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A multicentre European registry of intraluminal coronary beta brachytherapy

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Revised 13 August 2002; accepted 21 August 2002

KEYWORDS

Irradiation;
Restenosis;
Stent

Aims To assess the feasibility, safety and effectiveness of intravascular brachytherapy (VBT) in routine clinical practice.

Methods and results Between April 1999 and September 2000, 1098 consecutive patients treated in 46 European centres by intraluminal irradiation using a Sr/Y⁹⁰ source train (BetaCath™, Novoste, GA) were included in a registry, and follow-up data were obtained for 98.8% of them after 6.3±2.4 months. Eight hundred and forty (76.5%) patients were males, and mean age was 62.0±10.2 years. Two hundred and seventy-one (26.9%) had unstable angina, and 256 (23.5%) were diabetics. Nine hundred and thirteen lesions (77.7%) were the result of in-stent restenosis, 208 (17.7%) were de novo lesions and 48 (4.1%) non-stented restenotic lesions. Mean estimated reference diameter was 3.2±0.5 mm and mean estimated lesion length was 19.0±11.8 mm. The prescribed radiation dose was 18.8±3.2 Gy. Multivessel irradiation was done in 6.2% of cases, and a new stent was implanted in 29.6% of cases. Most patients received 6 or 12 months of combined aspirin and thienopyridin treatment after the procedure. Technical success was obtained in 95.9% of treated lesions, and the in-hospital major adverse cardiac event (MACE) rate was 1.8%. At follow-up, the MACE rate was 18.7% (1.9% deaths from any cause, 2.6% AMI, 13.3% TVR by PCI and 3.3% TVR by CABG).

Conclusion The major current application of VBT is the treatment of in-stent restenosis. The good results of VBT observed in recent randomized controlled trials can be reproduced in clinical practice.

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Introduction

Restenosis remains the main limitation of percutaneous coronary interventions (PCI). It occurs in 20–50% of cases within the first 6 months after the procedure,^{1,2} and is due to a combination of elastic recoil, negative remodelling and fibrointimal tissue proliferation.^{3,4} Several predictors of restenosis

have been identified,⁵ but only stents have been shown to partially limit it, by preventing both recoil and remodeling.^{6,7} However, when in-stent restenosis does occur as a result of excessive tissue proliferation, it often represents a major therapeutic challenge.⁸ The major predictors of in-stent restenosis are diabetes, a small stent diameter and a long stented length.^{9,10} Systemic medical treatment has generally been disappointing in preventing restenosis,^{11,12} and no mechanical percutaneous intervention has proven to be

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superior to balloon angioplasty alone^{13–17} in the treatment of in-stent restenosis. Until recently, when repeat angioplasty led to recurrent restenosis, surgery has often been the only option.

In contrast to this, intravascular brachytherapy (VBT), using either gamma or beta radiation sources, has been associated with a very significant impact on the restenosis process. The first patients were treated with gamma in 1994¹⁸ and with beta in 1995¹⁹ following PCI for de novo lesions. Since that time, five randomized trials,^{20–24} totalling over 1200 patients with in-stent restenosis, have conclusively demonstrated after 6–9 months follow-up that both gamma and beta VBT are associated with a significant decrease in angiographic restenosis and need for target vessel revascularization. For primary prevention of restenosis (VBT applied for de novo lesions), results have been less conclusive. One uncontrolled dose-finding trial²⁵ showed excellent results when a high dose of beta brachytherapy was given following balloon angioplasty without stent implantation, but a larger randomized controlled evaluation,²⁶ using a 30 mm long Sr/Y90 source train, suggested that the angiographic and clinical benefit of VBT was only small following balloon angioplasty alone, and was non-existent when a stent was implanted at the time of VBT.

The registry described here was set up to monitor the application of beta VBT for routine clinical practice in the first 46 centres in Europe, Turkey and Israel to use a Sr/Y90 coronary system (BetaCath™, Novoste, Norcross, GA). The main goals of the data collection were: (1) to comply with guidelines of good clinical practice concerning post-marketing surveillance of a new coronary device; (2) to ascertain whether the clinical results of the randomized controlled trials (RCT) would be reproducible in the 'real world'; (3) to determine whether predictors of treatment failure could be defined.

