Vascular Brachytherapy: Applications in the Era of Drug-Eluting Stents

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Vascular brachytherapy using beta and gamma emitters has revolutionized treatment of in-stent restenosis. We are witnessing a near-abolition of the restenosis problem for simple lesions, but the future of vascular brachytherapy depends on our success in improving efficacy and reducing complications such as late thrombosis and edge effects. Optimizing dosimetry, applying adequate radiation margins, and prolonging antiplatelet therapy should equalize brachytherapy results with those of drug-eluting stents. In this overview we examine issues related to progress and optimization of outcomes derived from the use of vascular brachytherapy. We also examine its potential to expand to other applications beyond in-stent restenosis, such as the treatment of de novo *lesions and peripheral vascular disease.*
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Coronary artery revascularization is currently in a phase of dynamic transition. The global application of percutaneous coronary interventions (PCIs), including the widespread insertion of coronary stents, continues to increase exponentially. The predominant limitation of stenting has been restenosis. Vascular brachytherapy using beta and gamma emitters has revolutionized treatment after PCIs, particularly of in-stent restenosis (ISR), and has demonstrated safety and efficacy. With the advent of drug-eluting stent technology and the lower reported restenosis rates, we are on the verge of a new era

in intervention cardiology. Clearly we are witnessing a near-abolition of the restenosis problem for simple lesions. This will lead interventionists to increase the number of coronary interventions being performed on more complex lesions and will set a new challenge for both vascular brachytherapy and drug-eluting stents. Despite encouraging reports from the initial trials, it appears that in the "real world" of coronary intervention there are potential limitations to drug-eluting stent technology, namely, edge effect, thrombosis, and late restenosis.

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Optimizing Efficacy with Vascular Brachytherapy

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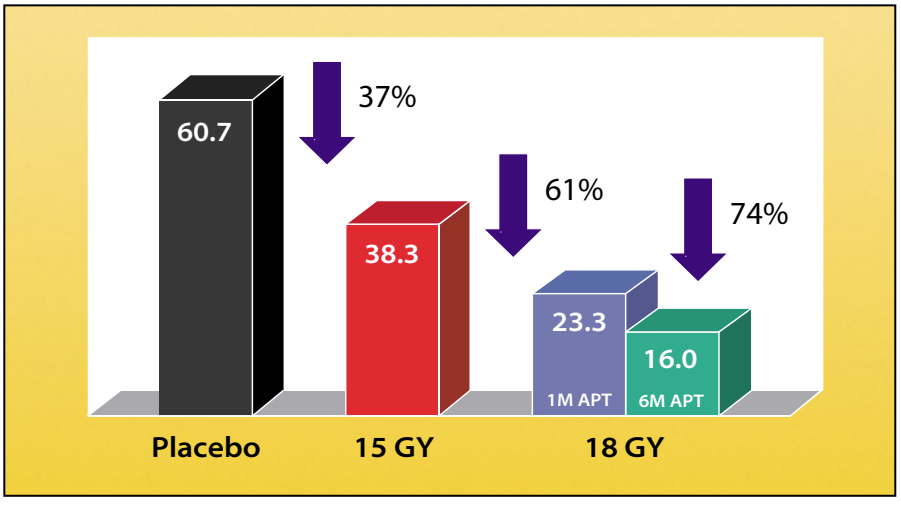
The Dose

