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CLINICAL INVESTIGATION **Benign Disease**

RENO, A EUROPEAN POSTMARKET SURVEILLANCE REGISTRY, CONFIRMS EFFECTIVENESS OF CORONARY BRACHYTHERAPY IN ROUTINE CLINICAL PRACTICE

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Purpose: To assess, by a European registry trial, the clinical event rate in patients with discrete stenotic lesions of coronary arteries (*de novo* or restenotic) in single or multiple vessels (native or bypass grafts) treated with *β*-radiation.

Methods and Materials: Between April 1999 and September 2000, 1098 consecutive patients treated in 46 centers in Europe and the Middle East with the Novoste Beta-Cath System were included in Registry Novoste (RENO).

Results: Six-month follow-up data were obtained for 1085 patients. Of 1174 target lesions, 94.1% were located in native vessels and 5.9% in a bypass graft; 17.7% were *de novo* lesions, 4.1% were restenotic, and 77.7% were in-stent restenotic lesions. Intravascular brachytherapy was technically successful in 95.9% of lesions. Multisegmental irradiation, using a manual pullback stepping maneuver to treat longer lesions, was used in 16.3% of the procedures. The in-hospital rate of major adverse cardiac events was 1.8%. At 6 months, the rate was 18.7%. Angiographic follow-up was available for 70.4% of the patients. Nonocclusive restenosis was seen in 18.8% and total occlusion in 5.7% of patients. A combined end point for late (30–180 days) definitive or suspected target vessel closure was reached in 5.4%, but with only 2% of clinical events. Multivariate analysis was performed for major adverse cardiac events and late thrombosis.

Conclusion: Data obtained from the multicenter RENO registry study, derived from a large cohort of unselected consecutive patients, suggest that the good results of recent randomized controlled clinical trials can be replicated in routine clinical practice. © 2003 Elsevier Science Inc.

RENO, Restenosis, Coronary, Radiation.

INTRODUCTION

Coronary artery disease remains the major cause of death in industrialized countries. Worldwide, >1 million procedures of percutaneous transluminal coronary angioplasty (PTCA) are performed each year. Even though PTCA is successful in 95% of cases and the complication rate is very low, restenosis remains the major limitation of percutaneous coronary interventions (PCIs).

Restenosis is the result of damage to the intima and media during PTCA, inducing a wound healing process with hyperproliferation and negative remodeling (constriction). Elastic recoil of the artery, local thrombus formation, vascular remodeling, and neointimal cellular proliferation are factors contributing to a progressive narrowing of the residual lumen (1).

Restenosis rates in short, type A and B lesions are reported to be 30–50% for conventional balloon angioplasty (2–4). Stent implantation after PTCA minimizes the elastic recoil and vascular remodeling, but does not reduce neointimal cellular proliferation; in fact, it tends to induce an increased proliferative response. Stents have been proved in clinical trials to reduce the restenosis rate to around 15–30%. For example, in the Stent Restenosis Study (STRESS) and Belgium Netherlands STENT Study (BENESTENT) trials, a 30% reduction in

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the restenosis rate was achieved after implantation of a single Palmaz-Schatz coronary stent (Cordis, Johnson and Johnson Company, Warren, NJ) for short lesions (5, 6). Nevertheless, the restenosis rate remains high after stent implantation in long lesions and small vessels.

Intravascular brachytherapy (VBT) has been proved an effective mode of preventing restenosis after PCI (7–13). The promising results of clinical trials and commercial availability of coronary radiation devices have led to the use of VBT in daily routine application. The Registry Novoste (RENO) registry allows the reporting of results of VBT using the Beta-Cath coronary system (Novoste, Norcross, GA) in routine clinical practice.

METHODS AND MATERIALS

Between April 1999 and September 2000, 1174 lesions were treated in 1098 consecutive patients in 46 centers in Europe and the Middle East with the Novoste Beta-Cath System and registered in RENO. All patients treated in routine clinical practice with this radiation device during the above-mentioned period were registered.

Patients with angina and/or objective evidence of ischemia due to an angiographically documented coronary artery lesion in a native vessel or bypass graft, who were candidates for percutaneous revascularization, were included in this registry. In patients with multivessel disease, only one lesion per vessel could be treated. The vessel diameter varied between 2.5 and 4.0 mm. All patients provided informed consent before inclusion.

