

Intravascular Brachytherapy Versus Drug-Eluting Stents for the Treatment of Patients With Drug-Eluting Stent Restenosis

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Drug-eluting stents (DESs), although promising technology, still are associated with restenosis; therefore, we evaluated the safety and efficacy of intravascular radiation therapy for the treatment of DES in-stent restenosis (ISR). Treatment of DES ISR has not been established, although intravascular radiation therapy is an effective treatment for patients with ISR of bare metal stents. Other modalities are conventional percutaneous coronary intervention (PCI), including restenting with DES. Radiation for Eluting Stents in Coronary FailUrE (RESCUE) is an international, Internet-based registry of 61 patients who presented with ISR of a DES and were assigned to intravascular radiation therapy with commercially available systems after PCI. Outcomes of these patients were compared with those of a consecutive series of 50 patients who presented with ISR of a DES and were assigned to repeat DES (r-DES) treatment. Baseline clinical and angiographic characteristics were similar between groups, except for more Cypher stents as the initial DES that restenosed in the r-DES group than in the intravascular radiation therapy group (88.5% vs 69%, $p = 0.01$). At 8 months there were fewer overall major adverse cardiac events in the intravascular radiation therapy group compared with the r-DES group (9.8% vs 24%, $p = 0.044$). The need for target vessel and target lesion revascularizations was similar in the 2 groups at 8 months. There has been no report of subacute thrombosis in either group. In conclusion, intravascular radiation therapy as adjunct therapy to PCI for patients presenting with ISR of a DES is safe and should be considered an alternative therapeutic option for this difficult subset of patients. © 2006 Elsevier Inc. All rights reserved. (Am J Cardiol 2006;98:1340–1344)

Drug-eluting stents (DESs) have proved to significantly decrease restenosis and the need for recurrent intervention compared with bare metal stents in pivotal trials.^{1–3} However, recurrence rates for more complex subsets of patients and lesions were higher and ranged from 17% to 50%.^{4–9} Causes of restenosis after implantation of bare metal stents and DESs are fundamentally similar: mechanical deformation of the stent, underexpansion, and neointima formation. The relative contributions of individual factors to the development of clinical restenosis, however, may differ and include resistance to the drug or inflammatory reaction to the polymer. Intracoronary radiation therapy for in-stent restenosis (ISR) of bare metal stents in native coronary arteries and saphenous vein grafts has substantially decreased the rate of recurrent restenosis compared with conventional percutaneous coronary intervention (PCI).^{10–13} The primary objectives of the present study were to assess the safety and effectiveness of vascular brachytherapy for patients with recurrent ISR after DES implantation. The secondary objective was to compare the outcome of intravascular radiation

therapy with repeat DES (r-DES) implantation for patients who presented with ISR of a DES.

Methods

Patient population: Since June 2002, 61 patients from 8 independent centers who underwent previous DES implantation, presented with recurrent anginal symptoms and/or angiographic documentation of ISR of the DES, and underwent PCI with adjunct brachytherapy were enrolled into an Internet-based registry, Radiation for Eluting Stents in Coronary FailUrE (the RESCUE registry). DES ISR was defined as a significant luminal stenosis (>50% diameter stenosis by visual estimate). The main inclusion criteria for the registry were patients >18 years of age who presented with stable or unstable angina, with documentation of ischemia, and with angiographic presentation of a restenotic lesion within ≥ 1 DES. The main exclusion criteria were patients who presented with ST-elevation myocardial infarction, cardiogenic shock, or visual thrombus involved in the stented segment, and those who were unable to take long-term antiplatelet therapy. These 61 patients were compared with 50 consecutive patients from Washington Hospital Center (Washington, DC) who met the inclusion/exclusion criteria and subsequently underwent PCI with additional DES implantation.

Vascular brachytherapy details: Selection of the radiation system was at the operator's discretion and was de-

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pendent on the system's availability. The following radiation systems and radiation doses were used in the registry: the Beta Rail system (Novoste, Norcross, Georgia), which had a strontium-90/yttrium- β source with a prescription dose of 18 to 23 Gy 2 mm from the center of the source based on vessel diameter, was used in 35 patients (56.5%); the Galileo system (Guidant, Santa Clara, California), which had a phosphorus-32 β source with a prescription dose of 20 Gy 1 mm from the balloon surface into the vessel wall, was used in 24 patients (38.7%); and the Checkmate system (Cordis, Miami, Florida), which had a γ source of iridium-192 with a dose of 15 Gy 2 mm from center of the source, was used in 3 patients (4.8%). Radiation therapy was performed after conventional PCI, with coverage of the treated segment and ≥ 5 mm from the injured segment.

