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In-stent restenosis in drug-eluting stents: issues and therapeutic approach

Abstract

Implantation of coronary drug-eluting stent (DES) became a predominant therapeutic strategy for coronary artery disease. One of the possible complications after DES implantation is in-stent restenosis (ISR) and today it becomes a significant issue for interventional cardiologists that requires further sustained and efficacious treatment. Widely accepted classification of DES-ISR is morphological classification proposed by Mehran et al. Currently available and effective therapeutic approach for DES-ISR include conventional balloon angioplasty, cutting or scoring balloon angioplasty, drug-coated/drug-eluting balloon angioplasty (DCB/DEB), DES in DES stenting (same or different), vascular brachytherapy and coronary artery bypass grafting (CABG). However, optimal treatment for DES-ISR remains unknown. Bioresorbable vascular scaffolds (BVS) offer initial hope, but further clinical studies are required to establish their long-term efficacy and safety.

Keywords: drug-eluting stents; in-stent restenosis

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Boshev Marjan, Otljanska Magdalena
University Clinic of Cardiology, Medical Faculty, University ?Sts. Cyril and Methodius?, Republic of Macedonia

Correspondence: Boshev Marjan, University Clinic of Cardiology, Medical Faculty, University Campus ☐Mother Theresa☐ ☐ Skopje, Republic of Macedonia, Tel +389 77 54 08 08, Email marjanboshev@gmail.com

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Introduction

Introduction of coronary stents in the field of interventional cardiology has significantly improved short- and long-term results of the percutaneous coronary interventions but in the same time they become responsible for development of a new entity called neointimal hyperplasia (NIH).[1] According to current available data, NIH is a process of vessel healing after stent implantation consisting of intimal proliferation as a result of local injury (barotrauma) which involves complex consecutive processes, like platelet activation and adhesion, smooth muscle cells activation, proliferation and migration to the intima, and deposition of excessive extracellular matrix.[2] If overexpressed, NIH can lead to so-called in-stent restenosis (ISR), i.e. renarrowing of a previously stented vessel segment.[3]

In the era of bare-metal stents (BMS), restenosis rates were present in 16-44% with predomination of restenosis in longer lesions and smaller vessel diameters.[1] The advent of drug-eluting stents (DES) was next logical step to eliminate the issue of NIH and ISR. DES are coated stents which release bioactive (cytostatic) agent into the surrounding areas. They were technologically invented with idea to suppress the excessive inflammatory vessel cell response to stent deployment. Unfortunately, although DES have significantly reduced restenosis rate, the entity of DES-ISR still exists and remains an issue. According to available literature reports, DES-ISR rate varies and ranges from 0-9%,[2] up to 16% with first generation of DES.[1]

The "ideal drug" should have some properties, like anti-proliferative and anti-migratory effects on the smooth muscle cells, and should be able to promote re-endothelialization as well as inhibition of anti-inflammatory response after vessel wall injury. The "ideal stent" in order to minimize ISR must also fulfill some criteria like: to be flexible, trackable, pushable, to have low profile, to be radio-opaque, thromboresistant, biocompatible, to have high radial strength, minimal foreshortening and good circumferential coverage (optimal scaffolding) as well as to be hemodynamically compatible. The "ideal drug-delivery stent" must have larger surface area, minimal gaps and minimal strut deformation after deployment.[3]

Definition and classification of ISR

Generally, there are two types of restenosis described in literature. "Angiographic" restenosis means recurrent diameter stenosis (late lumen loss – LLL) >50% within the stent segment or its edges (5mm segments adjacent to the stent) in follow-up.[4] "Clinical" restenosis means symptoms or ischemia recurrence with >50% diameter stenosis or >70% diameter stenosis without symptoms.[5] According to widely accepted Mehran system, morphological classification of ISR includes 4 patterns (types) of restenosis: pattern I – focal (ISR ≤ 10mm), pattern II – diffuse (ISR > 10 mm), pattern 3 – proliferative (ISR > 10 mm extending outside the stent) and pattern IV – occlusion (occlusive ISR).[2] This system was primarily created concerning BMS-ISR, but it also has prognostic value in DES-ISR[4] (Figure 1).

