

## Intracoronary Radiation Therapy (IRT) for In-Stent Restenosis

Dong-Hoon Cha, MD, PhD

Department of Cardiology, Pundang CHA Hospital, Pochon CHA University, Sungnam, Korea  
Vascular Brachytherapy Institute, Cardiology Research Institute, Washington Hospital Center,  
Washington, DC, USA

### ABSTRACT

The efficacy of beta and gamma emitters in reducing clinical and angiographic restenosis in patients with in-stent restenosis has been confirmed by a number of studies. This review is intended to give an overview of the individual trials, summarize pertinent lessons that have been learned and give insight into the future of intracoronary radiation. The encouraging results from the clinical trials have established vascular brachytherapy as a standard of care for patients with in-stent restenosis. (Korean Circulation J 2004; 34(1): 9-22)

**KEY WORDS :** Brachytherapy; Clinical trial; Coronary restenosis; Stents.

### Introduction

In-stent restenosis (ISR) has become a major clinical problem, with a rate of 7–37% of patients who undergo stent implantation, and is dependent on patient characteristics, lesion morphology, and procedural technique.<sup>1)</sup>

Annually, 800,000 new stents are deployed worldwide with 450,000 coronary angioplasties being performed on *de novo* and restenotic lesions in the US alone.<sup>2)</sup> The recurrence rate after treatment for ISR varies among reported series but remains high in the range 50–85% regardless of treatment modalities, including balloon angioplasty, rotational atherectomy, excimer laser ablation, and repeat stenting. Especially, the diffuse pattern of ISR (>10 mm) is associated with even higher rates of recurrence and presents a therapeutic challenge.<sup>3-6)</sup> Serial intravascular ultrasound studies have demonstrated that

ISR results primarily from neointimal tissue proliferation distributed either focally or diffusely over the entire length of the stent.<sup>7)8)</sup> The recently introduced drug coated stents have promised amazing results and offer an extraordinary cure for restenosis.<sup>9)</sup> However, the utility of drug coated stents for ISR remains unknown. Clinical feasibility studies in patients have suggested reduced postangioplasty restenosis after gamma and beta radiation therapy.<sup>10)11)</sup> Intracoronary radiation therapy (IRT) with gamma and beta sources for ISR has offered a therapeutic strategy that is more refined than conventional therapy.

### Gamma radiation for In-stent restenosis (ISR)

The only gamma emitter used in clinical trials for ISR is <sup>192</sup>Iridium (<sup>192</sup>Ir).

The efficacy of <sup>192</sup>Ir in reducing clinical and angiographic restenosis in patients with ISR has been confirmed by a number of studies, including two single-center trials, SCRIPPS and WRIST, a multicenter trial, GAMMA-1, and a registry, GAMMA-2 (Table 1). All of these trials were performed using a manual delivery system with a non-centering catheter with either IVUS-based or fixed depth dosimetry.

**Received :** February 19, 2003

**Accepted :** August 7, 2003

**Correspondence :** Dong-Hoon Cha, MD, Department of Cardiology, Pundang CHA Hospital, Pochon CHA University, Yatap-dong, Pundang-gu, Sungnam 463-712, Korea  
Tel : 82-31-780-5491, Fax : 82-31-780-5857  
E-mail : chadhmd@hotmail.com

**SCRIPPS (Scripps coronary radiation to inhibit proliferation post stenting)**

SCRIPPS was the first randomized trial of the safety and efficacy of intracoronary gamma radiation given as

adjunctive therapy to stents. In this study, 26 of 54 patients were randomized to receive  $^{192}\text{Ir}$  (8–30 Gy, dosimetry guided by IVUS) utilizing a ribbon (19–35 mm) delivered in a non-centered, closed-end, lumen catheter

**Table 1.** Clinical trials for in-stent restenosis using catheter-based systems with gamma radiation

Study name	Design	Radiation system	Dose (Gy)	Results and status
SCRIPPS	Single center, double-blind, randomized in 55 patients with restenosis.	Hand delivered 0.030" nylon ribbon with seeds (Best Medical) into a non-centered closed end lumen 4.5F catheter (Navius)	$\geq 8$ – $<30$ to media by IVUS	Completed. Showed reduction of restenosis in the irradiated group maintained at 3 years.
WRIST	Single center, double-blind, randomized in 130 patients with ISR. (100 natives, 30 vein grafts)	Hand delivered 0.030" nylon ribbon with Ir-192 seeds (Best Medical) into a non-centered closed end lumen 5.0F catheter (Medtronic)	15 at 2.0 mm for vessels 3–4 mm. 18 for vessels $>4$ mm	Completed. Showed reduction in restenosis (67%) and revascularization (63%). At 2 years reduction in TLR and TVR $<40\%$ .
LONG WRIST	Two center, double-blind, randomized in 120 patients with ISR lesions (36–80 mm)	Hand delivered 0.030" nylon ribbon with seeds (Best Medical) into a non-centered closed end lumen 5.0 F catheter (Medtronic)	15 at 2.0 mm for vessels 3–4 mm	Completed. At 6 months data restenosis rates lower in irradiated group 32% versus control 71%.
LONG WRIST HD	Single center, registry in 120 patients with ISR lesions (36–80 mm)	Hand delivered 0.030" nylon ribbon with seeds (Best Medical) into a non-centered closed end lumen 5.0 F catheter (Medtronic)	18 at 20 mm for vessels 3–4 mm	Enrollment completed. Initial results in 60 patients demonstrated further reduction of the restenosis rate compared to 15 Gy
SVG WRIST	Multicenter, double-blind, randomized in 120 patients with ISR	Hand delivered 0.030" nylon ribbon with seeds (Best Medical) into a non-centered closed end lumen 5.0F catheter (Medtronic)	15 at 2mm for vessels $<4.0$ mm	Completed. At 6 months, irradiated patients had reduced restenosis (15% vs. 43%, $p=0.004$ ) & MACE (20% vs. 55%, $p<0.05$ )
GAMMA-1	Multicenter, randomized double blind study in 252 patients with ISR	Hand delivered 0.030" nylon ribbon with seeds (Best Medical) into a non-centered closed end lumen 4.0F catheter (Cordis)	$\geq 8$ – $<30$ to media by IVUS	Completed. Patients with radiation therapy has significant reduction of the restenosis (22% versus 52%), and clinical TLR at 9 months.
GAMMA-2	Multicenter, registry in 125 patients with ISR	Hand delivered 0.030" nylon ribbon with seeds (Best Medical) into a non-centered closed end lumen 4.0F catheter (Cordis)	14 at 2 mm from the source	Completed. Similar to Gamma 1. MACE was reduced by 36% and TLR was reduced by 48% as compared to placebo.
ARTISTIC	Multicenter, double-blind, randomized in 110 patients with ISR	Mechanical delivery of 0.014" fixed wire 30mm (Angiorad) into a monorail closed end lumen with small balloon 3.2F catheter	12–15–18 at 2.0 mm from the source	Feasibility phase completed, with low restenosis rate. Pivotal study commenced.