The reference vessel diameter and lesion length were visually estimated. PTCA was performed according to standard clinical practice. To obtain a successful angiographic result ($<$50% residual stenosis), different approved PTCA techniques (balloon angioplasty, cutting balloon, mechanical or laser atherectomy, stent implantation) were applied.

After a successful PTCA procedure, the site of angioplasty was irradiated using source trains that consist of β-emitting $^{90}Sr/^{90}Y$ seeds with a stainless steel encapsulation. Each seed is 0.9 mm in diameter and 2.5 mm in length. The seeds are stored in the Novoste Transfer Device. This device incorporates a hydraulic, manual afterloading system, using sterile water to move the sources in a closed lumen of the radiation delivery catheter. Until January 2000, only source trains with 12 or 16 seeds were available that had active lengths of 30 or 40 mm, respectively. Investigators were instructed to pay attention to optimal positioning of the radiation source relative to the PTCA site to cover the entire interventional length, with a margin of at least 5 mm at each side. Interventional lengths $>$30 mm required multisegmental irradiation: a combination of two or three source train positions with one or two junctions. In March 2000, a 60-mm source train (24 seeds) became available, eliminating the junction of two 30-mm source trains. The delivery catheter (Beta-Cath, Novoste) is a 5F, triple-lumen, monorail, noncentered catheter. Before radiation, the Beta-Cath catheter was tested for fluid leakage and unhampered transfer of the dummy source train. The delivery catheter was advanced over the guidewire and positioned at the PTCA site. Proximal and distal radiopaque markers at the distal part of the delivery catheter delineated the position of the source train, allowing precise positioning at the PTCA site while providing sufficient margin. The radiation oncologist or technician uses the transfer device to advance the sources to the distal end of the delivery catheter and retrieve them when radiation is completed. Then, the catheter is removed, and a final angiogram is made.

The recommended radiation dose was determined by the vessel diameter and the presence of a stent. The dose has been prescribed at a distance of 2 mm from the source axis. The nominal diameter of the largest angioplasty balloon was considered to represent the reference diameter and was used for dose prescription. Without a stent, the dose prescription was as follows: 16.1 Gy for a maximal balloon diameter of $\geq$2.5 mm to $<$3.5 mm, 20.7 Gy for a balloon diameter of $\geq$3.5 to $<$4.0 mm, and 23 Gy for a balloon diameter of $\geq$4.0 mm. For in-stent restenosis or after stent implantation, the corresponding doses were 18.4, 23, and 25.3 Gy (i.e., 2.3-Gy extra to compensate for attenuation by the stent struts).

At discharge, per protocol, antiplatelet therapy was usually given for at least 3 months: aspirin with either clopidogrel 75 mg daily or ticlopidine 250 mg twice daily.

The primary end point of this registry trial was to assess the clinical success at 6 months, defined as procedural success without occurrence of major adverse cardiac events (MACE). Procedural success was achieved when at least 90% of the prescribed radiation dose had been delivered to the PTCA site and the final residual stenosis was not $>$50%. Geographic miss (14) was defined as incomplete coverage of the injured segment by the prescribed radiation dose; it was not evaluated according to a standard protocol. MACE included death, acute myocardial infarction (MI), or target vessel revascularization. Postprocedure measurements of creatine phosphokinase (CPK) and CPK-myocardial band isoenzymes were obtained 8 h after the procedure and every 6–8 h if the CPK was elevated. The highest level was recorded. Plasma CPK elevation to greater than twice the upper limit of normal and/or new Q waves on electrocardiography were scored as MI. Target vessel revascularization was defined as revascularization of a vessel that previously had undergone PCI by either coronary artery bypass grafting or repeat PTCA. Secondary end points were procedural success and clinical success at hospital discharge and at 12 months (optional). A follow-up coronary angiogram at 6 months was recommended.

The patient and lesion characteristics, indications for VBT, type of PCI and VBT performed, in-hospital events, and 6-month clinical and angiographic (if available) follow-up data were recorded. Case report forms were filled out and sent to the data coordinating center; no data monitoring was performed. An event committee evaluated and adjudicated all cases of death, MI, and MACE.

