# Direct Stenting Versus Direct Stenting Followed by Centered Beta-Radiation With Intravascular Ultrasound-Guided Dosimetry and Long-Term Anti-Platelet Treatment

## Results of a Randomized Trial: Beta-Radiation Investigation With Direct Stenting and Galileo in Europe (BRIDGE)

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| **OBJECTIVES** | We sought to assess the efficacy of vascular brachytherapy (VBT) combined with stenting for the primary prevention of restenosis. |
| **BACKGROUND** | Intravascular brachytherapy after stent implantation for de novo lesions has been abandoned for the present. We revisited this procedure by optimizing all procedural steps—the use of glycoprotein IIb/IIIa blockers, direct stenting, adequate radiation coverage, avoidance of edge damage, source centering, intravascular ultrasound-guided dosimetry, and continuation of a dual anti-platelet regimen for one year. |
| **METHODS** | The Beta-Radiation Investigation with Direct stenting and Galileo in Europe (BRIDGE) study is a multicenter, randomized controlled trial evaluating the long-term efficacy of VBT with P-32 (20 Gy at 1 mm in the coronary wall) after direct stenting. The primary end point was angiographic intra-stent late loss; secondary end points were six months binary restenosis and neo-intimal hyperplasia. Patients (n = 112) with de novo lesions (2.5 to 4.0 mm in diameter up to 15 mm long) were randomized to either VBT or no-VBT. |
| **RESULTS** | At six months, intra-stent loss was 0.43 and 0.84 mm (p < 0.001) in the irradiated and control groups, respectively. Intra-stent neo-intimal volume was reduced from 36 mm³ to 10 mm³. However, in the irradiated group there were six late occlusions as well as eight restenoses outside the stented and peri-stented area at the fall-off dose edges of the irradiated area. Accordingly, the target vessel revascularization and major adverse cardiac and cerebro-vascular events rates at one year in the VBT group (20.4% and 25.9%, respectively) were higher than in the control group (12.1% and 17.2%, respectively). |
| **CONCLUSIONS** | Despite the optimization of pre-, peri-, and post-procedural factors and despite the relative efficacy of the brachytherapy for the prevention of the intra-stent neo-intimal hyperplasia, the clinical outcome of the irradiated group was less favorable than that of the control group. (J Am Coll Cardiol 2004;44:528–37) © 2004 by the American College of Cardiology Foundation |

It has been shown that stents reduce restenosis by eliminating elastic recoil and negative remodeling, but they induce neo-intimal hyperplasia (1). Several randomized studies

**See page 538**

have confirmed the effectiveness of vascular brachytherapy (VBT) for the treatment of in-stent restenosis both with gamma (2–4) and beta (5–7) emitters, but its effectiveness

for de novo lesions, especially in combination with the use of stents, remains contentious (8–10).

A dose-finding study with yttrium demonstrated a dose-dependent reduction in restenosis in non-stented arteries (8), probably resulting from a beneficial effect of radiation on remodeling and an inhibitory effect on neo-intima formation (11,12). This trial, however, did not suggest any favorable impact of beta radiation on restenosis in stented de novo lesions. Restenosis adjacent to the target site (13,14) and late thrombotic events (15) were recognized as major limitations of VBT, especially in combination with the use of stents (9,10).

Geographical miss (GM) and edge restenosis frequently were associated with dilation and stenting occurring after radiation treatment (16). Therefore, it was advocated to complete the percutaneous intervention treatment *prior to*

**Abbreviations and Acronyms**
EIRS = effective irradiated segment
GM = geographical miss
IVUS = intravascular ultrasound
MACCE = major adverse cardiac and cerebrovascular
events
MI = myocardial infarction
MLD = minimal luminal diameter
QCA = quantitative coronary angiography
VBT = vascular brachytherapy

radiation to ensure complete radiotherapy coverage of the injury. Accordingly, direct stenting was viewed as an optimal approach to minimize the incidence of GM and edge restenosis. In addition, source centering and intravascular ultrasound (IVUS)-guided dosimetry, with theoretical advantages on dose delivery, were viewed as the methods of choice for radiotherapy treatment.

Because animal data have demonstrated increased thrombosis and the early presence of platelet activation after brachytherapy (17), the use of glycoprotein IIb/IIIa inhibitors was recommended as adjunctive therapy. Finally it was hypothesized that prolonged use of a dual anti-platelet medication reduces the incidence of late silent or thrombotic vessel occlusion (9,10,18,19). Thus, the purpose of the current study was to evaluate the efficacy of centered intra-coronary beta irradiation with $^{32}$P/Galileo after direct stenting of de novo lesions in patients undergoing extended anti-platelet treatment with aspirin and clopidogrel.

## METHODS

**Study design.** The Beta-Radiation Investigation with Direct stenting and Galileo in Europe (BRIDGE) trial is a multicenter, randomized, controlled clinical trial on the effect of brachytherapy after direct stenting. From February 2001 until March 2002, 112 patients were enrolled at 8 European centers. If the patient was eligible, a phone call was made to the central allocation service to register the patient, and the direct stenting procedure was performed. In cases of edge dissection or a stented length >18 mm, patients were subsequently not randomized. Once the direct stenting result was optimal based on quantitative coronary angiography (QCA) online criteria (residual diameter stenosis <15%), IVUS assessment was performed, and the patient was randomized during a second phone call, to either the VBT or control group.

