loss | Parameter | Standard Error | R2 | *P* |
|---|---|---|---|---|
| Treatment | 0.810123 | 0.058706 | 0.4653 | 0.0001* |
| MLD after procedure, mm | 0.196763 | 0.072959 | 0.4829 | 0.0076* |

Predictors were chosen by stepwise linear regression using an entry criterion of 0.20 and a stay criterion of 0.05.

*Significant *P* value.

## Conclusion

Sirolimus-eluting stents prevent neointimal proliferation and late lumen loss irrespective of the vessel size. The classic inverse relationship between vessel diameter and restenosis rate was seen in the bare stent group but not in the sirolimus-

eluting stent group. This finding with the sirolimus-eluting stent has the potential to considerably expand the use of these stents in smaller vessels and to eliminate the present difference in reintervention rates between patients treated with coronary artery bypass surgery and stenting.[20]

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## PART 3: DRUG ELUTING STENTS

*Chapter 12*

Degertekin M, *Regar E*, Tanabe K, Smits P, van der Giessen WJ, de Feyter P, Foley DP, Carlier SG, Ligthart JMR, Bruining N, Serruys PW:
**SIROLIMUS-ELUTING STENT FOR TREATMENT OF COMPLEX IN-STENT RESTENOSIS: THE FIRST CLINICAL EXPERIENCE.**
J Am Coll Cardiol. Accepted for publication.

# SIROLIMUS-ELUTING STENT FOR TREATMENT OF COMPLEX IN-STENT RESTENOSIS: THE FIRST CLINICAL EXPERIENCE

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## ABSTRACT

**Objectives.** In this study, we assess the value of sirolimus-eluting stent implantation in patients with complex ISR.

**Background:** The treatment of in-stent restenosis (ISR) remains a therapeutic challenge, since many pharmacological and mechanical approaches have shown disappointing results. Sirolimus-eluting stents 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 18.4mm) and objective evidence of ischemia were included. They received one or more 18mm sirolimus-eluting Bx VELOCITY stents. The stents were loaded with sirolimus in a slow release formulation (>28 days drug release). Quantitative angiographic and 3D IVUS follow-up was performed at 4 months and clinical follow-up at 9-months.

**Results:** Sirolimus-eluting stent implantation (n=26) was successful in all 16 patients. Four patients had recurrent restenosis following brachytherapy, and 3 had totally occluded vessels pre-procedure. The in-hospital course was uneventful. At 4-month follow-up, 1 patient had died and 3 patients had angiographic evidence of restenosis, (1 in-stent and 2 in-lesion). In-stent late lumen loss averaged 0.21mm and the mean percent volume obstruction of the stent by IVUS was 1.2%. At 9 months clinical follow-up, 3 patients had experienced 4 major adverse cardiac events (2 deaths, 1 acute myocardial infarction necessitating repeat target vessel angioplasty.

**Conclusion:** Sirolimus-eluting stent implantation in patients with severe ISR lesions effectively prevents neointima formation and recurrent restenosis at 4-month angiographic follow-up. The 9-month clinical follow-up showed a relatively low rate of major adverse cardiac events in a patient population with highly vascular disease.



## CONDENSED ABSTRACT

The outcome of sirolimus-eluting stent implantation in patients with complex ISR was evaluated. Sixteen patients with severe recurrent ISR (81% had diffuse, proliferative or totally occlusive lesions) in native coronary arteries received 26 sirolimus-eluting Bx-VELOCITY™ stents. All procedures were successful. At 4-months follow-up, in-stent late lumen loss averaged 0.20mm, percent volume obstruction of the stent was 1.2% and 3 patients had repeat restenosis. At 9-months clinical follow-up, 3 patients experienced 4 major adverse cardiac events (2 deaths, 1 MI, and 1 PTCA). Sirolimus-eluting stent implantation effectively prevents neointima formation and restenosis in a patient population with highly complex lesions.


## ABBREVIATIONS AND ACRONYMS

CABG= coronary artery bypass graft surgery
DS= diameter stenosis
ISR= in-stent restenosis
IVUS= intravascular ultrasound
MI= myocardial infarction
MLD= minimal luminal diameter
MACE= major adverse cardiac events
PCI: percutaneous coronary intervention
PTCA= percutaneous coronary angioplasty
QCA= quantitative coronary angiography

## INTRODUCTION

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). In-stent restenosis is mainly caused by neointimal hyperplasia [1] and in rare instances by mechanical factors such as incomplete stent expansion [2].

The treatment of ISR remains a therapeutic challenge, as all pharmacological [3] and mechanical treatment modalities have shown disappointing results. The recurrence rates after balloon angioplasty and stent-in-stent implantation [4], directional [5], rotational-directional or laser atherectomy [6] are reported to be in the range of 40%.

Intracoronary radiation is the only therapy for ISR proven to be effective in randomized clinical trials[7, 8, 9]. However, restenosis is not eliminated. Furthermore, the widespread use of intracoronary radiation therapy is limited by considerable logistic requirements [10,11] and potential side effects such as edge effects[12], geographic miss [13], delayed healing [14] and late thrombosis [15].

Attention is now focusing on the concept of local pharmacological 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 [16], [17]. Sirolimus is a potent immunosuppressive agent with antimigratory and antiproliferative effects on vascular smooth muscle cells, by blocking $G_1$/S transition. The inhibition of proliferation is mediated by sirolimus binding to its cytosolic receptor, FK506-binding protein 12, and associated with reduced cdk2 activity and protein retinoblastoma phosphorylation [18,19]. These findings suggest that sirolimus might also be useful for the treatment of ISR, which is further supported by findings in human carotid arteries [20]. A robust upregulation of FK506-binding protein 12 was detected in the neointimal tissue of restenotic lesions, whereas no FK506-binding protein 12 was detectable in smooth muscle cells from control media.

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

## METHODS

### Patient population

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

### In-stent restenosis definition

In-stent restenosis was defined as >50% diameter stenosis by quantitative coronary angiography within a previously (at least 4 months) stented vessel segment. In-stent restenosis was classified as focal (<10mm length), diffuse (>10mm length), proliferative (>10mm length and extending outside the stent edges) or totally occluded [21].

### Stent-in stent implantation and periprocedural medications

All in-stent restenotic lesions were predilated with conventional angioplasty balloons or cutting balloons. Then a sirolimus-eluting Bx VELOCITY™ stent (Cordis Waterloo, BL) was implanted 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 18mm long and 2.5-3.5 mm in diameter. Post-dilatation was performed as required.

During the procedure, intravenous heparin was given to maintain activated clotted time >300 seconds. All patients received aspirin (325 mg/d, indefinitely) and clopidogrel (300 mg loading dose immediately after stent implantation followed by 75 mg/d for 2 to 4 months at the discretion of the operator).

**Follow-up**

Angiographic and intravascular ultrasound (IVUS) follow-up were performed at 4 months and clinical follow-up at 9 months after the index procedure. Major adverse cardiac events (MACE) were defined as death, myocardial infarction, target vessel repeat percutaneous coronary intervention or coronary artery bypass grafting (CABG). Myocardial infarction (MI) was defined as a rise in creatine kinase enzyme level to more than twice the upper limit of normal values, accompanied by increased creatine kinase-myocardial band levels, in the absence or presence of pathological Q waves on the standard surface electrocardiogram.

**Quantitative coronary angiographic analysis**

Serial coronary angiography was performed at baseline (before and after intervention) and at 4-month follow-up. Intracoronary nitrates were administered before each angiographic acquisition. Post-procedure angiography was performed in at least 2 orthogonal projections, which were repeated at follow-up angiography.

Two coronary segments were subjected to quantitative angiography: in-stent and in-lesion. The in-stent analysis encompassed the length of the sirolimus-eluting stents, which covered the ISR segment. The in lesion segment was defined as the sirolimus-eluting stent plus 5mm proximal and 5mm distal to the stent or to the nearest side branch. Quantitative angiographic analysis was performed by an independent core laboratory (Brigham and Women's Hospital, Boston, Mass).

Minimal lumen diameter (MLD) and percent diameter stenosis (DS) were calculated for each segment. DS was defined as the minimal luminal diameter within the stented segment related to the interpolated diameter measured over the length of the stent. Late loss was calculated as MLD post-intervention minus MLD at follow-up. In-stent and in-lesion restenosis was defined as more than 50% DS at follow-up, located within the sirolimus-eluting stent and target lesion, respectively.

**Intracoronary ultrasound (IVUS) analysis**

Serial IVUS was performed with a mechanical 30mHz single element transducer system (CVIS, Boston Scientific Corp, Maple Grove, MN) at immediately after the intervention and 4-month follow-up. IVUS images were acquired using motorized pullback at a constant speed of 0.5 mm/s after intracoronary administration of isosorbide dinitrate. IVUS analysis included the sirolimus eluting stent as well as the vessel l segment beginning 5 mm distal to and extending 5 mm proximal to the stented segment. A computer-based contour detection program was used for automated 3-D 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. Feasibility, reproducibility and inter- and intra-observer variability of this system have been validated in vitro and in vivo[22, 23.] Volumetric changes of the vessel structures, from post-procedure (PP) to 4 month follow-up were compared. 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. Comparisons between immediately post procedure and the 4-month follow-up measurements were performed with a 2-tailed paired t test. A value of $p<0.05$ was considered statistically significant.

## 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 4 had diabetes mellitus. Four patients with recurrent in-stent restenosis after intracoronary beta-brachytherapy, and 1 heart transplant recipient with proliferative in-stent restenosis were included.

**Procedural data**

Lesion and procedural characteristics are shown in Table 2. The average length of the restenotic segment was 18.4±13.1mm: 3 lesions were focal (class I), 5 diffuse (class II), 5 proliferative (class III) and 3 showed total occlusion of the stent (class IV).

A total of 26 sirolimus-eluting stents were implanted. Nine patients received a single stent, and 6 received 2 stents to cover long lesions. In one patient with a totally occluded vessel, 5 sirolimus-eluting stents were implanted. All patients were discharged without complication 1 day after the procedure. No death, acute MI, repeat intervention of CABG occurred during this period.

**Angiographic outcome and 3D IVUS analysis**

Quantitative coronary angiography data are presented in Table 3. 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 Figure1.

