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Defeating In-Stent Restenosis: The Bugaboo of Percutaneous Coronary Intervention

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Abstract

Despite numerous advances in coronary intervention techniques, in-stent restenosis (ISR) remains the Achilles heel of interventional cardiology. The incidence of ISR varies from 10-50% and depends on the absence or presence of several risk factors such as small vessel size, longer lesions, and diabetes. Drug-eluting stents (DES) have dramatically reduced the rates of restenosis and target vessel revascularization in a wide spectrum of patients with varying lesion morphologies. The interventionists must do a strategic evaluation of their patient before doing angioplasty to prevent ISR. Intracoronary imaging might help to understand the mechanism and to decide the management. In this article, we describe and compare the contemporary treatment modalities in patients who develop ISR. We also describe the role of imaging in the evaluation and characterization of in-stent restenosis. Various modalities of treatment like balloon angioplasty, cutting and scoring balloon, rotational atherectomy, excimer laser coronary angioplasty (ELCA), drug-coated balloons, drug-eluting stents, brachytherapy, and the role of coronary artery bypass grafting (CABG) have been discussed.

Keywords: Restenosis, hyperplasia, elastic recoil,vascular remodeling, neoatherosclerosi, neointimal

Introduction

Restenosis is designated as the reduction in lumen diameter following percutaneous coronary intervention (PCI). This phenomenon is because of recoil if no stent is used; otherwise, it is determined by an excessive tissue proliferation in the lumen of the stented artery called "neointimal hyperplasia"or by a newly transpiring atherosclerotic process called "neoatherosclerosis" [1]. Due to different clinical, angiographic, and operative factors, the exact incidence of in-stent restenosis (ISR) is difficult to establish. In the pre-stent era, its incidence ranged between 32–55% of all PCI [2-5] and dropped too successively to 17–41% with the introduction of bare-metal stents (BMS) [6-8]. The novel innovation ofdrug-eluting stent (DES), especially 2ndgeneration, and drug-coated balloon (DCB) further reduced restenosis rate below 10% [9-10]. We hereby shed light on the main characteristics of ISR along with its treatment strategy in the current era.

Pathogenesis

The three major pathogenic mechanisms that underlie restenosis are:

Early elastic return (recoil)

Vascular remodeling

Neointimal hyperplasia

The first and the second mechanisms are typical of Percutaneous Old Balloon Angioplasty (POBA) before the stent era. On the other hand, the presence of metallic struts promotes a new mechanism called neointimalhyperplasia [11].

Elastic Recoil and vascular remodeling

Restenosis appears to be determined primarily by the direction and magnitude of vessel wall remodeling. An increase in the size of the external elastic membrane is adaptive, whereas a decrease in it contributes to restenosis. Stenting reduces acute recoil due to scaffolding. Vascular remodeling is a complex phenomenon including also medial and/or adventitial response to injury. On the other hand, after balloon angioplasty, the contribution of neointimal hyperplasia to restenosis is relatively limited, and lumen narrowing is mostly determined by vessel remodeling.

Neointimal hyperplasia

Higher levels of CRP were evidenced at follow-up in patients with in-stent restenosis than without, suggesting that inflammatory processes play a key role in the occurrence of in-stent restenosis [12]. The pathophysiology of restenosis is complex and incompletely

understood. Catheter-induced vascular injury causes an immediate and progressive release of thrombogenic, vasoactive, and mitogenic factors leading to platelet aggregation, thrombus formation, and inflammatory changes, with activation of macrophages and smooth muscle cells. These events induce the production and release of growth factors and cytokines, which in turn may promote their own synthesis and release from target cells. Thus, a self-perpetuating cascade is initiated that results in the migration of smooth muscle cells from their usual location in the media to the intima, where they undergo a phenotype change, produce an extracellular matrix, and proliferate. The restenotic lesion is therefore thought to be a proliferative lesion, with both cellular and matrix components causing an increased tissue mass [13]. Neoatherosclerosis is more frequent in DES as compared with BMS so that the drug released from the former seems to be one of the causative factors due to the incomplete endothelialization related to the drug itself [14-15]. Disruption of the necrotic core of lipid-rich plaques and lipid core penetration by stent struts are both associated with chronic inflammation. These factors are in turn associated with greater neointimal growth. Because some degree of arterial injury is unavoidable during stenting, therapies directed against local inflammation are a logical target to reduce neointimal growth [16-17]. Chronic inflammation is augmented by the presence of a foreign body (stent) and arterial injury. It is possible that the constant motion of the semirigid stent damages peri-strut neovessels resulting in local hemorrhage and fibrin deposition. The presence of neovessels within the neointima offers a potential target for anti-restenosis therapies [18].