Categorical data are presented as absolute and relative frequencies. For continuous variables, the arithmetic mean $\pm$ standard deviations are given as summary measures. The anal-

Table 1. Baseline clinical characteristics

Characteristic	All patients	ISR*	De novo*	Vein grafts	Native vessels	60-mm RST*	Pullback*
Patients	1098	878	188	67	1031	49	183
Lesions	1174	929	224	74	1100	56	208
Mean age (y)	62.0 ± 10.2	62.1 ± 10.4	61.2 ± 9.7	66.8 ± 9.9	61.7 ± 10.1	59.5 ± 9.2	62.0 ± 10.9
Male gender	840 (76.5)	668 (76.1)	149 (79.3)	58 (86.6)	782 (75.8)	39 (79.6)	153 (83.6)
Diabetes	256 (23.5)	209 (24.0)	36 (19.3)	21 (31.3)	235 (23.0)	9 (18.8)	41 (22.7)
Hypertension	688 (62.7)	563 (64.1)	98 (52.1)	45 (67.2)	643 (62.4)	32 (65.3)	108 (59.0)
Hyperlipidemia	852 (77.8)	700 (79.9)	123 (65.4)	52 (78.8)	800 (77.7)	44 (89.8)	151 (82.5)
Smoking	170 (15.9)	118 (13.8)	45 (24.7)	6 (9.4)	164 (16.3)	10 (20.4)	31 (17.4)
Unstable angina	271 (26.9)	203 (24.8)	54 (32.3)	26 (41.3)	245 (25.9)	14 (30.4)	43 (26.4)
Prior MI	395 (36.2)	331 (37.9)	52 (28.0)	21 (31.8)	374 (36.5)	28 (57.1)	85 (46.7)
Multivessel disease	548 (50.0)	433 (49.4)	100 (53.2)	62 (92.5)	486 (47.2)	28 (57.1)	109 (59.9)
Estimated mean lesion length (mm)	19.0 ± 11.8	19.4 ± 12.3	17.4 ± 9.5	17.8 ± 14.8	19.0 ± 11.6	31.0 ± 14.7	31.3 ± 18.7
Estimated mean reference diameter (mm)	3.2 ± 0.5	3.2 ± 0.5	3.2 ± 0.5	3.5 ± 0.62	3.2 ± 0.5	3.2 ± 0.4	3.2 ± 0.6
Target lesion in native vessel	1104 (94.1)	876 (94.4)	210 (93.8)	4 (5.5)	1100 (100)	54 (96.4)	191 (92.3)
Target lesion in bypass graft	69 (5.9)	52 (5.6)	14 (6.3)	69 (94.5)	0 (0)	2 (3.6)	16 (7.7)
De novo lesion	208 (17.7)	12 (1.3)	208 (92)	14 (19.2)	194 (17.6)	10 (17.5)	50 (24.2)
Restenotic lesion	48 (4.1)	4 (0.4)	2 (0.9)	4 (5.5)	44 (4.0)	3 (5.3)	14 (6.8)
In-stent restenosis lesion	913 (77.7)	913 (97.6)	14 (6.2)	54 (74.0)	859 (77.9)	43 (75.4)	143 (69.1)

Abbreviations: ISR = in-stent restenosis; RST = radiation source train; pullback = multisegmental irradiation; MI = myocardial infarction. Data presented as the number of patients with the percentage in parentheses, unless otherwise noted.

* In at least 1 vessel.

ysis was performed according to the intention-to-treat principle. Multivariate analyses consisted of logistic regression analyses based on the 980 patients treated in a single vessel, with complete data for 17 baseline variables. Automatic backward selection procedures based on maximal likelihood were performed, preserving variables that significantly contributed to prediction ($p < 0.05$). Calculations were performed using Statistical Package for Social Sciences, version 10.0.7.

RESULTS

The 6-month follow-up data were obtained for 1085 patients (98.8% of all included patients). Of these, 840 (76.5%) were men, and the mean age was 62.0 ± 10.2 years; 271 (26.9%) had unstable angina and 256 (23.5%) were diabetics. The target lesions were in a native vessel in 1104 (94.1%) and in a bypass graft in 69 (5.9%); 208 (17.7%) were *de novo* lesions, 48 (4.1%) restenotic, and 913 (77.7%) in-stent restenotic lesions. The mean estimated reference diameter was 3.2 ± 0.5 mm, and the mean estimated lesion length was 19.0 ± 11.8 mm (Table 1). A new stent was implanted at the time of the VBT procedure in 345 lesions (29.6%): 73.2% of *de novo* lesions and 18.4% of in-stent restenotic lesions (Table 2).