In one patient, who received two drug-eluting stents 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), non-compliant 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 2 sirolimus-eluting stents. Both IVUS and angiographic analysis revealed a gap of 2.2mm between the two drug-eluting stents. Neointimal proliferation occurred precisely at the bare segment between the two stents (Figure2). 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 on-line QCA. The second case was the heart transplanted recipient who had a 62% DS proximal to the stent. The vessel, which had TIMI 1 flow prior to implantation of the sirolimus-eluting stents, had been extensively ballooned during the procedure and the injured area was not completely covered by 2 stents. As the patient had no evidence of ischemia by radionuclide scintigraphy, repeat revascularization was not performed. Subsequent follow-up has been uneventful. All other patients showed only minimal late lumen loss. IVUS examination also showed minimal neointimal hyperplasia without any significant difference between the post-procedure and follow-up lumen volumes.

In one a patient who had previously undergone brachytherapy and showed restenosis at follow-up associated with a "black hole" [24,25] prior to sirolimus eluting stent implantation, IVUS showed re-

appearance of the “black hole” at 4-month follow-up. The eccentric, non-obstructive, echolucent luminal tissue was situated in the proximal portion of the stent-in stent segment.

**Nine-month 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 sirolimus-eluting stents in the RCA. Unfortunately, no clinical or autopsy information is available.

The second patient, who had received 5 sirolimus-eluting stents and had a residual in-stent stenosis of 34% post-procedure, showed no late lumen loss at 5 months follow-up, but developed an inferior myocardial infarction 7 months after the index procedure. This event occurred after the follow-up angiogram and IVUS, which may have damaged the endothelial lining of the stent and 3 weeks after discontinuing clopidogrel. Angiography revealed a proximal total occlusion of the artery. The patient was successfully treated with thrombus aspiration followed by balloon angioplasty. IVUS after thrombectomy showed a well-expanded stent without neointimal hyperplasia.

The third patient, who had failed brachytherapy, had no evidence of neointimal hyperplasia at 4 month follow-up IVUS, but died due to congestive heart failure 9.5 months after the index procedure. This 79 years old man with left main coronary artery disease and congestive heart failure had undergone coronary by-pass surgery twice and had percutaneous coronary intervention four times before the index procedure. He had also been treated with brachytherapy for his second ISR prior to receiving a sirolimus-eluting stent.

## DISCUSSION

We describe the first European experience with sirolimus-eluting stents for the treatment of ISR. We conclude that: 1) Sirolimus-eluting stents effectively prevent neointima formation at 4 month follow-up; 2) Late lumen loss is very low and comparable to that seen in de-novo lesions; 3) The relatively high clinical event rate at 9-months is related to the patient population treated, who had highly complex lesions and an intrinsically high rate of complications, and not due to failure of the device; and 4) Careful attention to implantation technique is requiring to avoid treatment failure.

**The drug and its clinical application in coronary arteries**

Sirolimus (rapamycin) is a FDA approved immunosuppressive drug for the prevention of renal transplant rejection. It has potent antiproliferative and antimigratory effects on vascular smooth muscle cells [26]. The first clinical application of sirolimus-eluting stents in simple de novo lesions proved feasibility and short term safety of this device. No adverse events attributable to the stent, the coating or the drug were seen and angiographic follow-up at 6 and 12 months showed impressive results without restenosis and minimal late lumen loss[16, 17,27.] These findings provoked considerable enthusiasm [28], but also profound skepticism [29]. The major criticism focused on the lack of data in complex lesions and on the lack of long-term data.

**Sirolimus eluting stents in in-stent restenosis**

In this report, we describe the application of sirolimus-eluting stents in a subset of patients presenting with extremely complex lesions and one of the most challenging therapeutic problems today, that of ISR. Our patients had been treated up to 4 times for restenosis after stent implantation, 81% had in-stent restenosis lesions longer than 10mm (average lesion length 18.4mm and 4 total occlusions),

and 25% had failed previous brachytherapy In addition, one patient was a heart transplant recipient with diffuse ISR and TIMI I flow. Notwithstanding the challenging population treated, we found strikingly similar results in terms of suppression of neointimal proliferation to that reported previously in de novo lesions in lower-risk patient populations[16 27]. The acute procedural success was excellent, and the in-hospital outcome was uneventful. At 4-month angiographic follow-up, only 1 patient with prior total occlusion showed repeat in-stent restenosis due to silent total re-occlusion of the vessel. In the remaining patients, late lumen loss averaged 0.08 mm and volume obstruction within the stent was 1.2%. This is similar to the findings in de-novo lesions and 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 1.36mm [30]. A registry of patients undergoing rotational atherectomy followed by beta radiation revealed a restenosis rate of 10% with a late lumen loss of 0.37mm [31]. The follow-up period is only 4 months in the present study, compared to 9 months in the other studies. However, the recently reported long-term data from the Sao Paulo group, which demonstrated that the 4 months results are preserved at one year in de novo lesions, support the notion that our 4-month angiographic and 3_D IVUS data may be predictive of the long-term findings. [27]

**Important clinical findings**

Despite our relatively small patient population, we witnessed some remarkable phenomena: First, neointimal hyperplasia in a gap between 2 sirolimus-eluting stents and at a site of injury that was not completely covered by the sirolimus-eluting stent. This case illustrates the therapeutic power of sirolimus- eluting stents, since the patient serves as his own control (Figure2).

Second the treatment of a patient with severe transplant vasculopathy. The patient presented with a small, diffusely diseased vessel and impaired flow (TIMI 1) and received 2 sequential, overlapping 2.5mm diameter sirolimus-eluting stents at the site of ISR. The vessel segment proximal to the stents was treated by balloon dilatation. At follow-up there was only minimal neointimal hyperplasia within the sirolimus-eluting stents, and angiographic restenosis occurred at the proximal adjacent vessel segment, outside the stents.

Third, the treatment of a patients after failed brachytherapy. We treated 4 patients who had failed brachytherapy, two of whom developed clinical events. First, silent occlusion occurred in a patient who had received 2 sirolimus-eluting stents for a total occlusion. The second patient, a 79 years old male, died due to congestive heart failure 9.5 months after sirolimus-eluting stent implantation. This patient suffered from extensive coronary artery disease with left main coronary artery disease, 2 previous CABG procedures, recurrent in-stent restenosis despite brachytherapy, and poor left ventricular function. Brachytherapy failure patients were responsible for 1/3 of all MACE, and represent a particular challenge. These patients can have prolonged endothelial dysfunction, which can increase the risk of thrombosis, and there are currently no data available on the combined effect of radiation and cytostatic drug therapy in coronary arteries.

Late vessel occlusion occurred in 2 additional patients who had not been treated with brachytherapy: One patient with 5 drug-eluting stents, experienced acute vessel closure and developed myocardial infarction after follow-up angiography and IVUS 3 weeks after discontinuing clopidogrel. IVUS performed at the time of the acute MI following primary PTCA showed no evidence of neointimal hyperplasia within the stents and thrombus formation as the cause for the occlusion. The second patient who had received 2 sirolimus-eluting stents died suddenly and we have to consider this as an acute cardiac and possibly thrombotic event[15]. Therefore, it seems wise to propose that patients receiving more than one sirolimus-eluting stent for the treatment of in-stent restenosis, particularly in

the setting of failed brachytherapy, total vessel occlusion, or poorly deployed stents, should receive clopidogrel for an extended period.

## CONCLUSION

Our findings suggest that sirolimus-eluting stent implantation is a highly effective treatment for patients with complex ISR, even when they are at an intrinsically high risk for complications. This may expand indication for drug-eluting stents in the future. As the use of drug-eluting stents increases, the number of interventional procedures will increase, and most importantly, their complexity and the range of indications will expand towards higher risk patient populations, including chronic total occlusions and left main stem lesions. In this setting, stenting the whole area injured by the balloon, overlapping sirolimus-eluting stents 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. Meticulous clinical, qualitative and quantitative IVUS and angiographic assessment are needed to understand the mechanisms of action and potential reasons for treatment failure.

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**TABLE 1**

**Baseline Clinical Characteristics**

| Variable | n (%) |
|---|---|
| Patients | 16 |
| Male sex | 12 (75) |
| Age, y | 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.

**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 eluting stent per lesion | 1.62 ± 1.02 |
| Implanted eluting stent length (mm) | 28.5 ± 18.0 |
| Implanted eluting stent 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, percutaneous coronary intervention.

**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 month after the procedure was not included in this analysis.
RD; reference diameter, MLD; minimal lumen diameter, DS; diameter stenosis

**TABLE 4 :**

**Volumetric VUS Measurements by Core Lab.**

| N=11 | Post-Procedure | 4-Month Follow-up |
|---|---|---|
| Stent length (mm) | 20.6 ±6.2 | 20.5 ±6.6 |
| Stent volume ($mm^3$) | 159.9±60.4 | 158.1 ±73.0 |
| Lumen volume ($mm^3$) | 159.9±60.4 | 156.5 ± 73.7 |
| NIH ($mm^3$) | NA | 1.6 ± 3.5 |
| Volume obstruction (%) | NA | 1.2 ± 2.7 |

P=NS

**TABLE 5**

**Individual 9-month Outcome in 16 Patients Treated with Sirolimus Eluting Stent for In-stent Restenosis**

| Case | ISR Pattern | Number of Previous PCI | Brachytherapy Failure | Lengthof Sirolimus ElutingStent (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 |

ISR; in-stent restenosis, PCI; percutaneous coronary intervention
*Events are Death, Myocardial infarction, Target vessel revascularization (PTCA/CABG).
†No repeat PCI were performed. Treatment strategies for restenotic vessels were explained in the Results section

**FIGURE LEGENDS**

**Figure 1.**
A chronically occluded LCX due to in-stent restenosis (Pre) was treated with a Sirolimus-eluting stent (Post). Follow-up angiography showed no restenosis; IVUS revealed no neointimal hyperplasia with the clear appearance of double stent struts.

**Figure 2.**
Angiograms: The long proliferative in-stent restenosis (Pre) was treated with two Sirolimus-eluting stents (Post). The follow-up angiogram showed focal repeat in-stent restenosis (62%DS) in the gap (arrow) which was not covered by the Sirolimus-eluting stents. No neointimal hyperplasia was evient in the 2 Sirolimus-eluting stents (A and C).
IVUS: Follow-up IVUS showed no neointimal hyperplasia in the proximal (A) and distal (C) Sirolimus-eluting stents with images of two layers of stent struts. Neointimal hyperplasia was noted in the gap region (B) where only 1 layer of (bare) stent struts can be seen..

