

CATHETER-BASED RADIOTHERAPY TO INHIBIT RESTENOSIS
AFTER CORONARY STENTING

PAUL S. TEIRSTEIN, M.D., VINCENT MASSULLO, M.D., SHIRISH JANI, PH.D., JEFFREY J. POPMA, M.D., GARY S. MINTZ, M.D., ROBERT J. RUSSO, M.D., PH.D., RICHARD A. SCHATZ, M.D., ERMINIA M. GUARNERI, M.D., STEPHEN STEUTERMAN, M.S., NANCY B. MORRIS, R.N., MARTIN B. LEON, M.D., AND PRABHAKAR TRIPURANENI, M.D.

ABSTRACT

Background In animal models of coronary restenosis, intracoronary radiotherapy has been shown to reduce the intimal hyperplasia that is a part of restenosis. We studied the safety and efficacy of catheter-based intracoronary gamma radiation plus stenting to reduce coronary restenosis in patients with previous restenosis.

Methods Patients with restenosis underwent coronary stenting, as required, and balloon dilation and were then randomly assigned to receive catheter-based irradiation with iridium-192 or placebo. Clinical follow-up was performed, with quantitative coronary angiographic and intravascular ultrasonographic measurements at six months.

Results Fifty-five patients were enrolled; 26 were assigned to the iridium-192 group and 29 to the placebo group. Angiographic studies were performed in 53 patients (96 percent) at a mean (\pm SD) of 6.7 ± 2.2 months. The mean minimal luminal diameter at follow-up was larger in the iridium-192 group than in the placebo group (2.43 ± 0.78 mm vs. 1.85 ± 0.89 mm, $P = 0.02$). Late luminal loss was significantly lower in the iridium-192 group than in the placebo group (0.38 ± 1.06 mm vs. 1.03 ± 0.97 mm, $P = 0.03$). Angiographically identified restenosis (stenosis of 50 percent or more of the luminal diameter at follow-up) occurred in 17 percent of the patients in the iridium-192 group, as compared with 54 percent of those in the placebo group ($P = 0.01$). There were no apparent complications of the treatment.

Conclusions In this preliminary, short-term study of patients with previous coronary restenosis, coronary stenting followed by catheter-based intracoronary radiotherapy substantially reduced the rate of subsequent restenosis. (N Engl J Med 1997;336:1697-703.)

©1997, Massachusetts Medical Society.

DESPITE its wide acceptance, coronary angioplasty is limited by rates of restenosis of 30 to 60 percent.¹ In recent years, much has been learned about the mechanism of restenosis, which can be divided into two broad components. The first component, recoil and remodeling, involves the mechanical collapse and constriction of the treated vessel. The second component, intimal hyperplasia, is the proliferative response to injury, which consists largely of smooth-muscle cells and matrix formation.²⁻⁵ Coronary stents provide a luminal scaffolding that virtually elimi-

nates recoil and remodeling and have been shown to reduce the likelihood of restenosis by approximately 30 percent.^{6,7} Stents, however, do not decrease and in fact increase the proliferative component of restenosis.

In recent years, several clinical trials using local, catheter-based ionizing radiation have demonstrated significantly reduced neointimal proliferation in animal models of restenosis.⁸⁻²⁰ Encouraged by these reports, we designed a double-blind, placebo-controlled, randomized trial to test this new treatment in patients with stented coronary arteries. The objective of our trial was to determine the safety and efficacy of catheter-based intracoronary gamma radiation to reduce intimal hyperplasia after coronary stenting in patients with previous restenosis.

METHODS

The trial was approved by both the Scripps Clinic Human Subjects Committee and the Radiation Safety Committee. Informed consent was obtained from each patient before enrollment in the trial.

The criteria for enrollment included a target lesion in a restenotic coronary artery that either already contained a stent or was a candidate for stent placement, and previous treatment of the lesion more than four weeks before enrollment. The reference vessel had to be between 3 and 5 mm in diameter, with a target lesion that was 30 mm or less in length. Patients were excluded if the coronary-revascularization procedure had been unsuccessful, a suboptimal result had been achieved, a stent had been implanted as an emergency procedure, or there was angiographic evidence of thrombus in the target lesion.

Procedure

The patients were given aspirin (325 mg), intracoronary nitroglycerin, and intravenous heparin in a dose sufficient to maintain an activated clotting time of more than 300 seconds. If the lesion was not already stented, single or, if required, tandem coronary stenting (Johnson and Johnson Interventional Systems, Warren, N.J.) was performed. If stents had been placed previously, redilation was undertaken, and, in many cases, additional stents were placed within the original stent to optimize the angiographic result. In all cases, high-pressure (≥ 18 atm) balloon dilations were performed in an attempt to achieve a 0 percent residual stenosis within the stented segment. Intravascular ultrasonography was then performed with the use of a 3.2-French catheter (Cardiovas-

