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Intracoronary Brachytherapy, a Promising Treatment Option for Diabetic Patients: Results From a European Multicenter Registry (RENO)

Christoph K. Naber,[1]* MD, Dietrich Baumgart,[1] MD, Raoul Bonan,[2] MD, Karl Wegscheider,[3] PhD, Patrick W. Serruys,[4] MD, PhD, Antonio Colombo,[5] MD, Sigmund Silber,[6] MD, Eric Eeckhout,[7] MD, Holger Eggebrecht,[1] MD, Raumund Erbel,[1] MD, and Philip Urban,[8] MD

Despite advances in the interventional treatment of coronary disease, diabetics still have double the case fatality rate as nondiabetics. The purpose of this analysis from the Radiation in Europe With Novoste (RENO) registry was to assess the clinical and angiographic 6-month outcome of diabetic patients in comparison to nondiabetic patients after localized β-radiation. A total of 1,098 patients (83.8% with in-stent restenosis) treated with the Novoste Beta-Cath system in Europe were enrolled in the RENO registry. Diabetes was, irrespective of the type of lesion treated, no significant risk factor for major adverse cardiac events or target vessel revascularization. Individuals with diabetes (n = 256) and without diabetes (n = 833) displayed no significant differences concerning clinical or angiographic endpoints. Vascular brachytherapy appears to be the first technique to even out the increased risk of diabetic patients undergoing percutaneous coronary interventions in the routine clinical setting. Thus, intracoronary brachytherapy represents a promising treatment option for diabetic patients. *Catheter Cardiovasc Interv 2004;61:173–178.* © 2004 Wiley-Liss, Inc.

Key words: in-stent restenosis; diabetics; brachytherapy; percutaneous transluminal coronary angioplasty

INTRODUCTION

Cardiovascular disease is the major cause of morbidity and mortality in patients with diabetes. Diabetic individuals have a two- to fourfold risk for vascular disease than nondiabetics. Diabetes mellitus has a negative impact on mortality and morbidity following catheter-based coronary procedures as well as coronary artery bypass surgery [1,2]. Recent advances in the treatment of coronary disease have improved survival for diabetics and nondiabetics, but diabetics still have double the case fatality rate as nondiabetics [3]. Determinants such as high atherosclerosis burden, complex lesion morphology, small target vessel size, and a higher rate of multivessel disease may predispose to the observed excess restenosis rates, which remain the major limitation of catheter-based coronary interventions among patients with diabetes mellitus, irrespective of whether the treatment is performed in native vessels [4–8], saphenous vein grafts [9], or in-stent restenosis [10–12]. Particular for the treatment of in-stent restenosis, intracoronary brachytherapy is currently the only effective tool to reduce the excess restenosis rates of 19–83% [13] significantly by 40–60% [14–18]. Interestingly, recent subanalyses from clinical brachytherapy trials demonstrated for the first time that diabetics appear to profit at least to the same extent from percutaneous interventions as compared to nondiabetic patients [19]. This finding was independent of the type of

[1]West German Heart Center, University Hospital Essen, Essen, Germany
[2]Institut de Cardiologie de Montreal, Montreal, Canada
[3]Institute for Statistics and Econometry, University of Hamburg, Hamburg, Germany
[4]Department of Cardiology, Thoraxcenter, Rotterdam, The Netherlands
[5]Department of Interventional Cardiology, Centro Cuore Columbus Hospital, Milan, Italy
[6]Cardiology Practice in the Dr. Muller Hospital, Munich, Germany
[7]Cardiology Clinic, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland
[8]Service de Cardiologie, Hopital de la Tour, Meyrin, Geneva, Switzerland

*Correspondence to: Dr. Christoph K. Naber, Department of Cardiology, University Clinic Essen, Hufelandstr. 55, 45122 Essen, Germany. E-mail: christoph.naber@uni-essen.de

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radiation and could be observed after β- as well as after γ-radiation [20,21]. It is thus tempting to speculate on whether such a favorable outcome of diabetic patients following catheter-based coronary procedures can be observed also in the clinical routine setting, besides the potential selection bias of controlled clinical trial populations. The purpose of this analysis was to assess the clinical and angiographic outcome 6 months after localized β-radiation (^{90}strontium/yttrium) in diabetic patients with predominantly long diffuse in-stent restenosis from the Radiation in Europe With Novoste (RENO) registry. RENO enrolled the first 1,100 patients treated with the Novoste Beta-Cath system in Europe and therefore perfectly mirrored the clinical routine situation during the enrollment period from June 1999 to September 2000. As the reduction of restenosis rate and target vessel revascularization (TVR) was well comparable to those of randomized brachytherapy trials, the RENO registry has proven that these results can be successfully achieved also in the routine clinical setting [22].

