Influence of device selection on angiographic outcomes for the treatment of in-stent restenosis. A sub analysis from the Washington Radiation for In-Stent restenosis Trial (WRIST)

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Key words:
Coronary angioplasty; Restenosis; Stent; Thrombosis, intravascular.

Background. **Treatment of in-stent restenosis is still a challenge. Despite promising results obtained with intracoronary brachytherapy (ICB), the ideal strategy of device selection has not been identified. The aim of this study was to evaluate the influence of device selection on ICB for the treatment of in-stent restenosis.**

Methods. **The outcomes of 130 patients from the Washington Radiation for In-Stent restenosis Trial (WRIST) were studied. Patients were analyzed on the basis of device selection, prior to randomization to γ-radiation (n = 65) or placebo (n = 65): balloon angioplasty (PTCA) (n = 15, 12%), rotational atherectomy (RA) (n = 40, 31%), excimer laser coronary angioplasty (ELCA) (n = 28, 22%) or additional stent implantation (n = 47, 36%).**

Results. **PTCA was less frequently used in lesions with prior in-stent restenosis (14.8%, $p < 0.05$); ELCA was less frequently used in saphenous vein grafts (57.1%, $p < 0.05$). The procedural outcomes and restenosis rates were similar among groups. In the RA group, patients assigned to Ir^{192} had a larger minimal lumen diameter (1.6 ± 0.5 vs 0.9 ± 0.4 mm, $p < 0.05$) and lower diameter stenosis (39 ± 17 vs 65 ± 16%, $p < 0.05$) at follow-up angiography and a reduced late loss (0.2 ± 0.5 vs 0.9 ± 0.5 mm, $p < 0.05$) and loss index (0 ± 0.4 vs 0.8 ± 0.4, $p < 0.05$) when compared to placebo. The incidence of delayed thrombosis was 7.7% in the ICB and 4.6% in the placebo group ($p = 0.71$); additional stenting, either alone (relative risk 12.36, 95% confidence interval 1.56÷94.43) or followed by ICB (relative risk 3.80, 95% confidence interval 1.02÷14.27), was correlated with an increased risk of late thrombosis.**

Conclusions. **ICB reduces the recurrence of in-stent restenosis through a reduction in late loss. In view of the higher risk of delayed thrombosis, additional stenting, either alone or followed by ICB, should be used with caution.**

(Ital Heart J 2002; 3 (4): 256-262)

Received January 7, 2002; revision received February 19, 2002; accepted March 4, 2002.

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Introduction

Stents have been found to reduce restenosis[1,2]. However, in-stent restenosis is a major limitation[3,4]. Any antirestenosis therapy under consideration must contend with the two basic mechanisms of vessel re-narrowing following coronary intervention. The first re-narrowing mechanism is vascular contraction, which can be mechanically blocked with a typical balloon expandable stent. The second re-narrowing mechanism, neointima proliferation, is a complex cellular reaction to the injury caused by the actions of mechanical devices such as balloons, stents, and atherectomy catheters.

Different treatment strategies have been tried to deal with this problem, including balloon angioplasty (PTCA), rotational atherectomy (RA), excimer laser coronary angioplasty (ELCA), and additional stent implantation. However, the recurrence rate after the currently available treatments for in-stent restenosis remains high[5-9]. Recently, intracoronary brachytherapy (ICB) has been successfully used to reduce or prevent in-stent restenosis in clinical studies[10-13].

The purpose of the present study was to evaluate the relative impact of γ-radiation ICB on the delayed outcome, in relation to the device selection for the treatment of in-stent restenosis.

Methods

The Washington Radiation for In-Stent restenosis Trial (WRIST) was a single-cen-

ter, randomized, double-blind study, performed at the Washington Hospital Center and designed to test the effectiveness of γ-radiation as an adjunctive treatment for in-stent restenosis. Between February 1997 and January 1998, 130 patients with in-stent restenosis in the native coronary arteries (n = 100) or in the saphenous vein grafts (n = 30) were included in this study; the patient's selection criteria and study design have been previously reported[11].

