Clinical Outcome Following Combination of Cutting Balloon Angioplasty and Coronary ß-Radiation for In-Stent Restenosis: A Report From the RENO Registry

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ABSTRACT: At present, vascular brachytherapy is the only efficient therapy for in-stent restenosis. Nevertheless, edge restenosis often related to geographical miss has been identified as a major limitation of the technique. The non-slippery cutting balloon has the potential to limit vascular barotraumas, which, together with low-dose irradiation at both ends of the radioactive source, are the prerequisite for geographical miss. This prospective study aimed to examine the efficacy of combining cutting balloon angioplasty and brachytherapy for in-stent restenosis. The Radiation in Europe NOvoste (RENO) registry prospectively tracked all patients who had been treated by coronary ß-radiation with the Beta-Cath™ System (Novoste Corporation, Brussels, Belgium) but were not included in a randomized radiation trial. A subgroup of patients with in-stent restenosis treated by cutting balloon angioplasty and coronary ß-radiation (group 1, n = 166) was prospectively defined, and clinical outcomes of patients at 6 months were compared with those of patients treated by conventional angioplasty and coronary ß-radiation (group 2, n = 712). At 6-month follow-up, there was a significant difference between groups 1 and 2 in target vessel revascularization (10.2% versus 16.6% respectively; $p = 0.04$) and in the incidence of major adverse clinical events (MACE) including death, myocardial infarction, and revascularization (10.8% versus 19.2%; $p = 0.01$). This observation was confirmed by a multivariate analysis indicating a lower risk for MACE at 6 months (odds ratio: 0.49; confidence intervals: 0.27–0.88; $p = 0.02$). Compared to conventional angioplasty, cutting balloon angioplasty prior to coronary beta-radiation with the Beta-Cath™ System seems to improve the 6-month clinical outcome in patients with in-stent restenosis. J INVAS CARDIOL 2003;15:5xx–5xx

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In recent years, intracoronary stents have become the primary treatment option in percutaneous coronary intervention.[1–3] The procedure is relatively simple with reliably higher clinical and angiographic success rates and lower restenosis rates than with any other coronary intervention.[1,2] Nevertheless, about 15–25% of patients who have received intracoronary stents experience clinical in-stent restenosis within 6 months.[4] Until a few years ago, this clinical condition was extremely difficult to treat by percutaneous intervention. Diffuse in-stent restenosis (defined as a lesion length within the stent of ≥ 10 mm) and even more occlusive restenosis had recurrence rates exceeding 50% in patients treated by conventional angioplasty.[5] Surgical revascularization, therefore, often was the only appropriate solution.

In 1997, Teirstein et al. published the first randomized trial that demonstrated the efficacy of coronary radiation, using a γ-irradiation source for the treatment of in-stent restenosis.[6] Meanwhile, a total of 1,455 patients have been treated in 7 published randomized trials using either ß or γ-radiation, establishing this technique as currently the only efficient treatment of in-stent restenosis.[7] Pioneers in the field of vascular brachytherapy, however, rapidly identified new stenotic lesions at one or both edges of the irradiated segment in patients with recurrent clinical symptoms.[8] This so-called "edge effect" (or edge restenosis) could be identified in a substantial number of patients as a consequence of "geographical miss," which is defined as low-dose radiation (at the borders of the radiation source), and vascular barotrauma by the balloon angioplasty catheter beyond the radiated segment of the artery.[9]

Currently available balloon catheters provide excellent trackability, due to a low profile and a slippery coating. Although not reported in clinical literature, catheter slippage at the site of an in-stent restenotic lesion is a common occurrence in clinical practice. The slippage is probably related to the distinct pathology of in-stent restenosis compared to *de novo* lesions. The cutting balloon was introduced initially as a primary restenosis prevention tool, but it has failed to demonstrate efficacy in this setting.[10] Because of the non-slippery design of this catheter and its potential to limit the geographical miss phenomenon, we prospectively investigated the efficacy of combining cutting balloon angioplasty and vascular brachytherapy for in-stent restenosis.

Methods

Patients. We prospectively performed a subgroup analysis of patients in the Radiation in Europe NOvoste (RENO) registry whose in-stent restenosis was treated by a combination of cutting balloon angioplasty and vascular brachytherapy using the Beta-Cath™ System (Novoste Corporation, Brussels, Belgium). The RENO multicenter registry tracked all patients treated by ß-radiation with the Beta-Cath™ System who were not included in a randomized radiation trial between April 1999 and September 2000 at a total of 46 European sites.[11] There was no randomized treatment allocation to either the use of cutting balloon or

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standard angioplasty. Either treatment was chosen by the cardiologist and was not site-specific. All patients with in-stent restenosis treated by cutting balloon or standard angioplasty were examined, and clinical follow-up was obtained at 6 months. Although not mandatory, a 6-month follow-up angiography was suggested. The study protocol had been approved by the local institutional regulatory board at all participating sites.