From the Divisions of Cardiovascular Diseases and Radiation Oncology, Scripps Clinic and Research Foundation, La Jolla, Calif. (P.S.T., V.M. S.J., R.J.R., R.A.S., E.M.G., S.S., N.B.M., P.T.); and the Division of Cardiology, Washington Hospital Center, Washington, D.C. (J.J.P., G.S.M., M.B.L.). Address reprint requests to Dr. Teirstein at the Division of Cardiovascular Diseases, SW-206, Scripps Clinic and Research Foundation, 10666 N. Torrey Pines Rd., La Jolla, CA 92037.

cular Imaging Systems, Sunnyvale, Calif.) and a motorized pull-back device at 0.5 mm per second to examine the stented vessel segment. The intravascular ultrasonographic examination ensured that an optimal result had been achieved, provided a basis for comparison at six months, and allowed an assessment of the lesion's geometry for dosimetric calculation by the radiation therapist (see below). A 4-French infusion catheter (United States Catheter Instruments, Billerica, Mass.) was then inserted to span the stented region. To reduce the risk of thrombus formation, heparinized saline was administered through the guide catheter, and ioxaglate (Hexabrix, Mallinckrodt Medical, St. Louis), an ionic contrast material, was administered.

The patient was then randomly assigned to receive a 0.76-mm (0.03-in.) ribbon (Best Industries, Springfield, Va.) containing sealed sources of either iridium-192 or placebo. All study personnel except one physicist from the Division of Radiation Oncology and one research nurse from the Division of Cardiology, who were not involved in the end-point analysis, were unaware of the randomization code. The radiation oncologist inserted the study ribbon into the infusion catheter. During this part of the procedure, the catheterization laboratory was cleared of all other personnel. Precise fluoroscopic positioning of the study ribbon to span the stented segment was performed by both the radiation oncologist and the interventional cardiologist. A 25-mm (1-in.) lead shield (Alpha-Omega Services, Bellflower, Calif.) was placed between the patient and the control room before treatment, and a radiation-safety officer performed multiple measurements of radiation exposure from various points inside and outside the catheterization laboratory throughout the procedure. The ribbon was left in place for 20 to 45 minutes, as required to administer the prescribed dose; it was then removed by the radiation oncologist and placed in an adequately shielded container. The femoral sheaths were removed two to four hours after the procedure, and the patient was discharged the following morning with instructions to take aspirin (325 mg daily indefinitely) and, if new stents had been implanted, ticlopidine (250 mg twice daily for two weeks).

Dosimetry

Dosimetry was calculated in the following manner. A series of tomographic sections obtained by intravascular ultrasonography with the use of a motorized pull-back apparatus were scanned, and measurements were performed along the length of the stent. The distance between the center of the ultrasonographic catheter (equivalent to the position of the radiation source) and the leading edge of the tunica media (the target) was measured at 1-mm intervals along the stented segment of the artery. Maximal and minimal source-to-target distances were determined. The radiation oncologist and the physicist combined this information with the specific activity of the radioactive sources to determine the time required to deliver 800 cGy to the target farthest from the radiation source, with no more than 3000 cGy delivered to the target closest to the source.

Radioactive and Placebo Sources

Discrete, shorter lesions were treated with a ribbon 19 mm long containing five sources of iridium-192 or placebo. Each source was 3 mm long and separated from the next source by 1 mm. Longer lesions were treated with a similar ribbon, 35 mm long and containing nine sources.

Quantitative Angiographic Analysis

After the ribbon had been removed, intracoronary nitroglycerin was administered and angiography was performed in two orthogonal projections. At the follow-up examination, identical angiographic techniques were used. All procedural and follow-up cineangiograms were forwarded to the Washington Hospital Center Angiographic Core Laboratory for analysis by observers who were unaware of the treatment assignments. Selected serial cine-

frames, obtained from two unforeshortened projections and matched for position within the cardiac cycle with the use of side-by-side projectors, were digitized with a cinevideo converter, with the contrast-filled catheter used as the calibration standard. The diameter of the reference vessel, the minimal luminal diameter within the axial length of the stent, and the minimal luminal diameter along the axial length of the radiation sources were determined with the use of a validated edge-detection program (Cardiovascular Measurement System, Medis Medical Imaging Systems, Nuenen, the Netherlands)²¹ at base line, after the procedure, and at follow-up. These measurements were used for serial calculations of the minimal luminal diameter within the stent and at its border (the area beyond the stent but exposed to the radiation sources). The immediate luminal gain was defined as the minimal luminal diameter immediately after the procedure minus the minimal luminal diameter before the procedure (in millimeters), and the late luminal loss was defined as the minimal luminal diameter immediately after the procedure minus the minimal luminal diameter at follow-up. The late-loss index was defined as the late luminal loss divided by the immediate luminal gain. Binary restenosis was defined as stenosis of 50 percent or more of the luminal diameter at follow-up.

