

Comparison of angiographic and clinical outcomes between rotational atherectomy and cutting balloon angioplasty followed by radiation therapy with a rhenium 188–mercaptoacetyltriglycine–filled balloon in the treatment of diffuse in-stent restenosis

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Background Rotational atherectomy (RA) and cutting balloon angioplasty (CBA) have been shown to effectively dilate in-stent restenosis (ISR). It is not known, however, which of these technique, when followed by β -radiation, is more effective. Therefore, we performed a prospective randomized study comparing RA and CBA before β -radiation therapy for diffuse ISR.

Methods Patients with diffuse ISR were randomly assigned to receive RA (group 1, $n = 58$) or CBA (group 2, $n = 55$) before β -radiation therapy with a rhenium 188–mercaptoacetyltriglycine–filled balloon, with the radiation dose being 18 Gy at a depth of 1.0 mm into the vessel wall. The primary end point was angiographic restenosis at 6 months, and the secondary end point was major adverse cardiac events (myocardial infarction, death, target lesion revascularization) at 9 months.

Results The 2 groups were similar in baseline characteristics. Mean lesion length was 21.0 ± 11.2 mm in group 1 and 20.8 ± 10.2 mm in group 2 ($P = .77$). Radiation was delivered successfully to all patients. We obtained 6-month angiographic follow-up in 90 patients (80%). The rates of angiographic restenosis were 14.9% (7 of 47) in group 1 and 14.0% (6 of 43) in group 2 ($P = .89$). No patient experienced myocardial infarction or death during the 9-month follow-up period. Rates of target lesion revascularization or major adverse cardiac events were 3.4% in group 1 and 3.6% in group 2 ($P = .94$) during the 9-month follow-up.

Conclusions Either RA or CBA, followed by β -radiation using a rhenium 188–mercaptoacetyltriglycine–filled balloon, is equally safe and effective for diffuse ISR in 6-month angiographic and 9-month clinical outcomes. (*Am Heart J* 2005;150:577-82.)

In-stent restenosis (ISR) develops in a significant proportion of patients after intracoronary stenting, particularly in those with multiple or long stents. In-stent restenosis remains an important clinical problem because the recurrence rate is high with conventional angioplasty, especially in diffuse ISR.^{1,2} When compared with con-

ventional treatment, intracoronary brachytherapy with γ - or β -irradiation in patients with diffuse ISR was recently shown to dramatically reduce the recurrence rate.³⁻⁵

Debulking therapies using excimer laser angioplasty or rotational atherectomy (RA) have been reported to yield better immediate angiographic results than balloon angioplasty through the removal of neointimal tissue.⁶ We previously reported results from 50 patients with diffuse ISR who underwent β -radiation using a rhenium 188–mercaptoacetyltriglycine (¹⁸⁸Re-MAG₃)-filled balloon after RA, showing that, at 6 months, the restenosis rate was 10% and the late loss index was 0.17.⁷

Recently, cutting balloon angioplasty (CBA), which has some theoretical advantages over balloon angioplasty, including the avoidance of balloon slippage, increased postintervention minimal lumen diameter, and inhibition of neointima proliferation, has been shown to effectively dilate the ISR.⁸⁻¹¹ One nonrandomized study demonstrated that the combination of CBA and β -radiation was

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effective in treating diffuse ISR.¹² A recent registry study reported the data on 878 patients who underwent either CBA (n = 166) or balloon angioplasty (n = 712) before β -radiation, in which CBA and β -radiation provided better 6-month clinical outcomes in patients with ISR compared with balloon angioplasty and β -radiation.¹³ However, because the synergistic effects of CBA before β -radiation therapy have not been sufficiently evaluated, we performed a prospective randomized study comparing RA and CBA before β -radiation therapy to identify the more effective treatment modality for diffuse ISR.

Methods

Study group

We enrolled 113 consecutive patients scheduled for radiation for diffuse ISR between June 2001 and January 2003. Eligible patients were randomly assigned to receive RA (group 1, n = 58) or CBA (group 2, n = 55) before β -radiation therapy with a ¹⁸⁸Re-MAG₃-filled balloon. Inclusion criteria were diffuse ISR (lesion length >10 mm, diameter stenosis >50%) in a native coronary artery with angina, demonstrable myocardial ischemia, and written informed consent. Exclusion criteria included acute myocardial infarction (MI) \leq 72 hours before treatment, poor renal function (serum creatinine >3.0 mg/dL), pregnancy, contraindication to antiplatelet therapy, and concomitant serious disease with expected survival of <2 years. In patients with multivessel ISR, only one lesion was treated with radiation therapy. Additional new stent implantation was strongly discouraged, although not contraindicated. The study was approved by our institutional review board.

