Intracoronary Brachytherapy to Prevent Restenosis Following Coronary Intervention: Is it Ready for Clinical Use?

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Summary

This article evaluates the current status of intracoronary brachytherapy for prevention of restenosis. First, experimental results obtained using porcine coronary arteries are reported. These are characterized by a complete suppression of intraluminal restenotic proliferation due to the deployed radiation dose. Second, currently available radiation devices are introduced and discussed in detail. Third, results from prospective randomized clinical trials on coronary brachytherapy are summarized. The article concludes with citations of published editorial comments on the most important clinical brachytherapy trials and reflects current opinions on brachytherapy held by leaders in the field.

Key Words

Restenosis, stents, radiation, brachytherapy, coronary arteries

Introduction

Since Grüntzig introduced percutaneous transluminal coronary angioplasty (PTCA) in 1977, a variety of catheter-based techniques for the treatment of coronary artery disease have been developed to overcome the limitations of the original balloon approach. Direct coronary arterectomy facilitates the removal of atherosclerotic material from bulky, soft, eccentric coronary lesions that cannot be easily treated by balloon angioplasty. Rotablation helps to crack rigid structures in long calcified lesions where balloons fail and flow-obstructing dissections frequently occur. Most importantly, stents provide an optimal initial result by scaffolding the artery, sealing dissections, and preventing elastic recoil and unfavorable late vessel shrinkage. These technical refinements have significantly improved initial procedural success rates to the extent that today virtually any lesion can be approached interventionally.

However, restenosis has not been effectively reduced by any of the new catheter techniques, and continues to be the Achilles' heel of interventional cardiology. Restenotic narrowing develops within the first 6 months following angioplasty and includes initial elastic recoiling, excessive migration, and proliferation of smooth muscle cells originating from angioplasty-induced tears through the muscular vessel wall. The end result of this process is late shrinkage of the entire artery. Depending on the patient's particular conditions and the catheter technique that is applied, restenosis rates can vary from 20 % – 50 %. Under a combination of unfavorable conditions, such as terminal renal failure or diabetes in combination with complex (type C) lesions, restenosis rates may be as high as 80 %. With an expected total number of 1,000,000 interventional procedures worldwide in the year 2000 and approximately 150,000 repeat procedures due to restenosis, the immense medical, social, and economic impact of the restenosis problem be-comes apparent.

A variety of preventive pharmacological approaches to restenosis have been proposed and tested over the last

two decades. Although some anti-proliferative drugs have shown promising experimental results, none of them has proven undisputed efficacy in humans. It was initially hoped that stents might reduce restenosis since they overcome elastic recoiling and late vessel shrinkage. However, it turned out that such a metallic "foreign body" stimulates smooth muscle cell proliferation so effectively that in-stent restenosis continues to be a serious problem.

The pathophysiologic and histologic appearance of a restenotic coronary lesion has much in common with a benign tumor, which consists mainly of rapidly proliferating smooth muscle cells. This understanding has stimulated the development of a novel therapeutic approach employing ionizing radiation, which has been successfully used to treat skin keloids [1-3]. Radiation is predominantly effective against rapidly proliferating rather than quiescent cells. The main mechanism is induction of DNA double strand breaks, either by direct hits to DNA or by creating free, aggressive radicals that in turn interact with DNA. Although classic radiation oncology mainly employs external beam irradiation to treat solid tumors, the special anatomy of a coronary artery has triggered the use of a more recently developed irradiation modality called brachytherapy. This term means "short-distance irradiation therapy" and is especially suited for hollow organs where a source can be inserted and exposed in direct contact with the target tissue. Thus, catheter-based, miniaturized sources were developed for application in coronary arteries.

To date, coronary brachytherapy to prevent restenosis is considered the only promising approach for widespread clinical application.