IVUS: intravascular ultrasound, ISR: in-stent restenosis, TLR: target lesion revascularization, TVR: target vessel revascularization, MACE: major adverse cardiac events

Table 1. Continued

Study name	Design	Radiation system	Dose (Gy)	Results and status
WRIST PLUS	A registry of 120 patients with ISR with 6 months of clopidogrel 75 mg QD	Hand delivered 0.030" nylon ribbon with Ir-192 seeds into a non-centered closed end lumen 4.0F catheter	14 at 2 mm distance from the source	Completed. 6 months angiography shows significant reduction of late total occlusion/thrombosis with 6 months clopidogrel
WRIST-12	A registry of 120 patients with ISR-12 months of clopidogrel & 15 months angiographic study	Hand delivered 0.030" nylon ribbon with Ir-192 seeds into a non-centered closed end lumen 4.0F catheter	14 at 2 mm distance from the source	Enrollment completed. Results available early 2002.
CURE	A registry of 120 patients with ISR not considered good candidates for CABG or medical therapy.	Hand delivered 0.030" nylon ribbon with Ir-192 seeds into closed end lumen 4.0F catheter (Cordis)	14 at 2 mm from the source	Enrollment extended. Clinical follow-up available for initial 120 patients. 31% TVR and 33% MACE at 6 months.
SCRIPPS-2	Single center randomized study for patients with diffuse ISR	Hand delivered 0.030" nylon ribbon with Ir-192 seeds into a non-centered closed end lumen 4.0F catheter (Cordis)	≥8–<30 to media by IVUS	Enrollment completed. Follow up will be available in the fall of 2000
SCRIPPS-3	A registry of 320 patients with ISR with 6 months of PLAVIX	Hand delivered 0.030" nylon ribbon with Ir-192 seeds into a non-centered closed end lumen 4.0F catheter (Cordis)	14 at 2 mm distance from the source	Enrollment completed. Clinical follow-up only will be available in 2001.
WRIST-12	A registry of 120 patients with ISR with 12 months of PLAVIX and 15 months angiographic study	Hand delivered 0.030" nylon ribbon with Ir-192 seeds into a non-centered closed end lumen 4.0F catheter (Cordis)	14 at 2 mm distance from the source	Enrollment completed. Results available early 2002.
GAMMA-5	Multicenter, registry in 600 patients with 12 months plavix for new stent & 6 months for no new stent	Hand delivered 0.030" nylon ribbon with seeds (Best Medical) into a non-centered closed end lumen 4.0F catheter (Cordis)	14 at 2 mm from the source	Study initiated in the summer of 2000.
EDGE WRIST	A registry of 120 patients with ISR with longer treatment margins	Hand delivered 0.030" nylon ribbon with Ir-192 seeds into closed end lumen 4.0F catheter (Cordis)	14 at 2 mm from the source	Study initiated in the fall of 2000.
Integrilin WRIST	Randomized 300 patient trial: radiation for ISR ± Integrilin	Hand delivered 0.030" nylon ribbon with Ir-192 seeds into closed end lumen 4.0F catheter (Cordis)	14 at 2 mm from the source	Study initiated in 2000. Preliminary results will be available early 2002.
RE-WRIST	30 patient registry of re-treatment with radiation for refractory ISR	Hand delivered 0.030" nylon ribbon with Ir-192 seeds into closed end lumen 4.0F catheter	15 at 2 mm from the source	9 patients enrolled. Complete 6-month follow-up available mid 2002.

ISR: in-stent restenosis, CABG: coronary artery bypass graft

at the treatment site (dwell time: 20–45 minutes). Only 35 patients in this cohort were ISR patients. This study demonstrated that at six-months the angiographic restenosis rate was reduced by radiation treatment (17% vs.

54%,  $p < 0.01$ ). At three years, these results remained consistent (33% vs. 64.3%,  $p < 0.05$ ). Subanalysis of the lumen diameter for patients who did not have further intervention demonstrated minimal reduction of the mi-

nimum lumen diameter (MLD) of the irradiated segments versus control at 3 years. There were no evident clinical complications resulting from the radiation treatment, and clinical benefits were maintained at three years with a significant reduction in the need for target lesion revascularization (TLR) ( $p=0.004$ ). A subgroup analysis for the 35 patients with ISR showed a 70% reduction of the recurrence rate in the irradiated group versus the placebo group.<sup>12)</sup>

#### **WRIST (Washington radiation for ISR trial)**

WRIST is a series of studies that were designed to evaluate the effectiveness of radiation therapy for ISR.<sup>13)</sup> The gamma radiation in these studies was composed of a ribbon with different trains of radioactive ( $^{192}\text{Ir}$ ) seeds, which was inserted manually into a closed-end lumen catheter. In the initial study, 130 patients (100 patients with native coronaries and 30 patients with vein grafts) with ISR lesions (up to 47 mm in length) were blindly randomized to treatment with either placebo or 15 Gy of  $^{192}\text{Ir}$  at 2 mm from the source of the vessel wall. At six months, clinical and angiographic follow-up showed a dramatic reduction of the restenosis rate between the irradiated group and the control group, 19% vs. 58%, respectively ( $p=0.0001$ ). There was a 79% reduction in the need for revascularization and a 63% reduction in major adverse cardiac events (MACE: death, Q-wave myocardial infarction or target vessel revascularization [TVR]) in the irradiated group compared to control. Intravascular ultrasound (IVUS) subanalysis demonstrated that 53% of lesions from the irradiated group had increased luminal dimensions and regression of neointimal tissue at 6 months. Between 6 and 48 months, the following interesting observation was noted: the IRT patients had more TLR (18% vs. 2%,  $p=0.001$ ) and TVR (19% vs. 3%,  $p=0.003$ ) than the placebo patients. This likely reflects an initial freezing of neointimal growth with IRT, with diminished effectiveness over time. However, at 4-year clinical follow-up, the IRT cohort continued to have markedly lower MACE rates than controls (40% vs. 65%,  $p=0.005$ ). The WRIST

study is considered to be a landmark in establishing gamma radiation for the treatment of ISR.

#### **LONG WRIST**

LONG WRIST is a randomized trial involving 120 symptomatic patients with diffuse ISR lesions 36 mm to 80 mm long (mean stent length: 70 mm) who received either a ribbon bearing  $^{192}\text{Ir}$  seeds or placebo seeds delivered to the target site via a noncentered, closed-lumen catheter. The radiation dosage consisted of 14–15 Gy at 2 mm distance from the center of the source. Quantitative angiography at six months disclosed rates of restenosis of 32% in the irradiated group and 71% in the control group within the stented segment only ( $p=0.0002$ ). Rates of restenosis considering only the segment containing the lesion were 46% and 78%, respectively ( $p=0.03$ ). The six-month MACE rates (death, nonfatal Q-wave or non-Q-wave myocardial infarction, TLR) were 38.3% and 61.7%, respectively ( $p=0.01$ ), with most of the significant difference accounted for by the TLR component, the rates for which were 30% and 60%, respectively ( $p=0.001$ ). The combined rate of total target-vessel occlusion or late thrombosis at any time during the follow-up was 15% of irradiated patients and 6.7% of controls.

