Stent Failure: The diagnosis and management of intracoronary stent restenosis (ISR)

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Abstract:

Introduction: Despite advances in stent technology for percutaneous coronary intervention (PCI) in the treatment of coronary disease, these procedures can be complicated by stent failure manifesting as intracoronary stent restenosis (ISR). Even with advances of stent technology and medical therapy this complication is reported to affect around 10% of all percutaneous coronary intervention (PCI) procedures. Depending on stent type (drug-eluting versus bare metal), ISR have subtle differences in mechanism and timing and offer different challenges in diagnosing the aetiology and subsequent treatment options.

Areas covered: This review will be visiting the definition, pathophysiology and risk factors of ISR.

Expert opinion: The evidence behind management options has been illustrated with the aid of real life clinical cases and summarised in a proposed management algorithm.

Keywords: coronary artery disease, in-stent restenosis, intracoronary stent restenosis, ischaemic heart disease, percutaneous coronary intervention

Article Highlights:

- The incidence of ISR varies by stent type and definition, but is reported to affect 2-20% of all PCI at 5 years.
- Factors influencing the development of ISR include pharmacology, biology, patient risk factors, lesion characteristics or mechanical variables relating to stent implantation
- The mainstay of diagnosis of ISR is coronary angiography with the aid of intracoronary imaging
- The management of ISR varies depending on the aetiology as often determined by intracoronary imaging.
- Once the aetiology is defined, treatment can be in the form of new stent implantation (third generation drug-eluting stent) or drug-coated balloon (DCB) treatment. An algorithm is presented in this article with example case studies (in Supplementary Reading).

INTRODUCTION:

Advances in percutaneous coronary intervention (PCI) have facilitated the management of a multitude of complex coronary artery lesions. These included the development of drug-eluting stents (DES) which superseded the use of bare-metal stents (BMS). Though, DESs have significantly reduced target vessel revascularisation (TVR) was reducing stent failure, both types of stents are at risk of intracoronary stent restenosis (ISR). ISR in BMS and DESs have subtle differences in mechanism and timing and offer different challenges in diagnosing the mechanism and subsequent treatment options. A recent report from the National Cardiovascular Data Registry in 2020 has estimated that ISR interventions represented 10% of all PCI procedures in USA, highlighting that though significantly reduced from the BMS era, prevalence of ISR is not uncommon and remains a challenge in modern practice[1].

In this article, we will be visiting the definition, pathophysiology and risk factors of ISR, and review the evidence behind management options illustrated with the aid of real life clinical cases.

DEFINITION OF ISR:

Following stent implantation in PCI, restenosis may take place in the form of a gradual narrowing of the stented segment which most commonly occurs in the first 3-12 months after PCI[2]. Clinically, this may present as recurrent anginal symptoms but could also present as an acute coronary syndrome (ACS) in approximately 10% of patients[3].

The definition of ISR varies, but the most recent consensus is summarised in the following three bulletpoints[3]:

- **Restenosis** – luminal dimeter reduction because of neointimal tissue proliferation.
- **Binary angiographic restenosis** – More than 50% percent luminal narrowing at subsequent angiography.
- **Clinical restenosis** – The presence of both binary angiographic restenosis and clinical symptoms or signs of ischemia (either at rest or with stress) **OR** restenosis with a ≥70% reduction in lumen diameter even in the absence of clinical symptoms or signs.

Signs of ischaemia in this definition include ECG changes, positive cardiac enzymes or limitation of coronary flow as measured by intracoronary physiology testing (such as fractional flow reserve [FFR])[3,4].

INCIDENCE OF ISR:

There has been a number of reports describing the incidence of ISR, but these vary depending on the definition of ISR used, the type of stent and the complexity of the stented lesion. As will be discussed in the following section (Factors influencing ISR development), restenosis rates are generally high in complex lesions such as small vessels, bifurcations and chronic total occlusions (CTO). The other main factor relates to the type of stents, which for the purposes of summarising the evidence has been split between BMS and DES.