Clinical Presentation

The neointimal proliferation induces gradual re-narrowing of a stented coronary artery called ISR [19]. The angiographic ISR has depicted a stenosis within the stented segment or its edge (5-mm segment proximal and distal to the stent) of more than 50% of the arterial diameter [20-21]. The Clinically ISR is defined as the presence of >50% diameter in-stent stenosis along with one of the following: symptoms of recurrent angina, objective signs of ischemia, ischemic fractional flow reserve (FFR) <0.80, the minimum cross-sectional area of < 4 mm2 (6 mm2 for left main) in intravascular ultrasound (IVUS) or restenosis with luminal diameter reduction even without clinical symptoms or signs.

ISR may be due to patient-related, lesion related, and procedure-related (Table 1) factors.Stent underexpansion, metal jacket, small vessel disease, and residual plaque burden at the stent edge constitute all major procedure-related factors of ISR [22]

Table 1: Predictors of in-stent restenosis

Patient-related	Diabetes mellitus Chronic renal failure Old age Female Genetic
Lesion-related	Chronic occlusion Bifurcation Ostial lesion Tortuous lesion Small vessel (< 3mm) Long lesion (>20 mm) Severe calcification Saphenous vein graft
Pharmacological	Resistance to stent drug Hypersensitivity to stent components
Biological	Plasma Proteolytic enzymes Matrix Metalloproteinases (MMPs)
Mechanical	Stent malappostion Stent under-expansion Edge trauma Geographical miss Stent fracture

The Mehran classification created for BMS-ISR lesions is the most widely used (Table 2) [20]. This has also been shown to have prognostic value in DES-ISR.Additionally, this morphological scheme has been validated in patients with ISR: The lesions B2 and C of the American College of Cardiology/American Heart Association classification demonstrate suboptimal acute results, a higher restenosis rate, and poorer long-term clinical outcomes [23].

Table 2: Classification of in-stent restenosis [12]

Type 1 focal (≤ 10 mm intrastent) • I A articulation or gap • I B margin • I C focal body • I D multifocal
Type 2 diffuse >10 mm intrastent
Type 3 proliferative 10 mm extending beyond the stent margins
Type 4 total occlusion
Restenotic lesions with TIMI flow grade of 0

The time course of neointimal hyperplasia differs considerably between DES and BMS. The vascular response to DES implantation is epitomized by delayed arterial healing [24]. DES-ISR tends to be focal, particularly at the stent edge or in areas of stent fracture. The diffuse intimal proliferation in DES is characterized by a lack of overall suppression of neointimal hyperplasia unless there is mechanical stent failure.Of note, focal neoatherosclerosis occurs earlier and more frequently in DES-ISR compared with BMS-ISR [25].

ISR represents a relatively benign clinical entity with a predominantly stable clinical presentation. However, many patients with ISR present with acute coronary syndrome secondary to neoatherosclerotic plaque rupture and thrombus formation [26]. The late stent thrombosis might represent a step in the continuum of the neoatherosclerotic process observed in DES-ISR. Conversely, as the natural history of asymptomatic patients with angiographic restenosis remains favorable [27]. Treatment of such patients based on oculostenotic reflex should be avoided whenever possible. A few studies validate the use of FFR for clinical decision making in ISR similar to de novo lesions and demonstrate that deferring intervention in patients with an FFR of> 0.75 is safe and appropriate.

