

Randomized Trial of $^{90}\text{Sr}/^{90}\text{Y}$ β -Radiation Versus Placebo Control for Treatment of In-Stent Restenosis

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Background—After conventional treatment of in-stent restenosis, the incidence of recurrent clinical restenosis may approach 40%. We report the first multicenter, blinded, and randomized trial of intracoronary radiation with the use of a $^{90}\text{Sr}/^{90}\text{Y}$ β -source for the treatment of in-stent restenosis.

Methods and Results—After successful catheter-based treatment of in-stent restenosis, 476 patients were randomly assigned to receive an intracoronary catheter containing either $^{90}\text{Sr}/^{90}\text{Y}$ (n=244) or placebo (n=232) sources. The prescribed dose 2 mm from the center of the source was 18.4 Gy for vessels between 2.70 and 3.35 mm in diameter and 23.0 Gy for vessels between 3.36 and 4.0 mm. The primary end point, ie, clinically driven target-vessel revascularization by 8 months, was observed in 56 (26.8%) of the patients assigned to placebo and 39 (17.0%) of the patients assigned to radiation ($P=0.015$). The incidence of the composite including death, myocardial infarction, and target-vessel revascularization was observed in 60 (28.7%) of the patients assigned to placebo and 44 (19.1%) of the patients assigned to radiation ($P=0.024$). Binary 8-month angiographic restenosis ($\geq 50\%$ diameter stenosis) within the entire segment treated with radiation was reduced from 45.2% in the placebo-treated patients to 28.8% in the $^{90}\text{Sr}/^{90}\text{Y}$ -treated patients ($P=0.001$). Stent thromboses occurred in 1 patient assigned to placebo < 24 hours after the procedure and in 1 patient assigned to $^{90}\text{Sr}/^{90}\text{Y}$ at day 244.

Conclusions—The results of this study demonstrated that β -radiation using $^{90}\text{Sr}/^{90}\text{Y}$ is both safe and effective for preventing recurrence in patients with in-stent restenosis. (*Circulation*. 2002;106:1090-1096.)

Key Words: restenosis ■ stents ■ angioplasty ■ trials

Coronary stents are used in 80% of percutaneous coronary interventions (PCIs); their use is based on their ability to reduce the occurrence of restenosis compared with balloon angioplasty.¹⁻⁶ Although restenosis occurs in only 10% to 30% of patients after initial stent placement, the incidence of recurrence after PCI for in-stent restenosis is much higher, ranging from 19% to 83%.^{7,8} Compared with balloon angioplasty alone, no mechanical therapies have been shown to lower the rate of recurrent restenosis.^{9,10}

Three clinical trials in patients with in-stent restenosis have shown that compared with conventional PCI, γ -radiation using ^{192}Ir lowers the frequency restenosis.¹¹⁻¹³ These favorable results were sustained at 9 months but were tempered by the occurrence of late (>30 -day) stent thrombosis in 5.3% of the patients.¹¹

Episodes of late stent thrombosis were related to both the short duration (14 to 30 days) of ticlopidine therapy and the frequent ($>80\%$) use of additional coronary stents.¹⁴

β -Radiation using ^{90}Y alone and ^{32}P may also reduce the frequency of restenosis,¹⁵⁻¹⁷ but the utility of $^{90}\text{Sr}/^{90}\text{Y}$ brachytherapy in the setting of in-stent restenosis has not been tested. The purpose of the present study was to compare the safety and effectiveness of intracoronary $^{90}\text{Sr}/^{90}\text{Y}$ β -radiation with placebo control after successful PCI in patients with in-stent restenosis.

Methods

Study Population

Between September 1998 and May 1999, 476 patients were enrolled into the Stents and Radiation Therapy (START) Trial at 50 clinical

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Dr Bonan serves as Medical Director of Novoste Corp.

*A complete list of institutions and investigators participating in the START trial is listed in the Appendix.

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centers (see Appendix). Patients were included in the trial if they had a single target site of in-stent restenosis in a native vessel between 2.7 and 4.0 mm. In-stent restenosis was defined as a visually determined $>50\%$ -diameter stenosis that was ≤ 20 mm in length and associated with objective evidence of myocardial ischemia. All patients were pretreated with aspirin (325 mg). After a successful angiographic result ($<30\%$ visual diameter stenosis) was obtained by using balloon angioplasty alone or in combination with rotational atherectomy, directional atherectomy, or excimer laser angioplasty, patients were randomly assigned to receive intracoronary treatment with $^{90}\text{Sr}/^{90}\text{Y}$ ($n=244$) or placebo ($n=232$). An activated clotting time between 275 and 300 seconds was obtained by using bolus unfractionated heparin. A 30-mm BetaCath radioactive source train (Novoste Corp) was used for lesions with a 20-mm balloon injury length ($n=452$); a 40-mm BetaCath source train was used for lesions with a 30-mm balloon injury length ($n=24$). Patients were excluded from the study if they had planned multivessel PCI, a recent (≤ 72 -hour) myocardial infarction (MI), unprotected left main coronary artery disease, 2 overlapping stents, a prior history of any chest radiotherapy, or prior stent placement for in-stent restenosis. Informed consent approved by a local institutional review board was obtained before the procedure in all patients.