Experimental Results

The porcine coronary overstretch model [4] that was developed at Emory University has been the preferred means for experimental study of the interaction between ionizing radiation and restenotic proliferation; of course, this assumes that much of the proliferative repair mechanism that occurs in pigs after intentional coronary overstretching resembles the pathophysiology of restenosis in humans. The model includes balloon-overstretching of a coronary artery with a balloon-to-artery diameter ratio of 1.3 : 1. This procedure creates tears through the muscular wall of the treated coronary artery that "heal" over a period of 28 days with the development of smooth-muscle-cell proliferation as well as negative vascular remodeling encroaching on the lumen.

We have used this model to evaluate new, short-lived, positron radiation emitting isotopes for coronary brachytherapy [5]. The key histologic findings of our experimental work are given in Figure 1. Panel a depicts a cross-sectional image of an untreated porcine coronary artery exhibiting "restenosis" as a dense cell-rich proliferation of smooth muscle cells derived from the media of the vessel. This formation developed 28 days after overstretch injury. Panel b shows an artery treated with a 24 Gy dose targeted at the adventitia of the vessel. This dose completely suppresses neointimal proliferation and leaves the transmedial tear free from any proliferative response that could diminish the lumen. Panel c gives a result obtained with a 16 Gy dose deployed to an artery prior to stenting. The treatment is so anti-proliferative that the stent struts are not endothelialized and remain exposed or "naked" to the blood stream. This phenomenon is the main reason for one particular side effect of brachytherapy, the late stent thrombosis that will be referred to below. Finally, panel d shows a porcine artery that was exposed to a 16 Gy dose of positron radiation without being previously subjected to overstretch injury. This artery cannot be distinguished from totally untreated controls by histological parameters. This finding is important since it provides the rationale for using radiation dose-fields that widely overlap with healthy adjacent coronary artery tissue.

Radiation Sources and Useful Isotopes

Gamma Radiation

^{192}Ir source ribbon (CheckMate system, Cordis, USA): The first source dedicated to intracoronary use is a 3F (diameter: 1.0 mm) nylon ribbon containing an array of cylindrical-shaped seeds with ^{192}Ir enclosed in a stainless steel capsule. The ribbon is manufactured in different lengths ranging from 19 to 80 mm. The ^{192}Ir source is advanced manually into a closed-end lumen of a non-centering delivery catheter. The source emits gamma radiation of 0.38 MeV and has a half-life of 74 days. This system is CE-certified and available for clinical use in Europe and in the United States.

Beta Radiation

Although gamma radiation was first shown to be effective, further source development has been focused on

