

## Radiation Therapy to Inhibit Restenosis: Early Clinical Results

PAUL S. TEIRSTEIN, M.D., VINCENT MASSULLO, M.D., SHIRISH JANI, PH.D., AND PRABHAKAR TRIPURANENI, M.D.

### Abstract

**Background:** Although several early trials indicate that treatment of restenosis with radiation therapy is safe and effective, the long-term impact of this new technology has been questioned. The objective of this report is to document angiographic and clinical outcome 3 years after treatment of restenosis of stented coronary arteries with catheter-based iridium-192 ( $^{192}\text{Ir}$ ).

**Methods:** A double-blind, randomized trial compared  $^{192}\text{Ir}$  with placebo sources in patients with previous restenosis after coronary angioplasty. Over a 9-month period, 55 patients were enrolled; 26 were randomized to  $^{192}\text{Ir}$  and 29 to placebo.

**Results:** At 3-year follow-up, target-lesion revascularization was significantly lower in the  $^{192}\text{Ir}$  group (15.4% vs. 48.3%;  $p < 0.01$ ). The dichotomous restenosis rate at 3-year follow-up was also significantly lower in  $^{192}\text{Ir}$  patients (33% vs. 64%;  $p < 0.05$ ). In a subgroup of patients with 3-year angiographic follow-up not subjected to target-lesion revascularization by the 6-month angiogram, the mean minimal luminal diameter between 6 months and 3 years decreased from  $2.49 \pm 0.81$  mm to  $2.12 \pm 0.73$  mm in  $^{192}\text{Ir}$  patients, but was unchanged in placebo patients.

**Conclusions:** The early clinical benefits observed after treatment of coronary restenosis with  $^{192}\text{Ir}$  appear durable at late follow-up. Angiographic restenosis continues to be significantly reduced in  $^{192}\text{Ir}$ -treated patients, but a small amount of late loss was observed between the 6-month and 3-year follow-up time points. No events occurred in the  $^{192}\text{Ir}$  group to suggest major untoward effects of vascular radiotherapy. At 3-year follow-up, vascular radiotherapy continues to be a promising new treatment for restenosis.

**Key Words:** Coronary artery angioplasty, restenosis, radiation therapy, clinical trials.

THE NEED FOR REPEAT PROCEDURES due to restenosis continues to be the Achilles heel of coronary angioplasty. Restenosis can be divided into two general concepts. The first, recoil and remodeling, refers to the mechanical collapse and constriction of the treated vessel. The second, intimal hyperplasia, refers to the proliferative response to injury, and consists largely of smooth muscle cells and matrix formation (1, 2). Coronary stents provide a luminal scaffolding that virtually eliminates classic recoil and remodeling; they have been shown to reduce restenosis by approximately 30% (3, 4). Stents, however, do not decrease but, in fact, increase the proliferative component of resteno-

sis. Other benign fibroproliferative disorders such as keloid formation and heterotopic ossification have been successfully treated with radiation therapy. In several animal models of restenosis, local, catheter-based ionizing radiation or radioactive stents have demonstrated significantly reduced neointimal proliferation (5–8). These reports have encouraged the initiation of several clinical trials. We designed the Scripps Coronary Radiation to Inhibit Proliferation Post-Stenting (SCRIPPS) trial as a double-blind, placebo-controlled, randomized trial to test this new treatment modality in restenotic stented human coronary arteries.

### Methods

In the SCRIPPS trial, patients with previous restenosis and stent implantation were randomized to receive a 0.03-inch ribbon containing either iridium-192 ( $^{192}\text{Ir}$ )-sealed sources at its tip (Best Industries, Springfield, VA) or a placebo ribbon with inactive sources. Iridium-192 dosimetry was calculated using intravascular

From the Division of Cardiovascular Diseases, Scripps Clinic, La Jolla, CA.

Address correspondence to Paul S. Teirstein, M.D., Division of Cardiovascular Diseases, SW206, Scripps Clinic, 10666 North Torrey Pines Road, La Jolla, CA 92037.

Adapted in part from a presentation made on November 30, 1998 to the Division of Cardiology, Department of Medicine, Mount Sinai School of Medicine, New York, NY.