VBT was technically successful in 1114 lesions (95.9%). Clinical sites reported geographic miss in 71 cases (6.1%). A mean radiation dose of 18.8 ± 3.2 Gy was delivered at 2 mm from the source axis using a source train of 30 mm (16.4%), 40 mm (79.1%), or 60 mm (4.3%). A multisegmental irradiation, performing a manual stepping procedure for the longer lesions, was used in 191 procedures (16.3%). The mean dwell time was 3.4 ± 0.5 min, excluding the mutisegmental irradiation. Fractionation due to ischemia was required in 41 procedures (3.5%) (Table 2).

The in-hospital MACE rate was 1.8% (20 of 1098 patients); details are listed in Table 3. At 6 months, after a mean follow-up period of 6.3 ± 2.4 months, 85% of patients experienced improvement of angina and the MACE rate was 18.7% (205 of 1098 patients; Table 4). Angiographic follow-up at 6 months was available for 764 (70.4%) of 1085 patients (Table 4). A combined end point for late (30–180 days) definite or suspected target vessel closure (defined as the sum of angiographic total occlusion at follow-up, MI, and death) was reached in 59 (5.4%) of 1085 patients, but with only 2% of clinical events (death or MI) (Table 4).

In the subgroup analysis, diabetic patients ($n = 256$) had a similar outcome compared with that of nondiabetics ($n = 833$): in-hospital MACE rate 2% vs. 1.8%, 6-month MACE rate

Table 2. Procedure-related parameters

Parameter	All patients	ISR*	De novo*	Vein grafts	Native vessels	60-mm RST*	Pullback*
Multivessel procedure	68 (6.2)	46 (5.3)	31 (16.5)	6 (9)	62 (6)	7 (14.3)	22 (12.0)
Nominal diameter of largest balloon† (mm)	3.3 ± 1.0	3.3 ± 1.1	3.2 ± 0.6	4.03 ± 3.77	3.22 ± 0.45	3.3 ± 0.4	3.5 ± 2.3
Atherectomy†	26 (2.2)	17 (1.8)	9 (4.0)	0 (0)	26 (2.4)	3 (5.4)	5 (2.4)
Cutting balloon†	177 (15.1)	171 (18.4)	8 (3.6)	11 (14.9)	166 (15.1)	15 (26.8)	21 (10.1)
New stent implanted†	345 (29.6)	170 (18.4)	164 (73.2)	24 (33.3)	321 (29.3)	20 (35.7)	90 (44.1)
Technical success of VBT†	1114 (95.9)	880 (95.7)	213 (96.4)	67 (91.8)	1047 (96.1)	54 (96.4)	199 (96.6)
Geographic miss†	71 (6.1)	55 (6.0)	16 (7.2)	4 (5.6)	67 (6.1)	2 (3.6)	11 (5.3)
Mean radiation dose at 2 mm (Gy)†	18.8 ± 3.2	19.0 ± 3.1	18.1 ± 3.4	20.1 ± 3.2	18.8 ± 3.1	20.7 ± 3.4	18.9 ± 3.0
30-mm source train†	193 (16.5)	136 (14.7)	51 (22.9)	22 (29.7)	171 (15.6)	1 (1.8)	36 (17.5)
40-mm source train†	929 (79.3)	753 (81.1)	165 (74.0)	51 (68.9)	878 (80)	7 (12.5)	159 (77.2)
60-mm source train†	50 (4.3)	39 (4.2)	7 (3.1)	1 (1.4)	49 (4.5)	48 (85.7)	11 (5.3)
Pullback maneuver†	191 (16.3)	137 (14.8)	44 (19.6)	18 (24.3)	173 (15.8)	11 (19.6)	191 (91.8)
Fractionated treatment†	41 (3.5)	33 (3.6)	8 (3.6)	4 (5.4)	37 (3.4)	0 (0)	12 (5.8)

Abbreviations: VBT = intravascular brachytherapy; other abbreviations as in Table 1.
Data presented as the number of lesions, with the percentage in parentheses, unless otherwise noted.
* In at least 1 vessel.
† Results per lesion.

20.3% vs. 18.2%, and late thrombosis rate 6.3% vs. 5.0%. The results in saphenous vein grafts were worse than in native vessels (Table 4).

