Radioactive Stents Delay but Do Not Prevent In-Stent Neointimal Hyperplasia

I. Patrick Kay, MBChB; Alexander J. Wardeh, MD; Ken Kozuma, MD; David P. Foley, MBBCh, PhD; A.H. Marco Knook, MD; Attila Thury, MD; George Sianos, MD; Willem J. van der Giessen, MD, PhD; Peter C. Levendag, MD, PhD; Patrick W. Serruys, MD, PhD

Background—Restenosis after conventional stenting is almost exclusively caused by neointimal hyperplasia. β-Particle–emitting radioactive stents decrease in-stent neointimal hyperplasia at 6-month follow-up. The purpose of this study was to evaluate the 1-year outcome of ^{32}P radioactive stents with an initial activity of 6 to 12 μCi using serial quantitative coronary angiography and volumetric ECG-gated 3D intravascular ultrasound (IVUS).

Methods and Results—Of 40 patients undergoing initial stent implantation, 26 were event-free after the 6-month follow-up period and 22 underwent repeat catheterization and IVUS at 1 year; they comprised half of the study population. Significant luminal deterioration was observed within the stents between 6 months and 1 year, as evidenced by a decrease in the angiographic minimum lumen diameter (−0.43±0.56 mm; $P=0.028$) and in the mean lumen diameter in the stent (−0.55±0.63 mm; $P=0.001$); a significant increase in in-stent neointimal hyperplasia by IVUS (18.16±12.59 mm^3 at 6 months to 27.75±11.99 mm^3 at 1 year; $P=0.001$) was also observed. Target vessel revascularization was performed in 5 patients (23%). No patient experienced late occlusion, myocardial infarction, or death. By 1 year, 21 of the initial 40 patients (65%) remained event-free.

Conclusions—Neointimal proliferation is delayed rather than prevented by radioactive stent implantation. Clinical outcome 1 year after the implantation of stents with an initial activity of 6 to 12 μCi is not favorable when compared with conventional stenting. **(*Circulation*. 2001;103:14-17.)**

Key Words: radioisotopes ■ restenosis ■ stents ■ angiography

Implantation of ^{32}P radioactive stents with activities ranging from 3.0 to 12 μCi in coronary artery lesions has been reported to inhibit neointimal hyperplasia within the stent at 6-month follow-up.[1,2] The major limitation of this therapy is significant renarrowing at the stent edges, which is called the "candy wrapper" or "edge effect."[1] Catheter-based radiation significantly reduces the recurrence of restenosis 6 months after percutaneous transluminal coronary angioplasty for in-stent restenosis, but 3-year follow-up reveals greater luminal deterioration in γ-radiation–treated patients.[3,4] Such findings indicate the need for longer follow-up beyond the traditional 6 months in patients treated with intracoronary radiation. The purpose of this study was to assess late results after the implantation of radioactive stents using repeat catheterization with quantitative coronary angiography and 3D intravascular ultrasound (IVUS) at 1 year.

Methods

Patient Population

The European ^{32}P Dose-Response Trial was a nonrandomized multicenter trial evaluating the safety and efficacy of implanting radioactive stents with activity levels of 3 to 12 μCi in single, native coronary artery lesions. All stents were implanted in de novo lesions, except for 1 case of in-stent restenosis. For the purposes of this analysis, this case was excluded. Other inclusion and exclusion criteria, as well as immediate and 6-month results, were previously reported.[1,2] Only patients undergoing 6-month angiographic and IVUS follow-up who did not experience major adverse cardiac events during the first 6 months were included. The study was performed in accordance with the Declaration of Helsinki and the European Guidelines for Good Clinical Practice. Ethical approval was provided by the Medical Ethical Committee of the University Hospital Rotterdam. All patients gave written, informed consent.

Radioactive Stent

The BX Isostent (^{32}P) (Isostent Inc), which is 15 mm in length and 3.0 or 3.5 mm in diameter, was used. The initial activity of the stents was measured and, thereafter, the date at which the radioactivity would have decreased to 6 to 12 μCi was calculated.