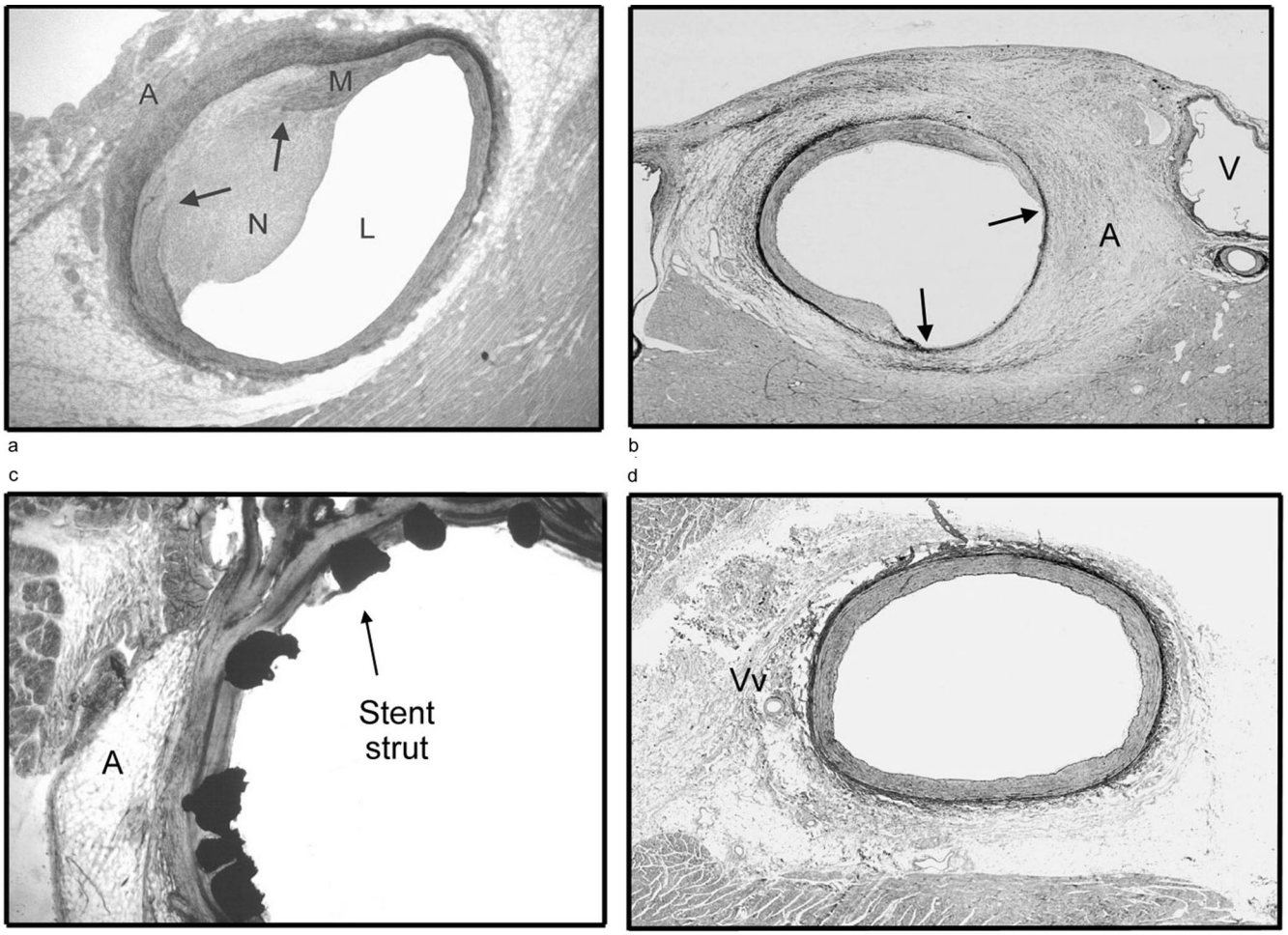

Figure 1. Cross-sections of porcine coronary arteries 28 days after initial balloon overstretch injury. All arteries were stained with Verhoeff-van-Gieson elastic staining.
a) Fully developed restenosis of an overstretched but nonirradiated control artery. Arrows indicate the free ends of the transmural tear. The gap in between is filled out by a cell-rich dense neointima (N) that encroaches upon the lumen (L). There is also a fibrotic reaction observed outside the vessel in the adventitia (A).
b) Complete suppression of neointimal growth of an artery subjected to 24 Gy of positron radiation targeted to the adventitia 1 mm away from the inner lumen surface. The transmedial tear is left without any proliferative response that would reduce the widely patent luminal area.
c) Stented porcine coronary artery that was treated with 16 Gy positron radiation immediately prior to stent placement. There is no neointimal tissue surrounding the stent struts, which thus remain "naked" in the blood stream.
d) Not overstretched, but irradiated (16 Gy) coronary artery that does not show any histologic abnormality.

emitters of beta radiation. The main reason was that the physical interaction between gamma radiation and a biological target is so weak that only a small fraction of radiation energy is deployed to the target itself while the bulk of the energy penetrates through the body. Thus, the results are long dwell times and significant radiation exposure for catheter laboratory personnel. In contrast, beta particles are readily absorbed by tissue and deploy their complete energy over a distance of only a few millimeters. These physical properties allow for a more effective use of energy and shorter dwell times without causing significant radiation exposure to the operators.