Procedural Details

The BetaCath source delivery system had 2 components, a transfer device used to deliver the radiation source train to the treatment site and a 5F "over-the-wire" triple-lumen delivery catheter with a closed source lumen. The delivery catheter was advanced over a 0.014-in guidewire, and radiopaque marker bands on the delivery catheter were positioned on either side of the injured segment. Sterile water was then injected by using a syringe locked to the transfer device, causing hydraulic pressure to advance the active or placebo source from the transfer device to the end of the BetaCath delivery catheter.

The radioisotope used for the present study was $^{90}\text{Sr}/^{90}\text{Y}$, which has a 28.1-year half-life. The mean activity of the 30-mm 12-source train was 39.96 ± 2.5 mCi, and the mean dose rate was 0.0923 ± 0.0058 Gy/s. The prescription point was 2 mm from the center line of the radiation source train. The dose prescription was 18.4 Gy for visual reference vessel sizes >2.7 mm and ≤ 3.35 mm and 23 Gy for visual reference vessel sizes >3.36 mm and ≤ 4.0 mm; the indwelling treatment time ranged from 3 to 5 minutes. After treatment, the sources were retrieved back into the transfer device, and the transfer device was separated from the delivery catheter and placed into a shielded storage. The use of PCI (including stents) after brachytherapy was discouraged and reserved for "bailout" indications (ie, $>30\%$ residual stenosis or a major dissection).¹⁸

After PCI, patients were given aspirin (325 mg daily) for the duration of the study. If a new stent was placed, patients enrolled from September 1998 until November 1998 also received ticlopidine (250 mg twice daily) for 14 days after the procedure. After November 1998, patients who received new stents were treated with ticlopidine (250 mg twice daily) or clopidogrel (75 mg daily) for at least 60 days after the procedure. Angiographic follow-up was obtained 8 months after the procedure, or sooner if recurrent symptoms developed.

Angiographic Analysis

All cineangiograms were forwarded to a central core laboratory for analysis with the use of standard criteria by observers blinded to the study protocol.^{19,20} Quantitative angiographic analysis was performed on 2 matched cine frames obtained before and after intervention and at follow-up. The following regions were analyzed by using a validated algorithm (Cardiovascular Measurement Systems; Leiden, the Netherlands)²¹: (1) the stent segment, which contained the entire axial length of the original stents; (2) the injured segment, which included the proximal and distal injured regions determined by the position of balloon; (3) the radiated segment, which included the proximal and distal location of the radiation source train; and (4) the analysis segment, which included a 5-mm segment proximal and distal to the regions of injury or radiation treatment. Semiquantitative measurements of the edges were obtained by using digital calipers.

Geographic miss was defined as proximal or distal balloon injury that was not covered with any radiation treatment. By using the contrast-filled injection catheter as the reference standard, quantitative measures were obtained from the average proximal and distal reference segment and minimal lumen diameter (MLD). Late loss was calculated by the post-PCI MLD minus the follow-up MLD. Binary angiographic restenosis was defined as $\geq 50\%$ follow-up diameter stenosis.

Clinical Outcomes

Death was reported as cardiac death and noncardiac death. MI was characterized as follows: Q-wave MI, defined as the development of new, pathological Q wave in ≥ 2 leads with postprocedural creatine kinase (CK) or CK-MB levels above normal, and non-Q-wave MI, defined as an elevation of the postprocedural CK levels to 2 times normal with CK-MB above normal. Device success was defined as the attainment of a $<50\%$ stenosis by quantitative analysis and the successful delivery of the radiation device. Procedural success was defined as the attainment of a residual stenosis $<50\%$ by quantitative analysis and no in-hospital major adverse cardiac events (MACEs), including death, MI, or emergency coronary artery bypass graft surgery (CABG) or repeat target-lesion PCI. Clinical stent thrombosis was defined as angiographic thrombus or subacute closure within the stented vessel at the time of clinically driven angiographic restudy due to chest pain or ECG changes.

Study End Points

The primary study end point was target-vessel revascularization (TVR), defined as clinically driven repeat revascularization (by symptoms or laboratory testing using PCI or bypass surgery), and a $\geq 50\%$ stenosis within the treated vessel on follow-up angiography. The occurrence of target lesion revascularization was determined as clinically driven ($\geq 50\%$ stenosis within 5 mm of the analysis segment associated with clinical ischemia or a $\geq 70\%$ stenosis in the absence of clinical indicators) repeat revascularization. The primary safety end point was the occurrence of MACEs, which included a composite of death, MI, or TVR.

