

INTRAVASCULAR GAMMA RADIATION FOR IN-STENT RESTENOSIS IN SAPHENOUS-VEIN BYPASS GRAFTS

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ABSTRACT

Background Intracoronary radiation therapy is effective in reducing the recurrence of in-stent stenosis in native coronary arteries. We examined the effects of intravascular gamma radiation in patients with in-stent restenosis of saphenous-vein bypass grafts.

Methods A total of 120 patients with in-stent restenosis in saphenous-vein grafts, the majority of whom had diffuse lesions, underwent balloon angioplasty, atherectomy, additional stenting, or a combination of these procedures. If the intervention was successful, the patients were randomly assigned in a double-blind fashion to intravascular treatment with a ribbon containing either iridium-192 or nonradioactive seeds. The prescribed dose, delivered at a distance of 2 mm from the source, was 14 to 15 Gy in vessels that were 2.5 to 4.0 mm in diameter and 18 Gy in vessels with a diameter that exceeded 4.0 mm. The primary end points were death from cardiac causes, Q-wave myocardial infarction, revascularization of the target vessel, and a composite of these events at 12 months.

Results Revascularization and radiation therapy were successfully accomplished in all patients. At six months, the restenosis rate was lower in the 60 patients assigned to the iridium-192 group than in the 60 assigned to the placebo group (21 percent vs. 44 percent, $P=0.005$). At 12 months, the rate of revascularization of the target lesion was 70 percent lower in the iridium-192 group than in the placebo group (17 percent vs. 57 percent, $P<0.001$), and the rate of major cardiac events was 49 percent lower (32 percent vs. 63 percent, $P<0.001$).

Conclusions The results of our study support the use of gamma-radiation therapy for the treatment of in-stent restenosis in patients with bypass grafts. (N Engl J Med 2002;346:1194-9.)

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SAPHENOUS-VEIN graft disease after coronary-artery bypass surgery results in a 40 percent rate of graft failure at 10 years.¹ Percutaneous treatment of saphenous-vein grafts is associated with high rates of procedural complications and restenosis, particularly as the age of the graft increases.²⁻⁴ Angiographic evidence of restenosis at six months has been reported in up to 45 percent of patients treated with directional atherectomy and in up to 37 percent of those treated with stenting.^{5,6} Stents

and laser and atherectomy devices have been improved in order to obtain better outcomes and reduce the high risk of repeated cardiac surgery in patients with saphenous-vein graft disease.⁶⁻¹⁰ Despite these improvements, in-stent restenosis remains a therapeutic challenge, and conventional therapies (balloon angioplasty, stenting, laser angioplasty, and atherectomy) continue to be associated with high rates of recurrence.⁵⁻¹¹ Graft failure leads to repeated coronary bypass grafting and is associated with increases in mortality and morbidity.¹²

Intracoronary radiation therapy for in-stent restenosis in native coronary arteries, with the use of gamma and beta emitters, has substantially reduced the rate of recurrent restenosis.¹³⁻¹⁵ We conducted a prospective, randomized, double-blind trial at three centers to evaluate the safety and effectiveness of adjunctive intravascular radiation therapy with the use of a gamma emitter, iridium-192, after successful revascularization in patients with in-stent restenosis of saphenous-vein grafts.

METHODS

The trial was sponsored by the Medlantic Research Institute, at the Washington Hospital Center, Washington, D.C. The investigators performed the data analysis independently of the sponsor, and the investigators had full access to the data. An Investigational Device Exemption was granted by the Food and Drug Administration. The study was approved by the institutional review boards and the radiation-safety committees at the participating centers and was monitored by an external data and safety monitoring board. Written informed consent was obtained from all patients before enrollment. An external committee independently adjudicated all clinical events in a blinded fashion.

Selection of Patients

Patients with symptoms of angina and angiographic evidence of in-stent restenosis of a saphenous-vein graft were eligible for the study. A 1:1 randomization scheme was generated by computer, without stratification. Enrollment criteria included an age of 30 to 80 years and a successful percutaneous intervention (defined by residual stenosis of less than 30 percent) in a vessel with a diameter of 2.5 to 5.0 mm, with a lesion that was less than 47 mm long.