Study protocol. The device selection was based on the lesion morphology and was left at the discretion of the operator in an attempt to optimize the final result. Focal lesions were mainly treated with PTCA, diffuse lesions with initial ablation, either with RA or ELCA, followed by balloon dilation; additional stenting was used with a provisional strategy to optimize the final angiographic result or to cover edge dissection. Interventional procedures included PTCA (n = 15, 12%), RA (n = 40, 31%), ELCA (n = 28, 22%) and re-stenting (n = 47, 36%). Patients were randomly assigned to receive a nylon ribbon containing placebo or Ir^{192} (Best Medical International, Springfield, VA, USA). Accurate positioning of the source placed in such a way as to cover the entire lesion site plus at least 4 mm overlap to normal segments at each end was documented by angiography. Patients were discharged on aspirin (325 mg daily indefinitely) and ticlopidine (250 mg twice daily for 1 month).

Angiographic analysis. For the purpose of the present study the results of the quantitative coronary angiographic analysis performed at the Washington Hospital Center laboratory (Washington, DC, USA), using the CMS-GFT system (Medis, Leiden, The Netherlands)[14] were used. The lesion length ("shoulder to shoulder"), minimal lumen diameter (MLD), reference diameter and percent diameter stenosis were measured using the same view prior to and following intervention and at 6 months of follow-up.

Procedural success was defined as < 50% stenosis without major in-hospital complications (death, myocardial infarction, or coronary artery bypass surgery). Myocardial infarction was defined as new pathological Q waves (> 0.4 ms) in two or more contiguous leads and a total creatine kinase elevation ≥ 2× normal value and/or elevated creatine kinase-MB fraction ≥ 2× normal value. Major complications and other secondary adverse events (abrupt vessel re-closure, repeated intervention, non-Q-wave myocardial infarction, vascular complications and delayed occlusion) were reviewed for adjudication by an independent committee.

Lesions were classified according to the modified American College of Cardiology/American Heart Association lesion classification score[15].

Angiographic binary restenosis at 6-month follow-up was defined as ≥ 50% diameter narrowing within the segment including the stent and its edges. For the purpose of the present study the measurements performed in the entire segment of artery covered by the ribbon were used. Acute gain (in mm) was calculated as the change in the stent MLD from baseline to the final procedural angiogram. Late loss (in mm) was defined as the change in stent MLD from the final to the follow-up angiogram. The arithmetic loss index was defined as late loss/acute gain.

Follow-up included clinical assessment for 1 year; target vessel revascularization was defined as a repeat percutaneous intervention or coronary artery bypass grafting involving the treated vessel. The indications to the latter procedures included clinical signs of ischemia in the presence of angiographic restenosis.

Statistical analysis. Data were prospectively recorded and forwarded to the data-coordinating center (Cardiology Research Foundation Data Analysis Center at the Washington Hospital Center, Washington, DC, USA). Outcomes were analyzed according to the "intention-to-treat" principle. Continuous variables were expressed as means ± SD and categorical data as percentages.

For analysis of the efficacy of ICB, the Student's t-test was used to compare continuous variables and the χ^2 test or Fisher's exact test were used to assess discrete variables. To test differences among the various treatment strategies, a one-way ANOVA was used with follow-up Bonferroni's correction for multiple testing of continuous variables and the χ^2 or Fisher's exact test for discrete variables. A value of $p < 0.05$ was considered statistically significant, except for the Bonferroni-corrected test ($p < \{0.05/6 = 0.0085\}$).

The relative risk (RR) with 95% confidence intervals (CI) was used for the assessment of differences between treatment groups to analyze the effect of various treatments, either alone or in association, on delayed thrombosis.

Results

In relation to device selection, baseline characteristics were similar among groups, except for the incidence of prior in-stent restenosis that was 43.1% in the overall population and as low as 13.3% in the PTCA group ($p < 0.05$); there was no difference between the ICB and the placebo groups (Table I).