The MACE rate was lower in patients treated with the 60-mm source train ($n = 49$) than in those treated with the 30- and 40-mm source trains ($n = 1049$): 12.2% vs. 19%. The MACE rate was relatively low in patients with in-stent restenosis (17.7%, $n = 878$) and when a cutting balloon was used (11.1%, $n = 171$).

In 183 patients, 191 lesions were treated with multisegmental irradiation because of lesion length, performing a manual stepping procedure. The mean estimated lesion length was 31.3 ± 18.7 mm. The mean radiation dwell time was 7.3 ± 1.3 min. The MACE rate was 27.9% vs. 16.8% in the nonmultisegmental irradiated patients.

Angiographic follow-up was performed in 177 of these patients (96.7%). The restenosis and late thrombosis rate were 37.1% and 9.8%, respectively, compared with 21.8% and 4.5% in the nonmultisegmental irradiated patients.

In patients irradiated with a geographic miss, the MACE

Table 3. In-hospital events

Event	All patients	ISR*	De novo*	Vein grafts	Native vessels	60-mm RST*	Pullback*
Any MACE	20 (1.8)	15 (1.7)	6 (3.2)	3 (4.5)	17 (1.6)	2 (4.1)	6 (3.3)
Death	3 (0.3)	3 (0.3)	1 (0.5)	2 (3)	1 (0.1)	0 (0)	2 (1.1)
MI	9 (0.8)	7 (0.8)	2 (1.1)	1 (1.5)	8 (0.8)	2 (4.1)	3 (1.6)
TVR revascularization	11 (1.0)	8 (0.9)	3 (1.6)	1 (1.5)	10 (1.0)	0 (0)	2 (1.1)
TVR by CABG	2 (0.2)	2 (0.2)	0 (0)	0 (0)	2 (0.2)	0 (0)	0 (0)
TVR by PCI	9 (0.8)	6 (0.7)	3 (1.6)	1 (1.5)	8 (0.8)	0 (0)	2 (1.1)

Abbreviations: MACE = major adverse cardiac event; TVR = target vessel revascularization; CABG = coronary artery bypass graft; PCI = percutaneous coronary intervention; other abbreviations as in Table 1.
Data presented as the number of patients, with the percentage in parentheses.
* In at least 1 vessel.

Table 4. Clinical and angiographic follow-up

	All patients	ISR*	De novo*	Vein grafts	Native vessels	60-mm RST*	Pullback*
Any MACE	205 (18.7)	155 (17.7)	47 (25.0)	18 (26.9)	187 (18.1)	6 (12.2)	51 (27.9)
Death (all causes)	21 (1.9)	18 (2.1)	4 (2.1)	8 (11.9)	13 (1.3)	1 (2.0)	7 (3.8)
MI	28 (2.6)	21 (2.4)	5 (2.7)	2 (3.0)	26 (2.5)	2 (4.1)	5 (2.7)
TVR revascularization	179 (16.3)	135 (15.4)	40 (21.3)	10 (14.9)	169 (16.4)	4 (8.2)	42 (23.0)
TVR by CABG	36 (3.3)	29 (3.3)	6 (3.2)	2 (3.0)	34 (3.3)	1 (2.0)	7 (3.8)
TVR by PCI	146 (13.3)	108 (12.3)	34 (18.1)	9 (13.4)	137 (13.3)	3 (6.1)	36 (19.7)
Angiographic follow-up	764 (70.4)	602 (70.9)	138 (79.3)	41 (67.2)	723 (72.7)	32 (66.7)	135 (76.3)
Restenosis (occlusive and non-occlusive)	185 (24.5)	141 (23.7)	39 (28.9)	13 (32.5)	172 (24.1)	5 (16.7)	49 (37.1)
Restenosis (total occlusion)	43 (5.7)	32 (5.4)	8 (5.8)	3 (7.5)	40 (5.6)	1 (3.2)	17 (12.6)
Composite end point late thrombosis	59 (5.4)	46 (5.2)	10 (5.3)	5 (7.5)	54 (5.2)	2 (4.1)	18 (9.8)
Angiographic total occlusion	42 (3.8)	32 (3.6)	8 (4.3)	3 (4.5)	39 (3.8)	1 (2.0)	17 (9.3)
MI	18 (1.6)	15 (1.7)	1 (0.5)	1 (1.5)	17 (1.6)	0 (0)	1 (0.5)
Cardiac death	4 (0.4)	3 (0.3)	1 (0.5)	1 (1.5)	3 (0.3)	1 (2.0)	1 (0.5)

