

# A case of in-stent restenosis-predictors of risk and treatment modalities

## Abstract

Undoubtedly, advancement in science has given many breakthroughs in the treatment of coronary artery disease, forgetting not, that it is at the cost of adverse effects and limitations do exist. Coronary stents are example of such advancements bringing along with it complications like in-stent restenosis (ISR). This phenomenon is becoming increasingly common at centres where bare metal stents (BMS) are frequently used. However, newer drug eluting stents (DES) are not completely devoid of such complications. ISR adds to financial burden and carries poor prognosis in terms of morbidity and mortality. Therefore, the need for more sophisticated technology, techniques and preventive modalities arise in order to alleviate the occurrence of ISR.

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**Abbreviations:** ISR, in-stent restenosis; BMS, bare metal stents; DES, drug eluting stents; LAD, left anterior descending; OM, obtuse marginal branch; RCA, right coronary artery; PCI, percutaneous coronary intervention; NSTEMI, non- ST elevation MI; ST, stent thrombosis; POBA, plain old balloon angioplasty; MLD, minimal luminal diameter; LLL, late lumen loss; EES, everolimus eluting stents; SES, sirolimus eluting stents

## History

A 42year of age young lady, married and housewife, recently diagnosed of hypertension and diabetes for the last 4 months when for the first time she presented with complaint of chest heaviness with radiation to neck and jaw which occurred only on exertion and relieved at rest. Her physical examination was unremarkable. Her baseline ECG, Echocardiography and blood tests were all normal except raised blood sugars for which she was put on sulfonylurea. She was planned for Coronary angiography which showed focal tight stenoses involving Left anterior descending (LAD), obtuse marginal branch (OM) and right coronary artery (RCA). Her percutaneous coronary intervention (PCI) with stenting (DES in LAD, BMS in OM and RCA coronaries) was performed successfully without any complication. TIMI III flow was achieved at the end of procedure. She was discharged a day after the procedure on tab Aspirin 150mg twice daily, Clopidogrel 75mg twice daily, Glucovance 5mg once daily before breakfast, Atorvastatin 20mg once daily at night time. Patient remained asymptomatic for 3months until when she presented with the complaint of recent new onset of chest pain which was relieved by sublingual nitrates and heaviness in chest after taking meals.<sup>1-5</sup>

## Examination

42years old lady of average built lying comfortably in bed with no obvious distress. She is breathing comfortably at room temperature. Her vitals were within normal limit with temp of 98F, pulse 80/min, B.P 136/80 mmHg and >96% oxygen saturation. Her neurologic, respiratory and abdominal examination, were all unremarkable. Her cardiovascular system was also normal with normal first and seconds heart sounds no added sounds.

## Diagnosis/differential diagnosis

- Unstable Angina
- Non- ST elevation MI (NSTEMI)

- In-stent restenosis (ISR)
- Stent Thrombosis (ST)

## Investigations and interventions

Her hemoglobin, blood sugar random, urea and electrolyte, urine R/E, Cardiac enzymes were all within normal limits. Her ECG and Echocardiography did not show any new change. Her repeat coronary angiography showed moderately tight ISR involving BMS in OM and RCA with TIMI II and TIMI III flow, respectively. To add to amazement, DES in LAD was not spared and showed mild ISR with TIMI III flow distally. She was planned for Plain old balloon angioplasty (POBA) for both BMS in OM and RCA.

## Treatment

Patient was treated with aggressive anti platelet and antithrombotic therapy along with optimal anti angina therapy was given for the time she remained admitted. Her blood pressure and blood sugar. Levels were kept within the normal range effectively. In stent restenoses were corrected with POBA for both BMS with TIMI III flow results at the end of procedure and no evidence of residual stenosis.<sup>6,7</sup>

## Discussion

Here is a brief discussion on the pathophysiological mechanism of causing ISR and the related factors with further discussion on the treatment options for ISR.

## Definition

In-stent restenosis is defined as the narrowing of more than or equals to 50% involving either the stented segment or adjacent 5mm segments on both sides of stent.