Lesion morphology and in-hospital outcome. The lesion characteristics were similar in both groups (ICB or placebo). There was no difference in relation to device selection, except for saphenous vein graft lesions ($p < 0.05$), that were more frequently treated by ELCA (Table II).

During RA procedures, 1.5 ± 0.5 burrs/procedure were used.

During ELCA procedures, 1.1 ± 0.4 fibers/procedure were used.

Table I. Baseline characteristics of patients according to radiation therapy and device selection.

	Overall		p	PTCA		RA		ELCA		ASI		p
	Ir^{192} (n=65)	Placebo (n=65)		Ir^{192} (n=6)	Placebo (n=9)	Ir^{192} (n=18)	Placebo (n=22)	Ir^{192} (n=14)	Placebo (n=14)	Ir^{192} (n=27)	Placebo (n=20)	
Age (years)	63 ± 11	62 ± 10	NS	64 ± 8	62 ± 11	58 ± 11	63 ± 11	68 ± 8	66 ± 6	64 ± 11	59 ± 10	NS
Males (%)	66.2	72.3	NS	66.7	88.9	61.1	68.2	71.4	85.7	66.7	60.0	NS
Smoking (%)	62.1	60.1	NS	66.7	66.7	66.7	63.6	78.6	57.1	51.9	65.0	NS
Hypertension (%)	72.3	67.7	NS	66.7	50.0	59.1	72.3	85.0	50.0	65.0	88.9	NS
Diabetes mellitus (%)	38.5	45.3	NS	33.3	44.4	27.8	31.8	28.6	57.1	51.9	52.6	NS
Unstable angina (%)	90.3	87.1	NS	50.0	85.7	93.8	90.5	100	78.6	92.3	90.0	NS
Previous MI (%)	44.6	44.6	NS	83.3	33.3	38.9	36.4	50.0	71.4	37.0	40.0	NS
Previous CABG (%)	56.9	50.8	NS	50.0	33.3	38.9	36.4	71.4	78.6	63.0	55.0	NS
Previous in-stent restenosis (%)	47.7	38.5	NS	0	22.2	44.4	36.4	50.0	35.7	59.3	50.0	< 0.05
LVEF (%)	47 ± 11	50 ± 10	NS	47 ± 4	50 ± 10	47 ± 12	49 ± 11	47 ± 13	51 ± 11	47 ± 11	48 ± 11	NS

Values are expressed as means ± SD or as percentages. ASI = additional stent implantation; CABG = coronary artery bypass grafting; ELCA = excimer laser coronary angioplasty; LVEF = left ventricular ejection fraction; MI = myocardial infarction; PTCA = balloon angioplasty; RA = rotational atherectomy.

Table II. Lesion characteristics and in-hospital outcome according to radiation therapy and device selection.

	Overall		p	PTCA		RA		ELCA		ASI		p
	Ir^{192} (n=65)	Placebo (n=65)		Ir^{192} (n=6)	Placebo (n=9)	Ir^{192} (n=18)	Placebo (n=22)	Ir^{192} (n=14)	Placebo (n=14)	Ir^{192} (n=27)	Placebo (n=20)	
Length (mm)	20 ± 10	22 ± 12	NS	13 ± 5	16 ± 10	20 ± 9	22 ± 6	21 ± 9	25 ± 17	21 ± 10	23 ± 11	NS
ACC/AHA B2-C	31.3	23.1	NS	33.3	44.4	22.2	31.8	28.6	14.3	38.5	10.0	NS
Saphenous vein graft	23.1	23.1	NS	16.7	11.1	0	0	57.1	57.1	22.2	30.0	< 0.05
Procedural success	100	96.9	NS	100	100	100	95.2	100	100	100	100	NS
In-hospital												
Death	0	0	NS	0	0	0	0	0	0	0	0	NS
CABG	0	0	NS	0	0	0	0	0	0	0	0	NS
Q-MI	0	0	NS	0	0	0	0	0	0	0	0	NS
Non-Q-MI	9.2	7.7	NS	0	0	7.1	4.5	11.1	14.3	11.1	10.0	NS
Vascular complications	10.8	10.8	NS	0	0	11.1	14.3	21.4	14.3	74	10.0	NS

Values are expressed as means ± SD or as percentages. ACC/AHA B2-C = B2-C lesion morphology according to the modified American College of Cardiology/American Heart Association classification[15]. Other abbreviations as in table I.