Pretreatment before β -radiation

Either RA and adjunctive balloon angioplasty or CBA was performed to obtain an optimal angiographic result (diameter stenosis <20%). For RA, single-burr approach was preferred, and burr size was determined to obtain burr/artery ratio about 0.7. Cutting balloon diameters ranged from 2.5 to 4.0 mm depending on original stent size. For long lesions, tandem balloon inflations were performed, with the maximum inflation pressure of the cutting balloon being 14 atmospheres. All patients were pretreated with aspirin 200 mg/d, clopidogrel 75 mg/d, and cilostazol 200 mg/d for 2 days. After irradiation, clopidogrel was given for 1 month, but aspirin and cilostazol were administered for >6 months.

Radiation delivery system, dosimetry, and procedure

The methods of brachytherapy have been described previously.⁷ The delivery system was a ¹⁸⁸Re-MAG₃-filled angioplasty balloon. Liquid ¹⁸⁸Re is a high-energy β -emitter that is available daily from a ¹⁸⁸W/¹⁸⁸Re generator (Oak Ridge National Laboratory, Oak Ridge, Tenn). We obtained coronary angiograms at each step to determine the actual segment treated with atherectomy or cutting balloon. The long conventional balloon (30 and 40 mm in length; Boston Scientific Corporation, San Jose, Calif), which was identical to that used for the dosimetric study, was selected to cover a proximal and distal uninjured margin of at least 5 mm. For long ISRs (>30 mm), which could not be covered by a single long balloon, manual stepping was

permitted, with minimal overlapping. From the dosimetry data, the irradiation time was calculated so as to deliver 18 Gy at 1.0 mm deep into the vessel wall from the balloon/artery interface. Fractionation was allowed in cases with severe angina or significant hemodynamic instability.

All patients were clinically evaluated during office visits at 1, 3, 6, and 9 months after brachytherapy. A repeat coronary angiogram was performed at 6 months after irradiation, or earlier if clinically indicated.

IVUS imaging protocol

Postintervention and follow-up intravascular ultrasound (IVUS) studies were performed in identical fashion. Intracoronary 0.2-mg nitroglycerin was administered. The ultrasound (US) catheter was advanced approximately 10 mm beyond the lesion site, and an imaging run was performed from beyond the lesion site to the aorto-ostial junction. Studies were performed with a commercially available system (Boston Scientific Corporation/Cardiovascular Imaging System, Inc) which used a 30-MHz single-element beveled transducer mounted on the end of a flexible shaft and rotated at 1800 rpm within a 3.2-F short monorail imaging sheath. With this system, the transducer was withdrawn automatically at 0.5 mm/s to perform the imaging sequence. Ultrasound studies were recorded on 1/2-in high-resolution s-VHS tape for off-line analysis. The postintervention IVUS imaging run was the final step in the intervention procedure. A follow-up IVUS imaging run was performed before any subsequent intervention.

Quantitative coronary angiography analysis

Coronary angiograms were analyzed by 2 experienced angiographers using an online quantitative coronary angiography system (ANCOR version 2.0, Siemens, Germany). Angiographic measurements were made during diastole after intracoronary nitroglycerin administration, using the guiding catheter for magnification calibration. Single matched views with the worst minimal lumen diameter and reference vessel diameter were compared. The reference vessel defined as the vessel segment 5 mm proximal and distal to the radiation sources was also compared. Lesion length was determined by the "shoulder-to-shoulder" extent of narrowing in the view with the least amount of foreshortening.

Quantitative IVUS measurements

Measurements were performed according the American College of Cardiology clinical expert consensus document on standards for acquisition, measurement, and reporting of intravascular US studies.¹⁴ Measurements included external elastic membrane (EEM), stent, lumen, plaque and media (P&M = EEM - lumen), and intimal hyperplasia (IH = stent - lumen) cross-sectional areas (CSA). Intimal hyperplasia burden (%) was defined as $100 \times (\text{IH}/\text{stent CSA})$. Serial IVUS comparisons between postintervention and 6-month follow-up were available in 42 of 58 patients in group 1 and 39 of 55 in group 2.