$^{90}Sr/^{90}Y$ source train (BetaCath system, Novoste, USA): The first beta radiation emitting system also uses a 3F non-centering delivery catheter that has

three lumens. The first is eccentrically placed for travel of the intracoronary guidewire. The second is a lumen for travel of a sealed source train consisting of $^{90}Sr/^{90}Y$ seeds. The second and the third lumina are designed for delivering the source train back and forth into the delivery catheter by hydraulic pressure forces created with a dedicated syringe containing sterile water. This syringe is functionally connected to a multiple-use handheld device that is also used as a shielded housing of the source. The source is a mother/daughter system: the mother has a half-life of 29 years and, consequently, must not be replaced; the daughter delivers the effective radiation energy. This system was the first in Europe to become CE-certified and is now commercially available in Europe and the United States.

^{32}P centered source wire (Galileo system, Guidant, USA): This system consists of three major components: a 0.018" nitinol source wire with ^{32}P hermetically sealed in the distal 27-mm tip. Second, a spiral centered balloon that eliminates the risk of inhomogeneous dose distribution to the vessel due to source-wire eccentricity in its curves. Third, an automatic computer-controlled afterloader that stores and seals the source wire and offers completely automated dose delivery and dosimetry with minimized operator interaction. Today, this system is probably the most technically advanced device, carries the CE-mark, and will probably soon become commercially available in Europe.

^{188}Re and ^{68}Ga in liquid-filled balloons: The design of all wire-based solid sources must specifically address the problem of how to center the source-wire within a coronary artery for achieving the best possible dose homogeneity along the vessel circumference. This is especially important for beta sources since the strong interaction between beta particles and the target tissue results in a steep dose decline over the distance from the center of the source. The best possible dose distribution can be achieved by filling a conventional angioplasty balloon with a liquid radiation source. Thus, the source is placed into in close contact with the vessel wall and irregularity is overcome due to the self-centering geometry of a cylindrical balloon. The first isotope suggested for use in liquid-filled balloons was the generator-produced beta-emitter ^{188}Re, which has a half-life of 17 hours. The ^{188}Re-filled balloons were tested in a safety and feasibility study and have demonstrated anti-restenosis efficacy in humans [6]. However, most cardiologists were concerned about the consequences of spilling liquid ^{188}Re in the catheter laboratory. They felt that an intracoronary loss of this isotope in case of an accidental balloon rupture might incur significant radiotoxicity to the patient. More recently, the short-lived positron-emitter ^{68}Ga has been suggested by our group, and has shown good anti-restenosis efficacy in the porcine coronary overstretch model [5]. We believe that this isotope, which has a half-life of only 68 minutes, may represent a safe alternative to source wire systems. In addition, because it is generator-produced, it permits on-site production of repeated single doses in or near the catheter laboratory.

^{32}P-labeled radioactive balloons (RDX system, Radiance, USA): This system employs balloons that carry radioactive ^{32}P sealed in the wall of the balloon. They combine the safety of a solid source with the favorable geometry of a liquid-filled balloon. Their one disadvantage is their relatively short half-life of 14 days. Since the source decays prior to use, strict and precise planning ahead of treatments is essential and creates potential for balloon wasting.

Radioactive stents: Stents were theoretically considered to represent an ideal platform for radiation delivery for prevention of coronary restenosis. They require only a very small amount of radioactivity (1 – 25 μCi, resp. 37 – 925 kBq) since their dwell-time is virtually infinite once a stent is deployed. However, there is a fundamental problem associated with radioactive stents that has not been overcome thus far. The stent delivery balloon is usually a little longer than the stent itself so that the injury length exceeds the axial length of the radiation dose field generated by the stent. Consequently, it turned out that both ends of the stent are inadequately treated with radiation due to the steep dose decline over the distance that is typical for beta-radiation. Thus, a special phenomenon was observed called the "candy wrapper effect" that describes the angiographic shape of stent restenosis, which looks like a piece of candy wrapped in foil on both sides. These severe bilateral edge stenoses create the particular angiographic appearance, which results in a complete functional loss of the benefit of stenting [7]. So far, the candy wrapper effect represents a major obstacle to further application of radioactive stents.