Methods

Population and data collection

One thousand and ninety-eight consecutive patients not enrolled in a RCT, and in whom VBT with the Beta-Cath™ system was attempted at any of the participating centres, were enrolled in this registry. Forty-six centres (see Appendix A) were initiated in a staggered manner between April 1999 and September 2000. Data were prospectively collected by local investigators and subsequently

entered into a central independently managed database. All serious adverse events were requested to be reported by fax within 48 h of their occurrence. Centres obtained Institutional Review Board or Ethic Committee approval as well as signed informed consent from the patients for the abstraction of medical records. Baseline clinical characteristics, indication for VBT, type of PCI and VBT performed, in-hospital events and 6 months follow-up data were recorded. A follow-up coronary angiogram was recommended but not mandatory, and the local operator's assessment of angiographic data was collected, both for the acute and the follow-up results. Compliance with consecutive patient enrolment at each centre was checked by monitoring the number of disposable delivery catheters that were supplied by the sponsor to the participants.

Definitions

Technical success was considered to have been achieved when 90% of the planned dose of radiation had been delivered to the target coronary segment and the residual stenosis was no greater than 50% at the end of the procedure. Geographical miss²⁷ was defined as incomplete coverage of the injured segment by the prescribed dose of radiation. Acute myocardial infarction (AMI) was defined as a plasma CPK rise above twice the upper limit of normal and/or new Q waves on the ECG. The infarction was considered related to the VBT procedure if it occurred in the territory of a treated coronary artery or if its localization could not be determined. Deaths were classified as cardiac or non-cardiac, and cardiac death was further defined as sudden (within 24 h of acute symptoms onset) or non-sudden. Deaths of undetermined cause were deemed to have been cardiac.

A major adverse cardiac event (MACE) was considered to have occurred if one or several of the following were documented: death, myocardial infarction or target vessel revascularization. For the latter, revascularization was counted as an endpoint if it was done together with the control angiogram but also if it was only planned at that time, whether by bypass surgery or by repeat percutaneous intervention. A surrogate composite endpoint for late thrombotic target vessel occlusion was defined as the occurrence of one or several of the following beyond the first 30 days following VBT: documented angiographic total occlusion within the irradiated segment, AMI in any location and cardiac death. Angiographic restenosis was considered present when the

operator reported a 50% or greater diameter stenosis in the target segment.

VBT procedure

Consent was obtained for the procedure according to local clinical practice. A femoral access was used in all cases. The mechanical part of the procedure was completed using any approved device or technique deemed appropriate by the operator. A satisfactory initial acute result was a prerequisite for subsequent brachytherapy, but a stent could be implanted either before or after irradiation. VBT was carried out through seven or eight French guiding catheters, using a monorail-type 5 French delivery catheter (Novoste, Norcross, GA) to hydraulically deliver a source train of Sr/Y90 seeds of 30, 40 or 60 mm in length by means of a hand-held transfer device. The procedure has been described in detail elsewhere.^{28,29} The recommended dose prescribed at 2 mm from the longitudinal axis of the source train, varied between 16.1 and 23 Gy for patients without, and between 18.4 and 25.3 Gy for patients with a previously implanted stent: 16.1 (or 18.4 with a stent) Gy were given to vessels with a reference diameter of 2.5–3.5 mm, 20.7 (23.0) Gy for >3.5–<4.0 mm, and 23.0 (25.3) Gy for ≥4.0 mm. The nominal diameter of the largest angioplasty balloon used prior to VBT was considered to represent the reference diameter. Investigators were instructed to pay meticulous attention to optimal positioning of the delivery catheter relative to the previously injured segment, so as to cover the entire length of the injury area, and to document the position of all balloon inflations and that of the delivery catheter by appropriate angiographic views, both with and without contrast injection. The 40 and 60 mm source trains only became available during patient recruitment, and several centres occasionally resorted to a 'pullback' manoeuvre to better cover long injured segments. This meant that the delivery catheter was positioned twice over adjacent segments of the target vessel, usually with a short overlap zone of a few millimetres. For patients with a clinically uneventful course after VBT, a single CPK blood level was requested at 12–24 h, prior to discharge. Following the procedure, patients were treated with aspirin together with either clopidogrel 75 mg daily or ticlopidine 250 mg twice daily. Based on the available information at the time of protocol design, a minimum of 90 days of combined antiplatelet treatment was recommended, but each investigator was free to prolong this if he/she thought it necessary.

