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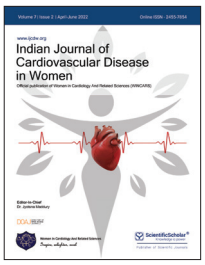

Cardiovascular Interventional Round

Management of In-stent Restenosis

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ABSTRACT

Despite recent improvements in percutaneous coronary intervention (PCI), in-stent restenosis (ISR) — which accounts for 5–10% of all PCI procedures in contemporary clinical practice remains a substantial problem and the most frequent reason for stent failure. While the absolute number of ISR-PCI operations performed in contemporary practice has increased as a result of rising procedural volume and complexity, the relative rate of ISR has decreased with newer-generation drug eluting stents (DESs) in comparison to the bare metal stent (BMS) period. While BMS ISR is usually early and characterized by neointimal hyperplasia, DES ISR tends to be late with neoatherosclerosis as a characteristic feature. According to recent research, drug-coated balloons or DESs are the most effective therapy options for the majority of ISR cases. Future ISR interventional paradigms may be influenced by intravascular imaging (IVI) ISR tissue patterns. IVI can provide useful information to guide treatment options in ISR-PCI.

Keywords: Stent restenosis, Neoatherosclerosis, Mangement

INTRODUCTION

The most common reason for stent failure is in-stent restenosis (ISR), which is defined as a significant decrease in the lumen diameter within the stent segment after a successful percutaneous coronary intervention (PCI). ISR management currently is accounting for 5–10% of all PCI procedures, despite the fact that the ISR related incidence is lower with newer drug eluting stent (DES) technologies vis a vis the bare metal stent (BMS) era. The present review highlight the pathophysiological mechanisms and management strategies of ISR in this era imaging and interventional advances.[1-6]

ISR

By traditional definition, ISR occurs when the lumen diameter of the stent or the artery 5 mm proximal and distal to the stent (stent edge) decreases by more than 50% as measured as quantified on coronary angiography.[7] Using three-dimensional data acquired by intravascular imaging (IVI), ISR has been defined as a reduction in vessel cross-sectional area to more than 75% of the reference vessel.[8-10]

Ischemic symptom recurrence is frequently referred to as "clinical restenosis." Clinical restenosis rates are lesser than ISR rates because not all ISR causes symptoms or indicators of ischemia ("silent restenosis"). Percutaneous interventional therapy for ISR may be recommended for individuals manifesting as acute coronary syndrome (ACS) or chronic coronary syndrome

(CCS), much as it is for patients with *de novo* coronary artery disease (CAD) (CCS).[11,12]

ISR has been referred to as Achilles heel of PCI. Treatment of ISR account for 10% and 5% of all PCI procedures in the United States (US) and Europe, respectively. Incidence-based risk is notoriously difficult to control. Although easy to treat percutaneously with excellent angiographic results, a high risk of recurring clinical events, such as repeated target lesion revascularization (TLR) has been reported. High MACE rates are often seen in patients with ISR presenting as ACS. ISR management can be challenging with the potential to enhance patient outcomes and minimize adverse outcomes.

ANGIOGRAPHIC PATTERNS

Observing angiographic patterns, Mehran *et al*.[13] created the most widely used ISR classification system. Patients with BMS-ISR were divided into subgroups according to three criteria: ISR length (<10 mm: Focal, >10 mm: Diffuse), ISR placement (inside or beyond stent boundaries), and occlusion (present or absent). Type I lesions are those localized within the stent (focal); Type II lesions are those that are with in stent (diffuse); Type III lesions are those that are both inside and outside the stent boundaries; and Type IV lesions are complete occlusions. Different angiographic patterns were linked to predictive value in relation to the subsequent need for TLR13. This categorization was developed for BMS-ISR and may not apply to DES-ISR, in which the majority of ISR is focal in origin.[14] Based purely on angiograph appearances, this categorization fails to identify insight into the underlying pathophysiology of ISR.[13]

ACTIOPATHOGENESIS

ISR can be attributed to a vast range of pathophysiological mechanism. It is hence imperative to, identify the underlying mechanisms while treating ISR. Moreover, one should attempt to address as many of the potential contributing mechanisms as one can during the ISR therapy, as it is probable that several of them will coexist.[14-16]

Stent undersizing, under expansion, vascular calcification, stent fracture, and geographic miss[17,18] are examples of potential stent related mechanical issues associated with ISR.

Neointimal hyperplasia and neoatherosclerosis[19] are biological processes of ISR. In Neointimal Hyperplasia: The intima accumulates an increased in the number of smooth muscle cells and the extracellular matrix. Accumulation of lipid-laden foamy macrophages within the neointima, in presence or absence of necrotic core development and/or calcification is diagnostic of neoatherosclerosis. This finding may have implications for the choice of percutaneous intervention[19-23] for patients with calcified neoatherosclerosis, which can be particularly difficult to treat.

The incidence of ISR in a stented coronary artery may be attributable to a combination of three groups of causes: extra-stent factors (such as vascular calcification calcific nodule, vessel size, or numerous stent layers), stent-related factors (such as stent undersizing or fracture), and intrastent factors. These factors can coexist simultaneously and are summarized in [Figure 1].

Recent research suggests that BMS-ISR and DES-ISR should be treated as separate pathogenic entities,[19] despite their clear outward similarities. Differences in angiographic appearances, late lumen loss (LLL) time course, IVI morphology, histology, and clinical response to interventions[10,16,19,20] may lend credence to this model.