Evaluation

The etiology of stent failure is critical to crafting the strategies for the most appropriate treatment while managing patients with ISR (Table 3). Depiction of ISR by angiography remains inadequate due to limited resolution and inherent deficiency in quantifying vessel

size, stent size, stent expansion, number of stent layers, in-stent calcific neoatheroslcerosis, and extra-stent calcific disease. Imaging modalities such as IVUS and OCT furnish in-depth evaluation of the native artery and stented segment and readily pin down the precise mechanism of stent failure (Table 3) in contrast to angiography. Both the US and European PCI guidelines endorse the use of such modalities in the diagnosis and treatment of stent failure (Class IIa recommendation, level of evidence C) [28-29]. Embracing IVUS and OCT during initial PCI is likely to attenuate the steady increase in ISR. This is especially important in light of recent imaging studies that demonstrate that suboptimal stent deployment occurs in 31% to 58% of patientsand this scenario confers an increased risk of adverse clinical outcomes [30-32]. Emerging data has recently demonstrated that the use of intravascular imaging during PCI is not only associated with stent failure and target lesion failure (TLF), but also with a reduction in cardiovascular mortality [33-34].

Table 3: In-stent restenosis intervention guided by intravascular imaging

Mechanism of in-stent restenosis	Potential interventions
Unstented/gap segment	Balloon angioplasty Drug-eluting stent
Severe neointimal hyperplasia	Balloon angioplasty Excimer laser coronary angioplasty Balloon angioplasty
Stent fracture	Balloon angioplasty Balloon angioplasty Brachytherapy
Undersized	High pressure balloon angioplasty Scoring/cutting balloon Larger DES
Underexpansion	High pressure balloon angioplasty Scoring/cutting balloon Excimer laser coronary angioplasty Rotational atherectomy Drug-eluting stent
Multilayered stent	Drug-coated balloon Brachytherapy Coronary artery bypass graft

A contemporary image-guided ISR treatment optimization ensures the treatment of modifiable entities predicting stent failure. The specific goals are to ensure final stent expansion/lumen area to > 90% of the proximal and distal reference segment, no inflow or outflow obstructions within 5 mm of the proximal or distal stent edge that has a minimal lumen area (MLA) < 5.0 mm2 by IVUS or MLA < 4.5 mm2 by OCT and, without any major edge dissections defined as > 60 degree, > 3 mm in length, or penetrating the media.(Figures 1 and 2)

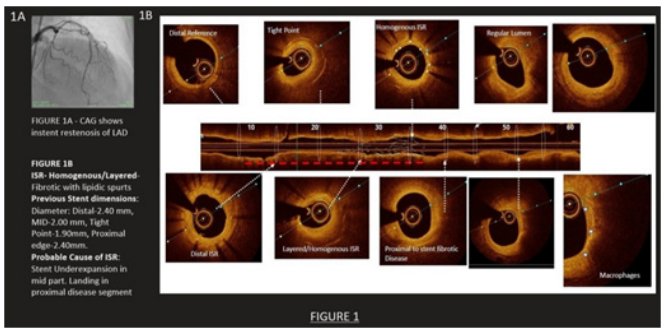

Figure: 1 (1A) Angiogram of in-stent restenosis in LAD; (1B)OCT findings of the same

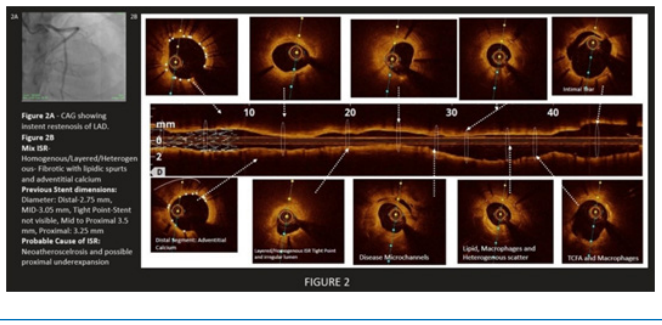

Figure: 2 (2A) Angiogram of in-stent restenosis in LAD; (2B) OCT findings of the same

Treatment of ISR

Balloon angioplasty (BA)

