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CLINICAL INVESTIGATION **Benign disease**

SUCCESSFUL REDUCTION OF IN-STENT RESTENOSIS IN LONG LESIONS USING β-RADIATION—SUBANALYSIS FROM THE RENO REGISTRY

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Purpose: Long lesions remain a challenging task in interventional cardiology, with a high propensity of restenosis, especially within the stented segment. Although intracoronary γ-radiation has been proved to reduce diffuse in-stent restenosis in long lesions, such an effect remains to be determined using β-radiation.
Methods and Materials: Of 1098 consecutive patients at 46 European centers treated with localized β-radiation (^{90}Sr, Novoste Beta-Cath System), 139 patients (mean age 61.5 ± 10.7 years, 84% male, 22% with diabetes mellitus) with lesions treated using a >40-mm source length underwent radiation using a single 60-mm source train (34%) or a stepping/pullback procedure with a 30-mm (12%) or 40-mm (87%) source length after conventional interventional procedures. The mean lesion length was 35.3 ± 17.9 mm.
Results: Technical success was achieved in 96% of cases. Geographic miss was noted in 9 patients (6.5%). The reference (placebo) group was obtained from the Washington Hospital Center for In-Stent Restenosis Trial (WRIST) and the WRIST Trial for long lesions (LONG WRIST) studies by selecting the cases (94 patients) that required a dummy source length ≥13 seeds (or >51 mm in length). Statistically significant improvement was noted in late angiographic restenosis (34.7% vs. 76.5%, $p < 0.0001$), target vessel revascularization (14.9% vs. 60.6), and major adverse cardiac events (i.e., death, myocardial infarction, or total vessel revascularization) (17.9% vs. 64.9%, $p < 0.0001$) at 6 months in reference to the nonradiation group.
Conclusion: This subanalysis from the Radiation in Europe with Novoste study confirms the safety and efficacy of β-radiation combined with conventional interventional procedures in patients with diffuse, long, in-stent restenosis **© 2004 Elsevier Inc.**

β-Radiation, In-stent restenosis, Long lesions.

INTRODUCTION

Diffuse in-stent restenosis with a lesion length >10 mm has been shown to be associated with a high recurrence rate of repetitive restenosis and remains a challenging task in interventional cardiology (1, 2). The revascularization rates in this subgroup of patients vary between 34% and >80% after percutaneous coronary intervention (PCI) (3), and conventional therapy has failed to reduce the recurrence rate effectively.

Randomized, placebo-controlled trials have established that β-based, as well as γ-based, vascular brachytherapy reduces the incidence of restenosis and clinical event rates after PCI for the treatment of focal in-stent restenosis of moderate length (4–7). For lesion lengths >30 mm, which are especially problematic, only vascular brachytherapy with γ-radiation has been demonstrated to benefit this group of patients most (8). One of the reasons for this success can be attributed to the variable ribbon length of γ-radiation sources, which can be easily adjusted to the lesion length to completely encompass the lesion, as well as adjacent areas (9). Consequently, the risk of a geographic miss can be minimized. Geographic miss has been identified as one of the major causes of failure after vascular brachytherapy because of edge restenosis (10). Also data from β trials have demonstrated the benefit of generously encompassing the lesion, as well as the balloon-injured area, with the radiation source. In the Stents and Radiation Therapy (START) trial, in which injury lengths of 20 mm were treated with a 30-mm source train, restenosis outside of the stent accounted for 51% of the treatment failures. However, in the START 40/20 trial, in which a 40-mm source train was used to treat a 20-mm lesion, the frequency of recurrence outside the stent was reduced to 22% (11).

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Based on approval by the U.S. Food and Drug Administration, only 30- and 40-mm source trains were commercially available for the Novoste β-radiation system at the beginning of intracoronary β-radiation. Before longer source trains (60 mm) came onto the market, patients with lesion lengths >25 mm had to be treated with a pullback procedure to ensure full coverage of the balloon-injured area.

The first 1100 patients treated with the Novoste Beta-Cath System were enrolled in a postmarket surveillance study, the Radiation in Europe with Novoste (RENO) trial, which clearly demonstrated an excellent overall clinical, as well as angiographic, outcome (12). Because the reduction in the restenosis and target vessel revascularization rates was quite comparable to that of other randomized clinical trials investigating the effect of brachytherapy, the RENO registry has proved that this treatment mode can also be successfully used in the routine clinical setting. The purpose of this study was to assess the safety and effectiveness of localized β-radiation (^{90}Sr/^{90}Y), using a single 60-mm source train or a stepping/pullback procedure combined with conventional interventional procedures, in a subgroup of patients with long, diffuse, in-stent restenosis at hospital discharge and 6 months after the initial procedure.

METHODS AND MATERIALS

The RENO registry was a postmarket, prospective, surveillance study enrolling 1098 consecutive patients at 46 European centers treated with conventional interventional therapies followed by localized β-radiation using the Novoste Beta-Cath System. Patients with *de novo* or restenotic lesions and objective evidence of ischemia were treated with approved interventional procedures (balloon angioplasty, percutaneous transluminal renal angioplasty, excimer laser coronary angioplasty, directional coronary atherectomy (DCA), and stenting) followed by ^{90}Sr radiation treatment (Novoste Beta-Cath System). Patient enrollment occurred between June 1, 1999 and September 27, 2000. In this report, we performed a subgroup analysis on 139 patients for diffuse in-stent restenotic lesions in single vessels treated by a radiation source train >40 mm. These included stepping (pullback) procedures using 30-, 40-, or 60-mm source trains or a single 60-mm source train.