While neo intimal hyperplasia is the usual pathophysiology in BMS. ISR neo atherosclerosis is commonly found in ISR of DES. In patient in DES ISR, it is relatively less common seen in the 1st year PCI (early DES ISR) in comparison to late DES ISR which develop after 1st year post PCI. Patients with BMS tend to develop ISR earlier following PCI in comparison to DES ISR. The ISR related neo atherosclerosis has an accelerated progress in comparison to native coronary artery disease. About 69% of neo intimal hyperplasia in BMS ISR versus 59% of neo atherosclerosis in DES ISR was reported in a study based on finding of intravascular ultrasound (IVUS). The study also reported stent under expansion in 14% and 18% of BMS ISR and DES ISR lesion, respectively. Moreover, 8% of BMS ISR and 16% of DES ISR reported co dominant pathophysiology. Second generation DES ISR lesions also had under expansion in 40% of cases and 66% of these also documented neo intimal hyperplasia of more than 50%. BMS ISR usually manifest with in first 6 months of the stent implantation whereas accelerated neo arthersoscleosis in patients with DES ISR continue after several year of stent deployment leading to incidence of late ISR. Silent ISR may be documented in patients with no clinical symptoms but undergoing routine angiographic

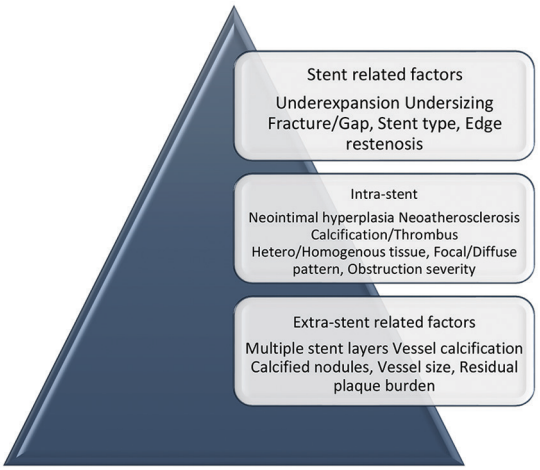

Figure 1: In-stent restenosis percutaneous coronary intervention - Etiological factors needing consideration.

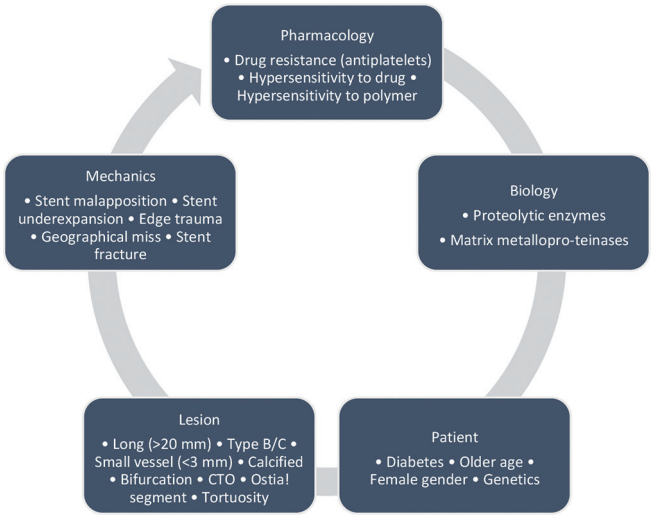

Figure 2A: Factors influencing the development of in-stent restenosis.

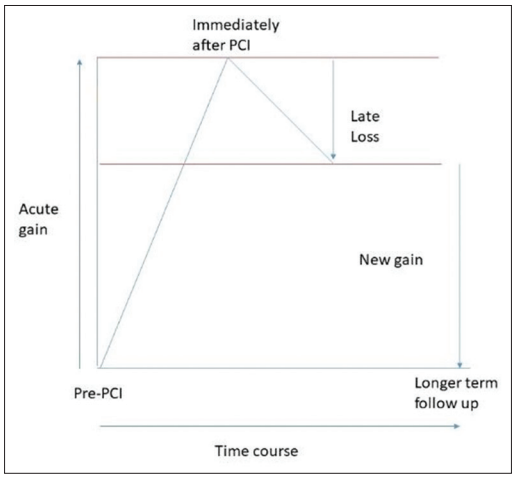

Figure 2B: Acute gain and late luminal loss in in-stent restenosis-percutaneous coronary intervention.

examination here by affecting the incidence of ISR. Initially believed to be a gradually progressing benign disease ISR has been know to present many a times a ACS. IVI has unfolded plaque rupture and stent thrombosis as the underlying pathophysiology of ISR presenting as ACS. ISR ACS has adverse prognosis as compared to stable presentation of ISR [Figure 2].

ISR IMAGING

Stent enhancement fluoroscopic techniques, for example, stent boost has been known to identify under expansion and stent fracture with relative ease in the Cath lab. Besides stent enhancement techniques, IVI place an important role in ISR imaging. In lack of RCT trials supporting the role of IVI in ISR management, the Guidelines recommend the use of IVI as class 2A and level B indication. By identifying the underlying pathophysiological mechanism, IVI affects the choice of therapy for ISR management.

Optical coherence tomography (OCT) in ISR

Given a higher spatial resolution OCT aids in neo intimal hyperplasia and neo atherosclerosis identification. However, the limitation of OCT includes the need of administering contrast media for a blood free field for image acquisition. This might be challenging in patients with tight or ostial instant restenosis. Moreover, in comparison with IVUS, OCT might not able to identify the external elastic lamina here by leading to difficulty in vessel sizing. This can specially be an issue in patients who have multiple stent layers. Higher contrast media OCT can be arrhythmogenic and also needs a watch for any acute injuries. The instant restenosis seen by OCT can be classified into four types: Homogeneous, Hetrogenous, Attenuated, and Layered. Homogeneous tissue pattern is a characteristic of early onset BMS ISR. The DES ISR is associated with attenuated, layered and heterogenous appearances which are reflective of underlying neoatherosclerotic disease process. The presence of these four patterns might be seen in both DES and BMS ISR while homogeneous tissue pattern is typical of BMS ISR. In very late BMS ISR, as 5 year after stent placement, heterogenous tissue pattern has been identified. Moreover, OCT also aids in identifying underlying pathophysiological mechanisms as plaque rupture in DES ISR presenting as acute coronary event with underlying neo atherosclerosis [Table 1].