DES systems (initial and repeat DES): Most DES restenoses occurred in patients who initially received the sirolimus-eluting stent, Cypher (Cordis), 43 (70.5%) in the vascular brachytherapy group and 44 (88%) in the r-DES group. With the paclitaxel-eluting stent, Taxus (Boston Scientific, Natick, Massachusetts), DES restenosis occurred in 11 patients (18.0%) from the vascular brachytherapy group and in 6 patients (12%) from the DES group. With the paclitaxel nonpolymeric stent, Achieve (Guidant), DES restenosis occurred in only 7 patients (11.5%) from the vascular brachytherapy group. Repeat DES selection was at the operator's discretion. From either of the 2 DES-approved systems for marketing by the Food and Drug Administration, the Cypher stent was implanted in 38 patients and Taxus in 12 patients. Repeat implantation of DES was sized to sufficiently cover from the healthy vessel proximally to the ISR lesion to the healthy vessel distal to the lesion. Among the 52 stents implanted, 10 of the Taxus stents were deployed on restenotic Cypher stents, and 4 Cypher stents were deployed on restenotic Taxus stents.

PCI procedure and anticoagulation therapy: Coronary angioplasty was performed by standard percutaneous techniques using the femoral approach and standard techniques for stent implantation. All patients were pretreated with 325 mg of aspirin orally before PCI and were encouraged to take it indefinitely. Patients were preloaded with 300 to 600 mg of clopidogrel before PCI if not on a maintenance dose, followed by 75 mg/day; and patients were instructed to continue this regimen for ≥ 12 months in the intravascular radiation therapy group and ≥ 6 months in the DES group. During PCI, patients received anticoagulation with bivalirudin (a bolus of 0.75 mg/kg, followed by an intravenous infusion of 1.75 mg/kg/hour) or unfractionated heparin (a bolus of 40 U/kg and additional heparin to achieve activated clotting time of 250 to 300 seconds). Glycoprotein IIb/IIIa inhibitors were administered at the operator's discretion. All patients routinely underwent pre- and postintervention 12-lead electrocardiography.

End points and clinical definitions: Clinical end points were freedom from target vessel revascularization and overall major cardiac adverse events. Major adverse cardiac events were defined as death, Q-wave myocardial infarction, and target vessel revascularization at 8 months. Q-wave myocardial infarction was defined as the presence of

Table 1
Baseline medical history and initial drug-eluting stent characteristics

Variable	IRT	DES	p Value
No. of patients	61	50	
Age (yrs)	61.6 \pm 13.5	62.0 \pm 11.2	0.867
Men	39 (64%)	32 (64%)	0.994
Diabetes mellitus	26 (43%)	22 (44%)	0.884
Smoker	36 (59%)	28 (56%)	0.749
Hypercholesterolemia*	48 (79%)	44 (88%)	0.195
Hypertension†	46 (75%)	39 (78%)	0.749
Previous coronary bypass surgery	22 (36%)	17 (34%)	0.821
Previous PCI	61 (100%)	50 (100%)	—
Previous myocardial infarction	33 (54%)	15 (30%)	0.011
No. of narrowed coronary vessels	1.75 \pm 0.89	1.69 \pm 0.76	0.707
Initial DES			
No. of patients	61	50	
No. of stents	71	52	
Indication for initial DES implantation			
Elective PCI	54 (89%)	46 (92%)	0.751
Acute myocardial infarction	7 (12%)	4 (8%)	0.751
Cypher	49 (69%)	46 (89%)	0.01
Taxus	13 (18%)	6 (12%)	0.31
Achieve	9 (13%)	0	0.01
Average stent size (mm)	2.92 \pm 0.39	3.01 \pm 0.47	0.249
Average stent length (mm)	21.66 \pm 6.68	23.43 \pm 6.96	0.146
Average stents/patient	1.17 \pm 0.41	1.04 \pm 0.20	0.02

* Previous diagnosis of hypercholesterolemia.

† Previous diagnosis of hypertension.

IRT = intravascular radiation therapy.

new pathologic Q waves on the electrocardiogram associated with an increased creatine kinase-MB level ≥ 3 times the upper normal value. Non-Q-wave myocardial infarction was defined as an increased creatine kinase-MB level ≥ 3 times the upper normal value without new Q waves. Target lesion revascularization was defined as a repeat revascularization within the stent or in the 5-mm distal or proximal segments adjacent to the stent. Target vessel revascularization was defined as a revascularization driven by any lesion located in the same previously treated epicardial vessel.

