Update on Radiation for Restenosis

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Coronary stenting is now used in most coronary interventions and reduces the restenosis rate to 20% or less. However, repeat in-stent restenosis occurs in 40%–60% of these patients. Radiation therapy, guided by intravascular ultrasound, can further reduce the incidence of repeat in-stent restenosis, and clinical trials have shown that all patient subgroups benefit from it. The mechanism appears to be reduction in neointimal hyperplasia. Studies are now evaluating use of medication with stents and radiotherapy, implantation of radiation-eluting stents, longer radiation sources to adequately cover lesions, and catheter balloons inflated with radioisotope solution. Intravascular radiation may soon be the standard of treatment for patients with in-stent restenosis and has the potential to reduce the recurrence rate to below 10%.
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The use of coronary artery stenting has continued to proliferate, and it is now estimated that more than 70% of all coronary interventions involve stent placement. Two well-known clinical trials, the STent REStenosis Study (STRESS) and the BElgian NEtherlands STENT study (BENESTENT), demonstrated that coronary stenting reduces restenosis.[1,2] However, restenosis continues to occur in up to 20% of patients.[3] Seven years ago, radiation was suggested as a potential way of reducing restenosis, because it is well known that low-dose radiation is highly effective and safe for preventing keloids and treating benign vascular malformations.[4] Also, low-dose radiation can delay normal wound healing and impair smooth muscle cell function.

Intravascular radiation has been accomplished by the use of a number of radioisotopes, including the gamma emitter iridium 192 (^{192}Ir) and the beta emitters phosphorus 32 (^{32}P), strontium 90 (^{90}Sr), yttrium 90 (^{90}Y), rhenium 188 (^{188}Re), technetium 99 (^{99}Tc), and xenon 133 (^{133}Xe).

Gamma Radiation versus Beta Radiation

The main difference between gamma and beta radiation is that gamma radiation consists of photons that originate from the middle of the nucleus, unlike beta radiation, which consists of electrons orbiting a nucleus that has too many or too few neutrons.[4] Gamma rays are not attenuated by calcium and penetrate much farther than beta particles; thus, their use requires special shielding. ^{192}Ir is the gamma emitter that is currently used; it also requires longer dwell times than do beta emitters.

Clinical Studies

Experimental studies have been remarkably positive, with a 20%–90% reduction in restenosis in a variety of animal models, using gamma and beta removable radiation sources, beta stents, and beta balloons. The sole exception, external radiation, appears to be much less effective and in some studies actually increases the degree of restenosis.[4,5]

The earliest results of clinical intravascular radiation come from Bottcher, who used ^{192}Ir in patients undergoing femoral artery angioplasty for restenosis.[6] Thirty patients each received a dose of 2000 cGy following dilation and stent placement. Clinical restenosis or occlusion occurred in 17.8%, and 10-year follow-up has shown the procedure to be safe, without any serious adverse events. Subsequently, a number of clinical trials have now been completed examining the use of intravascular radiation to prevent restenosis both within stents and in native unstented vessels. The most positive results have come from treatment of in-stent restenosis.[6]

Over 4000 patients have been enrolled in radiation trials such as the Scripps Coronary Radiation to Inhibit Proliferation Post Stenting (SCRIPPS) trial, the Washington Radiation for In-Stent Restenosis Trial (WRIST), GAMMA I, STents And Radiation Therapy (START), and the recently reported Proliferation REduction with Vascular ENergy Trial (PREVENT), INtimal Hyperplasia Inhibition with Beta In-stent Trial (INHIBIT), and Beta-Cath trials.[7–11] Although the entry criteria were different for each of the studies, all of these trials evaluating radiation for in-stent restenosis were remarkably consistent, showing a 30%–70% percent reduction in angiographic evidence of restenosis (Figure 1). Importantly, all patient subgroups have shown benefit, including patients with long lesions, diffuse disease, renal failure, or diabetes. The benefit appears to be entirely due to a reduction in neointimal hyperplasia.[10]