## Pathophysiology

Arterial vessels are abundant in elastic fibers which furnish it with the property of recoiling once distended by any means. However, this phenomenon is of note during balloon angioplasty (PTCA) which is resisted to some extent by the firm structure of stent. This occurs within seconds to minutes after the procedure. Deployment of stent at the lesion site requires inflation of the balloon to oppose it in approximation with the vessel wall, thereby stretching the plaque and vessel wall layers. This causes intima and media tear which initiates the controlled process of platelet migration and aggregation forming

a thrombus (thrombus redistribution). This phenomenon of thrombus redistribution along with neointimal proliferation makes significant contribution in decreasing the minimal luminal diameter (MLD). Neointimal proliferation is a process by which the smooth muscle cells and myofibroblasts are mobilized from media and adventitia of vessel wall, respectively. Redistribution an over growing of the smooth muscle cells on the stent struts causes luminal loss. This process takes months and is almost complete at 6 months after which there is a shift in the cellular distribution making Collagen and proteoglycan matrix the major component of the growing lesion. Interestingly, this shift of cellularity leads to relative decrease in the late luminal loss due to shrinkage in the width of lesion. This process occurs from 6months to 3years.<sup>8,9</sup>

## Predictors of ISR

There are certain factors which enhances the risk of restenosis. Those factors may be divided in to Patient factors, lesion factors and stent factors (Table 1). There is no ambiguity in the concept of prevention. Therefore, much of our efforts should be concentrated on preventing the occurrence of ISR at first place. Among the predictors from patient factor, history of in-stent restenosis is the major culprit in determining the chances of getting the stent restenosed and for target lesion revascularization (TLR). Clinically however, cardiologists face diabetes more often as a risk factor.

**Table 1** Predictors of In-stent Restenosis

Patient Factors	Lesion Factors	Stent Factors
Diabetes	Narrow lumen	BMS
Renal Impairment	Plaque burden	Increased Length of stent
Female	Long lesion	More number of stents
Gene		Overlapping of adjacent stents
History of re-stenosis		

Among the lesion factor not only the initial small sized vessel, plaque burden or length of lesion are the predictors of ISR but also the post procedural minimal luminal diameter (MLD). One of the studies which observed that the lesser the final MLD after the procedure, the higher the chances for ISR and therefore, the TLR. It is also agreed that the higher balloon pressures causes late lumen loss (LLL), however, studies have not been able to demonstrate the difference in outcome between the low and high pressure balloon deployment of stents. Now considerable evidence is available in support of a refined stent structure with improved results and outcomes in terms of ISR. Second generation drug eluting stents (DES) like Everolimus eluting stents (EES) to be better with decreased late luminal loss and ISR as compared to first generation stents like Sirolimus eluting stents (SES). There is not only the difference in the drug which is eluted by the stents but the lesser strut thickness and refined design.

## Patterns of IS

The patterns of ISR lesions can be divided for simplification purposes in to two broad categories,

- I. Focal:** Lesions localized within the stent confines with <10mm of length are said to be Type I lesions. These could be focal single or focal multiple.
- II. Diffuse:** Diffuse lesions are >10mm in length and may or may not be confined to the edges of stent.
  - i. Type II* diffuse lesions are confined to the stent edges
  - ii. Type III* diffuse lesions over hang the stent edges

*iii. Type IV* diffuse lesions are with total occlusion of stent and TIMI 0 flows distally

There shouldn't arise any doubt in accepting the notion that diffuse lesions have poor prognosis. There is study which compared the angiographic patterns of ISR lesions among BMS and DES. It was found that focal lesions occur in similar incidence in both BMS and DES however, the incidence of diffuse lesions are more in BMS and also in patients with Diabetes and history of previous ISR. Although the medicine is advancing still the data shows not much promise in the treatment options we have by now except for the newly emerging techniques with drug eluting balloons (DEB) and more sophisticated drug eluting stents (DES).

