

*Circulation. 2002;106:776.*

## **Twelve Versus Six Months of Clopidogrel to Reduce Major Cardiac Events in Patients Undergoing -Radiation Therapy for In-Stent Restenosis**

**Washington Radiation for In-Stent restenosis Trial (WRIST) 12 Versus WRIST PLUS**

**Ron Waksman, MD; Andrew E. Ajani, MD; Ellen Pinnow, MS; Edouard Cheneau, MD; Laurent Leborgne, MD; Regina Dieble, RN; Anh B. Bui, MD; Lowell F. Satler, MD; Augusto D. Pichard, MD; Kenneth K. Kent, MD; Joseph Lindsay, MD**

**B**ackground; Intracoronary-radiation reduces recurrent in-stent restenosis (ISR). Late thrombosis was attenuated with 6 months of aspirin and clopidogrel. We aimed to find out whether 12 months of aspirin plus clopidogrel is superior to a strategy of 6 months after radiation therapy for patients with ISR. **Methods and Results;** One hundred twenty consecutive patients with diffuse ISR in native coronaries and vein grafts with lesions <80 mm in length underwent PTCA, laser ablation, or rotational atherectomy. Additional stents were placed in 39 patients (33%). After the intervention, a ribbon with different trains of radioactive <sup>192</sup>Ir seeds was positioned to cover the treated site, and a dose of 14 Gy to 2 mm was prescribed. Patients were discharged with clopidogrel and aspirin for 12 months and followed up clinically. The cardiac clinical event rates at 15 months were compared with the -treated (n=120) patients of the WRIST PLUS study (only 6 months of antiplatelet therapy). Whereas the late thrombosis rates were similar (3.3% for the group given 12 months of antiplatelet therapy versus 4.2% for the group given 6 months, P=0.72), the group treated with 12 months of antiplatelet therapy had a rate of 21% for major adverse cardiac events and 20% for target-lesion revascularization compared with 36% (P=0.01) and 35% (P=0.009), respectively, in patients who were treated with only 6 months of clopidogrel. **Conclusions;** Twelve months of clopidogrel is superior to 6 months in reducing overall major cardiac events and revascularization rates at 15 months for patients with ISR treated with -radiation. At least 12 months of clopidogrel therapy should be recommended for patients undergoing radiation therapy for ISR.

*Circulation. 2002;106:2334.*

## **Delivered Dose and Vascular Response After $^{90}\text{Sr}$ -Radiation for In-Stent Restenosis. Retrospective Dosimetry and Volumetric Intravascular Ultrasound Analysis**

Yoshihiro Morino, MD; Hideaki Kaneda, MD; Tim Fox, PhD; Atsushi Takagi, MD; Ali H.M. Hassan, MD; Raoul Bonan, MD; Ian Crocker, MD; Alexandra J. Lansky, MD; Warren K. Laskey, MD; Mohan Suntharalingam, MD; Heidi N. Bonneau, RN, MS; Paul G. Yock, MD; Yasuhiro Honda, MD; Peter J. Fitzgerald, MD, PhD

**B**ackground: Observations from previous intracoronary radiation therapy trials noted a considerable discrepancy between the prescribed radiation dose and the dose actually delivered. The aims of this study were to investigate the effect of actual delivered dose on vascular changes and to test the appropriateness of the current dose prescription. Methods and Results; Serial volumetric intravascular ultrasound (IVUS) analysis was performed in 30 in-stent restenosis cases treated with a 40-mm  $^{90}\text{Sr}/\text{Y}$  source train. The fixed dose was prescribed at 2 mm from the centerline of the source train (18.4 Gy at 2 mm for reference diameter 3.35 mm and 23 Gy for diameter 3.36 mm). Only stent segments with full radiation coverage and device injury were enrolled and divided into 2-mm-long subsegments (n=202). DS90EEM (the minimum dose absorbed by 90% of the external elastic membrane surface) was calculated as the delivered dose corresponding to each segment, assuming that the radiation catheter occupied the same position in the vessel as the IVUS catheter. Mean DS90EEM of  $23.5 \pm 4.82$  Gy (range 12.3 to 41.7 Gy) was delivered to these subsegments. Overall, intimal hyperplasia volume remained constant from postintervention to follow-up ( $2.23 \pm 1.10$  to  $2.32 \pm 1.09$  mm<sup>3</sup>/m; P=NS). Regression analysis revealed there was no correlation between delivered dose intensity and changes in intimal hyperplasia volume. No particular dose-dependent complications were appreciated in this delivered dose range. Conclusions: The current dose-prescription protocol of  $^{90}\text{Sr}/\text{Y}$  radiation to native in-stent restenosis lesions may provide substantial inhibition of neointimal repopulation regardless of the actual delivered dose intensity.

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## How to Fix the Edge Effect of Catheter -Based Radiation Therapy in Stented Arteries

Edouard Cheneau, MD; Ron Waksman, MD; Hamid Yazdi, MD; Rosanna Chan, PhD; Jana Fourdnadjiev, PhD; Chalak Berzingi, MD; Vivek Shah, MS; Andrew E. Ajani, MD; Laurent Leborgne, MD; Fermin O. Tio, MD

**B**ackground; Edge stenosis remains a serious limitation of catheter-based vascular brachytherapy (VBT). This study aims to identify the mechanisms and evaluate strategies to minimize edge restenosis in patients treated with VBT. Methods and Results; Thirty-four porcine stented coronary arteries were irradiated (doses of 15 or 22 Gy) with  $^{192}\text{Ir}$  trains of either 6 seeds (23 mm) with 0 mm coverage at the distal stent edge and 10 mm at the proximal stent edge or 14 seeds (55 mm) centered at the distal edge of the stent with 27.5 and 14.5 mm coverage at the distal and proximal edges, respectively. After VBT, an additional 13-mm stent was positioned overlapping the distal margin of the first stent. Animals were killed at 28 days, and arteries were analyzed. Longer radiation margins were associated with reduced intimal area (IA) at the stent edge:  $2.3 \pm 0.9$ ,  $3.6 \pm 2.0$ , and  $5.3 \pm 2.2$  mm<sup>2</sup> with 15 Gy for a radiation margin of 14.5, 10, and -13 mm (-13 versus 10,  $P=0.06$ ; 10 versus 14.5,  $P=0.06$ ). Additional stenting was associated with an increase of IA:  $4.0 \pm 2.3$  mm<sup>2</sup> at the overlapped segment. Increasing the dose to 22 Gy resulted in a reduction of the IA at the overlap segment to  $1.31 \pm 0.57$  mm<sup>2</sup> with 14 seeds (27.5 mm coverage) but was not helpful with 6 seeds (0 mm coverage): IA,  $5.56 \pm 2.28$  mm<sup>2</sup>. Conclusions; Extending the radiation margins to 14.5 mm from each end of the stent minimized the edge-effect phenomenon. A higher dose is essential to eliminate further increases in IA at the overlapped segment with additional stents.

*Circulation. 2002;106:1090.*

## **Randomized Trial of 90Sr/90Y $\beta$ -Radiation Versus Placebo Control for Treatment of In-Stent Restenosis**

**Jeffrey J. Popma, MD; Mohan Suntharalingam, MD; Alexandra J. Lansky, MD; Richard R. Heuser, MD; Burton Speiser, MD; Paul S. Teirstein, MD; Vincent Massullo, MD; Theodore Bass, MD; Randall Henderson, MD; Sigmund Silber, MD; Peter von Rottkay, MD; Raoul Bonan, MD; Kalon K.L. Ho, MD; Alison Osattin, MPH; Richard E. Kuntz, MD for the Stents And Radiation Therapy (START) Investigators\***

**B**ackground; After conventional treatment of in-stent restenosis, the incidence of recurrent clinical restenosis may approach 40%. We report the first multicenter, blinded, and randomized trial of intracoronary radiation with the use of a 90Sr/90Y  $\beta$ -source for the treatment of in-stent restenosis. **Methods and Results;** After successful catheter-based treatment of in-stent restenosis, 476 patients were randomly assigned to receive an intracoronary catheter containing either 90Sr/90Y (n=244) or placebo (n=232) sources. The prescribed dose 2 mm from the center of the source was 18.4 Gy for vessels between 2.70 and 3.35 mm in diameter and 23.0 Gy for vessels between 3.36 and 4.0 mm. The primary end point, ie, clinically driven target-vessel revascularization by 8 months, was observed in 56 (26.8%) of the patients assigned to placebo and 39 (17.0%) of the patients assigned to radiation (P=0.015). The incidence of the composite including death, myocardial infarction, and target-vessel revascularization was observed in 60 (28.7%) of the patients assigned to placebo and 44 (19.1%) of the patients assigned to radiation (P=0.024). Binary 8-month angiographic restenosis (50% diameter stenosis) within the entire segment treated with radiation was reduced from 45.2% in the placebo-treated patients to 28.8% in the 90Sr/90Y-treated patients (P=0.001). Stent thromboses occurred in 1 patient assigned to placebo <24 hours after the procedure and in 1 patient assigned to 90Sr/90Y at day 244. **Conclusions;** The results of this study demonstrated that  $\beta$ -radiation using 90Sr/90Y is both safe and effective for preventing recurrence in patients with in-stent restenosis.

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## **Cost-Effectiveness of Gamma Radiation for Treatment of In-Stent Restenosis. Results From the Gamma-1 Trial**

**David J. Cohen, MD, MSc; Roberta S. Cosgrove, MS; Ronna H. Berezin, MPH; Paul S. Teirstein, MD;  
Martin B. Leon, MD; Richard E. Kuntz, MD, MSc on behalf of the Gamma-1 Investigators**

**B**ackground; Recently, several randomized trials have demonstrated that intracoronary brachytherapy can reduce the rates of both angiographic and clinical restenosis in patients undergoing percutaneous coronary intervention (PCI) for in-stent restenosis. Whether this practice is cost-effective is unknown. Methods and Results; Between December 1997 and July 1998, 252 patients with in-stent restenosis were randomized to receive brachytherapy or placebo after successful PCI as part of the Gamma-1 trial. We collected detailed resource utilization and cost data for each patient's initial hospitalization and for 1 year after randomization. Compared with conventional treatment, intracoronary brachytherapy increased procedure duration, physician services, and equipment costs. As a result, initial costs were increased by nearly \$4100 per patient (\$15 724 versus \$11 675,  $P<0.001$ ). Over the 1-year follow-up period, brachytherapy reduced the need for repeat revascularization by 21% and reduced the need for bypass surgery by 44%. Although follow-up medical care costs were \$2200/patient lower with brachytherapy, total costs remained higher at 1 year (\$28 543 versus \$26 737,  $P=0.46$ ). In a sensitivity analysis that incorporated recent technical modifications and the use of prolonged antiplatelet therapy to prevent late thrombotic occlusion, follow-up cost savings increased to \$3600/patient, and 1-year costs were slightly lower with brachytherapy (\$26 352 versus \$26 729,  $P=0.87$ ). Subgroup analysis demonstrated significant cost savings in patients with diabetes and patients who did not undergo repeat stenting. Conclusions; As performed in the Gamma-1 trial, coronary brachytherapy for in-stent restenosis improved clinical outcomes but increased 1-year costs compared with standard therapy. If late thrombosis can be eliminated, however, this technology has the potential to reduce overall medical care costs.

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## **Five-Year Clinical Follow-Up After Intracoronary Radiation Results of a Randomized Clinical Trial**

**Mark A. Grise, MD; Vincent Massullo, MD; Shirish Jani, PhD; Jeffrey J. Popma, MD; Robert J. Russo, MD, PhD; Richard A. Schatz, MD; Erminia M. Guarneri, MD; Stephen Steuterman, MS; David A. Cloutier, BS; Martin B. Leon, MD; Prabhakar Tripuraneni, MD; Paul S. Teirstein, MD**

**B**ackground; Several clinical trials indicate that intracoronary radiation is safe and effective for treatment of restenotic coronary arteries. We previously reported 6-month and 3-year clinical and angiographic follow-up demonstrating significant decreases in target lesion revascularization (TLR) and angiographic restenosis after radiation of restenotic lesions. The objective of this study was to document the clinical outcome 5 years after treatment of restenotic coronary arteries with catheter-based iridium-192 (192Ir). **Methods and Results;** A double-blind, randomized trial compared 192Ir to placebo sources in patients with restenosis after coronary angioplasty. Over a 9-month period, 55 patients were enrolled; 26 were randomized to 192Ir and 29 to placebo. At 5-year follow-up, TLR was significantly lower in the 192Ir group (23.1% versus 48.3%;  $P=0.05$ ). There were 2 TLRs between years 3 and 5 in patients in the 192Ir group and none in patients in the placebo group. The 5-year event-free survival rate (freedom from death, myocardial infarction, or TLR) was greater in 192Ir-treated patients (61.5% versus 34.5%;  $P=0.02$ ). **Conclusions;** Despite apparent mitigation of efficacy over time, there remains a significant reduction in TLR at 5 years and an improvement in event-free survival in patients treated with intracoronary 192Ir. The early clinical benefits after intracoronary radiation with 192Ir seem durable at 5-year clinical follow-up.