Intervention. Patients who presented with clinical in-stent restenosis and who were scheduled for vascular brachytherapy with the Beta-Cath™ System were treated with cutting balloon or standard angioplasty, as decided by the operator. Percutaneous intervention was performed in accordance with standard techniques, including adequate antiplatelet premedication and anticoagulation therapy during the intervention. Stenting was performed only in the case of either a flow-limiting dissection or an unacceptable elastic recoil. Thereafter, intracoronary brachytherapy was performed.

Vascular brachytherapy was performed using the Beta-Cath™ System. Briefly, the system consists of a shielding transfer device, which contains a train of unconnected radioactive seeds (strontium/iridium 90) to be connected to a 5 French (Fr) delivery catheter. This delivery catheter is a multi-lumen, non-centered, rapid-exchange device that accepts the radioactive seeds by hydraulic injection of water from the transfer device. The same hydraulic force (a syringe is locked onto the transfer device and operated by the physician) is required to return the seeds into the transfer device. Gold markers at both ends of the radioactive source train delimit the source train, which is available in lengths of 30, 40, and 60 mm. Operators were trained to avoid potential geographical miss by using an adequate source length or by applying a pull-back procedure (source withdrawal after a first application and proximal repositioning of the delivery catheter with a short overlap zone to deliver a second dose). The dwell time (and therefore radiation dose) was calculated according to the qualitative and/or quantitative estimation of the vessel's reference diameter. The prescribed dose was standardized, based on the manufacturer's recommendation, expressed in Grays delivered at a distance of 2 mm from the source center.

Operators were requested to angiographically document all steps of the procedure, taking angiograms adequate for performing a quantitative angiographic analysis. This analysis was performed on site during the intervention and off-line. Particular attention was given by an independent analyzer to the off-line measurements to judge the occurrence of a geographical miss.

Following an intervention, patients were treated with aspirin (≥ 100 mg daily) and prolonged combined antiplatelet therapy (ticlopidine 500 mg daily or clopidogrel 75 mg daily). Most patients treated by brachytherapy without a new stent implantation received combined antiplatelet therapy for 3-12 months, while the majority of patients treated by brachytherapy with stent implantation had this treatment prescribed for 6–12 months.

Study endpoint. The primary study endpoint was the incidence of serious adverse cardiac events at 6-month follow-up. These events were death from any cause, myocardial infarction, target vessel revascularization (MACE). Myocardial infarction was defined according to the World Health Organization guidelines.[12] This implied the appearance of new Q waves on the ECG and/or a CK rise above twice the upper limit of normal.

Table 1. Baseline clinical and angiographic characteristics

Variable	CB + VBT	BA + VBT	*p*-value
Number of patients	166	712	
Number of lesions	174	755	
Age (years)	62.2 ± 9.9	62.1 ± 10.5	0.97 (NS)
Male gender	123 (74.1%)	545 (76.5%)	0.50 (NS)
Diabetes	44 (27.2%)	165 (23.3%)	0.30 (NS)
Hypertension	117 (70.5%)	446 (62.6%)	0.06 (NS)
Hyperlipidemia	141 (86%)	559 (78.5%)	0.03
Smoking	24 (14.6%)	94 (13.6%)	0.87 (NS)
Unstable angina	22 (13.8%)	181 (27.5%)	0.01
Prior AMI	55 (33.1%)	276 (39.0%)	0.16 (NS)
Multivessel disease	82 (49.4%)	351 (49.4%)	0.99 (NS)
Estimated mean:			
lesion length (mm)	17.6 ± 13.2	19.8 ± 12.1	0.01
reference diameter (mm)	3.25 ± 0.39	3.16 ± 0.47	0.02
Target lesion in LMS	1 (0.6%)	10 (1.4%)	0.47 (NS)
Target lesion in LAD	75 (46.0%)	313 (44.2%)	0.57 (NS)
Target lesion in LCX	42(25.8%)	128 (18.1%)	0.07 (NS)
Target lesion in RCA	45 (27.6%)	256 (36.2%)	0.03
Target lesion in SVG	11 (6.3%)	41 (5.4%)	0.48