MATERIALS AND METHODS

The RENO registry was a postmarket prospective surveillance study enrolling 1,098 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 rotational atherectomy (PTRA), excimer laser coronary angioplasty (ELCA), directional coronary atherectomy (DCA), and stenting) followed by ^{90}strontium radiation treatment (Novoste Beta-Cath system). Patient enrollment occurred from 1 June 1999 to 27 September 2000.

Detailed proceedings have been published elsewhere [22]. In brief, baseline and clinical data were collected on standardized case report forms at the clinical sites. Clinical follow-up was mandated at 1 and 6 months. Angiographic follow-up at 6 months was not mandated, however, but is available on 72.4% of the patients.

The primary endpoint of the study was procedural success without occurrence of major adverse cardiac events (including death, myocardial infarction, revascularization of the target vessel) after 6 months. After successful completion of the interventional procedure, the angioplasty catheter was withdrawn. Next, the Beta-Rail delivery catheter was positioned and radiation therapy was performed as described [22] with a recommended dose prescription of 18.4 to 23 Gy at 2 mm from the radiation source depending on the vessel diameter.

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. From the steering committee, a 6-month combination treatment was recommended. Based on the results, 70% of patients received the combination treatment for longer than 6 months. The remaining patients received a combination treatment for 3–6 months.

Baseline demographic and clinical variables were descriptively summarized. Diabetic and nondiabetic patients were assessed for comparability at baseline and follow-up using chi-square tests or Fisher's exact test for nominal variables and exact Mann-Whitney U-tests for continuous variables. Odds ratios and 95% confidence intervals for diabetes vs. nondiabetes were calculated for the outcome variables 6-month MACE and TVR or 6-month binary restenosis using logistic regression models, either adjusted or unadjusted for 17 baseline variables (age, gender, unstable angina, bypass graft, in-stent restenosis, chronic total occlusion, new stent placement, cutting balloon used, final residual stenosis, reference diameter, lesion length, maximum balloon size, applied dose, total radiated length, ratio of lesion length to radiated length, pullback procedure used, and geographic miss). All statistical analyses were performed using SPSS 10.0.7 by SPSS. A P value of ≤ 0.05 is regarded as statistically significant.

RESULTS

Baseline demographic data are presented in Table I. There were more female patients and less current smokers in the diabetic group. Diabetics were slightly older, and there were more diabetic patients with multivessel disease.

Angiographic and interventional parameters are displayed in Table II. Lesion characteristics and procedural data were not significantly different between the groups. The pattern of in-stent restenosis categorized as focal, at the stent ends, or diffuse was similar between diabetic (18.3% vs. 3.3% vs. 78.4%) and nondiabetic patients (16.5% vs. 5.3% vs. 78.2%, respectively; $P = 0.4$). The applied dose was slightly lower in the diabetic patients, and a regression model with mean radiation dose as response variable and diabetes and vessel diameter as regressors reveals that this difference persists after adjustment for vessel diameter. The odds ratio for MACE was 0.94/Gy in diabetic and nondiabetic patients.