On playback of the postintervention and follow-up IVUS studies, the matching (postintervention and follow-up) IVUS image slices were acquired at 3 different sites of the nonstented adjacent segment at 1, 2, and 4 mm from the stent margin and at 5 equidistant sites within the stented segment. In practice, the 6-month follow-up target slices were first analyzed; then

Table I. Baseline characteristics of the study patients

Characteristics	Group 1 (n = 58)	Group 2 (n = 55)	P
Age (y)	58 ± 9	59 ± 10	.52
Male sex (%)	36 (62%)	37 (67%)	.69
Risk factors (%)			
Hypertension	21 (36%)	18 (33%)	.84
Diabetes mellitus	20 (34%)	14 (26%)	.31
Total cholesterol ≥200 mg/dL	13 (22%)	14 (26%)	.83
Current smoker	11 (19%)	15 (27%)	.37
Prior MI	1 (2%)	4 (7%)	.20
Unstable angina	19 (33%)	14 (26%)	.42
Left ventricular ejection fraction (%)	60 ± 7	62 ± 8	.22

the distance from each target slice to the closest identifiable axial landmark (ie, stent edge) was measured (using seconds or frames of videotape). Finally, this distance was used to identify the corresponding slices on the postirradiation IVUS studies. Vascular and perivascular markings were also used to confirm image slice identification. When necessary, the analysis was done side-by-side and the imaging runs were studied frame-by-frame to ensure that matching image slices were measured.

Primary and secondary end points

The primary end point was the angiographic incidence of restenosis (diameter stenosis >50%) by quantitative coronary angiography. The secondary end point was the occurrence of any major adverse cardiac event (MACE), including death, nonfatal MI, and repeat revascularization, during the 9-month follow-up period. Myocardial infarction was diagnosed when creatine kinase-MB was elevated ≥3-fold, with chest pain lasting >30 minutes, or with the appearance of new electrocardiographic changes.

Statistical analysis

The sample size was determined to give the study a power of 80% to detect 20% difference in restenosis rate with a *P* value of .05. Data are expressed as mean ± SD for continuous variables and as frequencies for the categorical variables. The differences between groups were assessed by χ^2 test or Fisher exact test for categorical variables and by paired or unpaired *t* test for continuous variables. A *P* value of < .05 was considered statistically significant.

Results

Baseline characteristics

The baseline clinical and angiographic characteristics of the patients are summarized in **Tables I and II**. There were no significant differences between the 2 groups with respect to any of these characteristics.

Inhospital outcomes and procedural results

Radiation therapy was successfully delivered to all patients. No in-hospital events, including stent throm-

Table II. Angiographic characteristics at baseline and 6 months

Characteristics	Group 1 (n = 58)	Group 2 (n = 55)	P
Artery treated			.76
Left anterior descending artery	43 (74%)	38 (69%)	
Left circumflex artery	5 (9%)	7 (13%)	
Right coronary artery	10 (17%)	10 (18%)	
Lesion length (mm)	21.0 ± 11.3	20.8 ± 10.2	.92
Reference vessel diameter (mm)	2.9 ± 0.4	2.9 ± 0.5	.67
Rotational atherectomy			
Mean burr size (mm)	2.0 ± 0.2		
Burr/artery ratio	0.69 ± 0.09		
Adjunctive balloon to artery ratio	1.08 ± 0.16		
Cutting balloon angioplasty			
Mean balloon diameter (mm)		3.33 ± 0.39	
Balloon to artery ratio		1.18 ± 0.19	
Radiation therapy			.43
Length of irradiated segment (mm)	39.9 ± 11.4	38.3 ± 11.7	
Overlap of balloons	9 (16%)	8 (15%)	.89
Fractionation	7 (12%)	6 (11%)	.85
Exposure time (s)	188.3 ± 89.5	180.4 ± 88.7	.64
Minimal lumen diameter (mm)			
Before intervention	0.76 ± 0.37	0.84 ± 0.41	.30
Immediately after intervention	2.59 ± 0.39	2.69 ± 0.53	.30
At 6 m	2.01 ± 0.66	2.22 ± 0.68	.15
Immediate gain (mm)	1.79 ± 0.54	1.85 ± 0.60	.58
Late loss (mm)	0.35 ± 0.52	0.54 ± 0.60	.25
Late-loss index	0.19 ± 0.36	0.29 ± 0.36	.34
Binary restenosis (%)	14.9 (7/47)	14.0 (6/43)	.89

bolism, Q-wave MI, emergency bypass surgery, or death, occurred in either group, and no patient had a creatine kinase-MB level of >3 times the baseline value.