Statistical methods

Categorical data are presented as absolute and relative frequencies. For continuous variables, arithmetic means±standard deviations are given as summary measures. Multivariate analyses consisted of logistic regressions based on the 980 patients treated in a single vessel, with complete data in 17 baseline variables. Automatic backward selection procedures based on maximum likelihood were performed, preserving variables that significantly contributed to prediction ($P<0.05$). Calculations were performed using spss 10.0.7.

Results

One thousand and ninety-eight patients were registered between April 1999 and September 2000; their baseline characteristics are shown in Table 1. Mean age was 62.0±10.2 years, and 23.5% were women. By far the most frequent indication for VBT was in-stent restenosis (913 lesions, 77.7%) followed by the treatment of de novo lesions (208, 17.7%) and restenotic lesions without previous stent implantation (48, 4.1%). Procedure-related parameters are listed in Table 2. The technical success rate was 95.9%, and most procedures (70.4%) did not include implantation of a new stent. The most frequently used source train length was the 40-mm, and a small minority of patients was treated with the 60-mm source train (only available since March 2000).

Since it was originally not fully realized that rigorous and prolonged antiplatelet therapy was a significant factor in determining the occurrence of late thrombotic complications, no data were gathered concerning the duration of antiplatelet therapy for individual patients. To compensate for this, two questionnaires were sent to the investigators in order to define the duration of antiplatelet therapy that was actually used. The first in July 1999 (3 months after patient recruitment had begun), and the second in April 2001 (at the time the last patients were followed-up for their 6-month visit). Results are given in Fig. 1. In-hospital events are listed in Table 3. Early complications were very rare. Follow-up data, obtained for 1085 (98.8%) patients after a mean period of 6.3±2.4 months, are given in Table 4. While the majority of patients saw their angina improve by at least one CCS class, the overall MACE rate was 18.7%, the need for target vessel revascularization 16.3% and the angiographic restenosis rate was 24.5% (non-occlusive restenosis 18.8% and target vessel occlusion 5.7%).

Table 1 Baseline clinical characteristics

	Overall	In-stent restenosis	Others
Number of patients	1098	878	220
Number of lesions	1174	929	245
Age (years)	62.0±10.2	62.1±10.4	61.5±9.3
Male gender	840 (76.5%)	668 (76.1%)	172 (78.2%)
Diabetes	256 (23.5%)	209 (24.0%)	47 (21.5%)
Hypertension	688 (62.7%)	563 (64.1%)	125 (56.8%)
Hyperlipidemia	852 (77.8%)	700 (79.9%)	152 (69.4%)
Smoking	170 (15.9%)	118 (13.8%)	52 (24.3%)
Unstable angina	271 (26.9%)	203 (24.8%)	68 (35.8%)
Prior AMI	395 (36.2%)	331 (37.9%)	64 (29.4%)
Multivessel disease	548 (50.0%)	433 (49.4%)	115 (52.5%)
Estimated mean lesion length (mm)	19.0±11.8	19.4±12.3	17.2±9.5
Estimated mean reference diameter (mm)	3.2±0.5	3.2±0.5	3.1±0.7
Target=chronic total occlusion	81 (6.9%)	54 (5.1%)	27 (11.0%)
Target lesion in LMS	14 (1.3%)	11 (1.3%)	3 (1.3%)
Target lesion in LAD	473 (43.0%)	388 (44.5%)	85 (37.3%)
Target lesion in LCX	236 (21.5%)	170 (19.5%)	66 (28.9%)
Target lesion in RCA	375 (34.1%)	301 (34.6%)	74 (32.5%)
Target lesion in SVG	69 (5.9%)	52 (5.6%)	17 (6.9%)

