Two-Year Follow-Up After Catheter-Based Radiotherapy to Inhibit Coronary Restenosis

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Background—Although early trials indicate the treatment of restenosis with radiation therapy is safe and effective, the long-term impact of this new technology has been questioned. The possibility of late untoward consequences, such as aneurysm formation, perforation, and accelerated vascular disease, is of significant concern. Furthermore, it is not known whether the beneficial effects of radiation therapy will be durable or whether radiation will only delay restenosis.

Methods and Results—A double-blind, randomized trial was undertaken to compare 192Ir with placebo sources in patients with previous restenosis after coronary angioplasty. Patients were randomly assigned to receive a 0.76-mm (0.03-in) ribbon containing sealed sources of either 192Ir or placebo. All patients underwent repeat coronary angiography at 6 months. All living patients were contacted 24 months after their index study procedure. Patients were assessed with respect to the need for target-lesion revascularization or nontarget-lesion revascularization, occurrence of myocardial infarction, or death. Over a 9-month period, 55 patients were enrolled; 26 were randomized to 192Ir and 29 to placebo. Follow-up was obtained in 100% of living patients at a minimum of 24 months. Target-lesion revascularization was significantly lower in the 192Ir group (15.4% versus 44.8%; \(P<0.01\)). Nontarget-lesion revascularization was similar in 192Ir and placebo patients (19.2% versus 20.7%; \(P=NS\)). There were 2 deaths in each group. The composite end point of death, myocardial infarction, or target-lesion revascularization was significantly lower in 192Ir-treated versus placebo-treated patients (23.1% versus 51.7%; \(P=0.03\)). No patient in the 192Ir group sustained a target-lesion revascularization later than 10 months.

Conclusions—At 2-year clinical follow-up, treatment with 192Ir demonstrates significant clinical benefit. Although further follow-up (including late angiography) will be necessary, no clinical events have occurred to date in the 192Ir group to suggest major untoward effects of vascular radiotherapy. At the intermediate follow-up time point, vascular radiotherapy continues to be a promising new treatment for restenosis. (Circulation. 1999;99:243-247.)

Key Words: restenosis ■ revascularization ■ radiotherapy ■ angioplasty ■ stent ■ radioisotopes

Intravascular radiation therapy is a promising new treatment for restenosis after angioplasty procedures.1-10 Several initial encouraging reports have recently sparked intense clinical investigation of this novel technology.7,11-18 Although early safety and efficacy have been demonstrated in numerous animal studies and in limited human trials, the long-term efficacy and, most important, safety of this technique have been questioned. The possibility of late untoward consequences, such as aneurysm formation, perforation, or accelerated vascular disease, is of significant concern.3,4 In addition, it is not known whether the beneficial effects of radiation therapy will be durable or whether radiation will only delay and not permanently reduce restenosis. With the exposure of increasing numbers of patients to intravascular radiation, it is essential to obtain long-term clinical follow-up.

The Scripps Coronary Radiation to Inhibit Proliferation Post-Stenting (SCRIPPS) trial was a double-blind, randomized trial comparing 192Ir with placebo sources. This clinical trial was approved by the Human Subjects and Radiation Safety committees of the Scripps Clinic. Patient inclusion criteria required a target lesion in a restenotic coronary artery that either already contained a stent or was a candidate for stent placement. The time interval between the

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Methods

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patient’s previous target-lesion intervention and the study intervention was required to be >4 weeks. The reference vessel was required to be between 3 and 5 mm in diameter and the target lesion to be ≤30 mm in length. Patients were excluded if the coronary revascularization procedure was unsuccessful, a suboptimal result was achieved, a stent was implanted as an unplanned emergency procedure, or the target lesion undergoing stent placement contained angiographic evidence of thrombus.

Before the procedure, patients were given aspirin (325 mg), intracoronary nitroglycerin, and intravenous heparin in a dose sufficient to maintain an activated clotting time of >300 seconds. If the lesion was not already stented, single or tandem coronary stenting (Johnson and Johnson Interventional Systems) 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 90% residual stenosis within the stented segment.