The efficacy of intracoronary gamma radiation therapy in reducing clinical and angiographic restenosis in patients with ISR has been confirmed by the Scripps Coronary Radiation to Inhibit Proliferation Post-Stenting (SCRIPPS),[1] Washington Radiation for In-Stent Restenosis (WRIST),[2] and the GAMMA-1[3] randomized trials. The only gamma emitter used in clinical trials for ISR is ^{192}iridium (^{192}Ir). Initial clinical studies recognize the limitations of gamma radiation, including high activity and radiation exposure, long treatment times, the need for special shielding, and the mandatory need to remove staff from the patient's side during the dwell time. These factors have driven the development of intracoronary radiation using beta emitters. Based on the Stents and Radiation Therapy (START)[4] and Intimal Hyperplasia Inhibition with Beta In-Stent (INHIBIT)[5] studies on ISR, progress of the technology has been rapid, with recent FDA approval of the ^{90}Sr/Y Beta-Cath™ (Novoste Corporation, Norcross, GA) and the P32 GALILEO® (Guidant Corporation, Indianapolis, IN) systems. Although gamma and beta radiation showed promising results when compared to conventional therapy, restenosis rates remained high at over 15%.

However, a few attempts to conduct dose-finding studies[6] have indicated that the dose in the initial clinical trials was suboptimal and that vessels can tolerate higher doses. In the LONG WRIST High Dose study (a registry of 120 patients with similar entry criteria to LONG WRIST), a higher radiation dose was prescribed; 18 Gy versus 15 Gy delivered at 2 mm distance from the center of the source. At 6-month follow-up, patients in the LONG WRIST High Dose group with 6 months of antiplatelet therapy had a strikingly low rate of target vessel revascularization (TVR) (17%) and major adverse cardiac events (MACE) (17%), compared to the overall MACE (36%) in the LONG WRIST group (Figure 1).

Intravascular ultrasound (IVUS) analysis post-intervention and at 6-month follow-up was performed in 25 patients from LONG WRIST High Dose and in 30 intracoronary radiation therapy (IRT) and 34 placebo patients from LONG WRIST.[7] At follow-up, the minimum lumen area was largest in the LONG WRIST High Dose patients (4.0 ± 1.4 mm^2); areas were 2.9 ± 1.0 mm^2 in IRT patients and 1.9 ± 1.1 mm^2 in placebo patients in LONG WRIST ($P < .005$ for all comparisons).[7,8] The dose-finding study utilizing the ^{90}Y source for de novo lesions demonstrated reduction of restenosis from 26% with 9 Gy to 9% with 18 Gy.[6] If this is the magnitude of reduction of

Figure 1. *Major adverse cardiac events at 6 months in the LONG WRIST studies. APT, antiplatelet.*



restenosis, we can estimate that 3 Gy more for each isotope will obtain single-digit restenosis and will equalize brachytherapy results and drug-eluting results.

Edge Effect

The first descriptions of the edge effect in the vascular brachytherapy field were related to the radioactive stent. Over the last few years numerous attempts have been made to improve the performance of radioactive stents; among those was the use of high-activity stents using cold ends or hot ends.[9] Unfortunately none of these attempts was successful in eliminating the edge-effect phenomenon. This lack of success can be simply explained by the fact that in the case of radioactive stents, the source cannot cover the entire longitudinal injured length, which occasionally extends a few millimeters beyond the stent, resulting in geographic miss and edge stenosis.

This phenomenon of geographic miss can also occur with catheter-based radiation therapy but can be controlled by extending the radiation margins beyond the injured segment.[10] Recent animal and clinical studies suggest that a minimum of at least 5–10 mm from each end of the injured segment will eliminate the edge-effect phenomenon.[11] This option is not easily achieved with drug-eluting stent technology because the drug is confined to the stent platform and can potentially leach from the proximal end of the stent. Thus it is conceivable that brachytherapy can be used for treatment of the edge-effect phenomenon in drug-eluting stents.

Late Thrombosis

Late thrombosis (more than 30 days after radiation therapy) is considered one of the major complications in vascular brachytherapy. In early clinical trials utilizing the technology, late thrombosis was reported in up to 14% of patients.[12] Late thrombosis also occurs with other vascular brachytherapy strategies and almost certainly relates to the healing arrest and lack of stent cover by cells. A fundamental strategy for preventing late thrombosis is to limit restenting at the time of index radiation. Our recent experience showed that it is essential to administer at least 12 months of antiplatelet therapy (clopidogrel) in addition to aspirin for all radiation cases (beta and gamma emitters).[13] Clopidogrel exerts its protective action by reducing fibrin and platelet aggregation, and it remains speculative as to whether it contributes to a reduction in neointimal proliferation and restenosis. Although late thrombosis is not yet a problem solved, we have gained greater understanding of this complex entity and need to continue to devise strategies to eliminate it.

