# Treatment options of in-stent restenosis: mini review

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In-stent restenosis (ISR) is the leading cause of the need for reintervention after percutaneous coronary intervention (PCI). Lumen diameter reduction may occur due to early elastic return, vascular remodelling, or aggressive neointimal hyperplasia in the luminal surface of the stent. Recent data also suggest that a newly occurring atherosclerotic process called „neoatherosclerosis" can play an essential role in the development of ISR. Numerous studies have shown a high incidence of acute coronary syndrome (ACS) as a clinical manifestation of ISR and its association with increased mortality and morbidity. Stent improvements, novel drug regimens, and technological advances have expanded the scope of treatment for ISR. Intracoronary imaging is also beneficial in guiding the intervention. The development of DES has been shown to reduce the incidence of ISR. However, target lesion revascularisation still exists and may occur within 5 years and 10 years (in 10% and 20%, respectively). Thus, it is necessary to consider the strategy to prevent and manage ISR optimally in order to avoid the possibility of another episode of restenosis. In this paper, we systematically reviewed ISR and its various treatments based on recent literature reviews.

**Key words:** ISR, definition, incidence, classification, mechanism, clinical presentation, management.

## Možnosti léčby in-stent restenózy: mini-přehled

In-stent restenóza (ISR) je hlavním důvodem nutnosti reintervence po perkutánní koronární intervenci (PCI). Ke zmenšení průměru lumen může dojít v důsledku časného elastického návratu, cévní remodelace nebo agresivní neointimální hyperplazie na luminálním povrchu stentu. Nedávné údaje rovněž svědčí o tom, že zásadní roli při vzniku ISR může hrát nově se vyskytující aterosklerotický proces označovaný jako „neoateroskleróza". Mnohé studie prokázaly vysokou incidenci akutního koronárního syndromu (AKS) jako klinického projevu ISR a jeho souvislost se zvýšenou mortalitou a morbiditou. Rozsah léčby ISR se zvýšil díky vylepšení stentů, novým farmakoterapeutickým režimům a pokroku v technologiích. Při provádění intervence je užitečné intrakoronární zobrazení. Bylo prokázáno, že rozvoj DES snížil incidenci ISR. Stále však existuje otázka revaskularizace cílové léze, která může vyvstat v rozmezí 5 nebo 10 let (u 10 %, resp. 20 %). Je tedy nutné zvážit strategii prevence a optimálního řešení ISR, aby se předešlo možnosti další epizody restenózy. V této práci systematicky hodnotíme ISR a její různé způsoby léčby na základě nedávných přehledů literatury.

**Klíčová slova:** ISR, definice, incidence, klasifikace, mechanismus, klinický obraz, léčba.

**DECLARATIONS:**

**Ethical principles compliance:**
The authors attest that their study was approved by the local Ethical Committee and is in compliance with human studies and animal welfare regulations of the authors' institutions as well as with the World Medical Association Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects adopted by the 18th WMA General Assembly in Helsinki, Finland, in June 1964, with subsequent amendments, as well as with the ICMJE Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals, updated in December 2018, including patient consent where appropriate.

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## 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 associated 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*

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).

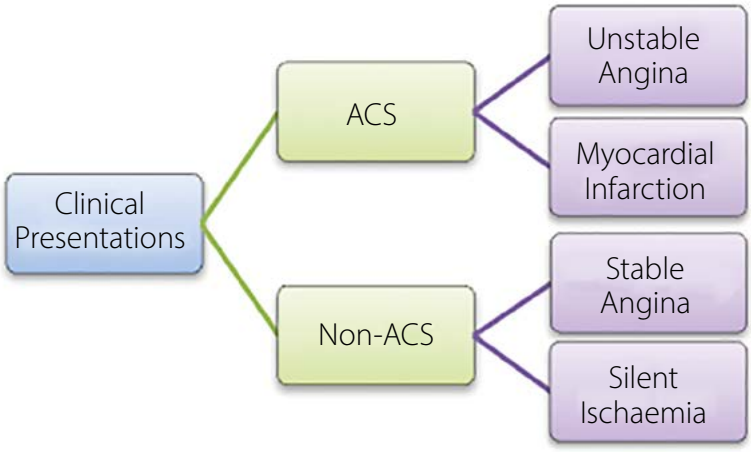
In addition, neoatherosclerosis is suggested as another cause of very late stent thrombosis and late target lesion revascularisation (12). It is related to incomplete regeneration of the endothelium leading to excessive uptake of circulating lipids and accelerated development of atherosclerotic plaques 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 angina 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).

