

Review Article

Coronary In-stent restenosis: Where are we Now?

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Abstract

Drug eluting stents (DES) have dramatically reduced the rate of in-stent restenosis (ISR) compared to bare metal stents (BMS). However ISR still occurs due to the widespread use of DES in complex lesions and high-risk patients, and it is not a benign phenomenon. Treatment of patients with ISR is still a challenge for interventional cardiologists. DES and BMS-ISR present different characteristics in terms of morphological pattern, time of presentation after stent implantation, underlying substrate and response to treatment. Treating DES-ISR is even more challenging than treating BMS-ISR. Several therapeutic options have been proposed, but a definite answer to this problem still has to be defined. In this paper we reviewed the data with currently available therapeutic modalities, in patients presenting with both BMS- and DES-ISR.

ABBREVIATIONS

BMS: Bare Metal Stents; PCI: Percutaneous Coronary Intervention; DES: Drug Eluting Stents; DEB: Drug-Eluting Balloon; MI: Myocardial Infarction; ST: Stent Thrombosis; TLR: Target Lesion Revascularization; OCT: Optical Coherence Tomography; POBA: Plain Old Balloon Angioplasty; SES: Sirolimus-Eluting Stents; PES: Paclitaxel-Eluting Stents; EES: Everolimus-Eluting Stents; BRS: Bioresorbable Vascular Scaffolds

INTRODUCTION

In-stent restenosis ISR was recognized to be an important issue for interventional cardiologists since the introduction of bare metal stents (BMS) in percutaneous coronary intervention (PCI) [1]. The advent of drug eluting stents (DES) had yielded the promise to solve this problem with no restenosis occurrence at 6 months follow-up [2]. However, despite these encouraging preliminary results, ISR occurs even in the DES era, due to the increase of PCI performed in more complex lesions and high-risk patients [3].

Management of patients with ISR represents a critical problem, particularly for those presenting with DES-ISR, whose treatment has proven to be particularly challenging [4], or in patients presenting with recurrent-ISR, with multiple stent layers, in whom previous treatments have already failed. To date several treatment options have been proposed for ISR as plain old balloon angioplasty, cutting balloons, repeat stenting, drug-

eluting balloon (DEB) inflation, and bioresorbable vascular scaffold (BRS) implantation [5]. However a definite answer to this problem is far to be defined. Here we discuss the currently available therapeutic options for ISR treatment.

Definition and incidence

ISR is defined as an angiographic reduction in lumen diameter after PCI, resulting from arterial damage with subsequent neointimal tissue proliferation, and is defined as the angiographic evidence of a luminal diameter stenosis >50% within the stent or within 5 mm of the stent edges [6]. It is morphologically classified by the Mehran system [7] (pattern I, focal; pattern II, diffuse; pattern III, proliferative; pattern IV, occlusion) that predicts the need for repeat revascularization for both BMS- and DES-ISR.

In-stent restenosis occurs in up to one-half of patients treated with BMS and its occurrence has a negative impact on the long-term survival, indeed 60% of patients require treatment with a repeat revascularization procedure [8].

DES showed to solve this problem with no restenosis occurrence at 6 months follow-up [2]. Thanks to their promising initial results to significantly reduce the rate of repeat revascularization compared to BMS, DES have been widely used in PCI, allowing more complex percutaneous procedures than in the preceding era. Subsequently the restenosis rate increased so that the current rate of ISR in clinical practice remains higher than 10% [9,10].

Causes and predictors of ISR

Many factors have been identified as possible causes of ISR, and recognizing the underlying mechanism of restenosis is of paramount importance in order to guide and optimize the repeated intervention. Stent under-expansion is considered the main mechanical trigger for both BMS and DES-ISR [11]. It is due to stent under deployment rather than from chronic recoil, resulting from under-sizing or poor expansion during implantation because of a low-pressure deployment or the presence of heavy vessel calcification [11,12]. It has to be differentiated from malapposition, in which stent is well expanded but stent struts are not apposed to the vessel wall. It cannot be detected by angiography and generally it occurs in vessels with tortuosity or different diameters within the treated segment [13]. In some patients, restenosis may be caused by technical factors as stent misplacement, a gap between two stents or a stent not covering the entire lesion [14]. Stent fracture may also cause ISR. It occurs more often in right coronary arteries and in closed-cell design stents. Local drug under-dosage and increased mechanical vessel irritation at the fracture site may both result in increased neointimal hyperplasia and restenosis [15]. Finally, drug resistance or hypersensitivity reactions are possible causes of ISR after DES implantation.

