Restenosis treatment in the drug-eluting stent era

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Despite recent advances, the in-stent restenosis (ISR) remains a challenging problem in interventional cardiology with an estimated overall restenosis rate of 20%, 25-30% in bare metal stents and 12% in drug-eluting stents (DES). In this review, we provide an overview of therapeutic options which include balloon angioplasty, cutting balloon, debulking techniques, brachytherapy and DES. Intracoronary brachytherapy using beta or gamma radiation had been considered the standard of care for some years. However, the use of DES to treat ISR has been shown to be safe, effective and ease-of-use for the prevention of recurrent restenosis. ISR after DES when focal angiographic pattern is present can be often treated with balloon angioplasty whereas if a non-focal pattern is recognized a new DES implantation is indicated. Waiting for a definitive answer regarding the optimal treatment of ISR from ongoing trials, we present our current approach to ISR.

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With more than 75 000 stent implantations per year of which 30% performed with drug-eluting stents (DES) and an estimated overall restenosis rate of 20% (25-30% in bare metal stents and 12% in DES), in Italy between 30 000-40 000 patients will require treatment for in-stent restenosis (ISR) in the year 2005[1]. On one hand the widespread use of DES will reduce the incidence of ISR, on the other more complex lesions and patients, such as multivessel diabetic patients, will be treated in the future so that restenosis will remain a challenging problem in interventional cardiology. Previous studies[2-4] supported the idea that patients with ISR who are asymptomatic without inducible ischemia have excellent long-term prognosis and may be managed medically. However, recent data indicate a significant negative impact of angiographic ISR on long-term survival even in asymptomatic patients[5].

Histologically, neointimal formation occurs in three phases. The first phase (the inflammatory phase) involves the deposition and activation of platelets on the stent surface, the second phase (granulation phase) is characterized by smooth muscle cell migration and proliferation within the neointima. The last phase shows an increase in proteoglycan extracellular matrix with a paucity of cell proliferation[6,7].

ISR has been classified according to length. Four types of ISR have been defined: I) focal (lesions are ≤ 10 mm in length); II) diffuse (lesions are > 10 mm within the stent); III) proliferative (lesions are > 10 mm extending beyond the margin(s) of the stent); and IV) occlusive ISR. Type I has been further subdivided into four types (IA to ID) based on the site of focal ISR in relation to the stent[8].

In our laboratory ISR treatment represents 14% of percutaneous coronary intervention procedures. Of these ISR lesions, 65% are focal, 25% diffuse intrastent, and 10% diffuse proliferative or total occlusions.

The clinical and morphological features of restenosis after DES implantation are less known; some authors have reported after sirolimus-eluting stent implantation a more frequently focal ISR pattern but multifocal or diffuse lesions have also been described especially with paclitaxel-eluting stents[9-12].

Besides the pattern and location (ostium, bifurcation, native coronary artery vs bypass) of ISR, patient-specific factors such as hypercholesterolemia, diabetes or failed brachytherapy, have been identified as predictors of recurrent clinical events or angiographic restenosis after any type of ISR treatment[13,14].

In the year 2003 a systemic review of 28 studies, including a total of 3012 patients with ISR treated with different modalities (balloon angioplasty, stent in-stent, direc-

tional coronary atherectomy, rotational atherectomy [ROTA], excimer laser angioplasty and intracoronary radiation), showed an estimated average probability of major adverse cardiac events after ISR treatment (with a follow-up of 9 ± 4 months) of 30%; the post-procedural diameter stenosis was the strongest and the only significant predictor of major adverse cardiac events, confirming the importance of the acute procedural result for the outcome[15]. The recent encouraging results of DES use in ISR seem to have settled the issue of the best treatment of in-stent bare restenosis, but opening a new one: "which is the best treatment of in-DES restenosis?".

Balloon angioplasty

Due to its simplicity and low cost, repeat balloon angioplasty remains the most common approach to treat ISR, yet its results have often been disappointing with a recurrence rate of 20 to 30% for focal lesions, but up to 80% for the proliferative and occlusive forms[6,16]. Mehran et al.[16] demonstrated by intravascular ultrasound (IVUS) that the mechanisms of luminal enlargement after balloon expansion include a combination of additional stent expansion (56% of area gain) and a compression and extrusion of the neointimal tissue through the stent struts (44% of area gain). A re-intrusion of the neointimal tissue through stent struts shortly after catheter-based treatment has been reported[17], so that the amount of neointimal tissue is the main cause of recurrence of restenosis. This explains the poor results after simple balloon dilation in the "aggressive" form of ISR where a large amount of neointimal proliferative tissue is present.