Intravascular Ultrasonographic Analysis

All ultrasonographic measurements were performed at an independent laboratory by one of us, who was unaware of the protocol and treatment assignments. Ultrasonographic studies were recorded on 12.7-mm (0.5-in.) high-resolution super VHS tape for off-line analysis. Motorized pullback of the transducer through a stationary imaging sheath was performed both immediately after the procedure and at follow-up. Computerized planimetry of ultrasonographic images at 1-mm axial increments along each stented segment permitted the measurement of cross-sectional areas of the stent, lumen, and intima (stent minus lumen). Stent, luminal, and intimal volumes were calculated with the use of Simpson's rule. The growth of tissue within the stent struts during the follow-up period was calculated as the intimal area (or volume) at follow-up minus the intimal area (or volume) immediately after the procedure.^{22,23}

End Points and Statistical Analysis

A successful procedure was defined as one resulting in less than 30 percent stenosis of the luminal diameter immediately after the procedure and successful delivery of iridium-192 or placebo for the prescribed time, without death, myocardial infarction, bypass surgery, or stent thrombosis within 30 days after the index procedure. Myocardial infarction was defined as an elevation of the MB fraction of creatine kinase to a value three times the upper limit of the normal range.

Clinical follow-up was performed at one and six months. All patients were requested to return for repeated coronary angiography and intravascular ultrasonographic examination at six months. Follow-up angiographic data obtained less than four months after the procedure were excluded unless restenosis was documented. Revascularization was repeated after follow-up angiography only if the patient had recurrent symptoms or a functional test demonstrating the presence of coronary ischemia.

Data were analyzed on an intention-to-treat basis. The predetermined primary end point was the late luminal loss and the late-loss index at six months, as measured by quantitative angiography. Secondary end points included clinical restenosis, defined as angiographic evidence of 50 percent or greater stenosis of the luminal diameter at six months, the need for revascularization of the target lesion at eight months, and a composite end point of death, myocardial infarction, and the need for repeated revascularization.

For the analysis of continuous data, two-tailed t-tests were used to assess differences between the two treatment groups. The results are expressed as means \pm SD. Categorical data were compared with the use of chi-square or Fisher's exact tests, except for

the composite clinical end point, which was analyzed by means of Kaplan–Meier survival curves, with differences between the two treatment groups compared with the use of a Wilcoxon test. Multiple logistic-regression analysis was used to assess the relation between angiographically identified restenosis (≥ 50 percent stenosis of the luminal diameter at the stent or stent border at follow-up) and multiple clinical and angiographic variables, including the number of stents placed, unstable angina, in-stent restenosis, diabetes, the diameter of the reference vessel, the post-procedural luminal diameter, and the location of the target lesion (vein graft, left anterior descending artery, or ostium).

Although approval was granted to enroll 100 patients, the study was terminated early by the Data Safety Monitoring Committee because an interim analysis showed significant differences in primary end points between the two groups that met prespecified rules for stopping the study.

RESULTS

Between March 24 and December 22, 1995, 55 patients were enrolled in the study; 26 were assigned to the iridium-192 group, and 29 to the placebo group. Base-line clinical and angiographic characteristics were similar in the two groups (Table 1). The mean number of previous occurrences of restenosis of the target lesion was 2.1 ± 1.4 in the iridium-192 group and 2.0 ± 1.3 in the placebo group (P not significant). Many patients had one or more base-line characteristics associated with an increased risk of restenosis, including diabetes, unstable angina, more than one previous restenosis, a target lesion in a vein graft, an ostial lesion, and a lesion length of 10 mm or more. These base-line characteristics were similar in the iridium-192 and placebo groups.

The mean time during which the iridium-192 ribbon was in place was 36 ± 7 minutes, and the mean specific activity of the iridium-192 was 3.6 ± 1.08 GBq (97.6 ± 29.2 mCi). The shortest mean distance from the source to the target was 1.02 ± 0.16 mm, resulting in the delivery of a mean maximal dose of 2651 ± 349 cGy. The longest mean source-to-target distance was 3.3 ± 0.47 mm, resulting in a mean minimal dose of 732 ± 83 cGy. Measurements of radiation exposure performed by the radiation-safety officer during treatment showed that the mean exposure was 1.19 ± 0.073 μ Sv per hour in the control room immediately adjacent to the catheterization laboratory and 132.3 ± 18.9 μ Sv per hour at the patient's right-hand side, where the radiation oncologist stood during the insertion of the study ribbon. Measurements performed during fluoroscopy associated with routine interventional cardiologic procedures in other patients showed mean radiation exposures of 0.236 ± 0.017 and 153.75 ± 143.95 μ Sv per hour, respectively. While positioning the study ribbon, the radiation oncologist was exposed to iridium-192 for less than five minutes per procedure, and during the final positioning, the interventional cardiologist was exposed for less than one minute. It should be noted that gamma radiation emitted by iridium-192 is not effectively blocked by lead aprons worn by catheterization personnel.