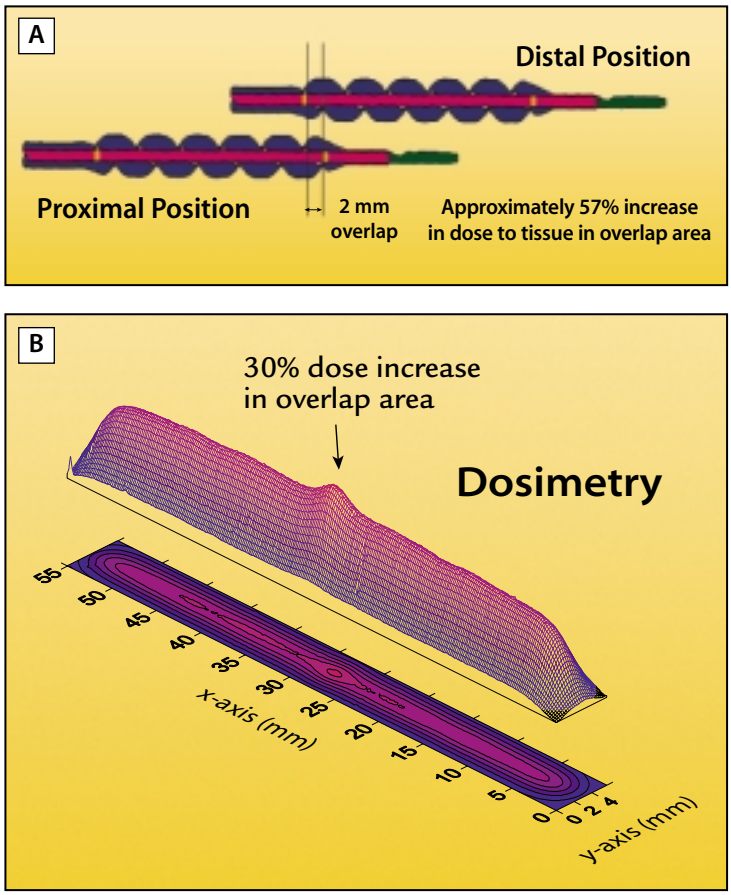


Figure 2. *Stepping of the GALILEO® system;* **(A)** *positioning of the source;* **(B)** *the dosimetry profile at the overlapped segment.*

In-Stent Restenosis

In 2002 vascular brachytherapy remains the standard of care for the treatment of ISR; it is currently in use in nearly 500 catheterization laboratories in the United States and is anticipated to be treating 40,000 patients with ISR by the end of 2002. This prediction is based on the results of seven randomized trials utilizing both gamma and beta emitters.

With the published results of the Washington Radiation for In-Stent Restenosis Trial for Saphenous Vein Grafts (SVG WRIST), there is now