Cutting balloon angioplasty

The cutting balloon is a non-compliant balloon catheter with 3 or 4 microblades (atherotomes) of 0.18 mm in depth and 0.70-0.76 mm in thickness that are fixed longitudinally on its surface. The mechanisms of cutting balloon rests on the action of the microblades intended to incise the atherosclerotic plaque or neointimal tissue at the beginning of balloon inflation and to develop a controlled fault line along which dilation occurs. The low-pressure balloon dilation makes the stent expansion minimal while most of the effect is the capacity of facilitating the maximum extrusion of the neointimal tissue out of the stent struts. It was initially reported in observational studies and then confirmed in IVUS studies[18,19]. Furthermore a lower trauma on the vessel wall (due to the low-pressure balloon dilation) could lead to less ISR.

On the basis of these evidences but most of all for its ease-of-use (identical technique to a regular balloon) cutting balloon angioplasty (CBA) was widely adopted by the interventional cardiology community. The Japanese Multicenter Registry of CBA for ISR reported data on 194 treated lesions. Angiographic restenosis occurred in 29% and target lesion revascularization in 22% of the lesions[20]. In contrast with previous retrospective studies suggesting that CBA might be superior to conventional percutaneous transluminal coronary angioplasty (PTCA) in the treatment of ISR, the recent randomized Restenosis Cutting Balloon Evaluation Trial (RESCUT) showed non-significant differences between the two approaches regarding: pattern of restenosis, recurrent angiographic binary restenosis (29.8 vs 31.4%) and major adverse cardiac events at 7 months (16.4 vs.15.4%)[21]. From this study the cutting balloon seems not to provide any additional benefit when adequate final lumen dimensions can be achieved with balloon angioplasty alone. The use of CBA in treating ISR is now confined: 1) to optimize the angiographic result after simple PTCA, 2) to prepare the vessel before brachytherapy because the instability of the standard balloon inside the restenotic segment ("water melon seeding effect") may damage the proximal and distal segments outside the stent with the consequent need for further stent implantation.

Debulking techniques

Following the idea that debulking of the neointima would lead to less remaining tissue inside the stent resulting in a reduction of neointimal proliferation and a decrease of recurrence, serial studies were conducted using atheroablative therapies (rotational atherectomy, excimer laser angioplasty, and directional coronary atherectomy).

Rotational atherectomy. Retrospective analysis reported a reduction in subsequent target vessel revascularization from 45 to 25% in patients with diffuse ISR treated with this technique compared with simple PTCA[22]. However, results of two subsequent randomized trials have provided conflicting data. The first, a single center Randomised Trial of Rotational Atherectomy versus Balloon Angioplasty for In-Stent Restenosis (ROSTER), was conducted in 150 patients and found a clinical restenosis rate of 20% in patients undergoing ROTA vs 43% in patients undergoing PTCA[23]. However, the Angioplasty Versus Rotational Atherectomy for Treatment of Diffuse In-Stent Restenosis Trial (ARTIST) failed to demonstrate in 298 randomized patients any advantages of ROTA. In this study the angiographic restenosis rate was 51.2% in the PTCA group vs 64.8% in the ROTA group[24]. In this trial ROTA was followed by low-pressure balloon dilation while in the PTCA arm high-pressure inflations were used resulting in stent expansion. Due to the absence of IVUS control in most of the population no information about the proportion of patients with suboptimally stent expansion in

the ROTA group is available. The superiority of the high-pressure balloon dilation alone group could have been related to the proper stent expansion. Taking into account that the device implies longer procedural times, higher costs, higher rates of peripheral vascular complications without demonstration of superiority vs PTCA alone in preventing restenosis it has now been confined to very particular cases, such as lack of balloon expansion even at high pressures.

Directional coronary atherectomy. Even if previous small series indicated a low rate of target lesion revascularization at 12 months, the recently reported data of the Flexicut Endovascular Atherectomy Treatment with Hyperplasia Eradication for Restenosis In-Stent study do not confirm this result, showing a high restenosis rate (65%) at 6-month angiographic follow-up[25,26]. At the present time directional coronary atherectomy as a stand-alone technique does not reduce the incidence of recurrent restenosis and cannot be considered as first-line treatment modality in patients with ISR. Its value for research purposes (analysis of biopsy specimen) and as an adjunctive technique has to be considered.

