

injury due to the persistent „abuse“ exercised by a foreign element causing chronic wall stress due to media damage and stent struts protrusion in tunica intima. These stimulate inflammatory processes and the migration of smooth muscle cells from tunica media and myofibroblasts from tunica adventitia to tunica intima. Simultaneously, the vessel discontinuity created by stent struts may facilitate contact between the two distal layers of the vessel wall with blood elements, resulting in various stimuli for neointimal proliferation (3). While DESs minimise neointimal proliferation compared with BMSs, hypersensitivity to the polymer and the drug, local inflammation, and delayed healing are the main contributors to neointimal formation with DES-ISR (1).

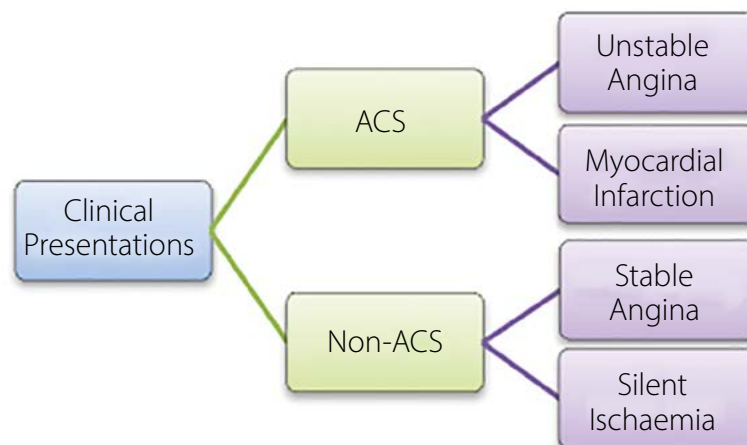
In addition, neoatherosclerosis is suggested as another cause of very late stent thrombosis and late target lesion revascularisation (12). It is related to incomplete regeneration of the endothelium leading to excessive uptake of circulating lipids and accelerated development of atherosclerotic plaques in the nascent neointima (3). It can occur years after stent placement and is characterised by accumulation of lipid foamy macrophages within the neointima, with or without necrotic core formation, and calcification (13).

Neoatherosclerotic change in the restenotic tissue is recognised earlier and more frequently in DES-ISR. An optical coherence tomography (OCT) study demonstrated that homogeneous and lipid-laden neointima was usually found in the BMS early phase (≤ 1 year) and late phase (> 1 year), respectively; heterogeneous neointima was observed more frequently in the DES early phase (≤ 1 year) compared with the BMS early phase (44% vs. 9%, $P < 0.05$) (12).

Clinical Presentation of ISR

ISR may remain asymptomatic or cause symptoms and any objective evidence related to myocardial ischaemia. Clinical presentation during hospitalisation is classified into ACS and non-ACS. Stable angina manifests as typical chest pain occurring on physical exertion and relieved by rest or nitrates. Silent ischaemia can be identified by abnormal results during stress tests (treadmill exercise test or dobutamine echocardiography). Unstable an-

Figure 1. Clinical Presentations of ISR



gina is defined as typical chest pain of recent onset or increasing in duration or intensity two weeks before hospitalisation. This type of angina is refractory to medications and is associated with ST-segment ECG abnormalities. MI is categorised into STEMI (ST-elevation myocardial infarction) and NSTEMI (non-ST elevation myocardial infarction) based on ECG dynamic abnormalities and elevations in high-sensitivity troponin levels. Magalhaes et al conducted an observational study to compare the clinical presentation among three generations of stents: BMS; first-generation DES; and second-generation DES. They showed that ISR clinical presentations in all groups were similar, with ACS accounting for 67.8%, 71%, and 66.7% in BMS, first-generation DES, and second-generation DES, respectively. Although not statistically significant, second-generation DES-ISR patients were less likely to present with MI compared with BMS and first-generation groups (5.2% versus 10.6% and 10.1%; $p = 0.273$) (14, 15).

Imaging for In-Stent Restenosis

Stent Enhancement

Conventional angiography may fail in detecting stent underexpansion and has low accuracy in assessing correct stent positioning. This technique works by identifying the two markers of a balloon positioned inside the stent. Throughout the respiratory and cardiac cycles, the two markers move in synchrony with the metallic struts. Stent Enhancement (SE) has 100% specificity compared to IVUS in

identifying stent underexpansion. The main limitation of SE is that it only visualises stent struts, and cannot provide information regarding the vessel wall and plaque (16, 17).

Intravascular Imaging: IVUS and OCT

Intravascular imaging can be a useful tool to guide coronary stent implantation because of angiography limitations (18). OCT and IVUS offer an anatomic assessment of the vasculature and allow visualisation into the heart. Both techniques are used to make measurements for lesion length and lumen size, but OCT is being shown in studies to be more accurate (19).

Intravascular Ultrasound (IVUS)

IVUS is a medical imaging method designed with a miniaturised ultrasound probe attached to the distal end of a catheter. It can show full-thickness visibility of the vessel wall by generating sound waves that penetrate 4–8 mm inside the vessel wall. This technique can evaluate the extent and distribution of neointimal tissue within the stented segment, but is limited to visualising its complex tissue structure as can be documented by histopathology. Therefore, it enables pre-PCI assessment of plaque burden, the extent of calcification, lesion length, and external elastic lamina diameter for stent sizing as well as post-PCI assessment of minimum stent area, malposition, underexpansion, tissue protrusion, edge disease, and edge dissection. A situation where IVUS is a suitable choice is