TABLE 1. BASE-LINE CLINICAL AND ANGIOGRAPHIC CHARACTERISTICS OF 55 PATIENTS WITH RESTENOSIS ASSIGNED TO RECEIVE IRIIDIUM-192 OR PLACEBO.*

| CHARACTERISTIC | IRIDIUM-192 GROUP (N=26) | PLACEBO GROUP (N=29) |
|--|-----------------------------|-------------------------|
| Age (yr) | 69.8 \pm 9.7 | 68.8 \pm 10.8 |
| Male sex | 73 | 76 |
| Elevated cholesterol level | 54 | 59 |
| Diabetes mellitus | 27 | 41 |
| Unstable angina | 42 | 55 |
| Previous myocardial infarction | 38 | 34 |
| History of hypertension | 65 | 69 |
| Previous restenoses | | |
| No. | 2.1 \pm 1.4 | 2.0 \pm 1.3 |
| >1 | 52 | 55 |
| >2 | 23 | 24 |
| In-stent restenosis | 62 | 62 |
| No. of stents in target lesion | | |
| 1 | 38 | 45 |
| 2 | 62 | 55 |
| Left ventricular ejection fraction (%) | 46.7 \pm 19.8 | 48.9 \pm 16.3 |
| Location of target lesion | | |
| Saphenous vein | 23 | 31 |
| Left anterior descending artery | 31 | 38 |
| Ostial | 31 | 41 |
| Aorto-ostial | 12 | 17 |
| Lesion length (mm) | 12.89 \pm 7.05 | 11.86 \pm 6.77 |
| Lesion length \geq 10 mm | 58 | 45 |

*Plus-minus values are means \pm SD. All other values are percentages of patients.

The angiographic results were excellent in both groups (Table 2), with an immediate luminal gain of 1.67 ± 0.67 mm in the iridium-192 group and 1.83 ± 0.97 mm in the placebo group (P not significant) and postprocedural stenosis of 7 ± 22 percent and 5 ± 23 percent, respectively (P not significant). In one patient in the placebo group, the study ribbon could not be advanced completely across the target region because of excessive tortuosity of the vessel. At 30 days, the initial procedure was successful in 96 percent of the patients in the iridium-192 group and 97 percent of those in the placebo group (P not significant). One patient in the iridium-192 group, who stopped taking ticlopidine on postoperative day 3, sustained a myocardial infarction due to stent thrombosis on day 18. There were no other myocardial infarctions and no deaths, and none of the patients underwent bypass surgery or had bleeding complications requiring blood transfusion or surgical intervention.

Follow-up

Angiographic follow-up data were obtained at six months in all patients except the patient in the iridium-192 group with stent thrombosis and one patient in the placebo group who refused follow-up angiography and died after eight months from cardiac arrest. Angiographic data from one additional

TABLE 2. ANGIOGRAPHIC RESULTS AT SIX MONTHS.*

| VARIABLE | IRIDIUM-192 GROUP (N=24) | PLACEBO GROUP (N=28) | P VALUE |
|---|-----------------------------|-------------------------|---------|
| Before the procedure | | | |
| Reference vessel (mm) | 2.88±0.58 | 2.78±0.47 | 0.50 |
| Minimal luminal diameter (mm) | 1.10±0.46 | 1.03±0.46 | 0.60 |
| Stenosis (% of luminal diameter) | 62±14 | 62±18 | 0.89 |
| After the procedure | | | |
| Reference vessel (mm) | 3.13±0.76 | 3.03±0.53 | 0.61 |
| Minimal luminal diameter (mm) | 2.82±0.60 | 2.88±0.83 | 0.78 |
| Stenosis (% of luminal diameter) | 7±22 | 5±23 | 0.74 |
| At six months | | | |
| Reference vessel (mm) | 3.08±0.75 | 2.94±0.49 | 0.41 |
| Minimal luminal diameter (mm) | 2.43±0.78 | 1.85±0.89 | 0.02 |
| Stenosis (% of luminal diameter) | 17±30 | 37±26 | 0.01 |
| Change in minimal luminal diameter† | | | |
| Immediate luminal gain (mm) | 1.67±0.67 | 1.83±0.97 | 0.49 |
| Late luminal loss (mm) | 0.38±1.06 | 1.03±0.97 | 0.03 |
| Late-loss index | 0.12±0.63 | 0.60±0.43 | <0.01 |
| Restenosis of stent and border (% of patients) | 17 | 54 | 0.01 |
| Restenosis of stent only (% of patients) | 8 | 36 | 0.02 |

*Plus-minus values are means ±SD.

†The immediate luminal gain is the minimal luminal diameter immediately after the procedure minus the diameter before the procedure. The late luminal loss is the minimal luminal diameter immediately after the procedure minus the diameter at follow-up. The late-loss index is the late luminal loss divided by the immediate luminal gain.

patient (in the iridium-192 group) were excluded from the analysis because one month after the study procedure a lesion proximal to the target lesion was treated with a stent that partly overlapped the target lesion, making angiographic analysis impossible. Follow-up angiography at 25 weeks showed no restenosis in this patient.