#### **LONG WRIST high dose**

LONG WRIST High Dose is a registry of 60 patients with similar entry criteria to LONG WRIST, except a higher radiation dose was prescribed with 18 Gy delivered at 2 mm distance from the center of the source and the second 60 consecutive patients of LONG WRIST High Dose received prolonged antiplatelet therapy (clopidogrel or ticlopidine) for 6 months instead of one month. Baseline clinical and angiographic details were similar in both study groups. At 6-month follow-up, MACE (death, Q-wave myocardial infarction or TVR) rates were reduced by 39% in the high dose group (23% vs. 38%,  $p=0.11$ ) compared to LONG WRIST and patients in the LONG WRIST High Dose group with 6 months anti-platelet therapy had a strikingly low rate of TVR

(17%) and MACE (17%) compared to one month of antiplatelet therapy and the LONG WRIST groups. IVUS analysis post-intervention and at 6-month follow-up was performed in 25 patients from LONG WRIST High Dose and in 30 IRT and 34 placebo patients from LONG WRIST.<sup>14)</sup> Stent length was longer in LONG WRIST High Dose than in placebo or treated patients in Long WRIST ( $p=0.006$  and  $p=0.013$ , respectively). At follow-up, the minimum lumen area was largest in the LONG WRIST High Dose patients ( $4.0 \pm 1.4$  mm<sup>2</sup>); areas were  $2.9 \pm 1.0$  mm<sup>2</sup> in IRT patients and  $1.9 \pm 1.1$  mm<sup>2</sup> in placebo patients in Long WRIST ( $p<0.005$  for all comparisons). The clinical and serial IVUS analyses show that IRT reduces recurrent in-stent neointimal hyperplasia in long, diffuse ISR lesions; furthermore diffuse lesions may require higher radiation doses and prolonged antiplatelet therapy to maintain the efficacy seen in focal lesions and minimize recurrent clinical events at 6 months.

#### **SVG WRIST (Washington radiation for ISR trial for saphenous vein grafts)**

SVG WRIST is an FDA approved, double-blinded, multicenter, randomized trial in patients undergoing post coronary bypass surgery with diffuse ISR in their saphenous vein grafts (SVG). SVG WRIST was the first study to examine the effects of gamma radiation therapy on patients with ISR in bypass grafts. One hundred and twenty patients with diffuse ISR in SVG underwent percutaneous coronary transluminal angioplasty (PTCA), laser ablation or rotational atherectomy, and or additional stents. After the intervention, a non-centered, closed end lumen catheter was positioned at the treated site, and patients were randomly assigned to a ribbon either with 192-Ir or with non-radioactive seeds both delivered by hand. Different ribbon lengths of 6, 10 and 14 seeds with a mean radiation length of  $34 \pm 22$  mm were used to cover lesions  $<47$  mm in length. The prescribed radiation doses were 14 or 15 Gy to a 2 mm radial distance from the center of the source for vessels with a diameter of 4 mm and 15 Gy at 2.4 mm for vessels  $>4$

mm in diameter. The patients with restenosis at follow-up were eligible to receive radiation if initially randomized to placebo. The closed end lumen catheter with either the active or the placebo seeds was delivered successfully to all patients. A mean dwell time of  $21.1 \pm 4.8$  minutes was well tolerated in irradiated patients. At 30 days, there were no adverse events related to the radiation therapy. At 6 months, the restenosis rate was significantly lower in the irradiated group than in the control (15% vs. 43%,  $p=0.004$ ). The need for repeat intervention at the treatment site was significantly reduced by 79% in the irradiated group compared to control (10% vs. 48%,  $p<0.001$ ), and the overall major cardiac events were reduced in the irradiated group (20% vs. 55%,  $p<0.001$ ). The rate of late thrombosis in the irradiated group was 1.7% versus 6.7% in the control ( $p=NS$ ), and there was no excess of edge effect in the irradiated group when compared to the control. IVUS analysis post-intervention and at 6-month follow-up was performed. In the irradiated patients there was no change in stent, lumen, or intimal hyperplasia (IH) area or volume. In the placebo patients there was an increase in intra-stent IH area ( $p<0.0001$ ) and volume ( $p<0.0001$ ) that caused a decrease in lumen area ( $p<0.0001$ ) and volume ( $p<0.0001$ ); these changes were significantly larger than in the irradiated group. Conventional treatment of ISR in bypass grafts is associated with a high recurrence rate. The SVG WRIST study demonstrated that catheter based gamma radiation therapy for ISR in bypass grafts was safe and effective in reducing the overall restenosis rate and the need for repeat revascularization. We examined 1142 patients (230 in SVG and 912 in native coronaries) from the WRIST series of studies and found that gamma IRT in SVG had similar outcome to native coronaries with equivalent rates of angiographic restenosis (22% vs. 29%,  $p=NS$ ) and TVR (27% vs. 23%,  $p=NS$ ) at 6-month follow-up.

#### **WRIST PLUS**

WRIST PLUS was driven by the late thrombosis risk seen in the early radiation trials. This was a registry of

120 patients with similar entry criteria to the WRIST protocol, but with 6 months of clopidogrel 75 mg QD in addition to aspirin, designed to evaluate whether prolonged antiplatelet therapy would reduce late thrombotic event rates.<sup>15)16)</sup> The TLR rate was 21%, TVR 23%, and cumulative MACE 23% at 6 months. Eight patients (5.8%) had late total occlusion at 6-month follow-up, of which 3 (2.5%) developed late thrombosis. When the WRIST PLUS group was compared to IRT patients in WRIST and LONG WRIST (1 month antiplatelet treatment), the strategy of prolonged antiplatelet therapy reduced the thrombosis rate (2.5% vs. 9.6%,  $p=0.02$ ), to levels seen in controls. No events have been reported to date in 29 patients who continued taking clopidogrel. The optimal duration of clopidogrel therapy to prevent late total occlusion beyond 6 months is still unknown, which led to the inception of WRIST 12.

#### **WRIST 12 (Washington Radiation for ISR Trial with 12 months of Clopidogrel)**

WRIST 12 is an FDA approved registry of 120 patients with diffuse ISR in native coronaries and vein grafts with lesions <80 mm in length. Patients underwent intervention using balloon, atheroablation and/or re-stenting (38% patients), and were then treated with IRT using 192-Iridium. Patients were discharged on 12 months of clopidogrel (75 mg QD) and scheduled for angiographic follow-up at 15 months. Enrollment of patients in WRIST 12 was completed in September 2000. Radiation was delivered successfully to all patients. Clopidogrel was tolerated well and there was no report of leukopenia. No deaths or Q-wave myocardial infarctions were reported at 6 months, and the MACE rate was 13%. We eagerly await comparison of the clinical and angiographic follow-up between 6 (WRIST PLUS) versus 12 months (WRIST 12) of clopidogrel. It is plausible that at least 12 months clopidogrel is required following IRT.

