Coronary In-Stent Restenosis: An Algorithmic Approach to Diagnosis and Treatment

Forward

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Even in the contemporary era of percutaneous coronary intervention using drug-eluting stents, in-stent restenosis (ISR) remains a common problem, occurring in 5% to 20% of cases, depending on several patient and lesion characteristics. Recurrent ISR can be a common problem in these subjects and adding layer upon layer of stent struts in the restenotic lesion may not be the optimal treatment option. Therefore, identification of the mechanism causing restenosis using intracoronary imaging, and optimization of the treatment of the restenotic lesion, are of paramount importance. This series provides our treatment algorithm, which was developed to systematically classify the pattern and underlying mechanism of ISR followed by suggestions for optimal treatment.

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In-Stent Restenosis: The Clinical Challenge

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In stent restenosis is the re-narrowing of a stented artery segment and is defined based on angiographic and/or clinical criteria (Table 1).[1] Mehran's classification system describes the morphologic classifications of ISR—focal, diffuse, proliferative, or occlusive—and has prognostic value in predicting the rate of revascularization.[2]

In-Stent Restenosis Incidence and Outcomes

Drug-eluting stents (DES) have revolutionized treatment of obstructive coronary artery disease improving the durability of percutaneous coronary artery interventions (PCI) by decreasing target lesion revascularization compared to bare metal stents (BMS). The safety and durability of DES is so favorable that BMS use has declined nationally, and contemporary discussions have centered around what role, if any, bare metal stents should have in CAD treatment.[3-6] Despite the advantages of DES over BMS in preventing in-stent restenosis (ISR) and target lesion failure, DES failure continues to be a clinical problem. Second-generation DES have failure rates at 1 year that average 5.7% and 8.7% in non-diabetic and diabetic patients, respectively.[7] Worse yet, DES TLF rates do not plateau at 1 year, and all modern DES trials show a gradual increase in major adverse clinical events (MACE) over time, such that 5-year TLF rates are in the 9% to 12% range in generally noncomplex lesions (Figure 1). In real world use, modern DES fare even less well with 5-year TLF rates that exceed 15% (Figure 1).[8] The cumulative rates of DES failure have created a major clinical problem so that > 10% of all PCIs done in the United States (US) are to treat ISR, and the number of ISR interventions appears to be increasing year over year (Figure 2).[9,10] The burden of ISR nationally generates significant cost to the US health care system, and it is increasingly recognized that PCI patients treated for ISR have an increased risk of death compared to non-ISR PCI patients. This elevated risk of death is present even in elective settings not complicated by acute coronary syndrome presentation (Figure 3).[11]

ISR patients suffer worse outcomes to some extent because treatments for ISR are not as effective as treatments for denovo coronary artery disease.[12-17] In the US, the contemporary treatment of initial ISR is to implant a second DES because DES therapy has superior efficacy over balloon angioplasty alone.[12,14,15] The failure rates for second layer DES are however quite high with clinical TLR rates of 12% to 16% at 12 months and 33% at 3 to 5 years.[12-18] There currently is an unmet clinical need for more effective treatments for ISR, especially in patients with multilayer stent failure.

Table 1. Definition and classification of in-stent restenosis.
Angiographic Restenosis and Classification
Diameter stenosis 50%
Type I focal: 10 mm in length
IA articulation or gap
IB margin
IC focal body
ID multifocal
Type 2 diffuse: 10 mm intrastent
Type 3 proliferative: 10 mm extending beyond the stent margins
Type 4 total occlusion: restenotic lesions with TIMI flow grade of 0
Clinical Restenosis: Assessed Objectively as Requirement for Ischemia-Driven Repeat Revascularization
Diameter stenosis 50% and one of the following:
Positive history of recurrent angina pectoris, presumably related to target vessel
Objective signs of ischemia at rest (ECG changes) or during exercise test (or equivalent), presumably related to target vessel
Abnormal results of any invasive functional diagnostic test (eg, coronary flow velocity reserve, FFR 0.80); IVUS minimum cross-sectional area 4 mm² (and 6.0 mm² for left main stem) has been found to correlate with abnormal FFR and need for subsequent TLR
TLR with diameter stenosis 70% even in absence of the above ischemic signs or symptoms
ECG = electrocardiography; FFR = fractional flow reserve; IVUS = intravascular ultrasound; MI = myocardial infarction; TIMI = Thrombolysis In Myocardial Infarction; TLR = target lesion revascularization. Adapted from Dangas GD, Claessen BE, Caixeta A, et al. In-stent restenosis in the drug-eluting stent era. *J Am Coll Cardiol*. 2010;56:1897-1907.

In-Stent Restenosis Causes and Implications for Treatment

The patient and procedural factors that are associated with increased risk of ISR are well characterized and have been reviewed in detail.[1,19,20] Patient characteristics that increase ISR risk include diabetes, chronic kidney disease, multivessel coronary artery disease, age, and female gender.[21] Lesion characteristics associated with ISR include complex lesions (B2/C, calcified stenoses, chronic total occlusion), longer lesion length, smaller artery diameter, bypass grafts, left anterior descending coronary artery location, and ostial stenoses.[22-24]

The biological factors that contribute to ISR are related to variable sensitivity to DES drugs[25] and/or potential
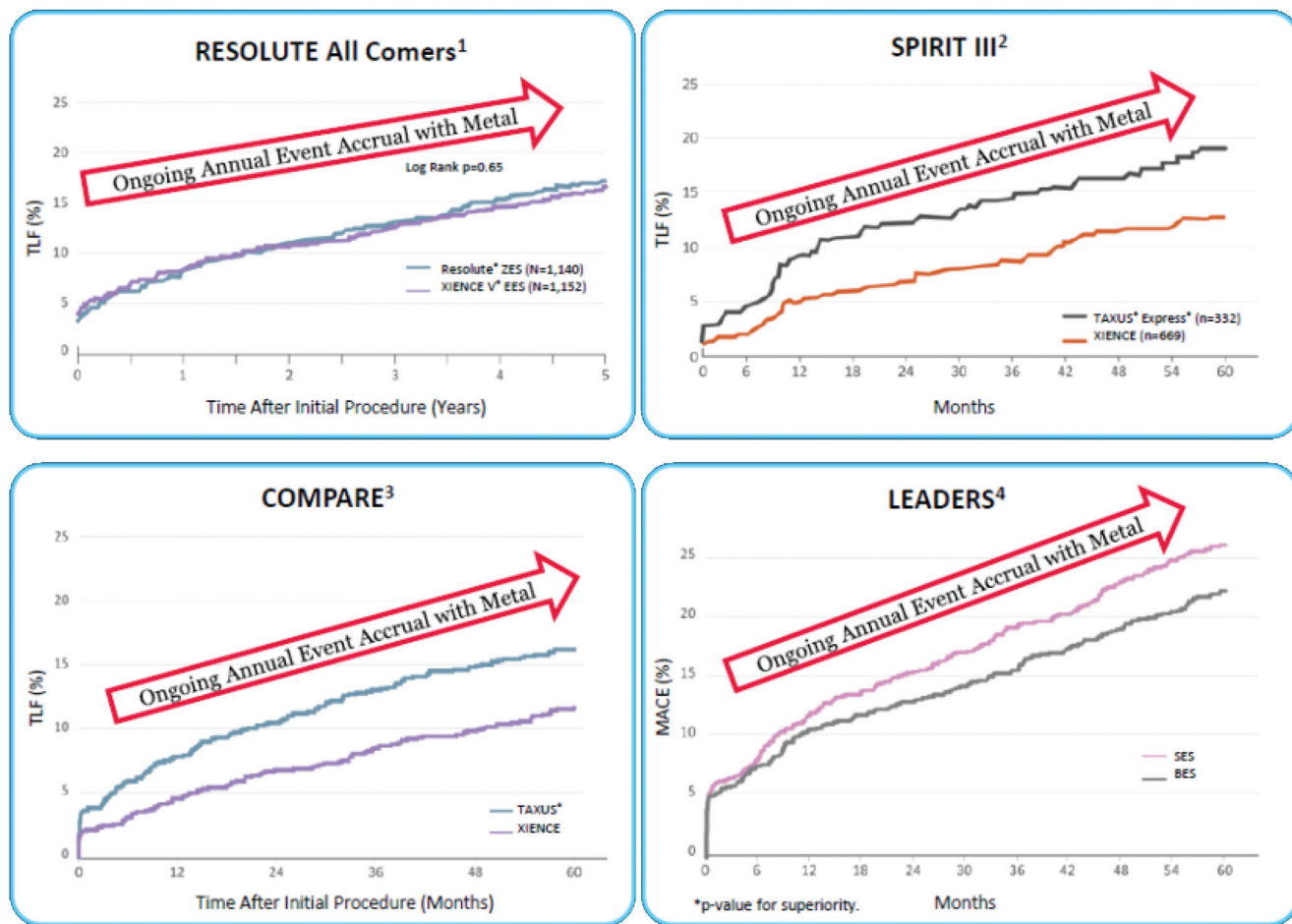
FIGURE 1. Five-year target lesion revascularization for second generation DES. *Windecker S. RESOLUTE all Comers 5 –year EuroPCR 2014; Gada H, et al SPIRIT III 5 year. JACC Cardiovasc Interv. 2013;1263-1266; Smits P. COMPARE 5-year TCT 2013; Serruys PW. LEADERS 5-year. TCT 2012; von Birgelen C, et al. TCT-572 Final 5-year Outcome After Implantation of Zotarolimus-Eluting RESOLUTE, J Am Coll Card. 2015;66[15_S]*