Clinical and angiographic predictors of ISR include small vessel size, increased stented length, complex lesion morphology, diabetes mellitus, and prior bypass surgery irrespective of the stent type (BMS, first or second generation DES) [9].

CLINICAL PRESENTATION

Because of its gradual and progressive onset, ISR has always been considered a benign phenomenon. However only few ISR are clinically silent, while the majority of patients with both BMS- and DES-ISR have symptoms as unstable angina (26% to 53% for BMS, 16% to 66% for DES) or even as myocardial infarction (MI) (3.5% to 20% for BMS, 1% to 20% for DES), leading to a poor clinical outcome [14,16].

Differences between BMS- and DES-ISR

There is increasing evidence showing that BMS- and DES-ISR present different characteristics in terms of morphological pattern, time of presentation after stent implantation, underlying substrate and response to treatment [4,17,18]. Particularly DES higher efficacy to prevent restenosis occurrence is counterbalanced by a delayed healing of the stented arterial segment that explains the different time course between DES and BMS-ISR [19]. As a consequence of the high neointimal growth inhibition DES-ISR tends to present as a focal pattern, often involving stent edges [4]. Moreover DES-ISR is characterized by hypo-cellular neointima rich in proteoglycan and fibrin, while BMS-ISR is more often homogenous tissue that is characteristic of neointimal hyperplasia rich in smooth muscle cells [5]. In addition, in-stent neoatherosclerosis appears to have an earlier and accelerated course in DES compared to BMS-ISR [18].

In this context intravascular imaging with optical coherence tomography (OCT) may be useful not only to differentiate between neointima hyperplasia from neoatherosclerotic tissue (that can be present in up to 50% of DES ISR) but also to detect

the presence of unstable features that may result essential to define the treatment strategy [5].

Treatment of ISR

Management of patients presenting with ISR is still challenging and although several therapeutic options have been proposed a definite answer to this problem still has to be defined. Plain old balloon angioplasty (POBA) is one of the oldest strategies for ISR treatment; it is simple and mainly associated with satisfactory acute results thanks to both axial and longitudinal tissue extrusion in association with stent expansion, especially for focal ISR patterns [20]. However on the long-term, results are poorer compared to DES [21,22]. Moreover, the geographic miss is a potential disadvantage of POBA, especially for edge-ISR. Finally, care is required for diffuse ISR lesions to avoid the balloon slippage outside the stent and the subsequent edge-related complications.

Cutting and scoring balloons are simple techniques that may overcome this problem; additionally the deep incisions into the neointimal tissue may favor its extrusion, so that their use might be helpful in restenosis lesions predilatation prior to DES deployment or DEB inflation. Theoretically the application of cutting or scoring balloons prior to DEB use may increase the bioavailability of paclitaxel within the restenotic tissue, and therefore may improve DEB efficacy. Preliminary data from the ongoing ISAR DESIRE 4 trial confirm the efficacy of their use before DEB for ISR lesions treatment.

Rotational atherectomy, the Excimer laser and noncompliant high-pressure balloon, (the OPN NC balloon) may still be considered preliminary to DES implantation in case of undilatable ISR lesions due to unexpanded stents or severe calcified intra stent neoatherosclerosis [23, 9].

Current guidelines on myocardial revascularization recommend the use of DES or DEB for the treatment of both BMS- and DES-ISR lesions [24]. The ISAR-DESIRE trial [25] was the first randomized trial assessing a reduction of recurrent restenosis rate of both sirolimus-eluting stents (SES, 14.3%) and paclitaxel-eluting stents (PES, 21.7%) over POBA (44.6%) for BMS-ISR treatment. Later the RIBS II trial [26] showed a significantly lower rate of restenosis (11%) of SES compared with POBA for BMS-ISR, associated with a superior long-term clinical outcome mainly derived from a reduction in the need of re-intervention. Treatment of DES-ISR is more challenging and associated with poorer outcomes compared to BMS-ISR [17,18,27]. The use of a second DES for DES-ISR became the strategy of choice however a debate raised on whether a different DES should be used rather than the same DES. The ISAR DESIRE 2 trial [28] showed no differences in terms of restenosis recurrence between SES and PES (16.6% VS 14.6%) for SES-ISR treatment. In the RIBS III trial [29] the hetero-DES strategy resulted superior to all other treatment strategies (that included also POBA, BMS and homo-DES), however no differences were found when hetero-DES strategy was directly compared to the homo-DES approach.

