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REVIEW

# Diagnosis and management challenges of in-stent restenosis in coronary arteries

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## Abstract

Over the course of the 3 decades, percutaneous coronary intervention (PCI) with stent implantation transformed the practice of cardiology. PCI with stenting is currently the most widely performed procedure for the treatment of symptomatic coronary disease. In large trials, drug-eluting stents (DES) have led to a significant reduction in in-stent restenosis (ISR) rates, one of the major limitations of bare-metal stents. Due to these favorable findings, DES was rapidly and widely adopted enabling more complex coronary interventions. Nevertheless, ISR remains a serious concern as late stent complications. ISR mainly results from aggressive neointimal proliferation and neoatherosclerosis. DES-ISR treatment continues to be challenging complications for interventional cardiologists.

**Key words:** Stent; In-stent; Restenosis; Percutaneous coronary intervention



**Core tip:** Percutaneous coronary intervention with stenting is currently the most widely performed procedure for the treatment of symptomatic coronary disease. In large trials, drug-eluting stents (DES) have led to a significant reduction in in-stent restenosis (ISR) rates, one of the major limitations of bare-metal stents. However, ISR remains a serious concern as late stent complications. ISR mainly results from aggressive neointimal proliferation and neoatherosclerosis. DES-ISR treatment continues to be challenging complications for interventional cardiologists. This review focuses on pathogenesis, diagnosis and treatment options for ISR in the current era of advanced intravascular imaging and intervention.

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## INTRODUCTION

Percutaneous coronary intervention (PCI) with stenting is currently the most widely performed procedure for the treatment of symptomatic coronary disease[1]. Over the course of the 3 decades, PCI with stent implantation transformed the practice of cardiology. In large trials, drug-eluting stents (DES) have led to a significant reduction in in-stent restenosis (ISR) rates, one of the major limitations of bare-metal stents (BMS)[2]. Due to these favorable findings, DES was rapidly and widely adopted enabling more complex coronary interventions. Nevertheless, ISR remains a serious concern as late stent complications.

## DEFINITION

ISR is defined as the gradual re-narrowing of a stented coronary artery lesion due to arterial damage with subsequent neointimal tissue proliferation[3,4]. Angiographically IRS is a binary event defined as recurrent diameter stenosis at the stent segment more than 50% of the vessel diameter as determined by coronary angiography[4]. The angiographic definition remains the main definition since it allows determination of ISR severity and morphological pattern. The clinical definition of ISR requires the presence of greater than 50% diameter in-stent stenosis and one of the following: Clinical symptoms of recurrent angina, objective signs of ischemia (EKG changes), positive coronary hemodynamic assessment with fractional flow reserve (FFR) less than 0.80, intravascular ultrasonography (IVUS) minimum cross-sectional area less than 4 $mm^2$ (6 $mm^2$ for left main), or restenosis with $\geqslant$ 70% reduction in lumen diameter even in the absence of clinical symptoms or signs.

## CLASSIFICATION

Multiple classification systems have been identified to address the severity of ISR. Mehran system[5] is a morphologic classification of ISR lesions in to four patterns. Pattern Ⅰ (focal) is ISR ($\leqslant$ 10 mm in length) lesion within the stent, pattern Ⅱ (diffuse) is ISR greater than 10 mm within the stent, pattern Ⅲ (proliferative) is ISR greater than 10 mm extending outside the stent, and pattern Ⅳ (occlusion) is totally occluded ISR. This classification system predicts the need for repeat revascularization after intervention (19%, 35%, 50%, and 98%, respectively)[5]. American College of Cardiology/American Heart Association lesion classification has been also validated in patients with ISR[6]. Type A lesions had a probability of success of more than 85% and a low risk of acute occlusion. Type B lesions had a probability of success of between 60% and 85% and a moderate risk of abrupt occlusion. Finally, type C lesions had a probability of success of less than 60% and a high risk of abrupt occlusion following the procedure (Table 1). Lesions B2 and C have been reported to be frequently associated with suboptimal acute results with a higher restenosis rate and poorer long-term clinical outcomes[7].

## INCIDENCE

In general, rates of ISR range from 3% to 20% with drug-eluting stents and 16% and 44% with BMS. This occurs mostly between 3 to 20 mo after stent placement[3,8]. The incidence of ISR depends on the definition, stent type, location, patient comorbidities and lesion complexity (*i.e.,* lesion length, vessel size, and bifurcation lesions). The introduction of DES has significantly reduced the occurrence of neointimal proliferation, which is considered the main mechanism for ISR. The decrease in ISR was translated into decreased clinical need for subsequent repeat revascularization[9-11]. A meta-analysis of 38 randomized controlled trials with more than 18000 patients showed significant reduction in TLR with both sirolimus-eluting stent (SES) and paclitaxel-eluting stents (PES) compared with BMS[10]. However, due to the complexity of ISR beyond device and stent design, the rates of ISR in both BMS and DES are still relatively high[12]. Routine angiographic surveillance 6 to 8 mo after stent implantation was done in one study that revealed ISR rates of 30.1%, 14.6%, and 12.2% for BMS, first-generation DES, and second-generation DES, respectively[13].