hypersensitivity to the stent, polymer, or drug component of the DES.[26] With newer biocompatible DES polymers and biodegradable polymers, the potential for hypersensitivity may be diminished compared to initial DES platforms. The technical and mechanical factors that contribute to DES failure include geographic miss, under-expansion, and stent fracture (Figures 4, 5C and D). Geographic miss occurs when the stent does not fully cover the injured or diseased segment. Under-expansion occurs more frequently in calcified stenoses and is seen more frequently with early DES failure within 1 year from implantation.[27] ISR in the BMS era was classically considered to occur from neointimal hyperplasia consisting of smooth muscle cells and extracellular matrix and compared to DES, BMS ISR tends to be more diffuse. More recently, it has become well established that in-stent neoatherosclerois is an important mechanism of stent failure that may occur more often with DES compared to BMS.[28] Neoatherosclerosis in-stent resembles classic atheroma with lipid deposition, foam cell macrophage infiltration, and in later stages marked calcification (Figures 5A and B).[28]

In-stent neoatherosclerotic thin cap fibroatheroma (TCFA) has been described, and rupture of in-stent TCFA are a potential source of very late stent thrombosis. Calcific neoatherosclerosis is particularly problematic for treatment because the calcific tissue is constrained by the stent, which makes it challenging to achieve expansion when treating the ISR segment. In some cases, calcific neoatherosclerosis requires debulking with atherectomy to enable maximal expansion during PCI of ISR lesions.[29]

Diagnosis of In-Stent Restenosis: Obligate Intravascular Imaging

In treating patients with ISR, diagnosing the cause of stent failure is critical to determining the most appropriate treatment. It is essential to understand the mechanism of stent failure because the mechanism of failure will directly impact the therapeutic decisions and devices needed to manage the ISR segment (Table 2). Angiography inadequately assesses ISR because of limited resolution and inherent deficiency in quantifying vessel size, stent size, stent expansion,
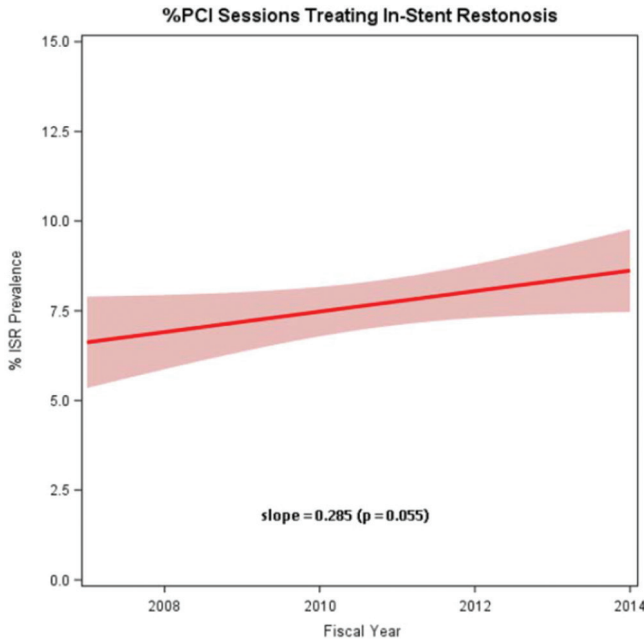
%PCI Sessions Treating In-Stent Restenosis

slope = 0.285 (p = 0.055)

FIGURE 2. Incidence of coronary in-stent restenosis: Insights from the National VA CART Program.[10]

Mortality Following Nonemergent, Uncomplicated Target Lesion Revascularization After Percutaneous Coronary Intervention

TLR versus no TVR: HR=1.40, 95% CI 1.16–1.69; p=0.0005
Non-TLR TVR versus no TVR: HR=1.48, 95% CI 1.08–2.04; p=0.02
TLR versus non TLR TVR: HR=0.93, 95% CI 0.65–1.32; p=0.67

— No TVR — TLR — Non-TLR TVR

12.2%
11.7%
8.9%

Risk Episodes						
No TVR	32524	27149	21641	17648	11543	4948
TLR	2330	1686	1324	987	768	1
Non-TLR TVR	810	600	426	260	157	0

Patients with nonemergent, uncomplicated target lesion revascularization (TLR) and non-TLR TVR had significantly higher rates of mortality compared with patients with no target vessel revascularization (TVR). The number at risk reported for each group identifies risk episodes. CI = confidence interval; HR = hazard ratio.

FIGURE 3. Technical and biological mechanisms of ISR.

Technical & Biological Mechanisms of ISR

FIGURE 4. Mortality following nonemergent, uncomplicated target lesion revascularization after percutaneous coronary intervention.[11]

number of stent layers, in-stent calcific neoatheroslcerosis, and extra-stent calcific disease. In contrast to angiography, intravascular ultrasound (IVUS) and optical coherence tomography (OCT) provide detailed assessment of the native artery and stented segment and readily identify the precise mechanism(s) of stent failure (Table 2). We firmly believe that all stent failures should be evaluated by intravascular imaging to diagnose the cause of in-stent restenosis, to inform therapeutic strategy, and to confirm effective treatment post PCI. The US and European PCI guidelines both support the use of intravascular imaging in the diagnosis and treatment of stent failure (Class IIa recommendation, level of evidence C).[30,31] Importantly, randomized studies clearly show that when treating denovo non-ISR stenoses, intravascular imaging reduces target lesion failure and ISR by 50%,[32,33] and over time we anticipate that increased adoption of IVUS and OCT during initial PCI will help to prevent the steady increase in ISR that is occurring in the US. This is especially important in light of recent intravascular imaging studies that demonstrate that (1) suboptimal stent deployment is common—occurring in 31% to 58% of patients[33-35] and (2) that suboptimal stent deployment confers an increased risk of adverse events.[35] Emerging data from several registry studies has recently demonstrated that use of intravascular imaging during PCI not only reduces stent failure and TLF, but is also associated with a reduction in cardiovascular mortality.[36,37]