Even though second DES implantation has shown good outcomes for ISR treatment, concerns have been raised on the addition of further permanent metallic layers into the arterial walls, particularly in patients with restenosis recurrence in

which additional layers had already been implanted. Indeed multiple layers may promote further endothelial growth in addition to mechanical complications such as stent fracture, malapposition and thrombosis. Thus, DEB have emerged as an attractive alternative to DES for ISR treatment, with the putative advantage of allowing the antiproliferative drug elution without the addition of an additional permanent metallic layer. The RIBS V trial [30] reported the first data on a randomized comparison of DEB and everolimus-eluting stent (EES) for the treatment of patients with BMS-ISR. In this study minimal lumen diameter at follow-up was better in the EES group compared to DEB (2.01 vs 2.36 mm; $p < 0.001$), but restenosis (4.7% vs 9.5%; $p = 0.22$) and clinical events at 1-year follow-up were similar in both groups. The use of DEB was tested also for the treatment of DES-ISR. In the ISAR DESIRE 3 trial [31] DEB were compared to PES and POBA for the treatment of DES-ISR. This study demonstrated that DEB is not inferior to PES and that both DEB and PES are superior to POBA. However when compared to EES for DES-ISR in the RIBS IV trial [32], DEB have resulted in lower minimal lumen diameter, lower net luminal gain, higher percent diameter stenosis and binary stenosis rates, and poorer clinical outcomes at one-year follow-up. Finally the pooled analysis of the RIBS IV and RIBS V trials [33] demonstrated the superior clinical and angiographic long-term outcomes obtained with EES compared with DEB for both DES and BMS ISR lesions. Despite these favorable results of EES over DEB, there are still concerns on adding a further permanent metallic layer in case of recurrent ISR already treated with multilayered stents. Kawamoto et al [34] compared for the first time the DEB vs. further second-generation DES implantation in patients with recurrent ISR, and showed that the results after both treatments were equivalent at one- and two-year follow-up (target lesion revascularization (TLR) at one year: DES 12.5% vs. DCB 10.9%; at two years: DES 27.7% vs. DCB 38.3%; $p = 0.40$). Finally, last generation DES (i.e. ultrathin struts), and newer DEB generations are emerging as an additional option for ISR treatment.

Recently attention has been focused on the possible use of BRS for ISR treatment [35]. BRS appear indeed very attractive in this setting as they may theoretically overcome both DES and DEB drawbacks, allowing transient vessel scaffolding combined with everolimus-drug elution. In this context, despite representing an off-label indication, BRS has shown good immediate and 15-months results following the treated of selected but complex ISR lesions irrespective of the ISR type (focal or diffuse, first or second recurrence, BMS or DES ISR) [35,36].

Antithrombotic treatment

Dual antiplatelet therapy (DAPT) with aspirin in association with clopidogrel (75 mg daily) or ticagrelor (90 mg twice a day) or prasugrel (10 mg daily) has to be used prior to ISR treatment. According to current recommendations [24] after any coronary intervention a 3- to 12-month duration of DAPT is recommended in patients treated with DES or DEB depending on a balance between the patient's clinical presentation and the bleeding risk profile.

Oral sirolimus was initially considered to be of potential value for the treatment of ISR, however subsequent experiences failed

to demonstrate its efficacy, and showed a higher rate of adverse drug effects so that its use cannot be recommended.

CONCLUSION

Despite the advent of DES, ISR still occurs and it represents a technical challenge. The underlying substrate differs between DES- and BMS-ISR, ranging from neointimal hyperplasia to neoatherosclerosis. To date second generation DES and DEB have shown good results for ISR treatment and are the currently recommended options. However last generation DES (i.e. ultrathin struts), newer generation DEB and BRS are emerging as possible alternative new tools for ISR treatment.

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