Excimer laser coronary angioplasty. Although previous reports have suggested a potential benefit of excimer laser angioplasty for patients with ISR, in later observational studies this technique failed to reduce recurrent restenosis showing an unacceptably high restenosis rate[27-29].

Brachytherapy

The rationale for delivering ionizing radiation in vessels for treating restenosis was driven by its use in inhibition of cellular proliferation in cutaneous scars. It has been used since 1994 in animal models and since 1998 in humans to treat neointimal proliferation occurring in ISR with similar mechanisms to those of tissue scar formation. Several clinical trials (Table I)[30-37] have reported with either gamma or beta-radiation a reduction of > 30% in further restenosis in treating ISR. Its use was found particularly effective in treating proliferative or occlusive forms of ISR. However these techniques present:

• technical limitations: gamma-radiation has a more deep and homogeneous tissue penetration, but was virtually never used in Italy because of very rigid protective regulations. The two systems of beta-radiation (Novoste ^{90}Sr-^{90}Y and Guidant Phosphore32) became available with small sources only late and the procedures were associated with more dissections and need for further stent implantation;

• side effects or complications of the technique: the delay of endothelialization which has been the cause of late thrombosis, leading to myocardial infarction. The prolonged use (up to 12 months) of dual antiplatelet treatment has decreased to 0.8-3% this dangerous event. Another complication has been a stenosis at the edges of the irradiated segment of the vessel (edge effect) due to the decreased irradiation at the extremities of the source often injured by balloon predilation of the stenotic segment. This was decreased with perfect covering with radioactive source of the entire zone treated with PTCA and 7 mm outside the extremities.

Finally a recent report on long-term efficacy of vascular brachytherapy for ISR shows at 5-year follow-up an alarming late restenosis rate up to 37%[38].

In a matched pair comparison of the procedural and long-term clinical and angiographic outcomes after treatment of diffuse ISR using a paclitaxel-eluting stent vs intracoronary beta-radiation therapy, Radke et al.[39] showed a non-significant difference: angiographic binary in-lesion restenosis at 6 months was 20% in the paclitaxel group and 16% in the beta-radiation therapy group.

Two comparative randomized studies, brachytherapy vs DES implantation, are currently underway: TAXUS V-ISR and SISR. The former is a prospective, randomized trial evaluating the slow-release formulation Taxus paclitaxel-eluting stent in the treatment of ISR vs intravascular beta-brachytherapy. The latter is a multicenter, randomized study of sirolimus-eluting stent vs intravascular brachytherapy (beta or gamma).

Table I. Radiation treatment for in-stent restenosis: clinical trials.

Study	Radiation source	No. patients	Lesion length (mm)	Radiation vs placebo (%)	
				Restenosis	MACE
WRIST[30]	Gamma	130	< 47	19 vs 58	32 vs 71
Long WRIST[31]	Gamma	120	36-80	46 vs 78	–
WRIST PLUS[32]	Gamma	120	< 80	34 vs 66	23 vs 64
GAMMA[33]	Gamma	252	< 45	33 vs 55	28 vs 44
WRIST 12[34]	Gamma	120	< 80	34	13
Beta WRIST[35]	Beta	50	< 47	34 vs 71	34 vs 76
START[36]	Beta	476	< 20	29 vs 45	19 vs 29
INHIBIT[37]	Beta	332	< 47	26 vs 52	24 vs 34

MACE = major adverse cardiac events.

Vascular brachytherapy, even in the DES era, has still some advantages:
• radiation source train can treat long lesions and in multiple vessels at a lower cost;
• radiation catheters (new-generation ones) can be used at sites where we would rather not deliver DES such as highly angulated, small vessels, very distal locations;
• radiation catheters can be used in bifurcations where a stent can "jail" a side-branch or will not allow normal artery bending.