- **BMS:** Data on this comes mostly from older studies, but remains relevant, as BMSs are still used, dependent on the financial modelling of different healthcare systems. A pooled analysis of 6,186 patients from six large clinical trials described the incidence of ISR in BMS stented lesions. This was defined as target lesion (TLR) or target vessel revascularization (TVR – combination of TLR, target vessel MI and cardiac death) beyond 30 days[5]. At 12 months, TLR was reported in 12% and TVR in 14.1%. Clinically relevant ISR (symptomatic / positive ECG or cardiac enzymes) occurred in half the patients with angiographic restenosis of greater than 50%. The incidence of TLR was much higher in angiographic restenosis of >70% (73%), compared to those with <60% restenosis (26%)[5].
- **DES:** The rates of ISR in DES stented lesions has been reported to be between 2-20%, varying by type of DES evaluated, lesion complexity and duration of follow up. First-generation DES (sirolimus / paclitaxel) has ISR rates of 13-16% at 5 years[6,7]. Second-generation DES (everolimus / zotarolimus) had TVR rates for ISR at 5-6%[8]. However, all types of DES have been reported in multiple studies to reduce ISR and TLR by 50-75% compared with BMS[8,9].

FACTORS INFLUENCEING DEVELOPMENT OF ISR:

Given the heterogeneity of ISR development and the difficulty in predicting its occurrence, a number of factors have been reported to influence its development[10-12]. These are summarised in Table 1 and include pharmacological, biological, patient-related, lesion-related and mechanical factors.

Some of these factors are difficult to predict (e.g. hypersensitivity to drug and / or polymer) or change (e.g. gender or age). However, the factors that can be influenced by PCI quality and operator experience are case selection based on lesion characteristics and operator expertise to optimize the mechanics of PCI. Thus use of adjunctive devices to optimally prepare lesions (e.g. calcium debulking) and ensuring optimal stent deployment (using intra coronary imaging and / or post PCI physiological assessment) are crucial to reducing incidence of ISR, especially in more complex lesions[12].

PATHOPHYSIOLOGY OF ISR:

There are a number of mechanisms involved in the pathological development of ISR - mostly a result of arterial damage and subsequent neointimal tissue proliferation. These also vary by type of stent, with ISR in BMS occurring mainly as a consequence of arterial damage in response to metallic stent struts leading to neointimal hyperplasia. To overcome this dysfunctional endothelial healing, DES technology was developed with the aim of introducing anti-proliferative pharmacological agents (e.g. paclitaxel, sirolimus) embedded within a carrier/polymer[13]. However, this did not remove the risk of ISR with DES which was still

evident due to an inflammatory response and potential hypersensitivity to polymer and / or drug leading to delayed endothelialisation and neo-atherosclerosis[14].

In general, endothelial healing in newly implanted stents (both BMS and DES) is achieved through a uniformly distributed neointimal proliferation along the length of the stent[15-17]. However, in some cases it can be relatively focal and is associated with leukocyte accumulation, neovascularisation and inflammation that leads to the formation of ISR. This was shown in histopathologic studies on hearts from post-mortem, repeat CABG or transplantation cases[18]. Within the first 2 weeks following PCI, there was accumulation of fibrin, platelets, neutrophils at the site of stent implantation indicating inflammation and thrombus formation. This was more pronounced in stent struts embedded in a lipid core and those in close contact with damaged media[18]. Older stents demonstrated neointimal growth with extracellular matrix accumulation which were more pronounced in mal-apposed stents or in stent struts associated with medial damage or in contact with plaque[19].

HISTOLOGY OF ISR:

Histological examination of ISR specimens vary by type of stent (BMS vs DES) but generally demonstrates luminal loss through proliferation of smooth muscle cells within a collagen-rich matrix[20]. ISR related to BMS shows greater cellular density in a homogenous fashion, whereas ISR related to DES shows a lower cellular density with a contractile phenotype embedded in a richer proteoglycan content[21,22].

Late DES ISR (greater than 12 months after implantation) is a consequence of neoatherosclerosis leading to both stenosis and possibly thrombosis[23]. Unlike native vessel

atherosclerosis however, neoatherosclerosis develops at a faster pace and represents an accelerated form of atherosclerosis related to defective endothelial healing over the stent scaffold[20,23]. Histologically, this is characterised by the presence of lipid-laden foam cells (macrophage origin) rich with or without calcifications and a necrotic core[23]. In addition to the stenosis posed by this process, it can progress further to form a thin cap plaque which could rupture and lead to thrombosis and myocardial infarction.