### *Bare-metal stents ISR*

Despite relatively high restenosis rates, bare-metal stents are still frequently used in clinical practice during PCI[14]. This is related to unaffordable prices of DES and more importantly, lower risk of bleeding due to shorter duration of dual antiplatelet therapy (DAPT) that is required after BMS compared with DES. BMS-ISR causes a significant therapeutic burden in current clinical practice. One pooled analysis reported a one-year TLR and TVR rates after BMS of 12% and 14.1% respectively[15,16]. Clinical restenosis was evident within 6-12 wk after BMS implantation[16]. Beyond 1 year, rate of BMS restenosis is negligible and most stenting events are related to disease progression in vessel segments other than the stented lesion[16].

### *Drug-eluting stents ISR*

Restenosis rate of DES increased in the recent years due to expanded use to include high-risk patients with complex coronary lesions. The DES-ISR rate has been reported in 3%-20% depending on DES type, the duration of follow-up, and the complexity of the lesions

**Table 1 ACC/AHA lesion-specific classification of the primary target stenosis**

| Lesion type | Lesion characteristic according to AHA/ACC classification | | | | | |
|---|---|---|---|---|---|---|
| Type A lesions | Discrete (< 10 mm length) | Concentric | Readily accessible | Non angulated segment < 45° | Smooth contour | Little or no calcification |
| | Less than totally occlusive | Not ostial in location | No major branch involvement | Absence of thrombus | | |
| Type B1 lesions | Tubular (10-20 mm length) | Eccentric | Moderate tortuosity of proximal segment | Moderately angulated segment, 45°-90° | Irregular contour | Moderate to heavy calcification |
| | Total occlusion < 3-mo-old | Ostial in location | Bifurcation lesions requiring double Guidewires | Some thrombus present | | |
| Type B2 lesions | Two or more "B" characteristics | | | | | |
| Type C lesions | Diffuse (> 2 cm length) | Total occlusion > 3-mo-old | Excessive tortuosity of proximal segment | Extremely angulated segments, > 90° | Inability to protect major side branches | Degenerated vein grafts with friable lesions |

in which the stents were placed[3]. When compared with BMS, DES is associated with lower ISR. At one-year follow up, SES markedly reduced the incidence TLR from 16.6% to 4.1% when compared with BMS[17]. For first-generation DES, j-Cypher registry of 12812 patients who received SES, the TLR rate was 7.3% at 1 year, and 15.9% at 5 years[18]. Ischemia-driven TLR was also the same in patients randomly assigned to SES or PES (13.1% *vs* 15.1%) in the SIRTAX LATE study[19]. Second generation stents have been associated with lower death and myocardial infarction compared with first-generation DES. However, zotarolimus-eluting stent (ZES) found to be noninferior to PES for TVR at 1 and 5 years[20]. In a pooled analysis of multiple studies comparing everolimus-eluting with ZES, the rates of TVR at up to five years of follow-up were 6.3% and 5.0%, respectively[21].

## PREDICTORS OF IN-STENT RESTENOSIS

Patient comorbidities, lesion characteristic, and procedural characteristics are the main predictors of ISR.

### *Patient characteristics*

Patient characteristics and comorbidities that are associated with higher rate of ISR include; metal allergy, local hypersensitivity reactions with immunologic and inflammatory response to the drug or the polymer, age, female gender, diabetes mellitus, chronic kidney disease (including hemodialysis), and multivessel coronary artery disease[3,22,23].

### *Lesion characteristics*

Lesion characteristics associated with ISR include; lesion length, smaller reference artery diameter, ostial lesion, initial plaque burden and residual plaque after implantation. In contrast with BMS, DES tends to have a more focal pattern of ISR, except in diabetics, where the ISR tends to be more confined to the stent edges[24,25]. Focal ISR (Mehran pattern Ⅰ) has been associated with a lower rate of ISR recurrence than nonfocal (Mehran pattern > Ⅰ) ISR[25].