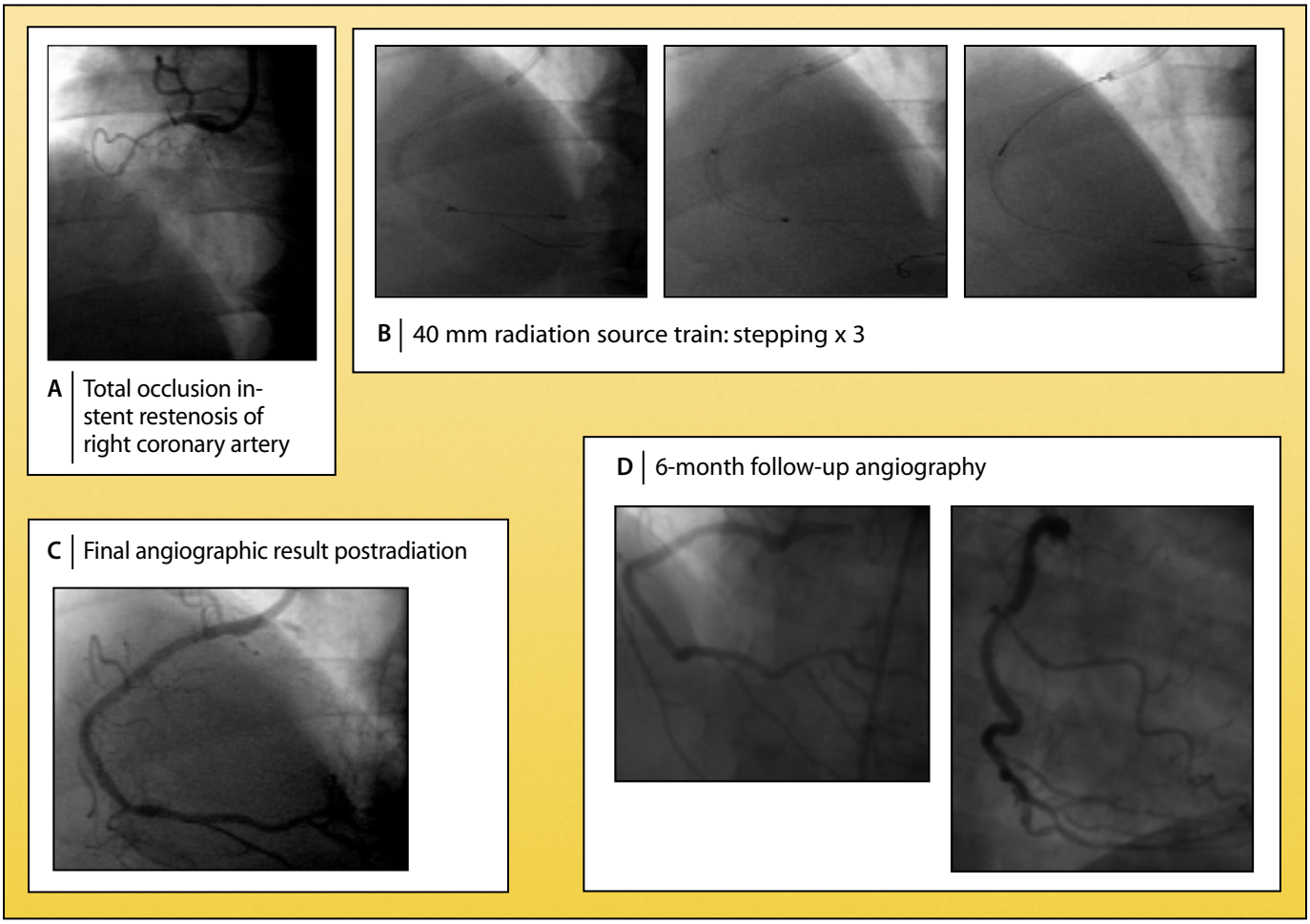


Figure 3. *An example of total occlusion of a "full metal jacket" in-stent restenosis lesion of the right coronary artery treated with laser and multiple stenting and stepping of the brachytherapy system.* **(A)** *Angiogram pretreatment,* **(B)** *positioning of the source to cover the entire treated segment,* **(C)** *angiogram after percutaneous coronary intervention and radiation,* **(D)** *6-month angiographic follow-up.*

evidence that the efficacy of the technology can be expanded to the treatment of ISR in vein grafts.[14] In contrast, there is not even a single randomized study to date on the use of drug-eluting stents for this application; preliminary results from the registries are mixed, with increased rates of late thrombosis and restenosis rates that vary from 0%–32%. By now we know that drug-eluting stents will further reduce the phenomenon of in-stent restenosis but will not eliminate it. Issues such as edge effect will require further treatment, and perhaps brachytherapy with catheter-based systems would be the best approach to treat these focal lesions. In addition, long lesions of in-stent restenosis and total occlusion would be better treated with long sources or the stepping technique, as demonstrated in Figure 2. This proved an excellent outcome, as shown in the case presentation in Figure 3.

