Vascular Brachytherapy from Investigation to Approval

Last November, a decade of preclinical and clinical investigations of vascular brachytherapy was completed, which led to the FDA's marketing approval of both the Checkmate System (Cordis) and the Beth-Cath System (Novoste) for the treatment of patients with in-stent restenosis. In recognition of the limited treatment options for these patients, the premarket approval applications for both systems were given expedited FDA review. Both approvals stipulated that the original cohort of patients in the trials used to prove safety and effectiveness (SCRIPPS,[1] WRIST,[2] GAMMA-1,[3] and START[4]) continue to be followed to assess the long-term effects.

The field of vascular brachytherapy, which emerged from the need to resolve the restenosis phenomenon seen following angioplasty, has been driven primarily by investigators who stimulated and directed industry to develop user-friendly devices that would allow safe delivery of radiation to coronary arteries following conventional intervention. Different sources and delivery catheters were designed to accommodate this radiation delivery. Initially, the main platforms for delivery were radioactive stents and catheter-based systems. Because of the high rate of edge effect (up to 40%) with the β-radioactive stent and the introduction of the drug-eluting stent, catheter-based systems became the sole platform for delivery of radiation into the coronary system.

Radiation catheters are designed with a closed-end lumen to accommodate a ribbon with radioactive seeds, a line source, radioactive seeds delivered hydraulically, or liquid- or gas-filled balloons. Although centering catheters seem to have an advantage by providing more homogeneous dose distribution surrounding the lumen of the vessel, benefit of this feature was not proved in the completed clinical trials. The radiation sources are delivered into the catheter either manually or via an automatic afterloader. This afterloader delivers and retrieves the source; calculates the dwell time, based on the vessel size and the activity of the source; and allows stepping of the radioactive source, for the management of long lesions. The Galileo system (Guidant) has a 0.018 radioactive wire, a helical balloon, and an automatic afterloader to deliver and retrieve a phosphorus P 32 β emitter with the option of automatic stepping. This system is next in line for FDA approval, based on results of the INHIBIT[5] studies. Soft x-ray catheters that may provide radiation on demand without the radioisotopes are in the pipeline.

During the past decade, much has been learned about the mechanisms by which radiation reduces restenosis; among these mechanisms are inhibition of smooth muscle cell proliferation and migration, vascular remodeling, apoptosis, and antiangiogenesis. While the target layer (adventitia, media, intima) has not been clearly determined, the dosimetry methods have been improved, and the therapeutic window has been identified.

Vascular brachytherapy is recognized as a multidisciplinary field involving radiation biology, radiation physics, device engineering, and clinical investigation. The introduction of vascular brachytherapy into the catheterization laboratory requires adequate shielding when using γ-radiation, scheduling of patients, along with full coordination of the radiation team.

While most US clinical trials have focused on in-stent restenosis, in Europe, β-radiation has been tested in de novo lesions; the dose-finding study yielded a single-digit rate of restenosis (3.9%) following balloon angioplasty using the yttrium Y 90 emitter (18 Gy).

The pivotal double-blind, randomized US trials for in-stent restenosis continue to demonstrate a reduction (35% to 66%) in the recurrence rate of restenosis when radiation is applied. To date, 4 randomized trials using γ-radiation (SCRIPPS, WRIST, GAMMA-1 [lesions smaller than 45 mm], and LONG WRIST[6] [lesions as long as 80 mm]) have shown a significant reduction in the recurrence rate (35% to 70%) for patients who were assigned to treatment with iridium Ir 192 (Table). The incidence of late thrombosis reported in these trials was diminished to background, with prolonged antiplatelet therapy (6 to 12 months) reported in the SCRIPPS III[7] and WRIST PLUS[8] studies. The 2 completed randomized studies using β emitters, START (strontium [Sr]/Y 90) and INHIBIT (P 32), proved the hypothesis that β-radiation has efficacy rates similar to those of γ-radiation and with 3 months of antiplatelet therapy, late thrombosis was nearly 0. In START, patients with lesions from in-stent restenosis as long as 20 mm were assigned to receive placebo or radiation; at 8-month follow-up, a significant treatment effect (31% to 66% reduction) was associated

Table
Reported Clinical Trials Using Vascular Brachytherapy for In-Stent Restenosis

				Restenosis (%)	
Trial	**Source**	**Length (mm)**	**Patients (N)**	**Placebo**	**Treated**
SCRIPPS[1]	Ir 192	15.3	35	70.5	11.1
WRIST[2]	Ir 192	23.7	130	58.3	19.0
GAMMA-1[3]	Ir 192	20.2	252	50.5	21.6
LONG WRIST[6]	Ir 192	32	120	71.0	32.0
START[4]	Sr/Y 90	17	476	42.2	14.2
INHIBIT[5]	P 32	17	332	48.0	16.0

with the use of Sr/Y 90 for all clinical and angiographic outcomes parameters examined. In the INHIBIT study, patients with diffuse in-stent restenotic lesions (up to 47 mm) were assigned to either placebo or radiation therapy; at 9-month follow-up, a significant radiation treatment effect (33% to 66% reduction) was noted with use of P 32 for all clinical and angiographic outcomes parameters examined.

Recent data from the PARIS[9] feasibility study demonstrate the effectiveness of vascular brachytherapy for management of de novo superficial femoral artery lesions (11% restenosis rate). In addition, the Vienna II study,[10] with a cumulative patency of 63.6% in the irradiated group versus 35.3% in the control group, indicates the potential of this therapy beyond the management of coronary in-stent restenotic lesions. Other applications for this therapy, such as small vessels; long, diffuse lesions; and vessels of diabetic patients, are awaiting further investigation.

Clinical experience using vascular brachytherapy has helped to identify the specific complications related to this technology: late thrombosis, edge effect, and delayed restenosis. The problem of late thrombosis appears to resolve with prolonged administration of antiplatelet therapy; solutions for edge effect and delayed restenosis are currently under investigation.

Although alternatives to brachytherapy are emerging, such as drug-eluting stents, gene therapy, photodynamic therapy, sonotherapy, and cryotherapy, presently, vascular brachytherapy is the only proven technology to reduce the restenosis rate following intervention. It should be used carefully and wisely.

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