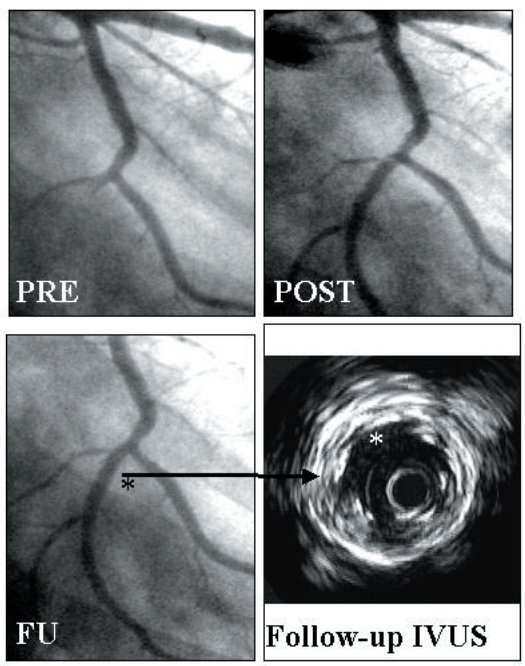
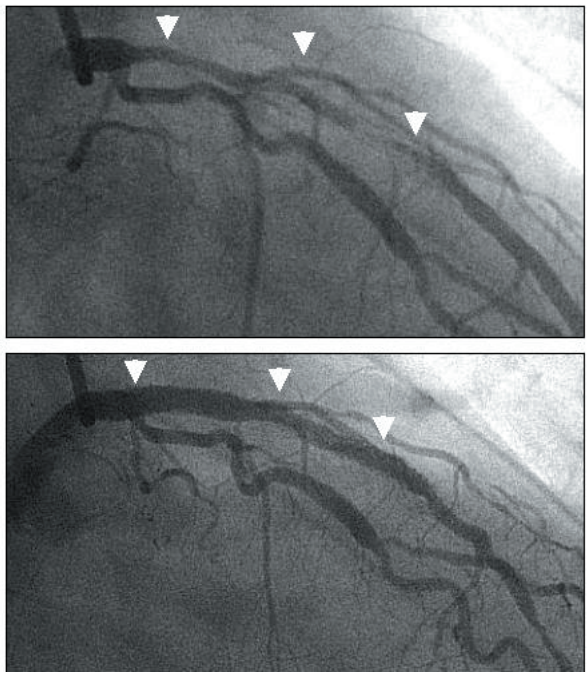



**FIGURE I**

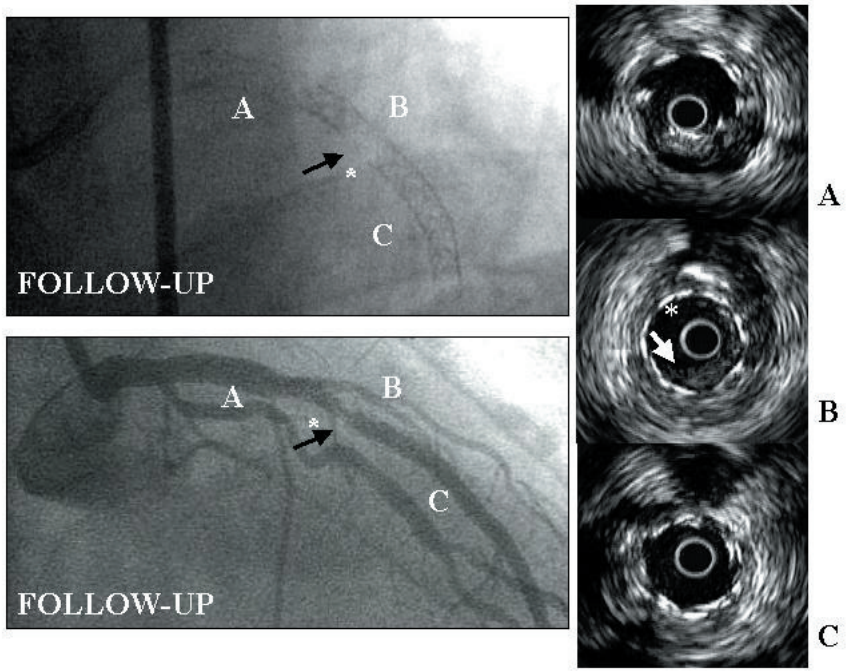
**FIGURE-II**



PRE-PROCEDURE

POST-PROCEDURE

**FIGURE-II**



## PART 3: DRUG ELUTING STENTS

*Chapter 13*

*Regar E*, Lemos PA, Degertekin M, Tanabe K, Lee CH, Sianos G, de Feyter P, van der Giessen WJ, Smits PC, van Domburg RT, Serruys PW:
**INCIDENCE OF THROMBOTIC STENT OCCLUSION AFTER RAPAMYCIN-ELUTING STENT IMPLANTATION IN 500 CONSECUTIVE PATIENTS TREATED IN THE "REAL WORLD".**
Submitted for publication.

# Incidence of Thrombotic Stent Occlusion After Rapamycin-Eluting Stent Implantation in 500 Consecutive Patients Treated in the "Real World".

The Rapamycin-Eluting Stent Evaluation At Rotterdam Cardiology Hospitals (RESEARCH)

Registry

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*Submitted for publication*

## ABSTRACT

Rapamycin (sirolimus )-eluting stents have proven to significantly reduce restenosis in highly selected patients. Sirolimus has potent anti-proliferative mechanisms of action but its impact on reendothelialization and endothelial function is not completely evaluated in the clinical setting.
Aim: To evaluate the incidence of thrombotic stent occlusion after sirolimus-eluting stent implantation in an unselected patient population.
Methods: Since 16th April 2002 the sirolimus-eluting stent (SES) is used in our institution for all percutaneous interventions, including unstable patients, acute myocardial infarction and brachytherapy failures with no anatomical exclusion criteria. Thrombotic stent occlusion was defined as "acute" within 24h, "subacute' between 24h and 30 days and "late" more than 30 days after the index procedure.
Results: From 16th April to 17th September 2002, 510 patients (pts) were enrolled. All pts had a minimum of 30 days of follow-up from the index procedure (mean follow-up period 101 ± 43 days [range 30 - 184 days]) and 298 pts had completed 3 or more months of follow-up. During follow-up 2 (0.4%) patients developed SES thrombosis, at 6 hours and at 11 days after the procedure. No late thrombotic occlusion was observed. Both cases of stent thrombosis occurred in diabetic females with complex coronary lesions. IVUS at reintervention revealed inadequate stent expansion and uncovered distal dissection as possible mechanical reasons.
Conclusions: Sirolimus-eluting stents show a low incidence of 0.4% of thrombotic occlusion in an unselected patient population. Stent thrombosis rate and time frame were comparable to that for bare metal stents.


## INTRODUCTION

Rapamycin (sirolimus )-eluting stents (SES) have proven to significantly reduce restenosis in highly selected patients with relatively simple lesion [1]. Persistent neointimal growth inhibition has been documented up to 2 years [2, 3]. Importantly, the favorable late outcomes observed after SES implantation were accomplished without compromising the well-established low incidence of acute complications with currently available bare stents.
However, the results derived from non-complex cases included in the initial trials may not be directly extrapolated to larger populations of unselected patients.
Sudden stent thrombosis is, even being rare, of considerable clinical importance as it is associated with major myocardial infarction in 60%-70% of the cases, with short-term mortality rates of 20% or higher [4]. Acute coronary syndrome, long stents, small vessels, chronic total occlusion and multi-vessel intervention are well-known predictors for (sub) acute stent thrombosis in bare metal stents [5]. The impact of these parameters on sirolimus-eluting stent implantation are unclear. We therefore evaluated the incidence of thrombotic stent occlusion after sirolimus-eluting stent implantation in a consecutive series of patients with complex clinical situations and coronary lesions.

## METHODS

### Patients and objectives

Since 16th April 2002, sirolimus eluting Bx VELOCITY™ stents (Cypher™; Cordis Corp., Johnson & Johnson, Warren, NJ, USA) implantation had been instituted as the default strategy for all percutaneous coronary interventions (PCI) performed at our institution as part of the Rapamycin-Eluting Stent Evaluation At Rotterdam Cardiology Hospitals (RESEARCH) registry. This registry evaluates the efficacy of sirolimus-eluting stent (SES) as the device of choice for all consecutive patients submitted to PCI in the daily practice. All clinical situations and lesion morphologies were considered eligible with no anatomical restrictions. The local ethical committee approved the study protocol and written informed consent was obtained in all patients.

### Stent implantation and periprocedural medication

SES was available in diameters from 2.25mm to 3.00mm and lengths of 8, 18, and 33mm. All SES contained 140µg sirolimus/$cm^2$ (±10%). All procedures were performed according to standard techniques and interventional strategy was left to the discretion of the individual operator. The aim of the procedure was to achieve a less than 20% residual diameter stenosis by on-line quantitative coronary analysis [6] with an antegrade TIMI 2-3 flow. Intravascular ultrasound, Doppler coronary flow reserve, and/or fractional flow reserve were allowed as a guidance for optimum stent deployment and high pressure stent deployment is highly recommended. Adjunctive ablative techniques, as well as direct stenting were allowed. Multiple stents, either in the same segment or in different locations were allowed to treat long and tandem lesions, border dissection, and multivessel disease.

All patients were on chronic aspirin medication (>75mg daily) and received a loading dose of clopidogrel (300mg). Weight-adjusted heparin was administrated to achieved an activated clotting time of >300 sec). GPIIb/IIIa inhibitors were given at the discretion of the operator.

Postprocedural antiplatelet regimen consisted in aspirin lifelong and clopidogrel 75mg/d for 3 months. Prolonged clopidogrel prescription (6 months) was recommended a priori defined subsets of lesions with in long stents (>3 stents or >36mm total stent length), chronic total occlusion, bifurcations and in-stent restenosis.

### Clinical follow-up

Clinical follow-up was performed by scheduled visits at the outpatient clinic or by direct contact (phone call or regular mail). Additional information was collected by contacting the patient's referring cardiologists, general practitioners or the Dutch Civil Registry.