Procedure and Clinical Follow-Up

Procedural details have been published previously.[5] All patients received either 250 mg of ticlopidine BID or 75 mg of clopidogrel per day for 3 months after stent implantation and 80 mg of aspirin per day indefinitely. Revascularization was performed on the basis of clinical symptoms and/or evidence of ischemia on exercise testing. Clinical end points were death, Q-wave myocardial infarction, non–Q-wave myocardial infarction (creatine kinase-MB rise >2

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From the Thoraxcenter, University Hospital Rotterdam, Dijkzigt, and the Daniel den Hoed Cancer Center (P.C.L.), Rotterdam, the Netherlands.
Correspondence to Prof Patrick W. Serruys, MD, PhD, Department of Interventional Cardiology, Thoraxcenter Bd 406, University Hospital Dijkzigt, Dr Molewaterplein 40, 3015 GD Rotterdam, The Netherlands. E-mail Serruys@card.azr.nl

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TABLE 1. Baseline Characteristics of the 22 Patients Studied

Male sex	20 (91)
Age, y	57 (38–73)
Risk factors	
Previous MI	12 (55)
Diabetes mellitus	3 (14)
Hyperlipidemia	18 (82)
Hypertension	9 (41)
Smoking	8 (36)
Family history	7 (32)
CCS class 3/4	15 (68)
Treated vessel	
LAD	12 (55)
LCx	5 (22.5)
RCA	5 (22.5)
Lesion type	
A	2 (9)
B1	10 (45.5)
B2	8 (36.5)
C	2 (9)
Lesion length, mm	10±3

Values are n (%), mean (range), or mean±SD. MI indicates myocardial infarction; CCS, Canadian Cardiovascular Society; LAD, left anterior descending coronary artery; LCx, left circumflex artery; and RCA, right coronary artery.

times normal upper limit), target vessel revascularization, non–target vessel revascularization, and early and late thrombotic occlusion of the target vessel.

Angiographic and IVUS Procedures

Angiography in multiple projections was performed before the procedure, after stenting, and at 6-month and 1-year follow-up. The stented vessel segments were examined with quantitative coronary angiography (CAAS II analysis system,[6,7] Pie Medical BV) and mechanical IVUS (CardioVascular Imaging System). IVUS images were acquired to coincide with the peak of the R wave by using an ECG-triggered pullback device with a stepping motor at 0.2 mm/step. This system eliminates the artifacts caused by the movement of the heart during the cardiac cycle.[8] The ECG-gated image acquisition and digitization was performed by a workstation designed for 3D reconstruction (EchoScan, Tomtec). A Microsoft Windows-based contour detection program was used for the volumetric 3D analysis.[8]

Core Laboratory Analysis Procedures

Quantitative coronary angiography using at least 2 orthogonal projections was performed. For analytical purposes, the following 3 regions of interest were defined: (1) stent, (2) target lesion, and (3) target vessel. The stent included only the radioactive stent. The target lesion was defined as the stent and 5 mm proximal and 5 mm distal to the edge. The target vessel was defined as the target lesion and the remaining segments of the treated vessel. Target lesion restenosis was defined as >50% diameter stenosis, located within the target lesion, at follow-up.[9] Edge restenosis was defined as >50% diameter stenosis, located at the proximal and/or distal edge, at follow-up.

Quantitative IVUS analysis of the stent and 5 mm proximal and distal to the stent was performed. Lumen and stent boundaries were detected using a minimum cost algorithm. Total stent and lumen volumes were calculated as previously described.[8] Neointimal volume was calculated as stent volume minus luminal volume. Feasibility, reproducibility, and interobserver and intraobserver variability of this system have been validated in vitro and in vivo.[8]

Statistical Analysis

Data are presented as mean±SD. Continuous data were compared using repeated measures ANOVA or a 2-tailed Student's *t* test as appropriate.