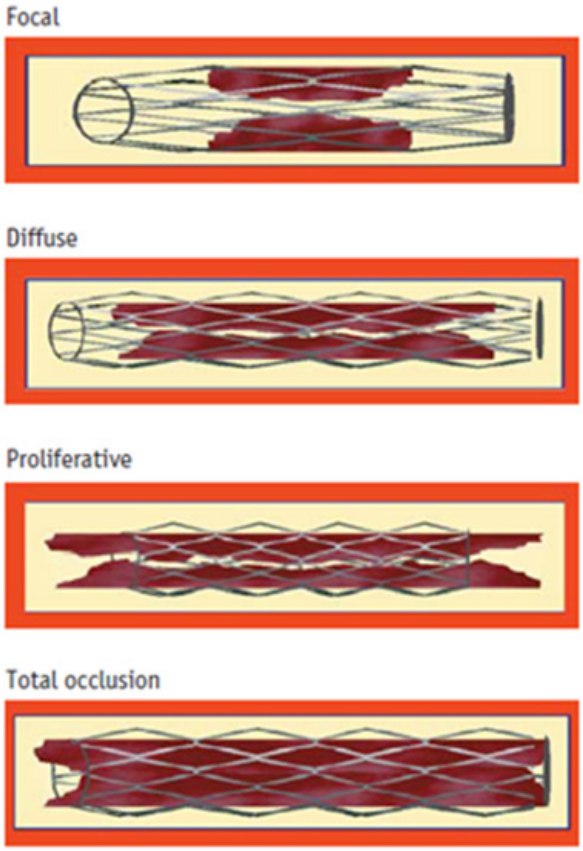

Figure 1 Classification of in-stent restenosis (ISR) in bare-metal stents according to Mehran et al.,[2]

In comparison to BMS-ISR, DES-ISR largely differs in terms of some important features like time of presentation, morphological characteristics, underlying substrate as well as response to further treatment.[4] For example, DES-ISR most frequently exhibits focal pattern (pattern I), usually involving stent edges. In addition, patients with DES-ISR develop earlier and more frequently neoatherosclerosis than those with BMS-ISR[4] (Table 1).

Table 1 Comparison of Principal Features of Restenotic Tissue after Bare Metal and Drug-Eluting Stent Implantation

	Bare-Metal Stent Restenosis	Drug-Eluting Stent Restenosis
Imaging features		
Angiographic morphology	Diffuse pattern more common	Focal pattern more common
Optical coherence tomography tissue properties	Homogeneous, high-signal band most common	Layered structure or heterogeneous most common
Time course of late luminal loss	Late loss maximal by 6-8 months	Ongoing late loss out to 5 years
Histopathological features		
Smooth muscle cellularity	Rich	Hypocellular
Proteoglycan content	Moderate	High
Pen-strut fibrin and inflammation	Occasional	Frequent
Complete endothelialization	3-6 months	Up to 48 months
Thrombus present	Occasional	Occasional
Neoatherosclerosis	Relatively infrequent, late	Relatively frequent, accelerated course

Etiopathogenesis of ISR

Etiopathogenetic mechanisms of DES-ISR are complex and arbitrarily can be divided into 4 main categories: biological factors, arterial factors, stent (mechanical) factors and implantation (technical) factors.[1] Very often DES-ISR develops as a result of interaction of more than one factor.

A. Biological factors: One of the most important biological factors for DES-ISR which cannot be controlled is resistance to antiproliferative (cytostatic) drugs. In literature there are documented many data on resistance to antiproliferative drugs, like sirolimus and paclitaxel which are used in most DES. There are some evidences that mutations of the gene polymorphism that encode mTOR (mammalian target of rapamycin) can lead to resistance to sirolimus (rapamycin). Hypersensitivity reactions to the polymer are also very important factors since they can provoke a prolonged inflammatory response which is associated with delayed healing and risk of restenosis. Animal models have shown that inflammatory response associated with sirolimus-eluting stents (SES) are present longer than 180 days and up to 2years, whereas newer generation of DES like everolimus-eluting stent (EES) have shown shorter period of inflammatory response persistence limited to 90days and 12months.[1] Hypersensitivity reactions to the metallic stent platform may sometimes contribute to development of DES-ISR. There is a suggestion for a possible link between nickel hypersensitivity and BMS-ISR but whether this is an issue with DES or not remains unclear.