PATTERNS OF ISR:

The patterns of ISR have been categorised into focal or diffuse. These were further classified angiographically in a study of 288 ISR in 245 patients who had received BMS stents[4].

- Pattern I: Focal (<10 mm in length) → rate of repeat TLR was 19%
- Pattern II: ISR >10 mm within stent → rate of repeat TLR was 35%
- Pattern III: ISR >10 mm extending outside stent → rate of repeat TLR 50%
- Pattern IV: Totally occluded stent → rate of repeat TLR 83%

With the advent of intravascular imaging, several classification emerged with Kang et al[24] describing an intravascular ultrasound (IVUS) based criteria that classifies ISR on the basis of luminal area, length and focus within the stent, as follows:

- Focal ISR: Lumen area <4 mm^2 and length ≤10 mm on IVUS
- Multifocal ISR: The presence of multiple focal ISR lesions within the body of the stent ('Multifocal body type') or the stent margins ('Multifocal marginal type')
- Diffuse ISR: Defined as MLA <4 mm^2 and length >10 mm

DIAGNOSIS AND ASSESSMENT OF ISR:

Patients who have had previous PCI and stent implantation who experience ISR may present with symptoms of stable ischaemia (angina) or with acute coronary syndrome. In both instances, the diagnosis of ISR can only be made post coronary angiography and if appropriate using adjunctive diagnostic modalities such as intracoronary imaging and / or physiological assessment. The indication for invasive coronary angiography will be similar to those without prior PCI[12]. Coronary angiography may also provide clues to the mechanism of ISR by demonstrated under-expanded stents or calcification outside the stent. Digital subtraction angiography may complement angiography and reveal stent fractures and/or geographic miss[4]. In more contemporary practice, intracoronary imaging (IVUS and OCT) has been found to be essential in providing the precise mechanism of ISR including stent under sizing, mal-apposition, geographical miss, as well as visualisation of neointimal hyperplasia, neoatherosclerosis, edge stenosis or underlying calcification. Consequently, these intravascular imaging modalities help the operator to better understand the mechanism of stent failure and thus tailor further treatment e.g appropriate lesion preparation, sizing stents, use of drug coated balloons (DCB) etc. [25]. For indeterminate cases where an objective assessment of ischaemia is required, especially in stable angina presentations or non-culprit vessel assessment as part of ACS presentation, a pressure-wire based index (e.g. FFR or iFR) may be used to demonstrate reduction in flow across the ISR lesion and further enforce the operators decision on whether to treat[26].

MANAGEMENT OF ISR:

Identification of the mechanism of ISR is essential in determining the best course of management[12]. For example, undersized stents may simply require balloon dilation, whereas more complex ISR lesions with neointimal hyperplasia or neoatherosclerosis may require debulking with tools such as atherectomy or scoring/cutting balloons. Consequently, the use of intravascular imaging is mandatory in these cases. Given the wide choice of revascularisation options, a number of studies have compared PCI strategies for the treatment of ISR. These are summarised in Table 2.

The majority of patients with ISR who undergo revascularisation will likely undergo repeat stenting. In fact, the 2014 European Society of Cardiology/European Association for Cardio-Thoracic Surgery guideline on myocardial revascularization recommends either DES or DCB for the treatment of ISR irrespective of stent type BMS or DES[27]. The role of surgical revascularisation in the form of coronary artery bypass grafting (CABG) remains uncertain, but should be considered in patients who are not suitable for PCI, who suffer from recurrent ISR despite DCB / DES re-implantation or who suffer from multi-vessel ISR / disease[28]. In these situations, the choice of revascularisation modality should always be guided by patient preference following an informed discussion.

If re-stenting is pursued, a newer generation DES should be used given the lower rates of ISR in DES compared with BMS. The recommended choice of DES here is an everolimus-eluting stent. This was shown to be superior to other devices in a network meta-analysis of 27 clinical trials (n = 5923)[29]. This analysis demonstrated lower extent of ISR on repeat angiography compared to DCB, sirolimus-eluting stents, paclitaxel-eluting stents, BMS or

balloon angioplasty. In addition, there was lower TLR with everolimus-eluting stents compared to all other strategies including other DES.