Additional stenting during radiation therapy was performed in 8 patients (7.1%), 4 in group 1 and 4 in group 2. All 4 patients in group 1 required additional stenting for dissection. In group 2, 1 patient required additional stenting for dissection, whereas 3 patients required additional stenting for angiographic diameter stenosis >20%.

Angiographic results

Quantitative angiographic data are shown in **Table II**. At baseline, the minimal lumen diameter of the target vessel and reference artery diameter did not differ between the 2 groups. Postintervention (2.59 ± 0.39 mm in group 1 vs 2.69 ± 0.53 mm in group 2, *P* = .30) and follow-up (2.01 ± 0.66 mm in group 1 vs 2.22 ± 0.68 mm in group 2, *P* = .15) minimal lumen diameters did not differ significantly between the 2 groups. In

Table III. IVUS findings at postradiation and 6 months

	Group 1 (n = 42)	Group 2 (n = 39)	P
Postradiation			
Distal segment			
Mean EEM CSA (mm ²)	11.5 ± 4.3	13.1 ± 3.2	.054
Mean lumen CSA (mm ²)	6.0 ± 2.5	6.9 ± 1.9	.085
Mean P&M CSA (mm ²)	5.5 ± 2.5	6.3 ± 1.7	.098
Stented segment			
Mean stent CSA (mm ²)	8.1 ± 2.3	8.8 ± 1.9	.112
Mean lumen CSA (mm ²)	5.9 ± 1.9	6.3 ± 1.5	.267
Mean IH CSA (mm ²)	2.1 ± 0.8	2.4 ± 0.8	.082
Mean IH burden (%)	26 ± 7	28 ± 7	.369
Proximal segment			
Mean EEM CSA (mm ²)	16.7 ± 5.3	16.9 ± 5.3	.797
Mean lumen CSA (mm ²)	8.7 ± 3.9	8.3 ± 2.7	.622
Mean P&M CSA (mm ²)	8.0 ± 2.2	8.7 ± 2.4	.208
6-m follow-up			
Distal segment			
Mean EEM CSA (mm ²)	11.6 ± 4.3	13.2 ± 3.3	.64
Mean lumen CSA (mm ²)	5.9 ± 2.5	6.7 ± 2.3	.170
Mean P&M CSA (mm ²)	5.7 ± 2.4	6.5 ± 1.8	.074
Stented segment			
Mean stent CSA (mm ²)	8.1 ± 2.3	8.8 ± 1.9	.109
Mean lumen CSA (mm ²)	5.8 ± 1.9	6.2 ± 1.8	.382
Mean IH CSA (mm ²)	2.3 ± 1.1	2.7 ± 1.2	.125
Mean IH burden (%)	28 ± 11	30 ± 12	.414
Proximal segment			
Mean EEM CSA (mm ²)	16.7 ± 5.3	16.9 ± 4.2	.865
Mean lumen CSA (mm ²)	8.5 ± 3.8	8.1 ± 2.7	.634
Mean P&M CSA (mm ²)	8.2 ± 2.6	8.8 ± 2.7	.365

addition, immediate gain, late loss, and loss index were not different between the 2 groups.

IVUS analysis

IVUS data are shown in Table III. There were no statistically significant differences in postintervention IVUS variables between 2 groups. At 6-month follow-up, there was no significant difference in stent CSA, lumen CSA, IH CSA or percent IH CSA between 2 groups. In both groups, Δ lumen CSA (-0.1 ± 0.7 mm² in group 1 vs -0.2 ± 0.9 mm² in group 2, $P = .753$), Δ IH CSA (0.1 ± 0.7 mm² in group 1 vs 0.2 ± 0.9 mm² in group 2, $P = .792$), and Δ IH burden ($1.5 \pm 10.1\%$ in group 1 vs $2.2 \pm 10.9\%$ in group 2, $P = .740$) were not statistically different.