Table 1 gives an overview of the isotopes used so far in coronary radiation treatment and lists their half-lives, radiation energy, and application in individual devices.

Isotope	Radiation	Energy (MeV)	Half-life	Device
^{192}Ir	γ	0.38	74 days	Source ribbon
^{90}Sr/^{90}Y	β	2.2	10 years	Source wire
^{90}Y	β	2.2	2.8 days	Source wire
^{32}P	β	1.7	14 days	Source wire
^{188}Re	β,γ	2.1	17 hours	Liquid-filled balloon
^{186}Re	β	1.1	3.8 days	Liquid-filled balloon
^{68}Ga	β^+,γ	2.9	68 minutes	Liquid-filled balloon
^{166}Ho	β	1.9	27 hours	Liquid-filled balloon
^{133}Xe	γ	0.074	5.2 days	Gas-filled balloon

Table 1. Radioactive isotopes used for coronary brachytherapy.

Results Reported from Clinical Application

Venezuelan Experience

The first brachytherapy of humans was performed in 1994 in Caracas, Venezuela, using an ^{192}Ir gamma source. A total of 21 patients presenting with single de-novo lesions were treated by PTCA followed by intracoronary radiation therapy with a target dose of 25 Gy deployed to the vessel wall. These patients have been followed clinically and angiographically since then, and have presented with an unexpectedly low restenosis rate at the 6-month follow-ups [8]. Moreover, it was demonstrated for the first time that intracoronary irradiation can be performed without acute procedural complications. However, an angiographic follow-up documented the development of occasional coronary pseudo-aneurysms at the treatment site and created significant concern over whether this was due to unintentional overdosing or an unavoidable weakening of the coronary artery wall after radiation treatment.

The SCRIPPS Trial

Fifty-five patients were enrolled in the first prospective, randomized, clinical trial of coronary brachytherapy performed at the SCRIPPS Clinic, San Diego, CA, in 1995. Patients presenting with restenosis after previous coronary intervention were randomized to either repeat PTCA with stenting and subsequent ^{192}Ir-radiation treatment, or to repeat PTCA with stent placement alone. At the 6-month follow-up, irradiated arteries had a significantly lower in-stent restenosis rate than did unirradiated control vessels (17 % vs. 54 %, P = 0.01) [9]. The benefit of this treatment persisted according to clinical parameters at the two-year follow-up [10], and this was confirmed angiographically at the three-year follow-up [11]. This represented an unprecedented success in restenosis prevention as a result of using brachytherapy in combination with stent placement.

The BERT Trial

Although it was not a randomized trial (using a comparison with historic controls), the BERT trial is important because it was the first application of beta-radiation in humans. The ^{90}Sr/^{90}Y BetaCath system was used to treat 21 patients with single de-novo lesions (no restenoses). Stenting was not required by the protocol, but provisional stenting was allowed in case of unacceptable post-PTCA results. Mean diameter stenosis was decreased through initial PTCA from 73 ± 7 % to 24 ± 12 %, and this value was found to be unchanged (26 ± 26 %) at the 6-month follow-up. Thus, the benefit of PTCA was preserved as a result of ^{90}Sr/^{90}Y-brachytherapy [12].

The Gamma-I Trial

The Gamma-I trial was the first randomized multicenter trial designed to investigate the safety and efficacy of intracoronary gamma-radiation treatment for restenosis. Restenotic patients (253) were randomized to receive repeat PTCA with or without stent placement either alone or in combination with post-procedural gamma-irradiation. The angiographic outcome was favorable, showing a 23 % reduction in restenosis rate (33 % vs 56 %, P = 0.006) and interestingly an even more significant 40 % restenosis reduction in diabetic patients (n = 79, restenosis 36 % vs 76 %, P = 0.002).