*Circulation. 2002;105:2465.*

## **Late Vascular Response to Repeat Stenting for In-Stent Restenosis With and Without Radiation. An Intravascular Ultrasound Volumetric Analysis**

**Yoshihiro Morino, MD; Thosaphol Limpijankit, MD; Yasuhiro Honda, MD; Alexandra J. Lansky, MD; Ron Waksman, MD; Heidi N. Bonneau, RN, MS; Paul G. Yock, MD; Gary S. Mintz, MD; Peter J. Fitzgerald, MD, PhD**

**B**ackground; Re-stenting of in-stent restenosis (ISR) improves acute angiographic results. Methods and Results; Volumetric intravascular ultrasound analysis was performed in 70 ISR lesions that received either placebo (n=36) or 192Ir radiation (n=34). ISR lesions treated by re-stenting were divided into 3 groups: old stent not re-stented (A), old/new stent overlap (B), and new stent only (C). ISR lesions treated without re-stenting were categorized as D. In placebo patients, postintervention lumen volume index (LVI) was significantly greater in re-stented segments B and C than in nonre-stented segment A ( $P<0.05$ ). At follow-up, however, LVI was similar in all 4 segments secondary to the increased intimal hyperplasia (IH) reaccumulation within the re-stented segments. In patients treated with 192Ir radiation, LVI was maintained from baseline to follow-up only in nonre-stented segments A and D. Conversely, there was a significant decrease in LVI in re-stented segments B and C ( $P<0.05$ ). Qualitatively, 79% of patients in the irradiated group had stent struts with undetectable neointimal versus only 27% in the placebo group ( $P<0.001$ ). Coefficient of variation of IH reaccumulation was greater in re-stented segments of 192Ir patients (B=57.3% and C=58.9%) than in re-stented segments in placebo patients (B=27.3% and C=26.8%) and nonre-stented segments in irradiated patients. Conclusions; Additional lumen gain from re-stenting ISR lesions is counteracted by exaggerated neointimal proliferation in placebo patients. Maximum effectiveness and safety of radiation can be achieved for ISR lesions when treated without re-stenting. Thus, regardless of supplementary intravascular brachytherapy, repeat stenting strategies provided little long-term advantage.

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## **High-Dose Intravascular $\gamma$ -Radiation After De Novo Stent Implantation Induces Coronary Artery Spasm**

**D. Scheinert, MD; V. Strnad, MD; R. Muller, MD; R. Burckhard, MD; S. Ropers, MD; R. Sauer, MD; W.G. Daniel, MD; R. Bonan, MD; J. Ludwig, MD**

**B**ackground; Intracoronary brachytherapy is effective in preventing restenosis after coronary interventions. However, in vitro and animal studies have shown that irradiation produces immediate and sustained endothelial dysfunction. This study assesses the clinical relevance of impaired vasomotoric function induced by brachytherapy. **Methods and Results;** We analyzed the occurrence of postradiation coronary artery spasms in 1 animal study and 2 clinical trials investigating the effects of high-dose intracoronary  $\gamma$ -radiation after de novo coronary artery stenting. Irradiated segments (IRSs) proximal and distal to the stent were studied by quantitative coronary angiography after stenting, after radiation, and at the end of the procedure. There was an 67% overall incidence of coronary artery spasm in the IRSs immediately after  $\gamma$ -radiation compared with 9% after sham treatment ( $P < 0.001$ ). Whereas in most cases this phenomenon was only minor or moderate, in 12 cases, 4 (22%) animals and 8 (28%) patients, severe coronary spasm ( $>90\%$  diameter stenosis) with significant ECG-changes or hemodynamic instability was observed. Relief of spasms was protracted (mean time until complete relief of spasm  $423 \pm 122$  seconds) and required repetitive intracoronary administration of nitroglycerin (mean dose:  $1.2 \pm 0.6$  mg). **Conclusions;** Vasoconstriction is a frequent reaction of coronary arteries after high-dose intracoronary  $\gamma$ -radiation, necessitating repetitive administration of vasodilators.

## **Balloon-based radiation therapy for treatment of in-stent restenosis in human coronary arteries: results from the BRITE I study.**

**Waksman R, Buchbinder M, Reisman M, Lansky AJ, Trauthen B, Whiting J, Li A.**

**C**atheter-based intracoronary radiation therapy demonstrated reduction of the recurrence rate of in-stent restenosis by 35%-50% when compared to conventional therapy. The objectives of this study were to determine the safety and feasibility of a new balloon-shaped source design and a higher applied dose to reduce the restenosis rates. Thirty-two patients with in-stent restenosis who met study eligibility criteria were successfully treated with standard PCI techniques. Following a successful intervention, a P-32 beta-balloon source was positioned to cover the angioplasty site and a dose of a 20 Gy at 1 mm from the surface of the source was administered. The primary endpoint was a composite of major adverse cardiac events (any death, MI, emergent CABG, or repeat target vessel revascularization) during 6 months of follow-up. At 6 months, only one patient underwent repeat PTCA to the target vessel (3%). There were no instances of death, emergency surgery, late thrombosis, total occlusions, or MI. Binary restenosis measured by QCA at the stented segment was 0% and for the whole analysis vessel was 7.5%. Beta-radiation delivered with a balloon P-32 source design for patients with in-stent restenosis results in lower than expected rate of angiographic and clinical restenosis and the absence of late complications.

**Twelve versus six months of clopidogrel to reduce major cardiac events in patients undergoing gamma-radiation therapy for in-stent restenosis: Washington Radiation for In-Stent restenosis Trial (WRIST) 12 versus WRIST PLUS.**

Waksman R, Ajani AE, Pinnow E, Cheneau E, Leborgne L, Dieble R, Bui AB, Satler LF, Pichard AD, Kent KK, Lindsay J.

**B**ACKGROUND: Intracoronary gamma-radiation reduces recurrent in-stent restenosis (ISR). Late thrombosis was attenuated with 6 months of aspirin and clopidogrel. We aimed to find out whether 12 months of aspirin plus clopidogrel is superior to a strategy of 6 months after radiation therapy for patients with ISR. **METHODS AND RESULTS:** One hundred twenty consecutive patients with diffuse ISR in native coronaries and vein grafts with lesions <80 mm in length underwent PTCA, laser ablation, or rotational atherectomy. Additional stents were placed in 39 patients (33%). After the intervention, a ribbon with different trains of radioactive <sup>192</sup>Ir seeds was positioned to cover the treated site, and a dose of 14 Gy to 2 mm was prescribed. Patients were discharged with clopidogrel and aspirin for 12 months and followed up clinically. The cardiac clinical event rates at 15 months were compared with the gamma-treated (n=120) patients of the WRIST PLUS study (only 6 months of antiplatelet therapy). Whereas the late thrombosis rates were similar (3.3% for the group given 12 months of antiplatelet therapy versus 4.2% for the group given 6 months, P=0.72), the group treated with 12 months of antiplatelet therapy had a rate of 21% for major adverse cardiac events and 20% for target-lesion revascularization compared with 36% (P=0.01) and 35% (P=0.009), respectively, in patients who were treated with only 6 months of clopidogrel. **CONCLUSIONS:** Twelve months of clopidogrel is superior to 6 months in reducing overall major cardiac events and revascularization rates at 15 months for patients with ISR treated with gamma-radiation. At least 12 months of clopidogrel therapy should be recommended for patients undergoing radiation therapy for ISR.

## **Cost-effectiveness of gamma radiation for treatment of in-stent restenosis: results from the Gamma-1 trial.**

**Cohen DJ, Cosgrove RS, Berezin RH, Teirstein PS, Leon MB, Kuntz RE; Gamma-1 Investigators.**

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## **Intravascular brachytherapy to prevent restenosis: dosimetric considerations.**

**Campos L, Stabin M.**

**A**cute myocardial infarction is often the result of occlusion of one or more coronary arteries. Occlusion and restenosis (re-closing of the vessel) are principal reasons that percutaneous transluminal coronary angioplasty (PTCA) may fail to provide long-term benefit. PTCA has been a popular treatment, which is less invasive than surgeries involving revascularization of the myocardium, promising a better quality of life for patients. Unfortunately, the rate of restenosis after balloon angioplasty is high (approximately 30-50% in the first year after treatment). Recent data suggest that intraluminal irradiation of coronary arteries in conjunction with balloon angioplasty and/or stent implantation reduces the proliferation of smooth muscle cells and neointima formation, thereby inhibiting restenosis. In order to study radiation dosimetry in the patient and for this therapy, dose distributions for electrons and photons, with discrete energies, were simulated for blood vessels of diameter 1.5, 3 and 4.5 mm irradiated with balloon and wire sources. Electron and photon transport was performed in a simple model representing the system used for irradiation using the MCNP 4B code (Monte Carlo N-Particles). Specific calculations for balloon and wire sources were also carried out for a few radionuclides. In this work, strengths and drawbacks concerning the use of each radionuclide simulated, as well as source geometries are discussed. The dosimetry performed in this study will improve understanding of the benefit-to-risk ratio in intracoronary brachytherapy.

## RADIATION

1. Twelve Versus Six Months of Clopidogrel to Reduce Major Cardiac Events in Patients Undergoing - Radiation Therapy for In-Stent Restenosis: Washington Radiation for In-Stent restenosis Trial (WRIST) 12 Versus WRIST PLUS

Ron Waksman, Andrew E. Ajani, Ellen Pinnow, Edouard Cheneau, Laurent Leborgne, Regina Dieble, Anh B. Bui, Lowell F. Satler, Augusto D. Pichard, Kenneth K. Kent, and Joseph Lindsay  
Circulation, Aug 2002; 106: 776 - 778.

2. Delivered Dose and Vascular Response After  $\text{Co}^{60}$ -Radiation for In-Stent Restenosis: Retrospective Dosimetry and Volumetric Intravascular Ultrasound Analysis

Yoshihiro Morino, Hideaki Kaneda, Tim Fox, Atsushi Takagi, Ali H.M. Hassan, Raoul Bonan, Ian Crocker, Alexandra J. Lansky, Warren K. Laskey, Mohan Suntharalingam, Heidi N. Bonneau, Paul G. Yock, Yasuhiro Honda, and Peter J. Fitzgerald.  
Circulation, Oct 2002; 106: 2334 - 2339.

3. How to Fix the Edge Effect of Catheter-Based Radiation Therapy in Stented Arteries

Edouard Cheneau, Ron Waksman, Hamid Yazdi, Rosanna Chan, Jana Fourdnadjiev, Chalak Berzingi, Vivek Shah, Andrew E. Ajani, Laurent Leborgne, and Fermin O. Tio  
Circulation, Oct 2002; 106: 2271 - 2277.

4. Randomized Trial of  $^{90}\text{Sr}/^{90}\text{Y}$   $\text{Co}^{60}$ -Radiation Versus Placebo Control for Treatment of In-Stent Restenosis

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Circulation, Aug 2002; 106: 1090 - 1096.

5. Cost-Effectiveness of Gamma Radiation for Treatment of In-Stent Restenosis: Results From the Gamma-1 Trial

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Circulation, Aug 2002; 106: 691 - 697.

6. Five-Year Clinical Follow-Up After Intracoronary Radiation: Results of a Randomized Clinical Trial

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Circulation, Jun 2002; 105: 2737 - 2740.

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#### Intravascular Ultrasound Volumetric Analysis

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Circulation, Mar 2002; 105: 1420 - 1423.

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Catheter Cardiovasc Interv 2002 Nov;57(3):286-94

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Circulation 2002 Aug 13;106(7):776-8

11. Cost-effectiveness of gamma radiation for treatment of in-stent restenosis: results from the Gamma-1 trial.

Cohen DJ, Cosgrove RS, Berezin RH, Teirstein PS, Leon MB, Kuntz RE; Gamma-1 Investigators.

Circulation 2002 Aug 6;106(6):691-7

12. Intravascular brachytherapy to prevent restenosis: dosimetric considerations.

Campos L, Stabin M.

Cell Mol Biol (Noisy-le-grand) 2002 Jul;48(5):429-3

Eur Heart J, 2001;22(8):669-75

Clinical and angiographical follow-up after implantation of a  $^{60}\text{Co}$  microCi radioactive stent in patients with coronary artery disease.