IVVS in ISR

The IVUS technique allows for more thorough tissue penetration than OCT does without the need for a blood-free field. IVUS cannot characterize tissues in great detail because of its limited wavelength (50 m) and axial resolution (150 m). IVUS can still show various ISR-related abnormalities, such as neointimal hyperplasia, mature neoatherosclerosis, stent under expansion, stent undersizing, and vascular calcification.[16,17] And the EEL is typically clearly defined at the reference segment and beyond the stent struts, allowing for precise vessel size. Neoatherosclerosis has been demonstrated in both BMS-ISR and DES-ISR using IVUS with virtual histology, however this technology is not yet extensively utilized in clinical practice.

Fractional flow reserve (FFR)/instantaneous wave-free ratio (iFR) in ISR

Repeated revascularization is warranted only if symptoms or evidence of ischemia attributable to the ISR lesion are present. Intracoronary physiology is sometimes recommended in the clinical setting, especially for patients with ISR of moderate severity or for those who are less symptomatic.

Table 1: BMS versus DES restenosis.

	BMS restenosis	DES restenosis
Imaging features		
Angiographic morphology	Diffuse pattern more common	Focal pattern more common
OCT tissue properties	Homogenous, high signal band most common	Layered structure or heterogenous most common
Duration of late luminal loss	Late loss maximal by 6–8 months	Ongoing late loss out to 5 years
Histopathological features		
Smooth muscle cellularity	Hypercellular	Hypo cellular, High common
Proteoglycan content	Moderate	
Peri-strut fibrin and inflammation	Occasional	
Endothelialization	Completed by 3–6 months	Completes upon months to 48
Thrombus	Occasionally	Occasional
Neoatherosclerosis	Unusual, late	Relatively common, accelerated course

OCT: Optical coherence tomography, BMS: Bare metal stent, DES: Drug eluting stent

However, there is a lack of information on the evaluation of ISR.[24] using FFR or iFR. Angiographically, moderate (40–70%) ISR lesions with an FFR value 0.75 can be safely managed with conservative treatment, according to previously published data with a 1-year follow-up.[25] To date, however, no randomized data have been found to back up an ISR treatment strategy based on FFR. The diagnostic process for patients with ISR should generally mirror that for patients with *de novo* CAD.[26]

TREATING ISR – APPROACH AND MANAGEMENT STRATEGIES

Concepts at large

To a large extent, the basic concepts for treating ISR are similar to those for treating native coronary stenoses. However, compared to *de novo* disease, caution is needed when dealing with a scaffold that is already in place. It may be necessary to identify and address the underlying conditions that led to the original stent failure to prevent a repeat event.

Quantitative angiographic metrics

Minimum lumen diameter (MLD), percentage diameter stenosis (%DS), acute gain, and Late luminal loss (LLL) are all quantitative coronary angiography metrics used to evaluate and compare the relative anti-restenotic efficacy of stent- and balloon-based therapy modalities. An individual's acute gain is calculated as the change in MLD between before and immediately after PCI. To calculate LLL, we compare the MLD post-procedure and MLD on follow-up. The goal of ISR treatment is to maximize acute gain while minimizing late luminal loss (LLL). [Figure 3] depicts the temporal distribution of acute gain and LLL following PCI. Notably, drug-coated balloon (DCB) treatment is related with lower rates of both acute gain and late loss than DES PCI, which is typically associated with higher rates of both acute gain and late loss. [Figure 3] illustrates that net gain is the most relevant metric when contrasting the two modalities, while minimal lumen diameter or % DS during long-term.[22,23] Follow-up may also be utilized.

Moreover several extraneous factors might affect acute gain and late luminal loss in patient with ISR. Stent under expansion secondary to vascular calcification, calcified neoatherosclerosis can be identified in a significant number with patients with ISR. In patients with DES ISR, a baseline stent under expansion is related to under expansion of the second stent which might be used to treat the ISR. This might be associated with recurrence of ISR and adverse MACE events on follow-up. In ISR treated with DCB, stent under expansion post procedurally is associated with higher occurrence of adverse events. Hence, it is imperative to identify the under lying factors of ISR so as to avoid re occurrence. An ISR treated suboptimally is associated with recurrent event here by entering into vicious cycle in which patients might receive extra drug eluting stent, also called as sandwich strategies, which might contribute to several layers of stent in the vessels causing the onion skin phenomenon. Hence identifying the underlying pathophysiogical causes is imperative to avoid recurrent events and failure in ISR management.

DES

DESs are very desirable for the therapy of ISR since they are recognized for having potent antiproliferative properties.[27] Because they have lower rates of restenosis than BMSs, DESs have actually surpassed them for the treatment of *de novo* CAD. DES implantation has been identified as the most successful treatment for ISR by network meta-analyses. The advantage of DES implantation over a number of alternative treatment modalities for ISR, including as intravascular brachytherapy (IVBT) and paclitaxel DCBs, has also been shown in head-to-head trials. The additional layer of stent that is placed during DES implantation may be a disadvantage. In the event of an ISR recurrence, this may result in additional therapeutic difficulties. Therefore, before the implantation of a new DES for the treatment of ISR, care

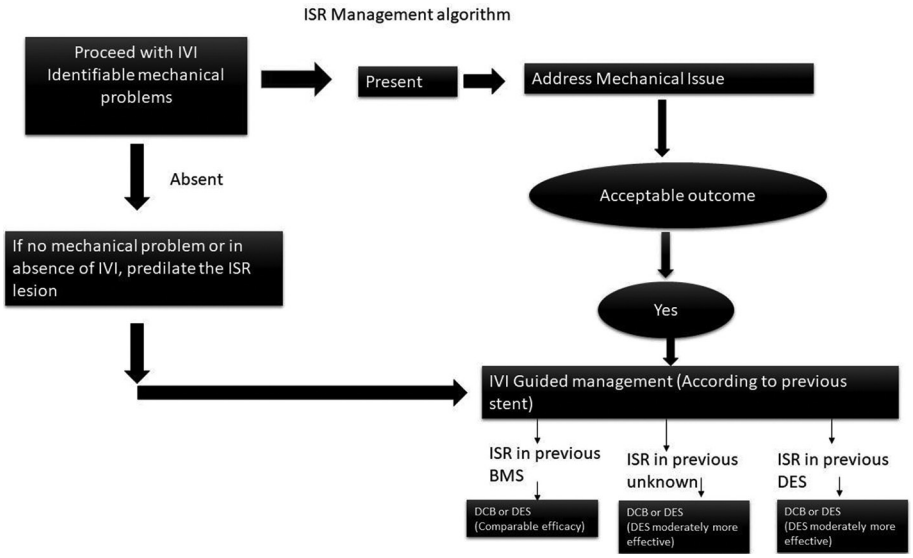

Figure 3: Algorithm for the management of in-stent restenosis.

