

LOCALIZED INTRACORONARY GAMMA-RADIATION THERAPY TO INHIBIT THE RECURRENCE OF RESTENOSIS AFTER STENTING

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ABSTRACT

Background Although the frequency of restenosis after coronary angioplasty is reduced by stenting, when restenosis develops within a stent, the risk of subsequent restenosis is greater than 50 percent. We report on a multicenter, double-blind, randomized trial of intracoronary radiation therapy for the treatment of in-stent restenosis.

Methods Of 252 eligible patients in whom in-stent restenosis had developed, 131 were randomly assigned to receive an indwelling intracoronary ribbon containing a sealed source of iridium-192, and 121 were assigned to receive a similar-appearing nonradioactive ribbon (placebo).

Results The primary end point, a composite of death, myocardial infarction, and the need for repeated revascularization of the target lesion during nine months of follow-up, occurred in 53 patients assigned to placebo (43.8 percent) and 37 patients assigned to iridium-192 (28.2 percent, $P=0.02$). However, the reduction in the incidence of major adverse cardiac events was determined solely by a diminished need for revascularization of the target lesion, not by reductions in the incidence of death or myocardial infarction. Late thrombosis occurred in 5.3 percent of the iridium-192 group, as compared with 0.8 percent of the placebo group ($P=0.07$), resulting in more late myocardial infarctions in the iridium-192 group (9.9 percent vs. 4.1 percent, $P=0.09$). Late thrombosis occurred in irradiated patients only after the discontinuation of oral antiplatelet therapy (with ticlopidine or clopidogrel) and only in patients who had received new stents at the time of radiation treatment.

Conclusions Intracoronary irradiation with iridium-192 resulted in lower rates of clinical and angiographic restenosis, although it was also associated with a higher rate of late thrombosis, resulting in an increased risk of myocardial infarction. If the problem of late thrombosis within the stent can be overcome, intracoronary irradiation with iridium-192 may become a useful approach to the treatment of in-stent restenosis. (N Engl J Med 2001;344:250-6.)

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ALTHOUGH coronary stents provide a metal scaffolding that reduces the risk of restenosis¹⁻⁴ by eliminating vascular contraction,^{5,6} stents do not inhibit neointimal proliferation but, rather, induce greater neointimal proliferation than do other coronary devices.^{7,8} Therefore, an effective treatment for restenosis within the stent requires the suppression of this neointimal response. The current treatments, including pharmacologic approaches,⁹ percutaneous transluminal coronary angioplasty (PTCA),¹⁰⁻¹² atheroablative techniques,¹³⁻¹⁵ and repeated stenting,¹⁶ have been disappointing. Radiation therapy, with its known antiproliferative effects in other diseases,¹⁷ has been proposed as a treatment for in-stent restenosis. The findings from two preliminary randomized, double-blind clinical trials from single centers^{18,19} have demonstrated a reduction of more than 50 percent in the incidence of clinical and angiographic restenosis with radiation therapy as compared with placebo. We conducted a multicenter, double-blind, randomized clinical trial, the Gamma-One Trial, to assess the feasibility, safety, and efficacy of intracoronary gamma radiation with iridium-192 for the treatment of in-stent restenosis.

METHODS

Study Design

The primary objective of this study was to compare the clinical outcome nine months after intracoronary radiotherapy with the clinical outcome after placebo therapy in patients with documented myocardial ischemia due to in-stent restenosis. The trial complied with the provisions of the Declaration of Helsinki regarding investigations involving human subjects and was approved for an Investigational Device Exemption by the Food and Drug Administration (FDA). All investigational sites received approval from their local institutional review boards. Written informed consent was obtained from all patients.

Criteria for Eligibility

Patients were eligible for the study if they had a history of angina and signs of myocardial ischemia, with a target lesion in which there was stenosis of more than 60 percent of the luminal diameter (according to a visual assessment of the angiogram); the lesion had to be no more than 45 mm long and had to be in a native coronary

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artery (2.75 to 4.0 mm in diameter) in which a stent had previously been implanted. Before randomization, the coronary intervention in the target lesion had to be considered by the operator to have been successful (i.e., the residual stenosis in the lesion had to be less than 30 percent of the luminal diameter). The principal criteria for exclusion from the study were a myocardial infarction within the preceding 72 hours; total occlusion of the vessel at the site of the in-stent restenosis; an intention on the part of the operator to use abciximab during the treatment of in-stent stenosis; and clinically significant impairment of left ventricular function (indicated by an ejection fraction of less than 40 percent).