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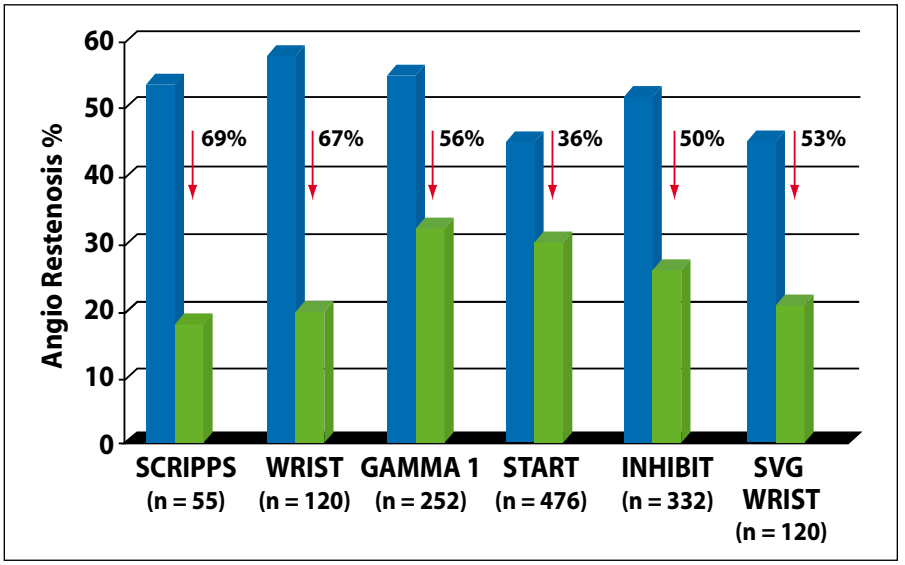
Gamma Radiation Trials

Three of the landmark trials of gamma radiation are the SCRIPPS, WRIST, and GAMMA I trials.[7–9] These were all double-blind, placebo-controlled trials that evaluated the effectiveness of gamma radiation therapy (8 to 30 Gy) for in-stent restenosis. As stated above, all three trials showed a remarkable reduction in restenosis with radiation compared to placebo (Figure 1). In the SCRIPPS study, 26 of 54 patients were randomized to receive ^{192}Ir. The dosage varied between 8 and 30 Gy;

Figure 1. *Six randomized trials comparing intravascular radiation (green bars) to placebo (blue bars) in patients with in-stent restenosis. See text for full names of trials.*



its administration was guided by intravascular ultrasound (IVUS). At 2 years, the treated group had a restenosis rate of 15.4%, compared to 48.3% in the control group.[7] The WRIST trial also showed impressive results. The gamma-irradiated group had a restenosis rate of 19%, compared to 58% in the control group at 6 months, and a 48% reduction in major adverse clinical events (MACEs) at 1 year (Figure 2).[8]

The GAMMA I trial demonstrated that lesion length has an effect on outcome. There was a 70% reduction in restenosis for lesions less than 30 mm long, compared to a 48% reduction for 30- to 45-mm lesions.[9]

Interestingly, in the GAMMA II Registry of 125 patients, rotational atherectomy was used in 45% of cases.[10] There was a 52% reduction in in-stent and a 40% reduction in total lesion restenosis. Previously unrecognized problems from radiation were identified by these studies, some of which included "geographical miss," edge effect, and late thrombosis, which will be discussed later.

The Saphenous Vein Graft (SVG) WRIST trial has shown a reduction in restenosis in vein grafts in the 30 patients that have been treated.[10] LONG (Long Lesions) WRIST showed a 32% incidence of restenosis in lesions 36–80 mm long that were irradiated, versus 71% in the control group.[10] PLAVIX WRIST showed a reduction in 6-month total occlusion rates when patients are placed on 75 mg of clopidogrel (Plavix) for 6 months. WRIST 12 will evaluate whether 12 months of clopidogrel is beneficial. Similarly, GAMMA V is a registry of 600 patients who will receive clopidogrel for 12 months if they have a new stent implanted and for 6 months if they do not receive a stent. The Columbia University Restenosis Elimination (CURE) study will be a registry for patients with in-stent restenosis who are not considered good candidates for medical or surgical therapy.