**Figure 1.** *Clinical Presentations of ISR*




## 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

in a patient with very severely compromised renal function and to minimise the use of contrast in PCI (18, 19).

### Optical Coherence Tomography (OCT)

OCT gives an image resolution 10 times greater than IVUS and is also easier and faster to set up and use. It reconstructs the vessel wall image by using infrared light. This light-based OCT technology can penetrate 2-3 mm inside the vessel wall. OCT is far better than IVUS for determining the vessel's luminal diameter and cross-sectional area. OCT can depict plaque morphology with a sensitivity close to that of histology. It can also assess calcium thickness, lipid, thrombus, fibroatheroma, plaque rupture, stent strut neointimal thickness and apposition, and edge dissections. It requires the use of contrast injection and may not be suitable in the case of patients with severe renal dysfunction (18, 19).

Based on restenotic tissue structure in the cross-sectional images captured by OCT, the patterns are categorised into (20):

1. Homogeneous intima: uniform optical properties of restenotic tissue showing no focal variations in the backscatter pattern
2. Heterogeneous intima:

a. Type 1 – Thin-cap fibroatheromas (TCFA)-like pattern: the presence of an area with marked signal attenuation with a diffuse border and fibrous cap thickness at the thinnest part ≤ 65 µm and an angle of lipidic tissue ≥ 180°
b. Type 2 – Layered pattern: restenosis tissue consists of concentric layers with different optical properties (a thick high scattering layer and a low scattering layer with a stent strut)
c. Type 3 – Patchy pattern: patchy and highly echolucent regions throughout the layers
d. Type 4 – Speckled pattern: restenotic tissue consists of a heterogeneous speckled band.

## Management of In-Stent Restenosis

The treatment of ISR remains a challenging clinical problem. Clinicians should carefully consider choosing the best type of treatment based on the original stent problem to prevent the possibility of another recurrence.

## Drug-Eluting Stent (DES)

Most previous studies consistently demonstrated relatively poor outcomes in patients treated for DES-ISR compared with BMS-ISR (21). In a meta-analysis assessing the treatment of DES-ISR, repeat DES implantation showed decreased target revascularisation and superior antirestenotic efficacy compared with angioplasty alone. DES implantation exhibited similar performance in both ISR types (BMS-ISR or DES-ISR) (1, 22).

A large meta-analysis was conducted to clarify which strategy is the best treatment modality for ISR. The study involved 27 trials with a total of 5,923 patients at 6 months to 1-year follow-up. Repeat stenting with everolimus-DES (EES) which is classified as second-generation DES was found to be statistically superior to all other modalities (23). The RIBS III trial (Restenosis Intrastent: Balloon Angioplasty Versus Elective Stenting) suggested that the use of second-generation and limus-type DES was associated with better angiographic outcomes although further studies with larger sample sizes would be required (21).

Nonetheless, the debate regarding whether to use a DES eluting the same or a similar type of drug (homo-DES approach) versus a switch to a different type of drug (hetero-DES approach) has continued. The hypothesis of the switch approach benefit is based on the possibility that it might overcome drug resistance or polymer-related problems (4). Furthermore, the RIBS III trial assessed the impact of selecting a different DES for the treatment of ISR. This study showed that, in patients with DES ISR, the use of a different DES yielded superior clinical and angiographic long-term results compared with those seen with other therapeutic modalities (21).

However, a potential drawback of DES implantation is that another layer of a stent is implanted, which can lead to ensuing therapeutic challenges in the event of ISR recurrence (22).

## Drug-Coated Baloon (DCB)

DCB offers the advantage of avoiding the implantation of an additional metallic layer when treating ISR, and is recommended by the European Society of Cardiology guidelines as a treatment option (Class I, Level of Evidence: A) (24).