Statistical Analysis

Binary variables are presented as rates, and continuous variables are presented as mean ± 1 SD. Binary variables were compared by χ^2 analysis, and continuous variables were evaluated by using the Student *t* test. Survival analyses were performed by Kaplan-Meier methods, and survival was compared by the log-rank test. All analyses were performed with the use of SAS for Windows (versions 6.12 and 8.0, SAS Institute). A 2-sided value of $P \leq 0.05$ was considered significant. The study power was sufficient to show a 38% treatment effect, assuming a 30% 8-month TVR rate in the placebo group and a 18.5% 8-month TVR rate in the treatment group, with $\alpha=0.05$ and $\beta=0.80$. This sample size was also sufficient to detect a 0.20-mm difference in the follow-up MLD between the $^{90}\text{Sr}/^{90}\text{Y}$ -treated patients and placebo-treated patients. The interaction between treatment assignment and diabetes, or use of an atherectomy device before brachytherapy, was tested by using regression models.

Results

Baseline Study Characteristics and Procedural Findings

Baseline characteristics were similar in the 2 arms (Table 1). Plaque-debulking devices were used with similar frequency in the 2 groups: rotational atherectomy was used in 39.8% of the placebo-assigned patients and in 43.9% of the $^{90}\text{Sr}/^{90}\text{Y}$ -assigned patients; excimer laser angioplasty was used in 7.4% of the placebo-assigned patients and in 5.7% of the $^{90}\text{Sr}/^{90}\text{Y}$ -assigned patients; and directional atherectomy was used in 0.9% of the placebo-assigned patients and in none of the

TABLE 1. Baseline Clinical and Angiographic Characteristics of 476 Patients With In-Stent Restenosis Assigned to Receive $^{90}\text{Sr}/^{90}\text{Y}$ or Placebo

Characteristic	$^{90}\text{Sr}/^{90}\text{Y}$ (n=244)	Placebo (n=232)
Age, y	61.5±11.5	61.1±10.4
Males	167 (68)	147 (63)
Diabetes mellitus	75 (31)	75 (32)
Current smoker	29 (13)	18 (8)
Hypertension	174 (72)	170 (74)
Hyperlipidemia	184 (77)	177 (77)
Prior myocardial infarction	113 (47)	110 (48)
Prior CABG	52 (21)	55 (24)
Unstable angina	180 (74)	183 (79)
Crescendo angina	101 (41)	91 (39)
Rest angina	75 (31)	87 (38)
Multivessel disease	90 (37)	103 (44)
LVEF	54.2±10.5	54.6±12.3

Values are mean±SD or n (%).

LVEF indicates left ventricular ejection fraction.

$^{90}\text{Sr}/^{90}\text{Y}$ -assigned patients. New stents were deployed in 19.8% of the placebo-assigned patients and in 20.9% of the $^{90}\text{Sr}/^{90}\text{Y}$ -assigned patients.

Quantitative Angiographic Results

The distribution of target coronary vessels was similar between the 2 arms (Table 2). For both arms, the overall stented segment length was 22.7±10.7 mm, the injured segment length was 25.2±9.2 mm, the radiated segment length was 30.0±5.3 mm, and the analysis segment length was 40.8±9.4 mm. The balloon/artery ratio was 0.97 for both placebo- and $^{90}\text{Sr}/^{90}\text{Y}$ -treated patients.

Acute and follow-up quantitative angiographic results are found in Table 3. Angiographic complications were uncommon in both groups: a final National Heart, Lung, and Blood Institute dissection grade >B was present in 3.0% of the placebo-assigned patients and in 2.4% of the $^{90}\text{Sr}/^{90}\text{Y}$ -assigned patients. Final Thrombolysis in Myocardial Infarction (TIMI) 3 flow grade was 99.1% in the placebo arm and 100.0% in the $^{90}\text{Sr}/^{90}\text{Y}$ arm.

Angiographic follow-up was obtained at 8 months in 188 (81.0%) of the placebo-treated patients and in 198 (83.2%) of the $^{90}\text{Sr}/^{90}\text{Y}$ -treated patients. There was no significant difference in the follow-up reference vessel diameter between the 2 arms (2.82±0.46 mm for the $^{90}\text{Sr}/^{90}\text{Y}$ arm and 2.85±0.44 mm for the placebo arm). Cumulative frequency distribution curves are presented for the MLD within the stent (Figure 1) and within the segment (Figure 2).

The lesion length at follow-up was significantly shorter in patients assigned to $^{90}\text{Sr}/^{90}\text{Y}$ compared with patients assigned to placebo (8.62±5.4 versus 12.5±10.7 mm, respectively; $P<0.001$). Asymptomatic late total occlusion was found with similar frequency between the 2 arms (4.0% in the $^{90}\text{Sr}/^{90}\text{Y}$ arm and 3.7% in the placebo arm, $P=0.872$). There were no new late aneurysms detected in either arm at the 8-month angiographic follow-up. Geographic miss was documented in