Coronary Intervention

The in-stent lesion was treated by means of conventional interventional techniques, usually consisting of high-pressure balloon dilation (pressure, >12 atm), atheroablative techniques (rotational atherectomy or ablation with an excimer laser), or both. All patients received oral aspirin (325 mg daily) and either oral ticlopidine (250 mg twice daily) or oral clopidogrel (75 mg daily) for more than 48 hours, whenever possible, before the index procedure to treat the restenosis within the stent. During the procedure, intravenous heparin was given to maintain an activated clotting time of at least 300 seconds. If the restenotic lesion was found to extend beyond the borders of the stent, if residual stenosis was not reduced to less than 30 percent of the luminal diameter, or if an extensive dissection was necessary, then one or two FDA-approved noncoiled coronary stents were implanted. Intravascular ultrasonography was then performed, with the use of a 3.2-French catheter (Cardiovascular Imaging Systems, Sunnyvale, Calif) and a motorized pull-back device, to examine the treated segment and the proximal and distal reference vessels.

Immediately after a successful coronary intervention, a short, monorail, closed-ended, noncentered, 4-French dedicated radiation catheter (Cordis, Warren, N.J.) was inserted over the intracoronary guidewire. Before the placement of the source wire, a 2.5-cm (1-in.)-thick lead shield was positioned between the patient's chest and the monitoring room to protect the caregivers from radiation. All catheterization personnel then moved into the monitoring room, where exposure to radiation was at background levels. Then, a 0.076-mm (0.030-in.) ribbon (Best Industries, Springfield, Va.) containing a sealed source of iridium-192 or a similar-appearing nonradioactive ribbon (placebo) was manually inserted into the delivery catheter by the supervising radiation oncologist. All patients and study personnel, except for the radiation physicist at each center who was involved in the clinical trial, were unaware of the treatment assignments. The radiopaque study ribbon within the delivery catheter was carefully positioned by the radiation oncologist and the interventional cardiologist so that the effective dose of radiation reached vessel segments of at least 4 mm at both ends of the target lesion. Confirmation that the study ribbon was positioned at the treatment site was provided by angiography. The study ribbons contained multiple 3-mm seeds (containing iridium-192 or placebo), each pair separated by a 1-mm space. The total length of the source ranged from 23 to 55 mm (for 6-, 10-, and 14-seed devices).

After delivering the prescribed dose of radiation to the target lesion, the ribbon was removed by the radiation oncologist and placed in an adequately shielded lead container. Angiography and intravascular ultrasonography were performed a final time, and if they revealed new dissections or extensive elastic recoil resulting in stenosis of more than 30 percent of the luminal diameter, then additional interventional therapy was recommended (repeated balloon dilation, a new stent, or both). After the procedure, patients were treated indefinitely with oral aspirin (325 mg daily) and with either oral ticlopidine (250 mg twice daily) or oral clopidogrel (75 mg daily) for eight weeks.

Dosimetry

The appropriate dose of radiation was determined with the use of tomographic sections of the coronary ultrasound images along the axial length of the stent. The maximal and minimal distances

from the center of the ultrasonographic catheter (representing the center of the radiation source) to the target segment of external elastic membrane (at the interface of the media and the adventitia) were calculated. The radiation oncologist and the radiation physicist used the data obtained by ultrasonography and the specific activity of iridium-192 to determine the time required to deliver 8 Gy to the target farthest from the source while ensuring that no more than 30 Gy would be delivered to the target closest to the source. If these calculations indicated that 8 Gy could not be delivered to the farthest target without exceeding the limit of 30 Gy at the near target, the dose was adjusted to provide 30 Gy or less to the near target, and a dose lower than 8 Gy to the far target was accepted.