A definite diagnosis of myocardial infarction required the presence of post-procedure enzymatic elevation in at least 1 sample (CKMB > 5X the upper limit for normal) or the identification of new pathologic Q-waves in the ECG. Such strict criteria was based on recent reports that demonstrated a prognostic importance only for large periprocedural infarctions (either diagnosed by the new Q-waves or substantial enzymatic elevation). In these studies, minor enzymatic release failed to influence the occurrence of in-hospital or post-discharge death [7, 8].

### Definition of thrombotic stent occlusion

Thrombotic stent occlusion was angiographically documented as a complete occlusion (TIMI flow 0 or 1) or a flow limiting thrombus (TIMI flow 1 or 2) of a previously successfully treated artery (TIMI flow 3 immediately after stent placement and percent in-lesion diameter stenosis=<30%).
Acute was defined as occurring =<24 hours, subacute as occurring > 24 hours to =<30 days following the study procedure. Late was defined as occurring > 30 days after the index procedure.

### Statistics

Continuous variables were expressed as mean ± 1 SD and compared by Student's T test. Discrete variables were presented as count and percentages.

## RESULTS

### Patient, lesion and procedural baseline characteristics

Between 16th April and 17th September 2002, 510 patients received at least one SES. In these patients a total of 860 lesions was treated using 1111 Cypher stents.
The baseline demographic, admission and angiographic data are shown in Table 1. It is of note that 15.7% of our patients presented with acute myocardial infarction and 32.4% with unstable angina while only 51.9% of patients were treated for symptomatic stable angina (Table 2).

### Antiplatelet therapy

52% of our patients received short-term combined aspirin-clopidogrel treatment, 48% long-term prescription (6months). Complex lesion subsets, antiplatelet treatment prescription and clinical outcome are summarized in Table 3.

### Thrombotic stent occlusion

All included patients had a minimum of 30 days of follow-up from the index procedure (mean follow-up period 101 ± 43 days [range 30 - 184 days]) and 298 patients had completed 3 or more months long follow-up.
During follow-up 2 (0.4%) patients developed SES thrombosis, at 6 hours and at 11 days after the procedure. Late thrombotic occlusion did not occur in any patient of the long follow-up subgroup.

### Case 1 - acute stent thrombosis (6h after the index procedure)

The patient was a 72-year old female with insulin-dependent diabetes mellitus, presenting at the index procedure with unstable angina, Braunwald class IB. She had 2-vessel disease with multiple lesions in the right coronary artery (RCA) and the distal left anterior descending (LAD) artery (Figure 1A). Treatment consisted in SES implantation in the RCA (Cypher 3.0/8mm), right

posterior descending artery (Cypher 2.5/18mm) and distal and periphery LAD (Figure 1B). Aspirin/clopidogrel combination therapy was prescribed for 6 month.
Six hours after the procedure, the patient developed chest pain and a ST-elevation myocardial infarction (peak CPK 2.8 X the upper normal limit). Acute coronary angiography showed the occlusion of the SES in the periphery LAD (Figure 1C). IVUS showed an under-expansion of the stent and a distal edge dissection that was not visible on the angiogram at the time of the index procedure.

**Case 2 - Subacute stent thrombosis**

The patient was a 61 year old female with insulin-dependent diabetes mellitus and stable angina (CCS class 2). She had 2-vessel disease with a spontaneous recanalized occlusion of the RCA and a total chronic occlusion of the LAD (Figure 2A). The index procedure consisted in the recanalization of the LAD and implantation of two SES stents (Figure 2B). Aspirin/clopidogrel combination was prescribed for 6 month.
2 Days after the procedure the patient suffered from repeated episodes of chest pain but did not seek for medical attention. After 11 days from the index procedure, a coronary angiography showed an occlusion in the distal portion of the stented LAD segment. IVUS revealed an under-expansion of the stent (Figure 2C).

## DISCUSSION

We describe the incidence of thrombotic stent occlusion after sirolimus-eluting stent implantation in a large series of unselected patients. The incidence of 0.4% (n=2) is low and comparable to that for bare metal stents. Both cases of stent thrombosis occurred in diabetic females with complex coronary lesions and IVUS revealed inadequate stent expansion and uncovered distal dissection as possible mechanical explanations. All thrombotic occlusions occurred within the first month after the procedure.

**Low incidence of stent thrombosis**

Coronary stent utilization was hampered in the early days by the excessive incidences of subacute stent thrombosis and hemorragic complications due to an aggressive anticoagulant regimens [9, 10]. However, systematic high-pressure stent implantation [11] and combined oral antiplatelet therapy [12] have substantially reduced the incidence of thrombotic occlusion with a minimum risk of bleeding. The low thrombotic rate of 0.4% after SES implantation observed in our series is remarkable in three aspects.
First, this clearly demonstrates that theoretic concerns derived from experimental data do not apply in clinical practice. Previous studies suggested that sirolimus could significantly enhance agonist-induced platelet aggregation [13] and induce endothelial function impairment [14]. Animal models showed focal remnants of residual fibrin deposition adjacent to the struts that may reflect a delay in arterial repair or simply impaired fibrin degradation secondary to the local effects of the drug [15]. Altogether, these features could potentially increase the risk of thrombotic complications

after SES implantation. However, neither our data nor the FIM series [16, 17] or the multicenter RAVEL trial [1] (both 0% stent thrombosis) support such worries.
Second, we observed this low stent thrombosis rate after SES implantation in an unselected patient population that included a large proportion of high risk patients with acute coronary syndrome, acute myocardial infarction (together 50% of our population), diabetes mellitus, long lesions[5], multivessel intervention [18], in-stent restenosis and failed brachytherapy. These risk factors represent exclusion criteria for many stent studies that, in consequence, are more likely to reflect the outcome in patients at lower risk for thrombotic events than our study population. Even when neglecting these potential confounders our result of 0.4% SAT compares favorable to contemporary bare stent trials that report SAT rates in the range of 1%-3% [19-22].
Third, all SES thrombosis occurred within 1 month after the index procedure, a time frame that matches exactly with previous reports for bare metal stents [23]. This is of note, as the question regarding possible late occurrence of thrombotic events induced by sirolimus has been raised as a result of the recent experience with intracoronary brachytherapy where a relatively high incidence of late stent thrombosis was documented, with approximately 70% of cases occurring between 1 and 3 months after the procedure [24, 25]. At the time of this analysis, 298 of our patients had completed a follow-up period of at least 3 months with no evidence of stent thrombosis. Importantly, these findings have to be interpreted taking into consideration the presence of several factors that could have even enhanced an eventual deleterious effect of sirolimus in our series, such as the high number of overlapping stents and the increased total length of implanted stent. Furthermore, none of the patients that have received a sirolimus eluting stent to treat repeat occurrence after failed brachytherapy had developed thrombotic stent occlusion.

**Impact of antiplatelet therapy**

Both stent occlusions occurred under combined antiplatelet medication. It can not completely be ruled out (and has not been tested) that both subjects were non-responder to acetyl salicylic acid, a entity that has been described to occur in up to 10% of angioplasty patients [26].
Up to date the optimal duration of antiplatelet therapy after sirolimus-eluting stent implantation is unclear. Our patients received combined antiplatelet therapy for at least 3 month, as it has been proven to be safe in the multicenter RAVEL and SIRIUS trial. We recommended prolonged antiplatelet therapy in higher risk patient subsets and in lesions, where we suspected a potentially longer re-endothelialization process because of the extent of injury. The compliance rate to the recommendations, however, indicates that there is a clear need to clarify the clopidogrel prescription, especially in patients with acute myocardial infarction. Controlled clinical trials are needed in the future to allow for optimal, evidence based instead of empirical antiplatelet treatment of our patients.

## LIMITATIONS

With this prospective, single-center registry of SES implantation, all the caveats of a registry study apply, including the absence of control group. Due to the limitation of availability, only SES with diameters 2.25 and 3.0 were implanted. Moreover, adverse effects may exhibit latency and escape clinical recognition until very late follow-up is completed.

## CONCLUSION

Sirolimus-eluting stents show a low incidence of thrombotic occlusion in an unselected patient population treated in the “real world” of interventional cardiology. The thrombotic rate of 0.4% and the time frame were comparable to that for bare metal stents.

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**Table 1: Patient, Lesions and Procedural Baseline Characteristics**

| | |
|---|---|
| Age | 61.4 ± 11.6 years |
| Male sex | 70.2 % |
| Diabetes | 18.6 % |
| Current smoking | 32.8 % |
| Hypertension | 43.8 % |
| Previous MI | 30.3 % |
| Previous PCI | 25.5 % |
| Previous CABG | 10.0 % |
| Previous brachytherapy | 2.7% |
| Coronary artery disease | |
| Single-vessel disease | 45.7 % |
| Double-vessel disease | 27.9 % |
| Triple-vessel disease | 24.6 % |
| Stable Angina, | 51.9 % |
| Unstable angina | 32.4 % |
| Acute MI | 15.7 % |
| IIBIIIA inhibitor use | 24.0 % |
| Treated vessel * | |
| LMC | 3.6 % |
| LAD | 56.8 % |
| LCx | 32.1 % |
| RCA | 34.7 % |
| Multi-vessel SES implantation | 25.0% |
| Number of SES per procedure | 2.1 ± 1.3 stents |
| Total length of the implanted stents | 37.8±26.7mm/patient (range 8-184mm) |
| Overlapping stents | 42.3 % |
| Small stent diameter (2.5 or 2.25mm) | 26.0% |
| Postdilatation performed | 53.0% |
| RD | 2.67±0.55 mm |
| MLD pre | 0.79±0.52 mm |
| DS pre | 70.8±19.4 % |
| MLD post | 2.28±0.54 mm |
| DS post | 15.0±12.5 % |
| Less than 30% residual stenosis and TIMI grade III flow | 88% |

MI myocardial infarction
PCI percutaneous coronary intervention
CABG coronary artery bypass graft
LMC left main coronary artery
LAD left anterior descending artery
LCx left circumflex artery
RCA right coronary artery
SES sirolimus-eluting stent
RD reference diameter

MLD minimal lumen diameter
DS diameter stenosis
Pre before intervention
Post after intervention

