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STATE-OF-THE-ART PAPER

In-Stent Restenosis in the Drug-Eluting Stent Era

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The introduction of the drug-eluting stent (DES) proved to be an important step forward in reducing rates of restenosis and target lesion revascularization after percutaneous coronary intervention. However, the rapid implementation of DES in standard practice and expansion of the indications for percutaneous coronary intervention to high-risk patients and complex lesions also introduced a new problem: DES in-stent restenosis (ISR), which occurs in 3% to 20% of patients, depending on patient and lesion characteristics and DES type. The clinical presentation of DES ISR is usually recurrent angina, but some patients present with acute coronary syndrome. Mechanisms of DES ISR can be biological, mechanical, and technical, and its pattern is predominantly focal. Intravascular imaging can assist in defining the mechanism and selecting treatment modalities. Based upon the current available evidence, an algorithm for the treatment approaches to DES restenosis is proposed.
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Restenosis after angioplasty and stent implantation has been historically considered the most significant problem in coronary interventional treatment (1). Drug-eluting stents (DES) have dramatically reduced the rates of restenosis and target lesion revascularization (TLR) compared with bare-metal stents (BMS) (2). However, a low rate of in-stent restenosis (ISR) after DES still exists, and its prevalence is not negligible because the population treated with DES is large. Although the low frequency of ISR events with DES makes clinical investigation difficult, many studies have addressed the incidence, mechanism, predictors, and optimal treatment of DES restenosis. We sought to provide a concise, comprehensive overview of the pathophysiologic mechanisms, clinical presentation, morphologic patterns, and management options of DES ISR.

Definition

Restenosis, or reduction in lumen diameter after percutaneous coronary intervention (PCI), is the result of arterial damage with subsequent neointimal tissue proliferation. Binary angiographic restenosis is defined as ≥50% luminal narrowing at follow-up angiography. Our group first proposed an angiographic classification of restenosis (Table 1) (3). The most widely accepted definition of clinical restenosis, assessed as a requirement for ischemia-driven repeat revascularization, was proposed by the Academic Research Consortium. This definition requires both an assessment of luminal narrowing and the patient's clinical context (Table 1) (4). In case of an intermediate lesion, the use of fractional flow reserve or intravascular ultrasound (IVUS) can guide the clinical decision (5–7).

Although a detailed discussion on stent thrombosis is beyond the scope of this review, it is important to distinguish it from ISR. Stent thrombosis frequently presents as myocardial infarction (MI), whereas ISR presents as MI in a small minority of cases (8). The Academic Research Consortium proposed a definition of stent thrombosis that found general acceptance (Table 1). The time course for a TLR occurring within 30 days after stent implantation is too short to be caused by neointimal hyperplasia but is more likely to be caused by a procedural complication or subacute stent thrombosis. Finally, it is still possible that restenotic and thrombotic processes may occasionally coexist. This can occur in cases characterized by neointimal hyperplasia plus focal thrombosis inside the stent. Many factors can provide useful tips in a particular case, including the time frame from original implantation (the longer the time, the greater the likelihood of neointimal hyperplasia), angiographic features (size of thrombus, length of stent, and ISR), IVUS (neointimal hyperplasia can be reliably seen and measured), and intraprocedural findings (neointimal tissue is hard and associated with balloon slippage, whereas thrombus is soft).

Incidence

The initial pivotal randomized trials comparing DES and BMS were conducted in patients with de novo native coronary artery lesions, and ISR was observed at follow-up in <6% of patients (9,10). After these promising initial

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Abbreviations and Acronyms

BMS = bare-metal stent(s)
DES = drug-eluting stent(s)
EES = everolimus-eluting stent(s)
ISR = in-stent restenosis
IVUS = intravascular ultrasound
MI = myocardial infarction
PCI = percutaneous coronary intervention
SES = sirolimus-eluting stents(s)
VBT = vascular brachytherapy
ZES = zotarolimus-eluting stent(s)

results, DES were rapidly and widely adopted, enabling more complex percutaneous procedures than in the preceding era. Subsequently, restenosis rates increased to the double-digit domain in randomized head-to-head DES comparisons including more complex patients and lesions (11,12). Moreover, a number of clinical registries and observational studies that included complex, unselected patients reported restenosis rates higher than 10% (13–15).

