Two-year clinical follow-up of $^{90}Sr/^{90}Y$ β-radiation versus placebo control for the treatment of in-stent restenosis

Sigmund Silber, MD,[a] Jeffrey J. Popma, MD,[b] Mohan Suntharalingam, MD,[c] Alexandra J. Lansky, MD,[d] Richard R. Heuser, MD,[e] Burton Speiser, MD,[f] Paul S. Teirstein, MD,[g] Theodore Bass, MD,[h] William O'Neill, MD,[i] John Lasala, MD,[j] Mark Reisman, MD,[k] Samin K. Sharma, MD,[l] Richard E. Kuntz, MD,[b] and Raoul Bonan, MD,[m] for the START Investigators ***Munich, Germany, Boston, Mass, Baltimore, Md, New York, NY, Phoenix, Ariz, La Jolla, Calif, Jacksonville, Fla, Royal Oak, Mich, St. Louis, Mo, Seattle, Wash, and Montreal, Quebec, Canada***

Background It is an ongoing concern that intracoronary brachytherapy may possibly just delay the problem of in-stent restenosis ("late catch up"). For γ-radiation, 3 placebo-controlled studies have shown the maintenance of the initially positive effect after 2 years, but similar data do not exist for β-radiation. STents And Restenosis Trial (START) was the first placebo-controlled randomized trial for in-stent restenosis with β-radiation; herein, we report the 2-year clinical follow-up.

Methods and Results Two hundred and forty-four patients were randomized to active treatment, 232 patients to placebo (nonactive source train) treatment. The primary end point of efficacy was target vessel revascularization (TVR); primary safety end point was any major adverse cardiac event (MACE) at 8 months and 2 years. Two-year clinical outcome in patients receiving brachytherapy was based on 195 of 244 original patients (79.9%) and in the placebo arm on 183 of 232 original patients (78.9%). TVR was significantly reduced by 25%; from 36.6% (placebo) to 27.5% (brachytherapy) remained significant after 2 years (RR .7 [.57–.98], 95% CI −9.2 [−17.5–0.8]). The Kaplan-Meier analysis for TVR and MACE showed improvement beginning approximately 90 days after radiation and remained almost constant for the 2 following years. Freedom from TVR was significantly increased from 62.4% ± 3.8% to 71.6% ± 3.3% ($P = .027$) and freedom from MACE from 58.9% ± 3.7% to 68.0% ± 3.4% ($P = .035$).

Conclusions The START trial shows for the first time that the initial beneficial effects of intracoronary brachytherapy with β-radiation using $^{90}Sr/^{90}Y$ are maintained at 2-year clinical follow-up period. (Am Heart J 2005;149:689-94.)

Despite the use of sirolimus- and paclitaxel-eluting stents for in-stent restenosis,[1-3] intracoronary brachytherapy is currently the only evidence-based medicine treatment for in-stent restenosis.[4-7] Today, there are 3 radiation delivery systems that the US FDA approved for routine clinical use (1 γ-emitting, ^{192}Ir, and 2 β-emitting, $^{90}Sr/^{90}Y$ and ^{32}P).

However, there is ongoing concern that intracoronary brachytherapy may possibly just delay the in-stent restenosis. Three placebo-controlled γ-radiation studies have shown the maintenance of the initially positive effect on clinical outcome at 2 to 5 years (Figure 1)[8-12]; but similar data had not been published for β-radiation in placebo-controlled studies.

STents And Restenosis Trial (START)[13] was the first placebo-controlled randomized trial for in-stent restenosis with β-radiation using $^{90}Sr/^{90}Y$. This study is the first to report the 2-year clinical follow-up for intracoronary treatment of in-stent restenosis with β-radiation.