TABLE 2. Baseline Qualitative Angiographic Findings

Characteristic	$^{90}\text{Sr}/^{90}\text{Y}$ (n=244)	Placebo (n=232)
Artery treated		
Left anterior descending	105 (43)	95 (41)
Left circumflex	63 (26)	55 (24)
Right coronary	70 (29)	77 (34)
Eccentricity	32 (13)	22 (10)
Calcification	60 (25)	51 (23)
Thrombus	4 (1.6)	1 (0.4)
Angulation >45°	11 (4.5)	16 (7.0)
Lesion length	16.3±7.2	16.0±7.6
0.1–10 mm	53 (23)	55 (25)
>10 and <20 mm	114 (48)	105 (47)
≥20 mm	68 (29)	63 (28)
ACC/AHA lesion class B2 or C	169 (69)	148 (66)
Reference diameter, mm	2.76±0.48	2.77±0.43
MLD, mm	0.98±0.38	0.98±0.37
Diameter stenosis, %	64.2±13.7	64.2±13.1
Previous interventions for stent restenosis		
Initial treatment	127 (52)	130 (57)
1 Prior procedure	82 (34)	74 (33)
2 Prior procedures	33 (14)	24 (10)

Values are n (%) or mean±SD.

ACC indicates American College of Cardiology; AHA, American Heart Association.

130 (34%) of 386 lesions available for follow-up angiographic analysis. Restenosis rates within the analysis segment in patients treated with $^{90}\text{Sr}/^{90}\text{Y}$ were similar in both groups (25.4% in patients with lesions with geographic miss and 29.4% in patients with no geographic miss). There were also no significant differences in the mean percent stenosis at the proximal or distal edges of the source train in patients treated with $^{90}\text{Sr}/^{90}\text{Y}$ or placebo.

The presence of diabetes mellitus or use of a debulking device did not influence the effect of $^{90}\text{Sr}/^{90}\text{Y}$ in reducing angiographic restenosis, as assessed by multivariable analysis. In patients who did not receive debulking therapy, the binary analysis segment restenosis rate was 38.5% in the placebo group and 27.3% in the $^{90}\text{Sr}/^{90}\text{Y}$ group ($P=0.094$). In patients who did receive debulking therapy, the binary analysis segment restenosis rate was 52.7% in the placebo group and 30.3% in the $^{90}\text{Sr}/^{90}\text{Y}$ group ($P=0.0017$). In patients without diabetes mellitus, the binary analysis segment restenosis rate was 45.3% in the placebo group and 26.9% in the $^{90}\text{Sr}/^{90}\text{Y}$ group ($P=0.0019$). In patients with diabetes mellitus, the binary analysis segment restenosis rate was 45.0% in the placebo group and 32.8% in the $^{90}\text{Sr}/^{90}\text{Y}$ group ($P=0.164$).

Early and Late Clinical Outcomes

There were no in-hospital deaths or differences in the rates of in-hospital MACEs between the 2 groups (Table 4). The procedural success (97%) and the device success (98%) rates were similar in

TABLE 3. Acute and Follow-Up (Based on Patients With Follow-Up) Quantitative Angiographic Results

Characteristic	⁹⁰ Sr/ ⁹⁰ Y (n=198)	Placebo (n=188)	P
Stented segment			
Postprocedural MLD, mm	2.17±0.42	2.15±0.42	0.650
Follow-up MLD, mm	1.96±0.66	1.47±0.60	≤0.001
Late loss, mm	0.21±0.61	0.67±0.61	<0.001
Postprocedural diameter stenosis, %	22.9±13.5	22.9±12.9	0.997
Follow-up diameter stenosis, %	30.4±22.7	47.9±20.8	≤0.001
Binary restenosis rate, %	14.2	41.2	≤0.001
Injured segment			
Postprocedural MLD, mm	2.10±0.41	2.11±0.42	0.788
Follow-up MLD, mm	1.85±0.67	1.44±0.61	≤0.001
Late loss, mm	0.27±0.59	0.67±0.62	≤0.001
Postprocedural diameter stenosis, %	25.4±12.5	24.4±12.1	0.390
Follow-up diameter stenosis, %	34.7±22.4	49.1±21.3	≤0.001
Binary restenosis rate, %	18.2	45.3	≤0.001
Irradiated segment			
Postprocedural MLD, mm	2.04±0.39	2.03±0.41	0.789
Follow-up MLD, mm	1.75±0.65	1.42±0.60	≤0.001
Late loss, mm	0.29±0.60	0.63±0.60	≤0.001
Postprocedural diameter stenosis, %	27.7±11.5	27.5±11.8	0.806
Follow-up diameter stenosis, %	38.2±21.2	50.0±20.1	≤0.001
Binary restenosis rate, %	24.4	45.9	≤0.001
Analysis segment			
Postprocedural MLD, mm	1.94±0.39	1.94±0.41	0.906
Follow-up MLD, mm	1.65±0.64	1.41±0.58	≤0.001
Late loss, mm	0.28±0.56	0.55±0.59	≤0.001
Postprocedural diameter stenosis, %	31.4±10.2	30.7±11.0	0.480
Follow-up diameter stenosis, %	41.7±20.7	50.1±19.7	≤0.001
Binary restenosis rate, %	28.8	45.2	0.001

Values are mean±SD or as indicated.