There were no differences between the groups regarding technical success rates and in-hospital events. The 6-month clinical and angiographic follow-up including the in-hospital events are displayed in Table III. With respect to the clinical and angiographic outcome after 6 months, no significant differences could be observed between the groups (Table III and Fig. 1). Odds ratios of

TABLE I. Demographic and Clinical Data

	All		In-stent restenosis		De novo lesions	
Parameter	Diabetes	No diabetes	Diabetes	No diabetes	Diabetes	No diabetes
n	256	833	209	657	35	143
Sex (male)	69.1[a]	78.8	70.3[a]	77.8	68.6	80.4
Age (years)	63.8 ± 9.8[a]	61.5 ± 10.2	64.1 ± 10.0	61.6 ± 10.5	60.9 ± 9.1	61.2 ± 9.5
Prior MI	35.2	36.3	36.7	38.2	26.5	27.5
Multivessel disease	62.1[a]	46.3	61.7[a]	45.1	62.9	50.3
>one vessel treated	4.3	6.6	3.8	5.2	8.6	11.9
Unstable angina	30.5	25.7	28.7	23.5	32.4	32.5
Hyperlipidemia	81.5	76.6	81.6	79.3	80.0	62.9
Current smoking	12.2[a]	17.0	11.0	14.7	23.5	26.1

[a]$P \leq 0.05$ vs. no diabetes.

TABLE II. Angiographic Data

	All		In-stent restenosis		De novo lesions	
Parameter	Diabetes	No diabetes	Diabetes	No diabetes	Diabetes	No diabetes
Treated vessels	267	897	217	694	38	168
Lesion length (mm)	18.7 ± 11.4	19.1 ± 11.9	18.9 ± 11.7	19.7 ± 12.6	18.0 ± 11.0	17.4 ± 9.3
Reference diameter (mm)	3.2 ± 0.5	3.2 ± 0.5	3.2 ± 0.4	3.2 ± 0.5	3.1 ± 0.5	3.2 ± 0.5
In-stent restenosis	80.8	76.7	100.0	100.0	0.0	0.0
Bypass	7.9	5.4	7.8	5.1	5.3	6.0
Cutting balloon	17.6	14.0	20.7	17.3	0.0	1.2
New stent	26.2	30.6	15.2	19.3	81.6	75.6
Technical success	96.9	95.5	96.7	95.2	97.3	96.4
Geographic miss	6.1	6.2	5.1	6.4	13.2	6.0
Mean dose (Gy)	18.4 ± 3.1[a]	19.0 ± 3.2	18.6 ± 3.2[a]	19.2 ± 3.1	17.4 ± 2.9[a]	18.4 ± 3.3

[a]$P \leq 0.05$ vs. no diabetes.

TABLE III. Six-Month Clinical and Angiographic Follow-Up Including In-Hospital Events

	All		In-stent restenosis		De novo lesions	
Parameter	Diabetes	No diabetes	Diabetes	No diabetes	Diabetes	No diabetes
n	256	833	209	657	35	143
Death	7 (2.7)	14 (1.7)	6 (2.9)	11 (1.7)	0 (0.0)	3 (2.1)
Cardiac	5 (2.0)	7 (0.8)	5 (2.4)	5 (0.8)	0 (0.0)	2 (1.4)
MI	10 (3.9)	18 (2.2)	7 (3.3)	14 (2.1)	2 (5.7)	3 (2.1)
Q-wave	4 (1.6)	7 (0.8)	3 (1.4)	5 (0.8)	1 (2.9)	1 (0.7)
Death or MI	15 (5.9)	30 (3.6)	11 (5.3)	23 (3.2)	2 (5.7)	6 (4.2)
TVR	44 (17.2)	136 (16.1)	31 (14.8)	102 (15.5)	10 (28.6)	28 (19.6)
MACEs	52 (20.3)	152 (18.2)	37 (17.7)	115 (17.5)	11 (31.4)	33 (23.1)

6-month MACE for diabetes were 1.14 (95% CI = 0.8–1.62) unadjusted and 1.30 (95% CI = 0.87–1.93) after adjustment for the baseline variables. For TVR or restenosis, odds ratios were 0.93 (95% CI = 0.65–1.34) unadjusted and 0.99 (95% CI = 0.68–1.45) after adjustment. There were no significant interactions between diabetes and any of the baseline variables included.

After stratification for the type of the treated lesion, there were also no significant differences between the groups (Table I and Fig. 2), although diabetic patients with de novo stenosis appeared to have somewhat higher rates of binary restenosis, TVR, and target vessel thrombosis. The odds ratios related to diabetes, stratified for the type of lesion treated, are displayed in Figure 3.