Drug-eluting stents

The mechanisms of action of DES in the treatment of ISR are:
• to obtain a greater post-interventional lumen dimension in comparison with that obtained after balloon angioplasty. This finding is consistent with previous reports that compared implantation of a bare metal stent with plain PTCA for ISR treatment. They showed in the stent group better immediate angiographic results because of a larger acute gain, but a similar follow-up lumen dimension due to the late proliferative response[40];
• to reduce the risk of procedure-related complications. Previous studies comparing balloon angioplasty with repeat stenting indicated a higher rate of major in-hospital complications in the balloon angioplasty group[40,41];
• to preserve acute procedural results by a potent and sustained inhibition of neointimal tissue growth by the antiproliferative drug applied to the stent. This action will be relevant since a large number of smooth muscle cells contained in ISR lesions are proliferating, as assessed by immunohistochemistry for proliferating cell nuclear antigen and other markers of proliferation[42]. In a recent study Nuhrenberg et al.[43] hypothesize that rapamycin effectiveness in reducing restenosis may depend on its capacity of reducing recruitment of leukocytes and hematopoietic progenitor cells after vascular injury. Not only an antiproliferative direct action but even an anti-inflammatory one is at the basis of sirolimus anti-restenosis effect[44].

The first two preliminary experiences with sirolimus-eluting stent implantation in patients with ISR were reported by Degertekin et al.[45] and Sousa et al.[46] in the year 2003. In the Rotterdam experience[45], a small series of 16 patients undergoing sirolimus-eluting stent implantation for complex ISR, the restenosis rate and the in-lesion late loss were 20% and 0.26 ± 0.67 mm respectively. In the San Paulo experience[46], a surprising 0% recurrent binary restenosis and an in-lesion late loss of 0.16 ± 0.47 mm were observed after sirolimus-eluting stent implantation for non-complex lesions in 25 patients. Promising results (angiographic restenosis rate of 16%) were reported by the TAXUS III study using the paclitaxel-coated stent[47]. The encouraging preliminary results and the ease-of-use led to a rapid widespread adoption of DES for ISR treatment, despite a lack of randomized trials. In the last year at least three observational studies and several abstracts (presented at the European Society of Cardiology Congress 2004 and at the Transcatheter Cardiovascular Therapeutics Meeting 2004) have confirmed these initial results (Table II)[45-52]. In a comparative retrospective analysis, Airoldi et al.[48] reported a 57% reduction in the incidence of recurrent restenosis in patients with ISR treated with sirolimus-eluting stent implantation compared with CBA. In the Rapamycin Eluting Stent Evaluated at Rotterdam Cardiology Hospital (RESEARCH) registry, 44 patients with unselected ISR were treated with sirolimus-eluting stent implantation, showing a binary restenosis of 14.6% (reaching 20-25% for more complex lesions) and a target lesion revascularization of 16.3%[49].

Recently, a randomized controlled trial (ISAR-DESIRE), compared two DES (sirolimus and paclitaxel) with conventional balloon angioplasty. It confirmed

Table II. Drug-eluting stent implantation for in-stent restenosis: clinical studies.

Study	Group	No. patients	Lesion length (mm)	Angiographic restenosis (%)	TVR (%)
Degertekin et al.[45]	Sirolimus	16	< 32	20	
Sousa et al.[46]	Sirolimus	25	< 20	4	
TAXUS III[47]	Paclitaxel	28	< 20	16	21
Airoldi et al.[48]	Sirolimus	55	< 25	13	11
	Cutting balloon	214		30	
RESEARCH[49]	Sirolimus	44	< 30	15	16
Iofina et al.[50]	Sirolimus	28	< 30	13	11
	Paclitaxel	24		20	8
	Balloon	25		61	32
ISAR-DESIRE[51]	Sirolimus	100	< 20	14	8
	Paclitaxel	100		22	19
	Balloon	100		45	33
TROPICAL[52]	Sirolimus	162	< 25	9.7	7

TVR = target vessel revascularization.

that a strategy based on sirolimus or paclitaxel-eluting stents is superior to conventional balloon angioplasty for the prevention of recurrent restenosis in patients with ISR. The incidence of angiographic restenosis was 44.6% in the balloon angioplasty group, 14.3% in the sirolimus-eluting stent group and 21.7% in the paclitaxel-eluting stent group. Although not included in primary analysis the comparison between sirolimus- and paclitaxel-eluting stents showed a significant lower target vessel revascularization in the sirolimus group than in the paclitaxel group (8 vs 19%, p = 0.02). In this study 60% of ISR lesions were focal[51]. Results from the TROPICAL study, a multicenter, non-randomized study of sirolimus-eluting stent in the treatment of patients with ISR in a native coronary artery lesion, are in press in *Circulation*[52]. The study was designed as a prospective multicenter registry, to assess the effectiveness and safety of sirolimus-eluting stents in the treatment of ISR (72% diffuse pattern). The 6-month angiography showed a late loss of 0.08 mm and a binary restenosis rate of 9.7%. These results represent a further confirmation of the high efficacy and safety of DES in the treatment of ISR. The ongoing randomized trials (TAXUS V-ISR; SISR and TAXUS VI) will give the answer about the best treatment for ISR.