In utilizing intravascular imaging to diagnose and treat ISR, the goal is to determine the reference segment size, lesion length, site of ISR (in-stent vs edge), nature of ISR (diffuse vs. focal), predominance of neotinima vs. neoatherosclerosis,
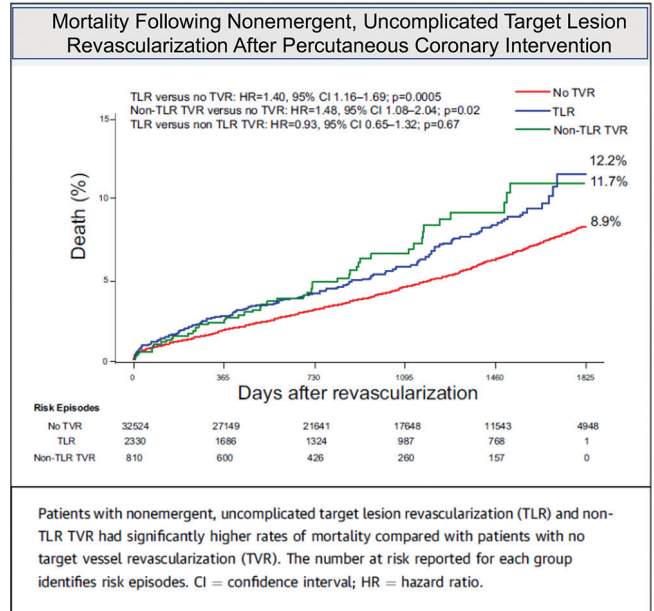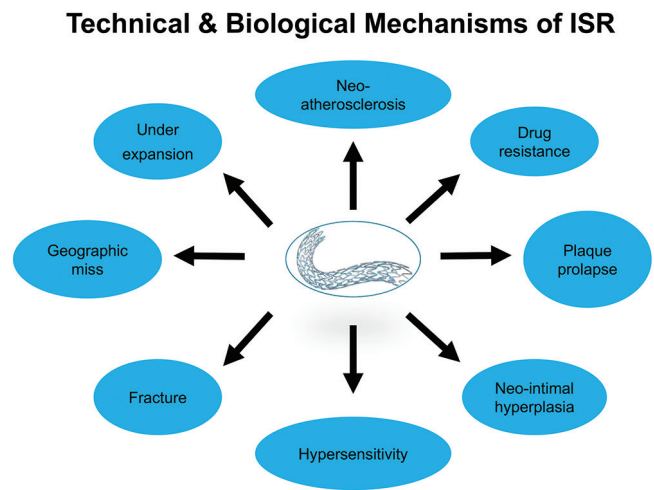
number of stent layers, prior stent expansion and apposition, presence/absence of stent fracture, and presence/absence of intra- and/or extra stent calcium. As outlined above, ISR treatments have much higher TLF rates compared to PCI of denovo stenoses, and we thus focus on utilizing an intravascular imaging–based strategy to maximize the likelihood that the ISR PCI will be durable. The strongest modifiable predictors of non-ISR stent failure are (1) under-expansion, (2) severe inflow and outflow disease proximal to or distal to the stent, and (3) presence of major dissection (> 3 mm or involving the media).[33,35] After identifying the causal mechanism of ISR,

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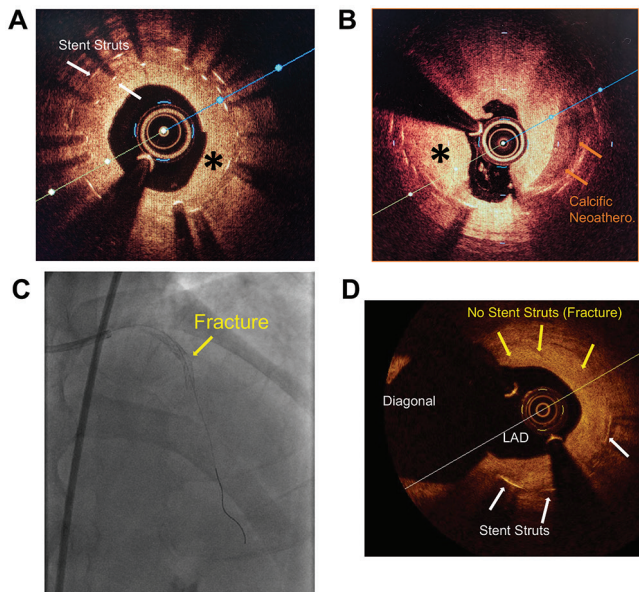**FIGURE 5.** Intravascular imaging of ISR tissue and stent fracture. [A] OCT image of multilayer ISR with neoinitima tissue and onion skin layer of neointimal between two stent layers (white arrows denote stent struts, * denotes neontima tissue) [B] OCT image of calcific neoatherosclerosis (in-stent) admixed with neoinitimal tissue (red arrows denote calcific neoatherosclerosis, * denotes neontima tissue). Angiogram (C) and OCT image (D) of stent fracture at the flexion point of an LAD and diagonal bifurcation with severe ISR (white arrows denote stent struts, yellow arrows denote region with no stent where stent has fractured at the bifurcation).

Table 2. Intravascular imaging is critical to guiding ISR intervention.

ISR Mechanism	Potential Treatments
Unstented/gap segment	BA, DES
Severe neointimal hyperplasia	BA, laser, DES
Stent fracture	BA, DES, brachytherapy
Undersized	BA high pressure, scoring balloon, larger DES
Underexpansion	BA high pressure inflation, scoring balloon, laser, atherectomy, DES
> 2 layers of stent	Laser, brachytherapy, outside US - DCB

*BA = balloon angioplasty; DES = drug-eluting stent; DCB = drug-coated balloon

Table 3. Image-guided ISR treatment optimization.

1. Final stent expansion/lumen area > 90% of the proximal and distal reference segment (demonstrated by IVUS or OCT)

2. No inflow or outflow obstructions within 5mm of the proximal or distal stent edge (defined MLA <5.0mm^2 by IVUS or MLA <4.5mm^2 by OCT)

3. No major edge dissections

(defined as >60 degree, >3mm in length, or penetrating the media)

we strongly advocate for an algorithmic approach to vessel preparation and treatment that is focused on (1) debulking the ISR tissue to facilitate expansion and maximize final stent area, (2) aggressively treating stent under-expansion if present, and (3) treating severe inflow and outflow disease (see ISR treatment algorithm, article two in this series by Dr. George Dangas). Multiple studies demonstrate that suboptimal minimal stent area (MSA) is the major predictor of stent failure, and an IVUS optimized MSA of > 5.0 mm^2 [33] or OCT optimized MSA of > 4.5 mm^2 [35] is often defined as the minimum goal for image optimized PCI. A more progressive approach to image-guided PCI that integrates reference vessel size is becoming the preferred strategy to preventing TLF in modern practice. Using this strategy, the target is to achieve an MSA at initial stent implantation that is > 90% of the closest proximal or distal reference segment.

Image-Guided Contemporary Treatment of In-Stent Restenosis

In a contemporary approach to image-guided ISR treatment optimization, we aim to treat the modifiable entities that predict stent failure. The specific goals are to ensure (1) final stent expansion/lumen area is > 90% of the proximal and distal reference segment, as demonstrated by IVUS or OCT, (2) there are no inflow or outflow obstructions within

5 mm of the proximal or distal stent edge that has a minimal lumen area (MLA) < 5.0 mm^2 by IVUS or MLA < 4.5 mm^2 by OCT and, (3) there are no major edge dissections defined as > 60 degree, > 3 mm in length, or penetrating the media (Table 3). If there is significant in-stent under expansion, it is critical to increase expansion by algorithmically applying high-pressure balloons, scoring balloons, and atherectomy technologies until the stent expands completely. It is particularly important that the initial ISR stent expands well prior to implantation of a new stent because, as discussed later in this ISR article series, multilayer (> two stents) under-expanded ISR is a particularly difficult problem to treat.[38,39] If intravascular imaging shows significant peri-stent inflow or outflow obstruction or an important edge dissection, then we treat with standard PCI technique often by placing an additional stent.