placebo-assigned patients and ⁹⁰Sr/⁹⁰Y-assigned patients. Emergency CABG was performed in 1 patient assigned to ⁹⁰Sr/⁹⁰Y and in no patient assigned to placebo therapy. The BetaCath delivery device was successfully placed in 98.7% of the patients, and the sources were successfully delivered in 98.1% of the patients. Source

drift was noted in 9% of the patients but was not associated with clinical sequelae. The temporary storage container was used in 5 patients because of the real or perceived inability to return the source train fully into the transfer device. None of these episodes was due

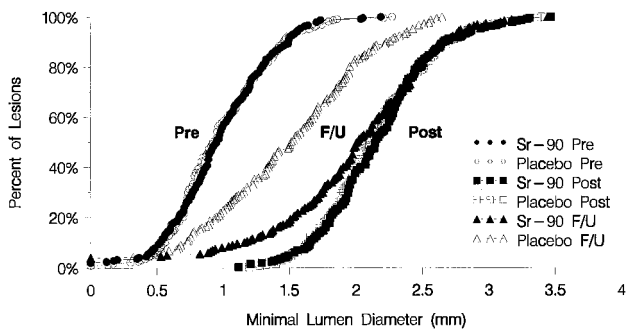


Figure 1. Cumulative frequency distribution curve of MLD within stented segment before treatment, after treatment, and late after treatment with ⁹⁰Sr/⁹⁰Y or placebo. Stent follow-up MLD is substantially larger in patients treated with ⁹⁰Sr/⁹⁰Y.

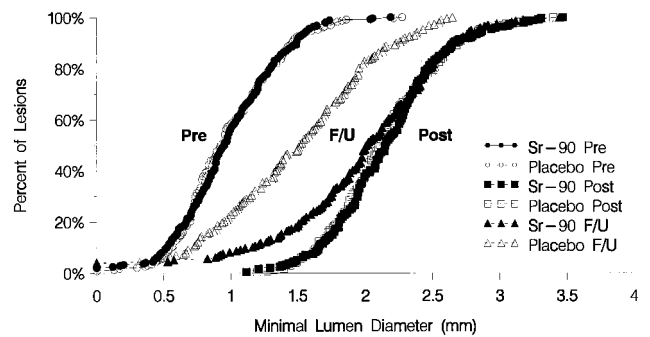


Figure 2. Cumulative frequency distribution curve of MLD within analysis segment before treatment, after treatment, and late after treatment with ⁹⁰Sr/⁹⁰Y or placebo. Stent follow-up MLD is substantially larger in patients treated with ⁹⁰Sr/⁹⁰Y.

TABLE 4. In-Hospital and Late (8-Month) Clinical Outcomes

Outcome	⁹⁰ Sr/ ⁹⁰ Y	Placebo	P
In hospital	(n=244)	(n=232)	...
Any MACE	6 (2.5)	5 (2.2)	0.99
Death	0 (0)	0 (0)	...
MI	4 (1.6)	4 (1.7)	0.99
Q wave	0 (0)	0 (0)	...
Non-Q wave	4 (1.6)	4 (1.7)	0.99
TVR	2 (0.8)	1 (0.4)	0.329
Vascular complications	3 (1.2)	2 (0.9)	0.694
Acute stent thrombosis (30-day)	0 (0)	1 (0.4)	0.49
240-Day outcome	(n=230)	(n=209)	...
Any MACE	44 (19.1)	60 (28.7)	0.024
Death	3 (1.3)	1 (0.5)	0.625
MI	4 (1.7)	7 (3.3)	0.364
Q wave	0 (0)	0 (0)	...
Non-Q wave	4 (1.7)	7 (3.3)	0.364
Emergency CABG	1 (0.4)	0 (0)	1.000
TVR	39 (17)	56 (26.8)	0.015
Target-vessel CABG	21 (9.1)	24 (11.5)	0.435
Target-vessel PCI	19 (8.3)	34 (16.3)	0.012
Target lesion revascularization	32 (13.9)	52 (24.9)	<0.001
Target lesion CABG	20 (8.7)	24 (11.5)	0.344
Target lesion PCI	12 (5.2)	30 (14.3)	<0.001
Late stent thrombosis	0 (0)	0 (0)*	...

Values are n (%).

*One patient had late stent thrombosis at day 244.

to faulty administration according to the Nuclear Regulatory Commission criteria.

Late clinical outcome at 240±30-day follow-up was assessed in 439 (92.2%) of the 476 patients enrolled in the study. The primary end point, 8-month TVR, occurred significantly less frequently in patients treated with ⁹⁰Sr/⁹⁰Y (Table 4), with an event rate at 240 days by Kaplan-Meier estimates falling from 26.2% in placebo-treated patients to 16.5% in ⁹⁰Sr/⁹⁰Y-treated patients ($P=0.012$). According to 240-day Kaplan-Meier estimates, the rates of target lesion revascularization were reduced from 24.4% in placebo-treated patients to 13.6% in ⁹⁰Sr/⁹⁰Y-treated patients ($P<0.001$), and the Kaplan-Meier rates of MACEs were lowered from 27.8% to 18.6%, respectively ($P=0.016$, Figure 3).