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 Procedure-related parameters

	Overall	In-stent restenosis	Other
Single vessel procedure	1029 (93.8%)	831 (94.8%)	198 (90%)
Multivessel procedure	68 (6.2%)	46 (5.3%)	22 (10%)
Nominal diam. of largest balloon ^a	3.3±1.0 mm	3.3±1.1 mm	3.2±0.6 mm
Atherectomy (DCA or rotabl.) ^a	26 (2.2%)	17 (1.8%)	9 (3.7%)
Cutting balloon ^a	177 (15.1%)	171 (18.4%)	6 (2.4%)
New stent implanted ^a	345 (29.6%)	170 (18.4%)	175 (71.7%)
Technical success of VBT ^a	1114 (95.9%)	880 (95.7%)	234 (96.7%)
Geographical miss ^a	71 (6.1%)	55 (6.0%)	16 (6.5%)
Mean dose at 2 mm (Gy) ^a	18.8±3.2	19.0±3.1	18.1±3.1
30 mm source train ^a	193 (16.5%)	136 (14.7%)	57 (23.4%)
40 mm source train ^a	929 (79.3%)	753 (81.1%)	176 (22.1%)
60 mm source train ^a	50 (4.3%)	39 (4.2%)	11 (4.5%)
Pullback manoeuvre ^a	191 (16.3%)	137 (14.8%)	54 (22%)
Fractionated treatment ^a	41 (3.5%)	33 (3.6%)	8 (3.3%)

^aResults per lesion. DCA=directional coronary atherectomy; Rotabl.=rotational atherectomy; VBT=vascular brachytherapy.

Factors predicting the occurrence of MACE, derived from multivariate analysis, are listed in Table 5, and those associated with late target vessel occlusion are given in Table 6.

Discussion

While VBT is now very solidly documented in five randomized trials^{20–24} as associated with a significant decrease in restenosis and clinical event rates when applied to treat in-stent restenosis, the present registry represents the first large cohort of patients having undergone coronary brachytherapy

during routine clinical practice. To our knowledge, this is also the first time that a multicentre registry of this size, including all consecutive patients of all centres using a new interventional modality, has been set up immediately after completion of the pivotal RCT^{20–26} proving efficacy. This approach allows assessment of effectiveness,³⁰ while also ensuring that feasibility, learning curve and safety issues are further evaluated in the 'real world'.

Based on the present data, the main indication for brachytherapy is now clearly in-stent restenosis, reflecting both the available evidence^{20–26} and the lack of a proven alternative treatment. There

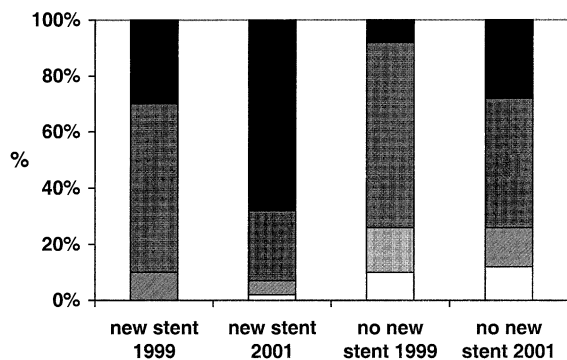


Fig. 1 Duration of combined antiplatelet regimen following VBT. □=less than 3 months; ▒=3 months; ▓=6 months; ■=12 months or more.

was low use of additional stenting overall (29.6% of procedures) and for in-stent restenosis in particular (18.4%). Such a strategy is distinctly unusual in today's PCI environment, and is probably a consequence of the reported risk of late thrombotic complications when stents and VBT are combined.^{22,31} The good results obtained, both acutely and after a 6-month follow-up period, confirm the feasibility and safety of VBT outside the constraints of a RCT. In-hospital complications were infrequent (1.8%), and the 6-month MACE rate of 18.7% (17.7% for patients with in-stent restenosis) observed in the present registry compares favourably to those reported in the radiotherapy arm of the currently available trials,^{20–26,32} where MACE rate varied between 18 and 29% for patients treated for in-stent restenosis and between 14 and 19% for de novo lesions. Similarly, need for target vessel revascularization was 16.3% in this registry, while it was 11–34% in the previously mentioned trials. It should also be stressed that several exclusion criteria often used in randomized trials (long lesions, chronic total occlusions, saphenous vein graft lesions, multivessel procedures, etc.) did not apply in this registry.