In summary from all available data, the recurrence rate after treatment of ISR with sirolimus-eluting stents is around 12-14% and with paclitaxel-eluting stents 18-20%. These rates seem to apply also to diffuse ISR. Since January 2002, DES implantation has been adopted as one of the possible strategies in patients with diffuse ISR at our Institution. One hundred patients with diffuse or proliferative ISR in a native coronary artery were treated with DES and were compared with 74 patients treated in the previous period with beta-brachytherapy. Thirty-three received a sirolimus-eluting stent and 77 a paclitaxel-eluting stent. At follow-up the restenosis rate was 12% for the sirolimus group, 13.8% for the paclitaxel group, and 37.8% for beta-brachytherapy. Mostly re-restenotic lesions in the DES group were focal while in the beta-brachytherapy group diffuse or occlusive patterns were present in half of the patients (Table III).

Alternative strategies

The initial failure of local approach in the treatment of ISR has raised major interest in the use of other therapies. Many pharmacological and even gene therapies as well as many trials were successful in animal models, but failed in human coronary arteries. After controversial data from two non-randomized studies with oral sirolimus therapy for the prevention of restenosis in *de novo* coronary arteries, the Oral Sirolimus to Inhibit Recurrent In-stent Stenosis (OSIRIS) trial showed encouraging results in the treatment of ISR. In this trial, a strategy based on a 2-day pre-treatment with high-dose rapamycin followed by a maintenance dose for 1 week after balloon angioplasty, resulted in a significant reduction of recurrences in patients with ISR[53-55]. Oral prednisone therapy has shown promising results in restenosis prevention in *de novo* coronary arteries but at the moment no data are available on their use for the prevention of recurrence in patients with ISR[56].

Current strategy for treatment of in-stent restenosis. Our approach

On the basis of the present knowledge, waiting for the results of ongoing trials, our recommendations are:
• to prevent ISR: a) optimize stent expansion: involving debulking calcified or bulky plaques before stent placement; b) use of IVUS or physiological assessment to confirm optimal stent dimensions and expansion. Many studies have identified in severely calcified lesions a lack of stent expansion as a cause of restenosis even in DES[9,57];

Table III. Humanitas database: baseline and follow-up angiographic data of 184 consecutive patients treated for diffuse in-stent restenosis.

Characteristics	Beta-brachytherapy group (n=74)	Sirolimus-eluting stent group (n=33)	Paclitaxel-eluting stent group (n=77)	p
Baseline procedure				
Age (years)	63.7 ± 8.12	68.8 ± 8.8	64.4 ± 9.8	NS
Diabetes (%)	28.7	28.1	31.7	NS
Reference diameter (mm)	2.65 ± 0.63	2.62 ± 0.52	2.67 ± 0.45	NS
Lesion length (mm)	18.4 ± 8.2	15.3 ± 10.5	17.7 ± 11.8	NS
9-month follow-up (%)				
Restenosis rate	37.8	12.1	13.8	< 0.001
Focal pattern	53.6	75	77.7	
Diffuse pattern	35.7	0	22.2	
Total occlusion	10.7	25	0	
TLR	33.3	9.1	12.3	< 0.001

TLR = target lesion revascularization.