All randomized patients underwent clinical follow-up at 1, 6, and 12 months and angiographic and IVUS follow-up at 6 months. An independent core laboratory assessed the angiographic and IVUS outcomes. Clinical end points were assessed by an independent masked end point committee. An independent data safety monitoring committee assessed the results with respect to patient safety at regular intervals.

**End points.** The primary end point was the angiographic intra-stent late loss. The secondary end points were event-free survival at one year, defined as the absence of major adverse cardiac and cerebrovascular events (MACCE). Major adverse cardiac and cerebrovascular events were defined as the occurrence of cardiac death and/or cerebrovascular events and/or myocardial infarction (MI) (Q-wave infarction as defined by Minnesota Code, non–Q-wave MI two times the upper limit of normal of creatine kinase and an abnormal level of creatine kinase, MB fraction) and/or target vessel revascularization.

All deaths were considered cardiac unless they were unequivocally documented to be non-cardiac. "Target lesion revascularization" was defined as revascularization of the stented segment. "Target vessel revascularization" was defined as a revascularization of any segment of the randomized coronary artery. Additional secondary end points were MACCE, binary angiographic restenosis at six months, and neo-intimal hyperplasia at six months as assessed by IVUS.

**Power calculation and sample size.** The sample size calculations were based on the results of the BElgium NEtherlands STENT (BENESTENT) II trial and the results of the dose-finding studies with the device under investigation (8,20,21).

One hundred and twelve patients were randomized to two groups of equal size. This number of patients would lead to a power of at least 84% to detect a 50% decrease in loss (from 0.80 in the control group to 0.40 in the treated group) with a two-sided type I error rate of 0.05.

**Patient selection.** Major inclusion criteria were: de novo lesions in one or two native vessels with a reference diameter of 2.5 to 4.0 mm and a lesion length of 15 mm suitable for direct stenting; stable (Canadian Cardiovascular Society class I, II, III, or IV) or unstable angina pectoris (Braunwald class I to III, B to C); or documented silent ischemia. Major exclusion criteria were: any MI within three days before inclusion and/or lack of normalization of the creatine phosphokinase; previous Q-wave MI in the territory supplied by the vessel to be treated and a large akinetic area in the same territory; stroke/gastro-intestinal bleeding within six months; ejection fraction <30%; severe hepatic disease; previous mediastinal irradiation; or known intolerance or contraindication to aspirin, clopidogrel, or glycoprotein IIB/IIIA inhibitors. Angioplasty exclusion criteria were: total occlusion (Thrombolysis in Myocardial Infarction flow grade 0); stenting of each arm of a bifurcation; and intended angioplasty of the ostium of the left anterior descending and left circumflex coronary artery to avoid impeding the flow in the main stem with the centering catheter. Written informed consent was obtained before patients were admitted to the interventional suite.

**Post-procedural anti-platelet treatment.** By protocol, a dual (clopidogrel 75 mg and acetylsalicylic acid 80 mg daily) anti-platelet treatment was used up to 11 months.

**Study device: stent and radiation delivery system.** The 18-mm MULTI-LINK RX TETRA Coronary Stent System (Guidant, Santa Clara, California) was used for direct
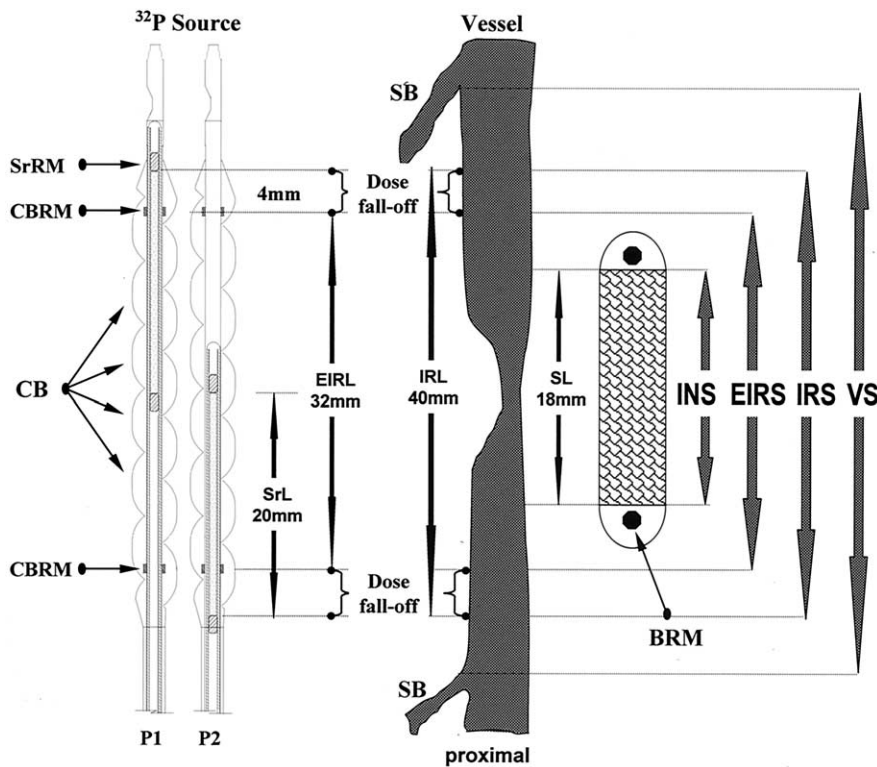
**Figure 1.** A schematic diagram of the tandem positioning of the $^{32}$P radiation source and an irradiated coronary artery with the anatomical and dose-based sub-segment definition. BRM = balloon radiopaque marker; CB = centering balloon; CBRM = centering balloon radiopaque marker; EIRL = effective irradiation length; EIRS = effective irradiated segment; INS = injured segment; IRL = irradiation length; IRS = irradiated segment; SB = side branch; SL = stent length; SrL = source length; SrRM = source radiopaque marker; VS = vessel segment.

stenting, and the GALILEO Intravascular Radiotherapy System (Guidant) was used for VBT.