### *Procedural characteristics*

Operator and technique dependent characteristics include stent undersizing, incomplete lesion coverage, stent under expansion, and malapposition. Mechanical properties of stents that may lead to recoil because of loss of radial force, stent fractures, and altering increase in shear stress are all associated with higher rates of ISR. For every 10 mm of excess stent length beyond lesion has been independently associated with increased post-procedural percent diameter stenosis by 4% and increased TLR at 9 mo (OR = 1.12, 95%CI: 1.02-1.24)[26-29]. Stent fracture, on the other hand, can trigger focal ISR or thrombosis[30-32] which can result in a reduction in drug delivery at the breakage point of the stent. Stent fracture occurs more frequently in the right coronary artery, overlapping stents, longer stents, SESs (because of the ridged closed cell structure), and excessively tortuous angulated vessels[33]. Malapposition, also known as incomplete stent apposition (ISA), is defined as the absence of contact between stent struts and the vessel wall not overlying a side branch. Malapposition seems to be related to procedural technique due to under-sizing the stent, use of low deployment pressures, and severely calcified lesions, which do not allow for homogenous stent expansion[34]. Oversized stents can also lead to extensive trauma to the vessel wall and increased proliferative reaction[35]. Geographic miss occurs when the stent does not fully cover the injured or diseased segment of the artery (axial miss) or the ratio of balloon to artery size is less than 0.9 or greater than 1.3 (longitudinal miss). Geographic miss is associated with increased risk of TLR and MI at 1 year[36]. DESs decrease neointimal growth. As a result, geographic miss or strut fracture may be larger factors of ISR in DESs compared with BMSs[12].

## PATHOGENESIS

The main mechanism of ISR following stent implantation is neointimal tissue proliferation because of arterial wall damage[21,22]. Neointimal tissue proliferation could be focal or distributed uniformly along the

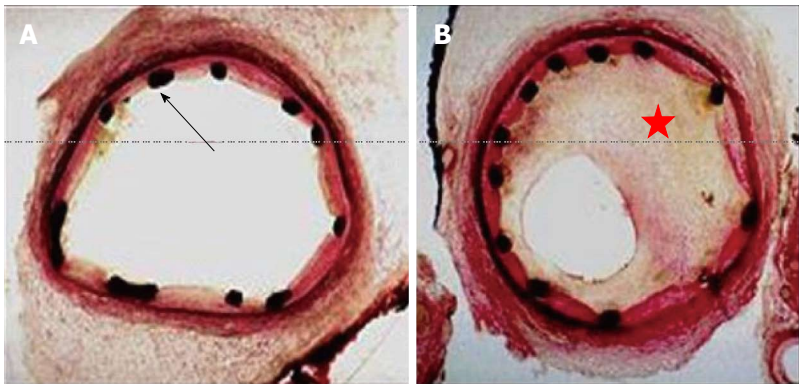



**Figure 1 The figure showing cross-section of coronary artery immediately after implantation of a bare metal stent black dots represent the stent struts (red arrow) (A); the figure showing significant in-stent restenosis with neointimal hyperplasia (red star) 6 mo after the implantation of a bare metal stent (B).**

length of the stent (Figure 1). ISR, which happens early within days of stent deployment, is due to elastic recoil and relocation of axially transmitted plaque. The causes of late (weeks to months) ISR commonly are reorganization of thrombus, neointima formation and remodeling[37].

Neoatherosclerosis yet is another contributing factor to ISR. The stimulation of neointima formation happens due to injury to the vessel during the PCI and stent deployment. A cascade of events are triggered by the intimal and medial damage, leading to proliferation and migration of vascular smooth muscle cells, extracellular matrix formation which ultimately activates the coagulation-fibrinolysis system[38]. The local inflammation can lead to the development of neoatherosclerosis characterized by accumulation of lipid-laden foamy macrophages within the neointima with or without a necrotic core formation and calcification, which can occur years after stent placement[39]. Neoatherosclerosis is associated with a higher proportion of in-stent atherosclerotic plaque, which could explain unstable symptoms and myocardial infarction presentation of patients with ISR years after PCI. The incidence of neoatherosclerosis was significantly greater in DES compared with BMS (31% *vs* 16%, $P < 0.001$)[40]. Younger age, longer implant durations, SES usage, PES usage and underlying unstable plaques, are independent risk factors for neoatherosclerosis[14,40].

## CLINICAL PRESENTATION

Due to the gradual and slow progression of ISR compared with stent thrombosis, majority of ISR presents as progressive recurrent angina[40]. The time for symptoms to develop due to DES-ISR is 3 to 12 mo after stent placement[41]. BMS stent on the other hand develop ISR symptoms sooner with reported average period of 6 mo post-PCI[42]. BMS-ISR presented as MI in 3.5%-20% of patients[43]. DES-ISR is similar to that of BMS with approximately 16%-66% of patients presenting with unstable angina and 1%-20% with MI[44,45].

## ANATOMIC ASSESSMENT

### *Routine surveillance*

Routine angiographic surveillance is not recommended because it has been shown to increase the rates of oculostenotic revascularization.