Methods

The study end points, methods, procedural details, angiographic, and statistical analysis as well as the angiographic and clinical results after 8 months have been previously published.[13] In brief, START was an international prospective, randomized trial performed between September 1998 and May 1999 at 50 clinical centers in the United State, Canada, and Europe. The main inclusion criterion was a single target 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 with a lesion length ≤20 mm and evidence of myocardial ischemia. A 30-mm BetaCath radioactive or nonactive source train (Novoste Corp, Norcross, Ga) was inserted

From the [a]Dr. Mueller Hospital, Munich, Germany, [b]Brigham and Women's Hospital, Boston, Mass, [c]University of Maryland, Baltimore, Md, [d]Lenox Hill Hospital, New York, NY, [e]Phoenix Heart Center, Phoenix, Ariz, [f]St. Joseph's Hospital and Medical Center, Phoenix, Ariz, [g]Scripps Clinic, La Jolla, Calif, [h]University of Florida, Jacksonville, Fla, [i]William Beaumont Hospital, Royal Oak, Mich, [j]Washington University School of Medicine, St. Louis, Mo, [k]Swedish Medical Center, Seattle, Wash, [l]Mount Sinai Hospital, New York, NY, and [m]Institut de Cardiologie de Montreal, Montreal, Quebec, Canada.
Submitted February 23, 2004; accepted May 14, 2004.
Reprint requests: Raoul Bonan, MD, Institut de Cardiologie de Montreal, 5000 Belanger St, Montreal, Quebec, Canada H1T 1C8.
E-mail: raoul.bonan@mmic.net
0002-8703/$ - see front matter

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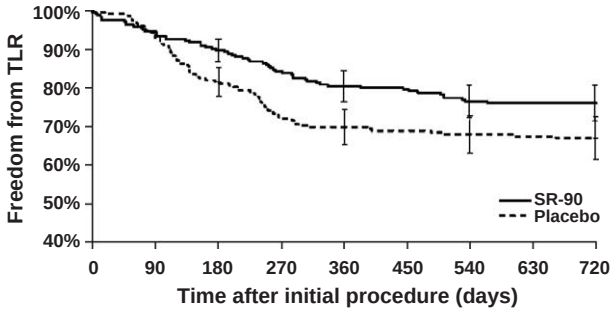
Figure 1



Freedom from TLR (at 720 days): event-free survival ± 1.5 SE; all lesions treated (n = 476).

for 3 to 5 minutes; 244 patients were randomized to active treatment, 232 patients to placebo (nonactive) treatment. In 24 patients, a BetaCath source train of 40-mm length was used. Main exclusion criteria were recent myocardial infarction (MI ≤ 72 hours), 2 overlapping stents, or prior stent placement for in-stent restenosis.

The Novoste BetaCath system has been previously described in detail.[13,14] The dose prescription was 18.4 Gy for visual reference vessel sizes >2.7 and ≤3.35 mm and 23.0 Gy for visual reference vessel sizes >3.35 and ≤4.0 mm. The use of stents after brachytherapy was discouraged and reserved for "bail-out" indications only.

With a continuous baseline treatment of aspirin, additional ticlopidine (250 mg twice daily for 14 days) was prescribed in patients enrolled between September and November of 1998. After November 1998, patients received ticlopidine (250 mg twice daily) or clopidogrel (75 mg daily) for at least 60 days after the procedure, if they had received a new stent. After April 1999, the recommended minimum duration for ticlopidine or clopidogrel ingestion was 90 days.

The primary end point of efficacy was target vessel revascularization (TVR) defined as clinically driven repeat revascularization (indication for re-PCI or coronary artery bypass surgery based on symptoms and/or laboratory testing) with an in-stent re-restenosis of ≥50% within the treated vessel at follow-up angiography. TVR not involving the target lesion was defined as TVR at a site other than the target site with or without concomitant target lesion revascularization. Secondary end points for efficacy were QCA parameters. Primary safety end point was 8-month major adverse cardiac event (MACE), including death, Q-wave or non–Q-wave MI, any bypass graft surgery (CABG), or repeat target lesion or target vessel PCI. Clinical stent thrombosis was defined as an angiographic thrombus or subacute closure within the stented vessel at a time of clinically driven angiographic restudy due to chest pain or electrocardiograph changes. Site thrombosis was defined as MI attributable to the target vessel. All MACEs were reviewed by the independent clinical events committee. The 2-year follow-up was mandated in the initial protocol with telephone contact, assessment of clinical status (including documentation of clinical events and angina status), and adverse-event monitoring. The time frame for the 2-year follow-up was defined as 720 days ± 1 month.