B. Arterial factors: Regarding arterial factors, the issue of wall shear stress should be first mentioned. The issue of wall shear stress is based on the biophysical principle that hemodynamics and vessel geometry may contribute to atherosclerotic plaque growth and neointimal proliferation. Namely, high-shear stress areas like carina of the bifurcation can potentially limit progression of atherosclerosis, while so-called low-shear stress areas like ostium of a bifurcation may lead to promotion of atherosclerosis or enhancement of neointimal proliferation. Positive vessel remodeling may be also a contributable factor for development of DES-ISR. In case of positive vessel remodeling, there is higher amount of NIH which cannot be accommodated between the stent and external elastic membrane which is reason for intraluminal growth of NIH and development of ISR. In case of absence of positive vessel remodeling, there is lower amount of NIH which can be accommodated between the stent and external elastic membrane, thus leaving the lumen patent. This phenomenon is commonly known as Glagov phenomenon[1] (Figure 2).

C. Stent factors: Stent (mechanical) factors include stent underexpansion, nonuniform stent strut distribution (stent malapposition), stent fracture, type of DES (type of drug and polymer release kinetics), nonuniform drug deposition/distribution, strut thickness and polymer disruption or peeling. These factors are mainly preventable and, what is more important can be recognized and solved during intervention. Stent underexpansion is considered to be a major risk-factor for ISR irrespective of stent type (BMS or DES). This issue involves stent underdeployment due to low pressures or as a result of undersized stent selection.[4] In addition, sometimes stents cannot be optimally expanded as a result of heavily calcified lesions even with high pressure atmospheres using non-compliant balloons. Stent underexpansion can be easily detected by using intracoronary imaging techniques, like IVUS or OCT which can reveal smaller stent cross-sectional area than the vessel cross-sectional area.[5] Another factor which is worth mentioning is stent malapposition which refers to incomplete stent strut apposition to the vessel wall. This issue usually cannot be detected angiographically, but we need additional intracoronary imaging techniques (IVUS or OCT). Sometimes stent underexpansion and stent malapposition may coexist. Stent fractures may be significant factor for development of ISR or thrombosis. ISR associated with DES fractures usually appears late and focally and is related to the mechanical fatigue of the metallic stent or to the stent design (closed- versus open-cell design). There are reports on stent fracture incidence of <0,1% for PES and 2,3% for SES.[1] Reasons for stent fractures include significant artery bending (curvature), long stents, calcified lesions, aggressive postdilatation with non-compliant balloons etc. Type of drug and polymer release kinetics may have also impact on the ISR occurrence. According to Schomig et al.,[1] in one meta-analysis, SES have shown benefit over DES in terms of significant reduction in TVR and stent thrombosis which is thought to be due to slower polymer release kinetics in SES. PISCES trial [6] showed that the duration of the drug release had greater impact on the NIH inhibition than the dose of drug delivered. Concerning stent strut thickness, generally thicker stent struts have been associated with an increased risk from ISR although in DES there is a complex interaction among several factors.[1] Polymer disruption, peeling and cracking may be real cause for exposure of the metallic layer of the stent, thus

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increasing the risk for ISR, although there are not sufficiently strong evidence which suggest that polymer coating damage is directly linked to ISR. Wiemer et al. showed that in DES which were unsuccessfully used to treat heavily calcified and tortuous lesions there were detected different grades of polymer damage.[7] Similar effects may be seen in cases of aggressive kissing-balloon postdilatation or after using non-compliant balloons on high pressure atmospheres.

D. Implantation (technical) factors: These include barotrauma outside stented segment, stent gap and residual uncovered atherosclerotic plaques. Barotrauma to unstented segments may lead to subsequent inflammatory vessel response which can be cause for ISR occurrence in the region of exposed stent margins. Stent gap refers to a short gap between two closely deployed DES which causes discontinuous presence of DES. Main issue here is that at the level of the gap local drug delivery from DES is minimal. Therefore, stent gaps in general should be as rare as possible.[5] Geographical miss (GM) is a term that is commonly used to express failure to complete cover of previously injured vessel or failure to complete coverage of the atherosclerotic plaque. STLLR study [8] investigated GM linked to SES implantation and showed that GM was found in 66,5% of the study group from which 47,6% of the patients experienced longitudinal GM and 35,2% of the patients experienced axial GM.[1] GM was linked to an increased risk for TVR and MI at 1year.[5] Longitudinal GM refers to an injured or diseased segment not fully covered by DES whereas axial GM refers to an undersized or oversized balloon[1] (Figure 3).

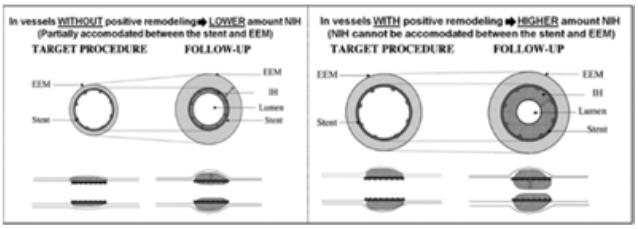

Figure 2 Explanation of the Glagov phenomenon (increased risk of ISR due to positive vessel remodeling).