In the group of patients who were submitted to additional stent implantation, previous ablation before ICB or placebo was performed in 36 patients (76.6%): in 11 (41%) and 9 cases (45%, p = NS) with RA and in 8 (30%) and 8 (40%, p = NS) cases with ELCA; 1.3 ± 0.6 stents/procedure were implanted.

The rate of procedural success was high (overall 98.4%) and was similar in all groups. There were neither deaths nor Q-wave myocardial infarctions and none of the patients underwent coronary artery bypass grafting.

One patient treated with RA underwent re-stenting for recurrent ischemia during his in-hospital stay. A non-Q-wave myocardial infarction was documented in 6 patients (9.2%) in the ICB group and in 5 patients (7.7%, p = NS) in the placebo group. There were 14 vascular complications: 7 subjects (10.8%) in the placebo group, 3 of them requiring transfusion, and 7 subjects (10.8%, p = NS) in the ICB group, 5 of them requiring transfusion.

Quantitative coronary angiography results (Table III). Among 130 patients, follow-up angiography was available for 115 (88%). In no case was a coronary perforation or pseudoaneurysm detected.

According to adjunctive ICB, reference diameters before, after intervention and at follow-up were similar among the groups. The MLD and diameter stenosis were also similar both before and after intervention. When compared to placebo, the MLD was larger ($p < 0.003$) and the diameter stenosis higher ($p = 0.000$) in the ICB group at follow-up. The acute gain did not differ among groups; when compared to placebo, patients who underwent adjunctive γ-radiation had a lower late loss (0.3 ± 0.7 vs 0.8 ± 0.6 mm, $p < 0.0001$) and a lower loss index (0.2 ± 0.7 vs 0.7 ± 0.4, $p < 0.001$).

Table III. Quantitative angiographic analysis according to device selection and radiation therapy.

	Overall		p	PTCA		RA		ELCA		ASI		p
	Ir^{192} (n=65)	Placebo (n=65)		Ir^{192} (n=6)	Placebo (n=9)	Ir^{192} (n=18)	Placebo (n=22)	Ir^{192} (n=14)	Placebo (n=14)	Ir^{192} (n=27)	Placebo (n=20)	
Reference diameter (mm)												
Pre	2.7 ± 0.7	2.7 ± 0.6	NS	3.3 ± 0.7	3.0 ± 0.7	2.8 ± 0.6	2.4 ± 0.4	2.8 ± 0.6	3.1 ± 0.6	2.7 ± 0.7	2.7 ± 0.5	< 0.05*
Post	2.9 ± 0.6	2.9 ± 0.5	NS	3.5 ± 0.8	3.2 ± 0.5	2.5 ± 0.4	2.6 ± 0.5	3.0 ± 0.5	3.1 ± 0.6	2.9 ± 0.6	2.9 ± 0.4	< 0.05*
Follow-up	2.9 ± 0.5	2.9 ± 0.6	NS	3.0 ± 0.5	3.2 ± 0.7	2.6 ± 0.4	2.7 ± 0.4	3.2 ± 0.6	3.1 ± 0.7	2.9 ± 0.5	2.8 ± 0.5	< 0.05*
MLD (mm)												
Pre	0.9 ± 0.4	0.8 ± 0.4	NS	1.3 ± 0.2	1.2 ± 0.5	1.1 ± 0.5	0.7 ± 0.3	1.1 ± 0.5	0.9 ± 0.3	0.9 ± 0.4	0.7 ± 0.5	< 0.05**
Post	2.0 ± 0.5	2.1 ± 0.4	NS	2.3 ± 0.6	2.2 ± 0.3	1.9 ± 0.4	2.2 ± 0.5	1.9 ± 0.4	2.2 ± 0.5	2.0 ± 0.5	2.1 ± 0.5	NS
Follow-up	1.6 ± 0.8	1.2 ± 0.7	0.003	2.0 ± 0.7	1.9 ± 0.8	1.6 ± 0.5§§	0.9 ± 0.4	1.9 ± 1.0	1.5 ± 0.8	1.4 ± 0.9	1.1 ± 0.8	< 0.05§
Diameter stenosis (%)												
Pre	65 ± 14	70 ± 15	NS	59 ± 12	61 ± 18	63 ± 13	71 ± 8	67 ± 16	71 ± 8	67 ± 15	74 ± 19	NS
Post	28 ± 12	27 ± 12	NS	36 ± 8	32 ± 11	29 ± 11	28 ± 10	29 ± 11	25 ± 12	29 ± 15	26 ± 15	NS
Follow-up	44 ± 23	59 ± 20	0.000	32 ± 13	43 ± 17	39 ± 17§§	65 ± 16	43 ± 23	53 ± 18	51 ± 28	62 ± 25	< 0.05**