Patients were then randomly assigned to receive a 0.76-mm (0.03-in) ribbon (Best Industries) containing sealed sources of either 192Ir or placebo. All study personnel except 1 physicist from the Division of Radiation Oncology and 1 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 the radiation oncologist and the interventional cardiologist. A 25-mm-thick (1-in) lead shield 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 of 800 to 3000 cGy; it was then removed by the radiation oncologist and placed in an adequately shielded container. The femoral sheaths were removed 2 to 4 hours after the procedure, and the patient was discharged the next morning with instructions to take aspirin (325 mg/day indefinitely) and, if new stents had been implanted, ticlopidine (250 mg twice daily for 2 weeks).

All patients were requested to return for repeat coronary angiography at 6 months. Revascularization was repeated after follow-up angiography only if the patient had recurrent symptoms or if functional tests demonstrated the presence of coronary ischemia. All living patients were contacted at or about 24 months after their index study procedure. Patients were queried regarding any hospitalizations or procedures that had occurred since their index procedure. Anginal class was assessed with the use of the Canadian Cardiovascular Society Scoring System. Medical records were obtained from each patient’s primary physician along with copies of hospital records from all admissions and procedures. The county coroner’s office was contacted as necessary to obtain data regarding the cause of death. Records from all admissions and procedures. The county coroner’s office was contacted as necessary to obtain data regarding the cause of death. All records and coronary angiograms were reviewed by an observer blinded to the patient's history and date of patient deaths. All records and coronary angiograms were reviewed by an observer blinded to the patient's history and date of patient deaths. All records and coronary angiograms were reviewed by an observer blinded to the patient's history and date of patient deaths. Kaplan-Meier survival analysis, with differences between the 2 treatment groups compared with the use of a Mantel-Cox test of significance.

Results

Between March 24 and December 22, 1995, 55 patients were enrolled in the present study; 26 were randomized to 192Ir and 29 to placebo. In-stent restenosis was present in 62% of both the treated and placebo groups. As previously reported,12 initial clinical follow-up obtained at a mean of 12.2±2.9 months demonstrated a reduction in target-lesion revascularization in 192Ir- versus placebo-treated patients (11.5% versus 44.8%; P<0.01). For the present report, clinical follow-up was obtained once again on or just after the 2-year anniversary of the index procedure (Table 1). Follow-up was obtained in 100% of living patients. Mean time from index study procedure to follow-up was similar in 192Ir- and placebo-treated groups (26.2±2.5 versus 25.7±2.6 months; P=NS). Follow-up times ranged from 24 to 33 months in 192Ir-treated patients and from 24 to 32 months in placebo-treated patients.

Anginal class at follow-up did not differ between the 2 groups (Table 2). Target-lesion revascularization remained significantly lower in the 192Ir group (15.4% versus 44.8%; P<0.01). Nontarget-lesion revascularization was similar in 192Ir- and placebo-treated patients (19.2% versus 20.7%; P=NS). Of the nontarget-lesion revascularization, 3 placebo-treated patients and 4 192Ir-treated patients had revascularization of the target vessel but not the target lesion. There were 2 deaths in each group. Both deaths in the placebo group were cardiac deaths associated with myocardial infarction. One death in the 192Ir group occurred in the immediate postoperative period of a patient who underwent bypass surgery for revascularization of a nontarget lesion 23 months after the

<table>
<thead>
<tr>
<th>TABLE 1. Two-Year Clinical Follow-up</th>
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<tbody>
<tr>
<td>Clinical follow-up</td>
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<tr>
<td>Time to follow-up, mo</td>
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<tr>
<td>Range of follow-up, mo</td>
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Kaplan-Meier survival analysis, with differences between the 2 treatment groups compared with the use of a Mantel-Cox test of significance.

<table>
<thead>
<tr>
<th>TABLE 2. Anginal Class and Clinical Events at 25.9±2.5 Months</th>
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<tbody>
<tr>
<td>Placebo (n=29)</td>
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<td>----------------</td>
</tr>
<tr>
<td>Anginal class, mean±SD</td>
</tr>
<tr>
<td>Death, %</td>
</tr>
<tr>
<td>MI, %</td>
</tr>
<tr>
<td>TLR, %</td>
</tr>
<tr>
<td>Non-TLR, %</td>
</tr>
<tr>
<td>TVR, %</td>
</tr>
<tr>
<td>Non-TVR, %</td>
</tr>
<tr>
<td>Death, MI, or TLR, %</td>
</tr>
<tr>
<td>Death, MI, TLR, or non-TLR, %</td>
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</tbody>
</table>