The GALILEO Intravascular Radiotherapy System comprises the $^{32}$P 0.018-inch source wire, a centering catheter, and the GALILEO source delivery unit. The source delivery unit is a high-dose rate afterloader designed specifically for coronary radiotherapy. It has a computer-controlled source wire handling device, which automatically advances the source wire to the most distal position of the centering catheter and subsequently moves to the next more proximal position in 20-mm increments (known as "steps"). Thus, the source wire makes two steps within the 32-mm long spiral-designed centering balloon catheter that is inflated to a pressure of $4 \pm 1$ atmospheres and has a nominal diameter of 2.5, 3.0, or 3.5 mm. Radiopaque markers (proximal and distal to the balloon) allow for the precise positioning of the centering catheter at the lesion site.

The appropriate diameter of the centering catheter is selected based on the intra-stent minimal luminal diameter (MLD) determined by online QCA. The dwell time required to deliver the prescribed dose (20 Gy at a depth of 1 mm in the vessel wall) is automatically computed, based on the average reference luminal diameter calculated from proximal and distal MLD acquired from online IVUS assessment. The length of the artery receiving full 20 Gy at 1 mm is 32 mm, whereas the whole radiated length is 40

mm ($2 \times 20$ mm). Fractionation of the treatment was required in three patients.

**QCA evaluation.** Quantitative coronary angiography was performed by means of the CAAS II analysis system (Pie Medical BV, Maastricht, Netherlands). A methodological approach, previously reported (9,14,16,22), was used to accurately depict the "geographic" relationship between the stent and the radioactive source, and the following sub-segments were defined (Fig. 1):

- Stented segment—defined by the radiopacity of the MULTI-LINK RX TETRA coronary stent.
- Peri-stent segments—defined by a length of 5 mm proximal and distal to the stent edge.
- Irradiated segment—defined as the segment encompassed by the inner edge of the radiopaque markers of the source wire. Two sub-segments of the irradiated segment are identified:
  1. Effective irradiated segment (EIRS)—the segment (32 mm) receiving full prescribed therapeutic radiation dose (90% isodose) is shorter than the irradiated segment (40 mm) as a result of the dose fall-off.
  2. Edge (dose fall-off) segments—vessel segments at the extremities of the irradiation source that do not receive the full therapeutic radiation dose. The length of each edge segment is approximately 4 mm.
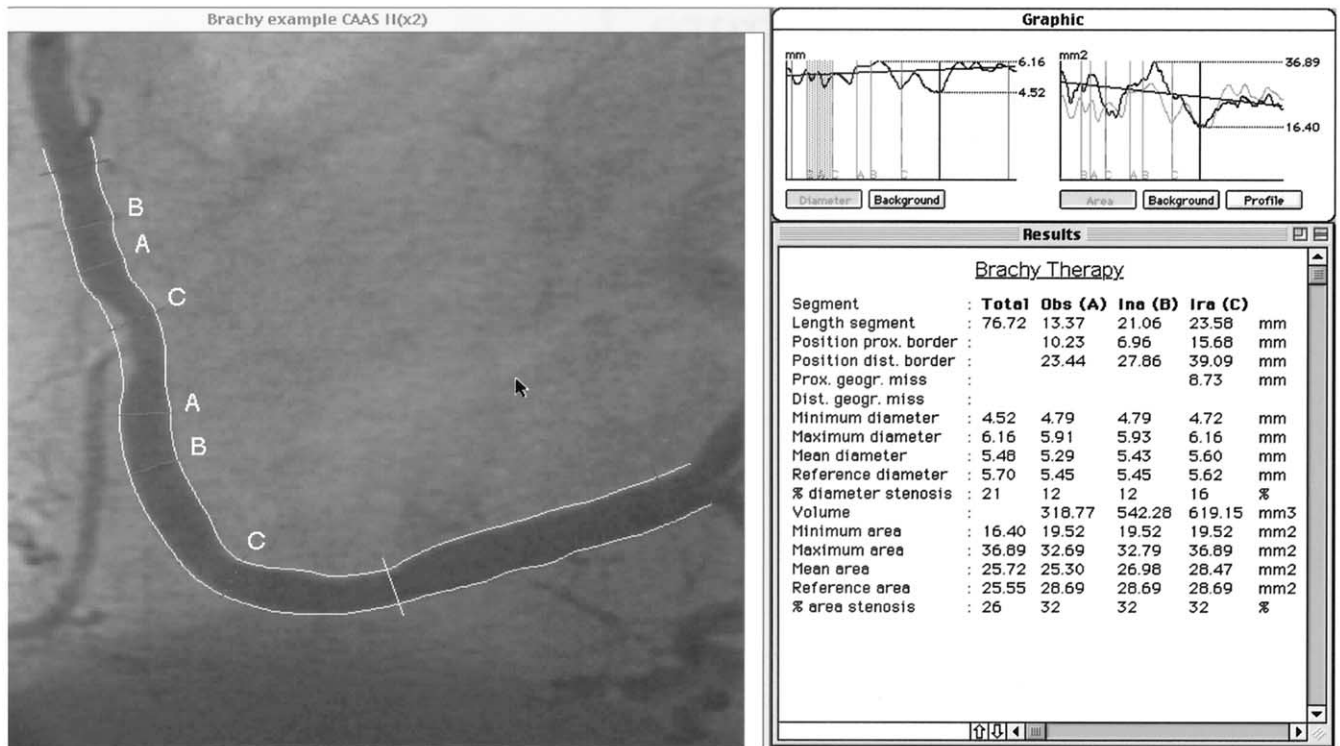
**Figure 2.** An example of quantitative coronary angiography depicting the automatic assessment of the anatomic relationship between the obstructed (A), the injured (B), and the irradiated (C) sub-segments, which allows the quantitative assessment of the length of the geographical miss, 8.73 mm at the proximal edge in this case.