CB + VBT = cutting balloon angioplasty + vascular brachytherapy; BA + VBT = standard balloon angioplasty + vascular brachytherapy; AMI = acute myocardial infarction; LAD = left anterior descending coronary artery; LCX = left circumflex coronary artery; LMS = left main stem coronary artery; RCA = right coronary artery; SVG = saphenous vein graft

Table 2. Procedural characteristics

Source length:	CB + VBT	BA + VBT	*p*-value
30 mm	18 (10.3%)	118 (15.6%)	0.09
40 mm	143 (82.2%)	610 (80.9%)	0.16
60 mm	13 (7.5%)	26 (3.4%)	0.07
Technical success	168 (97.7%)	712 (95.2%)	0.16 (NS)
Additional stent implantation	25 (14.4%)	145 (19.4%)	0.18 (NS)
Pullback maneuver	17 (9.8%)	120 (15.9%)	0.08 (NS)
Fractionated dose	10 (5.8%)	23 (3.1%)	0.14 (NS)
Obvious geographical miss*	4 (2.3%)	51 (6.8%)	0.03
Mean dwell time (minutes)	4.14 ± 1.47	4.12 ± 1.40	0.63 (NS)
Mean dose	20.35 ± 3.18 gray	18.73 ± 3.05 gray	0.07

CB + VBT = cutting balloon angioplasty + vascular brachytherapy; BA + VBT = standard balloon angioplasty + vascular brachytherapy

Follow-up, data collection and statistics. Clinical follow-up was provided for at least 6 months. A further extension of follow-up beyond 6 months was recommended, but not mandatory. Data were collected by an independent institution that reported directly to the study's safety committee. Groups were compared by means of a Student's t-test, while a multivariate analysis was conducted, which consisted of logistic regressions based on 980 patients treated in a single vessel using 17 baseline variables. Automatic backward selection procedures based on maximum likelihood were performed, preserving variables that significantly contributed to prediction ($p < 0.05$).

Results

Patients. Between April 1999 and September 2000, a total of 1,098 patients were included in the RENO registry, of whom

Table 3. In-hospital events

	CB + VBT	BA + VBT	*p*-value
Death	1 (0.6%)	2 (0.3%)	0.52 (NS)
Myocardial infarction	2 (1.2%)	5 (0.7%)	0.51 (NS)
Target vessel revascularization	1 (0.6%)	7 (1%)	0.64 (NS)
Major adverse clinical events	2 (1.2%)	13 (1.8%)	0.57 (NS)

CB + VBT = cutting balloon angioplasty + vascular brachytherapy; BA + VBT = standard balloon angioplasty + vascular brachytherapy

Table 4. Events at 6-month follow-up

	CB + VBT	BA + VBT	*p*-value
Death	2 (1.2%)	16 (2.2%)	0.39 (NS)
Myocardial infarction	2 (1.2%)	19 (2.7%)	0.27 (NS)
Target vessel revascularization	17 (10.2%)	118 (16.6%)	0.04
Major adverse clinical events	18 (10.8%)	137 (19.2%)	0.01

CB + VBT = cutting balloon angioplasty + vascular brachytherapy; BA + VBT = standard balloon angioplasty + vascular brachytherapy

878 patients were treated for in-stent restenosis. The baseline clinical and angiographic demographics of the study population are shown in Table 1. Except for the lower incidence of unstable angina in patients treated by conventional angioplasty, the clinical characteristics did not differ between both study groups. There were slight differences in the average estimated vessel size and lesion length.

Intervention and in-hospital outcome. In 166 patients with in-stent restenosis, a combined approach was performed, using cutting balloon angioplasty followed by vascular brachytherapy. In 712 other registry patients with in-stent restenosis, standard balloon angioplasty and vascular brachytherapy were performed. Procedural characteristics are shown in Table 2. The technical success, dosimetry, and source length were comparable between both groups. However, a higher incidence of obvious geographical miss was reported (6.8% with conventional angioplasty versus 2.3% with cutting balloon angioplasty; $p = 0.03$). In-hospital events, as shown in Table 3, were minimal for both groups and similar.