#### **CURE WRIST (Compassionate WRIST)**

CURE WRIST is an open label registry of patients

with ISR who had at least 2 episodes of restenosis at the target lesion and were not considered good candidates for coronary artery bypass graft (CABG) or medical therapy. Patients were eligible to participate if approved by all members of a committee (interventional cardiologist, radiation oncologist and cardiac surgeon). The angioplasty procedure involved  $\geq 1$  vessel (native coronary artery or SVG) followed by IRT with 192-Iridium (14 or 15 Gy to 2 mm). At this point in time, a total of 173 patients were enrolled. The mean age of the cohort was  $63 \pm 16$  years, 70% males, 45% diabetics, and 87% had previous cardiac bypass grafting. The target lesion involved a SVG in 40% of cases and 40% of patients received re-stenting. The IRT was delivered successfully in all cases with a mean source train length of  $61 \pm 19$  mm. Six month, 1 and 2 year events confirmed sustainable outcomes in this refractory patient cohort who did not respond to conventional standard of care.

#### **GAMMA-1**

GAMMA-1 is a multicenter, randomized, double-blind trial studying the effects of hand-delivered <sup>192</sup>Ir ribbon using IVUS to guide dosimetry (dose range 8–30 Gy) in 252 patients with ISR. Six-month angiographic results revealed significant reductions in the in-stent (22% vs. 52%) and in-lesion (33% vs. 56%,  $p=0.006$ ) angiographic restenosis rates of the radiation arm versus control. Subanalysis for lesion length demonstrated a 70% reduction in the angiographic restenosis rate for lesions <30 mm in length versus 48% for 30–45 mm lesions.<sup>17)</sup> In addition, edge effect was noted in patients who did not have enough coverage of the lesion by the radioactive seeds. Clinical events demonstrated a reduction in the TLR rate from 42% to 24%. However, the rate of death (3% versus 0.8%) and the rate of acute MI (12% versus 6%) were higher in the irradiated group than in the control. These complications were related in part to the late thrombosis phenomenon.

#### **GAMMA-2**

GAMMA-2 is a registry of 125 patients who were

treated for the same inclusion/exclusion criteria as GAMMA-1 but with a fixed dosimetry of 14 Gy at 2 mm from the center of the source. The treated lesions in GAMMA-2 were more heavily calcified, whereby 45% of patients required rotablation in contrast to 26% of patients in GAMMA-1. Despite the differences in lesions, the results between GAMMA-1 and -2 were remarkably similar. Both studies had similar and infrequent in-hospital adverse clinical events (2%). GAMMA-2 patients had a lower post-procedural MLD; perhaps due to increased lesion complexity and the fact that fewer stents were placed in GAMMA-2 patients than in GAMMA-1. Similar to GAMMA-1, there was a 52% in-stent and a 40% in-lesion reduction in restenosis frequency. TLR was reduced by 48% and MACE was reduced by 36%. The late thrombosis rate was 4% at 270 days with only eight weeks of antiplatelet therapy. It is believed that prolonged antiplatelet therapy will remedy the incidence of late thrombosis.

#### **ARTISTIC (Angiorad radiation technology for ISR trial in native coronaries)**

ARTISTIC is a blinded, randomized trial examining the benefits of using a flexible, 30 mm  $^{192}\text{Ir}$  wire source in 300 patients with ISR in native coronary arteries.<sup>18)</sup> The pilot phase of this study was recently completed and involved 26 patients at two centers, all of whom received radiation treatment. Inclusion criteria consisted of lesions <25 mm in length with a reference vessel diameter (RVD) between 2.5 and 5.0 mm and a degree of stenosis between 50–99%. Radiation was successfully delivered to 25 of 26 patients. At six-month angiographic follow-up, low binary restenosis rates of 14% were reported with a late loss index of 0.12, and a 15% rate of MACE. A randomized study using the same system was halted after enrolling 110 patients. Preliminary result of this study demonstrated significant reduction in the angiographic restenosis rate in the irradiated arm. A pivotal trial with the Angiorad system was in progress at the time of writing.

#### **EDGE WRIST**

EDGE WRIST is a single center registry, which is designed to address the question whether large margins (12 mm) from the injured segment will reduce the edge effect phenomenon. This study continues enrollment with projected completion in mid 2002. Edge restenosis may be a limitation of intracoronary irradiation to prevent ISR. Inadequate radiation source coverage of the injured segment which is so called “geographical miss” has been proposed as a cause of edge restenosis. We examined 506 patients from the WRIST series and found edge restenosis in 43 patients (8.5%). The majority of these lesions were focal (<10 mm). Event-free survival at 6 months was 85% and at 12 months 82%, which suggests encouraging outcomes after repeat intervention with conventional strategies. The coronary angiograms of 100 patients from WRIST were analyzed for edge restenosis (follow-up stenosis of  $\geq 50\%$  occurring  $\leq 5$  mm proximally and distally to the last seed of the radiation source) and geographic miss (injured segments not covered by the radiation source).<sup>19)</sup> Edge restenosis occurred in 10% of IRT patients and 4.7% of controls ( $p=\text{NS}$ ). In patients with geographic miss, edge restenosis occurred in 21% of IRT patients and 7% of controls. In both groups (IRT and controls), late edge lumen loss was greater in IRT patients than in controls ( $p<0.001$ ). A low radiation dose in the fall-off zone at the source ends in combination with vessel injury may stimulate neointimal formation. It is critical to ensure meticulous positioning of the source train in relation to the injured vessel segment in an effort to avoid edge restenosis.

#### **Integrilin WRIST**

Integrilin WRIST is also a single centered study of 300 patients, with randomization to glycoprotein IIb/IIIa antagonists (Integrilin) or placebo in patients receiving gamma radiation ( $^{192}\text{Ir}$ -Iridium) for ISR. This study specifically aimed to assess the impact of Integrilin in reducing early cardiac enzyme release after percutaneous intervention with the potential for improved longer-term clinical outcomes.

### Re-WRIST

Approximately one quarter of the patients enrolled in radiation studies for ISR required repeat revascularization to the irradiated site. Re-WRIST is a 30 patient registry evaluating the safety and efficacy re-treatment with IRT in patients with refractory ISR. Patients had to fail an additional angioplasty after the index radiation procedure to be eligible. The prescribed dose is 15 Gy to a 2 mm radial distance from the center of the source. All patients received 6 months of clopidogrel post-procedure. At present, 9 patients were enrolled in the Re-WRIST registry. The mean age of the cohort was  $65 \pm 10$  years (4 males, 3 diabetics and 7 patients had previous CABG). Six ISR lesions were in native coronary arteries and 3 in SVG. The mean time interval between radiation treatments was 18 months (range 6.4–28.9) and the mean number of previous interventions to the target lesion was  $4.1 \pm 1.5$ . The radiation was delivered successfully in all patients with no procedural or hospital complications. Balloon angioplasty alone was performed in 6 of 9 patients and no patient received additional stents. No clinical events were reported to 30-day follow-up. From this preliminary stage result, repeat radiation therapy appears feasible; however clinical follow-up is needed.

## Beta Radiation for ISR

### Physics of beta emitters

The beta isotopes currently in preclinical or clinical

use include 90-Yttrium ( $^{90}\text{Y}$ ), 90-Strontium ( $^{90}\text{Sr/Y}$ ), 32-Phosphorus ( $^{32}\text{P}$ ), 106-Ruthenium ( $^{106}\text{Ru}$ ), 133-Xenon ( $^{133}\text{Xe}$ ), 186-Rhenium ( $^{186}\text{Re}$ ), and 188-Rhenium ( $^{188}\text{Re}$ ) (Table 2). The majority of these isotopes are pure beta emitters, although some have weak gamma activity. Beta particles are free electrons that have been ejected from the nucleus of radioactive material. These high-energy beta particles travel meters in air but only millimeters in human tissue; therefore the radiation hazard of whole body exposure is minimal. Beta particles have a finite range in tissue proportional to their energy.<sup>20)</sup> A pure beta emitter provides an adequate dose distribution over the range of distances required for treatment of restenosis, with doses per emission up to fifty times higher than gamma sources.