- Vessel segment analysis—segment bordered by angiographically visible side branches encompassing lesion, stent, and radiation source.
- GM segment—this segment is present when the length of the stented and peri-stent segments (28 mm) are not covered by the EIRS (Figs. 2 and 3).

The above segment lengths were automatically measured by a customized software package specifically designed for the assessment of brachytherapy treatment. With this software, the anatomic relationship between the various (dose-related) sub-segments is automatically assessed, allowing the quantitative assessment of the length of the GM (Fig. 2).

At follow-up, the detection of any diameter stenoses >50% in the analyzed vessel segment was performed by analysts who were blinded to the allocated treatment. Subsequently, the boundaries of the above-mentioned sub-segments were superimposed on matched angiographic views using transparent sheets to locate the site of the MLD with respect to the irradiated area (9,14,16,22).
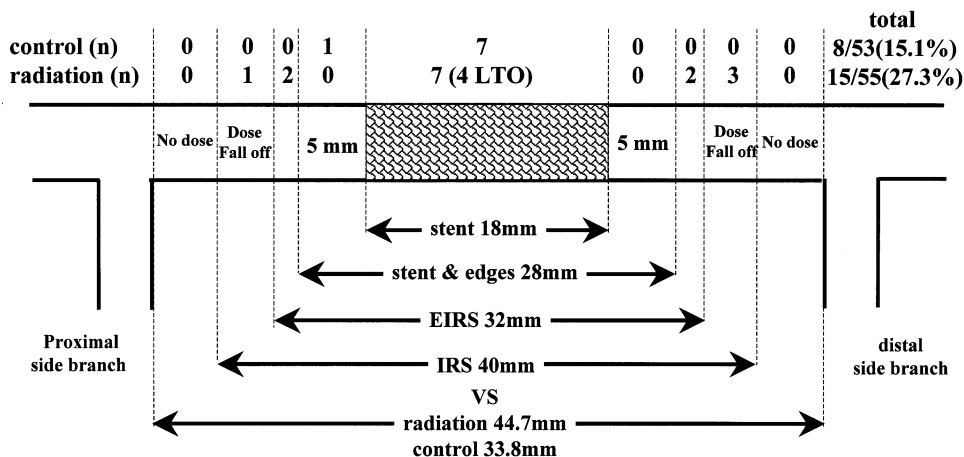


**Figure 3.** Location of the minimal luminal diameter at six months follow-up (±4 weeks) in patients with >50% diameter stenoses in relation to the dose-based sub-segments. Four instances of late total occlusion (LTO) were documented at the time of the angiographic follow-up, and two occurred later. EIRS = effective irradiated segment; IRS = irradiated segment; VS = vessel segment.

**Table 1.** Baseline Clinical and Angiographic Characteristics (Intention to Treat)

| | Irradiation (n = 54 Patients), n (%) | No Irradiation (n = 58 Patients), n (%) |
|---|---|---|
| Age, yrs (mean ± SD) | 61.2 ± 10.5 | 61.6 ± 10.5 |
| Gender, male | 41 (75.9%) | 48 (82.8%) |
| Previous MI | 16 (29.6%) | 19 (32.8%) |
| Diabetes mellitus | 8 (14.8%) | 13 (22.4%) |
| Hypertension | 32 (59.3%) | 31 (53.4%) |
| Current smoker | 12 (22.6%) | 12 (21.1%) |
| Angina pectoris* | | |
| CCS class I | 6 (11.1%) | 5 (8.6%) |
| CCS class II | 21 (38.9%) | 19 (32.8%) |
| CCS class III | 10 (18.5%) | 15 (25.9%) |
| CCS class IV | 0 (0.0%) | 1 (1.7%) |
| Glycoprotein IIb/IIIa inhibitors | 51 (94.4%) | 55 (94.8%) |
| Target coronary artery | | |
| LAD | 27 (50.0%) | 28 (48.3%) |
| RCA | 31 (57.4%) | 25 (43.1%) |
| LCX | 16 (29.6%) | 23 (39.7%) |
| Lesion type | n = 57 lesions | n = 59 lesions |
| A | 3 (5.3%) | 1 (1.7%) |
| B1 | 21 (36.8%) | 20 (33.9%) |
| B2 | 33 (57.9%) | 38 (64.4%) |
| C | 0 (0.0%) | 0 (0.0%) |
| Reference vessel diameter (mm) | 2.83 ± 0.59 | 2.87 ± 0.49 |
| Lesion length (mm) | 11.50 ± 3.85 | 11.73 ± 5.42 |

Plus-minus values are means ± SD. Unless indicated, all data are presented as percent of patients. *Angina was defined according to the classification of the Canadian Cardiovascular Society (CCS).
LAD = left anterior descending coronary artery; LCX = left circumflex coronary artery; MI = myocardial infarction; RCA = right coronary artery.