The newer DES, such as everolimus-eluting stents (EES), zotarolimus-eluting stents (ZES), and biolimus A9–eluting stents, are characterized by improvements in stent platform (i.e., thin-strut cobalt chromium vs. thick-strut stainless steel), polymer (thinner and/or biodegradable), and drug (biolimus A9 and zotarolimus were specifically designed for use in intracoronary stents), with the aim of minimizing the incidence of DES ISR and improving safety. Recent large randomized studies have shown that the next-generation EES is superior to the first-generation paclitaxel-eluting stent (PES) in terms of reducing repeat revascularization, MI, and stent thrombosis (16,17).

Clinical Presentation

Although some cases of ISR are clinically silent, the majority lead to recurrent symptoms. Given its gradual and progressive onset, ISR has been perceived as a benign phenomenon. Reports on the presentation of BMS ISR have shown that unstable angina is a frequent manifestation of ISR (26% to 53%). Moreover, depending on the definitions applied, BMS ISR presented as MI in 3.5% to 20% of patients (18,19). The presentation of DES ISR is similar to that of BMS ISR with approximately 16% to 66% of patients presenting with unstable angina and 1% to 20% with MI (18,19). The mechanism of late MI associated with ISR is multifactorial. First, a silent occlusive restenosis can

Table 1 Definitions and Classification of Restenosis and Stent Thrombosis

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 (e.g., coronary flow velocity reserve, FFR <0.80); IVUS minimum cross-sectional area <4 mm^2 (and <6.0 mm^2 for left main stem) has been found to correlate with abnormal FFR and need for subsequent TLR (5–7)
TLR with diameter stenosis ≥70% even in absence of the above ischemic signs or symptoms
Stent Thrombosis
Definite stent thrombosis
Angiographic confirmation of stent thrombosis
Presence of thrombus that originates in stent or in the segment 5 mm proximal or distal to stent *and* at least 1 of the following within a 48-h time window
Acute onset of ischemic symptoms at rest
New ischemic ECG changes that suggest acute ischemia
Typical rise and fall in cardiac biomarkers
Pathologic confirmation of stent thrombosis
Evidence of recent thrombus within stent determined at autopsy or via examination of tissue retrieved following thrombectomy
Probable stent thrombosis
Any unexplained death within first 30 days
Irrespective of time after index procedure, any MI related to documented acute ischemia in territory of stent thrombosis and in absence of any other obvious cause
Possible stent thrombosis
Any unexplained death from 30 days after intracoronary stenting

ECG = electrocardiography; FFR = fractional flow reserve; IVUS = intravascular ultrasound; MI = myocardial infarction; TIMI = Thrombolysis In Myocardial Infarction; TLR = target lesion revascularization.

be difficult to differentiate from a thrombotic event. In addition, a highly stenotic ISR lesion may also promote local nonocclusive thrombosis and lead to a clinical presentation of non–ST-segment elevation MI or troponin-positive unstable coronary syndrome. Based upon the wide variety in definitions and reported incidence of unstable angina and MI, it is impossible to definitively confirm or reject that ISR is indeed a benign phenomenon; a spectrum of the acuity of clinical presentation exists (20–23).

Certain studies have reported biomarker-positive acute coronary syndrome as presentation of ISR to be a predictor for further adverse events after treatment of ISR (23,24). In contrast, an observational study by Steinberg et al. (25) showed no differences in the occurrence of subsequent adverse events after treatment of ISR in patients presenting with acute coronary syndrome versus patients presenting with recurrent exertional angina.

Of note, in the BMS era, ISR has been reported to occur an average of 5.5 months after stent implantation, with a shorter interval for patients presenting with MI than those presenting with recurrent angina (26). Furthermore, diffuse ISR was more frequent in patients with MI and correlated with early ISR presentation (26). On the other hand, there is a paucity of detailed data on the timing of ISR related to DES. In one study of 39 ISR cases associated with DES, Lee et al. (27) showed that the mean time from PCI to ISR detection was approximately 12 months. The time frame to restenosis after DES may indeed be longer than that after BMS because antiproliferative drugs can delay the biologic response to injury.