The multivariate predictors of late target vessel occlusion were: younger age, chronically occluded target lesion and the occurrence of reported geographic miss. Chronically totally occlusive lesions (CTO) have long been known to have a higher propensity to develop recurrent total occlusion during the follow-up after PCI,^{33,34} and it is therefore not surprising for this also to be true after brachytherapy. Seven of the 55 (12.7%) CTO patients with angiographic follow-up had recurrent total occlusion at follow-up in the present series, vs 12% in the stent arm of the SICCO trial.³¹ Why geographic miss should be a predictor of late target vessel occlusion is less obvious. The incidence of

reported geographic miss was only 6.1% in the present series, and is most certainly an underestimation of the true magnitude of the problem,³⁵ with presumably only gross geographic miss being reported. This would seem to be supported by the fact that more stents were used in the geographic miss patients (44.2% of lesions vs 28.5%), suggesting perhaps a higher incidence of major dissections requiring bail-out stenting and thus a longitudinal extension of the injured segment. Implantation of a new stent only narrowly failed to appear among the multivariate predictors of late target vessel occlusion, and became one if geographical miss was forced out of the model. Duration of and compliance with the combined antiplatelet medication has previously been shown^{22,31,36,37} to be a major determinant for late thrombosis. This information was not collected for individual patients enrolled in this registry, however, and was therefore not evaluated as a potential predictor of late vessel occlusion. It should be noted that the surrogate endpoint for late subacute thrombosis that was used in the present series reflects a 'worst case scenario', since all documented target vessel occlusions were considered to have been thrombotic in origin, whether associated with clinical events or not,^{36,37} and conversely, in some cases, cardiac death or AMI occurring after 30 days may not have been related to target vessel occlusion but to disease progression elsewhere.

The multivariate predictors of MACE at follow-up (Table 5) are of particular interest since RENO is the largest single cohort of patients treated with VBT. Younger age is an interesting predictor, and may be contrasted with the well established disappointing long-term results observed with VBT in juvenile animal models.³⁸ Saphenous vein graft lesions are known to be associated with a markedly higher risk of MACE for PCI in general,³⁹ and this has also been seen with VBT in previous series.⁴⁰ The association of longer lesions and smaller reference diameters with an increased risk of MACE confirms what we know from randomized trials of both beta and gamma. Interestingly, for the 49 patients treated with the 60 mm source train for 56 lesions of 31 ± 14.7 mm in length, the 6-month MACE rate was only 12.2%, suggesting that perhaps an adequate ratio between lesion and source lengths may lead to improved results for longer lesions. Use of a cutting balloon was an independent predictor of a lower MACE rate. This may relate to the very stable balloon positioning that is obtained with the usually short (10–15 mm) cutting balloon, thus decreasing the likelihood of slippage and geographical miss.³⁵ Stent implantation increased MACE by 60%. This

Table 3 In-hospital events

	Overall	In-stent restenosis	Other
Death	3 (0.3%)	3 (0.3%)	0 (0%)
Q wave AMI	3 (0.3%)	3 (0.3%)	0 (0%)
Non-Q wave AMI	5 (0.5%)	3 (0.3%)	2 (0.9%)
PCI of target vessel	9 (0.8%)	6 (0.7%)	3 (1.4%)
CABG of target vessel	2 (0.2%)	2 (0.2%)	0 (0%)
Any of the above (=MACE)	20 (1.8%)	17 (1.7%)	5 (2.3%)

AMI=acute myocardial infarction; CABG=coronary artery bypass grafting, MACE=major adverse cardiac event, PCI↓5 percutaneous coronary intervention.