There was 1 episode of late clinical stent thrombosis in the ⁹⁰Sr/⁹⁰Y group at 244 days. After brachytherapy in this patient, an in-stent residual stenosis was noted, and a stent was placed, resulting in a 48% residual diameter stenosis. The patient received 3 months of therapy with aspirin and clopidogrel but presented with late subacute closure at day 244.

There were 4 late deaths in the present study. One patient underwent a successful treatment followed by ⁹⁰Sr/⁹⁰Y therapy but died 193 days after treatment because of complications subsequent to surgical resection of a colon polyp, including pneumonia. Another patient underwent successful treatment for in-stent restenosis followed by ⁹⁰Sr/⁹⁰Y therapy and expired 225 days later because of a metastatic prostate and rectal cancer. A

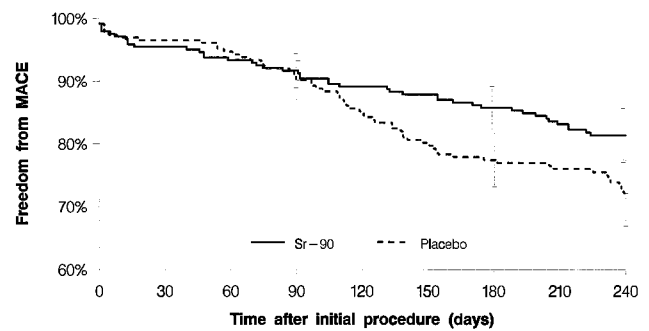


Figure 3. In patients treated with ⁹⁰Sr/⁹⁰Y or placebo, 240-day MACE-free survival curve. There was significant improvement in clinical outcome in patients in ⁹⁰Sr/⁹⁰Y arm compared with patients in placebo arm ($P=0.032$).

third patient underwent successful treatment for in-stent restenosis followed by ⁹⁰Sr/⁹⁰Y therapy and died 210 days after treatment that followed lung surgery. The fourth patient underwent successful treatment of in-stent restenosis, followed by placebo therapy. This patient died from cardiac causes 102 days after treatment.

Discussion

This multicenter, randomized, placebo-controlled trial was the first to demonstrate that intracoronary brachytherapy using ⁹⁰Sr/⁹⁰Y β -radiation reduced the frequency of angiographic and clinical recurrence in patients undergoing PCI for in-stent restenosis. Treatment with ⁹⁰Sr/⁹⁰Y lowered the frequency of the TVR by 37% and the incidence of angiographic restenosis within the treated segment by 36%. Intracoronary β -radiation also proved to be safe, inasmuch as there was only 1 case (0.4%) of late stent thrombosis 244 days after the procedure and no cases of new late aneurysm formation.

Outcomes After Stent Placement

Coronary stenting has reduced the frequency of clinical and angiographic restenosis compared with balloon angioplasty in most clinical subsets.^{1-6,22} The risk of clinical restenosis after stenting is between 10% and 30% and is increased with longer lesion or stent length,²³ smaller vessel size,²⁴ smaller posttreatment lumen diameter, and the presence of diabetes mellitus.²⁵ In-stent restenosis is due to excessive intimal hyperplasia within the stent and its edges.^{26,27} Conventional balloon angioplasty is a safe treatment for patients with stent restenosis,²⁸ although recurrence restenosis rates after PCI for in-stent restenosis are higher than with the initial stent placement, ranging from 19% to 83%.^{7,8} Recurrence rates are highest when the pattern of stent restenosis is diffuse, the reference vessel is small, the patient has diabetes mellitus, or the time to recurrence is short. Debulking techniques have been used in an attempt to lower restenosis rates, but none has proven to be more effective than balloon angioplasty alone.¹⁰

Vascular Brachytherapy for Treatment of Stent Restenosis

Intracoronary ¹⁹²Ir γ -brachytherapy is an effective method for reducing recurrent restenosis after PCI for in-stent restenosis,¹¹⁻¹³ particularly in patients with diffuse lesions and multiple

recurrent episodes of restenosis. The multicenter GAMMA-1 trial randomly assigned 252 patients to treatment with ^{192}Ir or placebo.¹¹ MACEs at 6 months were reduced by 36% with ^{192}Ir (from 43.8% in placebo-treated patients to 28.2% in ^{192}Ir -treated patients).¹¹ Angiographic restenosis was also reduced by 41% (from 55.3% in placebo-treated patients to 32.4% in ^{192}Ir -treated patients).¹¹ These ^{192}Ir trials were limited by prolonged dwell times (20 to 30 minutes), the need for extensive shielding apparatus, and the requirement for laboratory personnel to leave the room during brachytherapy administration. New stents were also commonly (>80%) used for the treatment of in-stent restenosis in these studies and resulted in frequent (5.3% to 8.3%) late stent thrombosis.^{11,13,14} Similar reductions in recurrence rates associated with PCI for in-stent restenosis were obtained with use of the ^{32}P β -source.¹⁶

Present Trial

In the present study, treatment with $^{90}\text{Sr}/^{90}\text{Y}$ after successful PCI for in-stent restenosis resulted in a 37% reduction in clinical restenosis by 240 days and a 36% reduction in angiographic restenosis. Control patients in this trial of in-stent restenosis had lower restenosis rates than did the control patients in the γ -source trials. Two factors likely contributed to these differences: (1) shorter lesion lengths (control group mean lesion length in the $^{90}\text{Sr}/^{90}\text{Y}$ study was 16.0 ± 7.6 mm versus 20.3 ± 10.3 mm in the GAMMA-1 trial) and (2) a higher incidence of "first-time" in-stent restenosis patients in the present study.