Wardeh AJ, Knook AH, Kay IP, Sabate M, Coen VL, Foley DP, Hamburger JN, Levendag PC, van der Giessen WJ, Serruys PW.

AIMS: This study is the contribution by the Thoraxcenter, Rotterdam, to the European(32)P Dose Response Trial, a non-randomized multicentre trial to evaluate the safety and efficacy of the radioactive Isostent in patients with single coronary artery disease. METHODS AND RESULTS: The radioactivity of the stent at implantation was 672 microCi. All patients received aspirin indefinitely and either ticlopidine or clopidogrel for 3 months. Quantitative coronary angiography measurements of both the stent area and the target lesion (stent area and up to 5 mm proximal and distal to the stent edges) were performed pre- and post-procedure and at the 5-month follow-up. Forty-two radioactive stents were implanted in 40 patients. Treated vessels were the left anterior descending coronary artery (n=20), right coronary artery (n=10) or left circumflex artery (n=10). Eight patients received additional non-radioactive stents. Lesion length measured 10+/-3 mm with a reference diameter of 3.07+/-0.69 mm. Minimal lumen diameter increased from 0.98+/-0.53 mm pre-procedure to 2.29+/-0.52 mm (target lesion) and 2.57+/-0.44 mm (stent area) post-procedure. There was one procedural non-Q wave myocardial infarction, due to transient thrombotic closure. Thirty-six patients returned for angiographical follow-up. Two patients had a total occlusion proximal to the radioactive stent. Of the patent vessels, none had in-stent restenosis. Edge restenosis was observed in 44%, occurring predominantly at the proximal edge. Target lesion revascularization was performed in 10 patients and target vessel revascularization in one patient. No additional clinical end-points occurred during follow-up. The minimal lumen diameter at follow-up averaged 1.66+/-0.71 mm (target lesion) and 2.12+/-0.72 (stent area); therefore late loss was 0.63+/-0.69 (target lesion) and 0.46+/-0.76 (stent area), resulting in a late loss index of 0.65+/-1.15 (target lesion) and 0.30+/-0.53 (stent area). CONCLUSION: These results indicate that the use of radioactive stents is safe and feasible, however, the high incidence of edge restenosis makes this technique currently clinically non-applicable. Copyright 2001 The European Society of Cardiology.

Circulation , 2001;103(14):1912-9

Late arterial responses (6 and 12 months) after (32)P beta-emitting stent placement: sustained intimal suppression with incomplete healing.

Farb A, Shroff S, John M, Sweet W, Virmani R.

BACKGROUND: Three-month studies of stent-delivered brachytherapy in the rabbit model show reduced neointimal growth. However, intimal healing is delayed, raising the possibility that intimal inhibition is merely

delayed rather than prevented. The purpose of this study was to explore the long-term histological changes after placement of beta-emitting radioactive stents in normal rabbit iliac arteries. **METHODS AND RESULTS:** Three-millimeter beta-emitting (32)P stents (6, 24, and 48 microCi) were placed in normal rabbit iliac arteries with nonradioactive stents as controls. Animals were euthanatized at 6 and 12 months, and histological assessment, morphometry, and analysis of endothelialization were performed. Morphometric measurements demonstrated a >50% reduction in intimal growth and percent lumen stenosis within 24- and 48-microCi stents versus control nonradioactive stents at both 6 and 12 months. However, the 24- and 48-microCi stents also showed delayed healing of the intimal surface, characterized by persistent fibrin thrombus with nonconfluent areas of matrix, incomplete endothelialization, and increased intimal cellular proliferation. Stent edge stenosis was present at 12 months in the 24- and 48-microCi stent groups, characterized by both intimal thickening and negative arterial remodeling. **CONCLUSIONS:** Inhibition of intimal growth is maintained 6 and 12 months after (32)P beta-emitting stent placement. However, delayed arterial healing, incomplete endothelialization, and edge effects are present.

Circulation , 2001;104(8):856-9

Serial intravascular ultrasound assessment of the efficacy of intracoronary gamma-radiation therapy for preventing recurrence in very long, diffuse, in-stent restenosis lesions.

Ahmed JM, Mintz GS, Waksman R, Mehran R, Leiboff B, Pichard AD, Satler LF, Kent KM, Weissman NJ.

**BACKGROUND:** The efficacy of coronary gamma-irradiation in preventing recurrent in-stent restenosis (ISR) is well established. However, brachytherapy may be less effective in very long, diffuse ISR lesions. **METHODS AND RESULTS:** We used serial intravascular ultrasound (IVUS) to study patients with long, diffuse ISR lesions (length, 36 to 80 mm) who were enrolled in (1) Long WRIST (Washington Radiation In-Stent Restenosis Trial), a double-blind, placebo-controlled trial of intracoronary gamma-irradiation (15 Gy at 2 mm from the source) and (2) high-dose (HD) Long WRIST, a registry that used a dose prescription of 18 Gy at 2 mm from the source. IVUS was performed using automated pullback (0.5 mm/s). Stent, lumen, and intimal hyperplasia were measured at 2-mm intervals. Complete postintervention and follow-up IVUS imaging was available in 30 irradiated and 34 placebo patients from Long WRIST and in 25 patients from HD Long WRIST. Stent length was longer in HD Long WRIST than in placebo or treated patients in Long WRIST (P=0.0064 and P=0.0125, respectively). Otherwise, baseline measurements were similar. At follow-up, the minimum lumen area was

largest in the HD Long WRIST patients (4.0 $\pm$ 1.4 mm<sup>2</sup>); areas were 2.9 $\pm$ 1.0 mm<sup>2</sup> in irradiated patients in Long WRIST and 1.9 $\pm$ 1.1 mm<sup>2</sup> in placebo patients in Long WRIST (P<0.005 for all comparisons). CONCLUSIONS:- Serial IVUS analysis shows that gamma-irradiation reduces recurrent in-stent neointimal hyperplasia in long, diffuse ISR lesions; however, it is even more effective when given at a higher dose.

J Am Coll Cardiol ,2001;38(2):415-20

Geographical miss during catheter-based intracoronary beta-radiation: incidence and implications in the BRIE study. Beta-Radiation In Europe.

Sianos G, Kay IP, Costa MA, Regar E, Kozuma K, de Feyter PJ, Boersma E, Disco C, Serruys PW.

**OBJECTIVES:** We sought to determine the incidence and causes of geographical miss (GM) and to evaluate its impact on edge restenosis after intracoronary beta-radiation therapy. **BACKGROUND:** Edge restenosis is a limitation of intracoronary beta-radiation therapy. Geographical miss is the situation in which the radiation source does not fully cover the injured segment and may lead to edge restenosis. **METHODS:** We analyzed 175 vessels treated according to the Beta-Radiation In Europe (BRIE) study protocol. The effective irradiated segment (EIRS) and both edges were studied with quantitative coronary angiography. The edges of the EIRS that were injured constituted the GM edges. Restenosis was defined as diameter stenosis >50% at follow-up. Geographical miss was determined by simultaneous electrocardiographic-matched, side-by-side projection of the source and balloons deflated at the injury site, in identical angiographic projections surrounded by contrast. **RESULTS:** Geographical miss affected 41.2% of the edges and increased edge restenosis significantly compared with non-GM edges (16.3% vs. 4.3%, respectively, p = 0.004). Restenosis was increased both in the proximal (p = 0.05) and distal (p = 0.02) GM edges compared with noninjured edges. Geographical miss associated with stent injury significantly increased edge restenosis (p = 0.006), whereas GM related to balloon injury did not significantly increase edge restenosis (p = 0.35). The restenosis in the EIRS was similar between vessels with and without GM (24.3% and 21.6%, respectively, p = 0.8). **CONCLUSIONS:** Geographical miss is strongly associated with restenosis at the edges of the EIRS. This effect is more prominent when caused by stenting. Geographical miss does not increase restenosis in the EIRS.

J Am Coll Cardiol ,2001;38(3):631-7

Treatment of diffuse in-stent restenosis with rotational atherectomy followed by radiation therapy with a rhenium-188-mercaptoacetyltriglycine-filled balloon.

Park SW, Hong MK, Moon DH, Oh SJ, Lee CW, Kim JJ, Park SJ.

**OBJECTIVES:** This study was done to evaluate the feasibility and efficacy of beta-radiation therapy with a rhenium-188-mercaptoacetyltriglycine ((188)Re-MAG(3))-filled balloon after rotational atherectomy for diffuse in-stent restenosis (ISR). **BACKGROUND:** Rotational atherectomy has been shown to be safe and efficient for the treatment of ISR, but the recurrence rate is still high. Intracoronary beta-irradiation after rotational atherectomy may be a reasonable approach to prevent recurrent ISR. **METHODS:** Fifty consecutive patients with diffuse ISR (length >10 mm) in native coronary arteries underwent rotational atherectomy and adjunctive balloon angioplasty, followed by beta-irradiation using a (188)Re-MAG(3)-filled balloon catheter. The radiation dose was 15 Gy at a depth of 1.0 mm into the vessel wall. **RESULTS:** The mean lengths of the lesion and irradiated segment were 25.6 +/- 12.7 mm and 37.6 +/- 11.2 mm, respectively. Radiation was delivered successfully to all patients, with a mean irradiation time of 201.8 +/- 61.7 s. No adverse event, including myocardial infarction, death or stent thrombosis, occurred during the follow-up period (mean 10.3 +/- 3.7 months), and nontarget vessel revascularization was needed in one patient. The six-month binary angiographic restenosis rate was 10.4%, and the loss index was 0.17 +/- 0.31. **CONCLUSIONS:** Beta-irradiation using a (188)Re-MAG(3)-filled balloon after rotational atherectomy is safe and feasible in patients with diffuse ISR, and it may improve their clinical and angiographic outcomes. Further prospective, randomized trials are warranted to evaluate the synergistic effect of debulking and irradiation in patients with diffuse ISR

Circulation, 2001;104(19):2358-62

Failure of a novel balloon-expandable gamma-emitting ((103)Pd) stent to prevent edge effects.

Hehrlein C, DeVries JJ, Arab A, Haller SD, Schloesser K, Tio FO, Fischell TA

**BACKGROUND:** Balloon-expandable beta-particle-emitting ( $^{32}\text{P}$ ) stents inhibit within-stent neointimal hyperplasia but induce lumen narrowing beyond the stent margins, ie, the so-called "edge effects."**METHODS AND RESULTS:** We prospectively investigated the performance of novel stents impregnated with the gamma-emitting isotope ( $^{103}\text{Pd}$ ), designed to reduce edge effects, in 24 rabbits. The stents had a length of 18 mm and were mounted on 20-mm-long delivery balloons for deployment. Angiograms were obtained immediately and 1 month after direct implantation of control and 1-, 2-, and 4-mCi ( $^{103}\text{Pd}$ ) stents into the iliac arteries without predilatation or postdilatation. Late lumen loss was measured with quantitative angiography. Neointimal hyperplasia and vascular remodeling were evaluated by histomorphometry. Late lumen loss was inhibited within ( $^{103}\text{Pd}$ ) stents (control 0.18 mm, 1 mCi 0.08 mm, 2 mCi 0.05 mm, and 4 mCi -0.03 mm,  $P < 0.05$  all activities versus control). Conversely, late lumen loss occurred at the edges of ( $^{103}\text{Pd}$ ) stents, correlating with areas of high balloon/artery ratios and vessel overstretch injury. Edge effects were primarily due to neointimal hyperplasia but were also caused by negative vessel remodeling at high stent activities. **CONCLUSIONS:** Edge effects after implantation of radioisotope stents can occur independently of the isotope chosen for stent impregnation.

Circulation, 2001;104(25):3020-2

Comparative efficacy of gamma-irradiation for treatment of in-stent restenosis in saphenous vein graft versus native coronary artery in-stent restenosis: An intravascular ultrasound study.