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The main exclusion criteria were acute or recent myocardial infarction (within the previous 72 hours), a left ventricular ejection fraction of less than 20 percent, angiographic evidence of thrombus, and prior treatment with irradiation of the chest.

Protocol

Before revascularization of the saphenous-vein graft, angiographic and intravascular ultrasound studies were performed to determine the length of the lesion and the size of the vessel. Revascularization was performed with the use of balloon dilatation, an excimer laser, rotational atherectomy, additional stenting, or a combination of these interventions; glycoprotein IIb/IIIa-receptor antagonists were not used. In preparation for radiation treatment, the patient was further sedated, and the activated clotting time was maintained at more than 300 seconds with heparin.

After a successful intervention, a closed-ended, noncentered catheter, either 4.0 French (CheckMate, Cordis) or 5.0 French (Medtronic AVE), was positioned to span the target lesion with at least a 5-mm overlap of a normal segment at each end to minimize the possibility of a geographic miss (i.e., failure to irradiate the entire lesion). The radiation oncologist hand-loaded a ribbon containing a train of placebo or iridium-192 seeds into the catheter (Best Medical International). The train consisted of 6, 10, or 14 seeds spaced to irradiate a vessel segment that was 23, 39, or 55 mm long. The patient, the cardiologist, and the radiation oncologist were unaware of the treatment assignment, but the radiation-safety officer and the radiation physicist were unblinded. Accurate positioning of the train was documented by angiography. Patients were monitored from the control room, since all personnel were required to be out of the procedure room while the dose of radiation was being delivered. Final angiographic and intravascular ultrasound studies were performed, and if required, a further intervention was undertaken to optimize the results. Routine care was provided after angioplasty, with no additional heparin therapy and early removal of the sheath. Antiplatelet therapy consisted of 325 mg of aspirin daily and either 250 mg of ticlopidine orally twice a day or 75 mg of clopidogrel orally daily for one month in the first 85 patients enrolled and for six months in the other 35 patients. (The regimen was extended because of cases of late thrombosis reported in other radiation trials.) All patients underwent clinical follow-up evaluations 1, 6, and 12 months after the procedure. Repeated coronary angiography was performed at six months.

Dosimetry

The prescribed dose of radiation, delivered at a distance of 2 mm from the source, was 14 to 15 Gy in vessels that were 2.5 to 4.0 mm in diameter and 18 Gy in vessels that were more than 4.0 mm in diameter. Each seed was 3 mm long, with a 1-mm space between seeds; the mean (\pm SD) length of the train of seeds was 44.3 ± 10.0 mm. The mean activity per seed was 25.7 ± 8.1 mCi, and the total seed activity was 293.3 ± 102.8 mCi.

Angiographic Analysis

The study personnel at the Washington Hospital angiographic core laboratory who performed the quantitative angiographic analysis were unaware of the treatment assignments. Restenosis at follow-up (a binary end point) was defined as angiographic evidence of at least 50 percent narrowing of the luminal diameter of the stented segment or of the segment exposed to radiation, including 5 mm at the proximal and distal edges (which we refer to as the analytic segment). Late loss was defined as a reduction in the minimal luminal diameter of the stented segment at six months, as compared with the diameter immediately after the procedure.

End Points

The primary end points were death from cardiac causes, Q-wave myocardial infarction, repeated revascularization of the target vessel,

and a composite of these events at 12 months. Secondary end points included angiographic evidence of restenosis (50 percent or more) and luminal loss at six months (late loss).

Statistical Analysis

The results are reported as means (\pm SD) for continuous variables and as percentages for categorical variables. Student's t-test was used to compare continuous variables; the chi-square test or Fisher's exact test was used to compare categorical variables. A P value of less than 0.05 was considered to indicate statistical significance. All reported P values are two-sided. A stepwise logistic-regression analysis was performed to determine independent predictors of major adverse events at 12 months. We included in the model all clinical and angiographic base-line characteristics and the angiographic results obtained immediately after the procedure that had a P value of less than 0.20. Cumulative frequency distributions of the minimal luminal diameter in the iridium-192 and placebo groups were determined before, immediately after, and six months after the procedure. Kaplan-Meier curves for survival without cardiac events (Q-wave myocardial infarction or revascularization of the target vessel) at 24 months were calculated.