Table I. Baseline clinical and angiographic characteristics of 476 patients with in-stent restenosis assigned to receive $^{90}Sr/^{90}Y$

Characteristic	$^{90}Sr/^{90}Y$ (n = 244)	Placebo (n = 232)
Age (y)	61.5 ± 11.5	61.1 ± 10.4
Men	167 (68)	147 (63)
Diabetes mellitus	75 (31)	75 (32)
Current smoker	29 (13)	18 (8)
Arterial hypertension	174 (72)	170 (74)
Hyperlipidemia	184 (77)	177 (77)
Prior MI	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
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 (mm)	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 procedure	33 (14)	24 (10)

Values are mean ± SD or n (%). *LVEF*, Left ventricular ejection fraction; *ACC*, American College of Cardiology; *AHA*, American Heart Association; *MLD*, minimum lumen diameter.

Binary variables are expressed as rates, continuous variables as mean ± SD. χ^2 analysis was used for binary variables as was the Student *t* test for continuous variables. The Kaplan-Meier test was used for clinical outcome analysis; survival was compared by the log-rank test.

Results

Table I shows the baseline clinical and angiographic characteristics for the 476 patients with in-stent restenosis assigned to receive either $^{90}Sr/^{90}Y$ or placebo. Table II shows the results for the clinical follow-up at 2 years (720 days) after discharge compared with inhospital outcome. Inhospital clinical outcome was obtained for all 244 treated and 232 placebo patients. Two-year follow-up was obtained for 195 (79.9%) treated and 183 (78.9%)

Table II. MACE in and out of hospital (up to 720 days)

	^{90}Sr (n = 244 patients)		Placebo (n = 232 patients)	
	Number	**%**	**Number**	**%**
Inhospital complications				
Any MACE (death, MI, emergent CABG, TVR)	6	2.5	5	2.2
Death	0	0.0	0	0.0
MI	4	1.6	4	1.7
Q-wave MI	0	0.0	0	0.0
Non–Q-wave MI	4	1.6	4	1.7
Emergent CABG	1	0.4	0	0.0
TLR	2	0.8	1	0.4
TL-CABG	1	0.4	0	0.0
TL-PTCA	1	0.4	1	0.4
TVR not involving the TL	0	0.0	0	0.0
TV-CABG	0	0.0	0	0.0
TV-PTCA	0	0.0	0	0.0
TVR	2	0.8	1	0.4
TV-CABG	1	0.4	0	0.0
TV-PTCA	1	0.4	1	0.4
Stent thrombosis (up to 30 d)	0	0.0	0	0.0
Abrupt closure	0	0.0	1	0.4
Subacute closure	0	0.0	0	0.0
Bleeding complications	4	1.6	4	1.7
Vascular complications	3	1.2	2	0.9
CVA	0	0.0	0	0.0
Out-of-hospital complications up to 720 d				
Any MACE (death, MI, emergent CABG, TVR)	72	29.5	91	39.2
Death	7	2.9	11	4.7
MI	6	2.5	9	3.9
Q-wave MI	3	1.2	3	1.3
Non–Q-wave MI	3	1.2	6	2.6
Emergent CABG	0	0.0	0	0.0
TLR	56	23.0	75	32.3
TL-CABG	36	14.8	37	15.9
TL-PTCA	26	10.7	49	21.1
TVR not involving the TL	26	10.7	27	11.6
TV-CABG	7	2.9	5	2.2
TV-PTCA	20	8.2	23	9.9
TVR	66	27.0	84	36.2
TV-CABG	39	16.0	40	17.2
TV-PTCA	38	15.6	56	24.1
Stent thrombosis (up to 30 d)	0	0.0	1	0.4
Site thrombosis (days 31-720)	1	0.4	0	0.0
Abrupt closure	0	0.0	0	0.0
Subacute closure	0	0.0	1	0.4
Bleeding complications	0	0.0	0	0.0
Vascular complications	1	0.4	1	0.4
CVA	4	1.6	5	2.2

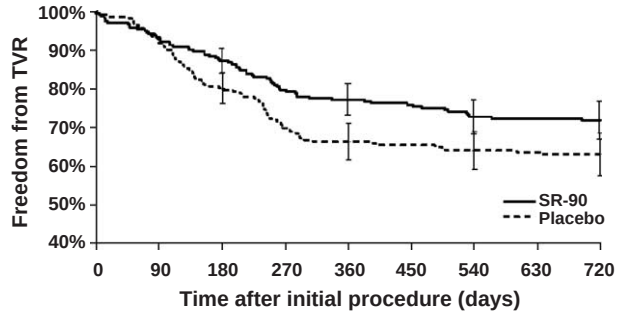
placebo patients. The combined in- and out-of-hospital complications up to 720 days are shown in Table III.