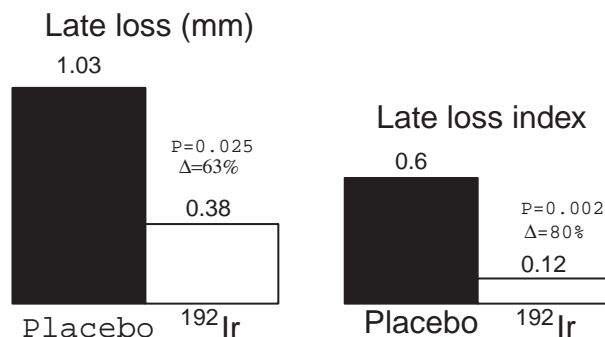
ultrasound (IVUS) measurements. The radiation oncologist and physicist used information from the IVUS image to determine a dwell time that provided 800 cGy to the internal elastic membrane furthest from the radiation source, provided that no more than 3,000 cGy was delivered to the internal elastic membrane closest to the radiation source. All angiographic and IVUS measurements were performed at an independent core ultrasound laboratory by investigators blinded to procedural information and patient assignment. Measurements that were captured included minimum luminal diameter, acute gain, late lumen loss, late lumen loss index and restenosis ( $\geq 50\%$  diameter stenosis at follow-up).

### Results

Between 3/24/95 and 12/22/95, 55 patients were randomized; 26 were assigned to  $^{192}\text{Ir}$  and 29 to placebo. Baseline clinical and angiographic characteristics were similar for both groups. Many study patients had one or more baseline characteristics associated with increased restenosis risk, including diabetes, unstable angina, more than one previous restenosis, ostial lesion location, vein graft target, and lesion length  $\geq 10$  mm.

At the 30-day endpoint, the initial procedure was successful in 96.2% of  $^{192}\text{Ir}$  and 96.6% of placebo patients ( $p = \text{ns}$ ). Six-month angiographic follow-up was obtained in all patients except one in the  $^{192}\text{Ir}$  group who sustained stent thrombosis and one in the placebo group who refused follow-up and died at 8 months due to cardiac arrest. One additional patient in the  $^{192}\text{Ir}$  group who had late angiographic follow-up (without evidence of restenosis) was disqualified from angiographic analysis for technical reasons.

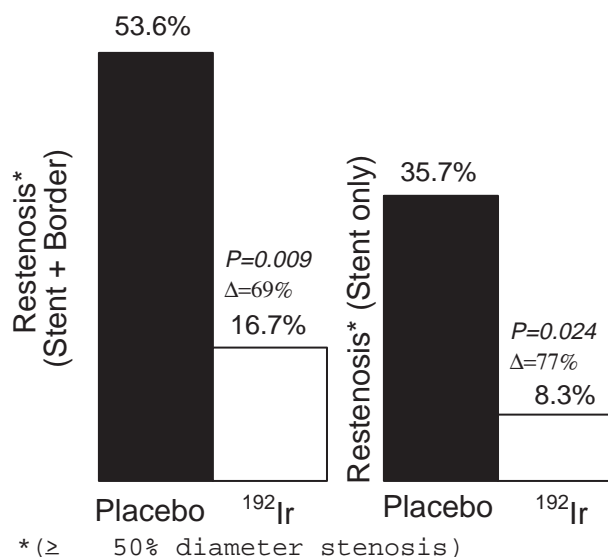
Angiographic indices of restenosis were markedly different in treated vs. placebo patients (Fig. 1). Late luminal loss was significantly lower in the  $^{192}\text{Ir}$  group ( $0.38 \pm 1.06$  mm vs.  $1.03 \pm 0.97$  mm;  $p = 0.009$ ). Notably, the late lumen loss index (9), a sensitive measure of a therapy's ability to preserve the post-procedural luminal diameter, was significantly lower in the  $^{192}\text{Ir}$  group ( $0.12 \pm 0.63$  vs.  $0.60 \pm 0.43$ ;  $p = 0.002$ ). Using a dichotomous definition, angiographic restenosis ( $\geq 50\%$  diameter stenosis at follow-up) either within the stent or at the stent border (outside the stent but still covered by the study ribbon) was only 16.7% in the  $^{192}\text{Ir}$  group compared to 53.6% for placebo patients ( $p = 0.025$ ) (Fig. 2). Restenosis limited to the stented segment oc-