Castagna MT, Mintz GS, Waksman R, Ahmed JM, Maehara A, Ajani AE, Bui AB, Satler LF, Suddath WO, Kent KM, Pichard AD, Weissman NJ

**BACKGROUND:** We used serial volumetric (post-irradiation and follow-up) intravascular ultrasound (IVUS) to compare the effectiveness of gamma-irradiation ( $^{192}\text{Ir}$ ) in saphenous vein graft (SVG) versus native coronary artery in-stent restenosis (ISR). **METHODS AND RESULTS:** The study population consisted of 47 patients with native coronary artery ISR from WRIST (Washington Radiation for In-Stent Restenosis Trial) and 31 patients with SVG ISR (12 from the WRIST and 19 from SVGWRIST). After irradiation and at 6-month follow-up, stent, lumen, and intimal hyperplasia (IH, stent minus lumen) areas were measured every 1 mm. ISR length was similar in the 2 groups (29 $\pm$ 12 versus 29 $\pm$ 14 mm,  $P=0.9$ ). Post-intervention measurements of stent (280 $\pm$ 154 versus 324 $\pm$ 270 mm<sup>3</sup>,  $P=0.4$ ), lumen (184 $\pm$ 91 versus 214 $\pm$ 172 mm<sup>3</sup>,  $P=0.3$ ), and IH (96 $\pm$ 77 versus 109 $\pm$ 119 mm<sup>3</sup>,  $P=0.5$ ) volumes were similar in the 2 groups. The post-intervention minimum

lumen cross sectional areas tended to be smaller in native artery ISR lesions (4.7±1.7 versus 5.4±1.6 mm<sup>2</sup>), P=0.11). During follow-up, there was a slight increase in IH volume (9±38 mm<sup>3</sup>) in native artery ISR lesions and a slight decrease in IH volume in SVG ISR lesions (-9±32 mm<sup>3</sup>), P=0.0463). There was also a slight decrease in minimum lumen area in the native artery ISR lesions versus a slight increase in minimum lumen area in the SVG ISR lesions (-0.8±1.7 versus 0.2±1.1, P=0.0087). As a result, the follow-up minimum lumen area in native artery lesions was smaller than in SVG ISR lesions (4.1±2.1 mm<sup>2</sup>) versus 5.6±2.2 mm<sup>2</sup>), P=0.0067). CONCLUSION: gamma-Irradiation with (192)Ir brachytherapy appears to be as effective in SVGs as it is in native artery ISR lesions.

J Am Coll Cardiol ,2002;39(2):274-80

Quantitative angiographic methods for appropriate end-point analysis, edge-effect evaluation, and prediction of recurrent restenosis after coronary brachytherapy with gamma irradiation.

Lansky AJ, Dangas G, Mehran R, Desai KJ, Mintz GS, Wu H, Fahy M, Stone GW, Waksman R, Leon MB.

**OBJECTIVES:** The study was done to investigate the relationship between clinical restenosis and the relative angiographic location of the recurrent restenotic lesion, after treatment of in-stent restenosis with vascular brachytherapy in the Washington Radiation for In-Stent Restenosis Trial (WRIST). **BACKGROUND:** Intracoronary radiation therapy reduces recurrence of in-stent restenosis. We investigated the above objective in patients enrolled in WRIST. **METHODS:** The WRIST study randomized 130 patients to double-blinded therapy with gamma irradiation (iridium-192 [(192)Ir]) versus placebo after interventional treatment of diffuse in-stent restenosis. After the intervention and at follow-up, three vessel segments were individually analyzed with quantitative coronary angiography: 1) the stent, 2) the radiation ribbon, and 3) the ribbon+margin segment (including 5 mm on either end of the injured or radiation-ribbon segment). Receiver operator curves (ROC) were used to assess the value of the follow-up percent diameter stenosis (DS) for each of the three analyzed segments in predicting target vessel revascularization (TVR). **RESULTS:** (192)Ir reduced recurrent restenosis (23.7% vs. 60.7%, p < 0.001) and the length of recurrent restenosis (8.99 ± 4.34 mm vs. 17.54 ± 10.48 mm, p < 0.001) at follow-up compared to placebo. Isolated stent edge (3.4%) and ribbon edge (1.7%) restenoses were infrequent in both groups. The best angiographic surrogate of TVR was the 50% follow-up DS obtained from the ribbon+margin analysis (ROC area 0.806). **CONCLUSIONS:** In WRIST, not only was (192)Ir therapy effective in reducing restenosis, but it also reduced the lesion length of treatment failures by

50%, and it was not associated with edge proliferation. The restenosis rate obtained from the vessel segment inclusive of the dose fall-off zones was the best correlate of TVR and should become a standard analysis site in all vascular brachytherapy trials.

Lancet ,2002;359(9306):551-7

Use of localised intracoronary beta radiation in treatment of in-stent restenosis: the INHIBIT randomised controlled trial.

Waksman R, Raizner AE, Yeung AC, Lansky AJ, Vandertie L

**BACKGROUND:** In-stent restenosis is a major limitation of intracoronary stenting. Ionising gamma radiation has been shown to reduce recurrence of restenosis after stent placement. We aimed to compare the effects of intracoronary beta radiation treatment with those of placebo for clinical and angiographic outcomes of patients with diffuse in-stent restenosis. **METHODS:** 332 patients with in-stent restenosis underwent successful coronary intervention, and were then randomly allocated to intracoronary beta radiation with a phosphorus-32 source (n=166) or placebo (166) delivered into a centreing balloon catheter through an automatic afterloader. Longer lesions (>22 mm of dilated length) were treated with tandem positioning of the study wire. The primary safety endpoint was major adverse cardiac events, defined as death, myocardial infarction, and repeat target-lesion revascularisation at 9 months. The primary efficacy endpoint was binary angiographic restenosis rate in the analysis segment during 9-months follow-up. Analysis was by intention to treat. **FINDINGS:** Procedural success, and in-hospital and 30-day complications were similar among the two groups. 24 (15%) patients in the radiated group had the primary safety endpoint of death, myocardial infarction, or repeat target-lesion revascularisation over 290 days compared with 15 (31%) in the placebo group (difference 16% [95% CI 7?5], p = 0.0006). Binary angiographic restenosis rate was lower in the radiated group than the placebo group for the entire analysed segment (difference 25% [14?7], p < 0.0001). **INTERPRETATION:** Vascular brachytherapy using pure beta-emitter <sup>32</sup>P delivered into a centreing catheter via an automatic afterloader can be used to reduce overall revascularisation in patients undergoing treatment for diffuse in-stent restenosis.

Am Heart J, 2002 ;143(2):342-8

Centered versus noncentered source for intracoronary artery radiation therapy: a model based on the Scripps Trial.

Arbab-Zadeh A, Bhargava V, Russo RJ, Levin CS, Jani SK, Lucisano J, Teirstein PS.

**BACKGROUND:** The Scripps Trial was a randomized study of intracoronary artery radiation therapy with iridium 192 used to treat restenotic vessels. We used the intravascular ultrasound data from the Scripps Trial to investigate whether a lumen-centered gamma or beta radiation source would reduce radiation dose heterogeneity compared with the noncentered source position used. **METHODS:** Analysis included 28 patients with stent placement in 20 native vessels and 8 saphenous vein grafts enrolled in this trial. Radiation dosimetry for gamma radiation was calculated to deliver 800 cGy to the far field target, provided the maximum dose to the near field target did not exceed 3000 cGy. Prescribed dosimetry for beta radiation by use of yttrium 90 was 1600 cGy at 2 mm distance from the source. **RESULTS:** The calculated average minimum source to target distance by use of a lumen-centered source increased by 0.18 mm from 1.70 +/- 0.25 to 1.88 +/- 0.36 mm, whereas the maximum distance decreased by 0.17 mm from 3.64 +/- 0.60 to 3.47 +/- 0.43 mm (P <.05). On the basis of these distances, the maximum radiation dose, as well as radiation dose heterogeneity (ratio of maximum to minimum), would have been reduced in 22 of 28 patients by use of a lumen-centered gamma or beta source (P <.005). The reduction in dose heterogeneity was substantially greater with a beta source compared with a gamma source (48% vs 16% reduction). **CONCLUSIONS:** Centering of the intracoronary artery radiation therapy delivery catheter within the vessel lumen can significantly reduce radiation dose heterogeneity when compared with a noncentered source position. This dose reduction is substantially greater for a beta compared with a gamma source

Circulation, 2002 ;105(5):550-3

Angiographical follow-up after radioactive ?old Ends?stent implantation: a multicenter trial.

Wardeh AJ, Albiero R, Kay IP, Knook AH, Wijns W, Kozuma K, Nishida T, Ferrero V, Levendag PC, van Der

Giessen WJ, Colombo A, Serruys PW.

**BACKGROUND:** Radioactive stents with an activity of 0.75 to 12 microCi have shown >40% edge restenosis due to neointimal hyperplasia and negative remodeling. This trial evaluated whether radioactive Cold Ends stents might resolve edge restenosis by preventing remodeling at the injured extremities. **METHODS AND RESULTS:** The 25-mm long (15-mm radioactive center and 5-mm nonradioactive ends) Cold Ends stents had an activity of 3 to 12 microCi at implantation. Forty-three stents were implanted in 43 patients with de novo native coronary artery disease. Two procedural, 1 subacute, and 1 late stent thrombosis occurred. A restenosis rate of 22% was observed with a shift of the restenosis, usually occurring at the stent edges of radioactive stents, into the Cold Ends stents. The most severe restenosis occurred at the transition zone from radioactive to nonradioactive segments, a region located in dose fall-off. **CONCLUSION:** Cold Ends stents did not resolve edge restenosis.

J Am Coll Cardiol , 2002 ;39(3):400-7

Vascular morphometric changes after radioactive stent implantation: a dose-response analysis.

Wexberg P, Kirisits C, Gyongyosi M, Gottsauner-Wolf M, Ploner M, Pokrajac B, Potter R, Glogar D.

**OBJECTIVES:** The goal of this study was to evaluate the dose-dependency of morphometric changes in the coronary arterial wall after radioactive stenting. **BACKGROUND:** Radioactive stents have been found to reduce intrastent intimal hyperplasia (IIH) but lead to a characteristic type of restenosis occurring predominantly at the stent edges. **METHODS:** Fifteen patients underwent intravascular ultrasound (IVUS) examination after implantation of a P-32 radioactive stent and at the six-month follow-up. The post-stent IVUS measurements on seven predefined locations of each lesion were subjected to a computer algorithm for the development of dose-volume histograms (DVH). Thus, we derived the radiation doses delivered to at least 10% and 90% of the adventitia (DV10, DV90). The IIH and vascular remodeling at follow-up were correlated with the doses in each segment. **RESULTS:** The IIH was most pronounced at the stent edges and lowest in the stent-body, whereas we detected a significant expansive remodeling within the stent body. The delivered doses correlated with a decreased IIH ( $r = 0.52$ ,  $p < 0.001$  for DV10 and  $r = 0.62$ ,  $p < 0.001$  for DV90) and with expansive remodeling ( $r =$

0.48,  $p = 0.009$  for DV10 and  $r = 0.50$ ,  $p = 0.006$  for DV90). A DV10 >90 Gy or a DV90 >15 Gy reduced IHH and induced expansive remodeling. Plaque growth was not reduced by radioactive stents. CONCLUSIONS: The DVH analysis reveals a dose-dependent increase of external elastic lamina area behind radioactive stents, whereas plaque growth is not reduced but inverted into an outward direction from the stent. A DV10 >90 Gy or a DV90 >15 Gy results in a beneficial long-term outcome after radioactive stenting. Wexberg P, Kirisits C, Gyongyosi M, Gottsauner-Wolf M, Ploner M, Pokrajac B, Potter R, Glogar D.

N Engl J Med 1997;336:1697-703.

### Catheter-Based Radiotherapy to Inhibit Restenosis after Coronary Stenting

Paul S. Teirstein, Vincent Massullo, Shirish Jani, Jeffrey J. Popma, Gary S. Mintz, Robert J. Russo, Richard A. Schatz, Erminia M. Guarneri, Stephen Steuterman, Nancy B. Morris, Martin B. Leon, Prabhakar Tripuraneni

**Background.** In animal models of coronary restenosis, intracoronary radiotherapy has been shown to reduce the intimal hyperplasia that is a part of restenosis. We studied the safety and efficacy of catheter-based intracoronary gamma radiation plus stenting to reduce coronary restenosis in patients with previous restenosis. **Methods.** Patients with restenosis underwent coronary stenting, as required, and balloon dilation and were then randomly assigned to receive catheter-based irradiation with iridium-192 or placebo. Clinical follow-up was performed, with quantitative coronary angiographic and intravascular ultrasonographic measurements at six months.

**Results.** Fifty-five patients were enrolled; 26 were assigned to the iridium-192 group and 29 to the placebo group. Angiographic studies were performed in 53 patients (96 percent) at a mean ( $\pm$ SD) of  $6.7 \pm 2.2$  months. The mean minimal luminal diameter at follow-up was larger in the iridium-192 group than in the placebo group ( $2.43 \pm 0.78$  mm vs.  $1.85 \pm 0.89$  mm,  $P = 0.02$ ). Late luminal loss was significantly lower in the iridium-192 group than in the placebo group ( $0.38 \pm 1.06$  mm vs.  $1.03 \pm 0.97$  mm,  $P = 0.03$ ). Angiographically identified restenosis (stenosis of 50 percent or more of the luminal diameter at follow-up) occurred in 17 percent of the patients in the iridium-192 group, as compared with 54 percent of those in the placebo group ( $P = 0.01$ ). There were no apparent complications of the treatment.