Table 4 Follow-up (after 6.3±2.4 months)

	Overall	In-stent restenosis	Other
No. of patients with follow-up	1085 (98.8%)	869 (99.0%)	216 (98.2%)
AP better by at least 1 CCS class	860 (85.0%)	699 (85.5%)	161 (83.0%)
Death (all causes)	21 (1.9%)	18 (2.1%)	3 (1.4%)
Non-cardiac death	9 (0.8%)	7 (0.8%)	2 (0.9%)
AMI (Q or non-Q)	28 (2.6%)	21 (2.4%)	7 (3.2%)
Q wave AMI	11 (1%)	8 (0.9%)	3 (1.4%)
TVR by PCI ^a	146 (13.3%)	108 (12.3%)	38 (17.3%)
TVR by CABG ^a	36 (3.3%)	29 (3.3%)	7 (3.2%)
Any MACE	205 (18.7%)	155 (17.7%)	50 (22.7%)
Surrogate composite for late thrombosis	59 (5.4%)	46 (5.2%)	13 (5.9%)
Cardiac death	4 (0.4%)	3 (0.3%)	1 (0.5%)
AMI >30 days	18 (1.6%)	15 (1.7%)	3 (1.4%)
Total occlusion >30 days	42 (3.8%)	32 (3.6%)	10 (4.5%)
Angio. follow-up obtained	764 (72.4%)	602 (70.9)	162 (78.6%)
Angio. restenosis (occl. and non-occlusive)	185 (24.5%)	141 (23.7%)	44 (27.7%)
Angio. occlusion	42 (3.8%)	32 (3.6%)	11 (4.5%)

^aRevascularization done or planned at the time of follow-up; AMI=acute myocardial infarction; CABG=coronary artery bypass grafting; CCS=Canadian Cardiovascular Society; MACE=major adverse cardiac event.

Table 5 Multivariate predictors of MACE during follow-up

	P value	Odds ratio	95% confidence
Age (1 year older)	0.03	0.98	0.981–0.998
Unstable angina	0.01	1.63	1.13–2.36
Native target (not SVG)	0.02	0.45	0.23–0.87
Lesion length (1 mm longer)	0.01	1.02	1.005–1.032
Balloon diameter (1 mm larger)	0.01	0.61	0.41–0.90
Cutting balloon use	0.02	0.49	0.27–0.88
New stent implanted	0.009	1.61	1.13–2.29

SVG=saphenous vein graft.

confirms prior data,^{22,31} and suggests that late thrombotic complications associated with stenting may have driven some of the MACE observed, but conversely, may also represent a selection of more complex cases with extensive dissection at the time of the index procedure, therefore increasing the possibility of geographical miss. As was previously shown,²² MACE rates do not significantly differ between diabetic (20.3%) and non-diabetic patients

Table 6 Multivariate predictors of late thrombosis during follow-up

	P value	Odds ratio	95% confidence
Age (1 year older)	0.01	0.97	0.94–0.99
Initial CTO target	0.003	2.66	1.38–5.14
Geographical miss	0.01	2.80	1.23–6.35

CTO=chronic total occlusion.

(18.2%). This is of particular interest, since diabetes is an important risk factor for adverse clinical outcomes following stenting⁴¹ and interventional procedures in general.⁴²

Since this registry was completed, drug-eluting stents have been shown to be highly effective in preventing restenosis when used to treat de novo coronary lesions.^{43,44} If such stents become widely used, they may decrease the need for brachytherapy by reducing the overall prevalence of restenotic lesions. Several randomized trials are also underway to evaluate the impact of drug-eluting stents in the treatment of in-stent restenosis, and at least three small uncontrolled registries^{45–47} have reported encouraging results in this indication. It is interesting to note, however, that both late thrombotic complications and recurrences ascribed to geographical miss^{45–47} have been reported in this setting. Drug-eluting stents are easy to use and do not require any additional personnel in the catheterization laboratory, but whether they will prove as effective as brachytherapy for the treatment of in-stent restenosis thus remains to be determined.