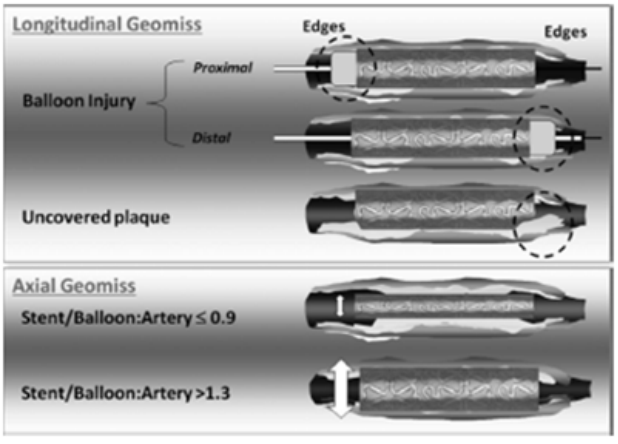

Figure 3 Description of the mechanisms of longitudinal and axial geomiss (GM).

Treatment options of DES-ISR

The optimal treatment for DES-ISR is not well established and remains unclear. There are available many procedures for treatment of DES-ISR with different rate of success:

a. Balloon angioplasty,

b. Cutting and scoring balloon,

c. Drug-coated/drug-eluting balloon (DCB/DEB),

d. DES for DES-ISR (same or different),

e. Vascular brachytherapy (VBT) and

f. Coronary artery bypass grafting (CABG).

In order to assess the possible mechanism for DES-ISR development as well as to serve as a guide for interventional cardiologist towards the optimal treatment, use of IVUS is highly recommended[5] (Figure 4). Conventional balloon angioplasty (BA) for DES-ISR is useful treatment option which is associated with satisfactory acute results and low incidence of complications, particularly in cases with focal pattern of DES-ISR. Nevertheless, long-term results especially in cases with diffuse pattern of DES-ISR are discouraging because of the high rates of recurrent ISR. This technique is preferable in patients with clearly underexpanded stents and in those cases high-pressure balloon dilation is recommended. In addition, operator should focus only on the narrowed segment of the stent, but not the whole stented segment. One of the most frequently seen effects in such cases is so-called "dog-bone" effect which usually means shifting to use high pressure noncompliant (NC) balloons instead of compliant balloons.[4] Possible complication of BA for DES-ISR is edge-related complication like edge-dissection. This can be avoided with careful and gradual balloon inflation. Commonly seen problem of BA during inflation in ISR is balloon slippage outside the stent, so-called "watermelon seeding" phenomenon, which usually occurs in cases of severe and diffuse pattern of ISR. Some authors recommend use of a buddy-wire technique to overcome this issue.[4,5] However, data supporting use of BA for treatment of DES-ISR are limited, especially after the advent of DCB/DEB which becomes dominant strategy for treatment of DES-ISR.[4] Cutting balloon is effective technique for treatment of DES-ISR which can prevent the issue of "watermelon seeding" phenomenon. This balloon device has tiny side blades which cut the neointima and enable balloon stabilization. Scoring balloons act on the same principle but they have superior flexibility and deliverability. Results achieved by cutting and scoring balloons are superior to those achieved by BA and they can be confirmed by some observational studies.[4]

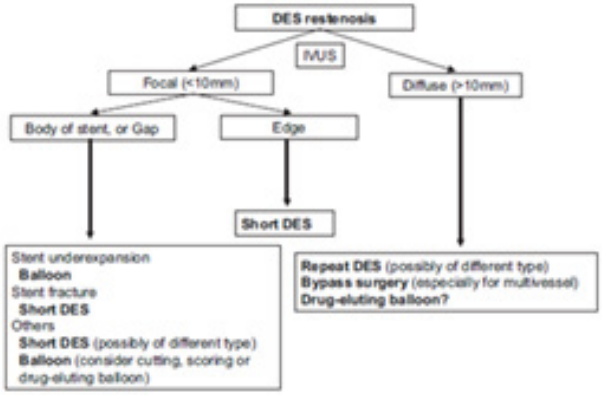

Figure 4 Algorithm for treatment of DES-ISR.[5]

DES: Drug-Eluting Stent; IVUS: Intravascular Ultrasound.