RESULTS

Characteristics of the Patients

A total of 120 patients were enrolled in the study between August 1998 and August 2000. The procedure was successful in all cases, with no unexpected adverse events. The base-line clinical, angiographic, and procedural characteristics were similar in the 60 patients assigned to the iridium-192 group and the 60 assigned to the placebo group (Table 1). The mean age of the patients was 66 ± 9 years. Forty percent had a history of diabetes, 76 percent had multivessel disease, and the mean left ventricular ejection fraction was 0.47 ± 0.14 . The majority of the patients (60 percent) had received more than one treatment for in-stent restenosis before enrollment.

The majority of patients had a diffuse pattern of in-stent restenosis. The length of the lesion exceeded 10 mm in 88 patients, with a mean length of 17.6 ± 10.2 mm in the iridium-192 group and 14.9 ± 10.0 mm in the placebo group ($P=0.15$) (Table 2). Coronary angioplasty was performed with an excimer laser in 53 percent of the patients, and in 50 percent additional stenting was required in order to optimize the final angiographic result, cover edge dissections, or both. The mean radiation-treatment time was 20.9 ± 6.6 minutes. All patients tolerated the radiation treatment.

In-Hospital Complications

There were no significant differences in in-hospital complications between the two groups (Table 3). One patient assigned to the placebo group died of a subarachnoid hemorrhage and cerebral infarction eight days after the procedure. The creatine kinase MB level was more than three times the base-line value in 7 percent of the iridium-192 group and in 10 percent of the placebo group ($P=0.51$).

TABLE 1. BASE-LINE CHARACTERISTICS OF THE PATIENTS.*

CHARACTERISTIC	IRIDIUM-192 (N=60)	PLACEBO (N=60)
Age (yr)	67±8	66±9
Male sex (%)	82	77
Previous myocardial infarction (%)	53	53
History of >1 treatment for in-stent restenosis (%)	57	63
Diabetes (%)	45	35
Hypertension (%)	80	75
Current or former smoker (%)	62	58
Hyperlipidemia (%)	90	90
Multivessel disease (%)	79	73
Left ventricular ejection fraction	0.48±0.12	0.46±0.16
Medications (%)		
Angiotensin-converting-enzyme inhibitor	40	41
Beta-blocker	60	75
Lipid-lowering agent	75	78
Treatment strategy (%)		
Balloon angioplasty alone	12	18
Angioplasty with an excimer laser	55	52
Rotational atherectomy	3	2
Additional stenting	50	50
Radiation therapy		
Length of seed train (mm)	44.6±9.7	44.1±10.3
Total activity of seeds (mCi)	305.4±86.2	—
Exposure time (min)	21.1±4.8	20.7±8.0

*Plus-minus values are means ±SD. None of the characteristics differed significantly between the two groups of patients.

TABLE 2. ANGIOGRAPHIC CHARACTERISTICS AT BASE LINE AND SIX MONTHS.

CHARACTERISTIC	IRIDIUM-192 (N=60)	PLACEBO (N=60)	P VALUE
Length of lesion (mm)	17.6±10.2	14.9±10.0	0.15
Diameter of reference vessel (mm)	2.88±0.55	2.90±0.56	0.85
Complex lesion (%)	36	38	0.80
Location of lesion (%)			
Ostial	17	10	0.28
Proximal	45	54	0.36
Middle	23	22	0.79
Distal	15	14	0.84
Minimal luminal diameter (mm)			
Before angioplasty	0.73±0.47	0.91±0.60	0.08
Immediately after angioplasty	2.20±0.39	2.29±0.47	0.27
At 6 mo	1.92±0.77	1.32±0.87	<0.001
>50% restenosis (%)			
Stented segment*	15	43	0.004
Analytic segment†	21	44	0.005
Late loss (mm)			
Stented segment*	0.23±0.75	1.14±0.85	<0.001
Analytic segment†	0.30±0.76	1.23±0.86	<0.001
Late-loss index‡	0.12±0.67	0.69±2.19	0.04

*The stented segment was defined as the stented portion of the lesion alone.