For the primary end point (TVR), a significant 25% reduction from 36.6% (placebo) to 27.5% (brachytherapy) was observed (RR .7 [.57–.98], 95% CI −9.2 [−17.5–0.8]). Target lesion revascularization (TLR) was also significantly reduced by 28% from 32.8% to 23.4% (Table III).

Table III. Combined inhospital and out-of-hospital MACE up to 720 days

Combined (inhospital and out-of-hospital) complications up to 720 d	^{90}Sr (n = 244 patients)		Placebo (n = 232 patients)	
	Number	**%**	**Number**	**%**
Any MACE (death, MI, emergent CABG, TVR)	76	31.1	93	40.1
Death	7	2.9	11	4.7
MI	10	4.1	13	5.6
Q-wave MI	3	1.2	3	1.3
Non–Q-wave MI	7	2.9	10	4.3
Emergent CABG	1	0.4	0	0.0
TLR	57	23.4	76	32.8
TL-CABG	37	15.2	37	15.9
TL-PTCA	26	10.7	50	21.6
TVR not involving the TL	26	10.7	27	11.6
TV-CABG	7	2.9	5	2.2
TV-PTCA	20	8.2	23	9.9
TVR	67	27.5	85	36.6
TV-CABG	40	16.4	40	17.2
TV-PTCA	38	15.6	57	24.6
Stent thrombosis (up to 30 d)	0	0.0	1	0.4
Site thrombosis (days 31-720)	1	0.4	0	0.0
Abrupt closure	0	0.0	1	0.4
Subacute closure	0	0.0	1	0.4
Bleeding complications	4	1.6	4	1.7
Vascular complications	4	1.6	3	1.3
CVA	4	1.6	5	2.2

Figure 2



Freedom from TVR (at 720 days): event-free survival ± 1.5 SE; all lesions treated (n = 476).

Figures 1 to 3 show the Kaplan-Meier curves for the primary efficacy (TVR) and safety (MACE) end points: the improvement begins around 90 days after treatment and remains almost constant for the following 2 years. Brachytherapy significantly improved freedom from TVR from 62.4% ± 3.8% to 71.6% ± 3.3% (P = .027) and

Table IV. Univariate and multivariate predictors of TVR up to 720 days

	Coefficient	SE	OR	P
Univariate predictors of TVR up to 720 d				
Age (per year)	−0.020	0.009	0.980	.0261*
^{90}Sr vs placebo	−0.424	0.198	0.655	.0322*
Calcification (moderate/severe vs none)	−.436	0.226	1.547	.0534
Prior MI	0.319	0.198	1.375	.1079
LAD	−0.317	0.202	0.729	.1177
Preprocedure RVD (per mm)	−0.327	0.220	0.721	.1369
History of peripheral vascular disease	−0.492	0.333	0.611	.1393
Male (vs female)	−0.266	0.205	0.766	.1939
ACC/AHA class B2 or C	0.279	0.215	1.322	.1951
	0.210	0.202	1.233	.2980
Adjunctive stent use	0.234	0.239	1.264	.3265
Lesion length (per mm)	0.007	0.014	1.007	.5954
Current smoker	0.087	0.326	1.091	.7883
Prior CABG	0.042	0.235	1.043	.8580
	0.058	0.421	1.060	.8901
Diabetes mellitus	0.005	0.212	1.005	.9830
Multivariable predictors of TVR up to 720 d				
^{90}Sr vs placebo	−0.449	0.201	0.638	.0254*
Age (per year)	−0.021	0.009	0.980	.0264*
Calcification (moderate/severe vs none)	0.506	0.230	1.658	.0279*

Predictors were chosen by stepwise logistic regression. *LAD*, Left anterior descending artery; *RVD*, reference vessel diameter.
*Significant *P* value.