Drug-coated/drug-eluting balloons (DCB/DEB) have been shown to be very effective in treatment of patients with DES-ISR.[4] According to a single-center, randomized study, DCB showed better clinical and

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angiographic results in treatment of DES-ISR in comparison to BA.[9] The PEPCAD-DES study, a prospective, multicenter, randomized trial of 110 randomly assigned patients, comparing the impact of paclitaxel-coated balloon angioplasty for treatment of DES-ISR versus conventional BA showed that paclitaxel-coated balloon angioplasty was superior to BA alone for treatment of DES-ISR.[10] In addition, ISAR-DESIRE 3 study, a prospective, randomized, multicenter clinical trial including 402 patients with "limus"-DES-ISR comparatively investigated the efficacy of paclitaxel-eluting balloon versus paclitaxel-eluting stent versus BA alone and confirmed that DCB/DEB was non-inferior to PES and that both DCB/DEB and PES were superior to BA alone in treatment of DES-ISR.[11] Available data from these studies suggest that DCB/DEB are superior to BA in treatment of DES-ISR. Unfortunately, RIBS-IV trial demonstrated that everolimus-eluting stents (EES) provide superior angiographic and clinical results compared with DEB in patients with DES-ISR.[12] Another important study, ISAR-DESIRE 4, randomizing 252 patients showed that lesion preparation with a scoring balloon before use of paclitaxel-coated balloon is linked to better outcomes than BA before paclitaxel-coated balloon in patients with limus-eluting stent-ISR.[13]

Available data from observational studies supports the opinion that DES offer significantly better results than other strategies including BA and cutting balloon angioplasty for treatment of DES-ISR. Whether to use DES with the same drug (homo-DES approach) or DES with different type of drug (hetero-DES approach) for treatment of DES-ISR remains an open issue and triggers wide debate in the scientific community. One of the trials in this field, the ISAR-DESIRE 2 trial which included 450 patients with sirolimus-DES-ISR has confirmed that there was no significant difference between antirestenotic efficacy and safety of sirolimus-DES (homo-DES) and paclitaxel-DES (hetero-DES) for treatment of sirolimus-DES-ISR.[5,14] This conclusion does not support the theory that switch DES strategy should be used for DES-ISR. Results from this trial suggest that focal pattern of DES-ISR might not be a consequence to drug resistance as previously thought, but most probably to some other causes like gap, stent fracture, localized polymer disruption, improper drug elution or even their combination, whereas diffuse pattern of DES-ISR is probably due to drug resistance.[5] Regarding bioresorbable vascular scaffolds as an option for treatment of DES-ISR, currently there are anecdotal cases only and we need data from large randomized clinical trials to confirm their efficacy and safety in these circumstances.[4]

There are a few observational studies that have investigated VBT for treatment of DES-ISR.[15,16] In general, vascular brachytherapy is effective therapeutic approach since it provides suppression of the proliferative process and reduces rates of clinical and angiographic restenosis. Torguson et al. suggested that VBT in patients with DES-ISR was clinically useful therapeutic approach. However, use of VBT for treatment of DES-ISR has been significantly reduced in last decade since high rates of restenosis and some technical problems have been experienced.[5] CABG remains the last treatment option when previously mentioned techniques have failed in attempt to solve the issue with DES-ISR. It is usually recommended for patients experiencing DES-ISR in a complex coronary lesion scenario and extended coronary artery disease (multivessel CAD) or patients with multivessel/recurrent DES-ISR.[5]

Conclusion

Despite the advent of newer generation of DES and improvement in the field of biotechnology of coronary stents, the issue of DES-ISR still exists and tends to grow due to increased use of second-generation DES worldwide. Typical morphological pattern for DES-ISR is focal and it is associated with better outcome. Incidence of diffuse pattern type is not negligible and it is usually linked to a higher incidence of recurrent DES-ISR. There are several possible treatment options for DES-ISR but the optimal treatment remains unclear. Evidences support DES and DCB/DEB as currently effective treatment approach for DES-ISR that provides acceptable clinical and angiographic results. Efforts should be made in direction to conduct large randomized clinical trials that could enlighten the mechanisms of DES-ISR and provide data on the optimal treatment approach for patients with DES-ISR. Initial hope exists with bioresorbable vascular scaffolds (BVS) but further studies are required in order to provide long-term safety and efficacy results.

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Conflicts of interest

Author declares there are no conflicts of interest.

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