The reference (placebo) group was obtained from the Washington Hospital Center for In-Stent Restenosis Trial (WRIST) and the WRIST Trial for long lesions (LONG WRIST) studies by selecting the cases that required ≥13-seed length (or >51 mm in length) dummy sources. Ninety-four patients in the placebo arms of the WRIST and LONG WRIST studies were matched by these criteria and used for comparison in this report. This control group served two purposes; namely, to select patients with appropriate lesion characteristics and to make the results comparable with previous brachytherapy trials.

Baseline and clinical data were collected on standardized case report forms by the clinical investigators at the clinical sites. Clinical follow-up was mandated at 1 and 6 months. Angiographic follow-up at 6 months was not mandated; however, the participating sites reported available angiographic follow-up data for 102 (73.4%) of the 139 patients. Of 102 follow-up angiograms, 49 angiograms were received and analyzed independently by the core laboratory. In the reference group, 6-month angiographic follow-up data were available for 81 (87.1%) of 93 patients. The primary end point of the study was clinical success, defined as procedural success without occurrence of a major adverse coronary event (MACE; i.e., death, Q or non-Q wave myocardial infarction, or target vessel revascularization by repeat percutaneous transluminal coronary angioplasty or coronary artery bypass graft) at 6 months of follow-up.

Angioplasty procedure

All potential candidates provided informed consent before the procedure. All patients enrolled in this registry are required to undergo medical evaluations, according to the local standards, before the procedure (e.g., medical history and physical examination, cardiac enzyme determination, and baseline electrocardiography).

Angioplasty was performed using conventional balloon catheter techniques with repeated balloon inflations (if necessary) until a successful angiographic result was obtained. Initially, the protocol instructed the investigator to ensure that the total balloon injury length was limited to a maximum of 30 mm when using the 40-mm source train. The balloon positions were angiographically documented to monitor the injured area. Atheroablative therapies (percutaneous transluminal renal angioplasty, excimer laser coronary angioplasty, DCA) before balloon angioplasty were allowed. However, it was very important to treat only the lesion. After undergoing PCI (balloon angioplasty, percutaneous transluminal renal angioplasty, excimer laser coronary angioplasty, or DCA), the operator could implant a stent.

It was also initially recommended that patients who were designated to receive a stent be treated with the Beta-Rail Delivery Catheter before stent placement. Regardless of how the patient was treated, all required patient data needed to be collected. The dose was prescribed according to the maximal balloon/stent diameter size used, as described below. A minimum of a 5–10-min (longer if clinically indicated) waiting period after the initial percutaneous transluminal coronary angioplasty was recommended to ensure the absence of dissection, thrombus, or spasm before placement of the Beta-Rail Delivery Catheter. Physicians were also required to ensure that the delivery catheter with source train was documented on cine film (with contrast injection) during the radiation procedure. The elective use of ReoPro was discouraged.

All RENO patients received a combination treatment of aspirin (100 mg) and clopidogrel/ticlopidine. The duration of treatment was, however, determined by the respective operator's routine use of this combination, because RENO was a registry. The steering committee recommended 6

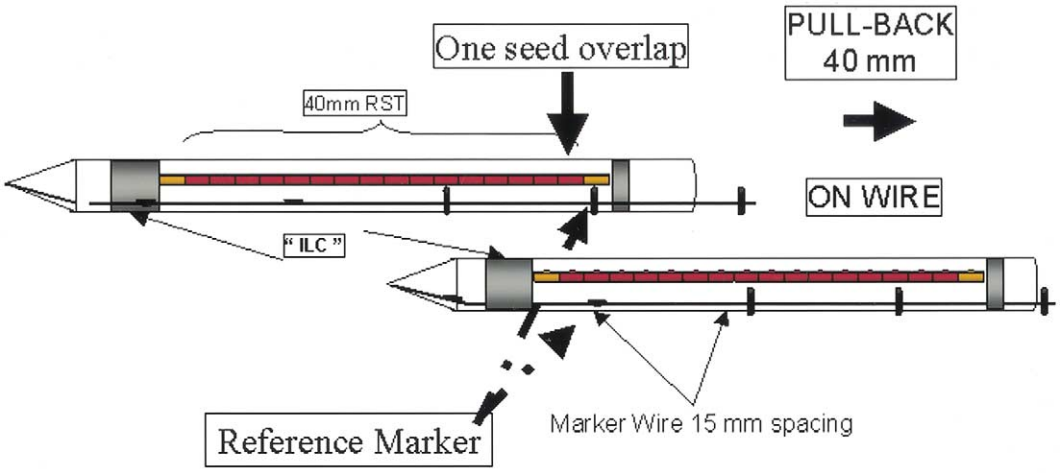


Fig. 1. Overlapping pull-back technique. Position of distal and proximal source chosen ideally to ensure an adequate radiation dose at site of overlap. Note, last active seed before gold marker carries only one-half the dose. Therefore, the last distal marker of the proximal train and the first proximal seed of the distal train must overlap. Marker wires assist in finding the exact source position.

months of combination treatment. According to the results, 70% of patients received the combination treatment for >6 months. The remaining patients received combination treatment for 3–6 months.

Radiation procedure

After successful completion of percutaneous transluminal coronary angioplasty or a prestent dilation procedure, the angioplasty catheter was withdrawn. Next, the Beta-Rail Delivery Catheter was positioned so that the radiopaque marker bands on the delivery catheter were equidistant from the center of the injured area and were recorded angiographically. The guidelines for lesion/balloon length and source train length, as well as dose prescriptions/guidelines, were followed (see below) to avoid the so-called edge effect. Therefore, all interventions, as well as the radiation procedure, were angiographically documented (using contrast injections) to monitor this phenomenon, as described previously.