must be made to ensure adequate lesion preparation has been performed, with special attention needed to address any under expansion of the original stent. In most situations, re-stenting will be necessary in the event of stent fracture.[28-41]

DES approach: Homo-DES versus hetero-DES

The selection of an anti-proliferative drug is one specific subtopic of interest with reference to DES treatment for DES-ISR. A DES combined with a different anti-proliferative agent (referred to as a "hetero-DES" method) has been proposed as a potential treatment for DESISR that may result in better results than a DES combined with the same anti-proliferative agent. Based on the idea that medication resistance might have contributed to the initial DESISR development is the theory. However, there is conflicting information in this area. The only randomized trial on this subject, ISAR DESIRE-2, failed to demonstrate a benefit for the treatment of sirolimus-eluting stent ISR[42] using the hetero-DES approach. In contrast, the RIBS-III trial had suggested that a hetero-DES method would offer better results, albeit this study was not randomized and the choice of the alternate treatment was left to the local investigators. A meta-analysis that suggested a hetero-DES method would be advantageous used data from a number of observational studies, which limited the validity of the conclusions. There are no longer any paclitaxel DESs available, and there have been no significant trials comparing the possible benefits of implanting a hetero-DES with an alternative -limus medication.

DCB

Standard angioplasty balloons are the main component of DCB catheters, and the surface of the balloons has a matrix coating.[43] The usual balloon coating consists of two components: A lipophilic active medication and a spacer or excipient that boosts the active drug's solubility and makes it easier for it to transfer from the balloon surface to the vessel wall.[43]

Anti-proliferative therapy is offered by DCBs without the need for an additional metallic scaffold. Given that it avoids using several stent layers; this method is logically appealing for the management of ISR. With several previous stent layers and the existence of a significant side branch, DCBs may be especially helpful in clinical settings when the insertion of another stent layer is undesired. They may also be well suited for settings where stent maldeployment is the cause of ISR. In addition, DCB-treated patients typically require a more condensed dual antiplatelet treatment (DAPT) regimen; therefore, this approach may be especially helpful in patients with a high risk of bleeding (Case 1) [Figures 4-6].

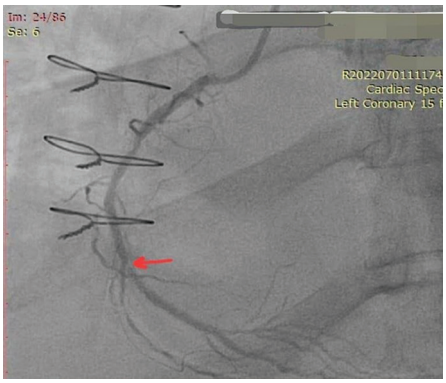

Figure 4: DES in-stent restenosis in post coronary artery bypass grafting patient, case of chronic kidney disease, for renal transplant with refractory angina (Arrow).

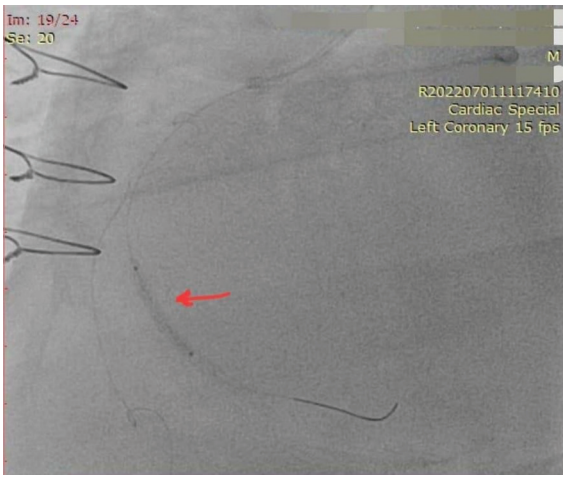

Figure 5: Sirolimus DCB balloon angioplasty done for DES in-stent restenosis, patient posted for renal transplant (lesser duration of dual antiplatelets) (Arrow).

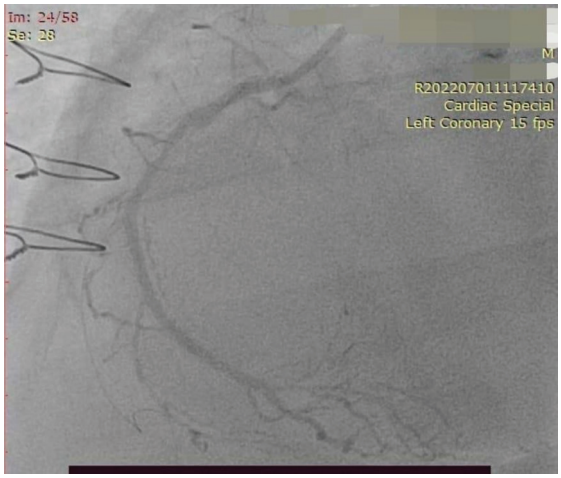

Figure 6: Post DCB treatment.