**Quantitative IVUS.** Post-procedure and six-month follow-up stented vessel segments were examined with mechanical intravascular ultrasound (Cardio Vascular Imaging System, CVIS, Sunnyvale, California) using automated pullback at 0.5 mm/s. A coronary segment beginning 5 mm distal to and extending 5 mm proximal to the stented segment also was examined. A computer-based contour detection program was used for automated three-dimensional reconstruction of the stented segment. Lumen, stent boundaries, and external elastic membrane were detected using a minimum-cost algorithm. Total vessel volume (TVV), stent volume (SV), and lumen volume (LV) were calculated according to Simpson's rule. Total plaque volume, plaque volume behind the stent struts, and neo-intimal hyperplasia were calculated as TVV − LV, TVV − SV, SV − LV, respectively. Percentage obstruction volume was calculated as neo-intimal volume/stent volume × 100. Feasibility, reproducibility, and inter- and intra-observer variability of this system have been validated in vitro and in vivo (23,24).

**Statistical analysis.** The primary analysis was performed according to the intention-to-treat principle (all randomized patients), and the QCA end point was assessed on a per-lesion basis. A secondary per-protocol analysis was performed; patients who did not receive brachytherapy treatment as planned were excluded.

Continuous parameters were presented as mean values and standard deviations, and discontinuous parameters as percentages. Continuous parameters were compared using the Student *t* test, whereas binary parameters were compared using the Fisher exact test. Patient survival curves were constructed according to the Kaplan-Meier method. The Wilcoxon rank sum test was applied to evaluate the difference in hierarchical ranking between the two groups. The statistical significance of all tests was defined at the $p < 0.05$ level.

## RESULTS

**Patient baseline characteristics.** Table 1 shows the baseline clinical and angiographic characteristics of each study group (54 patients with 57 lesions in the irradiation group versus 58 patients with 59 lesions in the control group). The number of diabetic patients enrolled in the irradiated and control groups were 8 (14.8%) and 13 (22.4%), respectively. The majority of patients were elective cases in functional class II or III, with a lesion Type B1/B2. In each group, 95% of the patients received abciximab.

**Serial QCA analyses.** STENT AND PERI-STENT SEGMENTS. A total of 116 lesions were randomized: 57 lesions were allocated to irradiation, and 59 to control. Quantitative angiographic follow-up was available in 55 lesions allocated to irradiation, and 53 allocated to conventional treatment. Three lesions in the irradiated group did not receive the allocated treatment: one lesion could not be crossed with the delivery catheter, one lesion could not be irradiated because of a technical defect, and one lesion occluded before irradiation. In an intention-to-treat analysis, the in-stent late loss was reduced from 0.84 ± 0.46 to 0.43 ± 0.75 mm (p < 0.001). Although the primary end point of the study was reached, the in-stent

**Table 2.** Serial QCA Analyses (Intention to Treat)

|  | Irradiation (55 Lesions) | No Irradiation (53 Lesions) | p |
|---|---|---|---|
| In-stent |  |  |  |
|   MLD post (mm) | 2.66 ± 0.44 | 2.69 ± 0.40 | 0.68 |
|   MLD follow-up (mm) | 2.23 ± 0.82 | 1.85 ± 0.52 | 0.006 |
|   Late loss (mm) | 0.43 ± 0.75 | 0.84 ± 0.46 | 0.001 |
|   DS follow-up (%) | 23 ± 25 | 30 ± 14 | 0.07 |
|   Restenosis, n (%) | 7 (12.7%) | 7 (13.2%) | 1.00 |
| Edges |  |  |  |
|   Prox MLD post (mm) | 2.50 ± 0.61 | 2.71 ± 0.62 | 0.09 |
|   Prox MLD follow-up (mm) | 2.49 ± 0.60 | 2.37 ± 0.55 | 0.28 |
|   Prox late loss (mm) | 0.01 ± 0.48 | 0.34 ± 0.50 | 0.001 |
|   Prox restenosis, n (%) | 0 (0.0%) | 1 (1.9%) | 1.00 |
|   Distal MLD post (mm) | 2.10 ± 0.58 | 2.28 ± 0.45 | 0.09 |
|   Distal MLD follow-up (mm) | 1.99 ± 0.61 | 2.12 ± 0.45 | 0.21 |
|   Distal late loss (mm) | 0.13 ± 0.57 | 0.16 ± 0.33 | 0.77 |
|   Distal restenosis, n (%) | 0 (0.0%) | 0 (0.0%) | 1.00 |
| Irradiated segment |  |  |  |
|   MLD (mm) | 1.77 ± 0.71 | NA | NA |
|   DS follow-up (%) | 37.87 ± 21.49 | NA | NA |
|   Restenosis, n (%) | 11 (21.6%) | NA | NA |
| Vessel segment |  |  |  |
|   MLD (mm) | 1.57 ± 0.65 | 1.71 ± 0.45 | 0.19 |
|   DS follow-up (%) | 44 ± 20 | 33 ± 1.3 | 0.001 |
|   Restenosis rate, n (%) | 15 (27.3%) | 8 (15.1%) | 0.16 |

DS = diameter stenosis; MLD = minimal lumen diameter; Prox = proximal; QCA = quantitative coronary angiography.

restenosis rates were similar; 12.7% (7 of 55; including 4 total occlusions) in the irradiated group versus 13.2% (7 of 53) in the control group. There was one patient with peri-stent restenosis in the control group (proximal edge), increasing restenosis to 15.1%, and none in the irradiated group. The location of the MLD in patients with restenosis at follow up is presented in Figure 3.