DISCUSSION

It is not yet clear why diabetic patients have such an unfavorable outcome following catheter-based coronary procedures. Van Belle et al. [23] concluded from their data that restenosis, especially in its occlusive form, is a major determinant of long-term mortality in diabetic patients after coronary balloon angioplasty due to a significant decrease in ejection fraction [24]. Serial IVUS analysis showed that the main reason for increased restenosis in diabetes mellitus was exaggerated intimal hyperplasia in both stented and nonstented lesions [25]. Histopathological analyses from coronary specimens from patients with diabetes mellitus yielded a reduced

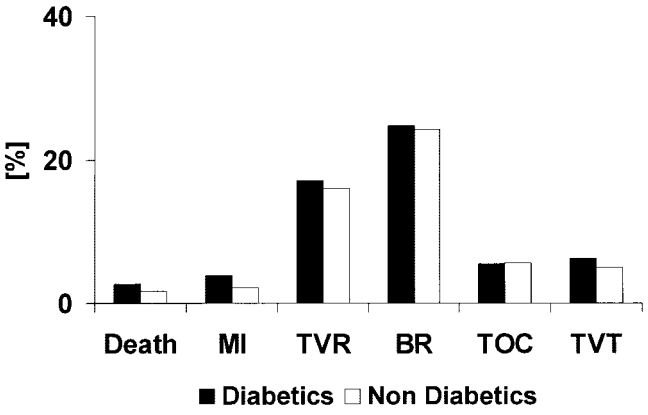

Fig. 1. Clinical and angiographic 6-month follow-up, all patients. BR, binary restenosis (> 50% diameter restenosis); TOC, total occlusion of target vessel in angiography; TVT, surrogate composite endpoint of target vessel thrombosis (target vessel-related cardiac death, MI after 30 days, total target vessel occlusion on angiography).

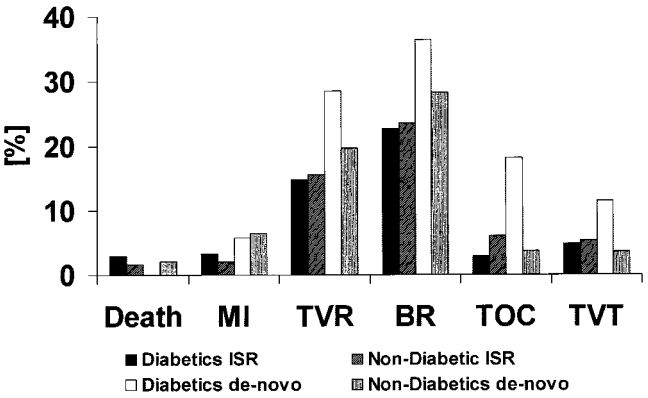

Fig. 2. Clinical and angiographic 6-month follow-up, stratified for initial lesion type. ISR, in-stent-restenosis.

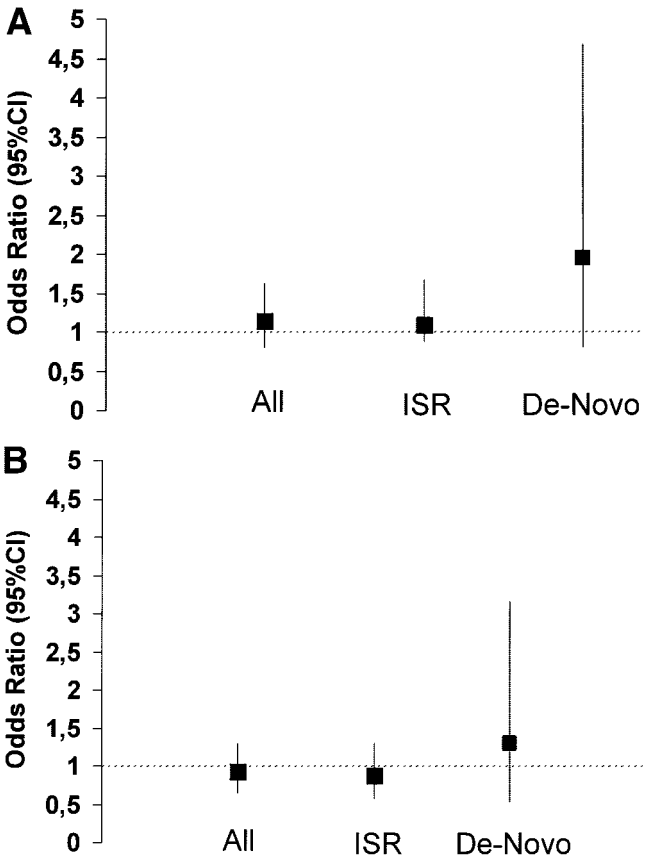

Fig. 3. Odds ratios for diabetes for (A) MACE and (B) TVR/restenosis.