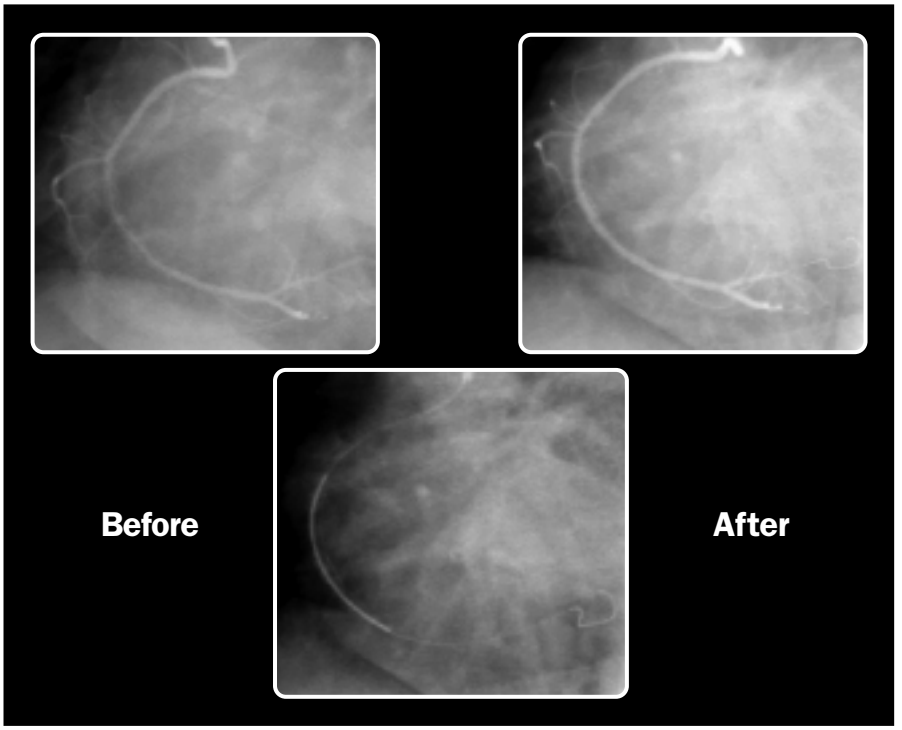


Figure 2. *An example of diffuse in-stent restenosis of the left anterior descending coronary artery, treated with cutting balloon angioplasty and iridium-192 source (Angiorad 0.014" gamma wire).*

Beta-Radiation Trials

The landmark beta-radiation trials are the Beta Energy Restenosis Trial (BERT), BETA-WRIST, INHIBIT, START, and Beta-Cath.[10,12–15] BERT was a feasibility study in 23 patients using a ^{90}SrY source.[15] The angiographic restenosis rate for the irradiated group was 17%. The BETA-WRIST trial used ^{90}Y with a source-centering balloon and showed a 22% restenosis rate at 6 months with a 12% late total occlusion rate.[12] START evaluated the Novoste Beta-Cath™ System (Figure 3) using a ^{90}SrY at a dose of 18–20 Gy at 2 mm from the source. At 8 months, the angiographic restenosis rate was 29% in the irradiated group and 45% in the placebo group. This study showed a 35% reduction in target lesion revascularization, target vessel revascularization, and MACE. Two similar studies are being conducted: the Beta Radiation to Reduce In-Stent Restenosis study (BRITE), with the Cordis radiance system, and INHIBIT, with the Guidant Galileo system (pictured in Figure 4).

In contrast to the treatment of in-stent restenosis, clinical studies evaluating intravascular brachytherapy for native-vessel nonstented coronary disease are much less compelling. The PREVENT Trial used a ^{32}P source and found a significant reduction in restenosis both in patients who received stents and in those who did not.[11] The Beta-Cath study has been presented but not yet published. In this study, 1455 patients were randomized to the Novoste Beta-Cath System or placebo. Stenting was permitted for bail-out or unsatisfactory result, which occurred in approximately 50% of the patients. At