Collection of Data and Analyses at the Core Laboratory

Case-report forms were completed at each site, monitored by independent study monitors, and submitted to the data-coordinating center (Cardiovascular Data Analysis Center, Harvard Clinical Research Institute, Boston). All events were classified by an independent clinical-events committee that was unaware of each patient's treatment assignment.

Angiograms obtained during the procedure and at follow-up six months later were submitted to the angiographic core laboratory (at the Cardiovascular Research Foundation, Washington Hospital Center, Washington, D.C.), where they were analyzed with a computer-based system (Medis, Leiden, the Netherlands). The diameter of the reference vessel and the minimal luminal diameter at the target lesion were determined before the procedure, immediately after the procedure, and at the follow-up examination six months later. The minimal diameter at the target lesion was determined in two ways; the first analysis was confined to the segment of the vessel in which the stent was implanted (the "in-stent" segment) and the second analysis included that segment plus an adjacent 5 mm of the nonstented region on each side of the stent, as well as any additional region occupied by the radiation ribbon during treatment (the "in-lesion" segment). The initial (acute) gain was defined as the minimal luminal diameter immediately after the procedure minus the minimal luminal diameter before the procedure. Late loss was defined as the minimal luminal diameter immediately after the procedure minus the minimal luminal diameter at the six-month follow-up. The late-loss index (a measure of late loss corrected for differences in initial gain) was defined as the regression slope of late loss plotted against initial gain.

Study End Points

Success of the procedure was defined as successful delivery of the iridium-192 or placebo, achievement of residual stenosis of less than 50 percent of the luminal diameter with Thrombolysis in Myocardial Infarction (TIMI) grade 3 flow on angiography, and survival to discharge from the hospital without a need for emergency bypass surgery. Procedure-related myocardial infarctions were defined as Q-wave infarctions if there was a new Q wave with a duration of at least 0.04 second in two or more contiguous electrocardiographic leads, and as non-Q-wave infarctions if, in the absence of new Q waves, the sampling of cardiac enzymes revealed an elevation of creatine kinase to more than two times the upper limit of normal plus an elevation of MB isoenzymes.

The prespecified primary end point after nine months was a composite of the following major adverse cardiac events: death, myocardial infarction (including late thrombosis), emergency bypass surgery, and the need for revascularization of the target lesion (either percutaneous revascularization or bypass surgery). Prespecified secondary end points included angiographic evidence of stenosis of 50 percent or more of the luminal diameter (a binary end point) at 6-month follow-up, myocardial infarction, acute thrombosis (angiographic evidence of thrombosis or subacute closure within the target vessel, or death in which acute thrombosis could not be ruled out by the adjudication committee — all within 30 days after the procedure), the need for revascularization of the target lesion within 9 months after the procedure, and the need for revascularization of the target vessel within 9 months after the procedure. Although

it was not a prespecified end point, we also evaluated the occurrence of late thrombosis (myocardial infarction attributed to the target vessel, with angiographic documentation of thrombus or total occlusion, occurring between 31 and 270 days after the procedure).

Statistical Analysis

The study was designed to have a power of 90 percent to reject the null hypothesis of no difference between the treatment groups with a 5 percent level of significance in two-tailed tests. On the basis of data from a previous single-center trial of coronary irradiation,¹⁸ it was assumed that the rates of the primary clinical events in the nine months after the procedure would be 40 percent or greater in the placebo group and 20 percent or lower in the iridium-192 group. Given these assumptions, it was determined that 250 patients would be needed. Randomization was stratified according to clinical center and the length of the treated lesion (≤ 30 mm vs. > 30 mm).

All comparisons were performed in accordance with the intention-to-treat principle. Continuous variables were compared with the use of Student's *t*-test if data were normally distributed and the Wilcoxon rank-sum test if they were not. Binary variables were compared with the use of the chi-square test with normal approximation or Fisher's exact test, when appropriate. A multivariable model of angiographic restenosis was constructed in which the dependent variable was the percent stenosis within the stent at the six-month follow-up and the independent variables were selected base-line covariates. A two-tailed *P* value of 0.05 or less was considered to indicate significance for all analyses performed with use of SAS software (version 6.12, SAS Institute, Cary, N.C.).

