CHAPTER 8

Challenges, Pitfalls, and Step-by-Step Techniques for Treating In-Stent Restenosis

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Introduction

Despite advances in stent technology, in-stent restenosis (ISR) remains a challenge. While incidence of restenosis is high with bare metal stents (BMS), drug-eluting stents (DES) are not without the risk of ISR. In fact, ISR remains the leading cause of treatment failure after any stenting.

Angiographically, ISR is defined as luminal narrowing that is greater than or equal to 50% of the vessel diameter within a previously placed stent or at its edges. While both lesions that have been previously treated with balloon angioplasty as well as those treated with stenting are at risk for restenosis, we will focus on the treatment of restenosis within previously stented lesions. Clinical presentation of ISR varies from recurrent stable angina to the spectrum of acute coronary syndromes, including acute myocardial infarction.

Causes and Mechanisms of ISR

After stenting, a vessel undergoes endothelial injury within the artery wall that consists of an inflammatory response. While the majority of vessels recover from this trauma during a healing process, some vessels undergo a pathologic response with abnormal healing that leads to narrowing of the vessel diameter, otherwise referred to as restenosis. This is a result of negative vascular remodeling with neointimal hyperplasia in the case of a BMS, while in-stent atherosclerotic plaque or "neoatherosclerosis" is felt to be the underlying factor leading to ISR within DES.[1]

Time Course of BMS-ISR vs DES-ISR

It is well-known that BMS-ISR and DES-ISR are quite different. Restenosis rates within BMS are significantly higher as compared to DES. In general, the incidence of ISR within BMS ranges from 16% to 44%, compared to less than 6% within DES. It is also well recognized that ISR within BMS occurs relatively early compared to DES, typically within 6 to 12 weeks post BMS deployment. The development of DES reduced the rates and time course of ISR, which typically occurs later (months to years post stenting) as compared to BMS.[2]

Classification System, Patterns of Restenosis, and Clinical Significance

Almost 2 decades ago, Mehran and colleagues developed a system to angiographically classify restenosis within bare metal stents.[3] This classification system, which uses four categories (**Table 1**), is still widely used today and is also now applied to ISR within DES. Also, it is important to note that restenosis within drug eluting stents is generally more focal in nature, as compared to the diffuse stenosis seen within BMS.

Importantly, this classification system has prognostic value as the need for repeat revascularization, or target lesion revascularization (TLR), increases with the increasing level of ISR classification as seen in **Figure 1**.

Predictors of Restenosis

One of the challenges that cardiologists face is the difficulty to predict restenosis, both clinically and angiographically. The potential underlying mechanism for the restenosis can be due to a number of factors, including those that are patient, procedure or lesion related. Several patient-specific factors have been associated with higher restenosis rates. The strongest independent predictor of restenosis is diabetes mellitus,[4] but restenosis can also be linked to hypertension, end stage renal disease and prior vein grafts.

The characteristics associated with the lesion can also warn of future restenosis, such as ostial lesions, diffuse lesions requiring stenting of long segments, vein graft disease, and small vessel size. Avoiding procedure-related factors such as stent under-deployment, over-expansion, or unacceptable residual stenosis can help prevent restenosis later. Thus, operator expertise and technical factors play an important role in prevention of the restenosis that may occur later.

Indications to Intervene

Universal guidelines that inform the appropriateness of screening for and intervening on restenotic lesions are not currently available. The general consensus from the literature has pointed toward proceeding with intervention for a restenotic lesion that is greater than 50% narrowed in the presence of symptoms and for all lesions that are greater than 70% stenosed.

For those lesions that are angiographically intermediate-appearing lesions, the use of fractional flow reserve (FFR) or instantaneous flow reserve (IFR) may be appropriate to guide treatment decisions.

Role of Intracoronary Imaging

Intracoronary vascular ultrasound (IVUS) or optical coherence tomography (OCT) is now increasingly being used to determine the characteristics of the restenosis as a means to guide appropriate therapy. IVUS is useful in identifying neointimal hyperplasia, stent underexpansion or problems at the stent edges, and its use is therefore recommended prior to definitive treatment of these lesions. OCT also offers favorable axial resolution, which can provide clear pictures of the neointimal surface, the interface between the vessel and the lumen, features of lesions instability, and the strut distribution. Overall, these imaging data help in evaluating for stent underexpansion, stent fracture, edge stenosis and neoatherosclerosis.

Approaches to Treatment, Challenges and Potential Treatment Strategies

Several strategies for the treatment of ISR have surfaced over the years including balloon angioplasty, atherectomy, and brachytherapy. More recent methods include repeat stenting and drug-coated balloons.