**Table 2: Angina status at index procedure**

| **Clinical presentation** | n | | **n** | **n** | **n** | **n** |
|---|---|---|---|---|---|---|
| **Acute MI** | 81 | Primary PTCA | 75 | ----- | ----- | ----- |
| | | Rescue PTCA | 6 | ----- | ----- | ----- |
| **Unstable angina** | 164 | **Braunwald class** | **I** | **II** | **III** | ----- |
| | | A | 0 | 1 | 1 | ---- |
| | | B | 21 | 50 | 39 | ---- |
| | | C | 1 | 21 | 29 | ---- |
| **Stable angina** | 245 | **CCS class** | **1** | **2** | **3** | **4** |
| | | | 3 | 97 | 119 | 26 |
| **Silent ischemia** | 20 | ---- | ---- | ---- | ---- | ---- |

MI myocardial infarction
CCS Canadian Cardiovascular Society

**Table 3: Complex lesion subsets, antithrombotic regimen and outcome**

| Subset# | % | Compliance to anti-platelet pro at 30 days (%) | Compliance to prolonged anti-platelet protocol (%) | Duration of anti-platelet therapy (month) | AT | SAT | Late ST* |
|---|---|---|---|---|---|---|---|
| Acute MI | 15.3 | 100 | 32.8 | 3.6±2.0 | 0 | 0 | 0 |
| Long stents (>36mm) | 17.8 | 100 | 87.2 | 5.8±1.7 | 0 | 0 | 0 |
| Multiple stenting (>2 Cypher stents) | 30.4 | 100 | 78.9 | 5.4±1.6 | 1 | 0 | 0 |
| CTO | 8.7 | 100 | 78.9 | 5.1±1.6 | 0 | 1 | 0 |
| Bifurcation stenting | 11.9 | 100 | 86.5 | 5.5±1.2 | 0 | 0 | 0 |
| In-stent restenosis | 9.6 | 100 | 73.8 | 4.9±1.6 | 0 | 0 | 0 |
| Left main stenting | 4.1 | 100 | 72.2 | 5.3±2.3 | 0 | 0 | 0 |
| Repeat stenosis after brachytherapy | 2.7 | 100 | 71.4 | 7.1±4.0 | 0 | 0 | 0 |

# subsets are not mutually exclusive
MI myocardial infarction
CTO chronic total occlusion
AT acute stent thrombosis
SAT subacute stent thrombosis
ST stent thrombosis
% proportion (%) of total study population

## FIGURE LEGENDS

**Figure 1:**
1A) Pre-intervention angiogram. Multiple lesions in the distal (I) and medial (II) RCA. Lesions in the distal LAD (lesion length 6.91mm; RD pre 2.63mm, MLD pre 1.58mm; DS pre 40%) and periphery LAD (lesion length 9.82mm; RD pre 1.71mm, MLD pre 0.89mm; DS pre 48%) (III).
1B) Final result after SES implantation in the distal LAD (Cypher 3.0/8mm, 2.25/18mm; RD post 2.51mm, MLD post 2.58mm; DS post 0%) and periphery LAD (Cypher 2.25/8mm; RD post 1.95mm; MLD post 1.75mm; DS post 10%).
1C) Acute coronary angiography 6h after the index procedure showed the occlusion of the SES in the distal LAD (I). IVUS showed an under-expansion of the stent (III; minimal stent area 2.00mm$^2$) in comparison to the proximal (II; lumen area 3.81mm$^2$) and distal (IV; lumen area 3.10mm$^2$) reference and a distal edge dissection (V, arrows) that was not visible on the angiogram at the time of the index procedure.

**Figure 2:**
2A) Pre-intervention angiogram showing a spontaneous recanalized occlusion of the RCA (I) and a total chronic occlusion of the LAD (II). The LAD is visualized by simultaneous contrast injection via a guiding catheter that is positioned in the left main stem and contrast injection via a diagnostic catheter that is placed in the ostium of the RCA, that gives collateral flow to the LAD.
2B) Final result after recanalization of the LAD and implantation of two SES stents (Cypher 3.0/33mm and 2.5/33mm; RD post 2.59mm; MLD post 1.79mm; DS post 33%).
2C) Coronary angiogram 11 days after the index procedure showed an occlusion in the periphery of the LAD (I, II). IVUS showed echolucent material within the lumen (IV) and revealed an under-expansion of the stent (V; minimal stent area 2.27mm$^2$) in comparison to the proximal reference (III, gap between two stents; lumen area 8.55mm$^2$) and distal reference (VI, lumen area 2.54mm$^2$).

| | |
|---|---|
| RCA | right coronary artery |
| LAD | left anterior descending artery |
| RD | reference diameter |
| MLD | minimal lumen diameter |
| DS | diameter stenosis |
| Pre | before intervention |
| Post | after intervention |