RESULTS

Between December 15, 1997, and July 21, 1998, 252 patients were enrolled at the 12 investigational sites; 131 patients were assigned to the iridium-192 group, and 121 patients were assigned to the placebo group. Block randomization was performed separately at each site, which resulted in the imbalance in numbers of patients between the groups.

Base-Line Characteristics

The base-line characteristics of patients and lesions were similar in the two groups (Table 1). The groups were well matched in terms of variables indicating a high risk of restenosis, including diabetes, unstable angina, location of the lesion in the left anterior descending artery, length of the lesion, and history of more than two previous interventions at the treatment site.

Characteristics of the Procedures

The lesions of the patients in both groups were treated similarly with the use of conventional interventional techniques, including PTCA alone, atheroablative techniques, and additional stents. A 14-seed source ribbon was used in 43 percent of the patients in the iridium-192 group and 40 percent of those in the placebo group. In the iridium-192 group, the average near-wall dose was 20.25 Gy and the average far-wall dose was 7.95 Gy. The mean (\pm SD) dose delivered to the portion of the vessel 2 mm from the source was 13.5 ± 2.2 Gy.

Early Results

Results within the first 30 days after the procedure were as follows. The procedure had a success rate of 98 percent in the iridium-192 group and 95 percent

TABLE 1. BASE-LINE CLINICAL AND ANGIOGRAPHIC CHARACTERISTICS OF 252 PATIENTS WITH IN-STENT RESTENOSIS ASSIGNED TO RECEIVE IRIIDIUM-192 OR PLACEBO.*

CHARACTERISTIC	IRIDIUM-192 (N=131)	PLACEBO (N=121)
Age — yr	58 \pm 12	61 \pm 11
Male sex — no. (%)	98 (74.8)	90 (74.4)
Diabetes mellitus — no. (%)	41 (31.3)	38 (31.4)
Dyslipidemia — no. (%)†	96 (73.3)	92 (76.0)
Hypertension — no. (%)	94 (71.8)	84 (69.4)
Prior myocardial infarction — no. (%)	70 (53.4)	57 (47.1)
Left ventricular ejection fraction	53.6 \pm 10.1	53.8 \pm 10.7
Unstable angina — no. (%)		
Exertional	72 (55.0)	63 (52.1)
At rest	33 (25.2)	39 (32.2)
No. of diseased native coronary arteries — no. (%)		
1	78 (59.5)	69 (57.0)
2	28 (21.4)	22 (18.2)
3	25 (19.1)	30 (24.8)
Previous interventions in target lesion		
Mean no.	1.6 \pm 0.9	1.8 \pm 1.4
>1 procedure — no. (%)	58 (44.3)	56 (46.3)
>2 procedures — no. (%)	13 (9.9)	21 (17.4)
Location of target lesion — no. (%)		
Left anterior descending	59 (45.0)	38 (31.4)
Left circumflex	27 (20.6)	36 (29.8)
Right coronary artery	40 (30.5)	44 (36.4)
Saphenous-vein graft	4 (3.1)	3 (2.5)
Lesion length (mm)	19.0 \pm 10.0	20.3 \pm 10.3

*Plus-minus values are means \pm SD.

†Dyslipidemia was defined as a low-density lipoprotein cholesterol level above 130 mg per deciliter.

in the placebo group. There was one episode of acute stent thrombosis in the placebo group, one death (due to a procedure-related coronary perforation) in the iridium-192 group, and three periprocedural myocardial infarctions in each group (Table 2). No specific complications, evident either clinically or angiographically, occurred as a result of the placement of the catheter that delivered iridium-192 or placebo or as a result of the radiation treatment itself.

The mean diameter of the reference vessel was 2.69 ± 0.51 mm for the iridium-192 group and 2.73 ± 0.50 mm for the placebo group (Table 3). The angiographic results after treatment of the in-stent restenosis were similar in the two groups: initial in-stent luminal gain was 1.51 ± 0.57 mm with iridium-192 for the 111 patients for whom follow-up data were available and 1.57 ± 0.60 mm with placebo for the 103 patients with follow-up data, resulting in postprocedural in-stent stenosis of 8.8 ± 17.9 percent and 8.9 ± 19.0 percent of the luminal diameter, respectively.