Beta particles interact with material to form electromagnetic photons called Bremsstrahlung radiation or 'braking radiation'.<sup>21)</sup> Bremsstrahlung is produced in dense target material such as lead or stainless steel, with penetration similar to X-ray sources. The importance of this radiation is appreciated in considering the use of  $^{90}\text{Sr/Y}$ ; two thirds of the exposure comes from beta particles and one third Bremsstrahlung.

A concept pertinent to beta emitters is radioactive equilibrium. This describes the state in which a parent isotope ( $^{90}\text{Sr}$ ,  $^{106}\text{Ru}$ ,  $^{188}\text{W}$ ) decays with a long half-life but low beta energy, into a daughter isotope ( $^{90}\text{Y}$ ,  $^{106}\text{Rh}$  or  $^{188}\text{Re}$ , respectively) with a short half-life but higher, and thus therapeutic, beta energy. These 'isotope pairs' have been used effectively. The catheter delivered source

**Table 2.** Beta isotopes

Isotope	Half-life	Energy maximum (MeV)	Energy average (MeV)	Activity required	Delivery/Catheter	Afterloader
$^{90}\text{Sr/Y}$	28 yrs	2.28	0.93	50 mCi	Noncentered	Manual
$^{90}\text{Y}$	64 hrs	2.28	0.93	50 mCi	Segmented balloon	Automatic
$^{32}\text{P}$	14 days	1.71	0.69	40 mCi	Helical balloon	Automatic
$^{32}\text{P}$	14 days	1.71	0.69	1–20 $\mu\text{Ci}$	Isostent	—
$^{186}\text{Re}$	90 hrs	1.08	0.38	300 mCi	Liquid balloon	Manual
$^{188}\text{Re}$	17 hrs	2.12	0.77	100 mCi	Liquid balloon	Manual
$^{133}\text{Xe}$	5.3 days	0.36	0.11	2–5 mCi	Gas balloon	Automatic
$^{106}\text{Rh}$	1 yr	3.54	1.18	30 mCi	—	—



of  $^{90}\text{Sr}/\text{Y}$  contains approximately 100 mCi of beta-emitting isotope. Currently, the most advanced system of  $^{90}\text{Sr}/\text{Y}$  delivers effective radiation in about 3 minutes.<sup>22)</sup>  $^{90}\text{Sr}$  decays with the emission of moderate beta energy (0.6 MeV) to  $^{90}\text{Y}$ , which in turn decays with the emission of high-energy beta (2.27 MeV).

Clinical Trials of Beta Radiation In parallel to the encouraging results of gamma radiation in the treatment of patients with ISR, there have been large scale clinical studies testing the effectiveness of beta radiation for de novo, restenotic and ISR lesions. Important early studies included the Geneva trial and the Dose Finding study

BERT (Beta Energy Restenosis Trial) which used  $^{90}\text{Y}$ . In these studies, radiation was delivered safely with low rates of angiographic binary restenosis. The BRIE (Beta Radiation In Europe) registry used  $^{90}\text{Sr}/\text{Y}$  (Novoste system) and in the initial 149 patients, 6-month and one-year rates of target vessel revascularization (TVR) with PTCA were 22% and 31%, respectively. In 2 early studies using  $^{32}\text{P}$ , PREV-ENT (Proliferation Reduction with Vascular Energy Trial) demonstrated a reduced late loss index and binary restenosis with active treatment (Table 3).

**Table 3.** Clinical trials for In-stent restenosis using catheter-based systems with beta radiation

Study Name	Design	Radiation system	Isotope and dose (Gy)	Results and status
BETA CATH	Prospective, randomized, multicenter trial in de novo lesions (balloon alone or provisional stenting)	Beta CATH system 30 mm source train	$^{90}\text{Sr}/\text{Y}$ , 18–20 Gy at 2 mm	Completed. Showed reduction in TLR, TVR & MACE in irradiated patients treated with balloon alone. Stented radiated patients had worse outcomes (presumed geographic miss).
BETA WRIST	Registry for 50 patients with ISR	Schneider System 90 Y source centering balloon and an afterloader	Dose 20.6 at 1 mm from the balloon surface	Completed. Restenosis rate 22% at 6 months. MACE 46 % at 2 years (similar results to the gamma WRIST group).
START	Multicenter, randomized, double blind design for 476 ISR lesions ( $\leq 20$ mm)	Beta CATH system 30 mm source train	$^{90}\text{Sr}/\text{Y}$ , 18–20 Gy at 2 mm	Completed. Showed reduction in TLR (41%), TVR (33%) & MACE (31%) in the irradiated group. No late thrombosis.
START 40/20	A registry of 207 patients with ISR	Beta CATH system 40 mm source train	$^{90}\text{Sr}/\text{Y}$ , 18–20 Gy at 2 mm	Completed. No deleterious effects of adding 10mm of length to the source train. Lack of a relationship between geographic miss and outcomes for ISR
INHIBIT	Multicenter, double blind randomized for 332 patients with ISR	Automatic afterloader (Nucletron) 0.018" 27 mm fixed wire via a helical centering balloon	$^{32}\text{P}$ , Dose 20 Gy at 1 mm into vessel wall	Completed. Demonstrated reduction of 50% in restenosis (analysis segment) and 55% in MACE.
GALILE OTM INHIBIT	International multicenter registry in 120 patients with ISR	Automatic afterloader (Guidant GALILEO system) via a helical centering balloon	$^{32}\text{P}$ , 20 Gy at 1 mm into vessel wall	Enrollment completed. Results available late 2001.
BRITE	Feasibility study in patients with ISR lesions $< 25$ mm	The Radiance system with a deployable P-32 balloon	$^{32}\text{P}$ , 20 Gy at 1.0 mm from the balloon	Enrollment completed. Demonstrated safety at 30 days & single-digit 6-month restenosis rates.
CURE	60 patient de novo registry; (30 patients balloon and 30 patients stented)	Liquid filled balloon	$^{188}\text{Re}$ , 20 Gy to the balloon surface	12-month event free survival (TLR) – 75%

ISR: in-stent restenosis, TLR: target lesion revascularization, TVR: target vessel revascularization, MACE: major adverse cardiac events

## BETA-CATH

The Beta-Cath system trial was the first prospective, randomized, multi-center trial investigating the use of vascular brachytherapy for the prevention of restenosis in *de novo* lesions using a 30 mm  $^{90}\text{Sr}/\text{Y}$  source train in conjunction with stand alone balloon angioplasty, or provisional stent placement in which balloon angioplasty was suboptimal.<sup>23)</sup>

The primary endpoint of the study was 8-month TVF (Target Vessel Failure: death, MI, TVR). The inclusion criteria included a single lesion and single vessel intervention with a *de novo* or restenotic lesion  $>50\%$  (by visual assessment) in vessels with a RVD between 2.7 and 4.0 mm. The radiation dose prescription point was calculated at 2 mm from the center of the source axis: 16.1 Gy in RVD  $\geq 2.7 - \leq 3.3$  mm and 20.7 Gy in RVD  $\geq 3.3 - \leq 4.0$  mm. Baseline demographic and angiographic characteristics were similar between groups.