MI indicates myocardial infarction; TLR, target-lesion revascularization; and TVR, target-vessel revascularization.
study procedure. The other death in the 192Ir group occurred in a patient who had self-terminated ticlopidine on day 3 and sustained a stent thrombosis resulting in acute myocardial infarction on day 18 after the index procedure. Angiography during the acute thrombotic event and again at 6-month follow-up demonstrated 100% occlusion of the target lesion. This patient died 18 months after the study procedure owing to complications of abdominal surgery for diverticulitis.

The composite end point of death, myocardial infarction, or target-lesion revascularization was also significantly lower in 192Ir-treated versus placebo-treated patients (23.1% versus 51.7%; P=0.03). These differences were driven entirely by differences in target-lesion revascularization. There were no significant differences in the occurrence of death or myocardial infarction. Similarly, the composite end point of death, myocardial infarction, target-lesion revascularization, or nontarget-lesion revascularization was lower in the 192Ir group (38.5% versus 72.4%; P=0.01). Life-table analysis of the composite end point of death, myocardial infarction, or target-lesion revascularization is displayed in the Figure.

Differences in clinical events were driven largely by differences in the need for target-lesion revascularization and became apparent at ~3 months. The 2 curves continue to diverge for 10 months, after which clinical events are infrequent.

Table 3 depicts changes in event rates for initial (12.2±2.9 months) and latest (25.9±2.5 months) clinical follow-up. Only 1 patient in the 192Ir group sustained a “late” target-lesion revascularization (at 11 months). The most significant change in clinical events between the 1- and 2-year follow-up periods was the rate of nontarget-lesion revascularization, which increased from 3.9% to 19.2%, respectively, in the 192Ir-treated patients and from 13.8% to 20.7% in placebo-treated patients.

### Discussion

At 2-year clinical follow-up, treatment with 192Ir continued to demonstrate significant clinical benefit. With 100% clinical follow-up and each patient followed up for ≥24 months, no unique safety issues have been identified. The composite clinical event rate (death, myocardial infarction, or any revascularization) in the treated group was 46.8% lower than that of the placebo group (38.5% versus 72.4%; P=0.01). Importantly, over the 2-year follow-up period, no events occurred in the 192Ir group that might suggest major untoward effects of vascular radiotherapy delivered in this manner. Although these results are encouraging, it should be emphasized that complications only evident on angiography (ie, pseudoaneurysm and accelerated vascular disease) could have been missed by this clinical follow-up study. The 2 deaths in the 192Ir group have clearly identified causes: 1 was a consequence of elective bypass surgery of a nontarget lesion, and the other was due to complications after abdominal surgery 18 months after a stent thrombosis. Although it is possible that the stent thrombosis was related to radiation exposure (in the absence of ticlopidine), this vessel was documented to be 100% occluded on angiography 6 months after the index procedure and was therefore unlikely to be a site of sudden coronary closure, perforation, or other acute cardiac event.

Late target-lesion revascularization rates were remarkably low in placebo and 192Ir group patients. The 1 case of target-lesion revascularization, which occurred since our previous follow-up report, occurred in a 192Ir-treated patient but only 11 months after the index procedure. Although 11 months is slightly later than the traditional 3- to 8-month window for clinical restenosis, it is not particularly unusual. At 2 years, the clinical event rate continues to strongly favor the treated group, with a 55.3% reduction in the composite end point of death, myocardial infarction, and target-lesion revascularization and a 65.6% reduction in the end point of target-lesion revascularization.

### Table 3. Clinical Events at 12.2±2.9 and 25.9±2.5 Months

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo (n=29)</th>
<th>192Ir (n=26)</th>
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<tbody>
<tr>
<td></td>
<td>12.2±2.9 mo</td>
<td>25.9±2.5 mo</td>
</tr>
<tr>
<td>Death, %</td>
<td>3.5</td>
<td>0</td>
</tr>
<tr>
<td>MI, %</td>
<td>3.5</td>
<td>3.9</td>
</tr>
<tr>
<td>TLR, %</td>
<td>44.8</td>
<td>11.5</td>
</tr>
<tr>
<td>Non-TLR, %</td>
<td>13.8</td>
<td>3.9</td>
</tr>
<tr>
<td>Death, MI, or TLR, %</td>
<td>48.3</td>
<td>15.4</td>
</tr>
<tr>
<td>Death, MI, TLR, or non-TLR, %</td>
<td>62.1</td>
<td>19.2</td>
</tr>
</tbody>
</table>