Results

Baseline demographics and lesion characteristics are shown in Table 1. Between 6 months and 1 year, target lesion revascularization and target vessel revascularization were performed in 4 patients (18%) and 5 patients (23%), respectively. No late occlusion was seen. No patient died or experienced myocardial infarction. In total, 21 of 40 patients (53%) were event-free through the 1-year follow-up.

Quantitative Coronary Angiography and IVUS Measurements

Quantitative coronary angiography data, presented as a subsegmental analysis of the stent area and the edges, are shown in Table 2. A significant decrease in the minimum and mean lumen diameters was noted between 6 months and 1 year ($P=0.028$ and $P=0.001$, respectively) compared with both edges. The late loss of mean lumen diameter was significantly larger after 6 months than before 6 months. Furthermore, in 11 patients (50%), the minimum lumen diameter at the edge at 6 months was detected within the stent at 1 year ("migration" from the stent edge to within the stent). Lesion progres-

TABLE 2. Subsegmental Quantitative Coronary Angiography Analysis

				Late Loss			
	Baseline	6 Months	1 Year	Baseline to 6 Months	6 Months to 1 Year	Total	*P* Between Periods
Minimum lumen diameter, mm							
Proximal edge	2.92±0.53	2.23±0.73*	2.08±0.50	0.69±0.80†	0.15±0.51‡	0.84	0.060
Stent	2.50±0.47	2.36±0.47*	1.93±0.52*	0.14±0.52†	0.43±0.56‡	0.57	0.16
Distal edge	2.29±0.61	2.17±0.58	2.08±0.49	0.36±0.49†	0.09±0.49‡	0.45	0.9
Mean lumen diameter, mm							
Proximal edge	3.19±0.56	2.73±0.57*	2.50±0.40*	0.39±0.62§	0.22±0.51‖	0.61	0.33
Stent	3.12±0.42	3.09±0.58	2.54±0.41*	0.03±0.62§	0.55±0.63‖	0.68	0.041
Distal edge	2.64±0.56	2.51±0.56	2.36±0.50	0.12±0.49§	0.16±0.52‖	0.28	0.9

*$P<0.05$, †$P=0.0041$, ‡$P=0.025$, §$P=0.028$, ‖$P=0.001$ by ANOVA.

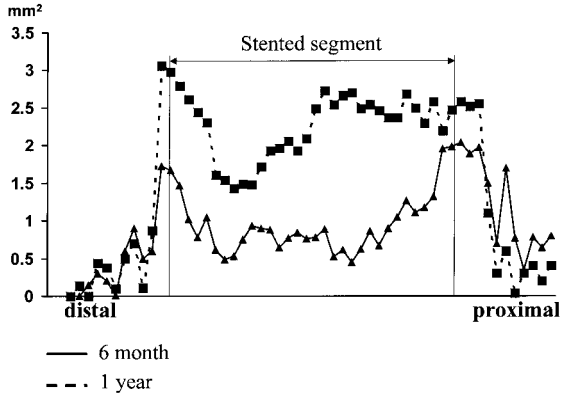

Figure 1. Mean neointimal area in stent at 6 months (■) and 1 year (▲) using IVUS.

sion to >50% diameter stenosis was observed in 5 patients. This was due to a progression of in-stent restenosis in 4 patients and a progression of a proximal stent-edge lesion in the other.

IVUS was completed in 19 patients; omissions were due to equipment failure[2] or patient clinical instability.[1] IVUS analysis demonstrated a significant increase in neointimal hyperplasia between 6 months and 1 year (18.16±12.59 mm^3 to 27.75±11.99 mm^3; increase of 52.8%; $P=0.001$), mainly in the mid and distal portions of the stent (Figure 1). An increase in neointimal hyperplasia >25% (range, 25% to 360%) occurred in 12 cases (63%), as shown in Figure 2. No change in lumen volume was noted at the stent edges between 6 months and 1 year.