### *Intravascular ultrasonography*

IVUS is considered a fundamental intracoronary imaging modality to assess ISR. The stent and procedures characteristics can be readily assessed as contributing mechanism of ISR using IVUS[35]. IVUS delineate external elastic lamina behind the stent struts very well, which provides valuable insights on vessel sizing for optimization of stent expansion (Figure 2F and G). IVUS does help detect the presence of neointimal hyperplasia obstructing the stent, stent underexpansion, stent fracture, or edge restenosis. In addition, it can provide insights into optimal vessel sizing for choosing the appropriate stent size (Figure 2K and L). However, IVUS has limited axial resolution (150 μm), which makes neointimal interface hard to define[12].

### *Optical coherence tomography*

Optical coherence tomography (OCT) provides better axial resolution (15 μm), allowing better resolution of the vessel lumen, neointimal tissue, and stent struts distribution. The morphology of ISR can be identified using OCT which could show macrophage infiltration, necrotic core, in-stent calcification and neoatherosclerotic plaque rupture[46,47]. The weakness of the OCT resides in the poor tissue penetration, which cause poor visualization of the residual plaque that is beyond the stent[12].

## HEMODYNAMIC ASSESSMENT

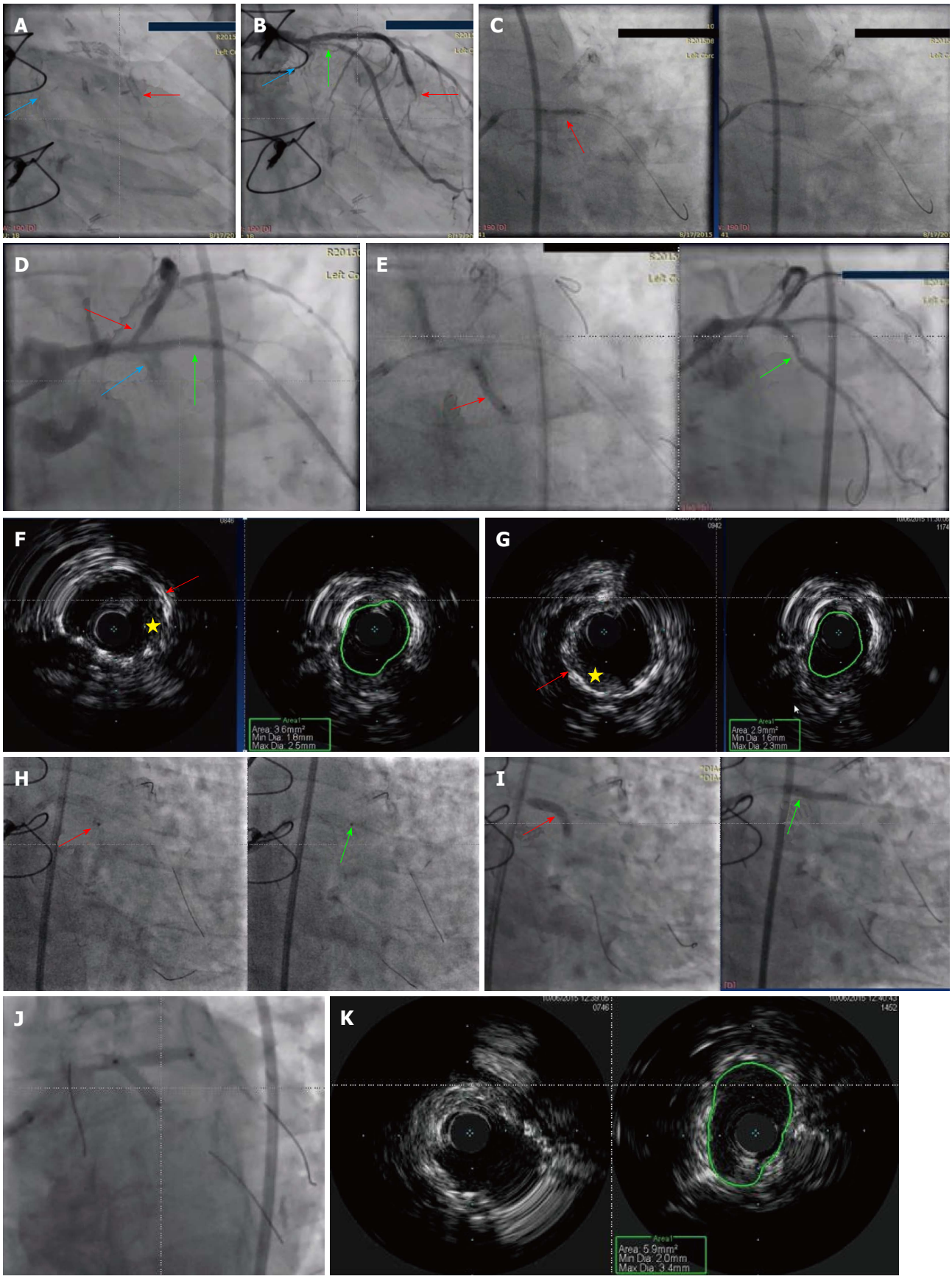
### *Fractional flow reserve*

FFR has been validated for clinical decision making in patients with ISR. The clinical outcome of patients with ISR with deferred interventions based on a FFR > 0.75 is excellent[48]. This diagnostic strategy is useful in controversial cases with angiographically moderate or inconclusive ISR.