DCB has a potential role in the treatment of DES-ISR by avoiding the placement of another layer of the stent and providing favourable results. DCB can be particularly suitable for clinical situations where it is not applicable to add another layer of the stent (i.e., multiple previous stent layers, the presence of a major side branch) or for bleeding events, and can be particularly suited to clinical situations where the mechanism of ISR is stent maldeployment (4, 5, 25).

DCB was ranked as the second most effective treatment for ISR based on meta-analyses conducted by Siontis et al (23). No significant difference in the risk of all-cause death, myocardial infarction, or target lesion thrombosis between treatments of DCB and DES was observed (8.7% vs. 7.5%; HR: 1.13; 95% CI: 0.65 to 1.96). However, DCB angioplasty showed a slightly better performance in BMS-ISR compared with DES-ISR in some studies (4, 22).

Furthermore, in DES-ISR, there was a borderline numerical trend toward a decreased risk after DCB angioplasty compared with DES implantation (9.5% vs. 13.3%; HR: 0.69; 95% CI: 0.47 to 1.00) (22, 26).

In recent years, sirolimus DCBs have also been developed, and a comparison of a novel SCB with a crystalline coating showed similar angiographic outcomes in the treatment of both coronary de novo disease and ISR compared with a clinically proven PCB (27, 28).

## Plain Old Balloon Angioplasty (POBA)

POBA is one of the initial treatments that has been used in patients with ISR. The procedure consistently shows satisfactory acute results and a very low occurrence of complications. The use of high-pressure balloons in ISR is most important for mechanical causes. It can be used for stent underexpansion with noncompliant balloons with a high pressure of approximately 40 atm. However, one of the limitations of POBA is that the acute gain is short-lived, and subacute tissue re-intrusion back to the lumen tends to occur within minutes of the last balloon inflation. The proce-

dure was also associated with edge-related complications and a high recurrence of ISR (> 50%) (1, 4). In regards to treatment strategy, nonetheless, observational studies and randomised trials have consistently shown that DCB and DES have relatively superior outcomes than POBA in ISR (29, 30).

## Cutting/Scoring Balloon

Cutting or Scoring balloons (CB or SB) were introduced to minimise barotraumas to the vessel wall and slippage of a conventional balloon when inflated over fibrotic scar tissue. They prevent balloon slippage-related complications using the lateral blades that anchor the balloon within the target lesion. In the treatment of ISR, cutting and scoring balloons may play an important role in lesion preparation preceding DES or DCB (1).

Neointimal modification with a scoring or cutting balloon has possible advantages over standard balloon pre-dilatation (31). Neointimal change of ISR with CB plus DCB vs. standard DCB lowers the 5-year rate of TLR, even though not statistically significantly. The benefit seems to be persistent in ISR after implantation of BMS and DES (32). In the ISAR-DESIRE 4 trial, neointimal modification with scoring balloon before DCB compared with DCB standard therapy showed superior results concerning angiographic outcomes at follow-up. However, at 1-year follow-up, there were no differences when the clinical events or TLR were assessed (16.2% vs. 21.8%; P = 0.26) (33). Both technologies are interfered with their inability to hinder neointimal proliferation and have limitations similar to balloon angioplasty (BA) (5).

## Bare Metal Stent (BMS)

During the BMS era, conventional balloon angioplasty or repeated BMS implantation was mostly used as the treatment for ISR. Recurring event rates after BA were approximately 20% by 1 to 2 years. The RIBS I (Restenosis Intra-stent Balloon Angioplasty Versus Elective Stenting) trial randomised 450 patients with BMS-ISR to undergo either BA or repeat BMS implantation. After 4 years of follow-up, target vessel revascularisation was as high as 25% and 29% (P = 0.35), and the major adverse cardiac event (MACE) rates were 31% and 37% for the BMS implantation and balloon angioplasty groups, respectively. Currently, BMSs have been replaced by DESs, and BMSs are only used in specific situations (eg, in patients with an extremely high bleeding risk, when short-duration antiplatelet therapy is required, or for economic reasons), and studies assessing the value of BMS in patients with DES-ISR are lacking and unlikely to be undertaken (31, 34).