The mean time to angiographic follow-up for the entire cohort was 6.7±2.2 months (6.9±1.8 and 6.4±2.7 months in the iridium-192 and placebo groups, respectively; P not significant). Angiographic indexes of restenosis were markedly different in the two groups (Table 2). Late luminal loss was significantly lower in the iridium-192 group than in the placebo group (0.38±1.06 vs. 1.03±0.97 mm; P=0.03). Notably, the index of late luminal loss (a sensitive measure of the ability of a revascularization procedure to preserve the postprocedural luminal diameter) was significantly lower in the iridium-192 group (0.12±0.63 vs. 0.60±0.43; P<0.01). The cumulative distributions of the minimal luminal diameter before and after the procedure and at follow-up in the two groups are shown in Figure 1. The curves overlap before and after the procedure, whereas at follow-up, the curve for the iridium-192 group is shifted to the right. The mean minimal luminal diameter at follow-up was larger in the iridium-192 group than in the placebo group (2.43±0.78 vs. 1.85±0.89 mm, P=0.02).

No aneurysms were observed on any follow-up angiograms in either the iridium-192 group or the placebo group. Angiographic restenosis (≥50 per-

cent stenosis of the luminal diameter) either within the stent or at its border (outside the stent but spanned by the study ribbon) was observed in 17 percent of the patients in the iridium-192 group, as compared with 54 percent of those in the placebo group (P=0.01). Restenosis limited to the stented segment occurred in 8 percent of the iridium-192 group but in 36 percent of the patients in the placebo group (P=0.02). A multiple logistic-regression analysis showed that treatment with iridium-192 was the only important predictor of freedom from angiographic restenosis (Wald chi-square = 4.9, P=0.03).

The angiographic results were confirmed by the independent analysis of intravascular ultrasonographic studies (Table 3). These studies showed no significant change in the stent area or volume between the period immediately after the procedure and the follow-up examination at six months. The decrease in the mean luminal cross-sectional area was smaller in the iridium-192 group than in the placebo group (0.7±1.0 vs. 2.2±1.8 mm², P<0.01), as was the cross-sectional area of tissue growth within the stent struts (0.7±0.9 vs. 2.2±1.8 mm², P<0.01). The decrease in the luminal volume was also smaller in the iridium-192 group (16.4±24.0 vs. 44.3±34.6 mm³, P=0.01), as was the volume of tissue growth within the stent struts (15.5±22.7 vs. 45.1±39.4 mm³, P=0.01).

Clinical follow-up data were obtained for all patients at a mean of 12.2±2.9 months (12.0±2.8 months in the iridium-192 group and 12.2±3.1

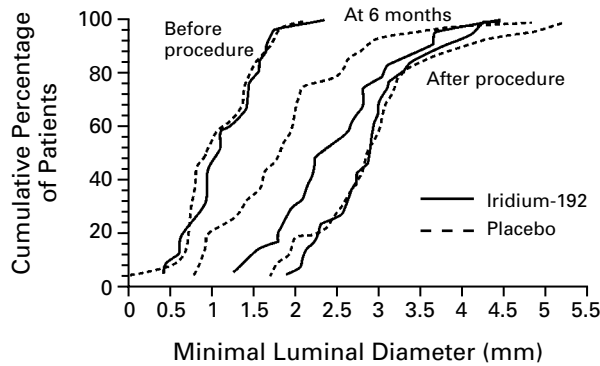


Figure 1. Cumulative Distribution Curves for the Minimal Luminal Diameter before and Immediately after Revascularization and at Six Months in 55 Patients with Restenosis Assigned to Receive Iridium-192 or Placebo.

The minimal luminal diameter at six months was larger in the iridium-192 group than in the placebo group (2.43 ± 0.78 vs. 1.85 ± 0.89 mm, $P=0.02$). The curves are similar for the two groups before and after the procedure, but at six months, the curve for the iridium-192 group is shifted to the right.

TABLE 3. INTRAVASCULAR ULTRASONOGRAPHIC RESULTS AT SIX MONTHS.

| VARIABLE | IRIDIUM-192 GROUP (N = 18) | PLACEBO GROUP (N = 18) | P VALUE |
|---|----------------------------|------------------------|---------|
| Change in mean stent cross-sectional area (mm^2) | 0.0 ± 0.3 | -0.1 ± 0.2 | 0.25 |
| Decrease in mean luminal cross-sectional area (mm^2) | 0.7 ± 1.0 | 2.2 ± 1.8 | <0.01 |
| Cross-sectional area of tissue growth (mm^2) | 0.7 ± 0.9 | 2.2 ± 1.8 | <0.01 |
| Change in mean stent volume (mm^3) | 0.6 ± 6.5 | -1.6 ± 4.7 | 0.25 |
| Decrease in mean luminal volume (mm^3) | 16.4 ± 24.0 | 44.3 ± 34.6 | 0.01 |
| Volume of tissue growth (mm^3) | 15.5 ± 22.7 | 45.1 ± 39.4 | 0.01 |

TABLE 4. CLINICAL EVENTS AT 12 MONTHS.

| EVENT | IRIDIUM-192 GROUP (N = 26) | PLACEBO GROUP (N = 29) | P VALUE* |
|--|----------------------------|------------------------|----------|
| | no. of patients (%) | | |
| Death | 0 | 1 (3) | NS |
| Myocardial infarction | 1 (4) | 0 | NS |
| Revascularization of target lesion | 3 (12) | 13 (45) | 0.01 |
| Death, myocardial infarction, stent thrombosis, or revascularization of target lesion | 4 (15) | 14 (48) | 0.01 |
| Death, myocardial infarction, stent thrombosis, or revascularization of target or other lesion | 5 (19) | 18 (62) | <0.01 |

*NS denotes not significant.