In treating ISR, it is critical to identify the presence of stent under expansion and multilayer ISR with intravascular imaging. In a series of "recalcitrant" ISR cases where patients with two layers of DES were treated with a third DES layer, IVUS demonstrated that two layer DES under expansion was common (average expansion, 64.5%) and severe calcification behind the stents was seen in all cases of under expanded multilayer DES ISR (Figure 6).[40] After reintervention in this ISR patient series, most stents remained under
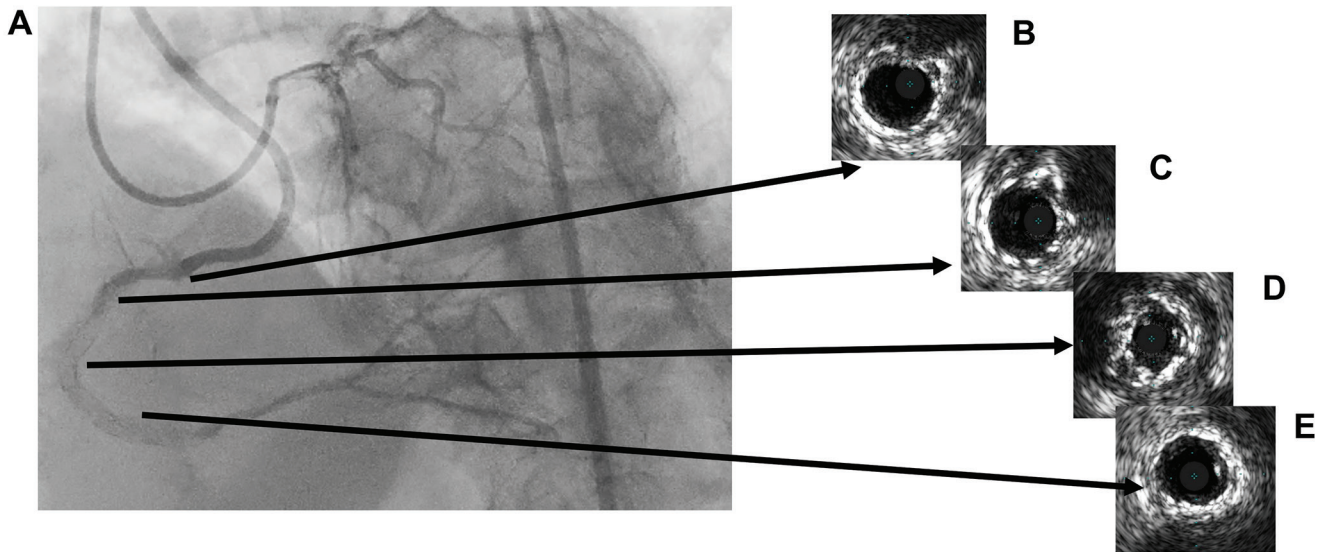
FIGURE 6. Multilayer DES ISR Chronic Total Occlusion. (A) Dual injection angiography showing mid RCA chronic total occlusion (CTO) in multi-layer DES ISR segment. (B-E vs C-E) Corresponding IVUS images showing multilayer stent under expansion in the ISR CTO region.

expanded (mean stent expansion, 67%).[40] In most cases, mechanical problems contribute to the development of DES ISR. With ISR interventions now accounting for > 10% of all PCIs in the US, and with the general experience that under expansion contributes to the majority of multilayer DES ISR, there is a tremendous opportunity to improve on PCI technique by optimizing the first stent implant with IVUS or OCT and to utilize atherectomy or other plaque modification techniques to ensure adequate stent expansion. It is well accepted that angiography underestimates the severity of calcium[41] and therefore, increased utilization of IVUS or OCT for pre-stent planning has the strong potential to identify situations where plaque modification will be required to facilitate maximal stent expansion. Emerging data suggest that in cases where intravascular imaging identifies an arc of calcium > 270 degrees or greater than 0.67 mm in thickness, atherectomy vessel preparation should be considered to optimize lesion and stent expansion.[42]

ISR interventions have failure rates that are higher than initial stent implantations. Thus, in an "ounce of prevention is worth a pound of cure" approach, the goal of initial PCI should be to maximize stent expansion to prevent the cycle of ISR reinterventions which are difficult to treat and have suboptimal long-term patency. Recurrent ISR is a major therapeutic dilemma. In the US, ISR is typically treated with reimplantation of another stent. Multiple layers of stents however compound the ISR problem by creating an "onion skin" layer of stent on neointima, which crowds the artery lumen, hinders complete expansion, and adversely impacts the ability to achieve an optimized final MSA (Figure 5). An artery encased in a multilayer stent is difficult to expand, and this stent compliance problem is further compounded

by the presence of peri-stent calcium or intrastent neoatherosclerotic calcium that likely hindered proper expansion during placement of the first or second stent. The function of DES is to provide scaffolding to prevent recoil and cover dissections and to deliver antiproliferative drugs that inhibit neointimal formation. In treating ISR, the main purpose of a second stent implant is to deliver antiproliferative drugs, and in many cases, the additional layer of stent further crowds the lumen with minimal benefit of additional scaffolding. In the complex multilayer ISR scenario, drug-eluting balloons provide an attractive opportunity to deliver antiproliferative drugs without adding an additional layer of stent. The 1-year DEB treatment outcomes for two- and three-layer stent treatment are however suboptimal, with MACE rates of 16.1% and 43.1%, respectively.[18] The challenges in treating multilayer ISR has led to a resurgence in coronary artery brachytherapy therapy for ISR in several referral centers. The coronary artery brachytherapy system available in the US (Novoste Beta-Cath) utilizes a strontium-90 source to deliver beta radiation to the ISR stenosis to inhibit neointimal proliferation without the need for placement of an additional stent. Two recent series evaluated the efficacy of coronary brachytherapy for recalcitrant multilayer ISR where in the best case, multilayer DES ISR brachytherapy TLR rates were 3.3% at 6 months, 12.1% at 1 year, 19.1% at 2 years, and 20.7% at 3 years.[43,44] In an effort to improve durability, we currently utilize an intravascular imaging guided approach with liberal use of atherectomy in all ISR and multilayer ISR brachytherapy cases. Contemporary, imaged-guided ISR treatment currently employs an algorithmic approach to vessel preparation and treatment that often utilizes scoring and cutting balloons, laser atherectomy, rotational or

orbital atherectomy, brachytherapy, and outside the US, lith–otripsy balloons and DEBs. An algorithmic approach to ISR treatment optimization is essential to improving outcomes in this difficult patient subset. Utility of specific devices and an ISR optimization algorithm will be the focus of subse–quent articles in this series.

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An Algorithmic Approach to the Treatment of Coronary In-Stent Restenosis

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Since the early days of percutaneous coronary intervention (PCI), restenosis has been one of the most frequent and severe complications.[1] The development of bare metal stents (BMS),[2] and subsequently of drug-eluting stents (DES),[3] has helped to reduce the incidence of restenosis, however patients undergoing stent implantation remain at significant risk for in-stent restenosis (ISR). Even with current-generation DES, ISR may occur after 5% to 20% of cases.[4] In the United States (US), a relatively modest number of treatment options are approved for ISR lesions by the US Food and Drug Administration (FDA), including the currently obsolete first-generation TAXUS paclitaxel-eluting stent, balloon angioplasty alone, scoring-balloon angioplasty, intravascular brachytherapy, and excimer laser coronary atherectomy (ELCA). This is reflected by the current AHA/ACC/SCAI guideline for PCI, which states a class IIb (may be considered) recommendation with level of evidence C for the treatment of DES ISR reading, "May be considered for repeat PCI with balloon angioplasty, BMW, or DES containing the same drug or an alternative drug if anatomic factors are appropriate and the patient is able to comply with and tolerate dual antiplatelet therapy (DAPT)."[5] The paclitaxel-coated balloon types are frequently used for this indication outside of the US but is not available in the US,[6] but involved in a broad controversy regarding their peripheral arterial applications.[7] Currently, DES implantation in ISR lesions, which holds a Class I level of evidence A indication in the European 2018 ESC/EACTS Guidelines on myocardial revascularization, has not been incorporated in the AHA/ACC/SCAI guidelines.[8] Hence, the most widely used treatment option for ISR in the US is balloon angioplasty, often followed by the off-label implantation of another DES.[9] Recurrent ISR can be a common problem in these subjects, and adding layer upon layer of stent struts in the restenotic lesion is not an attractive treatment option. Therefore, identification of the mechanism causing restenosis using intracoronary imaging, and optimization of the treatment of the restenotic lesion, are of paramount importance. This review introduces a treatment algorithm that will facilitate standardized classification of the pattern and mechanism of ISR with recommendations for optimal treatment according to various clinical scenarios. A recently introduced etiology-oriented ISR classification by