†The analytic segment was defined as the entire segment exposed to radiation, including 5 mm at the proximal and distal margins, beyond the source of radiation.

‡The late-loss index is the late loss divided by the change in the minimal luminal diameter (the diameter immediately after angioplasty minus the diameter before angioplasty).

TABLE 3. IN-HOSPITAL COMPLICATIONS.*

EVENT	IRIDIUM-192 (N=60)	PLACEBO (N=60)
	no. of patients (%)	
Death	0	1 (2)
Q-wave myocardial infarction	1 (2)	2 (3)
CABG	0	0
Repeated PTCA	0	0
Repeated catheterization	0	2 (3)
Creatine kinase MB, >3 times normal	4 (7)	6 (10)
Renal failure	1 (2)	0
Any vascular complication	5 (8)	4 (7)

*CABG denotes coronary-artery bypass grafting, and PTCA percutaneous transluminal coronary angioplasty.

Angiographic Results

Angiography was performed at six months in 85 percent of the patients in the iridium-192 group (47 of 55) and in 89 percent of those in the placebo group (48 of 54). The minimal luminal diameter at six months was significantly greater in the iridium-192 group (1.92 ± 0.77 mm, vs. 1.32 ± 0.87 mm in the placebo group; $P < 0.001$) (Table 2 and Fig. 1). The benefit of radiation was seen in the stented segment of the vessel, with an 80 percent reduction in late loss (0.23 ± 0.75 mm, vs. 1.14 ± 0.85 mm in the placebo group; $P < 0.001$). Furthermore, evaluation of the analytic segment confirmed the absence of stenosis at the edge of the treated segment ("edge effect"). The rate of restenosis in the stented segment was 65 percent lower in the iridium-192 group than in the placebo group ($P = 0.004$), and the rate of restenosis in the analytic segment was 52 percent lower in the iridium-192 group ($P = 0.005$). A geographic miss occurred in nine patients (8 percent). There were no perforations or evidence of aneurysm formation in the iridium-192 group.

In a limited subgroup of 45 patients who underwent intravascular ultrasound analysis at base line and at six months, the change in the cross-sectional area of in-stent intimal hyperplasia was significantly smaller in those treated with iridium-192 than in those treated with placebo (-0.07 ± 0.99 mm² vs. 2.03 ± 1.35 mm², $P < 0.001$).

Clinical Events

Clinical follow-up data were obtained at 12 months for all patients. The risk of a major cardiac event (the composite end point of death from cardiac causes, Q-wave myocardial infarction, and revascularization of the target vessel) was significantly lower in the irid-

ium-192 group than in the placebo group (19 patients treated with radiation had a major cardiac event, as compared with 38 patients in the placebo group; odds ratio, 0.27; 95 percent confidence interval, 0.13 to 0.57; $P < 0.001$) (Table 4). Although there were no significant differences in the rates of death from cardiac causes, Q-wave myocardial infarction, or non-Q-wave myocardial infarction, the rate of revascularization of the target lesion was 70 percent lower and the rate of revascularization of the target vessel 55 percent lower in the iridium-192 group ($P < 0.001$ for both comparisons). Radiation therapy was the only independent predictor of freedom from major cardiac events at 12 months (odds ratio, 0.26; 95 percent confidence interval, 0.11 to 0.59; $P = 0.001$). Figure 2 shows event-free survival over a period of 24 months.