The recommended dose prescription for a single application of radiation after PCI for the Novoste BetaCath system is 18.4 Gy at 2 mm from the centerline axis of the source for vessels <3.35 mm and 23 Gy at 2 mm from the centerline axis of the source for vessels between 3.35 and 4 mm.

For vessels treated with the pullback technique, the dose for the distal position of the radiation source train is determined by the proximal reference vessel diameter of the distal position, and the dose for the proximal position is determined by the proximal reference vessel diameter of the proximal position. The diameter of the reference vessel is determined visually (13).

Pullback technique

The extension of the radiation treatment length beyond the length of the Beta-Cath System Radiation Source Train (RST) required sequential positioning or "pullback" of the catheter. In an ideal situation, the proximal seed of the distal source train would be exactly juxtaposed to the distal seed of the proximal source train. Because precise positioning of the source train was impractical, the recommended technique was to attempt to achieve a "one seed" overlap to ensure that an adequate dose of radiation was delivered to the entire treated segment. At first, the total injury length was evaluated by reviewing all recorded interventions. Then, the distal and proximal position of the injury according to any landmarks was identified. The use of the marker guidewire allowed for accurate evaluation of the injury length (13).

The Beta-Cath Delivery Catheter was placed in the distal portion of the coronary artery to be treated, being careful to extend the radiation margin >5 mm beyond the distal injury margin. The area of "overlap" (proximal end of the RST in the distal position that overlaps the distal end of the RST in the proximal position) should be within the existing stent to minimize the possibility of local complications.

The RST was sent to the distal end of the delivery catheter and left in position for time required to deliver the desired dose of radiation. Using contrast, the position of the proximal RST marker relative to anatomic landmarks was recorded (or the Cordis marker wire was used). At the end of the designated dwell time, the RST was returned to the transfer device. The delivery catheter was then withdrawn over the guidewire and positioned in the proximal portion of the coronary artery to be treated. Care was taken to position the catheter to ensure a "one seed" overlap in the junction between the distal and proximal RST positions. It was ensured that the overlap was within the existing stent and that the proximal radiation margin extended >5 mm beyond the proximal injury margin. The marker wire aided in positioning the distal seed of the proximal source train such that an overlap existed with the proximal seed of the distal source train (Fig. 1). The RST was then sent to the distal end

Table 1. Demographics and risk factors

Variable	RENO (n = 139)	Control (n = 94)	Combined (n = 233)	Relative risk (95% CI)	Difference (95% CI)	p
Male gender	84.2 (117/139)	66.0 (62/94)	76.8 (179/233)	1.28 (1.09, 1.50)	18.22 (5.93, 30.50)	0.0015
Mean age ± SD (y)	61.45 ± 10.68	61.21 ± 9.84	61.36 ± 10.33	NA	0.24 (−2.48, 2.96)	0.8634
Smoking						
Current	14.1 (19/135)	16.0 (15/94)	14.8 (34/229)	0.88 (0.47, 1.65)	−1.88 (−12.28, 8.51)	0.7091
Prior	54.1 (73/135)	52.1 (49/94)	53.3 (122/229)	1.04 (0.81, 1.33)	1.95 (−12.16, 6.05)	0.7891
Never	31.9 (43/135)	30.9 (29/94)	31.4 (72/229)	1.03 (0.70, 1.53)	1.00 (−12.16, 14.16)	0.8861
Diabetes mellitus	21.9 (30/137)	37.2 (35/94)	28.1 (65/231)	0.59 (0.39, 0.89)	−15.34 (−28.27, −2.40)	0.0119
Hypertension	59.7 (83/139)	66.0 (62/94)	62.2 (145/233)	0.91 (0.74, 1.11)	−6.25 (−19.77, 7.28)	0.4087
Hypercholesterolemia	80.6 (112/139)	87.2 (82/94)	83.3 (194/233)	0.92 (0.83, 1.03)	−6.66 (−17.01, 3.70)	0.2127
Renal insufficiency	4.3	—	4.3	—	—	—
Diseased vessels (n)						
1	50.7 (70/138)	47.9 (45/94)	49.6 (115/232)	1.06 (0.81, 1.38)	2.85 (−11.20, 16.91)	0.6901
2	31.2 (43/138)	25.5 (24/94)	28.9 (67/232)	1.22 (0.80, 1.87)	5.63 (−7.04, 18.30)	0.3791
3	18.1 (25/138)	26.6 (25/94)	21.6 (50/232)	0.68 (0.42, 1.11)	−8.48 (−20.43, 3.47)	0.1440
Unstable angina	24.0 (31/129)	76.6 (72/94)	46.2 (103/223)	0.31 (0.23, 0.43)	−52.56 (−64.84, −40.29)	<0.0001

Abbreviations: RENO = Radiation in Europe with Novoste; CI = confidence interval; NA = not applicable.
Data presented as the percentage of patients with the number per total in parentheses, unless otherwise noted.

of the delivery catheter and left to dwell in place to deliver the intended dose of radiation. At the end of the designated dwell time, the RST was returned to the transfer device. After treatment completion, the delivery catheter was removed and the treated area assessed.

Angiographic assessment

After baseline nitroglycerin administration, cineangiograms of the target lesion were to be acquired in multiple angiographic projections before the procedure, before and after the randomized treatment, and at final completion of the intervention. Visual estimates were to be used by the site investigators to determine the percentage of diameter stenosis of the treated lesion before and after the assigned treatment.