Comparison of placebo and radiation treatment from pooled PTCA and stent (antiplatelet therapy  $\geq 60$  days) groups showed equivalent 8-month TLR (15.4% vs. 13.7%,  $p=0.37$ ) and TVF/MACE (20.6% vs. 18.7%,  $p=0.40$ ). This study was the first to identify the higher-than-expected rate of late stent thrombosis when radiation was used with new stent implantation. The primary clinical endpoint, TVF, was not shown to be significantly lower in the combined radiation arms compared with combined placebo arms. Secondary analyses of beta radiation in the PTCA branch showed a 34.6% reduction for  $^{90}\text{Sr}/\text{Y}$  in TVF/MACE ( $p=0.06$ ), and a 37.6% reduction for  $^{90}\text{Sr}/\text{Y}$  in restenosis rate of the lesion segment ( $p=0.003$ ). The results in angiographic restenosis were disparate in the combined stent branches; a 28.9% reduction for  $^{90}\text{Sr}/\text{Y}$  in lesion segment restenosis rate ( $p=0.004$ ) and a 30% increase for  $^{90}\text{Sr}/\text{Y}$  in the analysis segment ( $p=0.004$ ).

The paradox of positive treatment effect for  $^{90}\text{Sr}/\text{Y}$  seen in lesion segment analysis and the negative treatment effect of  $^{90}\text{Sr}/\text{Y}$  seen in the analysis segment likely explains the negative treatment effect of  $^{90}\text{Sr}/\text{Y}$  on clinical restenosis in stents, and merits further investigation.

Geographic miss may have contributed to the negative results of  $^{90}\text{Sr}/\text{Y}$ . The overall positive results in the lesion segment analysis and the strong trends in the clinical outcomes in the PTCA branch suggests a potential role for  $^{90}\text{Sr}/\text{Y}$  radiation in the treatment of *de novo* coronary lesions if the increase in restenosis in the 'analysis segment' can be solved.

## BETA WRIST

BETA WRIST examined the efficacy of beta radiation for prevention of ISR, with similar design to the original WRIST study.<sup>24)</sup> This registry included 50 patients who were treated for ISR in native coronaries, 2.5–4.0 mm in diameter with lesions  $<50$  mm in length. Beta radiation using a  $^{90}\text{Y}$  source was administered using a centering catheter and an afterloader system. Clinical outcomes were compared between these patients and those of the original WRIST cohort (randomized to either placebo or  $^{192}\text{Ir}$ ). Angiographic restenosis at 6 months in BETA WRIST was 22%, with a late total occlusion rate of 12%. In comparison to the historical control group of WRIST, Beta WRIST patients demonstrated a 58% reduction in the rate of TLR and 53% reduction in TVR at 6 months ( $p<0.001$ ). No differences were detected in comparison to the gamma-radiated patients of WRIST. The clinical benefit was maintained at 2-year follow-up with beta radiation reducing TLR (42% vs. 66%,  $p=0.016$ ), TVR (46% vs. 72%,  $p=0.009$ ) and MACE (46% vs. 72%,  $p=0.008$ ) compared to placebo. The efficacy of beta and gamma emitters for the treatment of ISR appeared similar at longer-term follow-up.

## START (Stents and radiation therapy) and START 40/20

A pivotal, multicenter, randomized trial, START involved 476 patients in over 55 centers throughout US and Europe, and was designed to determine the efficacy and safety of the Beta-Cath system for the treatment of ISR.<sup>24)</sup> Patients were randomized to either placebo or an active radiation train 30 mm in length. The inclusion criteria were single ISR lesions  $>50\%$  (by visual assessment) in native coronary target vessels between 2.7

and 4.0 mm in diameter. The target lesion ( $\leq 20$  mm) required treatment with a 20 mm balloon and a 30 mm source train. In the radiated patients, the mean lesion length was 16.3 mm, in arteries 2.8 mm in diameter. After successful angioplasty, these patients were treated with the Beta-Cath system containing  $^{90}\text{S}/\text{Y}$  seeds, delivering beta radiation through a closed-end lumen catheter. The dose prescribed at a point 2 mm from center of source axis was based on visual assessment of RVD; 18.4 Gy in RVD  $\geq 2.7 - \leq 3.3$  mm and 23 Gy in RVD  $> 3.3 - \leq 4.0$  mm. The duration of antiplatelet therapy was initially based on operator preference and was modified in early 1999 to at least 90 days of clopidogrel 75 mg/QD following recommendations from the Beta-Cath Trial Data Safety Monitoring Board, who first recognized late thrombosis as a complication of brachytherapy. At 8 months, angiographic restenosis rates in the irradiated segments were 24% vs. 46% in the placebo group ( $p < 0.001$ ). In the irradiated group, TLR was 13% as compared to 22% in control ( $p = 0.008$ ), with similar reductions of TVR (16% vs. 24%,  $p = 0.028$ ) and MACE (18% vs. 26%,  $p = 0.026$ ). There were late thrombotic events in radiated patients.

During multiple studies of radiation, including START, the medical community became aware of the mismatch between the interventional injury length and radiation length, the so called 'geographic miss' phenomenon, with the potential to compromise clinical outcome.<sup>25)</sup> The START 40/20 trial was a 207 patient registry that mirrored START, and ensured an adequate irradiation margin with 10 mm of radiation therapy applied proximal and distal to the injury zone (additional 5 mm each end). In comparison to the START population, START 40/20 patients were older, had more unstable angina and more prior treatments for ISR, with similar angiographic indices including RVD and lesion length. Compared to the control arm of START, patients in START 40/20 had: 1) a 44% reduction in restenosis in the analysis segment, compared to 36% in the radiated arm of START, a 50% reduction in TLR ( $p = 0.002$ ), compared to 42% in the radiated arm of START, a 34% reduction in TVR ( $p =$

0.03), compared to 34% in START and 4) a 26% reduction in MACE ( $p = 0.10$ ), compared to 31% in the irradiated arm of START. While the START 40/20 registry showed no deleterious effects of adding 10 mm of length to the source train, there was a lack of a relationship between 'geographic miss' and clinical or angiographic outcomes for ISR.