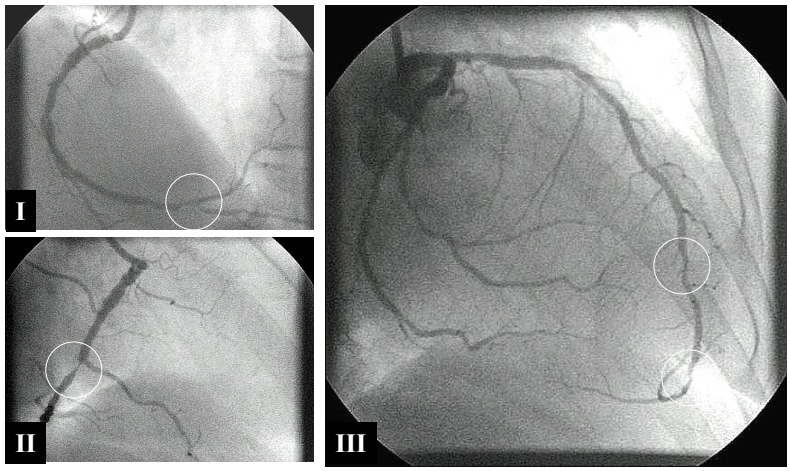


**FIG 1A**

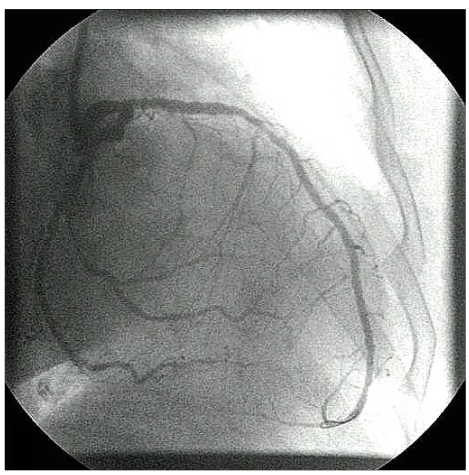

**FIG 1B**

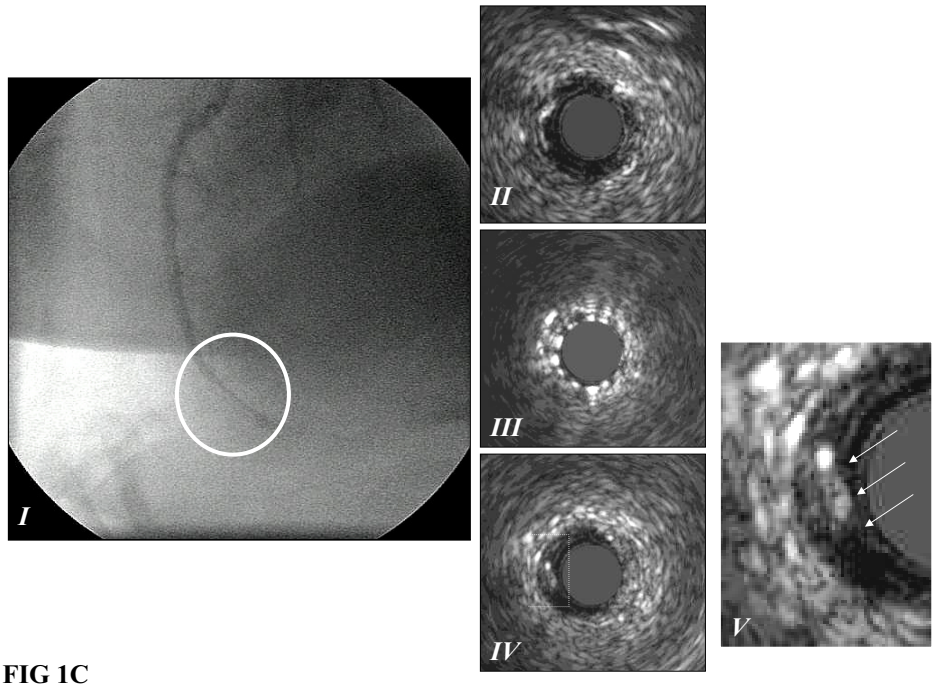


**FIG 1C**

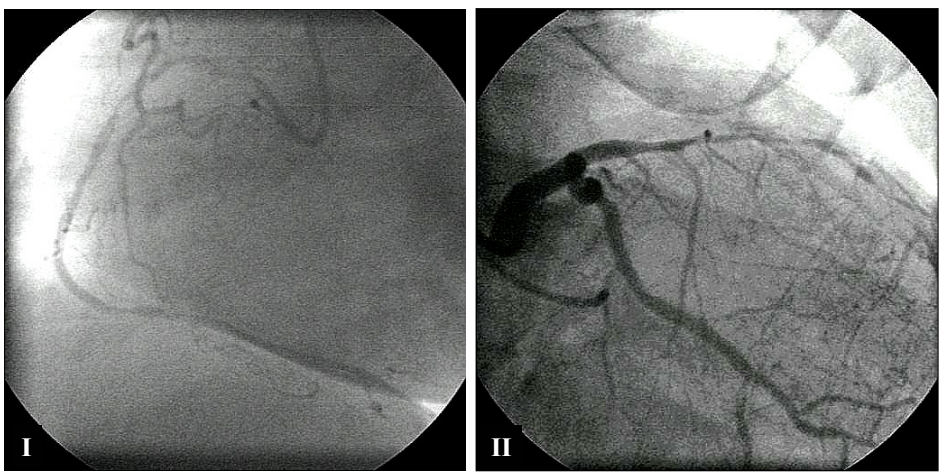


**FIG 2A**

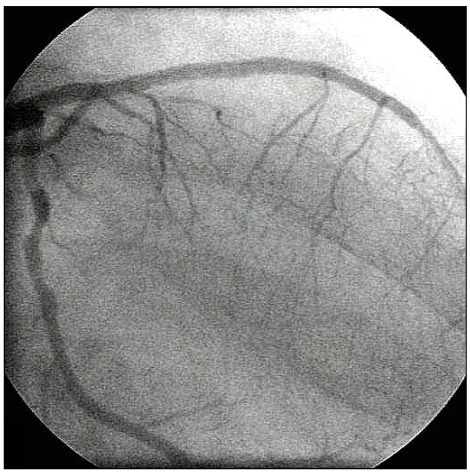

**FIG 2B**

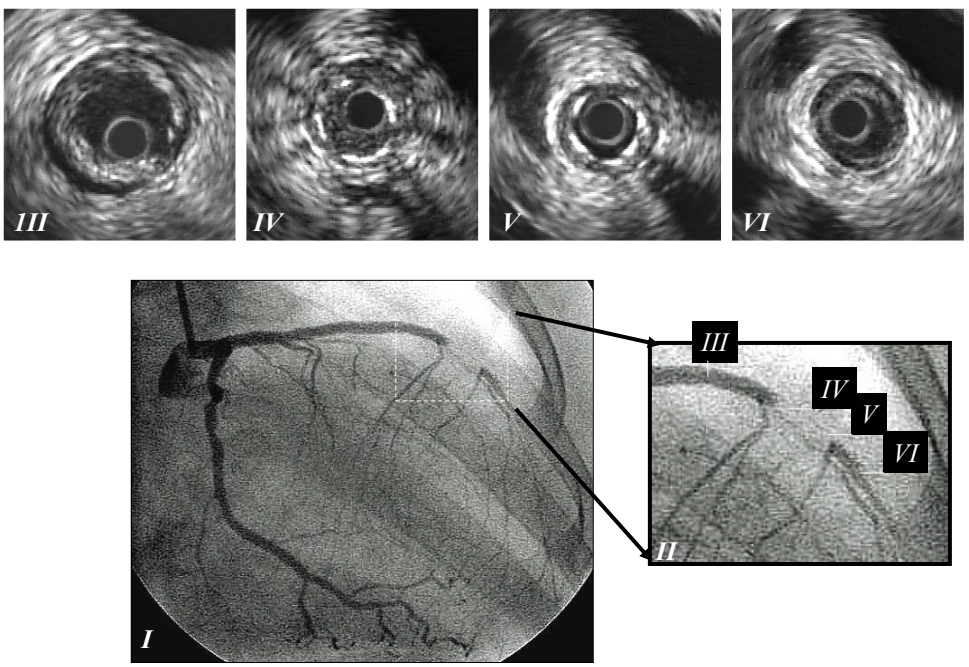


**FIG 2C**

## PART 3: DRUG ELUTING STENTS

*Chapter 14*

Serruys PW, *Regar E*, Carter AJ:
**RAPAMYCIN ELUTING STENT: THE ONSET OF A NEW ERA IN INTERVENTIONAL CARDIOLOGY.**
Heart. 2002;87:305-307.

EDITORIAL

# Rapamycin eluting stent: the onset of a new era in interventional cardiology

**P W Serruys, E Regar, A J Carter**

*Heart* 2002;**87**:305–307

Drug eluting stents represent one of the fastest growing fields in interventional cardiology today.

At the congress of the European Society of Cardiology in Amsterdam in 2000, I (PWS) was asked to give the Andreas Gruentzig Lecture. In the week preceding the lecture, we re-angiographied patients 32 and 33 of the initial cohort of patients who had received a rapamycin eluting stent in Sao Paulo and in Rotterdam. Scrutinising the 4–6 month angiographic and ultrasonic results of these patients, I became overwhelmingly convinced that we were the privileged witnesses of a new phenomenon: the almost complete abolition of intra-stent neointimal proliferation. Colleagues, invasive and non-invasive cardiologists, old friends, and financial analysts were surprised by the unusual "excess of enthusiasm" coming from somebody who has built over the years a reputation as a critical assessor, never one to be carried away by the hype of a new wave in interventional cardiology. In the history of this field I have recognised (and "got excited" by, as my American colleagues used to put it) only two revolutionary developments: the introduction of the moveable and steerable guidewire by John Simpson, and the advent of the stent (Palmaz-Schatz, Wallstent). The drug eluting stent is the third such development, and almost one year later I would like to restate the fact that we are entering a new era in interventional cardiology. Why? Because the principle of an eluting stent is sound, and because the three major technical challenges have been mastered—the controlled release of an efficient drug from a stable coating.

## THE PRINCIPLE

Drug administration for the prevention of restenosis has been tested in the past—with disappointing results throughout. A proposed explanation for the repeated failure of clinical drug studies has been that agents given systematically cannot reach sufficient concentrations in injured arteries, which has a signficant impact on the restenotic process. Local drug administration offers advantages. The active drug is applied to the vessel at the precise site and at the time of vessel injury. Local drug delivery is able to achieve higher tissue concentrations of the drug. No additional material or procedures are required. Systemic release is minimal and may reduce the risk of remote systemic toxicity.

## THE DELIVERY VEHICLE

The delivery vehicle must fulfil pharmacological, pharmacokinetic, and mechanical requirements. The release of the drug into the vessel must take place in a manner that is consistent with the drug's mode of action. Drug release must be predictable and in a controlled concentration and time. The delivery vehicle must be suitable for sterilisation; it must follow the geometric change of configuration during stent expansion and resist mechanical injury caused by the inflation of the balloon. Today these problems are controlled, guaranteeing intact coating during clinical application.

## THE DRUG

The drug should be one that inhibits the multiple components of the complex restenosis process. Uncontrolled neointimal tissue accumulation shows some parallels to tumour growth, thus the use of antitumorous strategies seems to be a logical consequence. Numerous pharmacological agents with antiproliferative properties have been tested for their potential to inhibit restenosis.

Rapamycin (sirolimus) has been approved by the US Food and Drug Administration for the prophylaxis of renal transplant rejection. It is a naturally occurring macrocyclic lactone which is highly effective in preventing the onset and severity of disease in several animal models of autoimmune disease, such as insulin dependent diabetes mellitus, systemic lupus erythematosus, and arthritis.

## RAPAMYCIN'S MECHANISM OF ACTION

The class of macrocyclic immunosuppressive agents (rapamycin, cyclosporin A, tacrolimus FK506) bind to specific cytosolic proteins called immunophilins (for example, FK506 binding protein 12) to gain their immunosuppressive activity. Rapamycin 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. mTOR is a key

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**Abbreviations:** FR, fast release; IL, interleukin; IVUS, intravascular ultrasound; mTOR, mammalian target of rapamycin; PBMA, polybutylmethacrylate; PCNA, proliferating cell nuclear antigen; PEVA, polyethylenevinylacetate; RAVEL, randomised study with sirolimus coated BX Velocity balloon expandable stent in the treatment of patients with de novo native coronary lesions; SR, slow release; VEGF, vascular endothelial growth factor

regulatory kinase and its inhibition 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/cyclinE complexes, essential for cell cycle progression. The mechanism of action is distinct from other immunosuppressive drugs that act solely by inhibiting DNA synthesis, such as mycophenolate mofetil and azathioprine. Rapamycin is synergistic with cyclosporin A and has much lower toxicity than other immunosuppressive agents.

Rapamycin prevents proliferation of T cells but also proliferation[1] and migration of smooth muscle cells. Gregory and colleagues demonstrated that intraperitoneal administration of rapamycin resulted in a dose dependent inhibition of arterial intimal thickening caused by either chronic alloimmune or mechanical injury in a rat model.[2 3] Subsequent studies reported that rapamycin inhibited both human and rat vascular smooth muscle cell proliferation in vitro by blocking $G_1$/S transition. The inhibition of proliferation was mediated by rapamycin binding to its cytosolic receptor, FK506 binding protein 12, and associated with reduced cdk2 activity and protein retinoblastom phosphorylation.[4 5]

Gallo and colleagues recently showed that systemic rapamycin treatment significantly reduces the proliferative response after coronary angioplasty in the porcine model.[6] The antiproliferative effects of rapamycin after angioplasty were attributed to an inhibition of the pRB phosphorylation preventing the down regulation of $p27^{kip1}$. Thus, the antiproliferative activity of rapamycin after balloon arterial injury in conjunction with its immunosuppressive properties suggests that this drug could also be useful for the prevention of in-stent restenosis.

This hypothesis is further supported by findings in human carotid arteries.[7] A robust upregulation of FK506 binding protein 12 was detected in the neointimal tissue of restenotic lesions, whereas no FK506 binding protein 12 was detectable in smooth muscle cells from control media.

## THE RAPAMYCIN ELUTING STENT

The rapamycin coated BX Velocity stent is fabricated from medical 316 LS stainless steel. It is available in a length of 18 mm and in two cell configurations (6 cell configuration: expanded diameter 2.5–3.25 mm) and 7 cell design (expanded diameter 3.5–3.75 mm). The stent contains 140 $\mu$g rapamycin/cm$^2$ which gives a total rapamycin content of 153 $\mu$g on the 6 cell stent and 180 $\mu$g on the 7 cell stent. The coating formulation consists of 30% rapamycin by weight in a 50:50 mixture of the polymers polyethylenevinylacetate (PEVA) and polybutylmethacrylate (PBMA).

## IN VIVO PHARMACOKINETICS

In vivo pharmacokinetics studies in the porcine coronary model demonstrated that the whole blood concentration of rapamycin peaks at 1 hour (mean (SD) 2.63 (0.74) ng/ml) after stent deployment and then declines below the lower limit of detection (0.4 ng/ml) by three days. The total arterial tissue concentration of rapamycin is 97 (13) ng/artery and the residual stent content is 71 (10) $\mu$g at three days. The amount of residual rapamycin on the stent at three days is 43% of the initial quantity loaded on the stent. A modification of the coating provides similar arterial tissue concentrations at 28 days. These data document the ability to deliver and achieve a potentially therapeutic arterial tissue concentration of rapamycin in the porcine model and insignificant concentrations in the systemic circulation using the non-erodible methacrylate and ethylene based copolymer matrix.