All preprocedure, postprocedure, and available 6-month follow-up cineangiograms were to be analyzed by an independent core laboratory (Angiographic Core Laboratory, Cardiology Research Foundation, New York, NY) using qualitative morphologic and quantitative angiographic methods, as described previously (14). Data collection was to have included assessment of Thrombolysis in Myocardial Infarction flow, eccentricity, calcification, thrombus, lesion length, American Heart Association/American College of Cardiology classification, and dissection grade. Recurrent in-stent restenosis was assessed using the dichotomous end point of >50% stenosis at 6 months.

Statistical analysis

The data were collected and analyzed according to an intention-to-treat method. All continuous variables were summarized using the mean and standard deviations, and nominal variables were described using frequencies and percentages. The reference group was selected from the WRIST and LONG WRIST studies by matching the patients on the basis of the radiation seed length used.

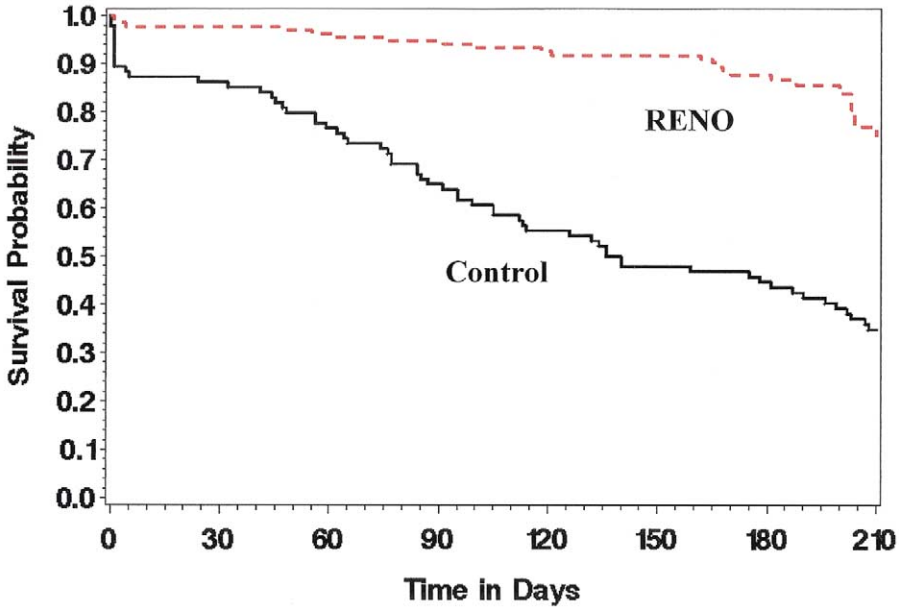
Baseline demographic and clinical variables were descriptively summarized for each of the treatment groups. The two treatment groups were assessed for comparability at baseline and follow-up using chi-square tests or Fisher's exact test for nominal variables and t tests for continuous variables. The differences between the treatment groups, with 95% confidence intervals, are presented.

The primary end point of this study (6-month MACE) is expressed as a percentage (count/sample size). The MACE rates between the two treatment groups were compared using a chi-square test. MACEs and total occlusions were also compared between the two groups using a Kaplan-Meier survival analysis. Wilcoxon and log–rank tests were used to test for differences between the survival curves. Multivariate logistic regression analyses were also applied to MACEs and total occlusions, controlling for the treatment group and any significant clinical characteristics. All statistical analyses were performed using the Statistical Analysis System.

The secondary end points of brachytherapy success, procedural success, and clinical success were expressed as a percentage (count/sample size). They were compared between the two groups using chi-square tests. Differences between the groups, along with 95% confidence intervals, are presented.

RESULTS

Baseline demographics and clinical characteristics showed a mean age of 61 years, with 84% (117 of 139) male participation, and 22% (30 of 137) with a history of diabetes mellitus in the β-radiation group and a mean age of 61 years, with 66% (62 of 94) male participation, and 37% (35 of 94) with of a history of diabetes mellitus in the reference (placebo) group. Clinical follow-up at 180 days was avail-



Summary Statistics

	Total	Events	Censored	Event Free %
RENO	134	24	110	82.09%
Control	94	61	33	35.11%

Tests Between Groups

	Chi-Square	d.o.f	P Value
Log-Rank	49.6	1	<.0001
Wilcoxon	55.2	1	<.0001

Fig. 2. Overall freedom from MACE in RENO registry. Total vessel revascularization and MACE rates from the RENO long lesion subset compared with those from WRIST control group. Clinical follow-up and lesion length were comparable and total vessel revascularization and MACE rates were significantly different.

able for 99.3% (138 of 139) in the radiation group. This report included all 6-month outcomes (Table 1).

Overall, in-hospital complications were significantly greater in the reference group (2.2% vs. 11.7%, $p < 0.005$). This result was mainly attributed to a reduction in non-Q wave myocardial infarction (0.7% vs. 11.7%, $p < 0.001$).

The MACE rate was also significantly lower during the 6-month follow-up (17.9% vs. 64.9%, $p < 0.0001$), which was a result of a lower total vessel revascularization rate (14.9% vs. 60.6%, $p < 0.0001$), and a lower rate of myocardial infarction (1.5% vs. 17.0%, $p < 0.001$), which could be attributed to the lower occurrence of non-Q wave myocardial infarction (0.7% vs. 16.0%, $p < 0.0001$). Multivariate analysis yielded radiation and lesion length as the only independent predictors of MACE, and the occurrence of total occlusions could not be predicted (Fig. 2).