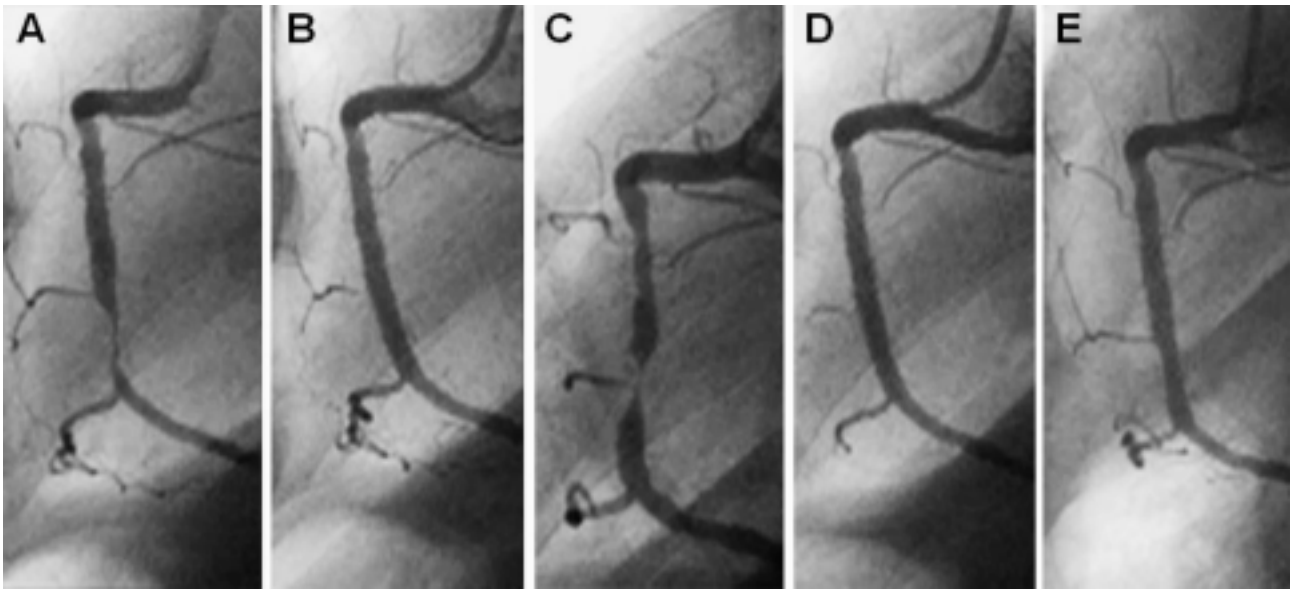

Figure 1. *Sirolimus-eluting stent implantation for in-stent restenosis after failed brachytherapy.* A: *diagnostic angiogram showing in-stent restenosis of the middle right coronary artery.* B: *final result after cutting balloon angioplasty and brachytherapy.* C: *12-month angiographic follow-up showing in-stent restenosis recurrence at the site of brachytherapy.* D: *final results after sirolimus-eluting stent implantation (3 × 18 mm).* E: *9-month angiographic follow-up showing persistence of the good result obtained previously.*

• if any doubt on conventional stent underexpansion exists, IVUS is mandatory to guide treatment strategy;
• due to the high cost of DES, a first-line treatment with balloon angioplasty may be chosen in focal ISR treatment. In this case an optimal angiographic result without residual stenosis should be achieved. For this purpose, CBA may be utilized;
• in diffuse ISR of a native coronary artery, DES implantation is recommended. DES should be 0.5 mm bigger than the one previously implanted. A recent IVUS study identified stent underexpansion as a significant cause of failure after DES implantation for ISR[58]. With the choice of a stent bigger than the one previously implanted, the routine post-dilation with high-pressure non-compliant balloon, as recently proposed by Blackman et al.[59], is not required;
• when proliferative ISR is treated with DES, always cover the entire length of the previously implanted bare metal stent and ensure even using IVUS guidance that the edges of the previous implanted bare stents be overlapped. TAXUS III Investigators hypothesized that barotrauma from balloon inflation in an area of preexisting in-stent neointima may trigger the local exuberant hyperplasia causing edge stenosis[47];
• when treating long ISR lesions with multiple DES, try to minimize the area of stent overlap. The sites of stent overlap could be the area at major risk of stent underexpansion;
• if a bifurcation or important side branches are involved in ISR either DES in the main branch and PTCA alone in the side branch or crush or reverse-crush techniques could be considered;
• in highly angulated, small vessels, very distal locations, brachytherapy should be used;
• recurrent restenosis after brachytherapy can be treated safely with DES implantation[60] (Fig. 1);
• in focal post-DES restenotic lesions, balloon dilation is recommended. In diffuse post-DES restenotic lesions repeat DES implantation can be chosen and has been so far reported as not harmful[61].

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