## TREATMENT

### *Balloon angioplasty*

Balloon angioplasty (BA) is one of the earliest interventions that were used to treat ISR by displacing in-


A
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Area 3.6mm²
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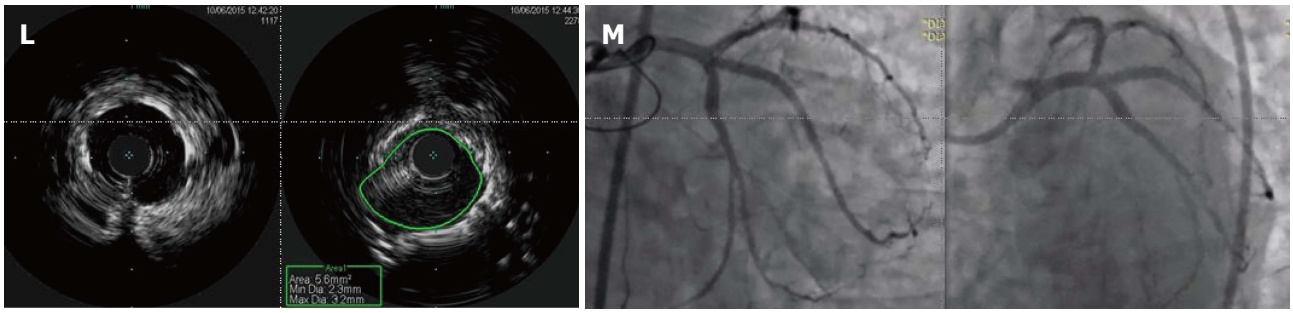


**Figure 2 Sixty-seven-year-old man presented with increasing chest pain at rest.** He has past medical history significant for coronary artery disease with PCI and coronary artery bypass grafting. He had PCI with (3.0 mm × 12 mm) DES to LCx, (2.5 mm × 16 mm) DES to RI and (2.5 mm × 16 mm) DES to obtuse marginal a year prior to his presentation. The left internal mammary artery to LAD is patent, however, he is known to have occluded SVG to RI and SVG to first diagonal (D1). Given his increasing chest pain, coronary angiogram was done. A: Coronary stents before contrast injection in LAD (red arrow), LCx (blue arrow); B: Coronary angiogram of the same patient showing severe proximal LCx ISR (blue arrow) with no flow, severe proximal RI ISR (green arrow) with slow flow, and mid LAD severe ISR (red arrow); C: Dilation of the RI coronary artery with 2.5 mm × 22 mm NC balloon with 22 atm inflation pressures was done; D: Coronary angiogram showing the proximal RI ISR (green arrow) post balloon dilation. Red arrow shows severe proximal LAD stenosis with poor flow. LCx has completely occluded ISR (blue arrow); E: The left circumflex ISR lesion (red arrow) was wired and with balloon dilation the flow was restored in the LCx (green arrow); F: IVUS imaging of the underexpanded stent in the proximal LCx lesion. Left panel shows stent struts (red arrow) with evidence of neointimal hyperplasia (yellow star). The right panel shows small stent CSA of only 3.6 $mm^2$ which is below the target 5 $mm^2$ in asians and 6 $mm^2$ in non-asians; G: IVUS imaging of the underexpanded stent in the proximal ramus coronary artery. Left panel shows severely under-expanded stent (red arrow) with evidence of neointimal hyperplasia (yellow star). The right panel shows small stent CSA of only 2.9 $mm^2$; H: Excimer Laser Coronary Angioplasty treatment of LCx (left panl - red arow) and ramus artery (right panel - green arrow) using 0.9 mm coronary laser and the heparinized flush technique. Laser catheter was advanced slowly at 0.2-0.5 m/s during laser emission with careful monitoring of heart rate and blood pressure. Vessel injury such as perforation, dissections and acute closure are the main side effects; I: Post laser balloon dilation with (3.5 mm × 20 mm) NC balloon of both LCx (red arrow) and ramus (green arrow) arteries; J: Sequential kissing stenting technique in the proximal LCx and ramus arties with DES 3.5 mm x 18 mm in Ramus and 3.5 mm × 15 mm in LCx; K: IVUS imaging of the stent in the proximal LCx coronary artery that shows good expansion of the stent with great increase in CSA to 5.9 $mm^2$; L: IVUS imaging of the stent in the proximal ramus coronary artery that shows good expansion of the stent with great increase in CSA to 5.6 $mm^2$; M: TIMI III flow was achieved in the LCx and Ramus coronary arteries without any compromise of LAD. PCI: Percutaneous coronary intervention; DES: Drug-eluting stents; LCx: Left circumflex; RI: Ramus intermedius; LAD: Left anterior descending artery; SVG: Saphenous vein graft; ISR: In-stent restenosis; NC: Non-compliant; IVUS: Intravascular ultrasound; CSA: Cross-sectional area.