**Conclusions.** In this preliminary, short-term study of patients with previous coronary restenosis, coronary stenting followed by catheter-based intracoronary radiotherapy substantially reduced the rate of subsequent restenosis.

Circulation 1997 96: 727-732.

### Long-term Angiographic and Clinical Outcome After Percutaneous Transluminal Coronary Angioplasty and Intracoronary Radiation Therapy in Humans

Jose A. Condado, Ron Waksman, Orlando Gurdiel, Raul Espinosa, Juan Gonzalez, Bruno Burger, Guillermo Villoria, Harry Acquatella, Ian R. Crocker, K. B. Seung, and Samuel F. Liprie

**Background.** Ionizing radiation has been shown to reduce neointimal formation after balloon angioplasty in experimental models of restenosis. This study was designed to evaluate the feasibility, safety, and effectiveness of intracoronary radiation therapy (ICRT) after percutaneous transluminal coronary angioplasty (PTCA) for preventing restenosis in human coronary arteries.

**Methods and Results.** Twenty-one patients (22 arteries) with unstable angina underwent standard balloon angioplasty. ICRT was performed with the use of an  $^{192}\text{Ir}$  source wire that was hand delivered to the angioplasty site. Angiographic follow-up was performed at 24 hours, between 30 and 60 days, and at 6 months. Angioplasty was successful in 19 of 22 lesions, and insertion of the radioactive source wire was successful at all treated sites. Angiographic study at 24 hours demonstrated early late loss of the luminal diameter from  $1.92 \pm 0.55$  to  $1.40 \pm 0.27$  mm. Between 30 and 60 days, repeat angiography demonstrated total occlusion in 2 arteries, a new pseudoaneurysm in 1 artery, and significant dilatation at the treatment site in 2 additional vessels. At 6 months' follow-up, all remaining arteries (n=20) maintained patent, with a mean lumen diameter of  $1.65 \pm 0.8$  mm. The calculated late lumen loss was  $0.27 \pm 0.56$  mm, and the late loss index was 0.19. Clinical events at 1 year included myocardial infarction in 1 patient, repeat angioplasty to the treated site in 3 patients, and persistent angina in 7 patients.

**Conclusions.** These preliminary results demonstrate that ICRT after coronary intervention is feasible and is associated with an acceptable degree of complications and lower rates of angiographic restenosis indexes.

Circulation 1998 98: 2024-2029.

### Intracoronary Radiation for Prevention of Restenosis : Dose Perturbations Caused by Stents

H. I. Amols, F. Trichter, and J. Weinberger

Background-Intravascular irradiation with  $\beta$ -emitters has been proposed for inhibition of restenosis in coronary arteries after balloon angioplasty or stent implantation. Previous studies have shown the effectiveness of  $\beta$ -radiation to prevent recurrent restenosis, even in the presence of an implanted stent. The limited range of  $\beta$ -particles compared with  $\gamma$ -radiation, however, opens the question of whether absorption and scattering of  $\beta$ -particles by stent struts will cause significant perturbations in the uniformity and magnitude of the radiation dose, which may in turn compromise treatment.

Methods and Results-Nine different stents were deployed with a balloon filled with a  $\beta$ -emitting radioactive liquid. Dose distributions were measured with Gafchromic film. Stents varied significantly in their absorption of  $\beta$ -particles. Some stents, constructed of fine meshed wires, produced minimal dose perturbations. Others, with thicker, high-atomic-number struts, induced cold spots in the dose distribution adjacent to the wires of 35%. Average dose reduction varied from 4% to 14% in the presence of various stents.

Conclusions-Radiation strategy may have to be tailored to stent design. Stents that minimally perturb the dose distribution may be deployed before irradiation. Those that significantly alter the radiation dose might be better deployed after irradiation. Dose prescriptions may require modification if such perturbations prove clinically significant. Observed dose perturbations, however, decreased rapidly with increasing distance from the stent, which may mitigate the clinical impact of these findings. This, as well as the effects of stents on dose distributions, requires further investigation.

Key Words: angioplasty ? restenosis ? brachytherapy ? stents ? beta rays

Circulation 1998 97: 2025-2030.

Endovascular  $\beta$ -Radiation to Reduce Restenosis After Coronary Balloon Angioplasty : Results of the Beta Energy Restenosis Trial (BERT)

Spencer B. King, David O. Williams, Prakash Chougule, J. Larry Klein, Ron Waksman, Richard Hilstead, Joan Macdonald, Kris Anderberg, and Ian R. Crocker

**Background**-In the porcine overstretch injury model of restenosis, endovascular  $\beta$ -radiation reduces neointima formation. To determine whether this therapy could be applied to patients with coronary artery disease, a special device was developed to allow delivery of 12 encapsulated  $^{90}\text{Sr}/\text{Y}$  sources, measuring a total of 30 mm, to various sites within the coronary arterial tree. This study was designed to evaluate the feasibility of the delivery of 12, 14, or 16 Gy at 2 mm after balloon angioplasty of stenoses of native coronary vessels.

**Methods and Results**-Delivery of  $\beta$ -radiation was attempted in 23 patients after successful balloon angioplasty. Source delivery was successful in 21 of the 23 patients (91%). There was no in-hospital or 30-day morbidity or mortality. Follow-up quantitative coronary arteriography in 20 patients demonstrated a late loss of 0.05 mm, a late loss index of 4%, and a restenosis rate of 15%. The use of the  $\beta$ -emitter  $^{90}\text{Sr}/\text{Y}$  significantly reduced treatment time and operator exposure compared with previous trials with the gamma-emitter  $^{192}\text{Ir}$ .

**Conclusions**-In this study, the administration of endovascular  $\beta$ -radiation after angioplasty was safe and feasible and substantially altered the postangioplasty late lumen loss, resulting in a lower-than-expected rate of restenosis. On the basis of these encouraging results, a multicenter, randomized trial with operators and patients blinded to treatment assignment is planned.

Circulation ,1999 ;100: 1623-1629

#### Preserved Endothelium-Dependent Vasodilation in Coronary Segments Previously Treated With Balloon Angioplasty and Intracoronary Irradiation

Manel Sabate, I. Patrick Kay, Willem J. van der Giessen, Angel Cequier, Jurgen M. R. Ligthart, Joan Antoni Gomez-Hospital, Stephane G. Carlier, Veronique L. M. A. Coen, Johannes P. A. Marijnissen, Alexander J. Wardeh, Peter C. Levendag, and Patrick W. Serruys

**Background**-Abnormal endothelium-dependent coronary vasomotion has been reported after balloon angioplasty (BA), as well as after intracoronary radiation. However, the long-term effect on coronary vasomotion is not known. The aim of this study was to evaluate the long-term vasomotion of coronary segments treated with BA and brachytherapy.

**Methods and Results**-Patients with single de novo lesions treated either with BA followed by intracoronary  $\beta$ -irradiation (according to the Beta Energy Restenosis Trial-1.5) or with BA alone were eligible. Of these groups, those patients in stable condition who returned for 6-month angiographic follow-up formed the study population (n=19, irradiated group and n=11, control group). Endothelium-dependent coronary vasomotion

was assessed by selective infusion of serial doses of acetylcholine (ACh) proximally to the treated area. Mean luminal diameter was calculated by quantitative coronary angiography both in the treated area and in distal segments. Endothelial dysfunction was defined as a vasoconstriction after the maximal dose of ACh (10-6 mol/L). Seventeen irradiated segments (89.5%) demonstrated normal endothelial function. In contrast, 10 distal nonirradiated segments (53%) and 5 control segments (45%) demonstrated endothelium-dependent vasoconstriction ( $-19 \pm 17\%$  and  $-9.0 \pm 5\%$ , respectively). Mean percentage of change in mean luminal diameter after ACh was significantly higher in irradiated segments ( $P=0.01$ ).

Conclusions-Endothelium-dependent vasomotion of coronary segments treated with BA followed by  $\beta$ -radiation is restored in the majority of stable patients at 6-month follow-up. This functional response appeared to be better than those documented both in the distal segments and in segments treated with BA alone.

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Real-time measurement of radiation exposure to patients during diagnostic coronary angiography and percutaneous interventional procedures

Jack T. Cusma, Malcolm R. Bell, Merrill A. Wondrow, Jerome P. Taubel, David R. Holmes, Jr.

#### Objectives

The aim of this study was to accurately assess the radiation exposure received by patients during cardiac catheterization in a large sample representative of the current state of practice in cardiac angiography.

#### Background

Radiation exposure to patients and laboratory staff has been recognized as a necessary hazard in coronary angiography. The effects on x-ray exposure of the increased complexity of coronary angiographic procedures and, in particular, the increasing use of coronary artery stenting, have not been adequately addressed in previous studies.

#### Methods

X-ray exposure measurements were performed on a consecutive series of 972 patients undergoing 992 diagnostic and interventional studies in the Mayo Clinic catheterization laboratory within an eight week period in late 1997. Data were acquired from 706 diagnostic procedures and 286 interventional procedures using a real-time exposure measurement system to continuously calculate and record the exposure rate and total exposure, reflecting all parameters relevant to the specific patient and procedure situation.

## Results

The median exposure for all 992 procedures was 41.8 mC/kg (162.1 R); the corresponding values for diagnostic and interventional procedures were 34.9 and 95.6 mC/kg, respectively (135.3 vs. 370.5 R). There were significant differences in the fluoroscopy exposure time between diagnostic and interventional procedures: 4.7 min vs. 21.0 min. Heavier patients (>83 kg) received x-ray exposures at a significantly higher rate than did lighter patients (<83 kg) during both fluoroscopy and cine; 44.9 mC/kg/min (173.9 R/min) vs. 27.9 mC/kg/min (108.3 R/min) for cine exposure rate and 2.3 mC/kg/min (8.8 R/min) vs. 1.5 mC/kg/min (5.8 R/min) for fluoroscopy exposure rate.

## Conclusions

Changes in practice have led to higher values for patient x-ray radiation exposures during cardiac catheterization procedures. The real-time display and recording of x-ray exposure facilitates the reduction of exposure in the catheterization laboratory.

Circulation,1999;99: 1660-1665.

## Effects of Intracoronary $\beta$ -Radiation Therapy After Coronary Angioplasty : An Intravascular Ultrasound Study

David Meerkin, Jean-Claude Tardif, Ian R. Crocker, Andre Arsenault, Michel Joyal, Guylaine Lucier, Spencer B. King, III, David O. Williams, Patrick W. Serruys, and Raoul Bonan

**Background-**Endovascular radiation is emerging as a potential solution for the prevention and treatment of restenosis. Its effects on the morphology of unstented vessels cannot be determined by angiography and therefore require the use of intravascular ultrasound.

**Methods and Results-**Through a 5F noncentered catheter for delivery of a  $^{90}\text{Sr}/\text{Y}$  source train, 12, 14, or 16 Gy at 2 mm was delivered to native coronary arteries after successful balloon angioplasty in 30 patients. Four patients required stent deployment in the first week. Quantitative coronary angiography and IVUS were performed during the initial procedure and at 6-month follow-up. Binary angiographic restenosis was present in 3 of 30 patients, with target lesion and vessel revascularization performed in 3 and 5 patients, respectively. Angiographic late loss was  $-0.02 \pm 0.60$  mm, with a  $-0.09 \pm 0.46$  loss index. IVUS demonstrated no significant reduction in lumen area (from  $5.69 \pm 1.72$  mm<sup>2</sup> after treatment to  $6.04 \pm 2.63$  mm<sup>2</sup> at follow-up), with no significant change in external elastic membrane area ( $13.71 \pm 4.54$  to  $14.22 \pm 4.71$  mm<sup>2</sup>) over the 6-month follow-up. Wall area was  $8.01 \pm 3.85$  mm<sup>2</sup> after radiation therapy and  $8.19 \pm 3.44$  mm<sup>2</sup> at follow-up (P=NS). No

significant differences were noted between the different dose groups.

**Conclusions**- $\beta$ -Radiation therapy resulted in a low restenosis rate with negligible late loss by angiography. By IVUS,  $\beta$ -radiation was shown to inhibit neointima formation, with no reduction of total vessel area at 6-month follow-up.

*Circulation*, 1999 ;99: 243-247

## Two-Year Follow-Up After Catheter-Based Radiotherapy to Inhibit Coronary Restenosis

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**Background**-Although early trials indicate the treatment of restenosis with radiation therapy is safe and effective, the long-term impact of this new technology has been questioned. The possibility of late untoward consequences, such as aneurysm formation, perforation, and accelerated vascular disease, is of significant concern. Furthermore, it is not known whether the beneficial effects of radiation therapy will be durable or whether radiation will only delay restenosis.