Follow-up Results

Follow-up angiographic studies were obtained six months after the procedure in 111 patients (84.7 percent) in the iridium-192 group and in 103 patients

TABLE 2. EARLY AND LATE CLINICAL EVENTS.

EVENT	IRIDIUM-192	PLACEBO	P VALUE
	(N=131)	(N=121)	
	no. (%)		
Early event (within 30 days)			
Death	1 (0.8)	0	0.52
Myocardial infarction	3 (2.3)	3 (2.5)	0.32
Q-wave	1 (0.8)	1 (0.8)	0.99
Non-Q-wave	2 (1.5)	2 (1.7)	0.99
Acute thrombosis	0	1 (0.8)	0.48
Death, myocardial infarction, or revascularization of the target lesion	3 (2.3)	4 (3.3)	0.26
Late event (through 9 months)			
Death	4 (3.1)	1 (0.8)	0.17
Myocardial infarction	13 (9.9)	5 (4.1)	0.09
Q-wave	6 (4.6)	3 (2.5)	0.50
Non-Q-wave	7 (5.3)	2 (1.7)	0.17
Late thrombosis (31-270 days)	7 (5.3)	1 (0.8)	0.07
Revascularization			
Target lesion	32 (24.4)	51 (42.1)	<0.01
Target vessel	41 (31.3)	56 (46.3)	0.01
Primary end point (death, myocardial infarction, or revascularization of the target lesion)	37 (28.2)	53 (43.8)	0.02

TABLE 3. INITIAL AND FOLLOW-UP ANGIOGRAPHIC RESULTS FOR PATIENTS WITH FOLLOW-UP DATA.*

VARIABLE	IRIDIUM-192 (N=111)	PLACEBO (N=103)	P VALUE
Before the procedure			
Reference-vessel diameter — mm	2.69±0.51	2.73±0.50	NS
Minimal luminal diameter — mm	0.98±0.45	0.96±0.38	NS
Stenosis — % of luminal diameter	63.3±15.7	64.6±13.4	NS
After the procedure			
Reference-vessel diameter — mm	2.77±0.47	2.81±0.49	NS
In-stent minimal luminal diameter — mm	2.49±0.50	2.52±0.51	NS
In-stent stenosis — % of luminal diameter	8.8±17.9	8.9±19.0	NS
In-lesion minimal luminal diameter — mm	2.09±0.42	2.12±0.49	NS
In-lesion stenosis — % of luminal diameter	23.9±11.9	24.5±11.4	NS
At six months			
Reference-vessel diameter — mm	2.70±0.48	2.79±0.52	NS
In-stent minimal luminal diameter — mm	1.78±0.87	1.37±0.64	<0.001
In-stent stenosis — % of luminal diameter	33.6±32.3	50.8±22.0	<0.001
In-lesion minimal luminal diameter — mm	1.47±0.74	1.31±0.62	0.07
In-lesion stenosis — % of luminal diameter	45.6±25.9	53.2±20.5	0.03
Change in minimal luminal diameter			
Initial in-stent gain — mm	1.51±0.57	1.57±0.60	NS
Initial in-lesion gain — mm	1.11±0.57	1.16±0.56	NS
Late in-stent loss — mm	0.73±0.79	1.14±0.65	<0.001
Late in-lesion loss — mm	0.64±0.69	0.83±0.66	0.05
In-stent late-loss index	0.52±0.70	0.75±0.41	0.01
In-lesion late-loss index	0.58±1.34	0.75±0.78	0.12
In-stent restenosis — no. (%)	24 (21.6)	52 (50.5)	0.005
In-lesion restenosis — no. (%)	36 (32.4)	57 (55.3)	0.01

*Plus-minus values are means ±SD. NS denotes not significant.