If the three lesions that did not receive the irradiation allocated treatment were deregistered from the intention-to-treat analysis (per protocol analysis), then the late loss was reduced to 0.38 ± 0.71 mm and the restenosis rate to 9.6%. Irradiation showed a beneficial effect in the intention-to-treat group on the late luminal loss at the proximal edge (Table 2).

**ANALYZED VESSEL SEGMENT.** At follow-up in the irradiated group, four additional sites with a diameter stenosis >50% were found in the EIRS, whereas four other restenotic sites were located at the edges of the EIRS (dose fall-off segments; one proximal and three distal). This resulted in an overall restenosis rate of 27.3%, whereas the restenosis rate in the control group remained 15.1%, p = 0.16 (no restenosis outside the stented and peri-stent segments) (Fig. 3).

**TOTAL OCCLUSIONS.** Overall, six patients presented with a late total occlusion (>30 days), four within the time window of angiographic follow-up (180 days ± 30 days; 103, 158, 169, and 171 days after irradiation) and two later (270 and 269 days after irradiation). In an intention-to-treat analysis, all six patients (10.9% per lesion) were in the irradiated group (p = 0.03). In a per-protocol analysis, five (9.6%)

were in the irradiated group, and one (1.8%) was in the control group (p = 0.10). All occlusions occurred within the stented segment. The two patients with occlusions outside the time window of the angiographic follow-up were not included in the QCA results at six months (Table 2). If included, the late loss and restenosis rates in the irradiated group were 0.51 ± 0.85 mm and 16.4%, respectively. There were no patients with a sub-acute thrombosis within the first 30 days after the procedure. Of the six total occlusions, two were late thrombotic (presented as acute MIs) and four were silent. Four of the six patients underwent repeat revascularization (one surgical and three percutaneous).

**INCIDENCE OF GM AND LOCATION OF RESTENOSIS WITH RESPECT TO THE IRRADIATED SEGMENT.** All 55 vessels were interpretable for the ascertainment of GM and/or location of restenosis outside the stent and peri-stent segments. The average length of GM was 4.68 ± 1.80 mm, with a range of 1.92 to 7.65 mm. There were 12 (21%) vessels with documented GM (10 proximal and 2 distal). Of these, one vessel was occluded, and three had a diameter stenosis >50%. Two of these were related because of the GM (13% of the overall restenosis observed in the irradiated group), and one showed progression of a pre-existing plaque proximal (12.12 mm) to the irradiated area. Sixty percent of the GM (7 of 12 vessels) were related to post-radiation intervention because of complications (persistent spasm, local thrombus formation, edge dissection) and the other 40% (5 of 12) was the result of inappropriate coverage of the stented segment by the radiation source. All the later cases were marginal, and they were not related to restenosis.

**Table 3.** IVUS Analyses (Intention to Treat)

|  |  | Irradiation (57 Lesions) | No Irradiation (57 Lesions) | p* |
|---|---|---|---|---|
| Stent |  |  |  |  |
| Stent length (mm) | Post | 18.2 ± 1.2 | 18.3 ± 1.8 | 0.60 |
| Stent volume (mm$^3$) | Post | 156 ± 43 | 160 ± 45 | 0.69 |
| Neo-intimal volume (mm$^3$) | F/Up | 10 ± 12 | 36 ± 26 | <0.001 |
| Change in PBS volumes (mm$^3$) | F/Up | 24 ± 28 | 14 ± 37 | 0.06 |
| Obstruction volume (%) | F/Up | 5 ± 6 | 21 ± 14 | <0.001 |
| Proximal edge |  |  |  |  |
| Change in EEM |  | 4.45 ± 15.82 | 0.49 ± 10.85 | 0.23 |
| Change in plaque volume (mm$^3$) |  | 5.28 ± 13.77 | 2.40 ± 9.04 | 0.31 |
| Change in luminal volume (mm$^3$) |  | −0.84 ± 12.10 | −1.96 ± 12.77 | 0.71 |
| Distal edge |  |  |  |  |
| Change in EEM |  | 4.36 ± 9.33 | 0.91 ± 9.89 | 0.15 |
| Change in plaque volume (mm$^3$) |  | 6.93 ± 7.41 | 1.73 ± 6.64 | 0.004 |
| Change in luminal volume (mm$^3$) |  | −2.56 ± 9.27 | −0.82 ± 10.67 | 0.48 |

*Student $t$ test.
EEM = external elastic membrane; F/Up = follow-up; IVUS = intravascular ultrasound; PBS = plaque volume behind the stent struts.

**IVUS.** The serial IVUS volumetric analysis confirmed the inhibition of the intra-stent neo-intimal hyperplasia within the irradiated group when compared with control (10 ± 12 mm$^3$ vs. 36 ± 26 mm$^3$; p < 0.001) with a concomitant reduction of the percentage volume obstruction from 21 ± 14% to 5 ± 6%; p < 0.001 (Table 3).

In addition, the change in the plaque behind the stent struts was greater in the irradiated group (p = 0.06) than in the control. However, at the proximal and distal edges of the irradiated group, there was an increase in plaque volume accompanied by a compensatory increase in the external elastic membrane volume (expansive remodeling), whereas both plaque and external elastic membrane volumes remained unchanged in the control group. The final result was that the luminal volume remained unchanged in both groups at follow-up.