Angiographic analysis by quantitative coronary angiography revealed a significantly greater postprocedural reference vessel diameter (2.88 ± 0.43 mm vs. 2.67 ± 0.40 mm, $p = 0.002$), and the postprocedural minimal lumen diameter (1.76 ± 0.54 vs. 1.81 ± 0.39, $p = 0.541$) was similar, resulting in a greater postprocedural percentage of diameter stenosis (27.15 ± 17.06 vs. 21.84 ± 15.87, $p = 0.043$) in the irradiated group. This result was similar in the stent segment (Table 2).

At follow-up, the reference diameter remained significantly larger in the irradiated group. The minimal lumen diameter, percentage of diameter stenosis, and late loss and late loss index ratio were significantly lower in the

Table 2. Baseline lesion characteristics

Variable	RENO (n = 139)	Control (n = 94)	Combined (n = 233)	Relative risk (95% CI)	Difference (95% CI)	p
Native vessel (%)	100.0 (139/139)	100.0 (94/94)	100.0 (233/233)	NA	0.00 (−0.89, 0.89)	NA
Mean reference vessel size (mm)	3.20 ± 0.48 (136)	2.56 ± 0.49 (93)	2.94 ± 0.58 (229)	NA	0.65 (0.52, 0.78)	<0.0001
Mean lesion length (mm)	35.33 ± 17.89 (135)	27.97 ± 11.84 (83)	32.53 ± 16.24 (218)	NA	7.37 (3.00, 11.73)	0.0003
Subtotal occlusion (99% DS) and total occlusion lesions (%)	26.1 (36/138)	13.0 (12/92)	20.9 (48/230)	2.00 (1.10, 3.64)	13.04 (2.04, 24.05)	0.0202
Mean reference vessel diameter (mm)	2.83 ± 0.49 (69)	2.56 ± 0.49 (93)	2.67 ± 0.51 (162)	NA	0.28 (0.21, 0.43)	0.0005
Mean minimal lumen diameter (mm)	0.68 ± 0.57 (69)	0.69 ± 0.40 (92)	0.69 ± 0.48 (161)	NA	−0.01 (−0.16, 0.14)	0.9061
Mean diameter stenosis (%)	76.00 ± 19.15 (69)	72.50 ± 15.50 (92)	74.00 ± 17.19 (161)	NA	3.50 (−1.90, 8.89)	0.2166
Mean lesion length (mm)	31.19 ± 10.91 (58)	27.97 ± 11.84 (83)	29.29 ± 11.54 (141)	NA	3.23 (−0.66, 7.11)	0.1026
In-stent restenosis pattern (%)						
Focal	4.4 (3/68)	12.9 (9/70)	8.7 (12/138)	0.34 (0.10, 1.21)	−8.45 (−19.20, 2.31)	0.1287
Diffuse	95.6 (65/68)	87.1 (61/70)	91.3 (126/138)	1.10 (0.99, 1.22)	8.45 (−2.31, 19.20)	0.1287

Abbreviations: DS = diameter stenosis; other abbreviations as in Table 1.
Numbers in parentheses are numbers of patients, unless otherwise noted.

irradiated group. This was observed in both the stented and the analyzed segments. In both segments, the binary restenosis rate was significantly lower in the irradiated group. The number of total occlusions was not significantly increased in the treatment group (Tables 3 through 5 and Fig. 3).

DISCUSSION

Safety and clinical efficacy are major issues for the acceptance of intracoronary radiation as a routine clinical therapy for the treatment of in-stent restenosis (15–18). The safety of intracoronary β-radiation has already been proven in the START (17) and Intimal Hypoplasia Inhibition with Beta In-stent Trial (INHIBIT) (18) trials, in which the overall MACE rates were impressively reduced by 31% and 56%, respectively. However, these randomized trials mainly included lesions with a mean length of around 17 mm. A subgroup analysis on longer lesions (21.8 ± 5.3 mm) in the START trial has already indicated that the restenosis rate in the analysis segment, as well as revascularization rate in the target vessel, may be also reduced effectively by 45% and 49%, respectively (16). Preliminary data from the first randomized trial, the LONG WRIST study, highlight the expected positive effects, because γ-radiation effectively reduced the MACE rate by 38% (15). The present analysis demonstrated that β-radiation is also highly effective for the treatment of long lesions. The MACE rates in the treated group were significantly lower than those in the reference group (17.9% vs. 64.9%). Although this was not a random-

Table 3. Procedural characteristics and outcomes

Variable	RENO (n = 139)	Control (n = 94)	Combined (n = 233)	Relative risk (95% CI)	Difference (95% CI)	p
New stent implantation (%)	31.2 (43/138)	50.0 (47/94)	38.8 (90/232)	0.62 (0.45, 0.86)	−18.84 (−32.52, −5.16)	0.0059
No postradiation dissection (%)	94.0 (63/67)	85.7 (78/91)	89.24 (141/158)	1.10 (0.99, 1.22)	8.32 (−2.20, 18.83)	0.1216
No postprocedure dissection (%)	98.6 (68/69)	91.3 (84/92)	94.4 (152/161)	1.08 (1.01, 1.16)	7.25 (−0.47, 14.96)	0.0792

Abbreviations as in Table 1.

Table 4. Procedural characteristics and outcomes: radiation group

Procedural characteristic	
Total radiation dose* (Gy)	
Mean ± SD	19.63 ± 3.02
Range	16.1–25.30
Actual time† (s)	
Mean ± SD	236.40 ± 61.15
Range	147–488
Pullback procedure (%)	77.7 (108/139)
Source train (mm)	
30	12.2 (17/139)
40	62.6 (87/139)
60	2.9 (4/139)
Single source train (60 mm)	21.6 (30/139)
Brachytherapy success	99.3 (138/139)

* $n = 132$.
† $n = 138$.

ized trial, the large difference outweighs any selection bias and highlights the effectiveness of β-radiation. Along the same line, the MACE rates using β- or γ-radiation (17.90% vs. 38.3%) are not directly comparable. Nevertheless, given a comparable reference group and matched-pair analysis, β-radiation does not seem to be inferior to γ-radiation in the treatment of long lesions. The superiority of any radiation regimen can, however, only be answered in a randomized, double- or triple-blind trial.