The WRIST Trial

Even more favorable results were obtained in the prospective randomized WRIST trial, comparing repeat PTCA vs. repeat PTCA with subsequent gamma-radiation treatment in 130 patients with in-stent restenosis in native coronary vessels as well as in saphenous vein grafts. As a result of brachytherapy, the in-stent restenosis rate was reduced by 38.7 % (22.0 % vs 60.7 %, P = 0.001). A parallel reduction of major adverse cardiac events was documented at the 6- and 12-month clinical follow-ups [13].

Study	Principal investigator	Lesion type	Patients	Restenosis rate (%)	Follow-up (months)
SCRIPPS	Teirstein	Restenosis	55	33 vs 64	36
GAMMA-I	Leon	In-stent restenosis	252	34 vs 56	6
START	Popma	In-stent restenosis	476	29 vs 45	8
WRIST	Waksman	In-stent Restenosis	130	19 vs 58	6
β-WRIST	Waksman	In-stent restenosis	50	22 vs 64	6
Long WRIST	Waksman	In-stent restenosis	120	46 vs 78	6
Geneva Dose-finding study	Verin	De-novo lesion	181	8 (highest dose)	6
PREVENT	Raizner	De-novo lesion	105	22 vs 50	6

Table 2. Prospective randomized clinical trials on intracoronary brachytherapy. Restenosis rate is given in the form: overall total-segment restenosis rate versus unirradiated controls.

Similar favorable results were gained in the ß-WRIST trial investigating treatment of in-stent restenosis with beta radiation [14], and in the Long-WRIST trial, which investigated the efficacy of gamma-radiation to treat long coronary lesions ranging from 36 – 80 mm in length [15].

The START Trial

The START trial was a large multicenter trial that investigated 476 patients with in-stent restenosis at 50 sites in the United States. Patients were randomized to either receive repeat PTCA or repeat PTCA with subsequent endovascular irradiation using the ^{90}Sr/^{90}Y device. The Study endpoints were 8-month target vessel failure, 8-month angiographic restenosis, in-stent minimal luminal diameter and late loss, as well as 8-month major adverse cardiac events and aneurysm formation. The angiographic outcome documented a 36 % reduction in total segment in-stent restenosis (28.8 % vs 45.2 %, P = 0.008) and a 49 % reduction in minimal lumen diameter late loss (0.28 mm vs 0.55 mm, P < 0.001). The clinical outcome was also favorable, with a 42 % reduction in the target lesion revascularization rate (13.1 % vs 22.4 %, P = 0.009) and a 31 % reduction in major adverse cardiac events (18.0 % vs 25.9 %, P = 0.039) at 8 months [16].

The Geneva Dose-Finding Study

The Geneva Dose-Finding Study was the first trial to evaluate the impact of beta radiation on de-novo lesions in combination with PTCA in a larger cohort of patients (n = 181). Using a centered ^{90}Y-beta source wire and an automated afterloader, this trial randomized patients to receive doses of 9 Gy, 12 Gy, 15 Gy or 18 Gy targeted to the vessel wall. It was shown that in the absence of stenting, very favorable results were also obtained and the restenosis rate in the highest dose-group was effectively reduced to the previously unattainable level of 8 % [17]. Unfortunately, the system (Schneider/Sauerwein) that was used is no longer available.

The PREVENT Trial

Just recently, the results of another prospective randomized trial were published [18] that characterized the impact of beta-radiation emitted by a centered ^{32}P beta source-wire on de-novo and restenotic lesions. 105 patients were treated with PTCA and/or stenting either alone or in combination with beta radiation. Restenosis rates were significantly lower in the irradiated arteries than in the unirradiated controls (22 % vs 50 %, P = 0.018). A compilation of the design and results of the most important prospective, randomized clinical trials is provided in Table 2.