intimal hypercellular tissue content in restenotic tissue from these patients, while collagen-rich sclerotic content was increased [26]. The authors concluded that these results suggest an accelerated fibrotic rather than a proliferative response in diabetic lesions from patients with restenosis after PTCA. On the other hand, Faries et al. [27] demonstrated that diabetic vascular smooth muscle cells (VSMCs) exhibit significantly increased rates of proliferation, adhesion, and migration as well as abnormal cell culture morphology suggestive of abnormal contact inhibition.

For the long term, diabetic patients have remained one of the most challenging tasks in interventional cardiology. The case fatality and restenosis rates were far worse in diabetic than in nondiabetic patients, irrespective of the treatment modality or the nature of the treated lesion [4–13].

Recent results from controlled intracoronary brachytherapy trials indicated for the first time that diabetic patients may profit significantly from a catheter-based interventional technique with long-term result comparable to nondiabetic patients. In the Scripps Coronary Radiation to Inhibit Proliferation Poststenting (SCRIPPS) trial, Teirstein et al. [19] showed that in the treatment group, late loss was particularly low in patients with diabetes, a vessel diameter < 3.0 mm, and in-stent restenosis. The authors concluded that in this study, patient characteristics associated with a more aggressive proliferative response to injury appeared to confer an enhanced response to radiotherapy. Similar results were published also for β-radiation [20,28], and even more surprising were the results from the GAMMA-I trial, which yielded after brachytherapy treatment a reduction in binary restenosis of 16% in the nondiabetic patients and of even 40% in the diabetic patients [21].

These findings are clearly supported by the data from the RENO registry reported here, which represents the largest single series of diabetic patients treated with brachytherapy to date. Common risk factors for resteno-

sis such as lesion length, reference vessel diameter, and type of target lesion were comparable between the groups. Although the diabetic group consisted of significantly more patients with multivessel disease, there were no statistically significant differences regarding the clinical and angiographic outcome between the groups after 6 months. Diabetes was no significant risk factor for MACE and TVR or angiographic restenosis in a multivariate analysis.

Subanalyses of the patients with in-stent restenosis and those with de novo lesions also yielded no significant differences between the groups, although diabetic patients with de novo stenosis appeared to have somewhat higher rates of binary restenosis, TVR, total occlusions, and target vessel thrombosis. On the other hand, these patients received also the lowest mean radiation dose, had the highest rate of geographic miss (inadequate radiation of the interventional injury length), and the highest number of new implanted stents. These facts, and the small number of patients in the RENO de novo group, indicate that the results of this subanalysis should be interpreted with caution.

In conclusion, the above findings indicate, with respect to the expected high case fatality in diabetic patients, that intracoronary brachytherapy represents a promising treatment option for diabetic patients. Vascular brachytherapy appears to be the first percutaneous interventional technique from which diabetic patients profit to at least the same extent that nondiabetic individuals do.

It appears reasonable to assume that the exaggerated intimal hyperplasia is counteracted by the antiproliferatory properties of intracoronary irradiation. Thus, it may be suggested that other antiproliferative therapies can be equally effective to even out the increased risk of diabetic patients undergoing percutaneous coronary interventions.

Study Limitations

The data entered into this analysis were taken from a large prospective multicenter registry. This registry was not designed to aim at differences between diabetics and nondiabetics undergoing intracoronary radiation. Thus, although our findings confirm findings from prospective studies in clinical practice, the power of the study, especially regarding the subgroup analysis, is not sufficient to show equivalence between the groups.

Another limitation is that due to the design of the RENO registry, there is no information on the type of diabetes or the antidiabetic treatment of the included patients available. Also, no information is available on the number or kind of previous treatments at the target lesion.

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