DISCUSSION

This study provides support for the therapeutic use of gamma radiation in patients with in-stent restenosis involving saphenous-vein grafts, for which acceptable alternative treatments are currently unavailable. In a cohort of patients at high risk for recurrent restenosis, gamma radiation with the use of iridium-192 was associated with angiographic and clinical outcomes that were superior to those associated with placebo. At six months, patients treated with iridium-192 had larger luminal diameters, less late loss, and a lower rate of recurrent stenosis. The radiation therapy was well tolerated in all patients, and its safety was demonstrated both at the time of the procedure and at 12 months. The iridium-192 group had improved clinical outcomes at 12 months, with a 49 percent reduction in the composite end point of major cardiac events ($P < 0.001$). In the group of patients who were evaluated at 24 months, the advantage of radiation therapy over placebo was maintained, despite a few adverse events that occurred after 12 months in both treatment groups.

Saphenous-vein graft disease continues to be a major therapeutic challenge. Recurrent stenosis involving vein grafts accounts for substantial morbidity and mortality, with cardiac events developing in 6 percent of patients per year.¹⁶ Although balloon angioplasty of saphenous-vein grafts has been associated with rates of recurrent stenosis that exceed 50 percent, stenting has not solved the problem of restenosis.^{6,7,10,11} Our findings confirm the efficacy of gamma radiation for the treatment of in-stent restenosis, even in patients with diffuse lesions. These data corroborate our initial findings in 15 patients treated for in-stent restenosis of saphenous-vein grafts; in that study, the rate of revascularization of the target vessel at six months was significantly lower in the gamma-radiation group than in the control group.¹³

Our findings with the use of gamma radiation for

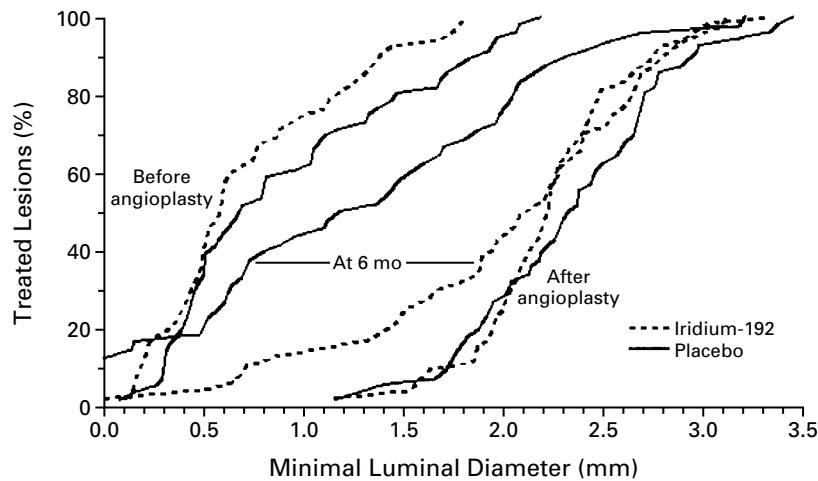


Figure 1. Minimal Luminal Diameter in the Iridium-192 and Placebo Groups before and after Angioplasty and at Six Months.

TABLE 4. MAJOR EVENTS AT 12 MONTHS.*

EVENT	IRIDIUM-192 (N=60)	PLACEBO (N=60)	P VALUE	ODDS RATIO (95% CI)
	no. (%)			
Primary end points				
Death	4 (7)	4 (7)	1.0	1.0 (0.24–4.20)
Q-wave myocardial infarction	1 (2)	2 (3)	1.0	0.49 (0.42–5.57)
Revascularization of target vessel	17 (28)	37 (62)	<0.001	0.25 (0.11–0.53)
Composite†	19 (32)	38 (63)	<0.001	0.27 (0.13–0.57)
Secondary end points				
Non-Q-wave myocardial infarction	6 (10)	7 (12)	0.77	0.84 (0.27–2.67)
Revascularization of target lesion	10 (17)	34 (57)	<0.001	0.15 (0.07–0.36)
Repeated PTCA	21 (35)	39 (65)	0.001	0.29 (0.14–0.61)
Cardiac bypass surgery	2 (3)	2 (3)	1.0	1.0 (0.14–7.30)
Rehospitalization for angina	28 (47)	40 (67)	0.03	0.44 (0.20–0.98)
Total occlusion	1 (2)	5 (8)	0.21	0.19 (0.02–1.65)
Late thrombosis	1 (2)	3 (5)	0.62	0.32 (0.03–3.19)

*CI denotes confidence interval, and PTCA percutaneous transluminal coronary angioplasty.

