New insights into coronary brachytherapy

A report from the American College of Cardiology Annual Scientific Session

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Prof. Sigmund Silber, Munich, Germany

Three studies presented at the ACC have increased our understanding of the clinical applications of intracoronary brachytherapy. These are: SVG WRIST (Washington Radiation for In-Stent restenosis Trial for Saphenous Vein Grafts); the Beta-Cath™ System Trial; and a matched analysis comparing beta and gamma radiation.

In-stent restenosis in saphenous vein grafts remains a therapeutic challenge. New devices and re-stenting have failed to reduce the recurrence rate so these patients continue to undergo multiple interventions or repeated surgery. Ron Waksman (Washington DC, USA) presented results from SVG WRIST, a recent multi-center clinical trial in which 120 patients with in-stent restenosis in saphenous vein grafts were randomized to receive either gamma radiation (^{192}Ir, CHECKMATE™ System, Cordis; a Johnson and Johnson company) or placebo. Main inclusion criteria for the study were: angina, vessel diameters of 2.5–5.0 mm and lesion lengths of up to 47 mm. The radiation dose prescribed was approximately 15 Gy for vessels of 2.5–4.0 mm and 18 Gy for vessels of 4.0–5.0 mm; results obtained at 6 months are shown in Figure 1.

A dramatic reduction (50–79%) in the angiographic and clinical recurrence rate of restenosis was observed with significantly lower incidence of major adverse cardiac events (MACE) when compared to placebo; no late thrombosis was observed when clopidogrel administration was extended.

The solution of extended antiplatelet regimens for the prevention of late thrombosis was proven in a much larger study: the Beta-Cath™ System Trial, initiated in July 1997 in 59 centers in the US and Europe. This trial represents the first and largest prospective randomized, masked placebo-controlled trial investigating the use of vascular brachytherapy for the treatment of *de novo* lesions; results were presented by Richard Kuntz (Boston, MA, USA). Inclusion criteria were *de novo* lesions in vessels of 2.7–4.0 mm that were treatable with a 20 mm balloon. 1455 patients underwent PTCA with or without stent implantation (at the discretion of the interventional cardiologist). Patients were then randomized to receive either placebo (n=744) or beta radiation (n=711) with the Novoste™ Beta-Cath™ System (^{90}Sr/^{90}Y; 16.1 Gy in vessels of 2.7–3.3 mm, 20.7 Gy in vessels of 3.3–4.0 mm). 504 patients received no stent, 499 received a stent and short-term

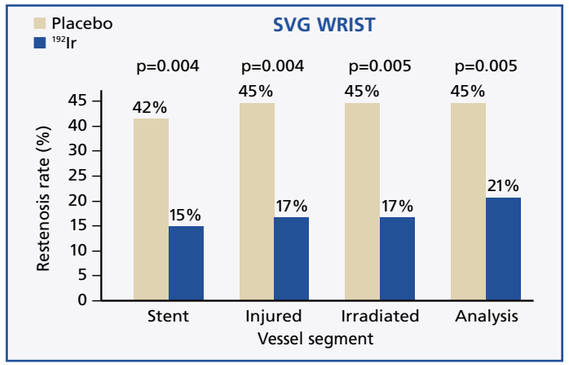

Figure 1. Restenosis rates by segment in SVG WRIST.

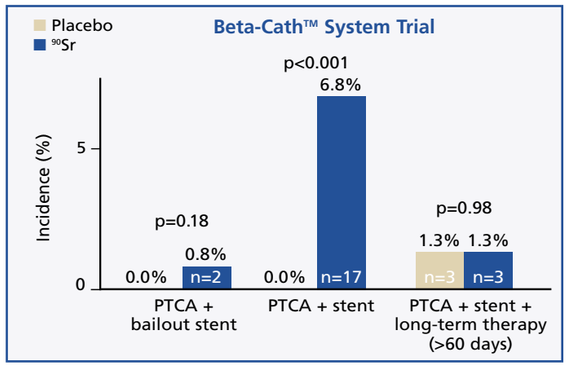

Figure 2. Incidence of late thrombosis in patients with de novo *lesions treated by PTCA with or without stenting plus short- or long-term antiplatelet therapy in the Beta-Cath™ System Trial.*

antiplatelet therapy with ticlopidine or clopidogrel, and 452 patients received a stent and long-term (>60 days) antiplatelet therapy.