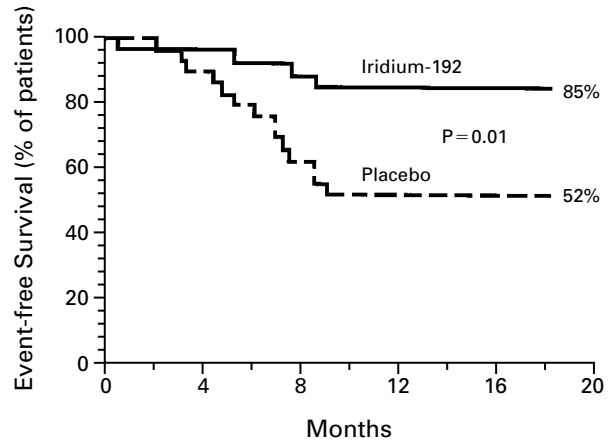


Figure 2. Kaplan-Meier Curves for Event-free Survival in the Iridium-192 and Placebo Groups.

Event-free survival was defined as survival without myocardial infarction or repeated revascularization of the target lesion. The curves diverge at three months, and the difference increases over the next six months.

months in the placebo group, P not significant). The difference in the rates of angiographic restenosis in the two groups was consistent with the difference in the proportion of patients undergoing revascularization of the target lesion (12 percent in the iridium-192 group and 45 percent in the placebo group, $P=0.01$) (Table 4). Significantly fewer patients reached the composite clinical end point (death, myocardial infarction, stent thrombosis, and revascularization of the target lesion) in the iridium-192 group (15 percent vs. 48 percent, $P=0.01$) (Fig. 2).

DISCUSSION

Our study group included patients at particular risk for restenosis because of such factors as the presence of diabetes, unstable angina, long lesions, and vein-graft or ostial lesions. In addition, all our patients had had at least one previous episode of restenosis, further increasing the risk of subsequent cardiac events.²⁴⁻²⁶ The patients treated with iridium-192 gamma radiation had a striking reduction in restenosis, as compared with those receiving placebo. This reduction was similar for the angiographic, ultrasonographic, and clinical end points. An independent, blinded analysis performed off site showed a 60 to 80 percent reduction in all the angiographic indexes of restenosis. Notably, the late-loss index, a sensitive measure of the proliferative response to injury,³ was reduced from 0.6 to 0.12 ($P<0.01$). Thus, of more than 50 clinically tested therapeutic agents,^{1,27} gamma radiation with the use of iridium-192 is one of the first found to reduce the rate of restenosis after coronary angioplasty.

The results of the independent, blinded, off-site ultrasonographic analysis in our study were consis-

tent with the results of the angiographic analysis and shed light on one mechanism of action of iridium-192. At six months, the stent volumes in both groups were similar to the volumes immediately after revascularization, whereas the volume of tissue growth within the stent struts (presumably neointimal formation) was 64 percent lower in the iridium-192 group. This finding confirms and extends previous observations that restenosis within stented coronary arteries is a consequence not of stent compression but of neointimal proliferation through the stent struts, which encroaches on the lumen.^{22,23,28,29}

Iridium-192 radiation also significantly reduced the frequency of clinical events. The frequency of revascularization of the target lesion (12 percent in the iridium-192 group and 45 percent in the placebo group, $P=0.01$) was reduced by 73 percent. Occurrence of the composite clinical end point was similarly reduced. However, it should be noted that the observed reduction in clinical events was almost entirely accounted for by the higher frequency of revascularization of the target lesion in the placebo group, which in turn was influenced by the protocol-mandated angiography at six months. Thus, the differences in the clinical outcome may have been artificially increased by the study design.

Data from previous clinical trials of intravascular radiation therapy to reduce restenosis are limited. In one study, Bottcher and colleagues^{30,31} used iridium-192 with angioplasty plus stent implantation in 13 patients with femoral-artery restenosis. Clinical follow-up indicated no recurrent restenosis over a period of 3 to 27 months. Steidle³² also used iridium-192 with stent implantation in patients with femoral-artery stenosis. Over a seven-month follow-up period, reocclusion occurred in 2 of the 11 patients who received radiation and in 5 of the 13 who did not. Most recently, Condado et al.³³ used iridium-192 in 21 patients undergoing coronary angioplasty, and Urban et al.³⁴ used yttrium-90, a beta emitter, in 15 patients undergoing coronary angioplasty. Both studies were uncontrolled feasibility trials. The results are pending.