Angiographic success was defined as a final residual stenosis $< 30\%$ with Thrombolysis In Myocardial Infarction flow grade 3 or improved from diagnostic angiogram. Stent thrombosis was adjudicated as angiographic documentation of partial or total stent occlusion with or without the presence of thrombus and was categorized as subacute (after the end of the procedure to 30 days) and late (> 30 days). Presenting ISR lesions were characterized as focal stenosis ≤ 10 mm, diffuse stenosis > 10 mm, or proliferative stenosis within and beyond the stented area.

Clinical follow-up: Patients were followed clinically by telephone contact or office visit. Clinical events were recorded at follow-ups after treatment. Outcomes were measured from the time of intravascular radiation therapy or r-DES implantation. In the radiation group, mean follow-up time was 7.14 \pm 1.81 months, with all patient follow-ups available. Mean follow-up time for the r-DES group was

Table 2
Baseline vessel characteristics

	IRT (n = 62 vessels)	DES (n = 50 vessels)	p Value
Coronary artery			
Left main	3 (5%)	1 (2%)	0.386
Right	17 (27%)	18 (36%)	0.368
Left anterior descending	22 (36%)	19 (38%)	0.846
Left circumflex	12 (19%)	6 (12%)	0.273
Saphenous vein graft	8 (13%)	6 (12%)	0.855
Average vessel treated/patient	1.02 ± 0.13	1.02 ± 0.14	1
Type of restenosis			
Focal	39 (63%)	32 (63%)	0.986
Diffuse	18 (29%)	11 (22%)	0.518
Proliferative	5 (8%)	7 (14%)	0.331
Diameter stenosis (visual)	0.81 ± 0.15	0.84 ± 0.09	0.213

Abbreviation as in Table 1.

8.86 ± 4.23 months, and 100% of follow-ups were available.

Statistical analysis: Results are reported as mean ± SD for continuous variables and as percentages for categorical variables. Student's *t* test was used to compare continuous variables, and chi-square test or Fisher's exact test was used to compare categorical variables. A *p* value <0.05 was considered statistically significant. All reported *p* values are 2-sided.

Results

Baseline clinical characteristics of patients in the RESCUE registry who presented with restenosis of a DES and were treated with intravascular radiation therapy were similar to the 50 patients who were treated with r-DES, although there was a significantly higher incidence of previous myocardial infarction in the radiation arm than in the r-DES arm (Table 1). This group of patients presented with high rates of diabetes (43.2%), smoking (57.7%), and after coronary artery bypass graft surgery (35.1%). The clinical presentation was recurrent angina in 77.1% of the radiation group and 88% in the r-DES group. Interestingly, time to treatment from original DES implantation was shorter in the vascular brachytherapy group than in the DES group (6.08 ± 2.77 vs 8.77 ± 4.9 months, *p* = 0.001). Angiographic characteristics were similar between groups and are presented in Table 2. Most ISR lesions were focal (63.4%); there were no differences for the vessel, vessel location, or complexity of lesions. In contrast, there were differences in devices used for the conventional PCI. Although most vascular brachytherapy lesions were treated with cutting balloons (54%), only 19% of lesions in the r-DES group were treated with cutting balloons. Nearly 39.2% of the r-DES lesions underwent direct stenting. Only 9% of patients in the radiation group underwent stenting with bare metal stents at the time of radiation therapy. The average irradiated length was 45.65 ± 12.09 mm, which is significantly longer than the average r-DES stent length of 17.19 ± 6.69 mm. The average stent size was 3.08 ± 0.36 mm.

Overall, procedural and in-hospital clinical outcomes were free of events, although 2 patients in the vascular

Table 3
Eight-month major adverse cardiac event rates

Variable	IRT	DES	p Value
No. of patients	61	50	
No. of vessels	62	50	
Major adverse cardiac events	6 (10%)	12 (24%)	0.044
Death	1 (2%)	2 (4%)	0.588
Q-wave myocardial infarction	1 (2%)	1 (2%)	1
Target vessel revascularization	6 (10%)	9 (18%)	0.198
Target lesion revascularization	6 (10%)	4 (8%)	1
Late thrombosis	0	0	—

Abbreviation as in Table 1.

brachytherapy group developed non-Q-wave myocardial infarction. There was no incidence of acute or subacute thrombosis seen in either group. At 8 months, the overall major adverse cardiac event rate was significantly lower in the vascular brachytherapy group (Table 3).

Discussion

This study evaluated the safety and efficacy of intravascular radiation therapy for the treatment of patients who presented with restenosis after DES implantation and compared this strategy with treatment with r-DES. The main findings of the present study suggest that, for DES ISR, radiation and r-DES treatments are effective and safe.