Primary and secondary end point

We obtained angiographic follow-up in 90 patients (80%), 47 in group 1 and 43 in group 2. Rates of angiographic restenosis were 14.9% (7 of 47) in group 1 and 14.0% (6 of 43) in group 2 ($P = .89$). The locations of the restenosis were similar, with 6 patients in group 1 and 5 in group 2 having restenosis within the irradiated segment, and 1 patient in group 1 and 2 in group 2 having restenosis at the distal edge of irradiation. One patient in group 2 had restenotic lesions in both the

irradiated segment and distal edge. The pattern of restenosis in both groups included 5 diffuse ISRs (3 in group 1, and 2 in group 2), 6 focal ISRs (3 in group 1, and 3 in group 2), and 2 edge restenoses (1 in group 1, and 1 in group 2). The incidence of geographic miss during index procedure was higher in group 1 (9 of 58, 15.5%) than group 2 (2 of 55, 3.6%, $P = .54$), although not to a statistically significant level. One edge restenosis at 6-month follow-up occurred in the irradiated edge, which was associated with geographic miss. We obtained angiographic follow-up in 6 of the 8 patients who underwent additional stenting, with restenosis noted in 1 patient (16%), an incidence of restenosis comparable to that in patients without additional stenting (12%, 10 of 82) ($P = .54$).

Nine-month clinical follow-up data were available in all patients. There was no cardiac death or nonfatal MI. Two patients in each group required target lesion revascularization, all of whom received repeated intervention. Therefore, the risk of a target lesion revascularization or a MACE was similar in both groups (3.4% in group 1 vs 3.6% in group 2, $P = .94$) during the 9-month follow-up period.

Discussion

The major finding of this study is that, for diffuse ISR, both RA and CBA, together with β -irradiation using a ¹⁸⁸Re-MAG₃-filled balloon, are equally safe and have similarly good 9-month clinical and 6-month angiographic outcomes. These findings indicate that both treatment strategies are valuable therapeutic options for the reduction of recurrent restenosis in patients with diffuse ISR.

A number of treatment strategies for diffuse ISR have been investigated to reduce recurrent restenosis. Diffuse ISR, however, has a relatively high rate of recurrence.¹⁵⁻¹⁷ Use of intracoronary radiation therapy in patients with ISR has demonstrated reduction of angiographic restenosis and subsequent target lesion revascularization.^{4,5,18} Although several studies of intracoronary radiation therapy have reported much reduced recurrence rates compared with conventional treatment, the restenosis rates still ranged from 19% to 45% even after radiation therapy.^{3-5,12,18} Therefore, current efforts have been aimed largely at lowering the rates of recurrent restenosis and clinical events, by avoidance of additional stenting and geographic miss, and by prolonged antiplatelet therapy.

It has been hypothesized that device selection before radiation therapy would influence short- and long-term results. Recently, previous studies have assessed the effect of device selection before radiation therapy on clinical and angiographic outcomes and provided conflicting results. The results from the START using β -radiation with strontium 90 (18.4 or 23 Gy at 2 mm from

source axis) and the γ -radiation trials using iridium 192 (15 or 18 Gy at 2 mm from the source) did not show any impact of device selection in combination with radiation therapy on recurrent restenosis in patients with ISR.^{19,20} However, START trial using β -radiation showed that in patients with diffuse ISR >15 and >19 mm in length, debulking with radiation group had a lower restenosis rate than non-debulking with radiation group, although not to a statistically significant level. Limitations of previous 2 studies^{19,20} are that they were not designed to evaluate the effect of device selection before radiation therapy, performed in a retrospective manner with uneven distribution of number of study population. Recently, results from the RENO registry using β -radiation showed that CBA before β -radiation improved the target lesion revascularization (10.2% vs 16.6%, $P = .04$) and MACEs (10.8% vs 19.2, $P = .01$) than conventional balloon angioplasty before β -radiation in patients with ISR.¹³ These inconsistent results of the role of pretreatment device may be attributed to different types of radiation sources, delivery methods, and interventional devices.