## Bioresorbable Vascular Scaffolds (BVS)

BVS has also been proposed as a treatment for patients with ISR. The main advantages are that the device eventually disappears from the vessel wall, avoids the presence of multiple stent layers, and prevents early lumen loss associated with tissue retraction seen in balloon angioplasty (4). Some studies suggest that the use of BVS implantation for the treatment of complex drug-eluting stent and bare-metal stent ISR lesions might be associated with acceptable long-term clinical outcomes (35, 36).

Based on Restenosis Intrastent: Bioresorbable Vascular Scaffolds Treatment (RIBS VI), target lesion revascularisation rates following BVS were similar to those seen with DEB (10.4%) but higher than with EES (3.2%; p < 0.001). After potential confounders in baseline characteristics were adjusted, results remained unchanged. It can be concluded that BVS yielded late angiographic and clinical results similar to DEB, but inferior to EES (37).

Potential limitations of BVS include lumen crowding due to thickness (particularly in small vessels), device flexibility that may influence access to restenotic lesions, and questions concerning radial strength and recoil, which may be particularly crucial in the management of ISR (34).

## Intravascular Brachytherapy (IVBT)

Intravascular brachytherapy is a technique that is intended to suppress cellular proliferation and migration by directing radiation at the site of the vascular intervention. It allows a localised delivery of radiation to inhibit the proliferative response seen after angioplasty (38). Condado et al conducted the first trial of coronary IVBT. They treated 21 participants with gamma irradiation after balloon angioplasty. The result was that 19 of 21 participants showed evidence of late occlusion at two-year angiographic follow-up (39). The final pathway of DES-ISR includes the formation of neointima with an accumulation of lipid macrophages within the neointima and subsequent calcification. IVBT inhibits neoatherosclerosis in DES-ISR. It impedes neointimal growth without affecting the surrounding healthy tissue. In a previous retrospective study, IVBT showed good outcomes for patients with DES-ISR. The incidence of target lesion failure (TLF) occurred in one in three patients at 2 years (40).In a systematic review and meta-analysis conducted by Megaly et al., the incidence of target vessel revascularisation occurred in approximately one in four patients at two--year follow-up, with an incidence rate of 29.2% (95% CI 18.0-40.4%) (41). Nowadays, the popularity of brachytherapy decreased after the introduction of DES because of logistic difficulties and lower restenosis events in the newer stents (42).

## Intravascular Lithotripsy (IVL)

Intravascular lithotripsy is a procedure for treating severely calcified plaques in the coronary and peripheral arteries. It generates sonic pressure waves through the vessel wall and produces calcium modification. This acoustic wave selectively fractures the intimal and medial calcium. This increases vessel compliance and optimises stent expansion (43). Some reports showed the safety and efficacy of IVL in treating in-stent restenosis. IVL can be promising to optimise the outcome of ISR in heavily calcified coronary artery disease (44–46).

## Ablative Strategies

### Excimer Laser Coronary Atherectomy (ELCA)

ELCA is a long-established adjunctive therapy that can be applied during PCI. Excimer laser generates pulses of short-wavelength, high-energy ultraviolet light that uses an active medium containing gas and halogen (47). It has been useful to facilitate stent ex-

pansion in balloon-resistant lesions. It has been effective for PCI of complex lesions, including stent restenosis, calcified lesions, and chronic total occlusion. It is both safe and effective for plaque modification. Ichimoto et al conducted a clinical study to investigate the outcomes after treatment with ELCA for ISR of des. The study showed that acute luminal gain was greater in PCI with the ELCA group than without ELCA. There was slightly less TLR in patients with ELCA for ISR compared to those without, and there was no significant difference in cardiovascular events between patients with and without ELCA (48).