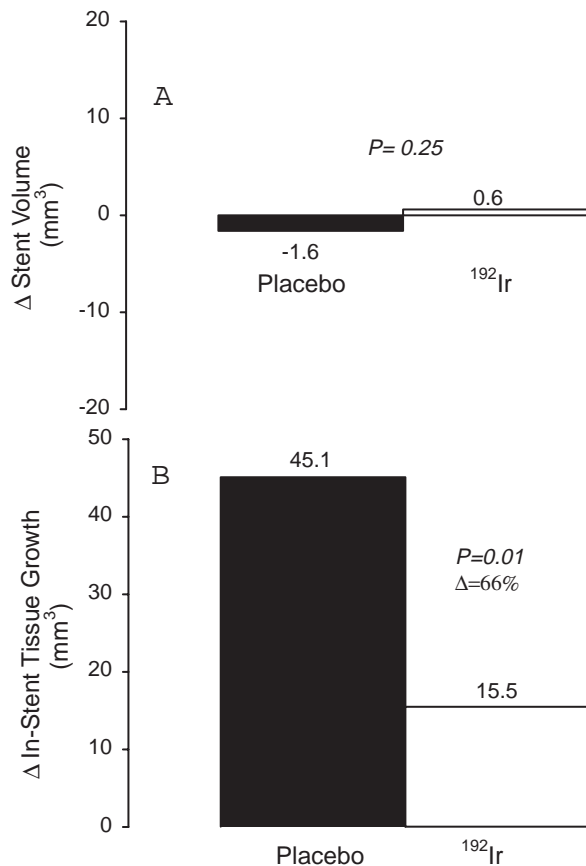
**Fig. 1.** Comparison of late luminal loss and late loss index in placebo versus  $^{192}\text{Ir}$  patients. Late loss was reduced by 63% while late loss index was reduced by 80%.

curred in only 8.3% of the  $^{192}\text{Ir}$  group compared to 35.7% of placebo patients ( $p = 0.024$ ).

The angiographic results were supported by independent intravascular ultrasound analysis (Fig. 3). By intravascular ultrasound analysis, there was no significant change in stent area or stent volume (Fig. 3A) between the immediate post-procedure and follow-up periods. The decrease in mean lumen area at follow-up was smaller in the  $^{192}\text{Ir}$  group ( $0.7 \pm 1.0$  mm<sup>2</sup> vs.  $2.2 \pm 1.8$  mm<sup>2</sup>;  $p = 0.003$ ), as was the increase in area of tissue growth (Fig. 3B) within the stent struts ( $0.7 \pm 0.9$  mm<sup>2</sup> vs.  $2.2 \pm 1.8$  mm<sup>2</sup>;  $p = 0.003$ ). The decrease in lumen volume was



**Fig. 2.** Comparison of a dichotomous definition of angiographic restenosis ( $\geq 50\%$  diameter stenosis) between placebo and  $^{192}\text{Ir}$  patients. Restenosis was reduced by 69% when both the stent and stent border were included in the analysis. Restenosis was reduced by 77% when only the stented region was measured.



**Fig. 3.** Intravascular ultrasound measurement of change in mean stent volume and change in the volume of tissue growth over a 6-month period in placebo versus <sup>192</sup>Ir patients. **A.** The stent volume did not change in either placebo or treated patients. **B.** Placebo patients demonstrated nearly three times the volume of tissue growth within stent struts at the follow-up examination.

also smaller in the <sup>192</sup>Ir group ( $16.4 \pm 24.0 \text{ mm}^3$  vs.  $44.3 \pm 34.6 \text{ mm}^3$ ;  $p = 0.008$ ), as was the increase in volume of tissue growth within stent

struts ( $15.5 \pm 22.7 \text{ mm}^3$  vs.  $45.1 \pm 39.4 \text{ mm}^3$ ;  $p = 0.0091$ ).

Clinical follow-up was obtained for all patients at a mean time of  $12.2 \pm 2.9$  months ( $12.0 \pm 2.8$  vs.  $12.2 \pm 3.1$  months in <sup>192</sup>Ir and placebo groups, respectively;  $p = \text{ns}$ ). The difference in angiographic restenosis rates was supported by a reduction in target lesion revascularization in the <sup>192</sup>Ir group (11.5% vs. 44.8%;  $p = 0.008$ ) (Table). Composite clinical events (death, myocardial infarction, stent thrombosis, or target lesion revascularization) were also significantly less frequent in <sup>192</sup>Ir patients (15.4% vs. 48.3%;  $p = 0.011$ ).