stent tissue from the lumen in axial and longitudinal direction to the outer portion of the vessel wall as well as further expanding the stent[49] (Figure 2). This intervention could be useful in focal ISR. The outcome of BA for focal ISR However, during balloon inflation, slippage or watermelon seeding can occur, leading to edge-related complications. Cutting or scoring balloons can help minimize this, but also have limitations in delivery through stented regions or distal areas[50]. Lateral blades or atherotomes anchor the balloon in the lesion and minimize slippage[51]. Progressive balloon dilations and small/short balloons can also prevent side effects from balloon slippage[52]. One of the limitations of BA is that subacute tissue re-intrusion back to the lumen tends to occur within minutes after the last balloon inflation. This explains the early lumen loss phenomenon detected in BA studies in this setting, a finding also associated with subsequent recurrent restenosis.

### *Vascular brachytherapy*

Brachytherapy inhibits neointimal formation within the stent, but not the stent edges, by delivering radiation to the areas of ISR. Brachytherapy effectively suppressed the proliferative response and significantly reduced clinical and angiographic restenosis rates (Figure 3C). Both beta and gamma radiation sources could achieve major reductions in the angiographic restenosis rates[53]. Gamma emitters had profound tissue penetration, whereas beta emitters had less tissue penetration (Figure 3E). Randomized clinical trials in patients with ISR demonstrated the superiority of brachytherapy compared with conventional BA or atheroablative techniques[53-55]. Adding an extra layer of metal to treat DES or BMS-ISR is not ideal and will continue to place patients at future risk for ISR. Therefore, DEB and vascular brachytherapy are better options compared with DES. Vascular brachytherapy is available in few centers in the United States and is used primarily for recurrence of DES-ISR, but logistic issues and lack of radiation oncology support impede its uses. Therefore, restenting with second-generation DES became the default therapy for DES-ISR.

### *Excimer laser angioplasty*

Excimer laser angioplasty (ELA) produces monochromatic light energy, which generates heat and shock waves that disrupt plaque (Figure 2H). Mehran *et al*[56] compared results of ELA *vs* rotational atherectomy (RA), both followed by percutaneous transluminal coronary angioplasty (PTCA). 119 patients with 158 ISR lesions were treated with ELA plus PTCA and 130 patients with 161 ISR lesions were treated with RA plus PTCA. Volumetric IVUS analysis showed a greater reduction in intimal hyperplasia volume after RA than after ELA (43 $mm^3$ *vs* 19 $mm^3$, $P < 0.001$). However, the 1-year TLR rates were similar: 26% with ELA plus PTCA *vs* 28% with RA plus PTCA ($P$ = nonsignificant). ELA is not currently a well-accepted treatment for ISR, but the ultimate role of this therapy