## Rotational Atherectomy (RA)

RA is an atheroablative technology that enables PCI for complex, calcified coronary lesions. The principal indication for RA is a modification of severely calcified de novo coronary stenoses which are unlikely to expand adequately with balloon angioplasty to allow for complete stent expansion (49). The randomised PREPARE-CALC Trial compared high-speed RA and modified balloons (MB) before DES implantation in severely calcified coronary lesions. After complete clinical follow-up over 9 months, the overall mortality was 2% in both groups (P = 1.00), spontaneous myocardial infarction occurred in 2 patients in the MB group and in none in the RA group, and TLR was twice as high in the MB group. It showed that there was no significant difference in clinical outcomes at 9 months between the MB and RA groups (50).

## Coronary Artery Bypass Graft (CABG)

In patients with symptomatic recurrent diffuse ISR with an indication for revascularisation, CABG can be advantageous over repeat PCI to reduce recurrent events (Level of recommendation 2a) (18). In a previous study, patients who underwent CABG had a significantly lower incidence of target vessel revascularisation (8%) and MACE (23%) before PCI (51, 52). Reports on the incidence of CABG due to restenosis after BMS or DES and the clinical outcomes are scarce in the literature.

## Adjunctive Medical Therapy

Systemic treatments have targeted different mechanisms that have been identified as potential factors in the development of restenosis. Platelets and thrombi were first attributed to the cascade of events leading to neointimal proliferation. However, antiplatelets and anticoagulants did not reduce neointimal hyperplasia and restenosis rates (53). Sirolimus or cilostazol may be of benefit in patients who had restenosis more than twice in the same area. They may reduce the amount of restenosis tissue that builds up. The double-blind, randomised, placebo-controlled Oral Sirolimus to Inhibit Recurrent In-stent Stenosis (OSIRIS) trial showed that restenosis can be reduced by short-term treatment with sirolimus. There was a significant correlation between sirolimus blood concentration on the day of the procedure with the late lumen loss at follow-up (P < 0.001) (54).

## Current Guidelines

The 2018 ESC/EACTS guidelines for myocardial revascularisation recommend either DES or DCB for both BMS-ISR and DES-ISR (Class I, Level of Evidence A). Intracoronary imaging such as IVUS and/or OCT should be considered to determine the most appropriate procedure prior to revascularisation (24).

Different guidelines by ACC/AHA/SCAI from 2021 propose DES implantation as the leading revascularisation method if anatomic factors are appropriate, and the patient can comply with and tolerate antiplatelet therapy (Class I, Level of Evidence A). Additionally, the guidelines suggest the use of vascular brachytherapy for patients with an artery that is unfavourable to receive another DES and who are not good candidates for bypass surgery (Class 2 b, Level of Evidence B-NR) (18).

Moreover, in patients with recurrent episodes of diffuse ISR in large vessels, multivessel disease, or in the presence of other complex lesions such as chronic total occlusions, both European and American guidelines suggest performing CABG over PCI (18, 24).

The 2022 EuroIntervention publication „Management of in-stent restenosis" proposes an ISR treatment algorithm. This algorithm is based primarily on the type of stent used in the initial procedure and the mechanical issues of ISR. If no mechanical issue is found, or IVI is unavailable, the recommendation is to focus on routine predilatation of ISR lesions such as POBA, RA, ELCA, IVL, cutting, and scoring balloons.

When mechanical issues are present, the operator can decide on the best approach to address the problem and how to treat the lesion. DCBs and DESs are used to treat the lesion in the majority of cases. When the type of stent is unknown and in DES-ISR, DES appears to be moderately more effective than DCB (5).

## Conclusion

Restenosis is much less common due to technical breakthroughs in stents and drugs. Nevertheless, ISR does still occur and remains a significant issue. Contrary to the lower incidence of ISR in DES, patients with DES-ISR display worse clinical outcomes than those with BMS-ISR after revascularisation.

While DES and DCB appear to provide the most benefit for ISR, the optimal strategy for managing ISR must be determined on a case-by-case basis. The underlying mechanisms of the lesion, patient profile, and prior treatment characteristics should always be considered before deciding on ISR therapy. Intravascular imaging aids in refining clinical decision-making strategies through a more detailed anatomical assessment of lesions.

Further research is needed to identify other possible clinical and anatomical predispositions and alternative therapies that can help improve selection and tailor treatment in each individual patient.

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