DCBs paclitaxel

The majority of clinical evidence relates to the use of paclitaxel-coated DCBs, particularly those based on iopromide. The first commercially available DCBs eluted paclitaxel. Due of its lipophilic characteristics, paclitaxel was chosen over other medications in DCBs. RCTs have shown that DCB therapy is superior than a number of different ISR treatment techniques, such as BA and BMS deployment. There is not much data comparing paclitaxel DCBs with various excipient coatings, however one small study revealed that iopromide and butyryl-tri-hexyl citrate-coated DCBs may produce similar results.[44-50]

It is important to note that higher mortality linked to paclitaxel-coated balloons and stents in femoropopliteal disease has drawn attention in a 2018 meta-analysis. These results in peripheral artery disease have been disputed by a number of subsequent researches however.

Importantly, the use of paclitaxel DCBs in the context of CAD has never been associated with safety concerns or excesses in mortality. A substantial meta-analysis that was recently published gave additional comforting data in this regard.

DCBs sirolimus

Sirolimus DCBs have also been created recently, and preliminary registry data show positive outcomes in both *de novo* CAD and ISR. Given that network meta-analysis suggests that paclitaxel-eluting DESs are linked with worse outcomes when compared to -limus-eluting DESs for the treatment of ISR, it is possible to speculate that similar benefits may exist when contrasting the two DCB technologies for the treatment of ISR. The technology to assure proper binding, persistence, and transfer of -limus-based medicines from DCBs to the artery wall was nonexistent until very recently. However, recent technological developments have made it possible to create -limus DCBs. Despite the potential appeal of -limus DCBs for the treatment of ISR, there is still a paucity of data on their safety and efficacy in this situation. According to a short RCT comparing a novel sirolimus DCB balloon to a paclitaxel DCB, the two groups' clinical results at 6 and 12 months were comparable. The fact that there are no published randomized data contrasting sirolimus DCBs and DESs for the treatment of ISR is noteworthy. Larger trials will be helpful in the future to assess the relative effectiveness of sirolimus DCBs to paclitaxel DCBs and DESs. Recognizing that more study would be helpful in this area given the lack of data that currently exists to back up the idea of a "class effect" for both limus- and paclitaxel-eluting DCBs.[51,52]

DCB: Lesion preparation is crucial

Regardless of the ultimate recommended treatment strategy, adequate lesion preparation is crucial when treating ISR. The quick initial drug transfer of the anti-proliferative medication and subsequent tissue retention in the restenotic area is essential for a DCB's effectiveness [Figure 7].

Therefore, impacting the ISR obstructive tissue with cutting or scoring balloons before DCB therapy may aid to increase the delivery of the anti-proliferative drug. The ISAR-DESIRE 4 experiment showed that DCB therapy's anti-restenotic effectiveness was enhanced by neointimal modification with a scoring balloon.[53] Interestingly, a scoring balloon with a medication coating has been created that combines both therapy modalities into a single instrument. When compared to an uncoated scoring balloon alone, this has shown good results in preliminary experiments, although it should be acknowledged that using the devices in sequence may be the most effective strategy.

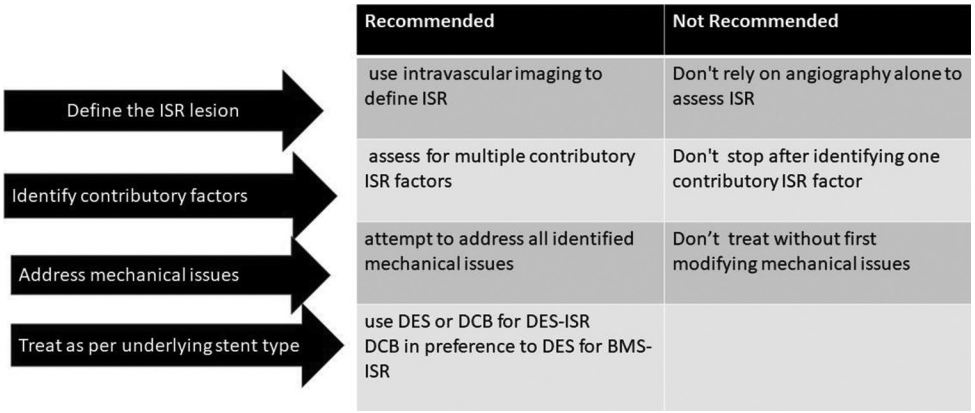

Figure 7: Recommendation of in-stent restenosis-percutaneous coronary intervention.

Direct evidence comparing DES and DCB for the treatment of ISR

For ISR, several studies have compared DESs to paclitaxel DCBs. A meta-analysis of randomized controlled data comparing DES with paclitaxel-DCB angioplasty has shown that repeat DES implantation for ISR is marginally more efficient in lowering the rate of TLR at 3 years, despite the putative advantages of DCBs in the management of ISR. Repeat DES implantation in this situation leads to better acute angiographic outcomes than DCB therapy, including increases in MLD and decreases in residual % DS. These superior acute angiographic findings with DES as opposed to DCB treatments are sustained at longer-term follow-up in the majority of head-to-head RCTs. In comparison to paclitaxel DCBs after 3 years, DESs reduced the need for future TLR, according to the DAEDALUS research, meta-analysis (n = 1976, 10 RCTs).

It is interesting to note that the underlying stent type may have an impact on the relative effectiveness of these two therapies for ISR. Clinical effectiveness and safety effects with DESs and DCBs seem to be equivalent in patients with BMS-ISR. This approach might be preferred in this situation since a DCB offers equivalent efficacy without requiring an additional stent layer. Contrarily, repeat stenting with a DES is marginally more effective than therapy with a DCB addressing the requirement for TLR[54] in the more difficult scenario of DES-ISR. This improved effectiveness must be evaluated against the need for an extra stent layer, though. Importantly, therapy of BMS-ISR is linked to better late angiographic and clinical results than treatment of DES-ISR, regardless of the chosen treatment technique.