Pathophysiologic Mechanisms

The clinical effect of a DES is highly dependent on its components: stent platform, active pharmacologic compound, and drug carrier. DES technology enables anti-inflammatory, immunomodulatory, and/or antiproliferative agents to be released in appropriate amounts and distributed at the site of arterial injury during the initial 30-day healing period. The precise reasons why DES restenose in some patients and in some segments within the same patient are still controversial. Biological, mechanical, and technical factors may contribute to ISR after DES implantation (Table 2).

Table 2 Possible Mechanisms of Restenosis After DES

Biological factors
Drug resistance
Hypersensitivity
Mechanical factors
Stent underexpansion
Nonuniform stent strut distribution
Stent fracture
Nonuniform drug elution/deposition
Polymer peeling
Technical factors
Barotrauma outside stented segment
Stent gap
Residual uncovered atherosclerotic plaques

Biological factors. DRUG RESISTANCE. Sirolimus and its analogs have a cytostatic effect. They inhibit the function of the mammalian target of rapamycin and suppress smooth muscle cell migration and proliferation by arresting the cell cycle in the G_1 phase (28). Paclitaxel has a cytotoxic effect, binding specifically to the beta-tubulin subunit of microtubules, and its principle action is to interfere with microtubule dynamics, preventing their depolymerization (28). Recent data indicate that genetic mutations can influence the sensitivity to these drugs, conferring resistance to sirolimus, its analogs, or paclitaxel (29,30).

HYPERSENSITIVITY. For BMS and first-generation DES, the predominant stent platform material is 316L stainless steel. In the BMS era, allergic reactions to nickel and molybdenum released from 316L stainless steel stents were potential triggering mechanisms for ISR (31). The platform material used in many novel DES (but not in the widely used PES and sirolimus-eluting stent [SES]) is cobalt chromium, which has a lower nickel content than 316L stainless steel, and does not appear to trigger the adverse proliferative response and hypersensitivity that accompanies the incorporation of other alloys.

However, because DES consist of 3 components (stent platform, antirestenotic drug, and polymer carrying the drug), hypersensitivity reactions can be caused by any one of these components. In the RADAR (Research on Adverse Drug/Device Events and Reports) project, 5,783 reports of adverse events after DES placement collected by the Food and Drug Administration were analyzed, and 261 reports described hypersensitivity reactions. Subsequently, 17 patients were identified for which the DES themselves appeared to be a probable cause of hypersensitivity (32). Of the 17 patients with DES hypersensitivity, 4 patients (24%) died of stent thrombosis between 4 and 18 months after stent implantation; this could have been isolated thrombosis or a combination with progressive/late restenosis. These deaths led to concern about a possible causative role of durable polymers that remain on the stent surface after drug elution. Because the exact incidence is unclear, any patient suspected of having a hypersensitivity reaction after DES implantation should be carefully monitored. New DES with biodegradable polymers and improved metal alloys would be expected to have fewer hypersensitivity problems.

Mechanical factors. STENT UNDEREXPANSION. Stent underexpansion results from poor expansion during implantation rather than from chronic stent recoil (Fig. 1) (33). Stent underexpansion may be undetectable angiographically in many cases; suspicion may be raised in an area of fluoroscopically underexpanded stent struts (compared with the rest of struts) in the context of a calcified lesion or an inability to fully expand the balloon inside the stent. However, the use of IVUS can be instrumental to detect