Limitations of the Study

These preliminary results must be viewed in the light of several factors. The most important is the unknown long-term effect of intracoronary gamma radiation delivered in this manner. Coronary arteries exposed to much higher doses of radiation (in multiple fractions administered to much larger volumes of tissue) used to treat cancers are associated with a small but finite risk of accelerated coronary disease over a period of 5 to 20 years.³⁵ Another factor is the exposure of sensitive distant tissues, such as sternal bone marrow and lymph nodes, to radiation, which we believe is mitigated by the low calculated dose (1.0 to 2.5 cGy) delivered at a distance of 5 to

10 cm from the iridium-192 sources used in this trial. In addition, further follow-up is required to ensure that the reduction in restenosis observed at six months in the iridium-192 group is maintained over time. This study also raises the practical question of how to protect hospital personnel from exposure to radiation. We took elaborate steps to provide protection from exposure. Although these steps were successful, the use of other isotopes that are less penetrating, such as beta emitters and beta-emitting radioactive stents, must be explored.

In this preliminary, short-term study of patients with previous coronary restenosis, stenting plus radiotherapy significantly reduced angiographic, ultrasonographic, and clinical indexes of restenosis. This benefit was achieved without an increase in adverse events at a mean follow-up of 12.2 ± 2.9 months. Gamma radiation with iridium-192 is thus a promising new treatment for patients with restenosis.

Supported in part by unrestricted grants from Johnson and Johnson Interventional Systems and SciMed Life Systems.

Dr. Teirstein owns patents on radiation-delivery catheters and is currently negotiating commercial interests in catheter-based radiation therapy.

We are indebted to Louis Gluck, M.D., physician, scientist, and pioneer, for his inspiration as our first patient treated with radiotherapy for restenosis; to Ronald A. Simon, M.D., James A. Koziol, Ph.D., and Sherry Mirakis, R.N., the members of the Data Safety Monitoring Committee; and to David A. Cloutier, B.S., Alexandra J. Lansky, M.D., and Samantha Russ, B.S., for their assistance in analyzing the data.

REFERENCES

1. Popma JJ, Califf RM, Topol EJ. Clinical trials of restenosis after coronary angioplasty. *Circulation* 1991;84:1426-36.
2. Kuntz RE, Safian RD, Levine MJ, Reis GJ, Diver DJ, Baim DS. Novel approach to the analysis of restenosis after the use of three new coronary devices. *J Am Coll Cardiol* 1992;19:1493-9.
3. Kuntz RE, Gibson CM, Nobuyoshi M, Baim DS. Generalized model of restenosis after conventional balloon angioplasty, stenting and directional atherectomy. *J Am Coll Cardiol* 1993;21:15-25.
4. Mintz GS, Popma JJ, Pichard AD, et al. Arterial remodeling after coronary angioplasty: a serial intravascular ultrasound study. *Circulation* 1996;94:35-43.
5. Mintz GS, Popma JJ, Pichard AD, et al. Intravascular ultrasound predictors of restenosis after percutaneous transcatheter coronary revascularization. *J Am Coll Cardiol* 1996;27:1678-87.
6. Serruys PW, de Jaegere P, Kiemeneij F, et al. A comparison of balloon-expandable-stent implantation with balloon angioplasty in patients with coronary artery disease. *N Engl J Med* 1994;331:489-95.
7. Fischman DL, Leon MB, Baim DS, et al. A randomized comparison of coronary-stent placement and balloon angioplasty in the treatment of coronary artery disease. *N Engl J Med* 1994;331:496-501.
8. Wiedermann J, Leavy J, Amols H, et al. Intracoronary irradiation acutely impairs endothelial and smooth muscle function as assessed by intravascular ultrasound. *Circulation* 1992;86:Suppl I:I-188. abstract.
9. Sheffer A, Eigler NL, Whiting JS, Litvack FI. Suppression of intimal proliferation after balloon angioplasty with local beta irradiation in rabbits. *J Am Coll Cardiol* 1993;21:Suppl A:185A. abstract.
10. Wiedermann JG, Marboe C, Amols H, Schwartz A, Weinberger J. Intracoronary irradiation markedly reduces restenosis after balloon angioplasty in a porcine model. *J Am Coll Cardiol* 1994;23:1491-8.
11. Waksman R, Robinson KA, Crocker IR, Smith R, Cipolla GD, King SB III. Effects of endovascular irradiation in a swine model of restenosis after angioplasty. *J Am Coll Cardiol* 1994;23:Suppl:473A. abstract.
12. Wiedermann JG, Marboe C, Amols H, Schwartz A, Weinberger J. Intracoronary irradiation: minimal effective dose for prevention of restenosis in swine. *Circulation* 1994;90:Suppl:I-59. abstract.