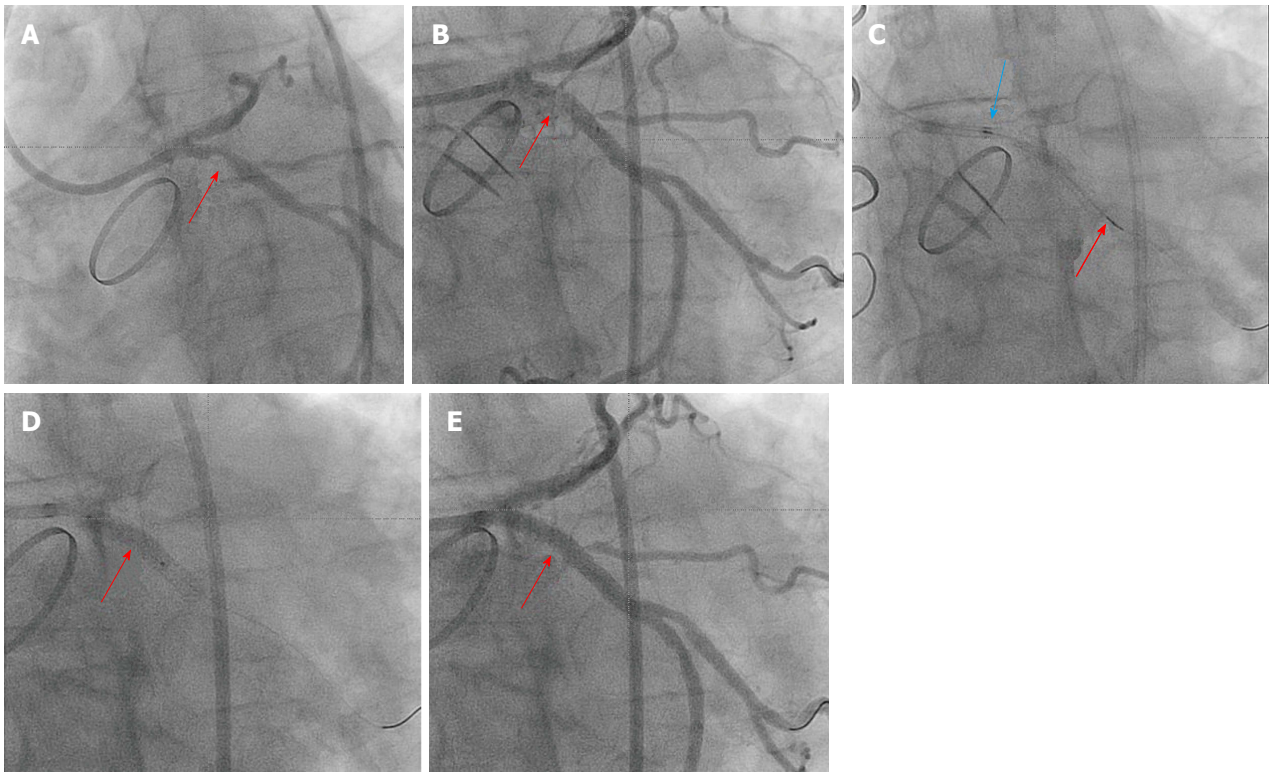


**Figure 3 Fifty-five-years-old caucasian male with mantle cell radiation for Hodgkin's lymphoma complicated with radiation heart valve disease with severe aortic valve stenosis status post mehanical aortic valve replacement surgery.** Few years later he presented with chest pain and had PCI to the proximal LAD and LCx with DES. However, both few months later he developed ISR and underwent another PCI with DES to the proximal LAD and LCx. Patient was referred for vascular brachytherapy for the treatment of ISR of the LCx due to increased chest pain at rest and recurrent ISR of proximal LCx. A: Coronary angiogram showing 90% focal proximal LCx ISR (red arrow); B: Balloon angioplasty of the proximal LCx lesion (red arrow) to prepare the lesion before brachytherapy delivery; C: Coronary angiogram showing the Novoste Beta-Cath™ System that was used to deliver a source train that contains 12 individual radioactive seeds blue arrow to red arrow). Once properly positioned, 23 Gy from the center of the source center was prescribed. The patient was monitored during the dwell time which required 4 min and 49 s; D: Another balloon angioplasty was done after the radioactive seeds are pulled from LCx; E: Final TIMI-III flow in the LCx. PCI: Percutaneous coronary intervention; LAD: Left anterior descending artery; LCx: Left circumflex; DES: Drug-eluting stents; ISR: In-stent restenosis.

is still unclear.

### *Drug-eluting balloon angioplasty*

It was proposed that repeat stenting for ISR raises concerns for creating multiple stent layers. Therefore, the use of DEB angioplasty should minimize the metal layer and eventually decrease future ISR. For that purpose, multiple randomized studies have been done to evaluate the efficacy and durability of DEB compared with DES in treating BMS or DES-ISR. Few studies have shown that DEB is non-inferior to DES for BMS and DES-ISR[52-61]. However, none of these studies have been powered for clinical endpoints. DEB is currently not available for use in the United States. In addition, their use has been associated with issues that may limit their use mostly related to the use of paclitaxel and potential of particulates showering to the distal vessel bed, as well as the high profile of the device. Comparison of DEB with DES for treatment of ISR will be discussed in the following section.

### *Drug-eluting stents*

Balloon angioplasty alone carries a high risk of recurrent stenosis, especially in diffuse and/or severe ISR[44,62,63]. The randomized trials Paclitaxel-eluting Stents *vs* Brachytherapy for In-stent Restenosis (TAXUS V ISR) and Sirolimus-eluting Stents *vs* Vascular brachytherapy (SISR) trial showed better outcomes for DES compared with brachytherapy[64,65]. Two major randomized trials compared DES with DEB for patients with ISR. The ISAR-DESIRE 3 trial randomized 402 patients with ISR in DES to paclitaxel-eluting balloon (PEB) *vs* first generation DES (PES) *vs* balloon angioplasty[52]. At a median follow-up of 3 years, the risk of TLR was similar with PEB *vs* PES (HR = 1.46, 95%CI: 0.91-2.33, $P$ = 0.11) and lower with PEB *vs* balloon angioplasty (HR = 0.51, 95%CI: 0.34-0.74, $P$ < 0.001). The risk of death/MI was lower, but not statistically significant, with PEB *vs* PES (HR = 0.55, 95%CI: 0.28-1.07, $P$ = 0.08). This finding was driven by a lower risk of death (HR = 0.38, 95%CI: 0.17-0.87, $P$ = 0.02). The risk of death/MI was similar with PEB *vs* balloon angioplasty (HR = 0.96, 95%CI: 0.46-2.0, $P$ = 0.91). Using the second generation DES, Restenosis Intra-Stent of Drug-Eluting Stents: Drug-Eluting Balloon *vs* Everolimus-Eluting Stent (RIBS IV) trial, evaluated the comparative efficacy of DEB and EES in patients presenting with DES-ISR[66,67]. A total of 309 patients with DES-ISR