Waksman et al largely utilizes intravascular imaging to identify and classify different stages of ISR.[10]

Rationale of an Imaging-Based Treatment Algorithm for ISR

Intravascular ultrasound to guide treatment

Both the current European and the North American guidelines state a Class IIa, level of evidence C indication for the use of IVUS to determine the mechanism of stent restenosis.[11,12] The use of IVUS can identify the presence of any stent- or lesion-related mechanical problems that may lead to restenosis, such as stent under-expansion (due to the presence of extensive peri-stent calcium or not), focal edge restenosis, stent fracture, or the presence of a stent gap. Furthermore, the extent of neointimal hyperplasia can be quantified using IVUS. The importance of identifying mechanical problems is underscored by the findings of Goto et al who analyzed 298 ISR lesions and reported that restenotic DES as compared to BMS were characterized by less neointimal hyperplasia, smaller stent areas, longer stent lengths, and more stent fractures.[13] As outlined in the treatment algorithm, each mechanical complication has its own specific suggested treatment aimed at correcting the original problem. Optical coherence tomography (OCT) imaging may be an alternative to IVUS in many ISR cases. OCT will allow for improved spatial resolution at the cost of limited tissue penetration. This trade-off will lead to improved imaging of the (neo–)intima but reduced image quality of deeper layers of the coronary artery.

Hence, intravascular imaging and accurate lesion characterization better defines not only the pattern but also the mechanism involved in the specific ISR case. In setting up a center of excellence for ISR treatment, attention should be paid to the detailed evaluation and a deep case understanding before treatment is offered. Therefore, a systematic algorithm for ISR makes a lot of sense.

Role of scoring and cutting balloons and atherectomy

An important objective in treating patients with ISR is obtaining as much acute lumen gain as possible by trying to maximize the immediate post-procedural minimal luminal area. The use of specialty balloons incorporating cutting or scoring elements has been shown to reduce balloon slippage and to result in superior acute angiographic outcomes as compared with conventional balloons.[14,15] A combination of both cutting- or scoring-balloon angioplasty

Table 1. Observational studies investigating excimer laser coronary atherectomy for the treatment of in-stent restenosis						
Study	Year	Treatment Arms (N)	ISR Type	Mortality	Repeat Revascularization Rates	Other Outcomes
Mehran et al[20]	1997	ELCA+PTCA (N = 54) PTCA (N = 54)	BMS	6 month: 2% 6 month: 2%	6 month: 21% 6 month: 38%	Greater lumen gain and greater cross-sectional area by IVUS analysis in ELCA group
Koster et al[21]	1999	ELCA+PTCA (N = 440)	BMS	In-hospital: 1.6%	In-hospital: 0.9%	n/a
Koster et al[22]	2000	ELCA+PTCA (N = 96)	BMS	6 month: 1%	6 month: 31%	n/a
Mehran et al[23]	2000	ELCA+PTCA (N = 119) RA+PTCA (N = 130)	BMS	1 year: 8% 1 year: 5%	1 year: 26% 1 year: 28%	Ablation efficiency was higher with RA, but 1-year clinical results were similar
Hirose et al[24]	2016	ELCA+SCB(12) SCB alone(11)	DES	6 month: 0% 6 month: 0%	6 month: 16.7% 6 month: 45.5%	Angiographic late lumen loss and diameter stenosis percent at 6-month angiographic follow-up significantly lower with in ELCA group
Ambrosini et al[25]	2017	ELCA+DEB (N = 80)	Not reported	6 month: 0%	6 month: 5%	
Ichimoto et al[26]	2018	ELCA+DES (N = 23) DES only (N = 58)	DES	2.5 year: 0% 2.5 year: 0%	2.5 year: 21.7% 2.5 year: 25.9%	n/a
Hashimoto et al[27]	2019	ELCA, DEB, OCT (N = 53)	BMS and DES	12 month: 0%	12 month: 26.4%	ELCA less effective in layered-type ISR on OCT analysis

BMS = bare metal stent; DEB = drug-eluting balloon; DES = drug-eluting stent; ELCA = excimer laser coronary atherectomy; ISR = in-stent restenosis; IVUS = intravascular ultrasound; OCT = optical coherence tomography; PTCA = percutaneous transluminal coronary angioplasty; RA = rotational atherectomy; SCB = scoring balloon.

and atherectomy (either rotational or excimer laser coronary atherectomy [ELCA]) will theoretically lead to optimized ablation and modification of any neointimal tissue. Table 1 shows an overview of baseline characteristics and clinical outcomes from published studies investigating the use of ELCA for ISR.

A Walk Through the iLASER Algorithm

Identifying patients who may benefit from coronary artery bypass graft surgery or intravascular brachytherapy

The patients presenting with ISR may still develop it within an old BMS. The treatment algorithm is shown in Figure 1 and includes several important steps. The first step encompasses the identification of clinical scenarios where patients may be better treated with non–percutaneous or non–conventional methods such as coronary artery bypass graft surgery (CABG) or intravascular brachytherapy (IVBT). For example in patients with recurrent ISR, rates of repeat revascularization have been reported to exceed 50% within two years.[16] Furthermore, the angiographic pattern of ISR according to the classification holds important prognostic implications.[17] In the original publication, patients were predominantly treated with repeat BMS implantation, often after rotational atherectomy (RA) or excimer laser coronary atherectomy (ELCA); 1 year target lesion revascu-

larization rates were 19.1% for focal ISR (type 1), 34.5% for proliferative ISR (type 2), 50.0% for proliferative ISR (type 3), and 83.4% for total occlusion ISR (type 4). This study reported significantly better outcomes after ISR if a patient was treated with CABG as compared to PCI. Constantini et al reported 6–month target lesion revascularization rates after treatment of ISR with IVBT in a cohort of 295 patients, the majority of whom had ≥ two prior interventions.[18] This study showed relatively favorable re-intervention rates in patients with type 3 and type 4 ISR of 30.2% and 8.3%, respectively.