#### **INHIBIT (Intimal Hyperplasia Inhibition with Beta Instant Trial)**

The INHIBIT was a multicenter randomized study involving 332 patients in 29 U.S. and international sites, examining the efficacy of the GALILEO system for the treatment of ISR.<sup>26)</sup> The GALILEO system uses a  $^{32}\text{P}$  source delivered in a centered delivery catheter with a dose of 20 Gy at a depth of 1 mm into the vessel wall, with potential advantages such as homogenous dose distribution, reduced radiation exposure and a perfusion balloon to ensure distal vessel flow was maintained. The study mandated at least 3 months of antiplatelet therapy and 307 patients completed 9 months clinical follow-up. Radiation was delivered successfully in 315 of the patients, tolerated well in all but 2 patients and there were no adverse effects related to the radiation procedure. At 9 months, treatment with  $^{32}\text{P}$  reduced the primary angiographic endpoint of binary restenosis by 67% ( $p = 0.0001$ ) in the stented segment and by 50% ( $p = 0.0003$ ) in the analysis segment. There were no differences in the edge effect rates between the active and the control treated groups. The radiated patients had reduced late loss (0.4 vs. 0.6 mm,  $p < 0.001$ ) and improved MLD (1.52 vs. 1.38 mm,  $p = 0.01$ ). At 9 months,  $^{32}\text{P}$  significantly reduced rates of TLR (11% vs. 29%,  $p < 0.001$ ) and MACE (14% vs. 31%,  $p < 0.001$ ). Tandem positioning to cover diffuse lesions  $> 22$  mm with  $^{32}\text{P}$  was safe and effective.

**GALILEO INHIBIT** is an international multicenter registry of 120 patients with ISR treated with an automatic afterloader (Guidant GALILEO system) via a helical centering balloon.  $^{32}\text{P}$  was delivered at 20 Gy at 1 mm into vessel wall.

### **BRITE (Beta Radiation to Prevent ISR)**

BRITE is a U.S. feasibility study to test the Radiance radiation system which uses a balloon catheter encapsulating a  $^{32}\text{P}$  radioactive sleeve for the treatment of ISR. In the BRITE Trial, 27 patients were treated with PTCA (26 balloon, 1 rotoblator) for lesions  $<25$  mm in length. Following intervention, the Radiance catheter was successfully delivered in all but one patient. The prescribed mean dose was  $19.8 \pm 0.4$  Gy at 1 mm from the inflated source surface and delivered in an average dwell time of  $482 \pm 39$  seconds. Seventy percent of the dose was administered when the balloon was inflated. The transit time was 8.5 seconds and no cases were interrupted. All patients were treated with 75 mg/QD clopidogrel for 3 months. There were no procedural complications or MACE at 30-day clinical follow-up. At 6-months, TVR (3.7%), MACE (3.7%), and angiographic binary restenosis rates (7.7%) were the lowest reported to date in any vascular brachytherapy series.<sup>27)</sup> The specific dosimetry and source apposition characteristics of the Radiance system may have contributed to these encouraging results.

BRITE II, a multicenter, double-blinded, randomized trial of 500 patients with  $\text{ISR} \leq 45$  mm in length in arteries 2.25–4.0 mm in diameter has been initiated. SVG ISR will also be addressed by this delivery system (SVG BRITE).

### **CURE (Columbia University Restenosis Elimination)**

The CURE study evaluated liquid  $^{188}\text{Re}$  injected into a perfusion balloon for *de novo* lesions; 30 patients were treated with balloon alone and 30 patients were stented with subsequent  $^{188}\text{Re}$  therapy. The delivered dose was 20 Gy to the balloon surface with a dwell time of  $6.9 \pm 2.2$  minutes. At 12-month follow-up in the first 37 patients, the rate of TLR-free survival was 75%.

## **Controversies of Vascular Brachytherapy**

### **Late thrombosis**

The phenomenon of late thrombosis following radia-

tion therapy relates to a number of potential triggers including delayed reendothelialization after injury, unhealed dissection, inadequate antiplatelet therapy and use of additional stents.<sup>28)</sup> While late thrombosis was first identified in the Beta-Cath trial, therapeutic preventive strategies have been driven by data obtained from gamma radiation studies.<sup>29)30)</sup> Analysis of 'WRIST Plus', a 120 patient registry using  $^{192}\text{Ir}$  and 6 months clopidogrel for ISR, suggests that at least 6 months of antiplatelet therapy is warranted after radiation therapy for ISR.<sup>31)</sup> The optimal duration of clopidogrel therapy beyond 6 months is unknown and is the subject of ongoing investigation (WRIST 12).

### **Edge effect**

The development of new stenotic lesions at the proximal and distal edge of the irradiated segment (edge effect) has been a major limitation of vascular brachytherapy which continues to remain unresolved.<sup>32)</sup> Edge effect has been seen in both catheter-based and radioactive stent platforms and may relate to either vessel injury (injured but not radiated i.e. 'geographic miss'), or low-dose radiation at the edges of the treatment zone inducing neointimal formation. In the irradiated group of WRIST, edge restenosis was observed in 21% of edges with geographic miss and in 4% of edges without geographic miss. Edge recurrence after  $^{192}\text{Ir}$  treatment of ISR was the result of neointimal hyperplasia (treatment failure) and lack of positive remodeling after radiation.<sup>33)</sup> Results of START 40/20 do not support longer source trains to reduce edge effect, as reducing geographic miss did not improve outcomes compared to START. Further uncertainty of 'edge effect' is supported by preliminary IVUS data from the START trial suggesting that edge restenosis was not increased in radiated patients compared to controls.<sup>34)</sup>

### **Long term safety**

Limited data is available pertaining to the long-term safety of beta radiation. Two-year follow-up of the Beta WRIST cohort appears favorable despite lack of angiographic follow-up. Potential for coronary aneurysms and

accelerated coronary atherosclerosis mandate at least yearly follow-up in all patients. Gamma radiation has an excellent safety profile to date, and if extrapolation can be made to lower energy beta sources, long-term safety appears assuring.<sup>35)36)</sup>

## Conclusion

The trials of coronary radiation therapy using gamma and beta emitters have demonstrated dramatic reduction in clinical and angiographic restenosis in patients with ISR. The encouraging results from the clinical trials have established intracoronary radiation as a standard of care for patients with ISR, despite the potential for relevant side effects (edge restenosis and late thrombosis). Interventional cardiology is entering a dynamic phase with the advent of drug-coated stents using anti-proliferative agents, and with the potential to eliminate restenosis, the future role of vascular brachytherapy is uncertain. Established ISR will remain a principal indication for this technology which requires additional 'fine-tuning' to achieve full optimization.