Plain old balloon angioplasty (POBA), with either compliant or noncompliant balloons, was the earliest technique. It is recommended to choose a balloon length that aims to treat the length of the restenosed segment rather than the length of the entire stented segment. In this way, it is perceived to be a more favorable option for focal lesions as compared to diffuse ones. While it has a relatively low complication rate, it did not prove to be an effective solution to the ISR. Rates of restenosis after POBA are high, around 30 to 60%.

Cutting and scoring balloons have also been attempted for the treatment of ISR as a way to debulk lesion buildup within the restenosed segment. These devices offer an abrasive surface on the balloon that prevents slippage and allows the separation of severely calcified and fibrotic lesions. Promising results surfaced from the ISAR-DESIRE 4 (Intra-coronary Stenting and Angiographic Results: Optimizing Treatment of Drug Eluting Stent In-Stent Restenosis 4) Trial in 2015, which compared treatment strategies with a scoring balloon versus a standard balloon in patients with DES-ISR. The investigators showed a reduction in restenosis rates at follow-up angiography for those treated with a scoring balloon as compared to regular balloon angiography at 6 to 8 months. However, there was no difference in target lesion revascularization or death between the two groups.[5] While the utility of these specialized balloons yielded slightly better results compared to POBA, they did not prove to be an answer to the restenosis dilemma and thus have also fallen out of favor as a primary means of treating ISR.[5]

Atherectomy is an effective tool to tackle severe calcific lesions. The success of rotational atherectomy in reducing restenosis rates has been controversial. The ROSTER (Randomized Trial of Rotational Atherectomy Versus Balloon Angioplasty for Diffuse In-Stent Restenosis) Trial showed promise in reducing the rates of restenosis when compared to balloon angioplasty alone. However, the ARTIST (Angioplasty Versus Rotational Atherectomy for Treatment of Diffuse In-Stent Restenosis Trial), which was much larger, challenged these findings, and actually demonstrated higher restenosis and complication rates in the atherectomy group as compared to balloon angioplasty alone.[5]

The so-called “sandwich” technique, in which restenosis inside a BMS is restented with another BMS, has also been trialed historically. This technique offered larger luminal gains as compared to POBA. However, with the introduction of DES, this method is now rarely used.

Vascular brachytherapy is a technique that utilizes radiation therapy within the vessel to prevent neointimal proliferation. This is effective at tackling ISR within the stent but not at the stent edges. Brachytherapy has been shown to be superior to POBA, but its use is limited to operator expertise, availability and lack of radiation oncology support in centers.[2]

Excimer laser coronary angioplasty is a technique that utilizes thermomechanics to attack rigid, calcific lesions within an ISR segment. While no trial has shown its strengths over traditional percutaneous transluminal coronary angioplasty (PTCA), it has been approved for use prior to brachytherapy when tackling ISR.[1]

With the introduction and maturation of DES technology, repeat stenting with a drug eluting platform or POBA with a drug-coated balloon technology adds to the armamentarium of management strategies for ISR. Repeat stenting with DES is the most widely used strategy and is performed in the majority of cases. It has been shown to be superior to POBA for BMS ISR in several studies.[5] However, ISR in DES-treated lesions is the most common scenario today and, unfortunately, has been the most challenging situation to treat. In the majority of cases, repeat stenting with another DES in a DES-ISR lesion is undertaken. The perceived challenges of repeat stenting include the unknown effect of repeatedly subjecting a vessel to antiproliferative therapies. However, while this is a perceived concern, long-term safety data are unknown at this time. There is also not a universal consensus regarding the type of DES to place as large randomized trials evaluating second generation DES for treatment of DES-ISR are currently lacking. It has been shown, however, that repeat stenting with newer generation, everolimus-eluting stents, is associated with a lower risk of TLR than all other strategies listed above.[6]

Drug-eluting balloons have shown promising results and are rising in use for both BMS-ISR and DES-ISR. This strategy is reasonable to use if available and may be an especially promising strategy in cases where repeat stenting should be avoided such as small vessel diameter, ostial lesions, and high bleeding risks with DAPT.[6]

As with de novo lesions, there should be a consideration for surgical intervention where appropriate. For instance, in a vessel that has undergone numerous repeat attempts at correcting restenosis or one in which there is concurrent obstructive disease in other major vessels, it may be appropriate to consider surgical revascularization. In these situations, a consultation with the "Heart Team" including cardiothoracic surgeons to evaluate for the candidacy of bypass surgery is recommended.

Summary of Techniques and Step-by-Step Guide

While no uniform treatment algorithm exists, the American College of Cardiology (ACC)/American Heart Association (AHA) guidelines for percutaneous coronary intervention have listed a Class I indication to treat a BMS restenosis with a DES. The ACC/AHA have also listed a Class IIb recommendation to use balloon angioplasty, BMS or DES for restenosis within a DES. As the treatment of a DES-ISR remains the most troublesome, here, we provide a step-by-step technique that we utilize for the majority of DES-ISR lesions. However, it should be emphasized that a patient-specific treatment plan is of utmost importance for individual success as seen in **Figure 2**.