Table V. Univariate and multivariate predictors of MACE up to 720 days

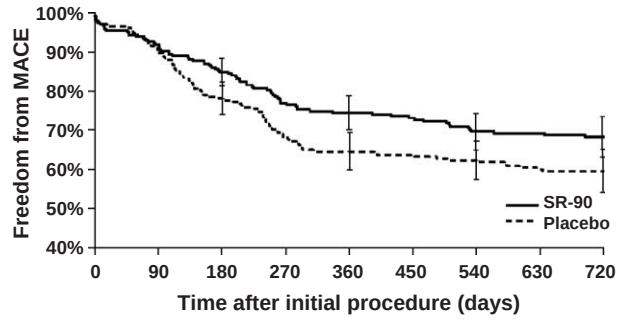
	Coefficient	SE	OR	P
Univariate predictors of MACE up to 720 d				
^{90}Sr vs placebo	−0.391	0.193	0.676	.0421*
Preprocedure RVD (per millimeter)	−0.438	0.216	0.645	.0423*
Prior MI	0.301	0.193	1.351	.1188
Calcification (moderate/severe vs none)	0.318	0.223	1.375	.1527
Male (vs female)	−0.262	0.200	0.769	.1905
CCS III and IV	0.242	0.196	1.273	.2184
Age (per year)	−0.011	0.009	0.989	.2196
LAD	−0.192	0.196	0.826	.3276
ACC/AHA class B2 or C	0.200	0.208	1.222	.3358
Current smoker	0.218	0.315	1.244	.4878
Adjunctive stent use	0.143	0.235	1.154	.5427
History of peripheral vascular disease	−0.170	0.304	0.844	.5761
Prior CABG†	0.101	0.228	1.106	.6579
Lesion length (per millimeter)	0.003	0.013	1.003	.8337
Angulation >45°	0.059	0.411	1.061	.8853
Diabetes mellitus	−0.011	0.206	0.989	.9579
Multivariable predictors of MACE up to 720 d				
^{90}Sr vs placebo	−0.411	0.194	0.663	.0347*
Preprocedure RVD (per millimeter)	−0.447	0.217	0.640	.0397*

Predictors were chosen by stepwise logistic regression.
*Significant *P* value.
†Stent use applies to patients who received stent(s) in the analyzed segment.

freedom from MACE from 58.9% ± 3.7% to 68.0% ± 3.4% (P = .035).

The ranking of predictors for TVR and MACE are delineated in Tables IV and V. For univariate analysis, patient age and radiation treatment were the only significant predictors for TVR (Table IV). Reference vessel size, lesion length, and diabetes mellitus were no longer predictors of TVR (Table IV). Multivariate analysis revealed the degree of calcification as an additional predictor for TVR (Table IV). For MACE, univariate and multivariate analysis revealed reference vessel size a stronger predictor than age but radiation treatment was the strongest predictor (Table V).

Figure 3



Freedom from MACE (at 720 days). Event-free Survival ± 1.5SE; All Patients Treated (n = 476).

Discussion

Intracoronary brachytherapy is the only nonsurgical treatment of in-stent restenosis proven superior to balloon angioplasty. In 7 randomized, placebo-controlled trials in 1530 patients with exclusively in-stent restenoses, intracoronary brachytherapy showed significant improvement in angiographic and clinical outcome (GAMMA-I,[8] SCRIPPS-II, WRIST,[15] LONG-WRIST,[16] SVG-WRIST,[17] START,[13] and INHIBIT[18]). Intracoronary brachytherapy has been shown to be effective for the treatment of in-stent restenosis with γ-radiation (5 studies, 364 patients in brachytherapy arms, 358 patients in the control groups) as well as with β-radiation (2 trials, 774 patients in brachytherapy arms, 756 patients in control arms).