## PRECLINICAL EFFICACY STUDIES

Preclinical efficacy studies demonstrated a 35–50% reduction in in-stent neointimal hyperplasia for the rapamycin coated stents as compared with bare metal stents at 28 days in the porcine and rabbit model.[8] Histological assessment revealed the presence of typical cellular components of the neointima and a similar degree of re-endothelialisation for the rapamycin as compared with the bare metal stents. The morphology of non-stented reference arterial wall sections, including the vessel area, neointimal area, and per cent area stenosis was similar for the metal and each of the drug coated stents. A semiquantitative histological grading system demonstrated less smooth muscle cell colonisation and more residual fibrin deposition for the rapamycin eluting stents as compared with the bare metal stents. Therefore, critical reparative events, such as endothelialisation and smooth muscle cell colonisation of the neointima, with rapamycin eluting stents occur in a similar temporal sequence as observed with bare metal stents. The focal remnants of residual fibrin deposition observed in the vessel with rapamycin coated stents may reflect a delay in arterial repair or impaired fibrin degradation secondary to the local effects of the drug.

## CLINICAL DATA

The first clinical application of the rapamycin coated stent was performed in Sao Paulo and Rotterdam. Thirty patients with angina pectoris were electively treated with two different formulations of the rapamycin coated BX Velocity stent (Cordis) (slow release [SR] n = 15, and fast release [FR], n = 15). All stents were successfully delivered, and patients were discharged without clinical complications. At four months' follow up, there was minimal neointimal hyperplasia in both groups as assessed by IVUS and quantitative coronary angiography (in-stent late loss, 0.09 (0.03) mm [SR] and 0.02 (0.3) mm [FR]). No in-stent or edge restenosis was observed. No major clinical events (stent thrombosis, repeat revascularisation, myocardial infarction, death) had occurred by 12 months.[9] At one year follow up, IVUS volumetric analysis and angiography indicated minimal amounts of neointimal hyperplasia that were scarcely different from the four month data in both groups, with some patients showing no evidence of hyperplasia whatsoever. There were no major adverse cardiac events and no restenosis in either of the groups. One late acute myocardial infarction occurred in the FR group at 14 months.[10] In Rotterdam,15 patients were treated, and quantitative angiography and three dimensional quantitative IVUS were performed at implantation and at six months' follow up. All stent implantations were successful; one patient died on day 2 of cerebral haemorrhage and one patient suffered subacute stent occlusion caused by edge dissection. At nine months' follow up no further adverse events had occurred and all patients were angina-free. Quantitative coronary angiography revealed essentially no change in minimal lumen diameter and per cent diameter stenosis by angiographic criteria, and hence no in-lesion or in-stent angiographic restenosis was observed. Quantitative ultrasound showed that intimal hyperplasia volume and per cent obstruction volume at follow up were negligible (5.3 mm$^3$ and 1.8%, respectively). No edge effect was observed in the segment proximal and distal to the stent.[11]

These first clinical results are spectacular, as they convincingly demonstrate the absence of neointimal proliferation in all patients within the first six months after coronary stent implantation, a phenomenon which has never been reported in the past. If this promise—namely, the elimination of restenosis—becomes reality we will witness the onset of a new era in interventional cardiology and the revolution of catheter based intervention, bypass surgery, and health care economics! These enormous potential implications are the key for

today's enthusiasm. However, more than 20 years of experience in the investigation of restenosis force us to think of a possible Achilles' heel. In fact, a lot of unanswered questions still have to be resolved. First of all, controlled clinical data are needed. Furthermore, long term studies are required to elucidate if the drug is permanently inhibiting neointima growth or simply delaying the formation of neointima. Additionally, the recent experience with vascular brachytherapy alerts us to search for "unexpected" phenomena such as positive remodelling, late stent malapposition, edge effect, or late thrombosis. Again, meticulous long term clinical, angiographic, and IVUS follow up will be mandatory.

## ONE YEAR LATER: DOES THE RAVEL STUDY REVEAL THE FULL STORY?

The randomised study RAVEL, using the rapamycin coated BX Velocity balloon expandable stent in the treatment of patients with de novo lesions in native coronary arteries, is a multicentre, prospective, randomised double blind clinical trial comparing a bare metal stent with the drug coated stent. Two hundred and twenty patients were randomised to a single rapamycin coated stent (140 $\mu g/cm^2$) versus a bare metal BX Velocity stent. At six months' follow up, the restenosis rate of the treated group was zero, the loss in minimal lumen diameter was zero, there was no target lesion reintervention, and the event-free survival was 96.5%.[12]

## UPCOMING CLINICAL TRIALS

The SIRIUS study is a multicentre, prospective, randomised double blind trial that is being conducted in 55 centres in the USA. Eleven hundred patients with focal de novo native coronary arterial lesions (2.5–3.5 mm diameter, 15–30 mm long) will be randomised to treatment with rapamycin coated or bare metal BX Velocity balloon expandable stents. The primary end points of the SIRIUS trial are target vessel failure (death, myocardial infarction, target lesion revascularisation) at nine months. In addition, secondary end points are core laboratory analysis of angiographic and IVUS data to determine treatment effects on neointimal hyperplasia and in-stent restenosis. Clinical follow up will extend to three years in order to assess for late events. In addition to the pivotal RAVEL and SIRIUS trials, feasibility studies are ongoing to assess efficacy of rapamycin coated stents in more complex lesion subsets such as in-stent restenosis.

Drug eluting stents represent one of the fastest growing fields in interventional cardiology today. The exploitation of different classes of drugs which are potential candidates for the inhibition of restenosis, in combination with novel drug delivery systems or local gene therapy (for example, local expression of proliferation regulatory genes, transfer of cytotoxic genes, vascular endothelial growth factor (VEGF)) will continue. The multicentre trials will help to answer some of the most important clinical questions and determine whether this really reflects the eve of a "new era" or just a "new vogue" in interventional cardiology.

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## SUMMARY AND CONCLUSIONS

# SUMMARY AND CONCLUSIONS

In-stent restenosis represents the major limitation of coronary stenting. We could demonstrate (chapter 2) that stents provide mechanical scaffolding that virtually eliminates recoil and remodeling and that neointimal growth is the major reason for in-stent restenosis. This thesis reports on three new approaches for the prevention of restenosis.

**Part 1: Intracoronary ionic radiation (brachytherapy)**

Particular physics and mechanisms of action of intracoronary brachytherapy forced us to adapt quantitative coronary angiographic analysis. Assessment of irradiated vessels should include the target segment, the injured segment and the irradiated segment (chapter 4). The need for such meticulous reporting is underlined by the finding that the restenosis rate observed at the lesion site is only half of that of the complete vessel segment (chapter 7). Furthermore, we could show that QCA is not sensitive in detection of morphologic changes of the coronary vessel wall (chapter 5).

Chapter 6 reports on the feasibility of intracoronary beta brachytherapy. Although the procedures for brachytherapy are more complicated than balloon or stent angioplasty, we demonstrated a high success rate in daily routine practice. The long-term outcome however, was hampered by delayed occurrence of major adverse cardiac events between 6 and 12 month after the index procedure.

Chapter 7 summarizes the European registry of gamma radiation for in-stent restenosis (Granite trial). This trial reflects the dynamic changes and experiences in the field of intracoronary radiation over the last two years. It showed an excellent procedural success rate, a remarkably low repeat restenosis rate at 6 month and a favorable long-term outcome at 1 year. Key issues were the reduction of geographic miss, the avoidance of implantation of new stents and a prolonged antithrombotic regimen.

During clinical application it became apparent that brachytherapy, although reducing restenosis in the irradiated area, introduced significant new disease at the edges of the treated lesions. We performed an experimental study, which aimed to discriminate between potentially contributing factors (radiation dose fall-off, dose fall-off plus injury, or injury per se). In a porcine coronary artery model we could demonstrate that the edge effect is associated with the combination of stent injury and radioactive dose fall-off.

**Part 2: Intracoronary non-ionic radiation (sonotherapy)**

We studied the intracoronary application of high intense ultrasound (sonotherapy) in patients with simple de-novo and with complex lesions (chapter 9). Intracoronary sonotherapy was applied safely and with high acute procedural success. We applied a similar methodology as in coronary brachytherapy for detailed angiographic assessment of treatment effects. At 6-month follow-up, late lumen loss and neointimal growth was similar to conventional PTCA. The sonotherapy segments showed a slight lumen loss over the complete length. The late loss was maximal at the site of the original obstruction. All restenoses occurred within the sonotherapy segments. There were no edge effects at the adjacent vessel segments.

**Part 3: Drug-eluting stents**

Sirolimus-eluting stents have proven to dramatically reduce in-stent restenosis in simple de-novo lesions. We investigated the efficacy of sirolimus-eluting stents in subsets of patients with complex lesions and/or at high risk for repeat occurrence.

In chapter 11, we analyzed the relationship between vessel diameter and angiographic outcome after sirolimus-eluting stent implantation. We could show that sirolimus-eluting stents prevent restenosis irrespective of vessel diameter, and do not show the "classical" inverse relationship of vessel diameter and restenosis rate that is seen with bare metal stents.

In chapter 12 we investigated the outcome of sirolimus-eluting stent implantation in patients with highly complex in-stent restenosis. Notwithstanding the challenging population treated, we found strikingly similar results in terms of suppression of neointimal proliferation to that reported previously in de novo lesions in lower-risk patient populations.
These promising results of sirolimus-eluting stents encouraged us to evaluate the efficacy in unselected patients. Since 16th April 2002 the sirolimus-eluting stent is used in our institution for all percutaneous interventions, including unstable patients and acute myocardial infarction with no anatomical exclusion criteria. Chapter 13 describes the incidence of thrombotic stent occlusion in the first 510 consecutive patients. Incidence (0.4%) and time frame of sirolimus-eluting stent thrombosis (at 6 hours and at 11 days after the procedure) were similar to that for bare metal stent thrombosis. No late thrombotic occlusion (>30 days) was observed.

***Intracoronary brachytherapy*** has proven to significantly reduce the repeat occurrence of in-stent restenosis. Beta radiation seems as effective as gamma radiation. Treatment failures can be reduced by the avoidance of geographic miss by usage of long sources, the avoidance of (late) thrombosis by prolonged antiplatelet therapy and the avoidance of implantation of new stents.
***Intravascular sonotherapy*** seems feasible and safe. It's efficacy for the prevention of restenosis is currently under investigation in randomized clinical trials (EURO-SPAH, SPLASH).
***Sirolimus eluting stents*** have proven to significantly reduce restenosis in simple de novo lesions. Observational studies in complex lesion subsets are promising, but need to be confirmed in randomized clinical trials.