Additional treatment approaches for ISR

While the majority of the time, the data currently available supports DCBs and DESs as the best first therapy modalities for ISR, other treatment modalities may still play a supplementary or adjunctive role. This might be especially true for ISR that occurs repeatedly. The data supporting these supplementary ISR treatments will be covered in this section, along with any potential specialized applications. Given the complicated and variable nature of ISR disease, having a variety of supplementary treatment choices in their toolbox may be advantageous for specialized centers doing complex ISR procedures.

The original treatment for ISR was balloon angioplasty BA; however, it was later determined to be subpar to a number of more recent alternative therapeutic modalities.[42-44] In addition to stent expansion, BA causes some acute gain as a result of tissue extrusion (both longitudinal and axial). The tissue re-intrusion that takes place soon after the final balloon inflation; however, indicates that this acute advantage is frequently fleeting. This method has also been largely abandoned in Europe as a curative therapy due to repeated significant tissue proliferation. Isolated conventional BA is still utilized in the US, where DCBs have not yet received approval, in cases of focal ISR when the risk of recurrence is thought to be minimal. Non-compliant or ultra-high-pressure non-compliant balloons (UHPNCBs) at high pressures should be employed in the case of a poorly deployed stent to enhance stent expansion. Isolated BA is not typically advised for the treatment of ISR, however, and this approach is best viewed as a tool for lesion preparation before the use of other therapies or for the final optimization of DES implantation, according to current research.

Scoring or cutting balloons

Cutting balloons are made up of regular balloon catheters fitted with lateral metallic blades that incise into the treated stenotic plaque on balloon inflation. Scoring balloons have a roughly identical mechanical foundation, but they use low-profile nitinol wires (on the order of 125 μm) arranged in a spiral pattern on the surface of the balloon catheter.

Their use has two main benefits: The blades' incision into the stenotic plaque may encourage future tissue extrusion, and their interaction with the plaque anchors the balloon in the plaque.

When treating ISR, cutting and scoring balloons may both be useful in lesion preparation before DESs or DCBs. Both approaches, however, share BA8889's shortcomings and are restricted by their inability to stop neointimal development when used alone. The use of a scoring balloon before a DCB has been demonstrated in the ISAR-DESIRE 4 to increase the anti-restenotic efficacy of the DCB. In the presence of severe or diffuse patterns of ISR, cutting or scoring balloons may also be helpful to prevent the "watermelon seeding" phenomena that can happen while dilating ISR lesions. Longer procedure times, poorer acute angiographic results, and worse long-term outcomes are all related to "watermelon seeding." It might cause a "geographic miss," which might then cause recurring edge-ISR. In lesion preparation prior to DCB treatment for ISR, a non-slip element balloon has also demonstrated similar efficacy to high-pressure non-compliant balloons.[55,56]

BRACHYTHERAPY

The delivery of targeted radiation inside the stent is referred to as IVBT. This therapy's goal is to stop neointimal cell proliferation in the targeted area without causing harm to the tissue around it. The radiation has this effect primarily through two mechanisms: direct injury caused by ionizing emissions and injury caused by the production of free radicals. IVBT was shown to be superior to the mechanical substitutes at the time in a number of randomized clinical trials.[57-59] Due to their increased simplicity and higher outcomes in the context of BMS-ISR, DESs quickly replaced IVBT once they were made available. On the utilization of IVBT in the DES-ISR environment, there are not any randomized statistics, though. According to observational data, IVBT might be involved in the recurrence of ISR. Since IVBT has been discontinued in the majority of centers, there is not enough data to support its widespread usage in the modern era.

ALTERNATIVE METHODS

Rotational atherectomy (RA) and excimer laser coronary angioplasty (ELCA) are examples of commercially accessible ablative therapies for the treatment of ISR. In the past, these methods were appealing for the treatment of ISR because they could remove the restenotic tissue that blocked the stent. When ablative techniques were compared to alternative therapy modalities, some of the early results in this regard were encouraging, but the results at late follow-up did not reveal any meaningful benefit compared to the control. As a result, their regular and organized use for ISR management was discontinued. When various traditional approaches have failed to treat undilatable ISR lesions, they may still have a place in the management of these conditions, particularly in the case of calcified neoatherosclerotic ISR.

ALTERNATIVE STRATEGIES: CORONARY ATHERECTOMY USING AN EXCIMER LASER

The debulking method known as ELCA ablates tissue using UV spectrum wavelengths. By producing heat and shockwaves, it achieves this. Despite several early historical studies showing the viability and safety of this technique, there are few current data to support the systematic use of ELCA as the primary treatment for ISR, and there are no randomized data on the use of ELCA for DES-ISR. But in other circumstances, it might serve as an addition to lesion preparation, especially for recurrent ISR in the presence of significant calcification. This approach may help with stent expansion for individuals with nondilatable ISR caused by substantially underexpanded stents because of a strongly calcified artery wall, especially if contrast is injected to cause additional barotrauma and microcavitation. Only short observational series may be used to support this claim, but it nonetheless offers a viable fallback alternative when other therapeutic approaches have failed.[60-62]

A further ablative approach that can be utilized to debulk ISR lesions and make it easier to apply future therapies is RA (as part of a combined strategy). Historical RCTs contrasting RA and BA can be found in BMS-ISR. The much larger ARTIST trial indicated poorer results with RA and a higher number of procedural-related complications,[63,64] but the ROSTER trial (which required the administration of IVUS throughout the intervention) suggested superior results with RA compared to BA. The trial methodology, which required lower balloon inflated pressures in the RA arm of this study, and the absence of systematic IVUS use to rule out severe under expansion may have contributed to this, should be highlighted. For the use of RA in the treatment of DES-ISR, there are no randomized data available. To prepare a lesion for DCB application or recurrent DES implantation, it may still be useful as an adjuvant technique. It should be regarded as a high risk technique, and burr entrapment within the ISR lesion[65,66] must be avoided with special care. Additionally, in the extremely rare instances of significantly underexpanded and nondilatable stents, the successful use of RA to ablate metal (also known as "stentablation" or "rotastenting") has been documented. However, considering that more appealing and safer approaches that are now available to address this particular problem, the indications for this procedure's use are likely to be quite limited (burr entrapment and vessel perforation).