BA is one of the earliest treatment modalities to be used in patients with ISR [35]. The axial and longitudinal tissue extrusion along with further stent expansion confers immediate angiographic improvement with BA [36-37]. Results are particularly favorable in patients with a focal ISR. In the setting of stent underexpansion, high-pressure noncompliant balloon inflations are the preferred strategy. In general, a balloon to artery ratio of 1.1 to 1 is recommended for sizing while treating ISR [38]. BA is often limited by sub-acute tissue re-intrusion back into the lumen that tends to occur within minutes of the last balloon inflation [39]. This explains the "early lumen loss" phenomenon associated with subsequent recurrent restenosis. Of note, edge-related complications should be carefully avoided during aggressive balloon dilations.Balloon slippage outside the stent (watermelon seeding) is sometimes encountered during oversized balloon inflation in severe diffuse narrowing leading to edge dissection. This phenomenon is prevented by the incorporation of a buddy wire, non-compliant balloon (Figure 3), shorter balloon length, slow inflation, or scoring/cutting balloon [40].

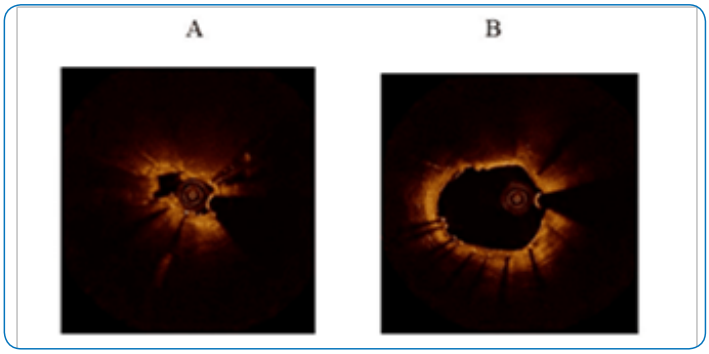

Figure 3: Optical coherence tomography depicting in-stent restenosis

(3A) Stent underexpansion; (3B) Excellent minimum stent area after dilatation with non-compliant balloon

Cutting and scoring balloon

One study reported lower rates of restenosis with the use of a scoring balloon compared with a conventional balloon prior to a DCB. Scoring and/or cutting balloons prevent balloon slippage, but their higher profile may limit device navigation [41].

Rotational atherectomy (RA)

RA compared to BA has demonstrated mixed results for the treatment of ISR [42-43]. Intracoronary imaging studies have confirmed the presence of calcium within neoatherosclerotic plaques, and RA might be an appropriate tool for lesions refractory to high-pressure balloon inflation. RA seems to play a pivotal role in undilatableunderexpanded stents [44].

Excimer laser coronary angioplasty (ELCA)

The stent expansion is materialized by an ELCA with contrast injection in ISR, secondary to stent underexpansion which refractory to high-pressure balloon inflation [45]. Recently, a study demonstrates a greater acute luminal gain in DES-ISR with ELCA [46].

Drug-coated balloon (DCB)

The European Society of Cardiology guideline has granted the use of DCB for the treatment of BMS or DES ISR (class I, level A). The innovation of DCB allows the release of anti-proliferative drugs to the area of ISR without leaving behind an additional layer of implant. Hence, many interventionistsprefer to use of DCBs over DES in patients presenting with first ISR, reserving the use of another DES layer for subsequent recurrences after DCB treatment. The use of DCB instead of repeat DES is particularly appealing in patients with multi-layered ISR, those with relevant side branches emerging from the stent with ISR, and those who may benefit from a shorter dual-antiplatelet therapy. The initial study of BMS-ISR demonstrated that DCB was superior to BA alone [47]. DES ISR represents a complex scenario of a high-risk population with primary failure of local drug delivery by the stent and the potential relative efficacy of DCBs versus DES according to the underlying tissue substrate (e.g neointimal hyperplasia vs. neoatherosclerosis) [48-49]. DCB provides superior clinical and angiographic outcomes in patients with DES-ISR compared with BA alone [50]. The efficacy of DCB in patients with DES-ISR has been subsequently confirmed in a randomized trial including patients with any type of DES-ISR [51]. Moreover, another controlled study suggests that DCB is equivalent to paclitaxel-DES in patients with DES-ISR [52]. Of note, DCB is superior to BA alone and similar to first-generation DES in patients with BMS or DES-ISR [53].