De Novo Lesions

In parallel to the encouraging results of beta and gamma radiation in the treatment of patients with ISR, there have been a handful of clinical studies testing the effectiveness of ionizing radiation for de novo lesions (Table 1). The first pilot study utilizing gamma radiation ^{192}Ir for *de novo* lesions was conducted on 21 patients and has now reached 7 years of follow-up. This study has demonstrated mixed results, with the presence of aneurysms between 60 days and 6 months, yet overall stability in the clinical and angiographic results. The initial beta studies—the Geneva trial[15] using ^{90}Y, the Beta Energy Restenosis Trial (BERT)[16] using ^{90}Sr/Y, and the ^{32}P Proliferation Reduction with Vascular Energy Trial (PREVENT)[17]—demonstrated reduced late loss index and binary restenosis with active treatment and showed the potential of

Table 1
Results of Beta Radiation Trials for the Treatment of *De Novo* Lesions

Study	No. Pts.	Source	Dose, Gy	Lesion length	Restenosis, %	MACE, %
BERT	20	^{90}Sr/Y	12, 14, 16	< 20 mm	15	15
BERT 1.5	35	^{90}Sr/Y	12, 14, 16	< 20 mm	11	9
PREVENT	96	^{32}P	16, 20, 24	< 22 mm	22	26
Dose Findings	181	^{90}Y	9, 12, 15, 18	< 15 mm	26 (9 Gy) 9 (18 Gy)	16 (9 Gy) 13 (18 Gy)
BRIE	149	^{90}Sr/Y	14, 18	< 20 mm	34	34
Beta-Cath (Stent)	764	^{90}Sr/Y	16	< 20 mm	44.3 (16 Gy) 34.1 (Control)	27.9 (16 Gy) 17.4 (Control)
Beta-Cath (Balloon)	504	^{90}Sr/Y	16	< 20 mm	31 (16 Gy) 36 (Control)	14.2 (16 Gy) 20.4 (Control)
ECRIS II	225	^{188}Re	22.5	< 20 mm	11.1 (22.5 Gy) 28.3 (Control)	5.6 (22.5 Gy) 26.4 (Control)
SVG BRITE	25	^{32}P	20	< 45 mm	11	4.2 (Control)

MACE, major adverse cardiac events.

this therapy with vascular remodeling. The Beta Radiation in Europe (BRIE)[18] registry and the Beta-Cath randomized trial, which had a high rate of geographic miss (up to 80%), demonstrated the edge-effect phenomenon, especially for the treatment of stented *de novo* lesions.

Nevertheless, there are strong indications from the dose-finding study[5] that with the right dosimetry and adequate coverage of the injured segment, binary restenosis can be minimized to 4.2% with balloon only and 15% with stents for stented lesions, with combined restenosis of 9%. In the Beta-Cath study, overall positive results in the lesion segment analysis and strong trends in the clinical outcomes in the PTCA branch suggest a potential role for ^{90}Sr/Y radiation in the treatment of de novo coronary lesions if the increase in restenosis in the "analysis segment" can be solved. A recent registry with direct stenting of *de novo* lesions, using the same dosimetry as in the Beta-Cath study, resulted in 15% restenosis for both the stented and the analyzed segment, suggesting that the edge effect can be eliminated. If so, the use of brachytherapy should be reexamined, especially for the treatment of unfavorable lesions subjected to stenting. Among these are small vessels, bifurcations, and long and diffuse lesions that may require multiple stenting.