Values are expressed as means ± SD. MLD = minimal lumen diameter; Post = after intervention; Pre = before intervention. Other abbreviations as in table I. * = PTCA vs RA; ** = PTCA vs RA, PTCA vs ASI; § = PTCA vs RA, PTCA vs ASI, ELCA vs RA; §§ = p < 0.05 Ir^{192} vs placebo in the RA group.

In relation to device selection, patients in the PTCA group had a larger reference diameter before and after intervention and at follow-up ($p < 0.05$) when compared to those in the RA group. The MLD before intervention was significantly larger in the PTCA group (1.2 ± 0.4 mm) when compared to both the RA (0.9 ± 0.5 mm, $p < 0.05$) and re-stenting groups (0.8 ± 0.5 mm, $p < 0.05$). The MLD at follow-up was larger in the PTCA group (1.9 ± 0.8 mm) when compared to the RA (1.2 ± 0.4 mm, $p < 0.05$) and the additional stent implantation groups (1.3 ± 0.8 mm, $p < 0.05$); when compared to RA, even the follow-up MLD in the ELCA group was significantly larger (1.7 ± 0.8 mm, $p < 0.05$). Similarly, the diameter stenosis at follow-up was lower in the PTCA (40 ± 15%) when compared to both the RA (53 ± 16%, $p < 0.05$) and additional stenting groups (56 ± 26%, $p < 0.05$).

There were no differences in acute gain, late loss and loss index according to the overall device selection (Fig. 1).

On the basis of the combined treatment strategy, in the RA group the patients assigned to Ir^{192} showed a larger MLD ($p < 0.05$) and a lower diameter stenosis ($p < 0.05$) at follow-up angiography and a reduced late loss ($p < 0.05$) and loss index ($p < 0.05$) when compared to placebo. Similar analysis in the other subgroups did not reveal any difference.

Long-term outcome (Table IV). When compared to placebo, patients treated with adjunctive ICB had a lower 6-month angiographic restenosis rate ($p = 0.000$) and a lower 1-year target vessel revascularization rate ($p = 0.000$). On the basis of device selection, restenosis and target vessel revascularization rates were similar among groups.