Drug-eluting stent (DES)

The ISAR-DESIRE (Intracoronary Stenting or Angioplasty for Restenosis Reduction-Drug-Eluting Stents for In-Stent Restenosis) trial is the first randomized trial to assess the value of DES in patients with BMS-ISR [54]. The rate of recurrent restenosis is found to be significantly lower with sirolimus- (14.3%) and paclitaxel- (21.7%) DES compared with BA alone (44.6%).A subsequent meta-analysis comparing these 2 DES for BMS-ISR reports similar results [55]. The clinical outcomes in patients requiring treatment for DES-ISR are worse compared with patients with BMS-ISR. DES provides superior results compared with other strategies such as BA or cutting balloon angioplasty in DES-ISR [56]. There does not any clear evidence on which type of DES should be used to treat ISR of a DES. The debate regarding whether to use a homo-DES approach versus a hetero-DES approach continues [57]. However, it is speculated that a switch approach might overcome drug resistance or polymer-related problems. One study suggests that there is no significant difference between the hetero-DES and homo-DES approach and the use of second-generation DES is superior to first-generation ones, and intravascular imaging guidance improves angiographic and clinical outcomes [58]. Despite these benefits of repeat stenting with DES in the management of DES-ISR, current data suggests that 10–20% of these patients will go on to develop recurrent ISR [59].

Brachytherapy

Brachytherapy effectively suppresses neointimal hyperplasia and significantly lowers clinical and angiographic restenosis rates. However, its use declined after demonstration of superior outcomes with DESs for the treatment of BMS-ISR in trials. Brachytherapy could be recommended in the setting of recurrent DES-ISR in view of favourable outcomes with several observational and prospective trials [60-61].

Coronary artery bypass graft (CABG)

CABG should be considered as the best means to prevent recurrences in patients with recurrent recalcitrant ISR and large areas of myocardium at risk.

Comparison of contemporary treatment modalities

A meta-analysis by Siontis et al. employed 27 trials with 5,923 patients at 6 months to 1-year follow-up. The primary outcome of this was percent diameter stenosis at follow-up, and the secondary endpoint included binary restenosis, rates of TLR, myocardial infarction, or death [62]. All modalities included BA alone, debulking techniques, brachytherapy, BMS, DES, and DCB. Repeat

stenting with everolimus-DES was found to be superior to all other modalities for both the primary outcome as well as for binary restenosis rates and TLR. DCB appeared to be the second most preferable treatment but did not achieve a significant difference over sirolimus or paclitaxel-eluting stents. Another meta-analysis reported that repeat stenting with DES was moderately more effective than DCB in ISR reducing the need for TLR at 3 years. The incidence of a composite of all-cause death, MI, or target lesion thrombosis was similar between groups. The rates of individual endpoints, including all-cause mortality, did not vary significantly between different groups [63].

Conclusion

Treatment of ISR remains a challenge despite the introduction of DES. Many cases of ISR in the modern era are focal in nature and can be treated in a simple fashion; however, the optimal approach for treating ISR must be ascertained on a case-by-case basis. The interventionists need to craft the strategy of treating the individual patient with consideration of lesion characteristics. Intracoronary imaging may play a pivotal role to understand the underlying mechanism of ISR, which also helps in decision-making. Amongst various contemporary therapeutic modalities, second-generation DES and DCB provide the best clinical and angiographic results. Multilayered recalcitrant ISR is a bugaboo of PCI that warrants major efforts to aggressively address residual underexpansion and optimize procedural results. DCB represents an elegant strategy for these patients but provides unsatisfactory long-term outcomes. Additional DES provides good acute results and midterm clinical outcomes but keeps on fueling a perverse vicious circle of ISR begetting ISR. Further research is warranted to solve this therapeutic conundrum. CABG may be recommended to such patient population.

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