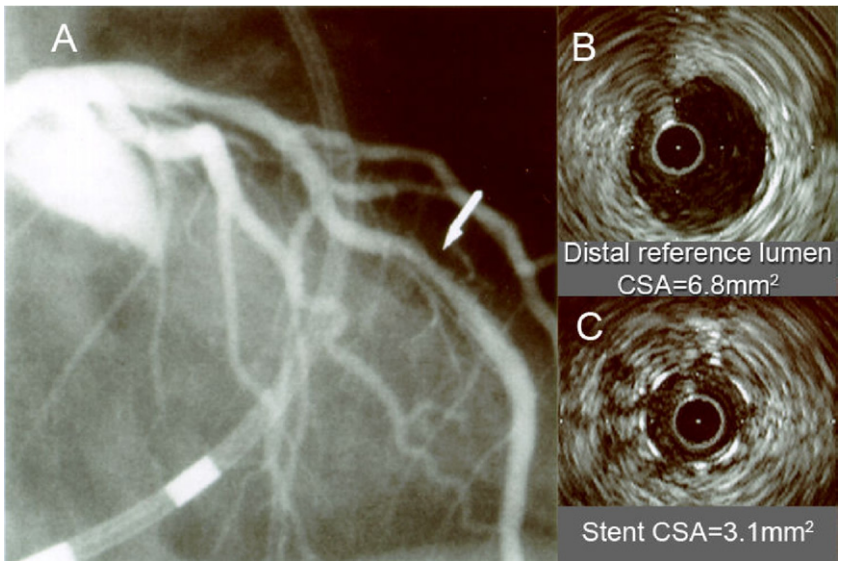

Figure 1 **Stent Underexpansion**

The **white arrow in A** shows a mid left anterior descending coronary artery lesion after stent implantation. **B** shows the intravascular ultrasound (IVUS) imaging of the distal reference lumen diameter, which measured 6.8 mm^2. **C** shows the IVUS imaging of the underexpanded stent in the treated lesion, which shows well-apposed stent struts, without evidence of neointimal hyperplasia but a small stent cross-sectional area (CSA) of only 3.1 mm^2; the vessel diameter is almost double the stent diameter.

underexpansion; despite good apposition of the stent struts to the vessel wall, the underexpanded site would be evident by a stent cross-sectional area significantly smaller than the vessel cross-sectional area in the same site, smaller than the stent cross-sectional area in other sites, and smaller than the reference lumen area. According to proposed strict criteria by de Jaegere et al. (34), excellent expansion is evident when the minimum lumen area in the stent is ≥90% of the average reference lumen area.

A condition that needs to be differentiated from underexpansion is stent malapposition; unlike underexpansion, there are stent struts not apposed to the vessel wall (i.e., space occupied by blood can be detected between the stent struts and the arterial intima). Malapposition cannot be judged angiographically (except in very few extreme cases), typically occurs with use of undersized stents or in arteries that have significant tortuosity and fluctuations of reference arterial lumen diameter within the treated segment, and is thought to predispose to stent thrombosis (35). However, a recent study by Steinberg et al. (36) found no association between early or late incomplete stent apposition and stent thrombosis in 1,580 patients enrolled in IVUS substudies of various TAXUS (Treatment of De Novo Coronary Disease Using a Single Paclitaxel-Eluting Stent) clinical trials. Because both malapposition and underexpansion affect selected regions of a stent, it is entirely possible that they coexist in 2 separate sites of the same stent (e.g., proximal struts can be malapposed owing to large and tortuous proximal reference sites, whereas the mid stent area at the original lesion site can be underexpanded) (37).

NONUNIFORM DRUG DISTRIBUTION. The effectiveness of local drug delivery requires transmural and circumferential distribution across and within the vessel walls. Physiologic and computational models have shown that local blood flow alterations, strut overlap, and polymer damage may hamper the uniformity of drug elution (38,39). Treating lesions in noncompliant vessels increases the odds of stent underexpansion, and difficult device delivery may strip the polymeric material with ensuing compromise in local drug elution. In addition, variability in vessel wall coverage among the different types of DES (reflecting the metal-to-artery ratio of their stent platforms) and variability in drug elution (e.g., stripping of coating or nonuniform/circular stent expansion) may produce focal areas within the stented segment with less than optimal drug distribution and contribute to increased ISR risk (40–42). Achieving drug elution from the metallic stent and from the stent delivery balloon during inflation may be a way to address this issue in the future.