Preliminary results from the Saphenous Vein Graft Beta Radiation to Prevent In-Stent Restenosis (SVG BRITE) study with the use of the RDX™ Coronary Radiation Delivery System (Radiance Medical Systems, Irvine, CA) utilizing ^{32}P source for the treatment of de novo lesions in saphenous vein grafts (mostly stented) are encouraging, with 0% restenosis and 11.1% late loss. If proven to be effective for *de novo* lesions, vascular brachytherapy can be a technology competitive with drug-eluting stents for high-risk lesions, especially for long lesions and multivessel disease. In addition, vascular brachytherapy can be utilized as an adjunct to ablative therapy (laser treatment and atherectomy when stents are not desired). With the use of contemporary and accurate dosimetry that is lesion specific, it would be feasible to obtain a single-digit restenosis rate for de novo lesions.

Peripheral Vascular Disease

Combating restenosis in the peripheral vascular system is contingent upon understanding the processes, mechanisms, and potential targets affected by using brachytherapy. In principal, vascular brachytherapy should limit neointimal formation following vascular injury. As such, it should find broad potential applications in the peripheral vascular system. Among them are the first and most frequently used application:

Table 2
Superficial Femoral Artery Radiation Trials

Study	No. Pts.	Randomized	Center cath.	Dose Gy	Dose at mm	Patency at 6 months, %
Frankfurt	40	–	–	12	3	82
Vienna I	10	–	No	12	3	60
Vienna II	113	Yes	No	12	r + 0	72
Vienna III	134	Yes	Yes	18	r + 2	–
Vienna IV	33	No	Yes	14	r + 2	–
Vienna V	98	Yes	Yes	14	r + 2	–
Swiss	120	Yes	–	12	r + 2	72
Paris	40	No	Yes	14	r + 2	88
PARIS	300	Yes	Yes	14	r + 2	–

treatment of superficial femoral arteries, first initiated by Liermann (Frankfurt, Germany). Known as the Frankfurt Experience, the first pilot study of endovascular radiation was conducted in 30 patients with in-stent restenosis in their saphenous femoral arteries.[19] Ten years after this first clinical trial, no safety issues related to the technology have been reported. Other potential applications for the use of vascular brachytherapy in the peripheral vascular system are ISR in renal arteries, arteriovenous (AV) dialysis shunt stenosis, subclavian stenosis, and to obtain patency of transjugular intrahepatic portosystemic shunt (TIPS) procedures. Several considerations should be addressed with the use of vascular brachytherapy in peripheral arteries. Among them are the use of a centering catheter, adjusting dose to vessel size, and treatment of long diffuse lesions.

The effectiveness of the micro-Selectron-HDR system (Nucletron BV, Veenendall, Netherlands) was tested in a randomized placebo-controlled trial in Vienna.[20] One hundred thirteen patients (63 men, 50 women; mean age 71 years) with *de novo* or recurrent femoropopliteal lesions were included in this randomized trial comparing the restenosis rate after percutaneous transluminal angioplasty (PTA) plus brachytherapy (BT) (57 patients) versus PTA (56 patients) without stent implantation. The mean treated length was 16.7 cm (PTA+BT group) versus 14.8 cm (PTA group). In patients randomized to PTA plus BT, a dose of 12 Gy was applied by a ^{192}Ir source 3 mm from the source axis. Follow-up examinations included measurement of the ankle-brachial index, color-flow duplex sonography, and angiography. The primary end point of the study was patency after 6 months. The overall recurrence rate after 6 months was 15 of 53 (28.3%) in the PTA+BT group versus 29 of 54 (53.7%) in the PTA group (X^2 test; $P < .05$). The cumulative patency rates at 12 months of follow-up were 63.6% in the PTA+BT group and 35.3% in the PTA group (log-rank test; $P < .005$).[20]