†The composite end point included death from cardiac causes, Q-wave myocardial infarction, and revascularization of the target vessel.

the treatment of in-stent restenosis in saphenous-vein grafts are similar to the reported results of this treatment in native coronary arteries. In our study, the rate of revascularization of the target lesion at 12 months was 17 percent; the rate was 24 percent in the Washington Radiation for In-Stent Restenosis Trial and 12 percent in the Scripps Coronary Radiation to Inhibit Proliferation Post Stenting trial.^{13,14} Radiation therapy has been the only consistent predictor of freedom from recurrent in-stent restenosis.¹³⁻¹⁵

In our study, the absolute rates of late thrombosis and total occlusion were lower in the iridium-192

group than in the placebo group, despite the use of additional stenting during the intervention in 50 percent of the patients in both groups. The phenomenon of late thrombosis, which has been reported in previous trials of radiation therapy, is explained in part by delayed re-endothelialization or unhealed dissection.^{17,18} Prolonged antiplatelet therapy (a six-month regimen) and avoidance of additional stenting when possible are two strategies that have minimized the incidence of late thrombosis.¹⁹ The saphenous-vein grafts in our study may have been less prone to late thrombosis than the grafts in previous studies because the treated ves-

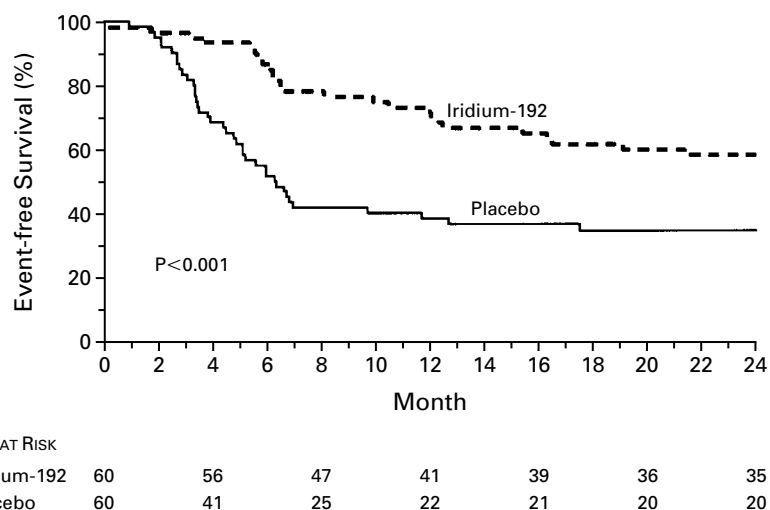


Figure 2. Event-free Survival at 24 Months. Event-free survival was defined as survival without Q-wave myocardial infarction or revascularization of the target vessel. Data were available for 79 of 120 patients at 24 months.

sels in our study were larger (mean reference diameter, 2.88±0.55 mm) and because 29 percent of our patients received antiplatelet therapy for six months.

One limitation of our study is the variation in the antiplatelet regimens assigned to patients in both treatment groups. In addition, although our findings confirm the efficacy of radiation therapy in reducing the risk of in-stent restenosis in saphenous-vein grafts at 12 months, substantially longer follow-up is required to determine whether the efficacy of this treatment can be sustained without long-term side effects. Our findings support the use of intravascular gamma radiation in patients with in-stent restenosis of saphenous-vein grafts.

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Dr. Waksman is a consultant to Cordis, the manufacturer of the system used in this study. Dr. Teirstein is a consultant for and has received research grants from Cordis and several other companies in the field of vascular radiotherapy. He also holds patents in the field of radiation therapy.

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CORRECTION

Intravascular Gamma Radiation for In-Stent Restenosis in Saphenous-Vein Bypass Grafts

Intravascular Gamma Radiation for In-Stent Restenosis in Saphenous-Vein Bypass Grafts . In the table of contents, the title should have read, "Intravascular," not "Vascular," as printed. We regret the error.