The use of drug-coated balloon (DCB) angioplasty is also reasonable in patients who may not be suitable for DES implantation. This is despite evidence from the RIBS IV study, which showed lower rates of the combined outcome of cardiovascular death, myocardial infarction and TLR in patients receiving EES compared with DCB (HR 0.57, 95% CI 0.34-0.96)[30,31]. The patient population who may benefit from DCB includes those who have optimal lesion preparation (<30% recoil) prior to deciding on usage of further stenting or DCB along with potential additive factors unfavourable towards further stenting e.g. not candidates for long-term dual antiplatelet therapy, who have multiple layers of metal or when compromise of a side branch is a concern[20].

Where debulking is required, the use of rotational or laser atherectomy may be indicated. More commonly however, scoring or cutting balloons are used in these circumstances given their wider availability and relative safety compared to atherectomy. The evidence for lesion preparation techniques in ISR is presented in Table 3.

A number of algorithms for the management of ISR have emerged[12,20]. As part our analysis of the evidence, we propose the management pathway shown in Figure 1 for the treatment of ISR lesions. We exemplify the application of this pathway with illustrated cases summarised in **Supplementary Reading**.

Conclusions

This article summarises the pathophysiology, mechanism and treatment modalities implemented in the management of ISR. It covers lesion modification, the evidence behind DES and DCB usage, and the importance of image-guided optimisation to avoid mechanical causes of ISR. We propose an algorithm which may be used by operators to approach these cases and stress the importance of intravascular imaging as part of the initial assessment and lesion stratification.

Expert Opinion

There is no one size fits all for the management of ISR. Identifying the aetiology of the lesion with the aid of intracoronary imaging is critical in deciding on the best treatment modality. We recommend that intracoronary imaging is performed in 100% of ISR cases to provide the best possible care for the patient. Barriers to using intracoronary imaging (cost, operator training, availability) should be mitigated by exploring the long term cost-effectiveness that imaging infers and referring to experienced operators if availability or training is an issue.

The key areas for improvement in the management of ISR is to employ newer generation stents and technologies such as DCB. The use of contemporary DES and DCB has revolutionised the field and reduces TVR and TLR compared to older technologies, and should therefore be available in all catheter labs taking on these cases.

Despite improvements in technology, diagnosis and treatment described in the article above, the problem of ISR persists and is unlikely to go away completely. However,

development of thinner strut stents, newer drug elution technologies and newer DCB (sirolimus, paclitaxel) may drive TLR/TVR rates lower than we currently have. Research into newer technologies and their effect on ISR management should continue to widen our knowledge into what is currently known about ISR PCI.

We suggest that algorithms such as the one presented in this article are taught to PCI trainees at the earliest opportunity in order to instil the notion of understanding the disease before making a decision about its management. A key point we would like to highlight to trainees is that just implanting another stent is not always the answer, and will depend on the aetiology which is often determined with the use of intracoronary imaging.

In the next five to ten years, it is likely that the use of intracoronary imaging will continue to rise (currently reported to be a mere ~10% utility in all PCI in the UK[32]) and may therefore lead to improved detection and treatment of ISR. Debulking devices are likely going to be more deliverable, stents technology continue to improve with associated better vessel healing and drug-elution technologies to improve lesion coverage which hopefully will further improve outcomes. The holy grail of research into ISR is being able to identify patients who are at risk of ISR before they develop it, which is where research efforts should be focused in the next decade by developing prediction models, biomarkers, imaging markers and precision medicine approaches.

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Table 1: Factors influencing the development of ISR.

Pharmacology	Biology	Patient	Lesion	Mechanics
Drug resistance (anti-platelets)	Proteolytic enzymes	Diabetes	Long (>20mm)	Stent mal-apposition
Hypersensitivity to drug	Matrix metalloproteinases	Older age	Type B/C	Stent under expansion
Hypersensitivity to polymer		Female gender	Small vessel (<3mm)	Edge trauma
		Genetics	Calcified	Geographical miss
			Bifurcation	Stent fracture
			CTO	
			Ostial segment	
			Tortuosity	

CTO = Chronic total occlusion

Table 2: Trials Evaluating the Treatment of In-stent Restenosis Using Contemporary DCB and DES.