Delayed thrombosis occurred in 8 patients (6.4%); the incidence of this complication was independent of adjunctive ICB ($p = 0.71$). However, the incidence of delayed thrombosis differed according to device selection ($p < 0.05$). In subjects who received ICB, a complete vessel occlusion was documented in 5 cases (7.7%): 1 patient in the ELCA group and 4 patients who received

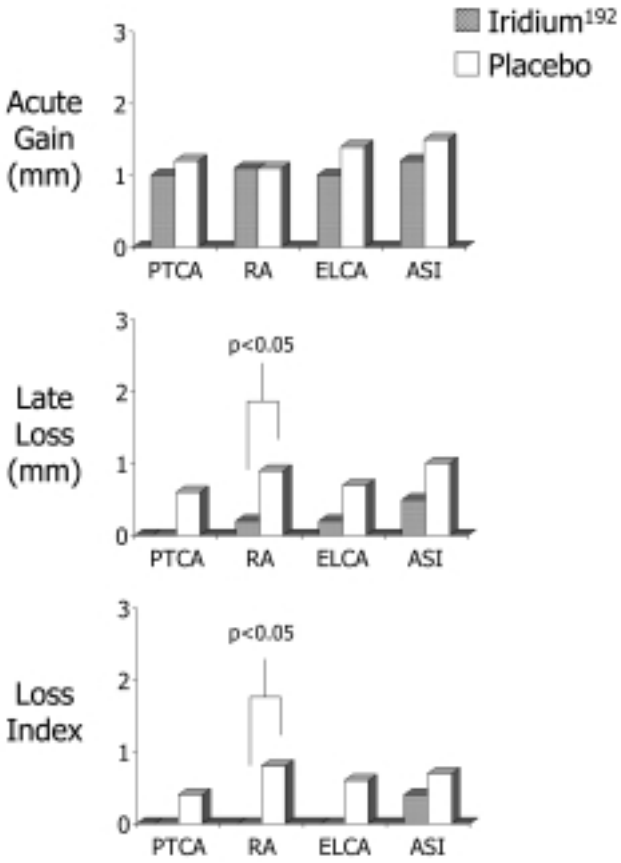

Figure 1. *Acute gain, late loss and loss index according to radiation therapy and device selection. ASI = additional stent implantation; ELCA = excimer laser coronary angioplasty; PTCA = balloon angioplasty; RA = rotational atherectomy.*

Table IV. Long-term outcome according to device selection and radiation therapy.

	Overall		p	PTCA		RA		ELCA		ASI		p
	Ir^{192} (n=65)	Placebo (n=65)		Ir^{192} (n=6)	Placebo (n=9)	Ir^{192} (n=18)	Placebo (n=22)	Ir^{192} (n=14)	Placebo (n=14)	Ir^{192} (n=27)	Placebo (n=20)	
Restenosis (%)	20.3	57.1	0.000	0	42.9	5.9	66.7	28.6	46.2	30.4	61.1	NS
One-year TVR (%)	27.7	67.7	0.000	16.7	44.4	22.2	81.8	28.6	78.6	33.3	55.0	NS
Delayed thrombosis (%)	7.7	4.6	NS	0	0	0	0	7.1	0	14.8	15.0	< 0.05

Values are expressed as percentages. TVR = target vessel revascularization. Other abbreviations as in table I.

additional stenting; 2 of the latter patients were admitted with acute myocardial infarction; in the remaining 3 patients vessel occlusion was asymptomatic. In the placebo group the 3 cases of delayed thrombosis (4.6%, p = 0.71 vs ICB) all occurred in the re-stenting group and were asymptomatic. ICB as an adjunctive therapy in the overall population of patients with in-stent restenosis was not correlated with an increased risk of delayed thrombosis; additional stent implantation, either alone in the overall population (RR 12.36, 95% CI 1.56÷94.43, p < 0.01) or followed by ICB (RR 3.80, 95% CI 1.02÷14.27, p < 0.05), was significantly correlated with an increased risk of delayed thrombosis (Fig. 2).

Discussion

The present study shows that ICB with γ-radiation is effective in reducing the recurrence after in-stent restenosis, mainly in extensive lesions previously treated with ablation devices; additional stent implantation as a treatment strategy for in-stent restenosis may increase the risk of delayed thrombosis, mostly when used in association with ICB.