START was the first randomized, controlled trial with β-radiation showing a significant reduction of clinically driven TVR after 8 months from 26.8% to 17.0%.[14] These results reflected the "real-world"

situation as confirmed by the European RENO registry in 1098 consecutive patients with a clinically driven TVR of 15.6%.[19]

Our results show for the first time that the initially beneficial outcome effects of intracoronary brachytherapy with β-radiation using $^{90}Sr/^{90}Y$ for in-stent restenosis are maintained during a 2-year follow-up period. Our follow-up rate at 2 years ± 1 month of approximately 80% in both the treatment and in the placebo arm is comparable to other radiation studies. At 2-year follow-up after brachytherapy, the clinical outcome remains significantly improved with a freedom from TVR of 71.6% and a freedom from MACE of 68% (Table III, Figures 1 and 2). Thus, the long-term beneficial effects of β-radiation with its 2-year MACE of 31.3% are comparable to those shown for γ-rays with 38.5% (SCRIPPS-1), 48.0% (WRIST-1[12]), and 41.0% (GAMMA-1,[11] Figure 3). The improvement of clinical outcome starts about 90 days after radiation (Figures 1 and 2). This is comparable to other β-emitters and to γ-radiation.[12,18]

Previously, many concerns have been raised regarding the possibility of late radiation-associated adverse events: the risk of delayed and accelerated vascular disease, aneurysm formation, late thrombosis, and late lumen loss. This study has shown that these did not manifest clinically during the follow-up period of 2 years. Only a single radiated patient developed a stent thrombosis between 1 month and 2 years (Table II). This rate of late stent thrombosis of 0.4% is well in the range of late stent thromboses of 0.7% in patients treated without brachytherapy.[20,21]

Our finding that the majority of radiated vessels remain stable for a 2-year follow-up confirmed the clinical follow-up of 50 nonrandomized patients radiated for in-stent restenosis with another β-isotope source[12,22] and with angiographic follow-up of 30 patients after radiation of de novo lesions.[23]

Interestingly, the vessel occlusion rate was very low and identical in both arms (0.4%). The low late stent thrombosis and the low vessel occlusion rate recognized at the 8-month angiographic follow-up may be related to the prolonged (60 days) regimen of ticlopidine/clopidogrel and the infrequent (20.4%) use of additional coronary stents to treat in-stent restenosis.[13]

In-stent restenosis is based on intimal hyperplasia within the stent and at its edges. Although balloon angioplasty is safe for the treatment of in-stent restenosis, it is associated with high recurrence rates up to over 80% (Figure 3).[24] Debulking techniques have been found superior to balloon angioplasty and in START were evenly used in both groups without demonstrable effects.[13,25] The use of a cutting balloon has not been shown to be superior to standard balloons in randomized trials (RESCUT Study).[26]

The risk factors for recurrence after treatment of in-stent restenosis are well delineated: mainly longer lesion length (>30 mm), longer stent length, smaller vessel diameter (<2.5 mm), smaller posttreatment lumen diameter, reopened chronic total occlusions, ostial/bifurcations location, and presence of diabetes mellitus.[27-29] Reducing stent length by using 2 single stents instead of one longer stent did not reduce in-stent restenosis rate.

In contrast to standard stent procedures, in this radiation study, lesion length could not be identified as a risk factor for revascularization (Tables IV and V). The nonimportance of lesion length as a risk factor for in-stent re-restenosis after radiation therapy has also been previously described for γ-radiation.[30] According to univariate and multivariate analysis, the only predictor of TVR and MACE in our trial was radiation treatment.

In conclusion, START is the first study to show that β-radiation for the treatment of in-stent restenosis can significantly reduce clinical need for reintervention (TVR) and MACE after 2 years. After treatment with intracoronary brachytherapy, lesion length and diabetes mellitus were no longer predictors of revascularization in this study.

Limitations

START did not include patients with very long lesions (>30 mm) because 60-mm source trains at the time the study was performed were not yet available, but such data have been reported in the RENO registry.[19] Data from a follow-up period longer than 2 years has not yet been collected. For γ-radiation, 5-year observational data has been published for a small series of patients.[10] Furthermore, the present data reflect the clinical outcome; conclusions for anatomic (angiographic) changes after 2 years cannot be drawn.

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Appendix

Institutions and investigators participating in the START as well as the data and safety monitoring board members have been previously published.