(85.1 percent) in the placebo group (Table 3). At the six-month follow-up, the incidence of the prespecified binary angiographic end point of in-lesion restenosis was significantly lower after radiation therapy (32.4 vs. 55.3 percent of patients, $P=0.01$). The incidence of other angiographic measures of restenosis was also significantly lower after radiation therapy, including in-stent restenosis (21.6 vs. 50.5 percent of patients, $P=0.005$), in-stent and in-lesion stenosis (as a percentage of luminal diameter), in-stent minimal luminal diameter, late loss in the stent and in the lesion, and in-stent late-loss index (Table 3). Irradiation with iridium-192 was found to be effective in reducing in-stent restenosis regardless of the length of the lesion, with a 60.0 percent treatment effect for lesions 30 mm or shorter (degree of restenosis, 18.0 percent in the iridium-192 group vs. 45.1 percent in the placebo group; $P<0.001$) and a 52.9 percent treatment effect for lesions longer than 30 mm (degree of restenosis, 35.3 percent vs. 75.0 percent; $P<0.05$). According to a multivariable model constructed in order to adjust for base-line variables, the independent predictors of angiographic restenosis at the six-month follow-up were assignment to placebo ($P<0.001$), a longer lesion ($P=0.002$), and a lesion within the left anterior descending coronary artery ($P=0.03$).

After nine months, the rate of progression to the prespecified composite primary end point of death, myocardial infarction, emergency bypass surgery, and revascularization of the target lesion was significantly lower in the iridium-192 group (28.2 percent, vs. 43.8 percent in the placebo group; $P=0.02$). The rate of revascularization of the target lesion was significantly lower in the iridium-192 group (24.4 percent vs. 42.1 percent, $P<0.01$), as was the rate of revascularization of the target vessel (31.3 percent vs. 46.3 percent, $P=0.01$).

Late thrombosis — defined as thrombosis occurring 31 to 270 days after the index procedure — was more frequent with radiation therapy than with placebo (5.3 percent vs. 0.8 percent, $P=0.07$) (Table 2). This increase in late thrombosis resulted in a trend toward more late myocardial infarctions in patients treated with iridium-192 (9.9 percent vs. 4.1 percent, $P=0.09$). Late thrombosis caused Q-wave myocardial infarction in three patients in the iridium-192 group and non-Q-wave myocardial infarction in four patients in the iridium-192 group and one patient in the placebo group. All patients in the iridium-192 group who had late thrombosis had new stents placed within the in-stent target lesion at the time of the radiation procedure. None of the late stent thromboses occurred while a patient was receiving ticlopidine or clopidogrel or within one month after discontinuing one of these drugs. In three of the seven patients with late stent thrombosis, ticlopidine was discontinued before the end of the eight weeks of therapy required by the study protocol.

Four of the iridium-192-treated patients (3.1 percent) and one patient in the placebo group (0.8 percent) died during the follow-up period. One death in the iridium-192 group was a suicide. The four other patients who died each had angiographically documented restenosis of the target lesion and died after repeated angioplasty (two in the iridium-192 group) or while waiting for bypass surgery (one in the iridium-192 group) or just after surgery (one in the placebo group). None of the patients who had a late thrombosis died during the study period.

DISCUSSION

Despite the use of multiple percutaneous revascularization techniques, including balloon angioplasty, repeated stenting, laser therapy, and atheroablation,¹⁰⁻¹⁶ approximately half of the 30 percent of patients in whom restenosis occurs after coronary stenting²⁰⁻²⁴ have recurrent restenosis. Our results demonstrate that gamma radiation is an approach that significantly reduces the need for repeated cardiac procedures in the short term in such patients.⁹⁻¹⁶ The rate of repeated revascularization of the target lesion was reduced by 42 percent, and the need for any revascularization within the target vessel was reduced by 33 percent. Other, nonrandomized trials have described encouraging results with the use of emitters of beta radiation as well as gamma radiation.²⁵⁻²⁹

Recently, late thrombosis has emerged as a major obstacle to the safety of vascular brachytherapy.^{30,31} Although the overall rate of major adverse cardiac events in this study was significantly lower in the iridium-192 group than in the placebo group, the rate of late thrombosis (thrombosis occurring after 30 days) was higher in the iridium-192 group. The occurrence of late thrombosis is clinically important; such an increase had not been previously observed in stent trials that did not have a radiation component,³² and it was largely responsible for a trend toward an increased rate of late myocardial infarctions (after 30 days) in irradiated patients. In the iridium-192 group, late thrombosis occurred only in patients who had received a new stent at the time of the radiation procedure and who had discontinued ticlopidine or clopidogrel a minimum of one month before the thrombosis occurred.