Abbreviations as in Table 2.
Presently, only a limited number of other clinical trials of vascular radiotherapy have been undertaken. Two-year angiographic follow-up after intracoronary \( \gamma \)-radiation was reported by Condado et al. The restenosis rate was low at 28%, but the study lacked a control group for comparison. Four coronary pseudoaneurysms were reported in the Condado et al series, possibly because the vessels were potentially exposed to much higher radiation doses (up to 9200 cGy) than our study patients. In addition, each target lesion in the present study received metallic, balloon expandable stents, which may limit aneurysm formation and remodeling. In another report, long-term follow-up documented high patency rates after femoropopliteal arteries undergoing angioplasty were exposed to intravascular \( \gamma \)-radiation. The long-term adverse events after radiation therapy for nonvascular indications have been well documented. Potential complications include accelerated vascular disease, coronary perforation (or pseudoaneurysm), and late malignancy. Accelerated vascular disease has been reported in patients irradiated for treatment of Hodgkin’s disease followed up beyond 9 years. The morphology of coronary artery disease appears to involve smaller (<0.5-mm) arteries and is similar to spontaneous coronary artery disease. Larger arteries (>0.5 mm) appear more resistant to radiation. In intravascular brachytherapy, the volume of irradiation is small, with significant radial dose fall-off from the lumen to the adventitia. Additionally, only a single vessel is radiated over a limited longitudinal segment, with much less exposure to the surrounding tissue. Therefore, the risk of radiation-induced fibrosis or atherosclerosis is believed to be much lower than that which occurs from the treatment of Hodgkin’s disease in which a much larger volume of tissue is irradiated. High doses of radiation could also lead to arterial rupture. Perforation and/or pseudoaneurysm of coronary arteries would likely be detected in the first few months after treatment. In the present study, the careful avoidance of the delivery of >3000 cGy to any 1 part of the luminal surface, with much lower doses delivered to the adventitia layers, probably reduced the risk of vessel perforation.

Secondary malignancies after radiation range from leukemia to solid tumors. Hematologic malignancies are usually seen within the first 3 to 7 years in cancer patients who receive combination chemotherapy and are often immunocompromised. Secondary solid tumors have a longer latent period of 7 to 10 years. These are occasionally soft-tissue sarcomas but are more often epithelial tumors of irradiated organs. Again, it is emphasized that the volume of radiation in intravascular brachytherapy is extremely small, making secondary malignancy unlikely. The application of radiation therapy in modest doses in other benign proliferative disorders (ie, heterotopic ossification and keloid scars) appears to be safe, with no apparent long-term complications.

Another finding in the present study was the high rate of nontarget-lesion revascularization that occurred in \( ^{192} \text{Ir} \) and placebo-treated patients (19% versus 21%; \( P = \text{NS} \)). It has been theorized that exposure to lower levels of radiation at sites remote from the target might stimulate vascular disease. Although our finding of similar nontarget-lesion revascularization rates in \( ^{192} \text{Ir} \) and placebo-treated patients does not support this theory, the high rate of late, nontarget-lesion revascularization in our study is disturbing. Despite the ability of radiation to significantly reduce restenosis, coronary disease appears to be an ongoing process, and patients will still likely require additional procedures, even after exposure of the treated lesion to ionizing radiation.

**Conclusions**

With 100% clinical follow-up 2 years after study entry, the clinical efficacy of \( ^{192} \text{Ir} \) appears durable. Target-lesion revascularization was reduced from 44.8% in the placebo group to 15.4% in the \( ^{192} \text{Ir} \)-treated group. Although late angiography has not been undertaken as yet, this clinical follow-up indicates no evidence of late untoward events, and no special safety issues have been identified. The need for nontarget-lesion revascularization, however, was frequent in both groups. At the intermediate follow-up time point, vascular radiotherapy continues to be a promising new treatment for restenosis.

**Acknowledgments**

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**References**

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