The reduction in MACEs is not simply an effect of a reduced total vessel revascularization rate but can also be attributed to the absence of any myocardial infarction in the treatment group. In the reference group, 6.4% ($p < 0.005$) experienced a Q or non-Q myocardial infarction. Total vessel revascularization itself was dramatically reduced by 75% to a rate of 14.9% and reached a rate similar to that observed in the START (16%) and INHIBIT (11%) trials (17, 18).

These positive clinical findings are further reflected by the quantitative coronary angiographic analysis. The restenosis rate was substantially reduced using intracoronary β-radiation when compared with the nontreated group. It might be argued that the absolute restenosis rate was still high (34.7%) and even higher than in the overall population (21.3%) of the RENO registry. However, on the basis of clinical studies, logistic regression analysis predicted a probability of restenosis of between 70% and 80% for this subgroup of patients with a lesion length of around 35 mm (19) (Fig. 4). Thus, the increased restenosis rate in the radiated group does not follow the expected steep linear relation between lesion length and restenosis rate. Therefore, brachytherapy seems to be even more effective in longer lesions.

The mere comparison of restenosis or target vessel revascularization rates seems to be too simple for the evaluation of the clinical success in complex, long, diffuse, in-stent lesions. Restenosis patterns of long lesions treated with brachytherapy rarely follow the diffuse nature of the original lesion, but rather recur as a focal short lesion, for which, most likely, the radiation dosage might not be effective (radial geographic miss). The therapy for these repetitive focal lesions has not been investigated but is expected to be effective with conventional balloon or cutting balloon techniques. In addition, anecdotal reports of successful repeat radiotherapy in these patients indicate that effective treatment solutions exist for this patient subset.

Long lesions, per se, increase the likelihood of an inhomogeneous dose distribution, especially given a noncentered system in a tortuous vessel and the relatively steep transverse dose decline of β-radiation (20, 21). Although the problem of vessel tortuosity within the stent is of lesser importance, unequal plaque distribution and variable vessel remodeling further enhance dose inhomogeneity in a longer segment. Other than the use of radiation, the lesion length was the only additional independent predictor of restenosis in the present analysis. In addition, the conically shaped coronary conduit arteries with decreasing lumen diameter from the proximal to distal segments add to the complexity of adequate dosimetry with increasing lesion length. In this respect, a pullback procedure using shorter source trains seems theoretically superior, because the dosage can be adjusted from distal to proximal; the 60-mm source train allows only one dose level. The present data indicate that patients treated with a single-step 60-mm source had an even lower restenosis rate (13.3%) than patients treated with pullback procedures (22.2%). One of the reasons for the better outcome in the 60-mm source group might have been the higher radiation dose (21.0 vs. 19.2 Gy). Nevertheless, it is unclear whether more individual dosing on the basis of meticulous intravascular ultrasound examination using a stepping procedure or a general dose increase will be the ultimate goal.

The inherent technical dose escalation associated with the pullback procedure applied in the current study rather encourages the latter consideration. Although the mean applied dose in the pullback group was ultimately lower, a critical technical concern was initially directed toward the up to twofold-increased dose at the overlapping zone. The clinical results, however, demonstrated that the dose increase did not result in any relevant vessel damage. Treatment with the Novoste system entails a dose prescription that is about one-half of what is currently recommended with the ^{32}P system from Guidant. If the entire treated segment can receive twice as much dose as is given with the Novoste device and show no evidence of negative clinical or angiographic outcomes, as in the INHIBIT trial, it is axiomatic that treatment of a small segment of vessel in which the sources overlap and receive 1.8 times the prescription dose should also be well tolerated (18). In addition, in the INHIBIT trial, approximately 40% of the patients were treated with a pullback procedure without apparent deleterious effects. The above observations support the idea that the doses presently prescribed are still at the lower range of the therapeutic window.