**Future directions**
Drug-eluting stents are one of the most promising fields in interventional cardiology today. Different classes of drugs, which are potential candidates for the inhibition of restenosis, will be further exploited. Further understanding of local vascular biology in specific lesion subsets such as unstable plaques, restenotic lesions or chronic total occlusions might allow the development of "tailored" modification by combination and controlled release of stent-based antithrombotic, anti-inflammatory and antiproliferative agents.
Local catheter-based gene therapy (e.g. local expression of proliferation regulatory genes, transfer of cytotoxic genes) will be another field of investigation, in which sonotherapy might also play a role in the enhancement of gene transfection.

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## SAMENVATTING EN CONCLUSIES

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Het ontstaan van restenose in een stent vormt de belangrijkste beperking van het gebruik van stents in kransslagaderen. We kunnen aantonen (hoofdstuk 2), dat stents het terugspringen van de vatwand ("elastic recoil" en " remodeling") mechanisch voorkomen en dat de neointimale groei de belangrijkste oorzaak is voor in-stent restenose. Dit proefschrift behandelt drie nieuwe methodes om restenose te voorkomen.

**Deel 1: Intracoronaire bestraling met ioniserende stralen (brachytherapie)**

Speciale fysische eigenschappen en de werking van ioniserende straling in de vatwand maakten het noodzakelijk, dat de kwantitatieve coronaire angiografische analyses aangepast moesten worden. Bij de beoordeling van bestraalde vaten dienen naast het behandelde deel ook het beschadigde deel en het bestraalde deel in de analyse mee genomen te worden (hoofdstuk 4). De noodzaak voor een dergelijke nauwkeurige verslaglegging wordt onderschreven door het feit, dat uit de waarnemingen blijkt, dat voor het definiëren van restenose het uitmaakt of alleen naar de stent lengte of naar de geheel behandelde vatwand sectie gekeken wordt ( hoofdstuk 7). Verder kon aangetoond worden, dat QCA niet gevoelig is voor het detecteren van morfologische veranderingen van de coronaire vatwand (hoofdstuk 5).

Hoofdstuk 6 handelt over de haalbaarheid van intracoronaire brachytherapie met beta bestraling. Alhoewel de behandelingen met brachytherapie ingewikkelder zijn dan ballon of stent angioplastie, kon deze therapie nagenoeg altijd in de dagelijkse praktijk toegepast worden. Bij de lange termijn resultaten werden echter tussen 6 en 12 maanden na de ingreep nadelige verschijnselen ("major adverse cardiac events') waargenomen.

Hoofdstuk 7 geeft een samenvatting van de Europese registratie van de behandeling van restenose met gamma bestraling (Granite studie). Deze studie geeft een afspiegeling van de dynamische veranderingen en ervaringen op het gebied van intracoronaire bestraling gedurende de laatste twee jaar. De studie toonde dat gamma brachytherapy uitstekend toegepast kon worden, een opvallend laag restenose percentage na 6 maanden had en een gunstig resultaat op lage termijn, na 1 jaar, had. De belangrijkste aandachtspunten waren de reductie van "geographic miss", het vermijden van het plaatsen van nieuwe stents en een verlenging van het antitrombose regiem.

Tijdens de klinische toepassing werd het duidelijk, dat de brachytherapie, ofschoon het restenose terug drong in het bestraalde gebied, nieuwe belangrijke verschijnselen aan de randen van de behandelde gebieden introduceerde. We hebben een experimentele studie uitgevoerd met het doel de invloed van verschillende potentiële factoren te onderzoeken (stralingsdoses fall-off, doses fall-off in combinatie met verwondingen of verwondingen alleen). In de coronairen van proefdieren (biggen) konden we aantonen dat het rand effect toegeschreven moet worden aan de combinatie van de verwondingen tijdens het plaatsen van een stent en de dose fall-off

**Deel 2: Intracoronaire bestraling met niet ioniserende straling (sonotherapie)**

We onderzochten de intracoronaire toepassing van hoog intensief ultra geluid (sonotherapie) bij patiënten met eenvoudige de-novo en met ingewikkelde laesies (hoofdstuk 9). Intracoronaire sonotherapie kon veilig en nagenoeg altijd toegepast worden. We hebben een overeenkomstige methode gevolgd als bij de brachytherapie om gedetailleerde angiografische beoordelingen van de behandelingseffecten te kunnen doen. Na 6 maanden waren de "late lumen loss" en de neointima groei overeenkomstig met die bij conventionele PTCA's. De met sonotherapie behandelde segmenten toonden een lichte lumen loss over de gehele lengte. Het "late loss" was het grootst aan de zijde van de originele vernauwing. Alle restenose verschijnselen werden waargenomen binnen de met sonotherapie behandelde segmenten. Randeffecten in de aangrenzende segmenten zijn niet waargenomen.

**Deel 3. Drug-eluting stents**

Stents voorzien van het medicijn sirolimus hebben aangetoond, dat zij de vorming van in-stent restenose drastisch terugdringen bij eenvoudige de-novo laesies. Wij onderzochten de doeltreffendheid van met sirolimus voorziene stents bij patiënten met complexe laesies en met een hoog risico op herhaling.

In hoofdstuk 11 zijn de resultaten gegeven van het onderzoek waarbij nagegaan, is welke de relatie is tussen de vatdiameter en de angiografische resultaten na de plaatsing van een met sirolimus voorziene stent. We kunnen aantonen, dat de stents voorzien van sirolimus, restenosis tegengaan, ongeacht de vatdiameter. Het klassieke omgekeerd evenredige verband tussen vatdiameter en restenose, zoals die optreedt bij kale metalen stents werd niet waargenomen bij stents voorzien van sirolimus.

In hoofdstuk 12 onderzochten we het resultaat van de stents met sirolimus in patiënten met zeer complexe vormen van instent restenose. Ook bij deze groep van, zeer moeilijke laesies, zijn vergelijkbare resultaten gevonden in termen van het onderdrukken van neointima groei ten opzichte van de eerder gerapporteerde resultaten bij de-novo laesies.

Deze belovende resultaten met de met sirolimus voorziene stents moedigden ons aan de uitwerking ervan na te gaan bij niet geselecteerde patiënten. Sinds 16 april 2002 wordt de met sirolimus voorziene stent in ons instituut gebruikt bij alle percutane interventies, ook bij onstabiele patiënten en bij patiënten met een hartinfarct, zonder anatomische uitsluitingscriteria. In hoofdstuk 13 wordt de frequentie van stent trombose in de eerste opeenvolgende 510 patiënten onderzocht. De frequentie (0.4%) en het tijdpad van de stent trombose (na 6 uur en na 11 dagen na de behandeling) van de met sirolimus voorziene stent waren verglijkbaar met kale metalen stents. Er werden geen late (na meer dan 30 dagen) afsluitingen gevonden.

*Intracoronaire brachytherapie* heeft aangetoond dat het herhaald terugkeren van restenose binnen de stent aanzienlijk teruggebracht kan worden. Met beta bestraling lijken dezelfde resultaten verkregen te worden dan met gamma bestralingen. Onvoldoende resultaten kunnen teruggebracht worden, door (1) te voorkomen dat er een "geographic miss" ontstaat (door langere bronnen te gebruiken), (2) het

voorkomen van trombose (door voortdurende antistollingstherapie) en (3) het niet inbrengen van nieuwe stents.

*Intravasculaire sonotherapie* lijkt haalbaar en veilig. Het voorkomen van restenose is nog steeds in onderzoek in gerandomiseerde klinische studies (EURO–SPAH, SPLASH).

*Stents voorzien van sirolimus* hebben bewezen dat zij het ontstaan van restenose in eenvoudige de-novo laesies kunnen terugdringen. De resultaten van studies met complexe laesies zijn belovend, maar moeten nog bewezen worden in gerandomiseerde studies.

**Toekomst perspectieven**

Stents voorzien van medicijnen zijn het meest belovend in het gebied van de interventie cardiologie. Verschillende klassen van medicijnen, die potentiële kandidaten zijn voor het remmen van restenose, zullen verder onderzocht moeten worden. Het begrijpen van de lokale vasculaire biologie in speciale laesies (zoals instabiele plaques, restenose laesies of chronisch totale afsluitingen) zouden de ontwikkeling van zeer specifieke modificaties mogelijk maken, bv. door combinatie en gecontroleerde afgifte van antistollings-, antiontstekings- of antiproliferatie geneesmiddelen uit stents.

Lokale, op het gebruik van catheter technieken gebaseerde, gen therapieën is een geheel ander gebied dat onderzocht zal worden, waarbij sonotherapie een mogelijke rol zou kunnen spelen in het verbeteren van de “gene transfection”.

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**CURRICULUM VITAE**

# CURRICULUM VITAE

Evelyn Regar graduated from Medical School, Technical University of Munich, Germany, in 1994. During 1994–1999, she performed her residency at the Medizinische Klinik Innenstadt, Ludwig-Maximilians-University, Munich, where her training included Internal Medicine and Cardiology. In 1999 she started a clinical and research fellowship at the Catheterization Laboratory of the Thoraxcenter, Erasmus MC Rotterdam, The Netherlands.

Evelyn Regar's research interest is the prevention of coronary restenosis and intravascular imaging. In 1996, she published her thesis (academic doctorate) on "Intravascular ultrasound imaging in patients with coronary artery disease and coronary stents" (Technical University, Munich). From 2000-2002, she received a research grant of the "Deutsche Forschungsgemeinschaft", Bonn, Germany for a project on "Mechanisms of action and efficacy of intravascular radiation therapy", that has been carried out at the Department for Experimental Cardiology, Erasmus MC, Rotterdam.

Evelyn Regar is member of the "German Scientific Working Group Health Technology Assessment" and the "German Society of Cardiology".

## LIST OF PUBLICATIONS

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## I) Original reports (peer reviewed articles)

1) Mudra H, Blasini R, *Regar E,* Klauss V, Rieber J, Theisen K: **Intravascular ultrasound assessment of the balloon-expandable Palmaz-Schatz coronary stent.** Coron Artery Dis 1993; 4:791-799

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