STENT FRACTURE. A stent fracture is defined as complete or partial separation of a stent at follow-up that was contiguous after the original stent implantation (43). A stent fracture eliminates the metal scaffolding support at the specific site and adversely impacts local drug delivery. It may occur in conjunction with restenosis (typically of a focal pattern), resulting from a decrease in local drug delivery at the fracture point; it may also be a marker of severe nonuniform stent expansion in a highly mobile and hard arterial area that ultimately separated the stent (Fig. 2). By IVUS, partial stent fracture is defined by the absence of at

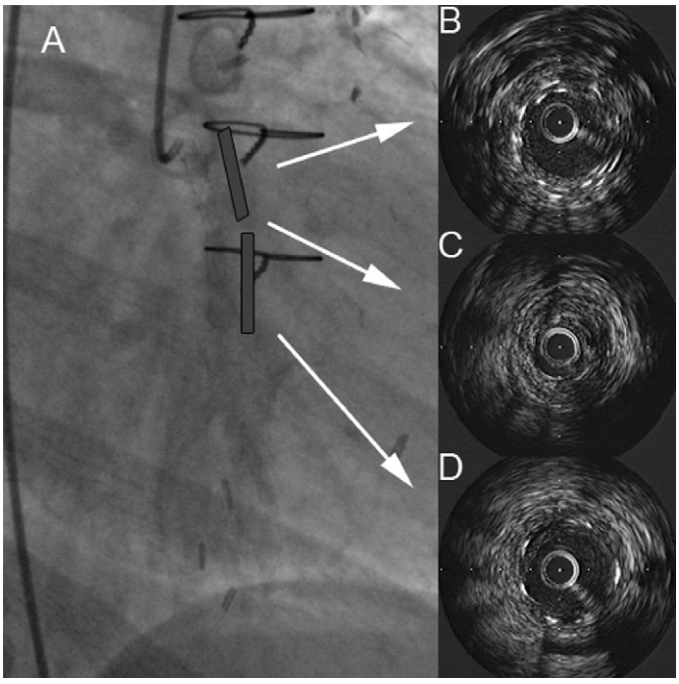

Figure 2 Stent Fracture

The **gray bars in A** are positioned adjacent to a fractured long stent in a right coronary artery. **B** shows the intravascular ultrasound cross section proximal to the stent fracture, with clearly visible stent struts across the circumference of the lumen. **C** shows the cross section at the site of stent fracture with no visible stent struts, indicating a complete fracture. **D** shows the cross section distal to the stent fracture, where stent struts are again visible across the circumference of the lumen.

least one-third or 120° of stent struts for at least 1 frame; complete stent fracture is defined by the complete absence of stent struts within the stented segment for at least 1 frame (43). Furthermore, a number of classification systems for the severity of stent fracture have been proposed (Table 3) (44–46). The incidence of DES fracture has been reported to range from 1% to 8% (47–49). The need for subsequent revascularization in fractured stents has been reported to range from 15% to 60% in these relatively small studies (47–49). Right coronary artery lesions, excessive tortuosity, angulation and torsion of the vessel, overlapping stents, longer stents, and SES (owing to its rigid closed-cell structure) have been associated with an increased risk of stent fracture (47–49).

Technical factors. BAROTRAUMA OUTSIDE STENTED SEGMENT. Subgroup analyses from an early SES randomized clinical trial indicated that the exposed margins of the stents that did not cover the entire region of the balloon injury were the primary sites of restenosis (10). Restenosis occurred predominantly at the proximal stent margin after SES placement. This was decreased in subsequent studies that employed the currently recommended technique of pre-dilation with shorter balloons, use of a single stent long enough to cover the entire area of balloon injury, and post-dilation within the stented regions using short, high-pressure balloons.

STENT GAP. Similar to stent fracture, stent gap causes discontinuous coverage with DES. A short gap between 2 DES

Table 3 Stent Fracture Classification Methods

Type	Popma et al. (45)	Allie et al. (44)	Scheinert et al. (46)
1	Single-strut fracture or gap between struts >2 times normal	Single-strut fracture only	Minor: single-strut fracture
2	Multiple strut fractures with V-form division of stent	Multiple single-stent fractures occurring at different sites	Moderate: fracture >1 strut
3	Complete transverse stent fracture without displacement of fractured fragments >1 mm during cardiac cycle	Multiple single-stent fractures resulting in complete transverse linear fracture but without stent displacement	Severe: complete separation of stent segments
4	Complete transverse stent fracture with abundant movement and displacement of fractured fragments >1 mm during cardiac cycle	Complete transverse linear type 3 fracture with stent displacement	

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Table 4 Predictors of ISR or TLR After DES Implantation