Plaque-debulking devices, particularly rotational atherectomy, were used in nearly 50% of the patients in this trial. The use of these debulking devices did not appear to influence angiographic or clinical outcomes, and there was no diminution of the treatment effect associated with the use of debulking devices. An important feature of the present study was the infrequent (20.4%) use of additional coronary stents to treat in-stent restenosis.

Although a relationship between the occurrence of geographic miss and angiographic or clinical restenosis could not be identified, edge effect and geographic miss were not specifically evaluated in the present study. The failure to identify a relationship between geographic miss and restenosis may be due to the fact that the effective radiation length of 25 mm for the 30-mm source (accounting for the dose falloff at the edges of the radiation source) was insufficient to adequately cover the margins in most injured zones. Additional studies are needed to understand the relationship between radiation doses at the edge of the treatment zone and late restenosis.

Radiation Exposure

Compared with γ -therapy, treatment with β -radiation results in shorter treatment times (3 to 5 minutes with the use of $^{90}\text{Sr}/^{90}\text{Y}$ in the present study versus 20 to 30 minutes for ^{192}Ir), which result in a significantly lower dose to nontarget tissue in the patient and allow the medical personnel to remain safely in the catheterization laboratory during the radiation treatment. The operator at the bedside receives $\approx 8.6 \times 10^{-7}$ C/kg per hour for β -radiation using $^{90}\text{Sr}/^{90}\text{Y}$. In comparison, cardiac fluoroscopy has an exposure rate of 3.9×10^{-3} C/kg per hour. Accordingly, the exposure risk seen in coronary brachytherapy using $^{90}\text{Sr}/^{90}\text{Y}$ is clinically insignificant compared with the routine exposure from cardiac fluoroscopy. Differences in treatment duration,

radiation exposure, and the ability to closely conform the dose to the target of interest may have important implications for the broader application of β -radiation for the treatment of in-stent restenosis.

Late Clinical Stent Thrombosis

Prior radiation stent studies have reported that late (>30-day) clinical stent thrombosis may occur in up to 6% of patients undergoing radiation treatment. Late stent thrombosis after radiation brachytherapy is generally manifested as an acute non-Q-wave or Q-wave MI.^{11,13,14} The occurrence of late stent thrombosis has been attributed to delayed endothelialization over the stent struts and has been observed up to 9 to 12 months after new stent implantation.¹¹ In the γ -radiation trials, this complication has also been related to the use of a new second stent within the initial lesion.¹⁴ The relatively short-term (≤ 4 -week) dosing of antiplatelet therapy with ticlopidine or clopidogrel may have also contributed to the incidence of late thrombosis. In this trial, the 20.4% use of additional stents was reserved for bailout indications, and this lower incidence of new stent use coupled with extended dual antiplatelet therapy may have translated into a reduced rate of late stent thrombosis in the radiation arm in the present study.

Limitations of the Study

The present study did not include patients with very long lesions (stenosis lengths >30 mm) because of the relatively short (30- and 40-mm) BetaCath source trains available for the study. Longer source trains (40 and 60 mm) are now available for clinical use. It is also recognized that a lower profile delivery catheter may enhance catheter delivery in smaller vessels and in those with tortuosity, angulation, and diffuse disease, and a 3.5F catheter has now been approved for clinical use. Another limitation of the present study is the intermediate duration (240 days) of follow-up after radiation therapy. Longer angiographic and clinical follow-up (up to 2 to 3 years or more) is required to address whether stent restenosis is prevented or simply delayed.

The present study demonstrated that $^{90}\text{Sr}/^{90}\text{Y}$ β -radiation is a safe and effective treatment for the prevention of recurrence in patients with in-stent restenosis. β -Radiation may be used as an alternative to γ -radiation in these patients. It provides the advantages of a shorter (3- to 5-minute) treatment time and allows laboratory personnel to remain at the patient's bedside during the procedure. Further studies are required to evaluate the long-term duration of the effect and to determine whether other β -sources may equally reduce recurrent restenosis after PCI for in-stent restenosis.