Nevertheless, an uncontrolled dose increase should be

Table 5. Principal effectiveness and safety results

Variable	Radiation (n = 139)	Control (n = 94)	Combined (n = 233)	Relative risk (95% CI)	Difference (95% CI)	p
Follow-up done (%)	96.4 (134/139)	100.0 (94/94)	97.9 (228/233)	0.96 (0.93, 1.00)	−3.60 (−7.60, 0.40)	0.0834
Procedure success (%)	89.9 (124/138)	81.7 (76/93)	86.6 (200/231)	1.10 (0.98, 1.23)	8.13 (−2.14, 18.41)	0.0805
Brachytherapy success (%)	99.3 (138/139)	89.2 (83/93)	95.3 (221/232)	1.11 (1.04, 1.20)	10.03 (2.65, 17.42)	0.0006
MACE-free at 6 mo (%)	82.1 (110/134)	35.1 (33/94)	62.7 (143/228)	2.34 (1.76, 3.11)	46.98 (34.39, 59.57)	<0.0001
TVR free at 6 mo (%)	85.1 (114/134)	39.4 (37/94)	66.2 (151/228)	2.16 (1.67, 2.81)	45.71 (33.18, 58.25)	<0.0001
MACE at 6 mo (%)	17.9 (24/134)	64.9 (61/94)	37.3 (85/228)	0.28 (0.19, 0.41)	−46.98 (−59.57, −34.39)	<0.0001
Death (%)	2.2 (3/134)	2.1 (2/94)	2.2 (5/228)	1.05 (0.18, 6.18)	0.11 (−4.66, 4.88)	>0.9999
Cardiac death (%)	0.7 (1/134)	2.1 (2/94)	1.3 (3/228)	0.35 (0.03, 3.81)	−1.38 (−5.56, 2.80)	0.5703
Noncardiac death (%)	1.5 (2/134)	0.0 (0/94)	0.9 (2/228)	3.52 (0.17, 72.46)	1.49 (−1.47, 4.46)	0.5133
MI (%)	1.5 (2/134)	17.0 (16/94)	7.9 (18/228)	0.09 (0.02, 0.37)	−15.53 (−24.35, −6.71)	<0.0001
Q-wave MI (%)	0.7 (1/134)	1.1 (1/94)	0.9 (2/228)	0.70 (0.04, 11.08)	−0.32 (−3.77, 3.13)	>0.9999
Non–Q-wave MI (%)	0.7 (1/134)	16.0 (15/94)	7.0 (16/228)	0.05 (0.01, 0.35)	−15.21 (−23.70, −6.72)	<0.0001
PTCA (%)	2.2 (3/134)	9.6 (9/94)	5.3 (12/228)	0.23 (0.07, 0.84)	−7.34 (14.73, 0.06)	0.0305
CABG (%)	12.7 (17/134)	56.4 (53/94)	30.7 (70/228)	0.23 (0.14, 0.36)	−43.70 (56.16, −31.23)	<0.0001
TVR at 6 mo (%)	14.9 (20/134)	60.6 (57/94)	33.8 (77/228)	0.25 (0.16, 0.38)	−45.71 (−58.25, −33.18)	<0.001
In-hospital MACE (%)	2.3 (3/131)	11.7 (11/94)	6.7 (14/225)	0.20 (0.06, 0.68)	−9.41 (−17.35, −1.48)	0.0050
Out-of-hospital MACE to 6 mo (%)	16.4 (22/134)	61.7 (58/94)	35.1 (80/228)	0.27 (0.18, 0.40)	−45.28 (−57.90, −32.66)	<0.0001
Core lab subset analysis						
In-analysis segment late loss at 6 mo	0.20 ± 0.70 (49)	0.85 ± 0.57 (81)	0.61 ± 0.70 (130)	NA	−0.65 (−0.87, −0.43)	<0.0001
Stent segment late loss at 6 mo	0.11 ± 0.90 (49)	1.00 ± 0.66 (80)	0.67 ± 0.87 (129)	NA	−0.89 (−1.16, −0.61)	<0.0001
In-analysis segment late loss index at 6 mo	−1.25 ± 7.32 (49)	1.37 ± 4.78 (80)	0.37 ± 5.99 (129)	NA	−2.62 (−4.73, −0.52)	0.0286
Stent segment late loss index at 6 mo	0.01 ± 0.60 (49)	0.86 ± 0.61 (79)	0.54 ± 0.73 (128)	NA	−0.85 (−1.07, −0.63)	<0.0001
In-analysis segment binary restenosis rate at 6 mo (%)	34.7 (17/49)	76.5 (62/81)	60.8 (79/130)	0.45 (0.30, 0.68)	−41.85 (−59.84, −23.85)	<0.0001
Stent segment binary restenosis rate at 6 mo (%)	20.4 (10/49)	70.0 (56/80)	51.2 (66/129)	0.29 (0.16, 0.52)	−49.59 (−66.47, −32.71)	<0.0001

Abbreviations: MACE = major adverse cardiac event; TVR = total vessel revascularization; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty; CABG = coronary artery bypass graft; other abbreviations as in Table 1.

Numbers in parentheses are numbers of patients, unless otherwise noted.

strictly avoided, and optimal sequential positioning is desirable (22). Because of the lack of anatomic landmarks, we recommend the use of a marker wire to optimize the sequential positioning of the source trains, which is particularly valuable in small vessels in which occlusion of contrast flow impairs one's ability to be guided by the position of side branches.

Limitations

This study was limited because the reference group was historical and the study was not randomized, which may constitute a certain selection bias. Nevertheless, the differences between the treatment and reference group were so enormous that any selection bias would not outweigh the positive benefits. It is possible that additional follow-up of