### Discussion

The SCRIPPS trial is the first double-blind, placebo-controlled, randomized trial of radiotherapy in patients undergoing coronary angioplasty. Although our patient numbers were small, we observed a striking reduction in restenosis when patients were treated with <sup>192</sup>Ir gamma radiation. This reduction in restenosis was similar for angiographic, ultrasonographic and clinical endpoints. Thus, gamma radiation using <sup>192</sup>Ir is the very first therapeutic agent, of more than 50 clinically tested (10), to demonstrate an impact on neointima formation after angioplasty.

Other clinical trials of intravascular gamma radiation therapy to reduce restenosis are limited, but data are rapidly accumulating. In one very early study, Bottcher (11, 12) used <sup>192</sup>Ir to treat 13 patients with angioplasty plus stent implantation for femoral artery restenosis. All 13 patients also received 12 Gy radiation immediately after the procedure. Clinical follow-up indicated no recurrent restenosis during the sub-

**TABLE**  
*Clinical Events at 12-Month Follow-up*

	<sup>192</sup> Ir (n = 26)	Placebo (n = 29)	p
Death	0	1 (3.4%)	ns
MI*	1 (3.8%)	0	ns
Target lesion revascularization	3 (11.5%)	13 (44.8%)	0.008
Death, MI, stent thrombosis or target lesion revascularization	4 (15.4%)	14 (48.3%)	0.011
Death, MI, stent thrombosis, target lesion revascularization or non-target lesion revascularization	5 (19.2%)	18 (62.1%)	0.002

\*MI = myocardial infarction

sequent 3–27 months. Steidle (13) also used  $^{192}\text{Ir}$  to treat 24 patients for femoral artery stenosis with stent implantation. Percutaneous radiation therapy with 2.5 Gy per day for 5 days, for a total of 12.5 Gy, was administered to 11 of these 24 patients. Over a 7-month follow-up period, reocclusion occurred in 2 of the 11 patients in the radiation group and 5 of the 13 patients in the no-radiation group. Condado et al. (14) treated 21 patients undergoing coronary angioplasty with  $^{192}\text{Ir}$ . While there was no control group, follow-up results were very encouraging, with a reported late loss index of 0.19 and restenosis rate of 27.3%.

Beta emitters differ from the gamma energy used in the above trials in that such radiation is less penetrating and more easily shielded, making it somewhat easier to handle in the catheterization laboratory environment. However, questions have been raised concerning the ability of a beta emitter to provide therapeutic radiation doses to the required depth. The results to date are conflicting (15). Verin et al. (16) treated 15 patients undergoing coronary angioplasty with  $^{90}\text{Y}$ , a beta emitter. The results were disappointing, with a loss index of 50% and restenosis rate of 40% at 6 months. These investigators are currently pursuing subsequent trials using higher dose prescriptions. King et al. (17) used  $^{90}\text{Sr}/\text{Y}$ , also a beta emitter, to treat 21 patients undergoing coronary angioplasty. Although there was no control group, the reported 6-month restenosis rate of 17% and loss index of 0.05% were very encouraging. These favorable results inspired a 1,400-patient, multicenter, randomized trial (the Beta-Cath<sup>TM</sup> trial) for *de novo* lesions and a 476-patient trial (the START trial) to test  $^{90}\text{Sr}/\text{Y}$  in patients with in-stent restenosis. The recently reported 6-month angiographic and clinical results of the START trial were strongly positive, providing significant confirmation of radiation's efficacy in limiting restenosis. Compared to the placebo group, patients with in-stent restenosis receiving radiation sustained a 36% reduction in subsequent restenosis, from 45% to 29% ( $p = 0.001$ ). Clinical results were also impressive, with the need for target vessel revascularization falling from 24% in the placebo group to 16% in treated patients ( $p = 0.026$ ) (NoVoste Announces Results of START TRIAL, NoVoste Press Release, March 12, 2000.)

Finally, clinical investigations of very novel radiation delivery systems are just beginning. A beta-emitting ( $^{32}\text{P}$ ) coronary stent has recently been tested in a small feasibility trial

(18), as has a beta-emitting ( $^{188}\text{Re}$ ) liquid-filled balloon catheter. The results of these trials are pending.