## REFERENCES

- 1) Bauters C, Hubert E, Prat A, Bougrimi K, van Belle E, McFadden EP, et al. *Predictors of restenosis after coronary stent implantation*. *J Am Coll Cardiol* 1998;31:1291-8.
- 2) Fischman DL, Leon MB, Baim DS, Schatz RA, Savage MP, Penn I, 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.
- 3) Serruys PW, de Jaegere P, Kiemeneij F, Macaya C, Rutsch W, Heyndrickx G, et al. *A comparison of balloon-expandable-stent implantation with balloon angioplasty in patients with coronary artery disease*. *N Engl J Med* 1994;331:489-95.
- 4) Casterella PJ, Teirstein PS. *Prevention of coronary restenosis*. *Cardiol Rev* 1999;7:219-31.
- 5) Reimers B, Moussa I, Akiyama T, Tucci G, Ferraro M, Martini G, et al. *Long term clinical follow-up after successful repeat percutaneous intervention for stent stenosis*. *J Am Coll Cardiol* 1997;30:186-92.
- 6) Mehran R, Mintz GW, Satler LF, Pichard AD, Kent KM, Bucher TA, et al. *Treatment of in-stent restenosis with excimer laser coronary angioplasty: mechanisms and results compared to PTCA alone*. *Circulation* 1997;96:2183-9.
- 7) Hoffmann R, Mintz GS, Dussailant GR, Popma JJ, Pichard AD, Satler F, et al. *Patterns and mechanisms of in-stent restenosis: a serial intravascular ultrasound study*. *Circulation* 1996;94:1247-54.
- 8) Hoffmann R, Mintz GS, Mehran R, Pichard AD, Kent KM, Satler LF, et al. *Intravascular ultrasound predictors of angiographic restenosis in lesions treated with Palmaz-Schatz stents*. *J Am Coll Cardiol* 1998;31:43-9.
- 9) Sousa JE, Costa MA, Abizaid A, Abizaid AS, Feres F, Pinto IM, et al. *Lack of neointimal proliferation after implantation of sirolimus-coated stents in human coronary arteries*. *Circulation* 2001;103:192-5.
- 10) Teirstein PS, Massullo V, Jani S, Popma JJ, Mintz GS, Russo RJ, et al. *Catheter-based radiotherapy to inhibit restenosis after coronary stenting*. *N Engl J Med* 1997;336:1697-703.
- 11) King SB 3rd, Williams DO, Chougule P, Klein JL, Waksman R, Hilstead R, et al. *Endovascular beta-radiation to reduce restenosis after coronary balloon angioplasty*. *Circulation* 1998;97:2025-30.
- 12) Teirstein PS, Massullo V, Jani S, Russo RJ, Cloutier DA, Schatz RA, et al. *Two-year follow-up after catheter-based radiotherapy to inhibit coronary restenosis*. *Circulation* 1999;99:243-7.
- 13) Waksman R, White RL, Chan RC, Bass BG, Geirlach L, Mintz GS, et al. *Intracoronary gamma-radiation therapy after angioplasty inhibits recurrence in patients with in-stent restenosis*. *Circulation* 2000;101:2165-71.
- 14) Ahmed JM, Mintz GS, Waksman R, Mehran R, Leiboff B, Pichard AD, et al. *Serial intravascular ultrasound assessment of the efficacy of intracoronary gamma radiation therapy for preventing recurrence in very long, diffuse, in-stent restenosis lesions*. *Circulation* 2001;104:856-9.
- 15) Waksman R. *Late thrombosis after radiation*. *Circulation* 1999;100:780-2.
- 16) Waksman R, Ajani AE, White RL, Pinnow E, Dieble R, Bui AB, et al. *Prolonged antiplatelet therapy to prevent late thrombosis after intracoronary gamma-radiation in patients with in-stent restenosis*. *Circulation* 2001;103:2332-5.
- 17) Leon MB, Teirstein PS, Lansky AJ. *Intracoronary gamma radiation to reduce in-stent restenosis: the multicenter GAMA 1 randomized clinical trial*. *J Am Coll Cardiol* 1999;33(Suppl):56A.
- 18) Waksman R, Porrazzo MS, Chan RC. *Results from the ARTISTIC feasibility study of 192-Iridium gamma radiation to prevent recurrence of in-stent restenosis*. *Circulation* 1998;98:17, 1-442:2327.
- 19) Kim HS, Waksman R, Cottin Y, Kollum M, Bhargava B, Mehran B, et al. *Edge stenosis and geographical miss following intracoronary gamma radiation therapy for in-stent restenosis*. *J Am Coll Cardiol* 2001;37:1026-30.
- 20) Amols HI. *Review of endovascular brachytherapy physics for prevention of restenosis*. *Cardiovasc Radiat Med* 1999;1:64-71.
- 21) Bass B. *Radiation safety requirements for cardiovascular brachytherapy*. *Cardiovasc Radiat Med* 1999;1:297-306.
- 22) Hillstead R. *Novoste intracoronary beta radiation system: vascular brachytherapy*. 2nd ed. Futura Publishing; 1999. p.489-97.
- 23) Kruntz R. *Beta Cath Trial Results*. ACC 2001.
- 24) Waksman R, White RL, Chan RC, Bass BG, Geirlach L,

## Intracoronary Radiation Therapy (IRT) for In-Stent Restenosis

- Mintz GS, et al. *Intracoronary gamma-radiation therapy after angioplasty inhibits recurrence in patients with in-stent restenosis*. *Circulation* 2000;101:2165-71.
- 25) Lansky AJ, Mehran R, Crockner IR. *The edge effect: the impact of vessel injury and dose fall-off after treatment of in-stent restenosis with Sr-90 radiation*. *Circulation* 2000;102 (Suppl.):II669.
  - 26) Gruberg L, Waksman R. *Intravascular radiation for the prevention of recurrence of restenosis in coronary arteries*. *Expert Opin Investig Drugs* 2001;10:891-907.
  - 27) Waksman R, Buchbinder M, Reisman M. *A feasibility study of a novel P-32 deployment balloon system for the treatment of in-stent restenosis*. *Circulation* 2000;102 (Suppl II):II669. Abstract
  - 28) Costa MA, Sabat M, van der Giessen WJ, Kay IP, Cervinka P, Ligthart JM, et al. *Late coronary occlusion after intracoronary brachytherapy*. *Circulation* 1999;100:789-92.
  - 29) Waksman R, Bhargava B, Mintz GS, Mehran R, Lansky AJ, Satler LF, et al. *Late total occlusion after intracoronary brachytherapy for patients with in-stent restenosis*. *J Am Coll Cardiol* 2000;36:65-8.
  - 30) Waksman R, Bhargava B, Leon MB. *Late thrombosis following intracoronary brachytherapy*. *Catheter Cardiovasc Interv* 2000;49:344-7.
  - 31) Waksman R, Ajani AE, White RL, Pinnow E, Dieble R, Bui AB, et al. *Prolonged antiplatelet therapy to prevent late thrombosis after intracoronary gamma-radiation in patients with in-stent restenosis*. *Circulation* 2001;103:2332-5.
  - 32) Sabate M, Costa MA, Kozuma K, Kay IP, van der Giessen WJ, Coen VL, et al. *Geographic miss: a cause of treatment failure in radio-oncology applied to intracoronary radiation therapy*. *Circulation* 2000;101:2467-71.
  - 33) Ahmed JM, Mintz GS, Waksman R, Lansky AJ, Mehran R, Wu H, et al. *Serial intravascular ultrasound analysis of edge recurrence after intracoronary gamma radiation treatment of native artery in-stent restenosis lesions*. *Am J Cardiol* 2001;87:1145-9.
  - 34) Morino Y, Bonneau HN, Fitzgerald PJ. *Vascular brachytherapy: what have we learned from intravascular ultrasound?* *J Invasive Cardiol* 2001;13:409-16.
  - 35) Teirstein PS, Massullo V, Jani S, Popma JJ, Russo RJ, Schatz RA, et al. *Three-year clinical and angiographic follow-up after intracoronary radiation: results of a randomized clinical trial*. *Circulation* 2000;101:360-5.
  - 36) Condado JA, Waksman R, Calderas C, Sucedo J, Lansky A. *Two-year follow-up after intracoronary gamma radiation therapy*. *Cardiovasc Radiat Med* 1999;1:30-5.