Abbreviations as in Tables 1 and 3.
Data presented as the number of patients, with the percentage in parentheses.
* In at least 1 vessel.

rate at 6 months was 19.7% vs. 18.6% in the adequately irradiated patients. The restenosis rate at 6 months, including total occlusions, was 28.8% vs. 24.2% and the late thrombosis rate was 12.9% vs. 4.7%, respectively. Table 5 shows the significant risk factors for MACE derived from the multivariate analysis. The risk of MACE was lower in older patients, in native vessels compared with saphenous vein grafts, in larger vessels, and when a cutting balloon was used for PTCA. The MACE rate was higher in patients with unstable angina, in longer lesions, and after implantation of a new stent. Multisegmental irradiation and geographic miss were not significant risk factors for MACE. For late thrombosis, the significant risk factors derived from the multivariate analysis are listed in Table 6. The risk in slightly decreasing with increasing age, is much higher in patients with an initial chronic total occlusion of the target lesion and in the case of a geographical miss. There was a strong trend toward a higher risk of thrombosis for patients in whom a new stent was implanted at the time of brachytherapy. Multisegmental irradiation did not increase the risk of late thrombosis.

Table 5. Multivariate predictors of MACE during follow-up

Risk factor	*p*	Odds ratio	95% Confidence interval
Age (1-yr older)	0.03	0.98	0.981–0.998
Balloon diameter (1-mm larger)	0.01	0.61	0.41–0.90
Cutting balloon use	0.02	0.49	0.27–0.88
Native vessel (not SVG)	0.02	0.45	0.23–0.87
Lesion length (1 mm longer)	0.01	1.02	1.005–1.032
New stent implanted	0.009	1.61	1.13–2.29
Unstable angina	0.01	1.63	1.13–2.36

Abbreviations: MACE = major adverse cardiac event; SVG = saphenous vein graft.

A lack of procedural success was reported in 48 lesions (4.1%). In 28 cases (2.6%), the cause of failure was related to VBT: ischemia due to obstruction of coronary flow by the delivery catheter ($n = 3$), inadequately functioning transfer device ($n = 5$), catheter failure ($n = 14$), unable to cross the lesion ($n = 4$), arrhythmia ($n = 1$), and unknown ($n = 1$). In 20 lesions (1.8%), the PTCA result was not satisfactory, but VBT was successfully delivered.

DISCUSSION

This study is the largest registry of consecutive patients with coronary artery disease treated with VBT. All patients treated in Europe during the registry period between April 1999 and September 2000 with the Novoste Beta-Cath System were registered.

Table 6. Multivariate predictors of late thrombosis during follow-up

Risk factor	*p*	Odds ratio	95% Confidence interval
Age (1-yr older)	0.010	0.97	0.94–0.99
Initial CTO target	0.003	2.66	1.38–5.14
Geographic miss	0.010	2.80	1.23–6.35
New stent	0.051		

Abbreviation: CTO = chronic total occlusion.

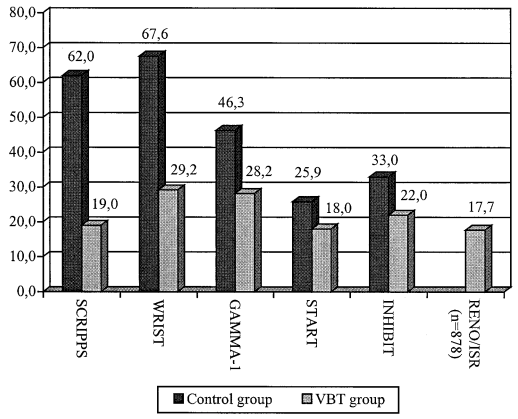

Fig. 1. Comparison of MACE rates (6–12 months) in randomized clinical VBT trials and RENO for in-stent restenosis. Inclusion and exclusion criteria were different among the various trials. MACE rate reported after a follow-up time varying from 6 to 12 months, depending on the trial.