Identification of mechanical/technical issues using intracoronary imaging and tailored treatment

After performing intracoronary imaging (IVUS or OCT) in the ISR lesion, the presence or absence of any mechanical/technical issues can be determined. For example, if stent underexpansion due to significant peri–stent calcium (> 90°) is diagnosed, we recommend ELCA, followed by high-pressure scoring balloon inflation. ELCA has been associated with calcium modification, even in ISR lesions, and may therefore be the preferred mode of atherectomy in this case.[19] If, even after ELCA, the (scoring- or cutting-) balloon is unable to dilate completely, CABG may be preferred, as this suggests that the underlying problem of under–expansion is insufficiently
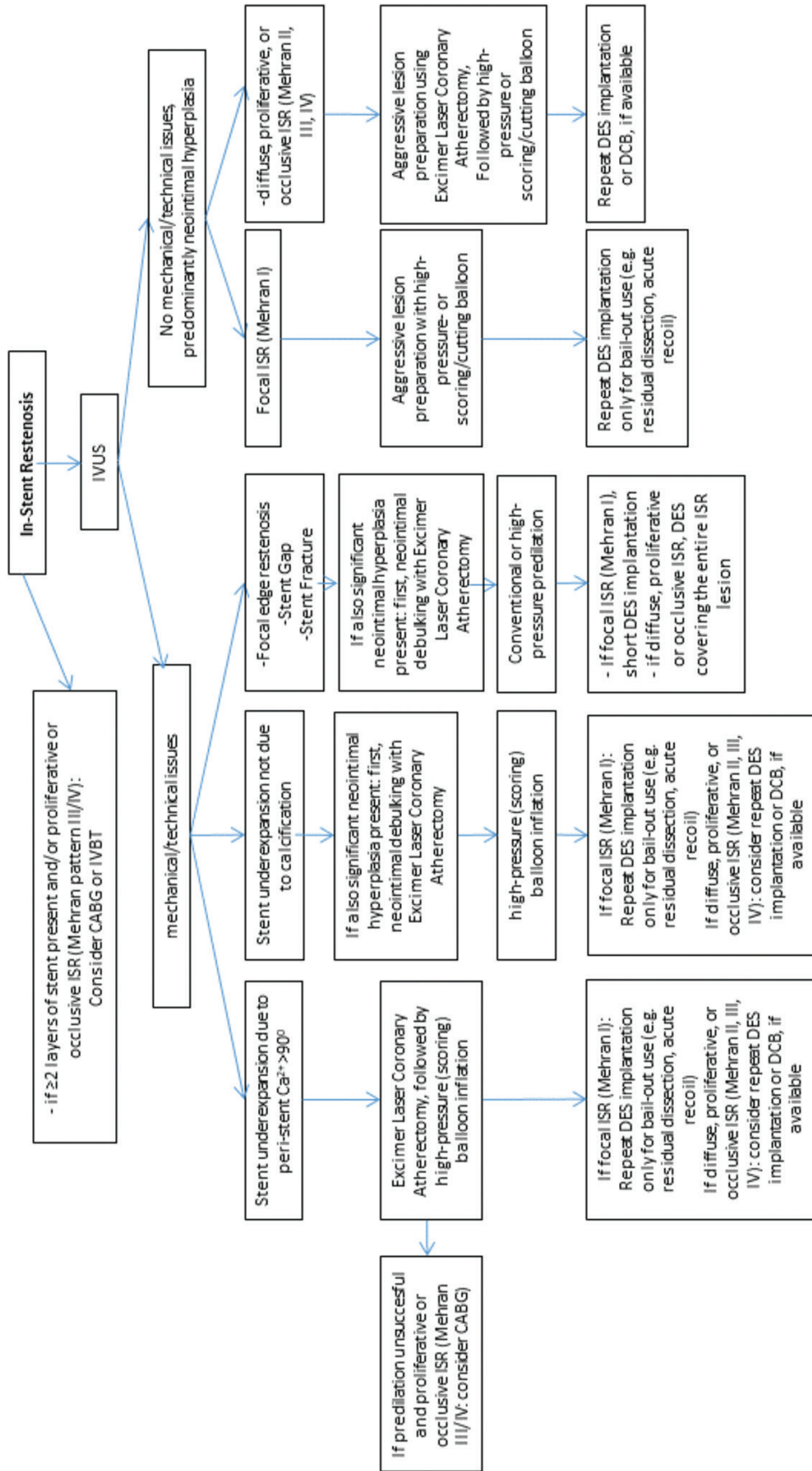
In-Stent Restenosis

IVUS

- if ≥2 layers of stent present and/or proliferative or occlusive ISR (Mehran pattern III/IV): Consider CABG or IVBT

No mechanical/technical issues, predominantly neointimal hyperplasia

- diffuse, proliferative, or occlusive ISR (Mehran II, III, IV)
  → Aggressive lesion preparation using Excimer Laser Coronary Atherectomy, Followed by high-pressure or scoring/cutting balloon
  → Repeat DES implantation or DCB, if available

Focal ISR (Mehran I)
  → Aggressive lesion preparation with high-pressure- or scoring/cutting balloon
  → Repeat DES implantation only for bail-out use (e.g. residual dissection, acute recoil)

mechanical/technical issues

- Focal edge restenosis
  - Stent Gap
  - Stent Fracture
  → If also significant neointimal hyperplasia present: first, neointimal debulking with Excimer Laser Coronary Atherectomy
  → Conventional or high-pressure predilation
  → - If focal ISR (Mehran I), short DES implantation
     - if diffuse, proliferative or occlusive ISR, DES covering the entire ISR lesion

Stent underexpansion not due to calcification
  → If also significant neointimal hyperplasia present: first, neointimal debulking with Excimer Laser Coronary Atherectomy
  → high-pressure (scoring) balloon inflation
  → If focal ISR (Mehran I): Repeat DES implantation only for bail-out use (e.g. residual dissection, acute recoil)
     If diffuse, proliferative, or occlusive ISR (Mehran II, III, IV): consider repeat DES implantation or DCB, if available

Stent underexpansion due to peri-stent Ca²⁺ >90°
  → Excimer Laser Coronary Atherectomy, followed by high-pressure (scoring) balloon inflation
  → If focal ISR (Mehran I): Repeat DES implantation only for bail-out use (e.g. residual dissection, acute recoil)
     If diffuse, proliferative, or occlusive ISR (Mehran II, III, IV): consider repeat DES implantation or DCB, if available

If predilation unsuccesful and proliferative or occlusive ISR (Mehran III/IV: consider CABG)

FIGURE 1. IVUS-based algorithm for the treatment of in-stent restenosis.

CABG = coronary artery bypass graft surgery; DES = drug-eluting stent; DCB = drug-coated balloon; ISR = in-stent restenosis; IVBT = intravascular brachytherapy; IVUS= intravascular ultrasound

addressed. If ELCA and cutting-/scoring-balloon angioplasty are successful, the decision to treat with additional DES implantation can be made based on the pattern of ISR. As focal ISR has a relatively good prognosis, DES implantation would only be recommended for bailout use, for example, in case of residual dissection. For diffuse, proliferative, or occlusive ISR, which are associated with higher rates of ISR, we recommend routine use of repeat DES implantation or DCB use (if available).

If stent underexpansion not due to calcification is diagnosed, we recommend the use of ELCA only if significant neointimal hyperplasia was also found to be present on IVUS imaging. If there was no or minimal neointimal hyperplasia, high-pressure (scoring) balloon inflation will be sufficient to dilate the lesion. Recommendations for additional stent implantation are similar to the prior scenario of stent under-expansion due to peri-stent calcium.

If focal edge restenosis, stent gap, or stent fracture is identified, we again recommend lesion debulking with ELCA only if significant neointimal hyperplasia is present. We always recommend conventional or high-pressure balloon predilation at the side of the mechanical complication, followed by a short repeat DES implantation in case of focal ISR or a long DES covering the entire lesion in case of diffuse, proliferative, or occlusive ISR.

If IVUS shows no mechanical/technical issues, and ISR is predominantly due to neointimal hyperplasia, treatment is dependent on the pattern of ISR. For focal ISR, aggressive lesion preparation, using a high-pressure or scoring/cutting balloon followed by DES implantation only for bailout use will be sufficient. On the other hand, for diffuse, proliferative, or occlusive ISR, we recommend atherectomy followed by scoring/cutting balloon angioplasty for optimal lesion debulking, followed by repeat DES implantation or DCB angioplasty, if available.