An overall thrombosis rate of 6.8% was observed in the stent + short-term therapy group, while in the stent + long-term therapy group there was no difference in thrombosis rates (1.3%) between patients administered radiation and those given placebo (see Figure 2).

Although the Beta-Cath™ System Trial demonstrated a significant treatment effect of brachytherapy on the angiographic outcome in the lesion segment, this effect was lost in the analysis segment, particularly in patients treated by stenting. This may have been due to 'geographic miss' — inadequate radiation coverage of the injury segment. Thus, the Beta-Cath™ System Trial complements earlier findings from a non-randomized European study (BRIE; Beta Radiation In Europe) that geographic miss may have a deleterious effect on clinical outcome.

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Is there a difference between gamma and beta radiation?

This was the purpose of a matched analysis performed at the Lenox Hill Hospital that was presented by Alexandra Lansky (New York, NY, USA). 227 patients receiving gamma radiation with ^{192}Ir were compared with 179 patients treated with beta radiation (^{90}Sr/^{90}Y) and 228 patients in the placebo group. The more diffuse the lesion at the baseline, the greater the reduction in lesion length at follow-up after both gamma and beta radiation treatments. Gamma radiation caused less untoward effects outside the stents, probably due to the use of longer radiation sources. Within the stents, however, beta radiation was superior.

In summary, data presented at the ACC indicate that the role of radiation in *de novo* lesions deserves more investigation. Brachytherapy has proven to be very effective for the treatment of in-stent restenosis in saphenous vein grafts. Brachytherapy has been dramatically reduced by prolonged administration of clopidogrel. However, if the radiation source is too short, the positive treatment effect is offset by an 'edge effect'; therefore longer radiation sources are preferred. Brachytherapy is the treatment of choice for the treatment of in-stent restenosis in native coronary arteries. Beta and gamma radiation are equally effective; however, beta radiation seems to be superior within the stent.

Current perceptions of VBT's role in today's cardiology practice

'Vascular brachytherapy is currently the only effective percutaneous therapy for combating in-stent restenosis. Five independent randomized controlled trials have consistently documented a major impact on angiographic and clinical endpoints, using either gamma or beta radiation, while the RENO registry indicated that similar results can be reproduced in routine clinical practice. These results have led to the approval and rapidly expanding use of several systems in Europe and the US. Late thrombotic complications have largely been eliminated by the administration of extended antiplatelet regimens, while the problem of geographic miss may be reduced by the use of longer radiation source trains and more meticulous positioning of balloon and source train. The potential of VBT for the treatment of *de novo* lesions awaits further study; major issues to be resolved are the identification of patient subsets most likely to benefit from VBT and determination of the optimal delivery dose.'

Dr Philip Urban, Cardiology Division, CHUV, Lausanne, Switzerland.

'Our utilization of vascular brachytherapy has been extremely high because we continue to have problems with restenosis after both percutaneous transluminal coronary angioplasty (PTCA) and stenting. These lesions would not be treatable with alternative technologies. Use of VBT has also been surprisingly high due to increasing indications for stenting in lesions that were previously treated by surgery.'

'I was encouraged by the results of the Beta-Cath™ System Trial, which showed that radiation reduces intimal hyperplasia. The study confirmed the importance of taking care when treating the injury area and providing adequate margins with the source train, something we learned when we completed the START trial.'

Dr Richard Heuser, Phoenix Heart Center, Phoenix, AZ, USA.

'The problem of restenosis and in-stent restenosis will be around for at least the next five years. The problem is a complex one and it is too simplistic to think that one treatment method alone will provide all the answers; such a multifactorial problem needs a multifactorial approach. Brachytherapy has already proven to be the only current safe and effective method of reducing in-stent restenosis. Other treatment regimes still need to show equivalency. Based on the newest data on stents, I am quite happy to see brachytherapy continue to be used in clinical practice for at least the next five years.'

Dr Dietrich Baumgart, University of Essen, Essen, Germany.