13. Mazur W, Ali NM, Dabaghi SF, et al. High dose rate intracoronary radiation suppresses neointimal proliferation in the stented and ballooned model of porcine restenosis. *Circulation* 1994;90:Suppl:I-652. abstract.
14. Wiedermann JG, Marboe C, Amols H, Schwartz A, Weinberger J. Intracoronary irradiation markedly reduces neointimal proliferation after balloon angioplasty in swine: persistent benefit at 6-month follow-up. *J Am Coll Cardiol* 1995;25:1451-6.
15. Waksman R, Robinson KA, Crocker IR, Gravanis MB, Cipolla GD, King SB III. Endovascular low-dose irradiation inhibits neointima formation after coronary artery balloon injury in swine: a possible role for radiation therapy in restenosis prevention. *Circulation* 1995;91:1533-9.
16. Waksman R, Robinson KA, Crocker IR, et al. Intracoronary radiation before stent implantation inhibits neointima formation in stented porcine coronary arteries. *Circulation* 1995;92:1383-6.
17. Hehrlein C, Gollan C, Dönges K, et al. Low-dose radioactive endovascular stents prevent smooth muscle cell proliferation and neointimal hyperplasia in rabbits. *Circulation* 1995;92:1570-5.
18. Verin V, Popowski Y, Urban P, et al. Intra-arterial beta irradiation prevents neointimal hyperplasia in a hypercholesterolemic rabbit restenosis model. *Circulation* 1995;92:2284-90.
19. Waksman R, Robinson KA, Crocker IR, et al. Intracoronary low-dose β -irradiation inhibits neointima formation after coronary artery balloon injury in the swine restenosis model. *Circulation* 1995;92:3025-31.
20. Laird JR, Carter AJ, Kufs WM, et al. Inhibition of neointimal proliferation with low-dose irradiation from a β -particle-emitting stent. *Circulation* 1996;93:529-36.
21. van der Zwet PMJ, Reiber JHC. A new approach for the quantification of complex lesion morphology: the gradient field transform: basic principles and validation results. *J Am Coll Cardiol* 1994;24:216-24.
22. Dussailant GR, Mintz GS, Pichard AD, et al. Small stent size and intimal hyperplasia contribute to restenosis: a volumetric intravascular ultrasound analysis. *J Am Coll Cardiol* 1995;26:720-4.
23. Hoffmann R, Mintz GS, Dussailant GR, et al. Patterns and mechanisms of in-stent restenosis: a serial intravascular ultrasound study. *Circulation* 1996;94:1247-54.
24. Teirstein PS, Hoover CA, Ligon RW, et al. Repeat coronary angioplasty: efficacy of a third angioplasty for a second restenosis. *J Am Coll Cardiol* 1989;13:291-6.
25. Meier B, King SB III, Gruentzig AR, et al. Repeat coronary angioplasty. *J Am Coll Cardiol* 1984;4:463-6.
26. Williams DO, Gruentzig AR, Kent KM, Detre KM, Kelsey SF, To T. Efficacy of repeat percutaneous transluminal coronary angioplasty for coronary restenosis. *Am J Cardiol* 1984;53:32C-35C.
27. Handley DA. Experimental therapeutics and clinical studies in (re)stenosis. *Micron* 1995;26:51-68.
28. Mehran R, Mintz GS, Popma JJ, et al. Mechanisms and results of balloon angioplasty for the treatment of in-stent restenosis. *Am J Cardiol* 1996;78:618-22.
29. Gordon PC, Gibson CM, Cohen DJ, Carrozza JP, Kuntz RE, Baim DS. Mechanisms of restenosis and redilatation within coronary stents: quantitative angiographic assessment. *J Am Coll Cardiol* 1993;21:1166-74.
30. Bottcher HD, Schopohl B, Liermann D, Kollath J, Adamietz IA. Endovascular irradiation — a new method to avoid recurrent stenosis after stent implantation in peripheral arteries: technique and preliminary results. *Int J Radiat Oncol Biol Phys* 1994;29:183-6.
31. Liermann D, Bottcher HD, Kollath J, et al. Prophylactic endovascular radiotherapy to prevent intimal hyperplasia after stent implantation in femoropopliteal arteries. *Cardiovasc Intervent Radiol* 1994;17:12-6.
32. Steidle B. Präventive perkutane Strahlentherapie zur Vermeidung von Intimahyperplasie nach Angioplastie mit Stentimplantation. *Strahlenther Onkol* 1994;170:151-4.
33. Condado JA, Gurdziel OG, Espinosa R, et al. Long-term angiographic and clinical outcome following balloon angioplasty and intracoronary radiation therapy in humans. *Circulation* 1996;94:Suppl I:I-209. abstract.
34. Urban P, Verin V, Popowski Y, et al. Clinical feasibility and safety of intraluminal beta irradiation to prevent restenosis after coronary balloon angioplasty. *Circulation* 1996;94:Suppl I:I-209. abstract.
35. Corn BW, Trock BJ, Goodman RL. Irradiation-related ischemic heart disease. *J Clin Oncol* 1990;8:741-50.