were randomly allocated to DEB, or second generation DES (EES) patients in the EES arm had a significantly larger minimal lumen diameter (2.03 ± 0.7 mm *vs* 1.80 ± 0.6 mm, $P < 0.01$) net lumen gain (1.28 ± 0.7 mm *vs* 1.01 ± 0.7 mm, $P < 0.01$), and lower percent diameter stenosis (23% ± 22% *vs* 30% ± 22%, $P < 0.01$) and binary restenosis rate (11% *vs* 19%, $P = 0.06$), compared with patients in the DEB arm. At the 1-year clinical follow-up (100% of patients), the main clinical outcome measure (composite of cardiac death, myocardial infarction, and target vessel revascularization) was significantly reduced in the EES arm (10% *vs* 18%, $P = 0.04$, HR = 0.58, 95%CI: 0.35-0.98), mainly driven by a lower need for target vessel revascularization (8% *vs* 16%, $P = 0.035$).

A meta-analysis looked into treatment of ISR comparing DEB, DES, and BA reported that treatment with DEB had a trend toward better outcomes than with DES[68-72]. The risk of TLR was lower in patients treated with DEB (OR = 0.22, 95%CI: 0.10-0.42) or DES (OR = 0.24, 95%CI: 0.11-0.47) than in those treated with BA. In a comparison of DEB and DES, the risk of TLR (OR = 0.92, 95%CI: 0.43-1.90) was similar. The risk of major adverse cardiac events, which was mainly driven by TLR, was also significantly lower in the DEB and DES groups (OR = 0.28, 95%CI: 0.14-0.53) than in the BA group, but it was similar between the DEB and DES groups (OR = 0.84, 95%CI: 0.45-1.50). For TLR, the probability of being ranked as the best treatment was 59.9% (DEB), 40.1% (DES), and 0.1% (BA).

There is no clear evidence on which type of DES should be used to treat ISR of a DES. Some experts argue that using a different type of DES helps to overcome drug resistance, but no strong data support this practice. A recently published network meta-analysis addressed the question of which strategy is preferred for the treatment of ISR, with the primary outcome defined as the percent diameter stenosis at angiographic follow-up[73]. This analysis suggested that PCI with second-generation DES (EES) was the most effective treatment, whereas percutaneous coronary intervention with DEB was ranked as the second most effective treatment but without significant differences from first-generation DES. Two additional similar design meta-analyses have reported similar findings suggesting second generation DES as treatment of choice for BMS and DES-ISR[74,75]. As a result, the 2009 update of the American College of Cardiology/American Heart Association/Society for Cardiovascular Angiography and Interventions guideline update for PCI and the 2005 European Society of Cardiology Task Force recommend DES for ISR whether the initial stent was BMS or DES[76-78].

A recently published pooled analysis of the RIBS V and RIBS IV compared the efficacy of EES in patients with BMS-ISR and DES-ISR[79-82]. The study detected clinical and morphological differences of ISR in BMS *vs* DES, including for the later more focal ISR pattern and delayed onset of presentation. Nevertheless, the outcome of the patients with DES restenosis was less favorable with regard to the angiographic indices, including lumen diameter post procedure and at follow-up. DES-ISR group treated with EES had both increased mortality and need for target vessel revascularization as compared with BMS-ISR group at one year follow up. The authors conclude that EES provides favorable outcomes in patients with ISR and that the results of EES are less satisfactory in patients with DES-ISR than in those with BMS-ISR.

## CONCLUSION

In-stent restenosis remains a prevailing clinical problem. The substrate of ISR includes a pathological spectrum ranging from smooth muscle cell proliferation to neoatherosclerosis. Optimal stent deployment, utilization of imaging-guided implantation by IVUS or OCT, adequate coverage of the lesion, verifying stent expansion and apposition to the vessel wall and minimal use of BMS are considered the main strategies to decrease ISR. Based on the currently available literature, the use of BMS should be minimal in clinical practice and replaced with second generation DES. For patients presenting with first ISR, vascular brachytherapy should be considered in patients with focal ISR, or high bleeding risk or requiring DAPT interruption. 2$^{nd}$ generation DES should be a second line therapy to avoid adding an extra layer of metal to treat DES. For patients presenting with recurrent ISR, second generation DES have better long-term outcomes specially if combined with DEB. DEB should be used as first line therapy for bifurcation restenosis to prevent excess metal at the carina.

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