Patient Characteristics	Lesion Characteristics	Procedural Characteristics
Age	ISR	Treatment of multiple lesions
Female sex	Bypass graft	Type of DES
Diabetes mellitus	Chronic total occlusion	Final diameter stenosis
Multivessel coronary artery disease	Small vessels	
	Calcified lesion	
	Ostial lesion	
	Left anterior descending coronary artery lesion	

DES = drug-eluting stent(s); ISR = in-stent restenosis; TLR = target lesion revascularization.

typically occurs in a zone of balloon injury owing to either pre- or post-dilation. Local drug deposition in the vessel wall is minimal at the gap site. In general, considering the reported safety and efficacy of overlapping DES, and the mechanism described previously, short stent gaps should be avoided (50).

RESIDUAL UNCOVERED ATHEROSCLEROTIC PLAQUES. The STLLR (Stent Deployment Techniques on Clinical Outcomes of Patients Treated With the Cypher Stent) trial evaluated the frequency of suboptimal PCI and its impact on the long-term outcomes of 1,557 patients treated with SES (51). The presence of geographic miss during the procedure (injured or diseased segment not covered by DES or balloon-artery size ratio <0.9 or >1.3) was associated with an increased risk of target vessel revascularization and MI at 1 year. Therefore, the risk and cost of implanting additional DES in such cases should be weighed against the risk of subsequent clinical events.

Predictors

Predictive factors for DES restenosis, such as diabetes mellitus, complex lesions (B2/C), small vessels, longer stents, and stent underexpansion, identified from real-world data seem to be similar to those for BMS restenosis (Table 4) (13,52,53). Because the post-procedural minimal lumen diameter is a major factor in restenosis, obtaining optimal acute angiographic results after DES implantation remains important.

Delayed Restenosis

After DES implantation, late restenosis and persistent neointimal growth have been reported. In the TAXUS II study, serial IVUS analyses were performed in 161 patients up to 2 years after deployment of BMS and PES (54). Whereas a modest late decrease in neointimal hyperplasia was observed in the BMS group, a small late increase in neointimal tissue was observed in the PES group. However, even at 2 years, the neointimal area remained significantly smaller in the PES arm compared with the BMS arm. This late "catch-up" phenomenon has also been observed in other DES types. Aoki et al. (55) reported serial IVUS neointimal volume measurements at 2 and 4 years in 23 patients receiving SES. A modest, nonsignificant increase in neointimal volume occurred between 2 and 4 years. Furthermore, the 2-year angiographic and IVUS results of the SPIRIT II (Clinical Evaluation of the Xience V Everolimus Eluting Coronary Stent System in the Treatment of Patients With De Novo Native Coronary Artery Lesions) trial suggested a limited late neointimal "catch up" in the EES group (56). This increase in neointimal hyperplasia did not translate into higher TLR in the EES group. A recent study comparing SES, ZES, and a polymer-free dual DES (eluting probucol and sirolimus) showed similar efficacy in terms of angiographic binary restenosis at 6 to 8 months between the SES (12.0%) and dual DES (11.0%), both of which performed significantly better than the ZES (19.3%, $p = 0.003$). A modest late "catch up" in terms of restenosis and TLR was observed with the first-generation SES but not with the dual DES or the ZES (which still had higher cumulative late lumen loss) (57).

The precise reason for the late increase in neointimal hyperplasia in DES is still unclear, but it may be related to a delayed healing response, persistent biological reaction caused by the drug soon after implantation, or a hypersensitivity reaction to durable polymer. Further study is warranted to investigate the clinical relevance of this persistent neointimal growth and establish the appropriate length of follow-up after DES implantation.

Morphologic Patterns

Both the incidence and angiographic patterns of restenosis differ between DES and BMS ISR. Table 5 shows morphologic patterns of ISR in SES, PES, and BMS. The predominant restenosis patterns in BMS are nonfocal types. Angiographic restenosis patterns following different types of DES may not be identical. The most frequent restenosis pattern after SES is focal, and the majority of ISR after PES is also focal (9,21,23,58–63). Interestingly, DES ISR patterns in the randomized SIRIUS (Sirolimus-Eluting Stent in Coronary Lesions) and TAXUS IV trials are relatively more often focal compared with DES ISR patterns in observational studies. These differences might be explained by the fact that patients included in the randomized trials had relatively less complex lesions.