1. The initial step in approaching an ISR lesion should be to perform intravascular imaging with IVUS or OCT. Imaging allows for evaluation of the size of the vessel and evaluates for structural etiologies of the restenosis, i.e. mal-expansion or mal-apposition of the prior stent.
    a. If a structure abnormality is identified, proceed with high-pressure balloon dilation. Then proceed to step #2 to determine if repeat stenting is feasible.
    b. If no structural abnormalities are identified on imaging, then determine if repeat stenting is feasible (proceed to step #2).
2. Determine if repeat stenting is feasible.
    a. DES deemed feasible: proceed to stenting with DES (step #3).
    b. Desire to avoid repeat stenting: proceed to alternate techniques (step #4). In certain situations, such as repeated restenosis with multiple layers of metal already present or the need to avoid long-term dual antiplatelet therapy due to high bleeding risk, repeat stenting with another DES is not desirable. In these situations, recommend proceeding with alternate methods (proceed to step #4).
    c. If recurrent stenosis: consider surgical revascularization if appropriate.
3. Repeat stenting with DES.
    a. In the majority of cases, repeat stenting is deemed feasible. Recommend placement of a newer generation DES.
4. Proceed to alternate methods, including drug-coated balloon, atherectomy or brachytherapy. These methods should be considered in situations in which it is ideal to avoid repeat layers of

metal/stenting within the vessel or situations in which avoiding prolonged dual antiplatelet therapy is necessary.

   a. Drug-eluting balloon (DEB) in lieu of a DES. While we recommend a DES to treat ISR in the majority of cases, there are situations in which sole use of a DEB may be considered. These include patients at high bleeding risk or other reasons that long-term dual antiplatelet therapy may not be appropriate, potential for increased layers of stenting > 3, or in cases that the geographic location of stenting may compromise flow to other vessels.
   b. Rotational atherectomy. Consider using atherectomy for severely calcified lesions.
   c. Brachytherapy. When above-mentioned techniques fail or are not available, brachytherapy can be considered.

5. Following intervention, follow recommendations for dual antiplatelet therapy in accordance with the most-updated ACC/AHA antiplatelet guidelines.[7]

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Table 1: Mehran Classification System of in-stent restenosis

Class	**Lesion Length**	**Lesion Location**	**Percentage of TLR**
Class I Focal	<10mm	At unscaffolded segment (1A), proximal or distal margin of stent (1B), body of stent (1C), or combination of these sites, i.e. multifocal (1D)	19%
Class II Diffuse Intrastent	>10mm	Confined to the stent without exceeding outside the margins of the stent	35%
Class III Diffuse Proliferative	>10mm	Extend beyond the margins of the stent	50%
Class IV Total Occlusion	>10mm	Totally occluded, TIMI 0 flow	98%