**MACE.** Table 4 shows the hierarchical ranking of MACE up to 12 months as well as the incidence of revascularization procedures (event per patient and total count of events). With the exception of the target lesion revascularization, the control group scored better than the irradiated group because of less frequent restenosis outside the target site in either the irradiated segment or the target vessel segment. The MACE-free survival curves are presented in Figure 4.

## DISCUSSION

The premises of the present trial were that in the stent era, with more than 85% to 90% of patients being stented, radiotherapy treatment has to demonstrate its efficacy as an adjunct to stent treatment of de novo lesions for primary

**Table 4.** Most Severe (Hierarchical) MACE, Revascularization Procedures (Event Per Patient), and Total Count of Cardiac Events Up to 12 Months

|  | Irradiation (n = 54 Patients) | No Irradiation (n = 58 Patients) | p |
|---|---|---|---|
| Death, n (%) | 0 (0.0) | 0 (0.0) | 0.36† |
| Myocardial infarction |  |  |  |
| Q-wave, n (%) | 3 (5.6) | 0 (0.0) |  |
| Non−Q-wave, n (%) | 3 (5.6) | 3 (5.2) |  |
| Revascularization procedures |  |  |  |
| CABG, n (%) | 0 (0.0) | 0 (0.0) |  |
| TLR RPTCA, n (%) | 2 (3.7) | 5 (8.6) |  |
| TVSR, non-TLR RPTCA, n (%) | 6 (11.1) | 1 (1.7) |  |
| TEVR, non-TLR, non-TVSR RPTCA, n (%) | 0 (0.0) | 1 (1.7) |  |
| MACE, n (%)* | 14 (25.9) | 10 (17.2) | 0.36‡ |
| Revascularization procedures, n (%) (CABG and PTCA, event per patient) | 11 (20.4) | 7 (12.1) | 0.31‡ |
| Total count of events, n | 19 | 10 | 0.09§ |

*Includes death, myocardial infarction, and revascularization. †Wilcoxon rank sum test. ‡The Fisher exact test (two-tail). §The student $t$ test. Total epicardial vessel revascularization (TEVR) is defined as a revascularization of any segment of the coronary artery that was in physical contact with any component (guiding catheter, guidewire, balloon catheter, or stent) of the angioplasty hardware during the initial (allocated) procedure. Target vessel segment revascularization (TVSR) is defined as a revascularization occurring within the treated vessel segment as defined by angiographic core laboratory analysis.
CABG = coronary artery bypass graft; MACE = major adverse cardiac events; PTCA = percutaneous transluminal coronary angioplasty; TLR = target vessel revascularization; RPTCA = repeat PTCA.
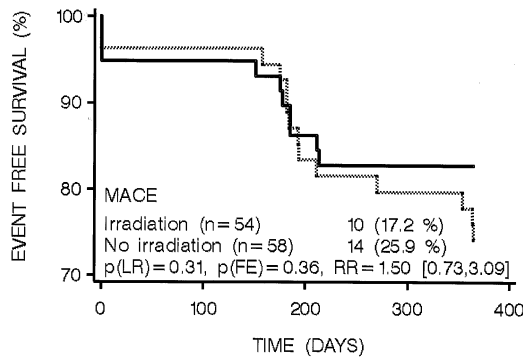
**Figure 4.** Event-free survival curves (Kaplan-Meier) at one year for the control and irradiated patients. MACE = major adverse cardiac and cerebrovascular events; p(FE) = p value Fisher exact test; p(LR) = p value log rank test; RR = relative risk.

prevention of restenosis. A large percentage of the balloon "geographic miss" cases are the result of balloon dilation applied before or after stenting; to avoid this phenomenon, a strategy of direct stenting with post-dilation performed strictly inside the stent was mandated before any randomization. Also, radiation treatment had to be performed as the last interventional procedure.

An IVUS investigation was performed after stent deployment to exclude incomplete deployment and apposition and/or edge dissection. A centering delivery system and IVUS-guided dosimetry of 20 Gy at 1 mm in the artery wall were used to theoretically preclude any radiation failure due to an insufficient dose administration and/or inhomogeneous dose distribution. An effective irradiation source length (32 mm) almost twice as long as the stent length (18 mm) was used to ensure adequate coverage of the lesion. Anti-thrombotic peri-procedural protection with glycoprotein IIb/IIIa inhibitors was systematically applied, and prolongation of the dual anti-platelet treatment was mandated for the prevention of late occlusion.

The main observations made in this study are the following: In-stent neo-intimal proliferation and restenosis are significantly reduced by beta irradiation. Peri-stent edge stenoses are eliminated by proper procedural technique and increased length of irradiation. Despite all efforts to reduce vascular damage and GM, total vessel analysis documents new stenosis toward the edges of the radioactive source (four within the effective irradiated segment, four at the edges). Despite peri-procedural administration of abciximab and thienopyridin for 11 months, vascular brachytherapy in patients with new stent implantation is associated with an excess of late coronary occlusion.

**Previous observational and randomized trials with beta-brachytherapy for de novo lesions.** The Proliferation REduction with Vascular ENergy Trial (PREVENT) also used a centered beta-emitting $^{32}$P source wire. In this small placebo-controlled, dose-finding study, the clinical and angiographic outcome was better in the irradiated patients (21). However, edge restenosis reduced the overall clinical benefit of radiotherapy. A 10% incidence of late vessel

occlusion also was reported with the one-month administration of double anti-platelet therapy.