**Methods and Results**-A double-blind, randomized trial was undertaken to compare  $^{192}\text{Ir}$  with placebo sources in patients with previous restenosis after coronary angioplasty. Patients were randomly assigned to receive a 0.76-mm (0.03-in) ribbon containing sealed sources of either  $^{192}\text{Ir}$  or placebo. All patients underwent repeat coronary angiography at 6 months. All living patients were contacted 24 months after their index study procedure. Patients were assessed with respect to the need for target-lesion revascularization or nontarget-lesion revascularization, occurrence of myocardial infarction, or death. Over a 9-month period, 55 patients were enrolled; 26 were randomized to  $^{192}\text{Ir}$  and 29 to placebo. Follow-up was obtained in 100% of living patients at a minimum of 24 months. Target-lesion revascularization was significantly lower in the  $^{192}\text{Ir}$  group (15.4% versus 44.8%;  $P<0.01$ ). Nontarget-lesion revascularization was similar in  $^{192}\text{Ir}$  and placebo patients (19.2% versus 20.7%;  $P=\text{NS}$ ). There were 2 deaths in each group. The composite end point of death, myocardial infarction, or target-lesion revascularization was significantly lower in  $^{192}\text{Ir}$ -treated versus placebo-treated patients (23.1% versus 51.7%;  $P=0.03$ ). No patient in the  $^{192}\text{Ir}$  group sustained a target-lesion revascularization later than 10 months.

**Conclusions**-At 2-year clinical follow-up, treatment with  $^{192}\text{Ir}$  demonstrates significant clinical benefit. Although further follow-up (including late angiography) will be necessary, no clinical events have occurred to date in the  $^{192}\text{Ir}$  group to suggest major untoward effects of vascular radiotherapy. At the intermediate follow-up time point, vascular radiotherapy continues to be a promising new treatment for restenosis.

Circulation , 1999 ; 100: 1182-1188

Geometric Vascular Remodeling After Balloon Angioplasty and  $\beta$ -Radiation Therapy : A Three-Dimensional Intravascular Ultrasound Study

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**Background-**Endovascular radiation appears to inhibit intimal thickening after overstretching balloon injury in animal models. The effect of brachytherapy on vascular remodeling is unknown. The aim of the study was to determine the evolution of coronary vessel dimensions after intracoronary irradiation after successful balloon angioplasty in humans.

**Methods and Results-**Twenty-one consecutive patients treated with balloon angioplasty and  $\beta$ -radiation according to the Beta Energy Restenosis Trial-1.5 were included in the study. Volumetric assessment of the irradiated segment and both edges was performed after brachytherapy and at 6-month follow-up. Intravascular ultrasound images were acquired by means of ECG-triggered pullback, and 3-D reconstruction was performed by automated edge detection, allowing the calculation of lumen, plaque, and external elastic membrane (EEM) volumes. In the irradiated segments, mean EEM and plaque volumes increased significantly ( $451 \pm 128$  to  $490.9 \pm 159$  mm<sup>3</sup> and  $201.2 \pm 59$  to  $241.7 \pm 74$  mm<sup>3</sup>;  $P=0.01$  and  $P=0.001$ , respectively), whereas luminal volume remained unchanged ( $250.8 \pm 91$  to  $249.2 \pm 102$  mm<sup>3</sup>;  $P=NS$ ). The edges demonstrated an increase in mean plaque volume ( $26.8 \pm 12$  to  $32.6 \pm 10$  mm<sup>3</sup>,  $P=0.0001$ ) and no net change in mean EEM volume ( $71.4 \pm 24$  to  $70.9 \pm 24$  mm<sup>3</sup>,  $P=NS$ ), resulting in a decrease in mean luminal volume ( $44.6 \pm 16$  to  $38.3 \pm 16$  mm<sup>3</sup>,  $P=0.01$ ).

**Conclusions-**A different pattern of remodeling is observed in coronary segments treated with  $\beta$ -radiation after successful balloon angioplasty. In the irradiated segments, the adaptive increase of EEM volume appears to be the major contributor to the luminal volume at follow-up. Conversely, both edges showed an increase in plaque volume without a net change in EEM volume.

Circulation ;1999 ;100(8):789-92

Late coronary occlusion after intracoronary brachytherapy.

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**BACKGROUND:** Intracoronary brachytherapy appears to be a promising technology to prevent restenosis. Presently, limited data are available regarding the late safety of this therapeutic modality. The aim of the study was to determine the incidence of late (>1 month) thrombosis after PTCA and radiotherapy. **METHODS AND RESULTS:** From April 1997 to March 1999, we successfully treated 108 patients with PTCA followed by intracoronary beta-radiation. Ninety-one patients have completed at least 2 months of clinical follow-up. Of these patients, 6.6% (6 patients) presented with sudden thrombotic events confirmed by angiography 2 to 15 months after intervention (2 balloon angioplasty and 4 stent). Some factors (overlapping stents, unhealed dissection) may have triggered the thrombosis process, but the timing of the event is extremely unusual. Therefore, the effect of radiation on delaying the healing process and maintaining a thrombogenic coronary surface is proposed as the most plausible mechanism to explain such late events. **CONCLUSIONS:** Late and sudden thrombosis after PTCA followed by intracoronary radiotherapy is a new phenomenon in interventional cardiology.

#### Summary

1. Sudden thrombotic events: 6.6% (6 patients; 2 balloon angioplasty and 4 stent).
2. Plausible mechanism: the effect of radiation on delaying the healing process

Circulation, 2000 ; 101: 1087-1090

The Effect of Endovascular Irradiation on Platelet Recruitment at Sites of Balloon Angioplasty in Pig Coronary Arteries

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Background-Endovascular irradiation (EI) inhibits balloon-induced neointima formation in animals and is now in clinical trials for restenosis prevention. However, little is known of the effect of EI on vessel thrombogenicity due to delayed arterial healing. We investigated EI effects on platelet recruitment in pig coronary arteries.

Methods and Results-EI was performed using  $^{90}\text{Sr}/\text{Y}$  at 0 Gray (Gy), 15Gy, or 30Gy at 2 mm after balloon overstretch injury. At 1 day, 1 week, and 1 month, platelet recruitment and thrombus formation were assessed using autologous  $^{111}\text{In}$ -oxine-platelet labeling and light and scanning electron microscopy. In balloon-injured nonirradiated vessels, there was complete reendothelialization at 1 month, and platelet recruitment was similar to normal uninjured arteries. In irradiated vessels, scanning electron microscopy showed incomplete reendothelialization at 1 month, and these areas demonstrated attachment of activated platelets. Light microscopy of irradiated coronaries showed adherent partially organized thrombi and incomplete resolution of intramural hemorrhages. There was a significant increase in platelet recruitment at 1 month in arteries receiving EI at 15Gy ( $5.1 \pm 2.8 \times 10^6$ ,  $P=0.02$ ) or 30Gy ( $12.5 \pm 9.9 \times 10^6$ ,  $P=0.005$ ) compared with nonirradiated controls ( $2.7 \pm 1.5 \times 10^6$ ); 30Gy was also higher than 15Gy ( $P=0.05$ ). Platelet recruitment was also increased for 30Gy compared with control at 1 day.

Conclusions-Endovascular irradiation at 15Gy or 30Gy after balloon angioplasty results in incomplete endothelial recovery, impaired resolution of intramural hemorrhage, and a dose-dependent increase in platelet recruitment at 1 month.

Key Words: balloon angioplasty ? restenosis ? radiation ? blood platelets ? thrombosis

Circulation, 2000 ;102: 951-958

Inhibition of Restenosis With  $\beta$ -Emitting Radiotherapy: Report of the Proliferation Reduction With Vascular Energy Trial (PREVENT)

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Background-Intracoronary  $\alpha$ - and  $\beta$ -radiation have reduced restenosis in animal models. In the clinical setting, the effectiveness of  $\beta$ -emitters has not been studied in a broad spectrum of patients, particularly those receiving

stents.

**Methods and Results-**A prospective, randomized, sham-controlled study of intracoronary radiotherapy with the  $\beta$ -emitting  $^{32}\text{P}$  source wire, using a centering catheter and automated source delivery unit, was conducted. A total of 105 patients with de novo (70%) or restenotic (30%) lesions who were treated by stenting (61%) or balloon angioplasty (39%) received 0 (control), 16, 20, or 24 Gy to a depth of 1 mm in the artery wall. Angiography at 6 months showed a target site late loss index of  $11 \pm 36\%$  in radiotherapy patients versus  $55 \pm 30\%$  in controls ( $P < 0.0001$ ). A low late loss index was seen in stented and balloon-treated patients and was similar across the 16, 20, and 24 Gy radiotherapy groups. Restenosis (50%) rates were significantly lower in radiotherapy patients at the target site (8% versus 39%;  $P = 0.012$ ) and at target site plus adjacent segments (22% versus 50%;  $P = 0.018$ ). Target lesion revascularization was needed in 5 radiotherapy patients (6%) and 6 controls (24%;  $P < 0.05$ ). Stenosis adjacent to the target site and late thrombotic events reduced the overall clinical benefit of radiotherapy.

**Conclusions-** $\beta$ -radiotherapy with a centered  $^{32}\text{P}$  source is safe and highly effective in inhibiting restenosis at the target site after stent or balloon angioplasty. However, minimizing edge narrowing and late thrombotic events must be accomplished to maximize the clinical benefit of this modality.

Circulation ,2000 ;101: 2355-2360

#### Intracoronary $\beta$ -Irradiation With a Liquid $^{188}\text{Re}$ -Filled Balloon : Six-Month Results From a Clinical Safety and Feasibility Study

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**Background-**Coronary irradiation is a new concept to reduce restenosis. We evaluated the feasibility and safety of intracoronary irradiation with a balloon catheter filled with  $^{188}\text{Re}$ , a liquid, high-energy  $\beta$ -emitter.

**Methods and Results-**Irradiation with 15 Gy at 0.5-mm tissue depth was performed in 28 lesions after balloon dilation ( $n=9$ ) or stenting ( $n=19$ ). Lesions included 19 de novo stenoses, 4 occlusions, and 5 restenoses. Irradiation time was  $515 \pm 199$  seconds in 1 to 4 fractions. There were no procedural complications. One patient died of noncardiac causes at day 23. One asymptomatic patient refused 6-month angiography. Quantitative angiography after intervention showed a reference diameter of  $2.77 \pm 0.35$  mm and a minimal lumen diameter of  $2.36 \pm 0.43$  mm. At 6-month follow-up, minimal lumen diameter was  $1.45 \pm 0.88$  mm (late loss index 0.57).

Target lesion restenosis rate (>50% in diameter) was low (12%; 3 of 26). In addition, we observed 9 stenoses at the proximal or distal end of the irradiation zone, potentially caused by the short irradiation segment and the decreasing irradiation dose at its borders ("edge" stenoses). The total restenosis rate was 46% and was significantly lower (29% vs 70%,  $P=0.042$ ) when the length of the irradiated segment was more than twice the lesion length.

Conclusions-Coronary irradiation with a  $^{188}\text{Re}$ -filled balloon is technically feasible and safe, requiring only standard percutaneous transluminal coronary angioplasty techniques. The target lesion restenosis rate was low. The observed edge stenoses appear to be avoidable by increasing the length of the irradiated segment.

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Methodological and clinical implications of the relocation of the minimal luminal diameter after intracoronary radiation therapy

Manel Sabate, Marco A. Costa, Ken Kozuma, I. Patrick Kay, Connie J. van der Wiel, Vitali Verin, William Wijns, Patrick W. Serruys on behalf of the Dose Finding Study Group

#### OBJECTIVES

The aims of the study were to determine the incidence of relocation of the minimal luminal diameter (MLD) after beta-radiation therapy following balloon angioplasty (BA) and to describe a new methodological approach to define the effect of brachytherapy on treated coronary stenoses.

#### BACKGROUND

Luminal diameter of coronary lesions may increase over time following angioplasty and irradiation. As a result, the MLD at follow-up may be relocated from its location preintervention, which may induce misleading results when a restricted definition of the target segment by quantitative coronary angiography (QCA) is performed.

#### METHODS

Patients treated with BA followed by intracoronary brachytherapy according to the Dose-Finding Study constituted the study population. A historical cohort of patients treated with BA was used as control group. To be included in the analysis, an accurate angiographic documentation of all instrumentations during the procedure was mandatory. In the irradiated patients, four regions were defined by QCA: vessel segment (VS), target segment (TS), injured segment (INS), and irradiated segment (IRS).