## Treatment of ISR in BMS

**PTCA:** Percutaneous transluminal coronary angioplasty is one of the most studied and easy to perform procedure with high recurrence rate of restenosis and less efficacious in achieving the initial gain in lumen as compared to stents. Balloon angioplasty shows good initial results in treating the restenotic lesion in BMS occurring later in contrast to the treatment of stent lesions occurring within 4months of stent implantation due to higher rates of adverse cardiac events. While performing procedure, special care is to be observed as to not induce dissection at the distal segments of stent. One of the determinants of success achieved through balloon angioplasty with recurrence rate is the type of lesion present. More focal, localized and simple the lesion is, higher becomes the chances of successful procedure and low recurrence rate. Lesions which do not produce any symptoms and occurring more than 6months post procedure generally do not herald any immediate threat and should be left alone because from this time on there is propensity for the lesion to decrease in size and therefore, in the late luminal loss.<sup>10</sup>

**Drug Eluting Balloon (DEB):** For this technique after studying various drugs, paclitaxel was chosen due to its lipophilic properties. Principle of using DEB is to directly expose and absorb the drug to proliferating segments of the vessel wall. This technique has emerged as a ray of hope in treating ISR. A study comparing Paclitaxel eluting balloon (PEB) to (plain old balloon angioplasty POBA) in the treatment of ISR showed a significant reduction in the late luminal loss in the PEB group with resultant reduction in the TVR. Another study by the same researcher confirmed the drastically beneficial effects of PEB as compared to Sirolimus eluting stent (SES) for the treatment of ISR. Study results showed significant reduction in the late luminal loss and adverse cardiac events in the PEB group.

**Cutting Balloon Technique:** Cutting balloon technique uses the rotational and directional atherectomy devices. The principle of using this technique is to reduce the bulk of lesion and achieve a final gain in the minimal luminal diameter. Despite the theoretical potential it holds in giving hope for the treatment of ISR, real world researches do not support the notion rather gives conflicting evidences as compared to the balloon angioplasty. Where one study shows promise in improving outcome with rotational atherectomy as compared to the balloon angioplasty, at the same time other studies show totally opposite results in contradiction. Adverse events included the damage it caused to the struts of stent.

**Repeat Stenting with BMS and DES:** BMS implantation in ISR has shown to be equal to POBA in terms of luminal loss at 6 months. However, BMS is superior to POBA in cases with edge ISR and larger vessel diameter with lesser adverse events. Repeat BMS also has better initial results DES whether SES or PES have shown to

be superior to POBA in following terms; DES reduces the rate of restenosis as compared to balloon angioplasty.

- a. TVR rate is reduced in DES treated ISR.
- b. IVUS proven inhibition of neointimal proliferation.

**Brachytherapy:** Brachytherapy is the use of irradiation in order to reduce the size of lesion. This therapy has shown initial bombastic results which sadly were cancelled out by the late catch up phenomenon and late thrombosis. Both of these complications lead to increased chances of TVR. Brachytherapy was compared head to head with the DES which also supported the fact the TVR increased in the former group demonstrating the superiority of DES over brachytherapy in ISR.

**Prevention of ISR:** First off, use of DES in high risk patients like diabetes mellitus and history of restenosis. Among DES newer generation stents have a better outcome and lesser chances of restenosis as compared to first generation DES and also BMS. After the use of DES, studies show that the use of “triple antiplatelet therapy” with Aspirin, Clopidogrel and Cilastazol for 6 months after placement of DES in diabetics lead to better outcomes in terms of reduced TVR and late lumen loss at 9 months as compared to the use of dual antiplatelet therapy in high risk individuals. There is also evidence that giving high dose oral Sirolimus, for two days before and a week after procedure, in addition to using a DES give additional benefits in terms of reducing the frequency of ISR and thereby reduction in TVR. Outcomes can be improved by the use of rotational atherectomy before stent implantation.<sup>11</sup>

## Learning points

The role of prevention cannot be stressed further as much as it is evident from this case report. There should be a careful synchronicity between the subject and chosen option. Simply speaking individualizing the therapy for coronary artery disease should be carefully considered. Predictors of ISR should be scrutinized before selecting a treatment option. Aggressive antiplatelet therapy with triple drug regime should be considered in selected patients to further reduce the chances of ISR. Off-label use of both BMS and DES should be avoided as it poses more risk of ISR and even late thrombosis in DES patients. Evidence for the use of DES in the treatment of BMS ISR is encouraging and should be confirmed further by large randomized trials. Even though DES shows promising effects in the prevention of ISR, it is not completely devoid of the complication and there is yet to be discovered a promising technique for the treatment of DES ISR.

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## Conflicts of interest

None.

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