Compared with γ -radiation, low penetration depth and rapid reduction of β -radiation energy within 2 to 5 mm may be associated with an inhomogeneous dose delivery.²¹ Furthermore, up to 15% attenuation of radiation doses by stent struts has been reported.²² Theoretically, therefore, plaque reduction in an ISR lesion can improve the penetration of radiation to the target tissue. In this regard, we have reported that β -radiation using a ¹⁸⁸Re-MAG₃-filled balloon (15 Gy at 1 mm from balloon surface) after RA has a low recurrent restenosis rate (10%) and late loss index (0.17).⁷ In the present study as well, the patients who underwent RA before β -radiation had a similar restenosis rate (14.9%) and late loss index (0.19), thus confirming the effectiveness of β -radiation after RA. These results, in addition to the theoretical advantage of plaque reduction by RA before β -radiation, may be explained, in part by the unique balloon centering system used here. Filling of a conventional balloon catheter with liquid ¹⁸⁸Re-MAG₃ provides self-centering radiation independent of the bending of the coronary artery, cardiac motion, and stenosis morphology.²³ When the size of the radiation balloon was matched to that of the coronary artery, direct contact between the radiation source and the inner vessel wall can occur, delivering more homogeneous and exact radiation energy to the in-stent restenotic lesion. START trial showed the lower incidence of restenosis after debulking plus β -radiation therapy in patients with diffuse ISR >15 and >19 mm in length, but in contrary to our results, it did not demonstrate the advantage of debulking in β -radiation therapy to a statistically significant level. This might be explained by the relatively higher dose and subsequent deeper penetration of radiation using β -radiation with strontium 90 (18.4 or

23 Gy at 2 mm from source axis). Debulking may not be critically important in β -radiation therapy with high dose and subsequent high penetration depth.

RA and CBA, both of which have been shown to effectively dilate ISR lesions, have been shown to be safe treatment modalities for ISR.^{8-11,17} Compared with RA, CBA provided larger postintervention minimal lumen diameters and inhibition of neointima proliferation in patients with ISR,^{10,11} but it is not clear whether this difference would also apply when combined with radiation. In the present study, we observed no significant between-group differences in angiographic restenosis and target lesion revascularization. Furthermore, IVUS analysis of the current study showed the small, nonsignificant change of IH burden within the stent during the follow-up period in both groups, which suggests that either RA or CBA, followed by β -radiation using a ¹⁸⁸Re-MAG₃-filled balloon is equally effective modalities to inhibit IH in patients with diffuse ISR.

In nonstented native lesions, after CBA, 55% of luminal enlargement was due to plaque compression and 45% was due to vessel expansion, whereas, after balloon angioplasty, 33% of luminal enlargement was due to plaque compression and 67% was due to vessel expansion,²⁴ indicating plaque compression was predominant mechanism of luminal enlargement with CBA. The previous intravascular US evaluation of the mechanism of lumen enlargement during CBA treatment of ISR showed that it was due entirely to in-stent neointima tissue reduction by neointimal hyperplasia extrusion through stent struts⁸ and its redistribution within enlarged stent²⁵ without the significant change of plaque burden external to stent, representing a significant decrease in plaque thickness within stent. Therefore, sufficient plaque compression of CBA may be attributed to facilitating penetration of the exact radiation dose to the target tissue. Moreover, further suppression of neointima proliferation by β -radiation therapy may reduce the differences of the effect of pretreatment devices before β -radiation therapy in this study, indicating both treatment strategies are useful tools for the prevention of recurrent restenosis in patients with diffuse ISR.

In conclusion, CBA and RA appear equally effective modalities to treat diffuse ISR in addition to intracoronary β -radiation using a ¹⁸⁸Re-MAG₃-filled balloon. From the viewpoint of technical simplicity, CBA could be a good substitute for RA in preparing patients with diffuse ISR for brachytherapy.

This study has several limitations. First, although it was a prospective randomized study, the number of patients was small to confirm the impact of device selection before radiation therapy, even if one exists. However, we performed serial IVUS analysis, resulting in similar changes of IH after radiation therapy, which may

counterbalance our limitation. Second, results using a $^{188}\text{Re-MAG}_3$ -filled balloon for β -radiation therapy cannot be extrapolated to other types of radiation sources, delivery methods, radiation doses, and interventional devices. Third, the clinical follow-up was only 9 months and the previous studies have shown a late “catch-up” restenosis phenomenon after brachytherapy.^{26,27} Therefore, longer-term follow-up study may be needed to elucidate the similar effectiveness of 2 treatment strategies. Fourth, we could not prove the efficacy of RA or CBA before β -radiation therapy in patients with diffuse ISR because of the lack of control group including brachytherapy after balloon angioplasty and balloon angioplasty alone groups.

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