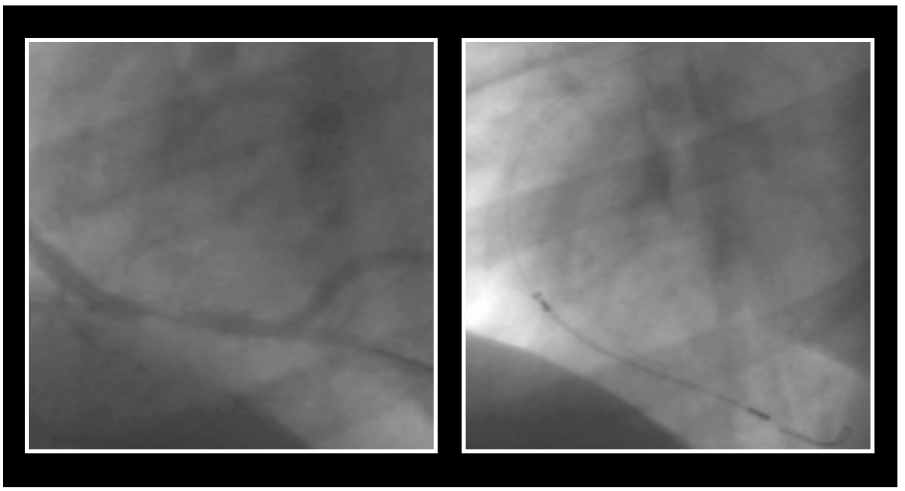


Figure 3. *An example of diffuse in-stent restenosis of the right coronary artery (left), treated with cutting balloon angioplasty and the Novoste Beta-Cath System (right).*

8 months, the primary endpoint of target vessel failure was not different between groups (17.4% for placebo and 15.6% for radiation). Part of the lack of benefit seen in the study may be due to a high incidence of geographical miss. Small nonrandomized studies have shown mixed results. Conclusions cannot be drawn at this time as to the effectiveness of radiation on nonstented coronary vessels.

Current Limitations

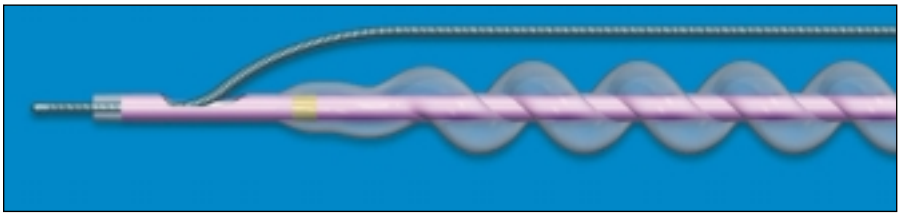
A new phenomenon, late stent thrombosis, has been reported from a number of studies. This appears to occur between 1 and 18 months following the procedure.[16] It is presumably related to a lack of reendothelialization and appears to be largely restricted to patients who receive a new stent. In the Beta-Cath study, stent thrombosis was identified by the Data and Safety Monitoring Board, and the protocol was changed to ensure at least 3 months of clopidogrel therapy in the irradiated group. With this change, the incidence of late stent thrombosis fell from 6.3% to 1.3%. In clinical trials in which prolonged antiplatelet therapy was used, such as the START and INHIBIT trials, late stent thrombosis appeared to be quite infrequent and not a significant problem.[6]

Another recognized problem of all radiation devices is what has been referred to as the "edge effect." This happens when the device fails to cover entirely the area damaged by the balloon or stent. Because there is a rapid fall-off in radiation at the edge of the source, this (edge) segment of vessel receives a significantly lower dose, which is inadequate to inhibit restenosis. Some experimental and clinical studies also suggest that very-low-dose radiation may actually increase intimal hyperplasia. This problem can be avoided by using a source long enough to cover the entire injured area, with at least 5 mm on each end of the radiation source extending beyond the injured area. Longer sources are now available to ensure adequate coverage of long lesions.

The issue of optimal dose remains unresolved. Experimental studies demonstrate a clear dose-response relationship, and clinical trials have validated this with similar findings. The GAMMA I study suggested that a dose of at least 15 Gy 2 mm from the source is the minimum necessary to inhibit restenosis.[9] The upper limit is also unclear, but current practice is to limit the dose to less than 50 Gy. The therapeutic window needs further definition to improve safety and efficacy. An excessive dose can occur when the radiation source is not optimally centered within the vessel. Several manufacturers use a centering balloon to reduce the possibility of exposing one wall of the artery to an excessive dose.

Based on the results of the five randomized clinical trials of intravascular radiation for in-stent restenosis, the U.S. Food and Drug Administration has now approved three devices for clinical use: the Guidant GALILEO System, the Novoste Beta-Cath System and the Cordis Gamma System. It is likely that with the widespread availability of these two radiation devices, intravascular radiation will become the standard of treatment for patients with in-stent restenosis.