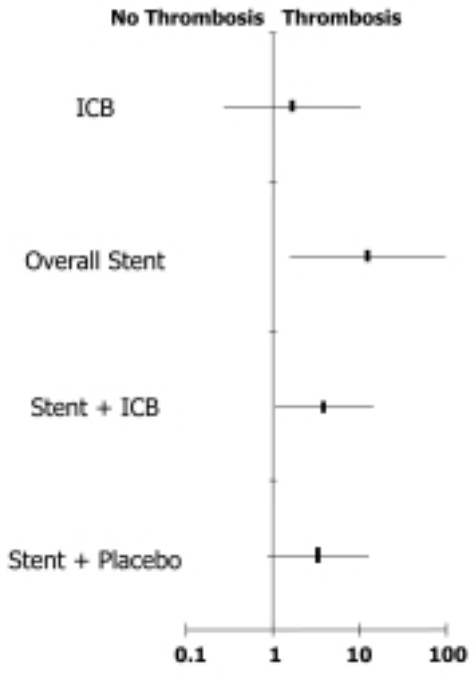

Figure 2. *Relative risks (95% confidence intervals) of the occurrence of delayed thrombosis for various treatment strategies. ICB = intracoronary brachytherapy.*

Radiation and conventional devices in the treatment of in-stent restenosis. The recurrence of in-stent restenosis is the result of neointima tissue proliferation[3]. Several percutaneous strategies have been tried: neointima extrusion with conventional balloon angioplasty, tissue removal with atherectomy or laser and lumen scaffolding with additional stent deployment, although safe and effective in discrete lesions, have been documented to have disappointing high rates of recurrence when applied to extensive lesions[4-9].

Endovascular γ-radiation therapy as an adjunct to traditional strategies has recently emerged as a promising option for the reduction of both balloon and stent restenosis[10-12]. Serial experimental observations showed a dramatic inhibition of endoluminal neointima formation in models of balloon-overstretch angioplasty and endovascular radiation[16].

The treatment of restenosis with vascular radiation appears to work through the inhibition of smooth muscle cell proliferation. The energy emitted from an active isotope is believed to block mitosis by causing a double-stranded break in the cell's DNA[17,18].

The WRIST trial was addressed to a high risk population, as 88% of patients had unstable angina, 43% had iterative in-stent restenosis, and 74% of lesions were extensive[11]: γ-radiation, used as an adjunctive therapy, resulted in a dramatic reduction in both the angiographic and clinical recurrences. Intravascular ultrasound studies from both the SCRIPPS[10] and WRIST trials documented that ICB significantly decreased neointima formation.

Recently, our group observed that there was no difference in survival among patients regardless of the device used in the coronary intervention. The results of this study support the notion that γ-radiation can be an equalizing factor for all the device used, and due to its robust inhibitory effect on neointima formation, radiation masks mild differences which may be related to device selection[19].

The present study confirmed that ICB was effective in that it resulted in a reduction in late loss as evaluat-

ed at quantitative angiographic analysis. Similarly, in the BERT trial a loss index as low as 4% has been reported in the group of patients receiving β-radiation after successful PTCA[20]. In our study the most striking results have been documented in the RA group, with an absolute 70% reduction in late loss in the Ir^{192} compared to the placebo arm. The ELCA + Ir^{192} subgroup had a slightly lower efficacy, with a 50% reduction in late loss (p = NS), but the extensive use of excimer laser in saphenous graft vein lesions may have flawed the results. We are not aware of any study which has reported the effectiveness of such a synergic strategy in which the acute gain obtained through tissue removal with ablation is maintained through adjunctive ICB. No coronary perforations or pseudoaneurysms were reported. The promising results obtained by combining atheroablation with ICB need to be confirmed in larger trials.