Recently Discovered Problems

Although the larger trials all documented significant reductions in overall restenosis rates, there were two phenomena observed that deserve more extensive consideration: edge stenosis and late thrombotic occlusion. Both are directly related to radiation in a particular way. Edge stenosis describes the phenomenon in which the border zones of the treated lesions exhibit a tendency to develop induced stenosis rather than restenosis suppression. This effect was observed not only with the above-mentioned radioactive stents, but also with catheter-based radiation therapy after PTCA and stenting. One reason may be that the radiation dose declines at the borders of the dose field to the extent that marginal parts of the lesion receive submaximal doses. In our own porcine experiments, we have observed a tendency for doses in the range between 5 and 10 Gy to possibly stimulate rather than suppress neointimal formation [5]. In addition we have not observed any detrimental effects of radiation on uninjured coronary arteries [5]. Thus, axial extension of the dose field to safely overlap both ends of the lesion was recommended. However, a three-dimensional intravascular ultrasound study in humans revealed that edge effects were also observed in marginal parts of lesions that were not irradiated. Therefore, it was concluded that non-measurable device injury rather than submaximal radiation doses may be a plausible alternative explanation of unfavorable edge effects [19]. Taking these findings into account, an extension of the dose field would also suppress edge effects if they were caused by device-induced micro injury. Thus, this problem may be solved with the use of catheter-based radiation delivery.

Late thrombotic occlusion first occurred in 6 out of 108 consecutive patients (6.6 %) between 2 and 15 months after irradiation and after the pharmacologic anti-platelet regimen had been discontinued [20,21]. Four of these patients had received a new stent at the time of radiation therapy. Half of them suffered an acute myocardial infarction.

Sudden stent thrombosis is not a new problem, but was known to occur only in the first 14 days following stent implantation. The generally accepted hypothesis to date is that radiation delays the process of healing at the lesion site such that stent struts remain uncovered by endothelium for a long time (Figure 1, panel c). Thus, they may pose a continued risk of fibrin and platelet activation that needs to be specifically addressed either by continuing anti-platelet medication or by developing a stent design that minimizes induction of clotting. Data that was presented more recently show that prolonged co-administration of Aspirin and Clopidogrel (Plavix, Iscover) at a 6- or even 12-month interval successfully prevents late thrombosis. The length required for re-endothelialization of irradiated segments is unknown to date.

Current Estimation of Coronary Brachytherapy by Leaders in the Field

The first editorial concerning intracoronary brachytherapy was published in 1997 by Teirstein [22], who commented on the first beta-emitter feasibility study undertaken in order to check on a centered ^{90}Y source wire system (Schneider/Sauerwein). This study failed to demonstrate any beneficial effect of radiation on clinical restenosis [23]. However, Teirstein takes into account that the most likely reason was underdosage and a potentially premature delivery of radiation. Consequently, he entitled the editorial "Too little, too soon?", but he concludes with the statement that "radiotherapy remains high on the list of potentially efficacious treatments" in the fight against restenosis.

Soon thereafter, Serruys wrote an editorial [24] to comment on the first reported clinical and angiographic outcome of patients treated with gamma-radiation in Venezuela [8]. Besides criticism of the prototype device used with respect to radiation safety issues and uncertainties of the selected dosimetry, Dr. Serruys found the described aneurysm formation worrisome and felt that it was far too early to comment conclusively on the total number of potential side effects. In his conclusion, he expresses doubt that brachytherapy as practised then was technically safe and efficacious.

King III wrote an editorial in 1999 [25] commenting on the favorable two-year results presented by the SCRIPPS trial [10]. He concludes by recommending further "watchful waiting", but speculated that with the expected results of larger randomized trials, the end of the reasonable waiting period may be rapidly approaching.

The most recently published editorial by Kuntz and Baim evaluates the evolving evidence base for intracoronary radiation by summarizing the results of recent randomized trials. They now conclude by stating that "intracoronary brachytherapy does seem to be a breakthrough treatment for patients with in-stent restenosis" [26].

Conclusion

After careful consideration of all the above-mentioned information, we would answer the question raised in the title of this article as follows: "Yes, coronary brachytherapy is now ready for clinical use". The theory behind preventing a rapidly growing, cell-rich proliferation by using ionizing radiation is sound. The equipment has been developed and perfected, and the evidence base from large, randomized clinical trials addressing radiation and in-stent restenosis is convincing.

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