Treatment was to be performed according to the good clinical practice of each participating center. This registry included patients with a high risk of restenosis, considering the prevalence of different risk factors, such as smoking, diabetes, hypertension, hyperlipidemia, and restenosis. Most patients (77.7%) were treated for in-stent restenosis. The 6-month clinical follow-up rate was extremely high (98.8%). The angiographic follow-up was similarly high and was obtained in 70.4% of patients, even though it was optional in this registry.

All trials, whether of β- or γ-radiation, demonstrated a benefit of radiation in patients with in-stent restenosis (9, 12, 13, 15, 16). In the SCRIPPS and GAMMA-I trials, the reduction in the restenosis rate was more important in the diabetic patients. The same trend was seen for diabetic patients in the subgroup analysis of RENO, with rates of 1.9% death, 2.6% acute MI, and 16.6% target vessel revascularization at 6 months. The 18.7% MACE rate at 6 months (17.7% for in-stent restenosis) compares favorably with the results of major randomized clinical trials for in-stent restenosis using either γ- or β-radiation (Fig. 1).

As expected, the MACE rate and restenosis rate were higher in vein grafts than in native vessels. In a recent randomized trial (17), the benefit of γ-radiation for in-stent restenosis in bypass grafts was demonstrated. Compared with the restenosis rate of 21% in the irradiated group after 6 months, the 32.5% rate obtained in RENO is rather disappointing.

The positive trends in the subgroup analysis also suggested a clinical benefit when longer source trains are used or when using a cutting balloon. These are available in a length of 10 or 15 mm, and it is assumed that their injury length is shorter than with a conventional angioplasty balloon of the same length, because they are anchored by the blades and do not slide during inflation, decreasing the risk of a geographic miss.

The geographic miss was site reported without using a standard protocol and therefore probably was underestimated. This may explain why no influence of geographic miss on the MACE rate could be demonstrated. The results could probably be improved further by irradiating with wider margins. In the current registry, a proximal and distal margin of 5 mm beyond the injured area was recommended. Taking into account that the PTCA injury exceeds the physical balloon length, the 50% dose falloff over the last seed (2.5 mm) of the source train, and the position uncertainty of the source (lack of landmarks and heart movement) (18), a 7.5–10-mm margin would be required to deliver the prescribed dose adequately to the whole injured length (19). In the Stents and Radiation Therapy 40 trial, the use of longer source trains, resulting in wider margins, reduced the incidence of edge restenosis and geographic miss compared with the initial Stents and Radiation Therapy trial. As determined by quantitative angiography, 46% had evidence of geographic miss. The restenosis rate among those patients was 32% compared with 18% for those whose injury length fell within the 90% isodose distribution ($p = 0.04$) (20).

According to the 6-month results, the multisegmental irradiation technique, although technically not satisfactory (21), can be performed safely with the Novoste Beta-Cath System. The follow-up events were acceptable, considering the lesion length and the high incidence of in-stent restenosis in the baseline population.

From this registry, no conclusions can be drawn concerning the radiation dose. The only dose-finding trial ever performed in coronary VBT was based on a ^{90}Y source wire and a centering delivery catheter, with a different dose prescription point. That trial showed a clear dose–response relationship (22). The dose prescription in this registry and in other trials using the Novoste Beta-Cath System was relatively low compared with trials using other radiation devices; however, because they demonstrated similar clinical results, the therapeutic window may be wide and there may be some gain in delivering a higher dose. The exact attenuation by stent struts is unknown; sparse data in literature vary between 10% and 15% (23–26). To simplify the dose calculation, a fixed dose of 2.3 Gy was recommended in the protocol, which means a 10–14% increase of the dose to compensate for the stent. This seems acceptable, taking into account the results of the published dosimetry studies. The question of adapting the dose prescription to the degree of calcification of the vessel wall has never been addressed in a clinical trial.

VBT was technically successful in 95.9% of lesions, and the in-hospital MACE rate was only 1.8%. Because of the low radiation hazard using β-radiation emitting isotopes, the personnel can remain in the cath-laboratory during the radiation procedure. It seems fair to conclude that coronary brachytherapy with β-radiation using a ^{90}Sr/^{90}Y source train is feasible and safe.