We could speculate that, in patients with moderate neointima proliferation and discrete in-stent restenosis, a conservative approach with PTCA followed by ICB seems a safe strategy, provided provisional stenting carries a high risk of delayed thrombosis; in patients with extensive neointima hyperplasia the effectiveness of tissue removal with atheroablative devices is enhanced by the subsequent inhibition of tissue healing with ICB that "freezes" the result obtained at the end of the procedure.

Radiation-related delayed complications. The initial enthusiasm for coronary vascular radiotherapy was dampened by reports of target lesion thrombosis, particularly thrombosis occurring late (> 30 days) after treatment[21]. In early trials, delayed thrombosis after brachytherapy was universally encountered, with an incidence of 3 to 10% independent of the isotope and delivery system tested.

Among patients enrolled in various β and γ ICB trials for in-stent restenosis, our group documented a 9.1% delayed occlusion rate in the irradiated group; additional stent implantation was the main independent predictor of delayed thrombosis[22].

Costa et al.[23] were the first authors to describe 6 cases of coronary occlusion late after β-radiation. There is evidence from animal studies that radiation induces thrombosis and that the thrombosis rate is related to the dose[24]. Even if comparisons between different doses and modalities of ICB cannot be made, in view of its clinical relevance the concern on delayed thrombosis after ICB remains. Condado et al.[25] described two silent episodes of thrombosis among 21 patients treated with γ-radiation after PTCA. Similarly, Tierstein et al.[26] reported a case of stent thrombosis after ICB in a patient who discontinued antiplatelet therapy. In the BETA WRIST trial, among 50 patients treated with β-radiation for in-stent restenosis, two delayed occlusions were documented[27]. There are several mechanisms deemed responsible for the occurrence of thrombosis after ICB: inhibition of neointima formation, delayed healing of the dissection as well as the lack of re-endothelization inside the stent struts[28]. In the present study, additional stent deployment followed by ICB was identified as the scenario at the highest risk of delayed thrombosis. Additional stent implantation adversely influenced the occurrence of thrombosis in the overall population. Re-stenting has been described as an effective primary strategy for the treatment of in-stent restenosis[29]; however, Elezi et al.[30] reported a delayed occlusion rate (6.8%) similar to that described in the present study when stents were used on a provisional basis without adjunctive brachytherapy. In our series, apart from additional stent implantation, only one delayed occlusion occurred in a patient in the radiation group after laser angioplasty, but the fact that antiplatelet therapy was withdrawn can be considered responsible. During the study, ticlopidine was administered for only 1 month after additional stent implantation; in patients with impaired stent endothelization a longer period (at least 6 months) of full antiplatelet therapy with aspirin + thienopyridines is now mandatory. In the WRIST PLUS study a period of 6 months of therapy with aspirin + clopidogrel after adjunctive ICB for in-stent restenosis was well tolerated and resulted in a reduced delayed thrombosis rate[31].

Limitations of the study. The WRIST study was not specifically designed to test the effectiveness of γ-radiation combined with different percutaneous devices and an operator-dependent bias clearly occurred in the selection of these strategies. Therefore these results cannot be generalized.

A 6-month follow-up is too short to draw definitive conclusions on the absolute efficacy of ICB; however, there actually are reports documenting the safety and effectiveness of this strategy with a 2-year follow-up[25,26].

Delayed thrombotic occlusion was not included as an endpoint, even if mortality, morbidity and repeat target revascularization at 6 months were primary endpoints. Moreover, the study was not designed to test any efficacy in employing an antiplatelet strategy for the prevention of thrombotic occlusion.

In conclusion, intracoronary γ-radiation as an adjunctive strategy in the treatment of patients with in-stent restenosis is associated with a significant clinical benefit at 1-year of follow-up. The reduction in the rate of in-stent restenosis is obtained through a significant reduction in late loss, that is more evident in patients undergoing extensive mechanical plaque ablation. In the setting of ICB, additional stents should be cautiously deployed due to an extremely high rate of delayed thrombosis; regardless of the possibility or otherwise of avoiding re-stenting, prolonged full antiplatelet therapy is mandatory.

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