## RESULTS

Sixty-five patients from the Dose-Finding Study and 179 control patients were included. At follow-up, MLD was relocated more often in the radiation group (78.5% vs. 26.3%;  $p < 0.0001$ ). The rate of >50% diameter stenosis differed among the four predefined regions: 3.1% in the TS; 7.7% in the INS; 9.2% in the IRS and 13.8% in the VS.

## CONCLUSIONS

Relocation of the MLD is commonly demonstrated after BA and brachytherapy, and it should be taken into account during the analysis of the results of radiation clinical trials.

Cathet. Cardiovasc. Intervent. 51:147-153, 2000

How long is enough? Defining the treatment length in endovascular brachytherapy

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The International Commission on Radiation Units and Measurement (IRCU) 50 has clearly defined treatment volumes in radiation therapy in the management of neoplasms. These concepts are applied to the field of endovascular brachytherapy (EVBT) for the prevention of postangioplasty restenosis. The following definitions are proposed: gross target length (GTL) is defined as the narrowed segment of the artery that requires intervention. Clinical target length (CTL) is defined as the intervened or injured length, which could be due to angioplasty, stent strut injury, stent deployment, or debulking procedures. Planning target length (PTL) is the CTL plus a margin to account for heart/catheter movement and uncertainty in target localization. The final treatment length (TL) is the PTL plus the effect of penumbra. The accurate specification of treatment length serves several important purposes. Based on an understanding of the different factors constituting the treatment length, adequate margins can be provided beyond the GTL; this will avoid geographic misses and minimize edge failures. These definitions of target length ensure treatment consistency and provide a standard terminology for communication among practitioners of EVBT, something of critical importance in the conduct of multi-institutional trials in this new and multidisciplinary therapy. Finally, since the efficacy of EVBT is critically dependent on the precision of radiation delivery, these guidelines ensure that the benefits of EVBT seen in prospective randomized trials can be translated into daily clinical practice at the community level.

Circulation, 2000 ;101: 2454-2457

### Edge Restenosis After Implantation of High Activity $^{32}\text{P}$ Radioactive $\beta$ -Emitting Stents

Remo Albiero, Takahiro Nishida, Milena Adamian, Antonio Amato, Marco Vaghetti, Nicola Corvaja, Carlo Di Mario, and Antonio Colombo

**Background-**A high restenosis rate has been reported at the edges ("edge restenosis") of  $^{32}\text{P}$  radioactive stents with an initial activity level of 3 to 12  $\mu\text{Ci}$ . This edge effect might be due to balloon injury and to a low dose of radiation at the stent margins. The aim of this study was to evaluate whether the implantation of  $^{32}\text{P}$  radioactive stents with a higher activity level (12 to 21  $\mu\text{Ci}$ ) combined with a nonaggressive stent implantation strategy could solve the problem of edge restenosis.

**Methods and Results-**We compared the results of lesions treated with single radioactive BX stents with an activity of 12 to 21  $\mu\text{Ci}$  (group 2, n=54 lesions) with the results of lesions treated by single radioactive BX stents with an initial activity level of 3 to 12  $\mu\text{Ci}$  (group 1, n=42 lesions). There were no procedural events. At the 6-month follow-up, no myocardial infarctions, deaths, or stent thromboses had occurred. Intrastent binary restenosis was 0% in group 1 versus 4% in group 2 (n=2, both at the ostium of the right coronary artery, P=NS). Intrastent neointimal hyperplasia was significantly lower in group 2 than in group 1. The intralesion (intrastent plus peri-stent) restenosis rate was 38% in group 1 versus 30% in group 2 (P=NS).

**Conclusions-**Single  $^{32}\text{P}$  radioactive stents with an initial activity level of 12 to 21  $\mu\text{Ci}$  reduced intrastent neointimal hyperplasia compared with stents of 3 to 12  $\mu\text{Ci}$ , but they did not solve the problem of edge restenosis, even if a nonaggressive stent implantation strategy was used.

Circulation , 2000 ;101: 1895-1898.

### Intracoronary $\beta$ -Radiation Therapy Inhibits Recurrence of In-Stent Restenosis

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Background-Intracoronary  $\beta$ -radiation therapy reduces recurrent in-stent restenosis (ISR). This study, BETA WRIST (Washington Radiation for In-Stent restenosis Trial) was designed to examine the efficacy and safety of the  $\beta$ -emitter 90-yttrium for the prevention of recurrent ISR.

Methods and Results-A total of 50 consecutive patients with ISR in native coronaries underwent percutaneous transluminal coronary angioplasty, laser angioplasty, rotational atherectomy, and/or stent implantation. Afterward, a segmented balloon catheter was positioned and automatically loaded with a 90-yttrium, 0.014-inch source wire that was 29 mm in length to deliver a dose of 20.6 Gy at 1.0 mm from the balloon surface. In 17 patients, manual stepping of the radiation catheter was necessary for lesions >25 mm in length. The radiation was delivered successfully to all patients, with a mean dwell time of  $3.0 \pm 0.4$  minutes. Fractionation of the dose due to ischemia was required in 11 patients. At 6 months, the binary angiographic restenosis rate was 22%, the target lesion revascularization rate was 26%, and the target vessel revascularization rate was 34%; all rates were significantly lower than those of the placebo group of -WRIST.

Conclusions- $\beta$ -Radiation with a 90-yttrium source used as adjunct therapy for patients with ISR results in a lower-than-expected rate of angiographic and clinical restenosis.

Circulation , 2000 ;101: 2467-2471.

Geographic Miss : A Cause of Treatment Failure in Radio-Oncology Applied to Intracoronary Radiation Therapy

Manel Sabate, Marco A. Costa, Ken Kozuma, I. Patrick Kay, Willem J. van der Giessen, Veronique L. M. A. Coen, Jurgen M. R. Ligthart, Pedro Serrano, Peter C. Levendag, and Patrick W. Serruys

Background-A recognized limitation of endovascular  $\beta$ -radiation therapy is the development of new stenosis at the edges of the irradiated area. The combination of injury and low-dose radiation may be the precursor of this phenomenon. We translated the radio-oncological concept of "geographic miss" to define cases in which the radiation source did not fully cover the injured area. The aims of the study were to determine the incidence and causes of geographic miss and evaluate the impact of this inadequate treatment on the outcome of patients treated with intracoronary  $\beta$ -radiation.

Methods and Results-We analyzed 50 consecutive patients treated with  $\beta$ -radiation after percutaneous

coronary intervention. The prescribed dose ranged between 12 and 20 Gy at 2 mm from the source axis. By means of quantitative coronary angiography, the irradiated segment (IRS) and both edges were studied before and after intervention and at 6-month follow-up. Edges that were injured during the procedure constituted the geographic miss edges. Twenty-two edges were injured during the intervention, mainly because of procedural complications that extended the treatment beyond the margins of the IRS. Late loss was significantly higher in geographic miss edges than in IRSs and uninjured edges ( $0.84 \pm 0.6$  versus  $0.15 \pm 0.4$  and  $0.09 \pm 0.4$  mm, respectively;  $P < 0.0001$ ). Similarly, restenosis rate was significantly higher in the injured edges (10% within IRS, 40.9% in geographic miss edges, and 1.9% in uninjured edges;  $P < 0.001$ ).

**Conclusions**—These data support the hypothesis that the combination of injury and low-dose  $\beta$ -radiation induces deleterious outcome.

Circulation, 2000 ;101(4):360-5

Three-year clinical and angiographic follow-up after intracoronary radiation : results of a randomized clinical trial.

Teirstein PS, Massullo V, Jani S, Popma JJ, Russo RJ, Schatz RA, Guarneri EM, Steuterman S, Sirkin K, Cloutier DA, Leon MB, Tripuraneni P

**BACKGROUND:** Although several early trials indicate treatment of restenosis with radiation therapy is safe and effective, the long-term impact of this new technology has been questioned. The objective of this report is to document angiographic and clinical outcome 3 years after treatment of restenotic stented coronary arteries with catheter-based  $(^{192}\text{Ir})$ . **METHODS AND RESULTS:** A double-blind, randomized trial compared  $(^{192}\text{Ir})$  with placebo sources in patients with previous restenosis after coronary angioplasty. Over a 9-month period, 55 patients were enrolled; 26 were randomized to  $(^{192}\text{Ir})$  and 29 to placebo. At 3-year follow-up, target-lesion revascularization was significantly lower in the  $(^{192}\text{Ir})$  group (15.4% versus 48.3%;  $P < 0.01$ ). The dichotomous restenosis rate at 3-year follow-up was also significantly lower in  $(^{192}\text{Ir})$  patients (33% versus 64%;  $P < 0.05$ ). In a subgroup of patients with 3-year angiographic follow-up not subjected to target-lesion revascularization by the 6-month angiogram, the mean minimal luminal diameter between 6 months and 3 years decreased from  $2.49 \pm 0.81$  to  $2.12 \pm 0.73$  mm in  $(^{192}\text{Ir})$  patients but was unchanged in placebo patients. **CONCLUSIONS:** The early clinical benefits observed after treatment of coronary restenosis with  $(^{192}\text{Ir})$  appear durable at late follow-up. Angiographic restenosis continues to be significantly reduced in  $(^{192}\text{Ir})$ -treated patients, but a small amount of

late loss was observed between the 6-month and 3-year follow-up time points. No events occurred in the (192)Ir group to suggest major untoward effects of vascular radiotherapy. At 3-year follow-up, vascular radiotherapy continues to be a promising new treatment for restenosis.

## Summary

Circulation, 2000;101(1):18-26

Short- and intermediate-term results of (32)P radioactive beta-emitting stent implantation in patients with coronary artery disease: The Milan Dose-Response Study.

Albiero R, Adamian M, Kobayashi N, Amato A, Vaghetti M, Di Mario C, Colombo A

**BACKGROUND:** Radioactive (32)P beta-emitting stents have been shown to reduce intrastent neointimal hyperplasia in a substantial dose-related manner in the animal model. The aim of this dose-response study was to evaluate, in the clinical setting, the safety and efficacy at 6-month follow-up of this approach to reducing restenosis. **METHODS AND RESULTS:** A total of 122 (32)P radioactive beta-emitting stents (initially the Palmaz-Schatz and later the BX Isostent) with an activity level of 0.75 to 3.0 microCi (group 1), 3.0 to 6.0 microCi (group 2), and 6.0 to 12.0 microCi (group 3) were implanted in 91 lesions in 82 patients. There were no procedural events. At 6-month follow-up, no deaths had occurred, and only 1 patient had stent thrombosis. Pure intrastent binary restenosis was 16% in group 1, 3% in group 2, and 0% in group 3. However, intralumen restenosis was 52% in group 1, 41% in group 2, and 50% in group 3. **CONCLUSIONS:** The use of (32)P radioactive beta-emitting stents in patients with CAD is feasible. At 6-month follow-up, intrastent neointimal hyperplasia was reduced in a dose-related manner. However, in the 3 groups, intralumen restenosis was high because of a high late lumen loss in the reference segments at the stent edges, possibly as a result of a low activity level of radiation at the edges of the stent combined with an aggressive approach to stenting. We called this "edge effect" the "candy wrapper."

## Summary

Table 3. Baseline and Postprocedure Quantitative Angiographic Results

Data are mean±SD.

1 Significant difference between group 3 and group 1.

2 Significant difference between group 3 and group 2.

Table 4. Clinical Events at 6-Month Follow-up

Data are mean±SD or number (%) of patients.

Table 5. Follow-up Intralesion Quantitative Angiographic Measurements

1 Significant difference between group 3 and group 1.

Table 7. Predictors of Edge Restenosis by Univariate Analysis

B/A indicates balloon-to-artery ratio; Prox., proximal; Ref., reference; and Dist., distal.

Heart, 83(3):332-7 2000

Outcome from balloon induced coronary artery dissection after intracoronary beta radiation.