Follow-up. Table 4 illustrates the clinical outcome at 6-month follow-up. There was a significant difference in the incidence of MACE favoring the cutting balloon approach (10.8% versus 19.2% for conventional PTCA; $p = 0.01$). This difference is related to a greater need for target vessel revascularization in the conventional angioplasty group (16.6% versus 10.2% for cutting balloon angioplasty; $p = 0.04$), as differences in the incidence of death and myocardial infarction were found to be insignificant. Angiographic follow-up was performed for slightly more patients who were treated by cutting balloon angioplasty (127 [79.9%]) than for patients who received treatment with conventional angioplasty (475 [68.8%])($p = 0.005$). In concordance with the clinical findings, there was a trend toward more frequent angiographic restenosis in the conventional angioplasty group (119 patients, 25.3%), compared to the cutting balloon cohort (22 patients, 17.5%) ($p = 0.06$). The use of cutting balloon angioplasty resulted in a lower occurrence of MACE, according to results of the multivariate analysis, with an odds ratio of 0.49 (confidence intervals: 0.27–0.88; $p = 0.02$).

Figure 1. ***(A)*** *Diffuse in-stent restenosis in the proximal right coronary artery.* ***(B)*** *A 40 mm radiation source in place.* ***(C)*** *Final result at the end of the procedure.* ***(D)*** *Six-month follow-up angiography showing a patent stent without restenosis.*

Discussion

The present study demonstrated improved clinical outcome at 6-month follow-up in patients treated with cutting balloon angioplasty, compared to conventional angioplasty, prior to ß-irradiation for in-stent restenosis.

The RESCUT trial is a randomized, multicenter trial of cutting balloon angioplasty versus conventional angioplasty in 428 patients with in-stent restenosis.[13] The primary end point of the trial was angiographic restenosis at 7 months. There were no significant differences in restenosis rates (29% versus 31.3%, respectively; $p = 0.82$), indicating that the use of a cutting balloon only was not sufficient in preventing recurrent restenosis. There were however significant less balloon slippages in the cutting balloon group (6.5 versus 25.1, respectively; $p < 0.01$).

Vascular brachytherapy is currently established as the only efficient therapy for diffuse in-stent-restenosis.[7] This has been confirmed by seven published randomized trials comparing angioplasty and brachytherapy, demonstrating a reduced need for target vessel revascularization varying between 34% and 73%.[7] A major limitation in the early experience of the technique was the occurrence of the so-called "edge restenosis" mostly believed to be related to geographical miss. With increasing experience, operators understood the need to cover the entire "balloon"-traumatized lesion segment by an effective irradiation dose to prevent this restenotic edge effect. This could practically be realized by the use of an adequate source length.

The RENO registry of 1,098 patients is the largest post-marketing surveillance study worldwide in the field of vascular brachytherapy, reflecting "real-life" practice. While the registry was started, operators recognized the importance of further preventive measures for geographical miss. The cutting balloon provides a potential optimal angioplasty tool for in-stent restenosis prior to irradiation therapy, given the availability of a short (10 mm), non-slippery balloon segment. Therefore, we postulated that this balloon catheter could improve the clinical outcome of patients with in-stent-restenosis treated by irradiation. In the present observation, we reported a greater incidence of obvious geographical miss with conventional angioplasty (6.8% versus

2.3% with cutting balloon angioplasty; $p = 0.03$). This may be explained by the characteristics of the cutting balloon, taking in account however that the true incidence of geographical miss might have been underestimated by the investigators and that this observation may only partially explain the study results.

Slight differences appeared in a few baseline clinical and angiographic characteristics, raising questions about the comparability of the two groups. In particular, vessel size and lesion length (which negatively affect MACE rates with increasing values) were slightly larger in the cutting balloon group. Nevertheless, a multivariate analysis (considering all these confounding factors) demonstrated that cutting balloon use remained an independent predictor for a lower MACE rate at 6-month follow-up. The intervention's major impact was a reduced need for target vessel revascularization (10.2% versus 16.6% with conventional angioplasty), with no significant differences between study groups in death or myocardial infarction rates.

While this registry reflects "real life" practice, the present observation has several limitations. First, the clinical follow-up is limited to 6 months which is relatively short as events may occur beyond 6 months following intervention. Secondly, the absence of a central angiographic core lab indicates only semi-quantitative assessments and a possible underestimation of the incidence of geographical miss (despite the fact that the operators were fully trained to anticipate this problem). Thirdly, although repeat angiography was not requested according to protocol, quite a substantial proportion of patients underwent this investigation with a significant larger cohort in the cutting balloon group. This probable hazard could have been anticipated by imposing a systematic control in all patients. Finally, the same positive result might have been observed with any other short, non-compliant balloon.

In conclusion, the present study indicates an additional clinical benefit in patients with in-stent-restenosis treated by cutting balloon angioplasty compared to standard angioplasty prior to coronary ß-radiation therapy. The practical implications of this observation are that the use of a short, non-slippery balloon prior to irradiation therapy for in-stent restenosis is recommended to minimize the risk for geographical miss and its consequent adverse effects.

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