Restenosis after DES is lower compared with bare metal stents and was reported as a single digit in the pivotal trials with Cypher and Taxus DESs.^{2,3} However, when implanted in more difficult subsets of patients and lesions, such as diabetic patients with multivessel disease, diffuse long lesions, or small vessels, the need for repeat revascularization is >10%.⁵⁻⁹ In the Sirolimus Eluting stents for Compassionate Use REgistry (SECURE), a compassionate-use protocol treating patients with lesions in degenerated vein grafts or at a site of failed vascular brachytherapy, restenosis was reported to be up to 50%.⁵ With the dissemination of DESs to many vessels, left main arteries, and more complex lesions, it is projected that with an average recurrence rate of 10%, there will be ≥100,000 patients annually who will present with ISR of a DES.⁹

The etiology of DES restenosis is multifactorial. It could result from mechanical factors such as stent underexpansion or strut fracture or from biologic factors, including drug resistance, insufficient dose, or lack of response to the drug.¹⁴ Other factors could be related to the polymer, which may cause long-term inflammation or hypersensitivity reaction.^{15,16} It is important to verify the mechanism of DES restenosis to match an appropriate treatment. Intravascular ultrasound could help to determine if the restenosis is related to neointima formation or to a mechanical factor. Although the pattern of restenosis of DES ISR is more focal and less diffuse compared with that of bare metal stents, the treatment is not necessarily simple.¹⁷ For example, balloon angioplasty alone was associated with a recurrence rate of nearly 40%. Even repeat sirolimus-eluting stent implantation was associated with a recurrence rate of 18%.¹⁸⁻²⁰ Within our data, placing a different type of DES on a DES that restenosed was not associated with any additional ad-

verse events compared with the restenosis rates of placing the same DES on a DES that restenosed. Based on the success with the use of intravascular radiation therapy for treatment of bare metal stent ISR, we proposed the use of intravascular radiation therapy for the treatment of ISR of DES. Intravascular radiation therapy is proved technology for the treatment of ISR of a bare metal stent. This was shown in numerous, randomized studies irrespective of the complexity of the patients and lesions. Intravascular radiation therapy is best performed in relatively focal lesions such as those seen with DES ISR.^{10–13} However, there are no data available on the safety and efficacy of intravascular radiation therapy for DES ISR. In vitro testing of β -radiation on Taxus stents demonstrated integrity of the stent and polymer without any effect on drug elution.²¹

DESs have recently demonstrated efficacy and safety for the treatment of bare metal stent ISR, with similar and perhaps better results than with intravascular radiation therapy.²² Thus, the question of which strategy is favorable for the treatment of DES ISR is valid and not yet answered. The present study showed for the first time that intravascular radiation therapy was safe and effective for treatment of ISR of a DES in this cohort. Fewer than 10% of patients required repeat target lesion revascularization, and there were no adverse events or thrombosis related to the intravascular radiation therapy.

When compared with the cohort treated with r-DESs, intravascular radiation therapy suggested an improved major adverse cardiac event outcome at 8 months, with a trend toward less target vessel revascularization also at 8 months. This was mainly driven, however, by higher nontarget lesion target vessel revascularization in the r-DES group. We previously reported a similar observation for patients with failed vascular brachytherapy, i.e., superiority of intravascular radiation therapy over DESs in terms of late recurrences.²³ When intravascular radiation therapy and DES fail in these groups, intravascular radiation therapy should be considered as an alternative therapy because it is associated with low recurrences without compromising safety. We attribute the good results of the intravascular radiation therapy group to the intravascular radiation therapy being performed in experienced centers; there was minimal usage of restenting as the method of PCI, an adequate dose was given, and there was no incidence of geographic miss.

The question remains: what should be the anticoagulation regimen of patients undergoing intravascular radiation therapy on DES ISR? In this registry, we recommended ≥ 12 months of clopidogrel and indefinite treatment with aspirin. Although the cohorts in our study did not develop stent thrombosis, it would probably be safer to keep these patients on indefinite dual antiplatelet therapy, specifically if new stents are implanted with or without intravascular radiation therapy. Applying more antimitotic therapy to a vessel that was already treated with delayed healing modality is a concern at this point. We recommend indefinite use of dual antiplatelet therapy until further studies can shed light on reendothelialization with this dual antiproliferative therapy.

The present study carries limitations. It was based on 2 small registries (1 multicenter and 1 single center), it lacked systematic angiographic follow-up, clinical follow-up was

limited to 8 months, and it did not reflect the long-term durability of these strategies. Nevertheless, the study suggests safety for strategies and supports the use of intravascular radiation therapy for this indication in those centers that still have the intravascular radiation therapy technology available. The control group using r-DES and the historical controls suggest that treatment of DES failures may not be trivial, and a randomized study of intravascular radiation therapy versus repeat DES is warranted to assess the preferred therapy for this difficult subset of patients.

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