These findings are similar to those in earlier reports from several other trials of vascular irradiation that used different isotopes,^{19,31,33} in which therapy with antiplatelet drugs (ticlopidine or clopidogrel) was used for only one to two months after the radiation procedure. Previous studies have demonstrated the potent benefit of antiplatelet therapy for the prevention of stent thrombosis.³² Of the seven patients in the iridium-192 group who had late stent thrombosis, only four had received the complete eight-week course of antiplatelet treatment specified in the protocol. Stent thrombosis occurred in six patients three to four months after radiation and in one patient nine months

after radiation. These new phenomena might be caused by a radiation-induced delay in endothelialization over the stent struts or by the effects of radiation on endothelial-cell function.

Thus, although radiation therapy may eventually prove useful in patients with recurrent in-stent restenosis, this treatment also presents patients and interventional cardiologists with the new problem of late stent thrombosis. The data, however, point to a potential solution. The occurrence of late thrombosis was limited to patients in whom a new stent was implanted at the time of the radiation procedure and who were not receiving antiplatelet therapy at the time of stent thrombosis. Thus, we speculate that a strategy that limits the use of new stents and prolongs antiplatelet therapy to six months or longer may be of value.

In summary, our trial demonstrated the efficacy of iridium-192 for the treatment of in-stent restenosis, a problem that affects approximately 150,000 patients in the United States annually. However, the reduction in major adverse cardiac events was determined solely by a diminished need for revascularization of the target lesion, not by reductions in death or myocardial infarction. The new problem of late stent thrombosis, resulting in an increased rate of myocardial infarction, was observed in 5.3 percent of iridium-192-treated patients, possibly because, in the absence of antiplatelet therapy, the radiation inhibited neointimal growth over freshly implanted stent struts. Until the problem of late stent thrombosis can be overcome, gamma radiation will not be a viable treatment for patients in whom stenotic lesions recur after a stent has been implanted.

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Dr. Leon has been a consultant and a recipient of research grants in the field of vascular radiotherapy from companies including Cordis (a Johnson & Johnson subsidiary). In addition, he and members of his family own stock in Johnson & Johnson, which manufactures the radiotherapy catheters used in the clinical trial. Dr. Teirstein serves as a consultant for several companies working in the field of vascular radiotherapy, including Guidant, Cordis, and Boston Scientific. He has received research grants from a number of companies working in the field of radiation therapy, including Guidant, Cordis, Boston Scientific, Novoste, and Isostent. Dr. Teirstein also holds patents in the field of radiation therapy and may receive royalties from the sale of radiation-delivery devices.

APPENDIX

In addition to the authors, the following institutions and investigators participated in the Gamma-One Trial: *Coronary Angiographic Core Laboratory*, Cardiovascular Research Foundation, Washington, D.C. — A.J. Lansky; *Data Coordinating and Statistical Center*, Cardiovascular Data Analysis Center, Harvard Clinical Research Institute, Boston — E. Catapano, K. Ho; *Data and Safety Monitoring Committee* — S. Smith, Jr. (chairman), D.E. Cutlip, D. Diver, E. Norouzi, J. Orav (statistician); *ECG Core Laboratory*, Cardiovascular Data Analysis Center, Harvard Clinical Research Institute, Boston — S. Ho, V. Korley; *Study Investigators* — L. Korcuska, Cleveland Clinic, Cleveland; C. Banks, Christ Hospital, Cincinnati; B. Kluck and L. Phillips, Lehigh Valley Hospital, Allentown, Pa.; R. Wade, Lenox Hill Hospital, New York; D. Shelstad, Mayo Clinic, Rochester, Minn.; M. Brown, New York Hospital, New York; B. George and J. Brooks, Riverside Hospital, Columbus, Ohio; K. Sirkin, Scripps Clinic, La Jolla, Calif.; J. Willerson, N. Strichman, J. Bennis, and M. Harlan, Texas Heart Institute, Houston; J. Hermsiller and K. Howard, St. Vincent's Hospital, Indianapolis; M. Taaffe, Washington Hospital Center, Washington,

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