Conclusion

ISR remains a relatively frequent adverse outcome after PCI, even in the modern era of DES, and rates of repeat restenosis remain unacceptably high. A systematic treatment approach aimed at optimizing the acute and long-term results of PCI of ISR lesions using current best practices may be one important step towards improved outcomes. In order to optimize percutaneous treatment of ISR, a systematic approach as outlined in the iLASER algorithm is of paramount importance. This algorithm includes the assessment of the pattern of ISR, the use of intravascular imaging to determine the mechanism of ISR, optimal lesion preparation using scoring balloons and/or ELCA, and finally, repeat DES implantation if deemed necessary or DCB angioplasty if available. In the near future, the iLASER registry will provide insight into clinical outcomes and angiographic and IVUS follow-up of treatment of ISR using the iLASER algorithm.

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In-Stent Restenosis: Tools and Techniques

Jasvindar Singh,MD, FACC; and Adam Shpigel, MD

The mechanisms of in-stent restenosis (ISR) are varied, with the most common causes including neointimal hyperplasia, neoatherosclerosis within the stent, stent underexpansion, and stent fracture. Each of these etiologies requires a distinct therapeutic strategy in order to treat the immediate clinical presentation and prevent future recurrence. In this portion of the supplement, the tools and techniques for treatment of in-stent restenosis will be examined, offering the interventionalist a broad armamentarium for the treatment of this common phenomenon.

Intravascular Ultrasound

The use of intracoronary imaging is integral to the treatment of in-stent restenosis for several reasons. Our lab makes frequent use of intravascular ultrasound (IVUS) for this purpose, the Eagle Eye Platinum digital IVUS catheter (Philips), in particular. This is necessary for establishing the etiology of the ISR, establishing the size of the vessel, and determining a treatment strategy. Following treatment of the lesion, either by angioplasty or stenting, we perform repeat IVUS to establish adequacy of treatment and appropriate stent expansion and apposition.

Specialty Balloons

In our practice, we make extensive use of specialty balloon angioplasty for the treatment of in-stent restenosis. These balloons can be used for controlled high-pressure inflation for dilation of an underexpanded stent. Additionally, these balloons can be inflated at high pressure in the setting of neointimal hyperplasia or neoatherosclerosis. Depending on the circumstance, we will sometimes use specialty balloon angioplasty as a standalone technique, particularly if the angiographic result is adequate or in vessel segments that have already been stented multiple times. In other cases, these balloons are used for predilation prior to placement of an additional drug-eluting stent. The two balloons that we commonly use in clinical practice are the AngioSculpt PTCA balloon (Philips) (Figure 1) and the Chocolate balloon (Teleflex) (Figure 2).

AngioSculpt PTCA Balloon

The AngioSculpt PTCA balloon is a specialty scoring balloon often used in the treatment of in-stent restenosis, particularly when caused by neointimal hyperplasia. The defining feature of the AngioSculpt PTCA balloon is the presence of three nitinol scoring edges running down the length of the balloon. These scoring edges are rectangular in cross section and are designed to lock into fibrous tissue or atherosclerotic plaque. These edges limit the incidence
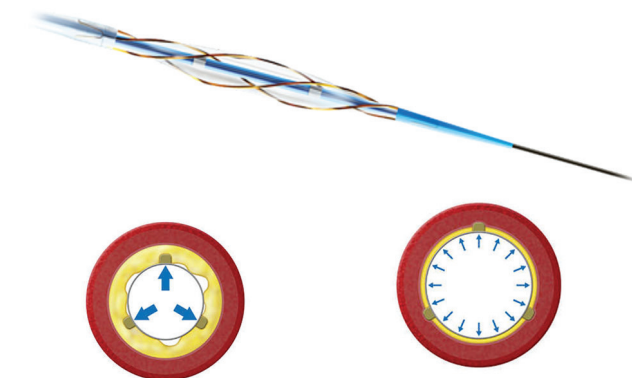

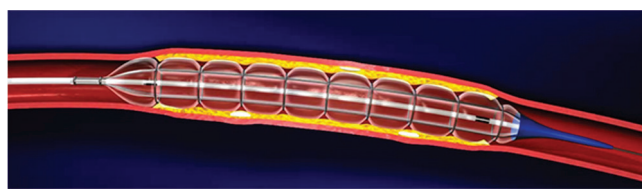**FIGURE 1.** The AngioSculpt PTCA scoring balloon cathter.

FIGURE 2. The Chocolate balloon.

of device slippage or "watermelon seeding," even within highly fibrotic tissue within a stent. Additionally, the leading edges of the scoring elements exert a force of up to 15 to 25 times that of a conventional angioplasty balloon at the point of contact. The coronary AngioSculpt PTCA balloon is available in diameters from 2 to 3.5 mm and in a variety of lengths. The newest iteration of the AngioSculpt PTCA balloon has smooth transitions, substantially improving deliverability. All sizes are compatible with a 6-F guide catheter. In our practice, the AngioSculpt PTCA balloon should be inflated slowly, at approximately one atmosphere every 5 seconds, to optimize the engagement of the atherotomes and provide the most effective angioplasty. In our experience, the AngioSculpt PTCA balloon is a very useful tool in the treatment of in-stent restenosis, both as a standalone treatment and for lesion dilation prior to placement of a stent.

Chocolate Balloon

The Chocolate balloon is a unique angioplasty balloon design which we use extensively in settings of in-stent restenosis caused by neointimal hyperplasia and stent underexpansion.
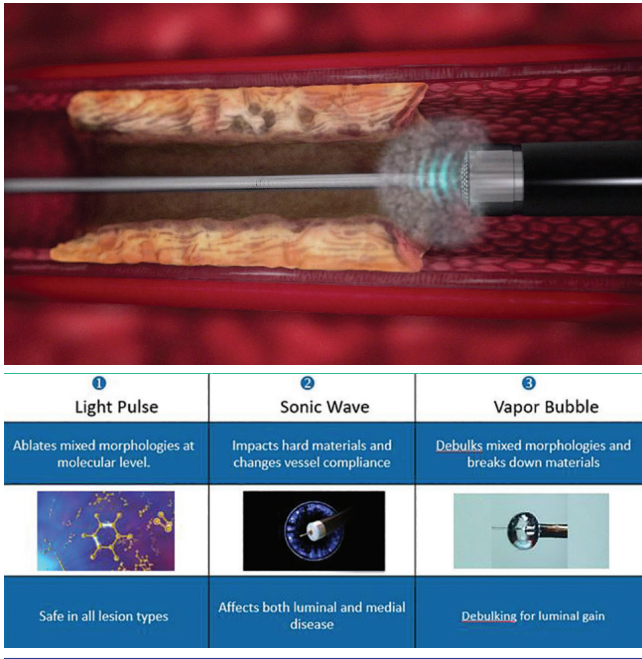
❶ Light Pulse	❷ Sonic Wave	❸ Vapor Bubble
Ablates mixed morphologies at molecular level.	Impacts hard materials and changes vessel compliance.	Debulks mixed morphologies and breaks down materials
Safe in all lesion types	Affects both luminal and medial disease	Debulking for luminal gain

FIGURE 3. Laser atherectomy.

The unique structure of the Chocolate balloon consists of a nitinol constraining structure surrounding the balloon. As evident from the figure, this creates a series of alternating pillows and grooves. These are designed to provide predictable and uniform dilatation while minimizing the risk of dissection. Conventional angioplasty applies radial, longitudinal, and torsional force during expansion, which can cause trauma to the vascular wall and possible dissection. By its design, the Chocolate balloon can ameliorate these traumatic forces while still providing robust vessel dilation and lesion modification. Sizes from 2 to 3.5 mm are available in a variety of lengths, with the 2- and 2.5-mm sizes 5-Fr compatible, and the larger sizes 6-Fr compatible.

Noncompliant Balloons

Noncompliant coronary balloons are widely used in the predilation of restenotic lesions, especially in the setting of prior stent underexpansion. We use the NC Emerge and Sapphire balloons predominantly in our cath lab. These lesions often require high-pressure inflations in the setting of prior stent underexpansion.

Laser Atherectomy

Laser atherectomy has emerged as an invaluable tool for treatment of in-stent restenosis. Neointimal hyperplasia is particularly well treated by laser atherectomy (Figure 3). In our lab, laser atherectomy is frequently used for the treatment of in-stent restenosis, particularly in the setting of multiple layers of stent or a heavily fibrotic segment of disease.