INTRAVASCULAR LITHOTRIPSY

Intravascular lithotripsy (IVL) is a recently developed technique that circumferentially alters vascular calcium using localized pulsatile sound waves.[67] In *de novo* CAD,[68] IVL has proven to be secure and efficient. It has been described

to employ IVL to assist stent expansion in ISR, although there are few data on this technique, and it is thought to be off-label. However, numerous observational studies have shown that IVL can be utilized successfully in individuals with non-dilatable ISR who are resistant to traditional treatments, particularly when the stent is under expanded because of circumferential coronary artery calcification. Similar to ELCA, the energy generated alters the calcified plaque's compliance, leading to fractures outside or inside the stent. The use of IVL in patients with ISR is significantly more user-friendly and less reliant on operator experience than ELCA and RA.

SIMPLE METAL STENTS

In comparison to BA, BMS implantation showed some promise in terms of acute luminal gain. BMS implantation was utilized after BA for the treatment of BMS-ISR. However, at the 6month follow-up in the RIBS-I trial, BMS implantation did not outperform BA for the treatment of BMS-ISR. In that trial, only the selected subset of patients with large (>3 mm) arteries showed that BMSs were superior to traditional BA. In addition, BMSs showed superiority than BA in patients who had edge-ISR. Since there are no studies evaluating the effectiveness of BMSs in the management of DES-ISR, the majority of their contribution to ISR management is historical.[69,70]

BIORESORBABLE VASCULAR SCAFFOLDS(BVS)

For the treatment of ISR, BVS were thought to hold some promise. However, compared to the outcomes seen with DESs in earlier studies, the use of BVS for patients with ISR was linked to a greater TLR rate. Polymeric BVS are no longer offered for sale commercially.[70] Some early preliminary studies[71,72] looked into the possible benefits of magnesium-based BVS, but more analysis is needed to establish whether they will eventually be used to treat individuals with ISR.

Treatment of BVS-ISR patients

The treatment of patients with BVS-ISR was prospectively registered in the RIBS VII study. Patients with BVS-ISR and patients with restenosis of metallic stents experienced clinical outcomes that were comparable overall and after controlling for potential variables.

Coronary artery bypass grafting (CABG)

In some patients, CABG may be a viable therapy option, but there are no RCTs contrasting CABG with other ISR treatment techniques. But according to certain observational assessments, individuals who underwent CABG for ISR (85% of whom had multivessel disease) had better results than those who underwent percutaneous therapies. Patients with ISR of the left main stem (LMS), intractable ISR in a major artery, concomitant multivessel illness, or ISR in the ostial LAD may also be candidates for CABG.[73,74]

Patients with ISR, especially those who come with recurrent ISR, have been advised to use a number of supplementary anti-inflammatory or anti-proliferative drugs. It was believed that using supplemental medicinal treatments might lower the likelihood of ISR recurrence. Oral sirolimus significantly improved 6-month angiographic parameters in the OSIRIS research. However, after longer follow-ups, this initial advantage was diminished, and interest in this therapy decreased due to worries about potential side effects. There is currently no conclusive evidence in favor of treating these patients with additional systemic anti-proliferative medications.

CLINICAL SITUATIONS THAT POSE CHALLENGES

Recurrent ISR, ISR in the presence of significant calcification, LMS ISR, ISR chronic complete occlusion (CTO), and stent fracture are few particular clinical circumstances with relevance for ISR.

RECURRENT ISR

ISR that has recurs following the initial course of treatment is referred to as recurrent ISR. The recurrent ISR lesion will have two stent layers if the ISR was initially treated by repeat stent insertion. More than two stent layers may be present in some ISR lesions. Under expansion of the first stent appears to be regularly linked to these occurrences. Those with three layers of stents have been shown to have worse outcomes from ISR-PCI than with DCB patients with one or two layers of stents. Although DES implantation has been found to be safe and effective in recurrent ISR with two stent layers, it may be prudent to avoid a third layer of stent when treating ISR. According to a different study, DES implantation was superior than BA in patients with recurrent ISR who had previously received DES treatment. To help with therapy choices in this difficult lesion subset, there aren't much dedicated randomized data available. A meta-analysis reveals that TVR still happens in roughly 1 in 4 patients at 2 years in this context, despite the fact that IVBT has been reported to be an effective treatment for recurrent ISR with multiple stent layers.[75-77] Although the 1-year TLR incidence was reported as 14.5% in the 1-stent layer group, 14.9% in the 2-stent layer group, and 41.2% in the 3-stent layer group in a study by Yabushita *et al*.,[75] DCBs may also be helpful in this difficult situation.

It is crucial to identify any residual mechanical problems that were not sufficiently addressed during the initial ISR treatment procedure and may have led to the ISR recurrence when handling recurrent ISR. Future TLR will probably be more likely if these recurring mechanical problems are not fixed.

Underexpanded stents appear to be the cause of recurrence in the majority of instances, but localized stent fractures (such as those at hinge sites) may also play a role in some situations. In this case, it is crucial to ensure optimal final stent expansion. It is unknown whether the routine use of IVL in these patients will enhance clinical outcomes in patients with recurrent ISR. Finally, as was already mentioned, individuals with multivessel disease and recurrent ISR affecting the LMS or ostial LAD should be evaluated for CABG.

SEVERE UNDER-EXPANSION AND SEVERE CALCIFICATION IN THE CONTEXT OF ISR

One well-known significant risk factor for ISR is coronary artery calcification. Calcium modification may be needed for ISR when there is calcification and stent under expansion. In this situation, calcium can be modified by RA, ELCA, and IVL. It may be helpful to perform intra vascular imaging again after calcium modification to make sure it was successful, especially if DES implantation is intended as a final form of therapy. There are few data comparing the different calcium modification procedures, thus the choice will probably be based on availability and expertise. Referral to an expert facility may be required if this cannot be done locally. To guarantee that a wide range of ISR lesions may be treated, specialized ISR tertiary referral centers should ideally have numerous calcium modification techniques available.