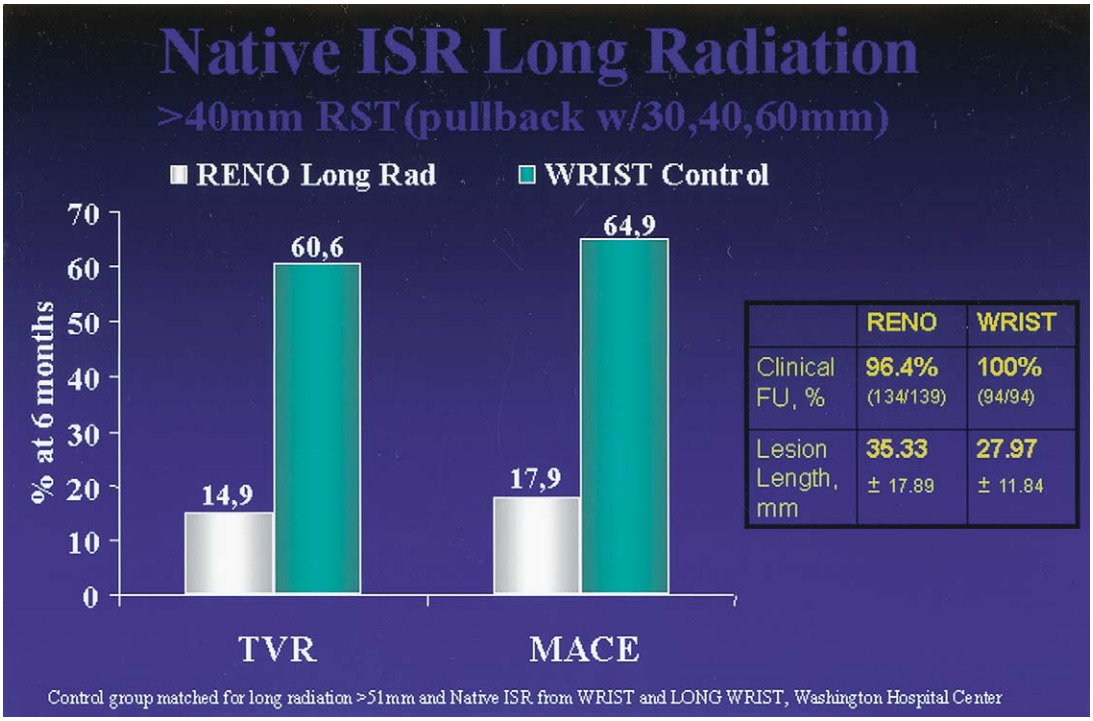


Fig. 3. Comparison of target vessel revascularization and MACE at 6 months between RENO long lesion group and respective control group from WRIST study. Note: lesion length and clinical follow-up were comparable.

these patients might reveal late effects not evident at the 6-month end point. Given the degree of benefit already observed in other clinical observations and the lack of adverse events, it is unlikely that late effects will negate the benefit of treatment.

The overall positive results of β-radiation in long lesions should be interpreted on the basis of the nonrandomized registry investigation. Thus, selection bias with respect to the treatment group cannot be excluded. Additional differences might arise from differences in the interventional ap-

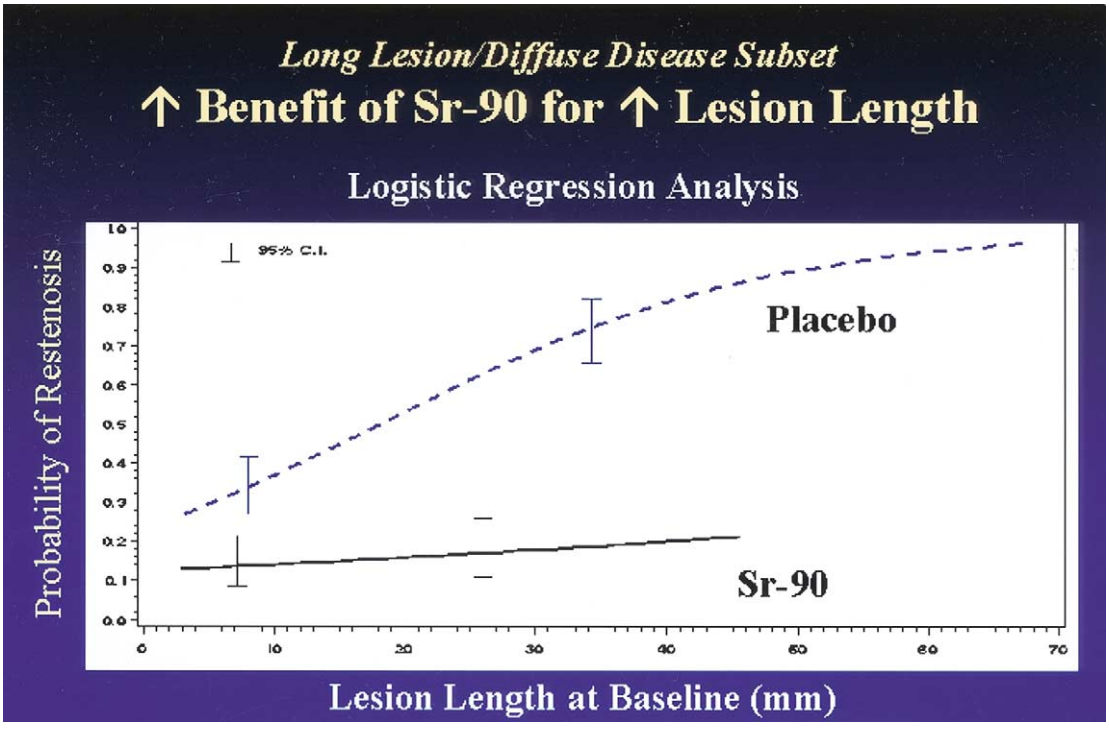


Fig. 4. Logistic regression analysis for probability of restenosis in relation to lesion length demonstrating superiority of β-radiation, especially with longer lesions (19).

proaches in the RENO registry, which was gathered in Europe, and the LONG WRIST study, which was mainly conducted in the United States. Therefore, the matched-pair analysis was chosen to account, at least in part, for these limitations and to ensure better comparability between the investigational groups. Although direct comparisons of MACE rates and radiation regimens seem problematic, the absolute numbers of clinical and angiographic outcome parameters are convincing and underline the effectiveness of β-radiation. We are, nevertheless, fully aware that only randomized trials will give adequate answers with respect to the effectiveness and superiority of any treatment option.

A further limitation seems to be the long-term follow-up, a limitation of any radiation trial to date. In particular, serious negative long-term effects such as aneurysm formation, thrombosis, or fibrosis can only be judged after 5–10 years (23). Although previous trials have indicated an increase in MACE rates with a duration of up to 5 years, the respective treatment groups were still superior to the control group.

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APPENDIX
Radiation in Europe with Novoste

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