Coronary lasers are classified as excimer lasers, using a gas mixture as a medium to generate high-energy ultraviolet light. There are three mechanisms by which the laser operates to ablate fibrous tissue and plaque. The light pulse mechanism is that by which the energy from the laser breaks carbon–carbon bonds in the fibrous tissue, thus ablating it. The sonic wave mechanism is that by which pulsed waves are generated by the laser "cracking" hard materials and changing vessel compliance. The sonic waves affect both luminal and medial disease. The third mechanism action is driven by the vapor bubble at the distal tip of the catheter. When this vapor bubble expands and bursts, it addresses mixed lesion morphologies and debulks for luminal gain. The small size of the released particles generally does not obstruct the distal circulation.

The ELCA (excimer laser coronary atherectomy) catheter and CVX–300 laser system (Philips) is used frequently in our cath lab. This laser uses XeCl as the gas medium for production of the laser. The catheter comes in various diameters, and there are different guidelines for selecting a size for a given vessel. In our practice, the 0.9-mm laser is the most frequently used in the coronary circulation. The size of the vapor bubble is approximately 2.5 times the diameter of the catheter. The 0.9-mm laser is 6-Fr guide compatible and has a short monorail segment. Prior to use, the laser must be calibrated per manufacturer instructions.

The laser's fluence and rate must be chosen prior to atherectomy. Fluence is the energy of the laser and rate is the number of pulses per second. We frequently use a fluence of about 45 and rate of 45, but these can be adjusted according to clinical circumstance, up to a fluence of 80 and a rate of 80.

Importantly, the rate of laser advance must be very slow. The recommended speed is approximately 1 mm per second. If the laser is advanced too quickly, it is unlikely to have time to properly modify the lesion. Several runs may be undertaken at the operator's discretion.

Other Atherectomy

There are occasional reports of rotational atherectomy being used for treatment of in-stent restenosis. This is associated with risks including damage to the stent, embolization of metallic debris, and damage to the rotational atherectomy system. This should only be considered as a salvage approach and only by operators experienced in the use of rotational atherectomy for other lesion types.

The use of orbital atherectomy in in-stent restenosis is listed as a contraindication per manufacturer guidelines and has not been widely attempted given concern for damage to the stent or orbital atherectomy system.

Miscellaneous Tools and Techniques

Delivery of balloons and stents can be difficult across previously placed stents. When difficulty delivering equipment is encountered, a number of approaches can be taken. Angioplasty of a stented segment, when possible, often improves delivery of subsequent equipment, especially if the previously placed stent is underexpanded.

In some cases, difficulty with advancing balloons or stents can be attributable to unfavorable wire bias. In these cases, because of the orientation of the wire within the vessel, the leading edge of the balloon or stent that is being delivered may be obstructed by a previously placed stent. It can be helpful to place another coronary wire, a "buddy wire," alongside the initially placed wire, in these cases. This may straighten the vessel and potentially offer more favorable wire bias for advancing equipment. If a stent is being placed, it is imperative to remember to remove the other wire prior to stent deployment, otherwise the wire will be trapped between two layers of stents and may be very difficult to remove.

If we are having difficulty advancing equipment in the setting of previously placed stents, we will frequently reach for a guide extender, such as the Guidezilla (Boston Scientific) or the Guideliner (Teleflex) (Figure 4). The Guideliner is shown in the figure for illustration. These can be advanced to, or even distal to, the area causing delivery difficulty. If there is difficulty advancing the guide extender, we frequently make use of the inchworm technique, in which a balloon is advanced immediately distal to the guide extender and inflated. The balloon is then deflated, and during deflation, forward pressure is applied to the guide extender in an effort to slide the extender over the balloon. If a stent is to be placed, we will often leave the guide extender distal to the lesion, place the stent in approximately the right position, and then withdraw the guide extender so that the stent may be deployed.

The Wiggle Wire (Figure 5) is an interesting piece of technology which we have increasingly started to use in the setting of difficult delivery. The Wiggle Wire has a shaped distal segment starting 6 cm proximal to the tip and consisting of three "waves" with an amplitude of approximately 3 mm, as can be seen in the figure. These bends can improve deliverability by moving the balloon or stent to be delivered away from the wall of the vessel and the previously placed stent. We generally reserve use of the Wiggle Wire for delivery difficulty despite use of the previously noted techniques.
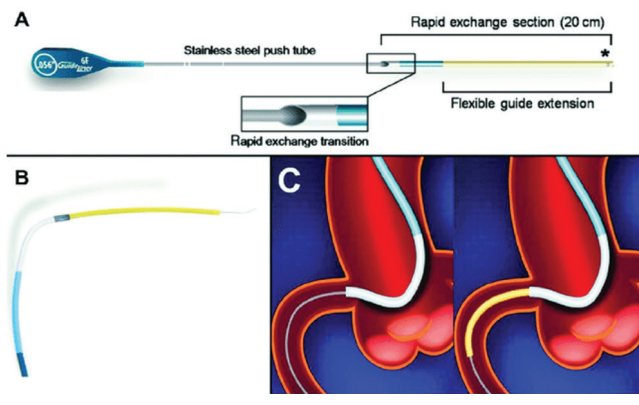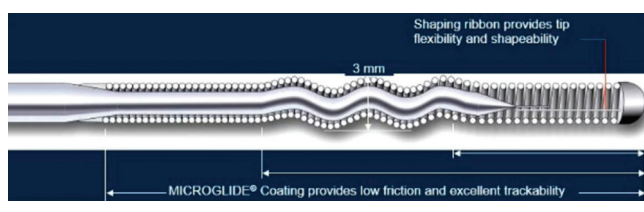

FIGURE 4. The Guideliner device.

FIGURE 5. The Wiggle Wire device.

Conclusion

While the rate of in-stent restenosis has dropped dramatically in the era of drug-eluting stents, it remains an important clinical entity with which the interventional cardiologist must be familiar. We cannot overstate the importance of intracoronary imaging in identifying the etiology and correctly addressing the likely cause. We now have a plethora of tools for managing in-stent restenosis including specialty balloons, noncompliant angioplasty balloons, and laser atherectomy, and several ways to overcome the difficulty in delivering these devices. While in-stent restenosis can be challenging to treat, our variety of tools and techniques will, in the hands of a thoughtful operator, result in procedural success.
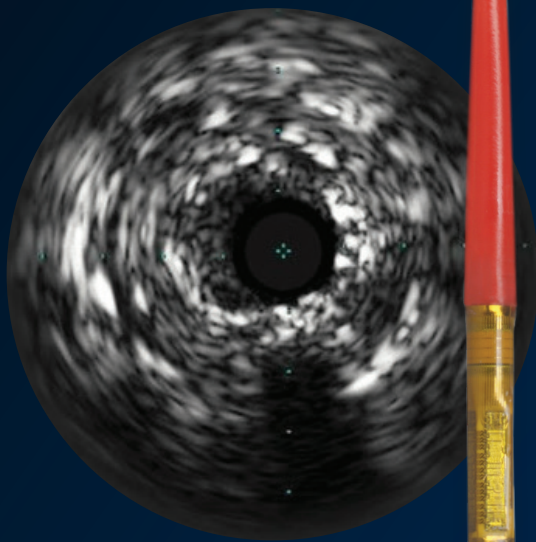
Defeat ISR

Treat in-stent restenosis (ISR) using IVUS guidance and the only scoring balloon and atherectomy system indicated for ISR.

ELCA laser
atherectomy catheter

Eagle Eye Platinum
digital IVUS catheter

AngioSculpt PTCA
scoring balloon catheter

See clearly.
Treat optimally.

Refer to full device labeling and instructions for important safety information. Caution: Federal law restricts these device to sale by or on the order of a physician.