Appendix

Institutions and Investigators Participating in START Trial

Institutions and investigators that participated in the START trial are as follows (the number of patients enrolled is given in parentheses): Scripps Clinic and Research Foundation, La Jolla, Calif (40): P. Teirstein, V. Massullo; University of Florida, Jacksonville (29): T. Bass, R. Henderson; Dr. Mueller Hospital, Munich, Germany (26): S. Silber, P. von Rottkay; St. Luke's Hospital, Kansas City, Mo (20): B. Rutherford, A. Elman; Piedmont Hospital, Atlanta, Ga (18): C. Wilmer, C. Brown, F. Schwaibold; Cardiology Research Foundation, Washington, DC (17): M. Leon, R. Waksman, L. White; William Beaumont, Royal Oak, Mich (17): W. O'Neill, A. Martinez; University of Alabama, Birmingham (16): L. Dean, R. Kim; Mercy

General Hospital, Sacramento, Calif (16); R. Low, M. Leinbent; Ochsner, New Orleans, La (15); S. Jenkins, R. Kuske; Beth Israel Deaconess Medical Center, Boston, Mass (14); R. Kuntz, A. Abner; St. Francis Hospital, Roslyn, NY (14); A. Berke, L. Farber; Washington University School of Medicine, St. Louis, Mo (13); J. Lasala, C. Perez; Thomas Jefferson University Hospital, Philadelphia, Pa (12); M. Savage, R. Valicenti; Swedish Medical Center, Seattle, Wash (12); M. Reisman, T. Barnett; University of Maryland School of Medicine, Baltimore (11); W. Laskey, M. Suntharalingam; Mid Carolina Cardiology, Charlotte, NC (11); G. Neiss, D. Cox, M. Kirsch; Seattle Cardiac Research, Seattle, Wash (11); J. Werner, S. Cole; Rush Presbyterian/St. Luke's Medical Center, Chicago, Ill (11); G. Schaer, J. Snell, C. Nguyen; Emory University School of Medicine, Atlanta, Ga (10); J. Douglas, Z. Ghazzal, J. Keller; Loyola University, Maywood, Ill (9); B. Lewis, E. Grassman, B. Emami; New York Hospital/Cornell Medical Center, New York, NY (8); M. Parikh, A. Shaknovich, D. Nori; Medical College of Virginia, Richmond (8); G. Vetrovec, D. Arthur; University of Chicago, Chicago, Ill (8); T. Feldman, A. Mundt; Brigham and Women's Hospital, Boston, Mass (8); J. Popma, D. Simon, J. Harris; Mount Sinai Hospital, New York, NY (7); S. Sharma, R. Stock; Albany Medical Center, Albany, NY (7); A. DeLago, H. Keys; Rhode Island Hospital, Providence (6); D. Williams, P. Chougule; Phoenix Regional Medical Center/Columbia HCA, Phoenix, Ariz (6); R. Heuser, B. Speiser; University Hospital, Augusta, Ga (6); L. Walters, B. Dasher; University of Rochester, Rochester, NY (6); R. Pomerantz, P. Rubin; University of Florida, Gainesville (6); C. Pepine, R. Kerensky, N. Mendenhall; Mayo Clinic, Rochester, Minn (5); D. Holmes, S. Stafford; Johns Hopkins Hospital, Baltimore, Md (5); J. Brinker, L. Kleinberg, J. Welsh; University of Wisconsin, Madison (5); M. Wolff, P. Mahler; Marshfield Clinic, Marshfield, Wis (5); K. Wolschleger, M. Fallon; Vanderbilt University, Nashville, Tenn (5); R. Myers, A. Cmelak; LDS Hospital, Salt Lake City, Utah (5); S. Sorensen, W. Sause; Iowa Methodist Medical Center, Des Moines (4); P. Bear, H. McBride; Brooke Army Medical Center, Ft. Sam Houston, Tex (4); T. Carlson, M. Beat; University of Texas Health Science Center, San Antonio (3); S. Bailey, J. Marbach; Jewish Hospital, Louisville, Ky (3); M. Leeser, O. Jose; Center Hospitalier University of Montreal, Montreal, Canada (3); F. Reeves, D. Donath; Crouse Health Hospital, Syracuse, NY (3); R. Caputo, C. Chung; University of Iowa Hospital, Iowa City (2); J. Rossen, K. Zhen; Indiana University, Indianapolis (2); V. Pompili, J. Dillon, R. Timmerman; Duke University Medical Center, Durham, NC (1); M. Sketch, G. Bowen; Wake Forest University, Winston-Salem, NC (1); M. Kutcher, E. Shaw; Ottawa Heart Institute, Ottawa, Canada (1); M. Labinaz, L. Eapen; and Catharina Hospital, Eindhoven, the Netherlands (1); H. Bonnier, M. Lybeert.

Data and Safety Monitoring Board Members

Data and Safety Monitoring Board members are as follows: Thomas Ryan (chairman), Bernard Gersh, David Faxon, John Hirshfield, Stuart Pocock (statistician), and Don Cutlip (Cardiovascular Data Analysis Center [CDAC] representative); CDAC/Harvard Clinical Research Institute Staff: Kalon Ho, William Smith (nurse reviewer), Alison Osattin, Matthew Pietruszewicz, and Lisa Beck; Angiographic Core Laboratory, Cardiology Research Foundation: Alexandra Lansky, MD; and ECG Core Laboratory, CDAC/Harvard Clinical Research Institute: Peter Zimetbaum and Shiu Ho.

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