This registry recommended antiplatelet therapy for at least 3 months (aspirin with either clopidogrel 75 mg daily or ticlopidine 250 mg twice daily). Because late thrombosis was defined as a composite end point of angiographic total occlusion, any acute MI, or death, 5.4% was probably an overestimation; the clinically related events were low (0.4% death and 1.6% MI). Implantation of a new stent is not a significant risk factor for late thrombosis, although multi-

variate analysis showed a strong trend. A higher rate of late thrombosis after brachytherapy has also been reported in other trials (27), especially when a new stent was implanted at the time of brachytherapy. Antiplatelet therapy is now generally prescribed for at least 6 months, and more often 12 months.

This registry has certain limitations. No core laboratory was involved to analyze the fluoroscopic images of treatment procedure and follow-up. No accurate measurements were performed to assess any geographic miss. Additional treatment after irradiation was not registered. The late thrombosis rate could have been overestimated, because it was defined as a composite end point of angiographic total occlusion, any acute MI, or death.

The data derived from this largest cohort of unselected consecutive patients treated with VBT in the coronary arteries suggest that the excellent results of recent randomized, controlled, clinical trials, including patients with in-stent restenosis, can be replicated in "routine clinical practice." The results can probably be improved by using wider margins. The optimal radiation dose is still unknown but should be the subject of additional investigation.

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Appendix 1. Organization of the registry

Steering Committee:	P. Urban (principal investigator) A. Gerschlick R. Bonan D. Baumgart A. Zeiher R. Schilcher L. Verhees
Data Coordination Center:	Wegscheider, Biometrie und Statistik GmbH, Berlin, Germany
Sponsor:	Novoste Europe SA/NV

Appendix 2. List of participating centers

Participating centers	Interventional Cardiologist	Radiation Oncologist
Lausanne, C.H.U.V.	Eeckhout	Coucke
Antwerp, UZA	Vrints	De Bal
Aalst, OLV	Wijns	Verbeke
Brussels, St Jean	Vandormael	Burette
Brussels, St Luc	Debbas	Scalliet
Dresden, Weisser Hirsch	Dörr	Herrmann
Eindhoven, Catharina	Bonnier	Schmeets
Hasselt, Virga Jesse	Benit	Brosens
Milan, Columbus	Colombo	Orecchia
München, Professor Silber	Silber	von Rottkay
Rotterdam, Thoraxcenter	Serruys	Levendag/Coen
Antalya, Akdeniz UH	Sancaktar	Garipagaoglu
Haifa, Rambam	Beyar	Rosenblatt
Tel Aviv, Ichilov	Miller	Ron
Mont Godinne UCL	Gurné	Vandeput
Erlangen, Universitätsklinikum	Ludwig	Strnad
Chemnitz, Herzzentrum	Kleinertz	Schubert
Hamburg, UKE	Brockhoff	Krüll
München, Klinikum Innenstadt	Klaus	Pöllinger
Dortmund, St. Johannes	Heuer	Donsbach
Glenfield General Hospital	Gershlick	Benghiat
Berlin, Charité Mitte	Rutsch	Buchali/Matnjani
Jerusalem, Shaari Zedek	Meerkin	Hayne
Essen, Universitätsklinikum	Baumgart	Sauerwein
Århus, Skejby	Thuesen	Overgaard
Kayseri, Erciyes	Basar	Karahacyoglu
Lübeck, Universitätsklinikum	Katus	Feyerabend
Bad Oeynhausen, Herzzentrum	Wiemer	Lindner
Hamburg, St Georg	Küchler	Ehnert
Kaiserslautern, Westpfalz-Klinikum	Glunz	Herbig
Aachen, Universitätsklinikum	vom Dahl	Schubert
Berlin, Benjamin Franklin	Schultheiss	Hinkelbein
Bochum, St. Joseph	Mügge	Kißler
Athens, Onassis	Voudris	Efstathopoulos
Varese, Circulo	Verna	Novario/Bianchi
Frankfurt, UNI	Auch-Schwelk	Schopohl
Nijmegen Acad. Ziekenhuis	Aengevaeren	Pop
Bochum, Augusta Krankenhaus	Altmaier	Dürscheidt
Vienna, AKH	Glogar	Pötter/Pokrajac
Milano, Humanitas	Presbitero	Orecchia
Potsdam, Ernst von Bergmann	Ohlmeier	Koch
Ioaninna University	Michalis	Tsekeris
Barcelona Clinico	Serra	Penaranda
London, King's College	Thomas	Calman
Hamburg, Mathey-Schofer	Schofer	Thelen
Saarbrücken, Klinikum	Görge	Treitz