Kay IP ; Sabate M ; Van Langenhove G ; Costa MA ; Wardeh AJ ; Gijzel AL ; Deshpande NV ; Carlier SG ; Coen VL ; Levendag PC ; Van der Giessen W ; de Feyter PJ ; Serruys PW

**OBJECTIVE:** To evaluate the healing of balloon induced coronary artery dissection in individuals who have received beta radiation treatment and to propose a new intravascular ultrasound (IVUS) dissection score to facilitate the comparison of dissection through time. **DESIGN:** Retrospective study. **SETTING:** Tertiary referral centre. **PATIENTS:** 31 patients with stable angina pectoris, enrolled in the beta energy restenosis trial (BERT-1.5), were included. After excluding those who underwent stent implantation, the evaluable population was 22 patients. **INTERVENTIONS:** Balloon angioplasty and intracoronary radiation followed by quantitative coronary angiography (QCA) and IVUS. Repeat QCA and IVUS were performed at six month follow up. **MAIN OUTCOME MEASURES:** QCA and IVUS evidence of healing of dissection. Dissection classification for angiography was by the National Heart Lung Blood Institute scale. IVUS proven dissection was defined as partial or complete. The following IVUS defined characteristics of dissection were described in the affected coronary segments: length, depth, arc circumference, presence of flap, and dissection score. Dissection was defined as healed when all features of dissection had resolved. The calculated dose of radiation received by the dissected area in those with healed versus non-healed dissection was also compared. **RESULTS:** Angiography (type A = 5, B = 7, C = 4) and IVUS proven (partial = 12, complete = 4) dissections were seen in 16 patients following intervention. At six month follow up, six and eight unhealed dissections were seen by angiography (A = 2, B = 4) and IVUS (partial = 7, complete = 1), respectively. The mean IVUS dissection score was 5.2 (range 3-8) following the procedure, and 4.6 (range 3-7) at follow up. No correlation was found between the dose prescribed in the treated area and the presence of unhealed dissection. No change in anginal status was seen despite the presence of unhealed dissection. **CONCLUSION:** beta radiation appears to alter the normal healing process, resulting in unhealed dissection in certain individuals. In view of the delayed and abnormal healing observed, long term follow up is indicated given the possible late adverse effects of radiation. Although in this cohort no increase in cardiac events following coronary dissections was seen, larger populations are needed to confirm this phenomenon. Stenting of all coronary dissections may be warranted in patients scheduled for brachytherapy after balloon angioplasty

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Radiation safety of personnel during catheter-based Ir-192 coronary brachytherapy.

Jani SK ; Steuterman S ; Huppe GB ; Chu GL

Catheter-based brachytherapy using Ir-192 seed sources has shown significant reduction in the rate of

restenosis among patients with coronary in-stent restenosis. High-energy gamma rays from Ir-192 raise some radiation safety issues of personnel. The aim of this study was to fully analyze the radiation safety issues associated with Ir-192 brachytherapy in the cardiac cath lab environment. Measurements were made to assess the penetrating ability of Ir-192 gamma rays through tissues, concrete and lead. Radiation exposure levels were measured around a large number of patients undergoing Ir-192 brachytherapy. Personnel were carefully monitored for any additional dose received from brachytherapy for the last five years covering > 500 cases. Our results showed that with a proper radiation safety program in place, the dose to cath lab staff was negligible. It was concluded that radiation safety of personnel was easy to maintain during catheter-based coronary brachytherapy using Ir-192 seed sources.

Int J Radiat Oncol Biol Phys, 46(4):1019-24 ,2000

The 90-day coronary vascular response to (90)Y-beta particle-emitting stents in the canine model.

Taylor AJ ; Gorman PD ; Hudak C ; Tashko G ; Sweet W ; Farb A ; Virmani R

**PURPOSE:** Long-term preclinical studies using continuous, low-dose-rate vascular brachytherapy with (32)P beta-emitting stents have yielded largely disappointing results. In contrast, a shorter half-life, higher dose-rate (90)Y beta-emitting stent more closely mimics the delivery dose rate characteristics of clinically effective beta- and gamma-wire and balloon brachytherapy devices. We evaluated the dose response characteristics of a (90)Y beta-emitting stent in the canine coronary injury model and hypothesized that this device would reduce neointimal formation. **METHODS:** Seventy-seven (90)Y beta-emitting coronary stents (15 mm BXTM, 3.0- and 3.5-mm diameter) were implanted in 26 normal dogs (20-25 kg) using a randomized, blinded study design. Stent activity included nonradioactive controls (n = 24), 4.5 microCi (n = 15), 8 microCi (n = 12), 16 microCi (n = 18), and 32 microCi (n = 8). Histologic endpoints were assessed at 3 months. **RESULTS:** Luminal stenosis and neointimal area were similar in control stents and low-activity (4.5 and 8 microCi) (90)Y stents. Higher activity stents (16 and 32 microCi) were associated with significant adverse effects. Frequent total occlusions (5 of 18 stents, 28%; p = 0.008) and a 40% increase in neointimal area (p = 0.024 vs. control) occurred in the 16 microCi group. Incomplete neointimal healing and a trend for reduced neointimal cell density were evident only in the 16- and 32-microCi group. **CONCLUSION:** Despite unique characteristics (2.7 day half-life and a higher dose rate) of (90)Y beta-emitting coronary stents, they have an adverse effect on neointimal formation, including frequent total occlusions at high activity levels. Incomplete healing, present 90 days (33 half-lives) after stent

placement, indicates prolonged recovery from radiation injury.

Eur J Nucl Med, 27(1):76-82, 2000

Dosimetry of rhenium-188 diethylene triamine penta-acetic acid for endovascular intra-balloon brachytherapy after coronary angioplasty.

Lee J ; Lee DS ; Kim KM ; Yeo JS ; Cheon GJ ; Kim SK ; Ahn JY ; Jeong JM ; Chung JK ; Lee MC

To examine the possibility of using rhenium-188 diethylene triamine penta-acetic acid (DTPA) for endovascular intra-balloon brachytherapy after angioplasty, dose distribution around the balloon was calculated and validated by film dosimetry. Medical internal radiation dosimetry (MIRD) was calculated assuming that the balloon had ruptured and that the contents had been released into the systemic circulation. <sup>188</sup>Re-perrhenate eluate from the <sup>188</sup>W/<sup>188</sup>Re generator was concentrated using an ion column and used to label DTPA. The dose distribution around the angioplasty balloon (20 mm length, 3 mm diameter cylinder) was estimated by Monte Carlo simulation using the EGS4 code. The time required for 17.6 Gy to be absorbed at 1 mm from the balloon's surface following application of 3700 MBq/ml of <sup>188</sup>Re was found to be 278 s. Fifty percent of the energy was deposited in the first millimetre of the vessel wall from the balloon's surface. The calculated radiation absorbed dose agreed with that measured by film dosimetry, which was performed using a water phantom, with errors ranging from 9.4% to 17%. Upon balloon rupture the total amount of <sup>188</sup>Re-DTPA was presumed to enter the systemic circulation. The resulting radiation absorbed dose was calculated using the MIRDOSE3 program and residence times obtained from dogs and amounted to 0.0056 mGy/MBq to the whole body and 4.56 mGy/MBq to the urinary bladder. The absorbed dose of <sup>188</sup>Re-DTPA to the whole body was one-tenth of that of <sup>188</sup>Re-perrhenate. A window-based program was developed to calculate the exposure time and the radiation dose absorbed as a function of the <sup>188</sup>Re concentration and the arbitrary distance from the balloon to the surrounding tissues. We conclude that <sup>188</sup>Re-DTPA is easy to prepare, safe to use and suitable for intra-balloon brachytherapy after coronary angioplasty.

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Preserved endothelium-dependent vasodilation in coronary segments previously treated with balloon angioplasty and intracoronary irradiation.

Sabat M ; Kay IP ; van Der Giessen WJ ; Cequier A ; Ligthart JM ; Gomez-Hospital JA ; Carlier SG ; Coen VL ; Marijnissen JP ; Wardeh AJ ; Levendag PC ; Serruys PW

**BACKGROUND:** Abnormal endothelium-dependent coronary vasomotion has been reported after balloon angioplasty (BA), as well as after intracoronary radiation. However, the long-term effect on coronary vasomotion is not known. The aim of this study was to evaluate the long-term vasomotion of coronary segments treated with BA and brachytherapy. **METHODS AND RESULTS:** Patients with single de novo lesions treated either with BA followed by intracoronary beta-irradiation (according to the Beta Energy Restenosis Trial-1.5) or with BA alone were eligible. Of these groups, those patients in stable condition who returned for 6-month angiographic follow-up formed the study population (n=19, irradiated group and n=11, control group). Endothelium-dependent coronary vasomotion was assessed by selective infusion of serial doses of acetylcholine (ACh) proximally to the treated area. Mean luminal diameter was calculated by quantitative coronary angiography both in the treated area and in distal segments. Endothelial dysfunction was defined as a vasoconstriction after the maximal dose of ACh ( $10^{-6}$  mol/L). Seventeen irradiated segments (89.5%) demonstrated normal endothelial function. In contrast, 10 distal nonirradiated segments (53%) and 5 control segments (45%) demonstrated endothelium-dependent vasoconstriction ( $-19\pm 17\%$  and  $-9.0\pm 5\%$ , respectively). Mean percentage of change in mean luminal diameter after ACh was significantly higher in irradiated segments ( $P=0.01$ ). **CONCLUSIONS:** Endothelium-dependent vasomotion of coronary segments treated with BA followed by beta-radiation is restored in the majority of stable patients at 6-month follow-up. This functional response appeared to be better than those documented both in the distal segments and in segments treated with BA alone.

Table 2. Coronary Vasomotor Response (Mean Luminal Diameter)

Data are presented as mean  $\pm$  SD (in mm).

1  $P=0.03$ ,

2  $P=0.0004$ ,

3  $P=0.01$  with respect to baseline values.

Long-term coronary vascular response to (32)P beta-particle-emitting stents in a canine model.

Author

Taylor AJ ; Gorman PD ; Farb A ; Hoopes TG ; Virmani R

**BACKGROUND:** The arterial placement of (32)P beta-particle-emitting stents in various experimental animal models results in discordant effects on neointimal formation. We studied the vascular effects of beta-particle-emitting stents in normal canine coronary arteries because compared with pigs and rabbits, the canine model may more closely mimic the vascular response of humans. **METHODS AND RESULTS:** Thirty stents (control nonradioactive, n=10; low-activity (32)P, 3.5 to 6.0 microCi, n=11; high-activity (32)P, 6.5 to 14.4 microCi, n=8) were implanted in normal canine coronary arteries through the use of a single balloon inflation at nominal pressure. Histological analysis after 15 weeks included the measurement of neointimal and adventitial area and thickness. Neointimal fibrin area was measured with the use of computer-assisted color segmentation on Movat pentachrome sections. Luminal stenosis was significantly increased in (32)P stents compared with control stents (44.6+/-16.8% versus 32.7+/-10.8%; P=0.05) and was highest in the high-activity group (45.5+/-24.3%). No evidence of an "edge effect" was seen in adjacent, nonstented coronary segments. All (32)P stents showed incomplete vascular healing as indicated by a dose-dependent increase in fibrin area with increasing stent activity. Arterial radiation resulted in a decrease in adventitial size, which was maximal for high-activity (32)P stents, indicating an inhibitory effect on the adventitial response to injury. **CONCLUSIONS:** (32)P beta-particle-emitting stents have adverse vascular effects at 15 weeks in the canine normal coronary artery model. Vascular brachytherapy with this device causes increased neointimal formation and prominent, dose-dependent lack of healing.

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The effect of 32P beta-radiotherapy on both vessel remodeling and neointimal hyperplasia after coronary balloon angioplasty and stenting: a three-dimensional intravascular ultrasound investigation.

Costa MA ; Sabate M ; Serrano P ; van der Giessen WJ ; Kozuma K ; Kay IP ; Coen VL ; Ligthart JM ; Wardeh A ; Levendag PC ; Serruys PW

Intracoronary radiation is a promising therapy to decrease restenosis after percutaneous intervention. The aim of this pilot study was to determine the mechanism of intracoronary beta-radiation after balloon angioplasty

and stenting in a double-blind placebo-controlled randomized fashion. Twenty-six patients were randomized to either placebo (n = 6) or 3 doses (28, 35 and 42 Gy) of beta-radiation (n = 20) using the Guidant brachytherapy system (27 mm long 32P source wire). Of these, 21 patients underwent post-procedure and 6-month follow-up three-dimensional intravascular ultrasound (IVUS) assessment. Volumetric quantification was performed by means of a semi-automated contour detection system after an ECG-gated motorized pullback IVUS imaging and three-dimensional reconstruction. We compared the volumetric changes (Delta) of total vessel volume (TVV), plaque volume (PV) and lumen volume (LV) after 6 months between placebo (dummy wire) and irradiated patients. In addition, the volume of neointimal hyperplasia was quantified within the stented segments. There was an opposite behavior of TVV and LV change between placebo (DeltaTVV = -24 mm<sup>3</sup> and DeltaLV = -42 mm<sup>3</sup>) and irradiated (DeltaTVV = +18 mm<sup>3</sup> and (DeltaLV = +5 mm<sup>3</sup>) patients. The mean neointimal formation within the stented segment in the irradiated patients (n = 7) was 1.9 mm<sup>3</sup> (1.5%). Our results suggest that beta-radiation affects vessel remodeling after percutaneous intervention and inhibit neointimal formation in stented patients.

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