The excitement generated by these results must be tempered by several concerns. Most important are the unknown long-term effects of intracoronary radiation. While previous experience with radiation therapy for benign disorders suggests no significant increased risk at these doses, patients treated in these early clinical trials must continue to be followed carefully over a longer time period. Further follow-up must also be undertaken to assure that the reduction in restenosis reported above is durable and will not dissipate over time.

The work ahead necessary to develop and refine clinically useful vascular radiotherapy systems is daunting. There are many unanswered questions. What will be the most practical catheter-based gamma radiation system? Can beta radiation penetrate deep enough into the diseased vessel wall to provide clinical efficacy? Will radioactive stents be effective, or will they be limited by dose heterogeneity, edge effect, and/or thrombotic events? If radiation is proven to have long-lasting efficacy, should it be used for all patients undergoing angioplasty or confined only to patients with restenosis and/or other subgroups? Will radiation therapy be so effective that it will replace coronary stents, or will it always be used as an adjunct to a stenting strategy?

These questions provide a foundation for the next decade of investigation. After the past decade of failures in the struggle against restenosis, the next decade promises more success.

### Acknowledgment

The author is indebted to the extensive help and collaboration of his co-workers: 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 Steuteran, M.S., Nancy B. Morris, R.N., and Martin B. Leon, M.D., as well as Krishnan Suthanthiran of Best Industries, Inc.

### References

1. 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.
2. Mintz GS, Popma JJ, Pichard AD, et al. Arterial remodeling after coronary angioplasty. A serial intravascular ultrasound study. *Circulation* 1996; 94:35–43.

3. Serruys PW, de Jaegere P, Kiemeneij F, et al. for the Benestent Study Group. A comparison of balloon-expandable stent implantation with balloon angioplasty in patients with coronary artery disease. *N Engl J Med* 1994; 331:489–495.
4. 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.
5. Wiedermann JG, Marboe C, Amols H, et al. Intracoronary irradiation markedly reduces restenosis after balloon angioplasty in a porcine model. *J Am Coll Cardiol* 1994; 23:1491–1498.
6. Waksman R, Robinson KA, Crocker IR, et al. 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; 91:1533–1539.
7. 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; 92:1570–1575.
8. Laird JR, Carter AJ, Kufs WM, et al. Inhibition of neointimal proliferation with low-dose irradiation from a  $\beta$ -particle-emitting stent. *Circulation* 1996; 93:529–536.
9. Teirstein PS, Massullo V, Jani S, et al. Catheter-based radiotherapy to inhibit restenosis after coronary stenting. *N Engl J Med* 1997; 336:1697–1703.
10. Handley DA. Experimental therapeutics and clinical studies in (re)stenosis. *Micron* 1995; 26:51–68.
11. Bottcher HD, Schopohl B, Liermann D, et al. 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; 29:183–186.
12. Liermann DD, Bottcher HD, Kollatch J, et al. Prophylactic endovascular radiotherapy to prevent intimal hyperplasia after stent implantation in femoropopliteal arteries. *Cardiovasc Intervent Radiol* 1994; 17:12–16.
13. Steidle B. Preventive percutaneous radiotherapy for avoiding hyperplasia of the intima following angioplasty together with stent implantation [German]. *Strahlenther Onkol* 1994; 170:151–154.
14. Condado JA, Waksman R, Gurdziel O, et al. Long-term angiographic and clinical outcome after percutaneous transluminal coronary angioplasty and intracoronary radiation therapy in humans. *Circulation* 1997; 96:727–732.
15. Teirstein P. -radiation to reduce restenosis. Too little, too late. *Circulation* 1997; 95:1095–1097.
16. Verin V, Urban P, Popowski Y, et al. Feasibility of intracoronary  $\beta$ -irradiation to reduce restenosis after balloon angioplasty. A clinical pilot study. *Circulation* 1997; 95:1138–1144.
17. King SB 3rd, Williams DO, Chougule P, et al. Endovascular beta-radiation to reduce restenosis after coronary balloon angioplasty: Results of the beta energy restenosis trial (BERT). *Circulation* 1998; 97:2025–2030.
18. Fischell TA. The radioactive beta-emitting stent (Isostent): Animal studies and planned clinical trials. *Am J Cardiol* 1996; 78:45–50.