Figure 1: Schematic image of lesion classes

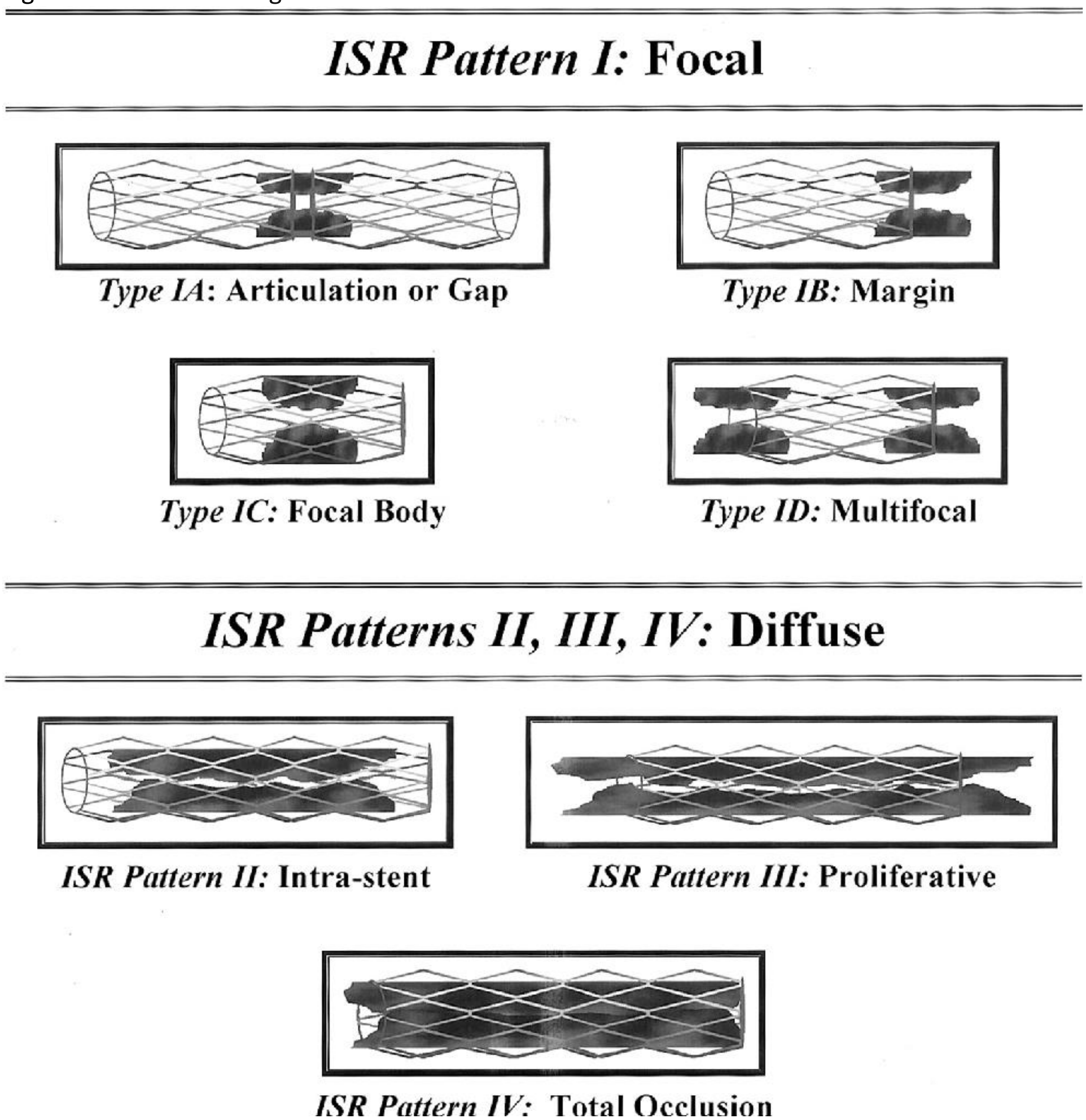

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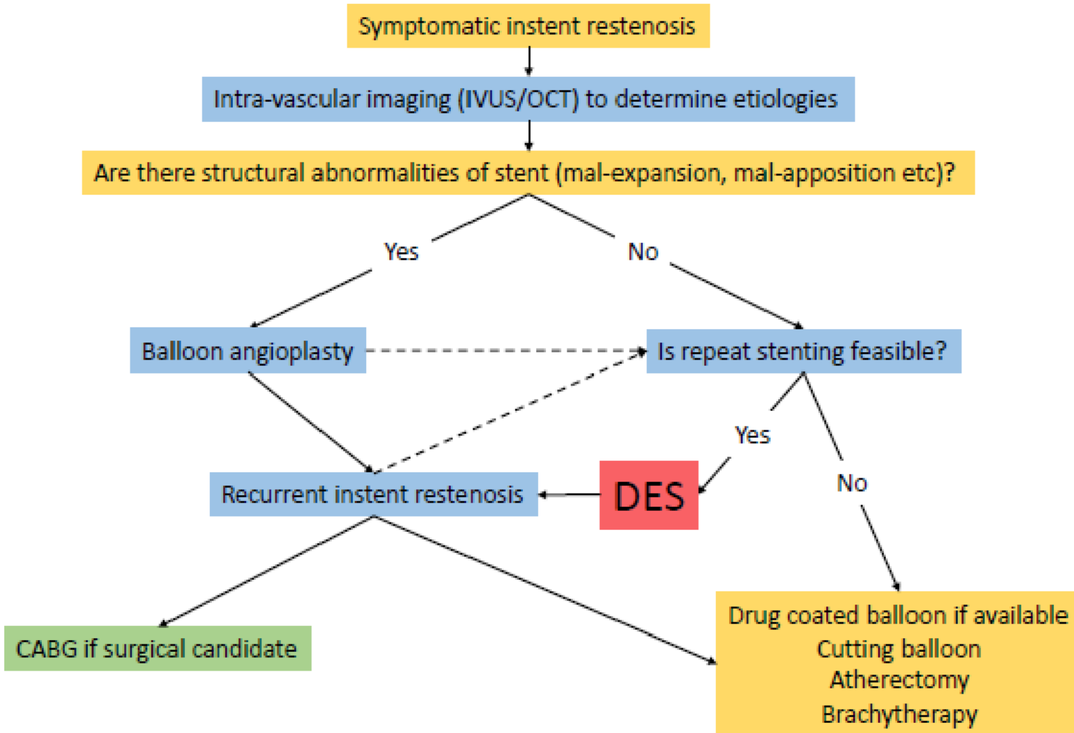
Figure 2: Step-by-step guide



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