

Definition

Despite advances in interventional cardiology, the risk of developing in-stent restenosis remains a challenging clinical problem in stent implantation. ISR has been described as a luminal stenosis with 50% or more diameter narrowing of a stented coronary segment or within 5 mm of the proximal and distal ends of the stent.

From the clinical perspective, restenosis is often associated with recurrent angina symptoms or acute coronary syndrome; this condition is called „clinical restenosis“ and is usually associated with the necessity to repeat target lesion revascularisation or target vessel revascularisation. By contrast, ISR with no symptoms or signs of ischaemia is referred to as „silent restenosis“ (1, 2, 3).

Incidence

In the pre-stent era, ISR incidence ranged from 32% to 55% of all angioplasties, and dropped to 17–41% in the bare-metal stent (BMS) era. A further step to reduce restenosis was undertaken with the advent of drug-eluting stents (DES), with a reduction to 5–10%. The widespread use of DES for small arteries, long lesions, complex coronary lesions, diabetes, and a history of bypass surgery have all resulted in significant numbers of patients representing with DES restenosis in clinical practice (3, 4, 5).

Classification

The angiographic classification by Mehran divides ISR into four types: I-focal; II-diffuse; III-proliferative; IV-occlusive with occurrence rates of 42%, 21%, 30%, and 7%, respectively. This angiographic classification of ISR provides the means for appropriate and early detection for investigational purposes. This classification scheme was based on prognostic predictors of repeat revascularisation for BMSs. Mehran's morphological character of ISR is a predictor of clinical events, with the necessity of repeated target vessel revascularisation among groups I-IV in 19%, 35%, 50%, and 83% of cases, respectively ($P < 0.001$) (1, 2, 6).

Coronary angiography is a commonly used method to evaluate ISR lesions; on the other hand, intracoronary imaging provides a more precise assessment to detect and

characterise ISR while giving insight into its mechanism. Intravascular imaging data have demonstrated the relation between ISR lesion morphology, future events, and the importance of optimisation of restenosis treatment. Lesion stratification according to Waksman ISR Classification can direct treatment for specific lesion characteristics. The Waksman In-Stent Restenosis Classification characterises different patterns of ISR to best delineate the type of restenosis, help guide treatment, and is more specific to DES-ISR (1, 7).

Time Course and Predictors

The occurrence of ISR is dependent on the underlying stent type and may have relevance for the follow-up of patients after coronary stent implantation. In the BMS era, ISR has been reported to occur on average 5.5 months after stent implantation, with a shorter interval for patients presenting with ACS. DES-ISR is associated with the neoatherosclerosis mechanism and increases steadily after stent implantation (8, 9).

Assessing the underlying aetiology of ISR is important for guiding and optimising repeat interventions to prevent repeated ISR (4). DES and BMS seem to share similar predictive factors for restenosis occurrence. Several predisposing factors have been asso-

ciated with restenosis and can be categorised into lesion-related, procedure-related, and patient-related. Vessel and lesion characteristics that could predict a high probability of ISR are vessel size, tortuosity, calcification, total occlusion, and lesions in the left anterior descending coronary artery (LAD). Stent underexpansion, long stenting, small reference diameter, stent malposition, and stent fracture are all major procedure-related factors of ISR. Among the patient-related predictors identified, diabetes mellitus has consistently emerged as a high-risk clinical predictor of ISR (3, 10). Genetic factors, such as the PIA polymorphism of glycoprotein IIIa, the insertion/deletion polymorphism, and the plasma activity of angiotensin I-converting enzyme, have been reported to be other important patient-related risk factors of ISR (11).

Mechanism

Major pathogenic mechanisms that underlie restenosis are: early elastic return (recoil); vascular remodelling; and neointimal hyperplasia. The first two mechanisms are typical of angioplasty in the pre-stent era. However, a new mechanism called neointimal hyperplasia develops in the presence of metallic struts. ISR pathogenesis is primarily a non-specific inflammatory response to vessel wall

Table 1. Mehran's classification of ISR

Type of ISR	Characteristics
I-focal	Length less than 10 mm
IA	The articulation or gap
IB	Margin
IC	Focal body
ID	Multifocal
II-diffuse	Length more than 10 mm, intrastent
III-proliferative	Extending the edges of the stent
IV-occlusive	Total occlusion

Table 2. Waksman ISR Classification and Treatment Recommendation

Type		Definition	Treatment recommendation
I	Mechanical	IA : stent underexpansion	High pressure balloon, ELCA, or IVL
		IB : stent fracture	DES
II	Biological	IIA : Neointimal hyperplasia	Balloon, DCB, DES or VBT
		IIB : Neoatherosclerosis, noncalcified	DCB or DES
		IIC : Neoatherosclerosis, calcified	Scoring balloon, ELCA, OA or RA
III	Mixed: Combined mechanical and biological aetiology		High pressure balloon with DCB, DES or VBT
IV	Chronic total occlusion		DCB or DES, VBT for multiple layers, CABG
V	> 2 layers of stent		Balloon, DCB, VBT or CABG

DCB: drug-coated balloon; ELCA: excimer laser coronary atherectomy; IVL: intravascular lithotripsy; VBT: vascular brachytherapy; OA: orbital atherectomy; RA: rotational atherectomy; CABG: coronary artery bypass graft