ISR OF LMS

Data on the management of LMS ISR are scarce. According to the FAILS trial, LMS ISR could typically be treated percutaneously. According to a retrospective investigation, DES and DCB treatments can produce comparable results in this situation. However, given the substantial mortality following TLR for LMS stent failure that has been documented, CABG should be taken into consideration in the right individuals.

ISR-CTO

According to the Mehran classification, ISR-CTO was proposed to stand for its own unique class of ISR13. According to certain reports 1, ISR-CTO PCI has a higher risk of complications and unfavorable events during follow-up than CTO-PCI. However, compared to *de novo* CTO-PCI, additional studies have found similar outcomes.

A road map that may make it easier for the progression of specialized wires within the actual lumen is provided by the visualization of the stent in various projections during the ISR-CTO PCI procedure. Operator experience may have an impact on operation outcomes, and ISR-CTO PCI should be viewed as a highly specialized, high-risk technique.[78-81]

STENT FRACTURE

The general definition of stent fracture, which may be detected in conjunction with ISR, is the full or incomplete separation of the stent strut on an angiography and/or the lack of a stent strut on at least one slice of IVUS. Repeat stenting will typically be necessary for ISR lesions brought on by stent fracture, albeit it must be remembered that there are not any high-quality, randomized data to back up this recommendation.[82-84]

TREATMENT STRATEGY FOR ISR

We give a suggested ISR treatment algorithm based on the data covered in this review. In contrast to edge-restenosis, which typically necessitates repeat stenting, it should be highlighted that this method is designed to manage restenosis within the stent.

According to the scientific data compiled in this review, the type of stent implanted during the index procedure (BMS or DES) and the existence or absence of mechanical problems that would prevent adequate stent expansion are two of the most crucial factors to take into account when determining how to treat ISR. This is because failure to appropriately address mechanical difficulties appears to increase the chance of future ISR recurrence, and the ideal therapy for ISR (DES or DCB) appears to be influenced by the underlying stent type.

We would advise the use of IVI for all ISR cases because it is the most effective tool for identifying mechanical faults and is in line with current recommendations 3940144. To detect mechanical problems like stent fracture and stent under expansion, improved fluoroscopic imaging approaches, such as StentBoost, may also be helpful.

The operator can then choose the optimum way to handle mechanical concerns (if any) and set up the ISR lesion based on the results of the IVI. The anticipated underlying disease and the available local skill expertise should both be taken into account when determining the appropriate lesion preparation, which is a significant factor in procedural success. IVI can be performed again after lesion preparation to confirm that mechanical problems have been resolved before more aggressive therapy. Operators should concentrate on predilating the ISR lesion enough and maximizing stent expansion if IVI is not accessible. UHPNCBs and noncompliant balloons may be used in this. Cutting or scoring balloons can also be helpful and, whenever possible, should be done before DCB therapy to maximize DCB efficacy.

After that, the operator can choose how to handle the lesion. The majority of the time, DCBs or DESs should be utilized to treat ISR based on the available scientific evidence. In some instances, despite repeated attempts at predilatation, poor outcomes (i.e., large dissections or chronic residual stenosis

>40%) are seen. DCBs should be utilized with caution because they may produce outcomes comparable to those of the original balloon predilatation in these circumstances. Repeat DES implantation may be preferred as a therapy option in this situation since it is marginally more successful than DCBs for DES-ISR. In addition, given that DESs have been demonstrated to be generally moderately more effective than DCB treatment for the management of ISR, operators should choose them if the type of underlying stent is unknown. Operators must, however, weigh the risk benefit ratio advantage against the placement of an additional stent layer. Therefore, in some circumstances, such as when there are already two layers of stent present, initial treatment with DCBs may be preferred. Given that the results of DCB and DES implantation in BMS-ISR are equivalent, DCB might be preferred initially. In this case, other factors may also have an impact on clinical decision-making (i.e., presence of a significant side branch). The use of DCBs may also enable a DAPT to last for a shorter period of time in individuals with a high bleeding risk.

A second round of IVI post-treatment should typically be carried out to check whether an acceptable procedural outcome has been obtained. If not, additional steps may be necessary to improve the outcome, and this procedure can be repeated until a suitable outcome is obtained.

In some patients, CABG may be a viable therapy option, but there are no RCTs contrasting CABG with other ISR treatment techniques. But according to certain observational assessments, individuals who underwent CABG for ISR (85% of whom had multivessel disease) had better results than those who underwent percutaneous therapies. Patients with ISR of the LMS, intractable ISR in a major artery, concomitant multivessel disease, or ISR in the ostial LAD may also be candidates for CABG.

SUPPLEMENTAL MEDICAL CARE

Patients with ISR, especially those who come with recurrent ISR, have been advised to use a number of supplementary anti-inflammatory or anti-proliferative drugs. It was believed that using supplemental medicinal treatments might lower the likelihood of ISR recurrence. Oral sirolimus significantly improved 6-month angiographic parameters in the OSIRIS research. However, after longer follow-ups, this initial advantage was diminished, and interest in this therapy decreased due to worries about potential side effects. There is currently no conclusive evidence in favor of treating these patients with additional systemic anti-proliferative medications.[85,86]

CONCLUSION

Despite recent improvements in PCI, ISR — which accounts for 5–10% of all PCI procedures in contemporary clinical practice remains a substantial problem and the most frequent reason for stent failure. While the absolute number of ISR-PCI operations performed in contemporary practice has increased as a result of rising procedural volume and complexity, the relative rate of ISR has decreased with newer-generation DESs in comparison to the BMS period. According to recent research, DCBs or DESs are the most effective therapy options for the majority of ISR cases. Future ISR interventional paradigms may be influenced by IVI ISR tissue patterns. IVI can provide useful information to guide treatment options in ISR-PCI.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

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