Minar and colleagues continued with a series of registries and randomized studies.[20] Among them are Vienna I–IV, which use intravascular gamma radiation as adjunct therapy to angioplasty of lesions in superficial femoral arteries to optimize the dosing and to investigate the utility of the technology for stented arteries. A list of radiation trials in superficial femoral artery (SFA) lesions is shown in Table 2. The Peripheral Arteries Radiation Investigational Study (PARIS) pilot study demonstrated the lowest restenosis rates (<13%) published so far, which can be attributed to more accurate dosimetry and the use of a centering catheter.[21] If the randomized study duplicates these results, it is anticipated that vascular brachytherapy will be expanded for the use of *de novo* lesions in SFA lesions.

Recently two trials utilizing beta radiation have been initiated to explore the potential use of beta emitters for the treatment of SFA disease. These are the Radiation After PTCA Is Done (RAPID) study using the RDX system (^{32}P emitter) and the More Patency with Beta for In-Stent Restenosis in the Lower Extremity (MOBILE) study for the treatment of in-stent restenosis in SFA lesions using the Corona device with the ^{90}Sr/Y emitter. The Corona system will be tested for the treatment of AV dialysis shunt stenosis in a randomized study that will begin in the last quarter of 2002. If

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the outcomes of these studies mimic the results of the gamma emitters, expansion of the use of vascular brachytherapy for peripheral vascular disease is anticipated.

Conclusion

The field of vascular brachytherapy is now entering maturity. The technology is cost-effective and reimbursed appropriately. In the midst of this progress, a promising new player is evident in the combat to eradicate restenosis: drug-eluting stents. Initial trials with the use of drug-coated stents have demonstrated the potential to reduce the restenosis rate further. This, however, will increase the frequency of interventional procedures for coronary artery disease and reduce the need for cardiac bypass surgery, but the use of drug-coated stents may still be associated with restenotic lesions that in the past would not have been interfered with. The utility of drug-eluting stents for in-stent restenosis is unknown; trials are currently under way to address this important issue. At present, drug-eluting stents await clinical interrogation and are prohibitively costly, which may impact on their widespread applicability. Although drug-eluting stents may have a great future, there are still issues that need to be resolved. Who knows what problems may emerge as these stents go through the regulatory and clinical processes? Perhaps in the future both radiation and coated stents will be used in the catheterization laboratory in the battle to eliminate restenosis. For those who may be worried about the future of vascular brachytherapy in the era of drug-eluting stents, it is suggested that they do not prematurely dismiss brachytherapy because it may be needed for the treatment of restenosis and drug-eluting stent failures. ■

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Main Points

- Potential limitations to drug-eluting stent technology include the edge effect, thrombosis, and late restenosis.
- The future of vascular brachytherapy depends on optimizing dosimetry, applying adequate radiation margins, and prolonging antiplatelet therapy.
- Limitations of gamma radiation include high activity and radiation exposure, long treatment times, the need for special shielding, and the mandatory need to remove staff from the patient's side during dwell time.
- In radioactive stents, the source cannot cover the entire longitudinal injured length, which occasionally extends a few millimeters beyond the stent, resulting in geographic miss and edge stenosis.
- Geographic miss can also occur with catheter-based radiation therapy but can be controlled by extending the radiation margins beyond the injured segment; recent studies suggest that a minimum of at least 5–10 mm from each end of the injured segment will eliminate the edge-effect phenomenon.
- Late thrombosis (more than 30 days after radiation therapy) is considered one of the major complications in vascular brachytherapy and has been reported in up to 14% of patients.
- A fundamental strategy for preventing late thrombosis is to limit restenting at the time of index radiation; in addition, at least 12 months of clopidogrel exerts a protective action by reducing fibrin and platelet aggregation.
- Vascular brachytherapy should limit neointimal formation following vascular injury; potential applications in the peripheral vascular system include treatment of superficial femoral arteries, in-stent restenosis in renal arteries, arteriovenous dialysis shunt stenosis, and subclavian stenosis.

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