Limitations

Although the results of the present series are very encouraging, they suffer from the limitations of all registries. While they accurately reflect current practice in 'real life' situations, and are consistent with previous RCT, they cannot be seen as direct evidence of the efficacy of VBT, especially in a mixed population with a variety of indications for PCI.

No angiographic core laboratory was available, and the angiographic data should therefore only be seen as semi-quantitative. However, the present results are consistent with previous series that did use systematic quantitative angiographic analysis, and both a measure of vessel reference diameter and lesion length were confirmed as predictors for MACE in this registry, as would have been expected. When the protocol was finalized in February 1999, a recommendation for a course of aspirin together with either ticlopidine or clopidogrel for at least 90 days was made for all patients, but no data concerning antiplatelet management was collected for individual patients. The exact nature and duration of treatment as well as compliance with the prescribed regimen could thus not be assessed for their impact on late vessel occlusion and on MACE in general. Others^{36,37} have shown that prolonged treatment is associated with very low late thrombotic complications, knowledge which became

available during this registry's enrolment phase. As a result, a majority of patients received combined antiplatelet treatment for 6 months or more.

Conclusions

Vascular brachytherapy in Europe is currently being used mainly to treat in-stent restenosis. It is both feasible and safe in a variety of clinical environments, with an excellent technical success rate. At the 6 months follow-up mark, good results are obtained in routine clinical practice, and MACE rates are similar to those obtained in the VBT arms of RCT. Longer source trains (40 and 60 mm) are increasingly used, together with a strategy of limited new stent implantation and prolonged combined antiplatelet treatment.

Appendix A

Steering committee: D. Baumgart, R. Bonan, A. Gershlick, P. Urban (Chair), A. Zeiher.

Database management and statistical analysis: Wegscheider Biometrie und Statistik GmbH, Berlin, Germany.

Participating centres: [country, names of cardiologist and radiotherapist and number of patients included (in brackets)].

Rotterdam Thoraxcenter, The Netherlands; Serruys, Levendag/Coen (130)—Essen Universitätsklinikum, Germany; Baumgart, Sauerwein (101)—Milan Columbus, Italy; Colombo, Orecchia (90)—München Müller, Germany; Silber, von Rottkay (49)—Lausanne C.H.U.V., Switzerland; Eeckhout, Coucke (48)—Dortmund St. Johannes, Germany; Heuer, Donsbach (39)—Antalya Akdeniz UH, Turkey; Sancaktar, Garipagaoglu (37)—Hamburg St. Georg, Germany; Küchler, Ehnert (37)—Kaiserslautern Westpfalz-Klinikum, Germany; Glunz, Herbig (33)—Chemnitz Herzzentrum, Germany; Kleinertz, Schubert (32)—München Klinikum Innenstadt, Germany; Klauss, Pöllinger (32)—Aalst OLV, Belgium; Wijns, Verbeke (29)—Aachen Universitätsklinikum, Germany; vom Dahl, Schubert (25)—Antwerp UZA, Belgium; Vrints, de Bal (24)—Kayseri Erciyes, Turkey; Basar, Karahacyoglu (24)—Berlin Benjamin Franklin, Germany; Schultheiss, Hinkelbein (24)—Mont-Godinne UCL, Belgium; Gurné, Vandeput (23)—Hamburg UKE, Germany; Brockhoff, Krüll (22)—Berlin Charité Mitte, Germany; Rutsch, Buchali/Matnjani (21)—Frankfurt UNI, Germany; Auch-Schwelk, Schopohl (20)—Jerusalem Shaari Zedek, Israel; Meerkin, Hayne (19)—Hasselt Virga Jesse, Belgium; Benit, Brosens (18)—Lübeck Universitätsklinikum, Germany;

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Sponsor: Novoste Europe SA/NV, Brussels, Belgium. Special thanks to Nick van Dyck for his tireless endeavours in helping to collect all data from all centres.

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