Figure 4. *A centering catheter, part of Guidant Corporation's GALILEO System™, used in the INHIBIT (INtimal Hyperplasia Inhibition with Beta In-stent Trial) study.*



Radiation and Stents

Numerous experimental studies have demonstrated that radioactive

stents can reduce neointimal formation. One study recently reported that in a rabbit iliac artery, using a gamma-emitting palladium 103 (^{103}Pb) as the radioactive source, at doses ranging from 1.0 to 4.0 mCi, there was a significant dose-dependent reduction in restenosis.[17] The clinical results of radioactive stents have been somewhat disappointing. Pilot studies using varying doses of beta radiation have failed to show a significant reduction in restenosis. This has largely been because of the so-called "candy wrapper effect," or edge effect (described above), which appears to result from an inadequate degree of radiation at the edges of the stent, where vascular injury from the balloon has occurred. Future considerations will include use of new isotopes with low activity and long half-life and a solution of the problem of edge effect. Hybrid stents that are radioactive and elute drugs may be created.[17]

Conclusions cannot be drawn at this time as to the effectiveness of radiation on nonstented coronary vessels.

Liquid- and Gas-Filled Balloon Systems

A limited number of reports have described using low-pressure liquid-filled balloons for vessel wall irradiation. Rhenium 188 (^{188}Re) perrhenate, rhenium 186 (^{186}Re) perrhenate, holmium 166 (^{166}Ho), and samarium 153 (^{153}Sm) have been used in animal models. There is, of course, the reasonable fear of rupture of the balloons in the coronary artery, with spilling of the radioactive contents. The CURE study will be a single-center, open-label study designed to evaluate the feasibility and safety of liquid ^{188}Re. A total of 48 patients have been treated with a balloon inflated with this radioisotope solution. The dose administered to the balloon surface was 20 Gy, and the dwell time was approximately 7 minutes. The technique appears feasible and safe; confirmation will have to await randomized double-blind studies.

The BRITE trial and the Beta Radiation Trial To Eliminate Restenosis (BETTER) examined the use of ^{32}P, a beta emitter, in the balloon material with a trilayer, sealed-source design. This design eliminates the risk of contaminating the coronary system with radioactive material in case of rupture. The treatment protocol consisted of a dose of 20 Gy 1 mm from the source. The 6-month data in 47 patients demonstrated low target vessel revascularization and major adverse cardiac event rates.

Korean investigators have established a registry, which has evaluated the feasibility and efficacy of beta radiation with an ^{188}Re-mercaptoacetyltriglycine $(MAG)_3$-filled balloon after rotational atherectomy for diffuse in-stent restenosis more than 10 mm long. Fifty patients were enrolled, and the restenosis rate was 10.2%.[17]

We will also await results of the Xena-Cath study, which uses an ^{133}Xe gas-filled balloon. This study will examine the potential benefit of using local irradiation with the ^{133}Xe radiogas contained within the Cook Xena-Cath coronary balloon catheter to reduce safely the incidence of future restenosis in de novo and restenotic lesions.[17]

A number of newer devices currently undergoing clinical trials may provide either safer or easier delivery of radiation. These include the Angiorad 0.014" gamma wire (Figure 2), ^{188}Re liquid balloons, ^{32}P trilayer balloons, and ^{133}Xe gas-filled balloons, as well as soft x-ray systems. Clearly radiation is here to stay and will become part of the armamentarium for preventing restenosis. It is likely that it will not become the

Main Points

- Restenosis occurs in up to 20% of patients who undergo coronary interventions with stent placement, but repeat in-stent restenosis can occur in 40%–60%.
- Treatment with intravascular radiation can reduce the rate of in-stent restenosis by 50%.
- Intravascular radiation is performed using either beta- or gamma-emitting radioisotopes.
- Problems from radiation include "geographical miss," edge effect, and late thrombosis.
- Although the optimal radiation dose is unclear, studies show a dose-response relationship.
- Late stent thrombosis may occur 1–18 months after stent placement; clopidogrel or antiplatelet therapy appears to reduce its incidence.

sole treatment for restenosis in the future but will be one of several new therapies, such as improved stents, particularly drug-eluting stents, and pharmacologic therapy. For the first time in 20 years, it seems likely that a significant impact is being made on the problem of restenosis. ■

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