Trial	Treatments Compared	Results
Use of drug-coated balloons in bare metal stent in-stent restenosis		
PACCOCATH ISR I and II[33,34]	DCB versus POBA	MACE: 11% versus 46%; p=0.001
		Binary restenosis: 6% versus 51%; p≤0.001
PEPCAD II[35]	DCB versus PES	MACE: 9% versus 22%; p=0.08
		Binary restenosis: 7% versus 20%; p=0.06
RIBS V[36]	DCB versus EES	MACE: 8% versus 6%; p=0.60
		Binary restenosis: 9.5% versus 4.7%; p=0.22
TIS[37]	DCB versus EES	MACE: 10.29% versus 19.12%; p=0.213
		Binary restenosis: 8.7% versus 19.12%; p=0.078
Use of drug-eluting stents in bare metal stent in-stent restenosis		
SISR[38]	SES versus brachytherapy	Binary restenosis: 19.8% versus 29.5%; p=0.07
TAXUS V ISR[39]	PES versus brachytherapy	MACE: 11.5% versus 20.1%; p=0.02
		Binary restenosis: 14.5% versus 31.2%; p≤0.001
ISAR-DESIRE[40]	DES (SES + PES) versus POBA	Binary restenosis: 14.3% (SES) and 21.7% (PES) versus 44.6% (POBA); p≤0.001
RIBS II[41]	SES versus POBA	Binary restenosis: 11% versus 39%; p≤0.001
Use of drug-coated balloons in drug-eluting stent in-stent restenosis		
PEPCAD-DES[42]	DCB versus POBA	MACE + stent thrombosis: 16.7% versus 50.0%; p<0.001
		Binary restenosis: 17.2% versus 58.1%; p<0.001
PEPCAD China ISR[43]	DCB versus PES	LLL: 0.46 ± 0.51 versus 0.55 ± 0.61 mm; p for non-inferiority = 0.0005
ISAR-DESIRE 3[44]	DCB versus PES versus POBA	Diameter stenosis, PEB versus PES: 38 ± 21.5% versus 37.4 ± 21.8%; p for non-inferiority = 0.007
RIBS IV[31]	DCB versus EES	Clinical outcome: 20.1% versus 12.3%; p=0.04
Use of drug-eluting stents in drug-eluting stent in-stent restenosis		
ISAR-DESIRE 2[45]	SES versus PES	LLL: 0.40 ± 0.65 mm versus 0.38 ± 0.59 mm; p=0.85
		Binary restenosis: 19.6% versus 20.6%; p=0.69
RESTENT-ISR[46]	EES versus ZES	LLL: 0.40 ± 0.56 versus 0.45 ± 0.61 mm; p=0.57
		MACE: 15.8% versus 22.6%; p=0.276
RIBS III[47]	Hetero-DES versus control	Binary restenosis: 22% versus 40%; p=0.008
		MACE: 23% versus 35%; p=0.039

BMS = bare metal stent; DCB = drug-coated balloon; DES = drug-eluting stent; EES = everolimus-eluting stent; ISR = in-stent restenosis; LLL = late lumen loss; MACE = major adverse cardiac events; PEB = paclitaxel-eluting balloon; PES = paclitaxel-eluting stent; POBA = plain old balloon angioplasty; SES = sirolimus-eluting stent; ZES = zotarolimus-eluting stent.

Table 3. Trials Evaluating the Use of debulking techniques in the treatment of ISR

Trial	Treatments Compared	Results
ISAR-DESIRE 4[48]	Scoring balloon versus POBA	In-segment percentage diameter stenosis: 35.0 ± 16.8% versus 40.4 ± 21.4%; p=0.047
ROSTER[49]	Rotablation versus POBA	Repeat stenting: 10% versus 31%; p≤0.001
ARTIST[50]	Rotablation versus POBA	Restenosis rate: 64.8% versus 51.2%; p=0.039
Ichimoto et al.[51]	ELCA versus no ELCA	Acute luminal gain: 1.64 ± 0.48 mm versus 1.26 ± 0.42 mm; p≤0.001

ELCA = excimer coronary laser atherectomy; ISR = in-stent restenosis; POBA = plain old balloon angioplasty

Figure 1: Proposed algorithm for investigating and managing ISR