Radiation Doses

The radioactive stents had a mean activity of 8.6±1.6 μCi at implantation and delivered 58±10 Gy to a depth of 1 mm from the stent at 100 days, with a dose rate of >15cGy/h. There was no correlation between stent activity or delivered dose and changes in minimum or mean lumen diameter at 6-month or 1-year follow-up.

Discussion

A worrying late progression of in-stent neointimal hyperplasia was observed between 6 months and 1 year after the implantation of radioactive stents, leading to target vessel or lesion reintervention in 5 of 26 patients (19%) who had been event-free at 6 months. The event-free rate at 1 year after the implantation of 6 to 12 μCi radioactive stents was 21 of 40 patients (53%), which compares poorly to the expected outcome after the implantation of a nonradioactive stent.[10]

In contrast to the tissue growth seen in malignancy, the DNA synthesis that occurs after nonradioactive stenting in experimental models terminates after 6 weeks.[11] At this time point, the activity of the radioactive stent used in this study would have been sufficient to inhibit cellular proliferation. Thereafter, the majority of lumen deterioration occurs in the first 3 months after conventional stent implantation, with minimal change between 6 months and 1 year,[12–14] and actual regression of neointimal hyperplasia between 1 and 3 years after stenting.[15] This latter phenomenon has been attributed to a reduction in the proteoglycan content of hyperplastic tissue.[16] Accordingly, the findings reported here of "breakthrough" or "rebound" hyperplasia causing further lumen deterioration between 6 months and 1 year must be interpreted as being specific to the effects of radioactivity, presumably due to a fall- off in radiation levels. The observation that the radioactive stent may provide a substrate for atherosclerosis may well have been predicted by Carter et al's porcine model.[17]

Because no significant stenosis progression was observed at the stent edges among our patients, the candy wrapper effect may be considered a short-term healing response to vessel wall injury beyond the stented vessel segment combined with the effects of low-dose radiation.[18,19]

Unexpected late luminal deterioration has also been reported between 6 months and 3 years among patients treated by catheter-based γ-radiation after repeat intervention for in-stent restenosis (mean loss of 0.37 mm with 4 of 17 patients [26%] progressing to restenosis [diameter stenosis >50%]), compared with no major changes in the placebo group.[4] The difference in the time frame of this virtual "rebound hyperplasia" between radioactive stenting and catheter-based γ-radiation therapy may be a function of the biological effects of and response to the type and dosage of radiation administered. Alternatively, late loss may also have

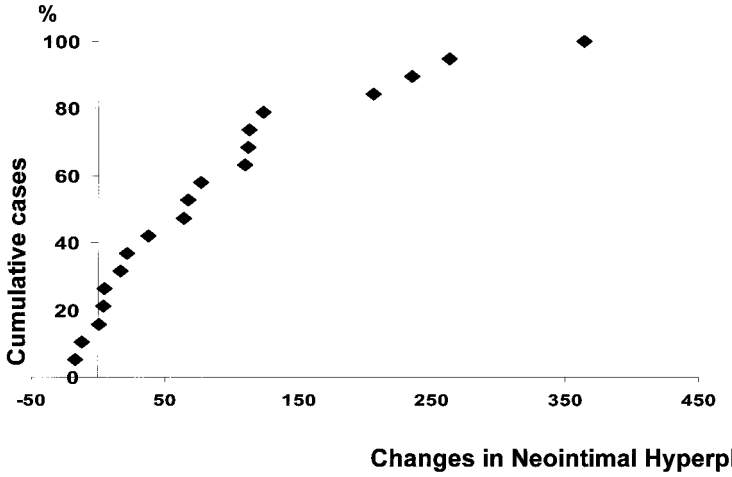

Figure 2. Cumulative distribution curve of percent changes in late neointimal growth after 6 months, as measured by IVUS.

occurred between 6 months and 1 year and remained subclinical in the catheter-based study.

Conclusions

Neointimal hyperplasia is delayed rather than prevented by radioactive stent implantation. The combination of this phenomenon of rebound hyperplasia with the established phenomenon of edge restenosis calls into question the clinical applicability of radioactive stenting using current approaches.

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