In the Beta Radiation In Europe (BRIE) registry, 149 patients received 14Gy of beta radiation. Restenosis and MACE rates were 34% (9). In this trial, the problem of edge restenosis was related to the occurrence of GM (16). A 5.7% late vessel occlusion rate was reported, and the prolongation of anti-platelet treatment reduced its incidence. Patients that received a new stent in combination with radiation had worse clinical and angiographic outcomes than patients who were treated with balloon angioplasty and radiotherapy. The same was observed during the European Dose-Finding study (8).

The BetaCath trial was the largest randomized trial of beta radiation and stenting in de novo lesions (951 patients). It failed to show any difference in the primary end point in the radiation arm compared with the control arm (10). The late vessel thrombosis, edge restenosis, and the incompatibility of radiation with the use of stents for de novo lesions were the main lessons learned from this study. However, this negative result could be attributed to the lack of source centering, low prescription radiation dose, and the high incidence of GM.

**Edge restenosis.** Restenosis at the edges of the radioactive source was first described after radioactive stent implantation and (25) was seen subsequently in all brachytherapy trials. By IVUS, edge restenosis is a combination of increase in plaque volume without adaptive remodeling (26,27).

In concordance with known cell biological effects and animal data, low-dose radiation at the extremities of the source (dose fall-off) and angioplasty-induced vessel injury, referred to as "geographical miss," seem to play a key role in edge restenosis and treatment failure for beta (16) and gamma (28) brachytherapy. The fall-off dose at the source edges is an inherent characteristic of all sources, beta or gamma.

**Safety margins.** The safety margins after brachytherapy for avoidance of GM and edge restenosis have not yet been defined. Many factors, such as the extent of the peri-vascular injury (up to 10 mm away from a microscopic point of view) (29), the barotrauma caused by the balloons (up to 2.5 mm away from the actual stent margins) (30), the source displacement during the cardiac cycle (up to 5.4 mm) (31), and the fall-off dose at the margins of each source, must be considered.

It has been proposed that for an 18-mm lesion treated with a 20-mm balloon, a 39-mm iridium source should be used (32). In an animal model, a safety margin of 14.5 mm was sufficient to eliminate edge restenosis (33). Recently a 10-mm safety margin per vessel was found to have 95% specificity for avoidance of GM (34). As a simple rule, a ratio of one to two for the lesion to source length is advised. This advice was applied in the present trial, with the result of eliminating any significant loss in the peri-stent segment (5 mm proximal, 5 mm distal). However, eight sites of restenosis were documented around the edges of the irradiated area. The physio-pathological mechanism of narrowing remains elusive because no injury has been imparted on this vessel wall segment, and

the spiraled balloon of the radiation therapy delivery system cannot be implicated in a potential traumatic injury, because it is slightly undersized, inflated at low pressure, and shorter than the radioactive source (centering balloon length 32 mm and radiation source length 40 mm [2 × 20 mm]). The only remaining explanatory hypothesis is the potential stimulating effect of a low dose on a pre-existing atherosclerotic plaque (35). Low-dose radiation (±2 Gy) has been shown to potentiate cellular metabolic activities and immunological responses in various tissues (36–39).

**Late vessel occlusion.** In the first brachytherapy trials, the phenomenon of late occlusion, silent or symptomatic, of the irradiated vessel became apparent (15). Initial clinical trials prescribed a combined anti-thrombotic treatment (aspirin and clopidogrel or ticlopidine) for two to four weeks after irradiation. First, they reported that most events occurred after discontinuation of the double anti-platelet treatment (9). In consequence, prolonged combined anti-thrombotic treatment was recommended. Two trials have addressed the issue of prolonged anti-platelet treatment for the prevention of late occlusion/thrombosis. In the Washington Radiation for In-Stent Restenosis trial (WRIST) (18), clopidogrel and aspirin were prescribed for 6 months (WRIST PLUS), and in WRIST 12 (19) for 12 months. Both showed good results at 6 months follow-up, but at 15 months, the incidence of occlusion/thrombotic rates were unacceptably high: 15.9% in WRIST PLUS and 13.5% in WRIST 12. Second, they reported that new stent implantation was related to late thrombosis both in de novo (40) and restenotic lesions (9,10).

In the present study, six late occlusions occurred despite the use of prolonged dual anti-platelet treatment. Poor compliance with anti-platelet medication, edge dissection, and incomplete stent apposition at baseline were excluded as direct mechanisms of thrombosis or occlusion. The most likely explanation is long-term endothelial dysfunction and delayed vascular healing, two established drawbacks of vessel irradiation previously documented in animal models (41).

**Study limitations.** This study is a well-randomized study but not a double-blind trial, and the effect of a sham source on injured coronary segments has not been evaluated. Stent implantation was considered as the only source of injury. Minor injuries from guiding catheters, guide wires, or the radiation-centering catheter cannot be completely ruled out.

**Conclusions.** Optimized application of vascular brachytherapy with adequate coverage of vascular injury and use of IVUS-guided dosimetry did succeed in preventing in-stent neo-intimal proliferation and peri-stent edge restenosis. However, the lower doses that are delivered at the fall-off zones, which is a phenomenon inherent in any brachytherapy source (short or long), seems to promote the progression of pre-existing plaque and results in new stenoses toward the edges of the irradiated segment. The increased radiation source length and dose were most likely responsible for the observed excess in vessel thrombosis despite prolonged anti-platelet medication. This narrow therapeutic window

precludes any use of brachytherapy as a therapeutic tool for the primary prevention of restenosis in de novo lesions treated with bare metal stents.

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