Prognostic implications of morphologic patterns of ISR. After BMS implantation, the classification of angiographic patterns of ISR has important prognostic significance (3). After DES implantation, the morphologic pattern of DES ISR remains an important predictor of clinical outcomes after ISR treatment (23,64). Cosgrave et al. (64) reported the rate of ISR recurrence following previous successful DES ISR treatment to be 18% in the focal group and 51% in the nonfocal group; the incidence of TLR at a median of 14 months was 10% and 23%, respectively. Rathore et al. (23) reported that a focal pattern of SES ISR was an independent predictor of lower recurrent restenosis rate,

Table 5 Morphologic Pattern of SES, PES, and BMS ISR

Study/First Author (Ref. #)	Year	SES			PES			BMS		
		n	Focal	Nonfocal	n	Focal	Nonfocal	n	Focal	Nonfocal
Randomized trials										
SIRIUS	2004	31	83.9%	16.1%	—	—	—	128	43.0%	57.0%
TAXUS IV	2004	—	—	—	16	62.5%	37.5%	65	30.8%	69.2%
Observational studies										
Lemos et al. (59)	2003	20	75.0%	25.0%	—	—	—	—	—	—
Colombo et al. (62)	2003	14	100.0%	0.0%	—	—	—	—	—	—
Iakovou et al. (60)	2005	—	—	—	98	50.0%	50.0%	—	—	—
Corbett et al. (61)	2006	150	71.3%	28.7%	149	51.7%	48.3%	—	—	—
Park et al. (21)	2007	97	76.3%	23.7%	80	51.3%	48.7%	—	—	—
Kitahara et al. (63)	2009	124	79.0%	21.0%	—	—	—	—	—	—
Rathore et al. (23)	2010	487	47.0%	53.0%	—	—	—	351	19.3%	90.7%

BMS = bare-metal stent(s); ISR = in-stent restenosis; PES = paclitaxel-eluting stent(s); SES = sirolimus-eluting stent(s).

with a hazard ratio of 0.47 in a cohort of 351 patients treated for SES ISR.

Clinical Approach and Treatment Options

The optimal treatment for DES restenosis remains undefined. The variety of treatment options (conventional balloon angioplasty, cutting or scoring balloon, drug-eluting balloon, BMS, same DES, different DES, vascular brachytherapy [VBT], or bypass surgery) and the variable etiologies of DES restenosis make it difficult for interventional cardiologists to determine the optimal therapy for this condition, except for the almost uniform avoidance of VBT. So far only 1 randomized clinical trial investigating the treatment of DES ISR has been published. Many observational studies have evaluated clinical and angiographic outcomes after percutaneous treatment for DES restenosis. However, the numbers of enrolled patients in these studies have been too small, the treatment modalities too diverse, and the results too inconsistent to draw any definitive conclusions about the optimal treatment of DES ISR (Table 6) (20,22,23,64–75).

An intravascular imaging technique (ultrasound being the most common) may reveal the mechanism of DES ISR in a specific case and guide further therapy. From a technical point of view, a larger high-pressure balloon may be useful in ISR cases owing to original stent underexpansion. A common technical problem of balloon angioplasty in ISR is the slippage during inflation, which can be avoided with use of a cutting or scoring balloon; however, the cutting or scoring balloon may in turn be somewhat more difficult to deliver in distal areas through stented segments. Drug-eluting balloons provide the theoretic advantage of avoiding

Table 6 Clinical and Angiographic Outcomes After Percutaneous Treatment of DES ISR

Study/First Author (Ref. #)	Year	No. of Lesions	Type of DES	Follow-up Duration	TLR	Angiographic Restenosis	Treatment Modalities Used
Randomized trial							
ISAR-DESIRE 2	2010	450	SES	6–8 months	16.7%	18.0%	PES 50%, SES 50%
Observational studies							
Lemos et al. (68)	2004	24	SES	9.3 months	20.8%	42.9%	BA 11%, BMS 4%, PES 41%, SES 44%
Moussa et al. (70)	2006	22	SES	12 months	23.0%	N/A	BA 13.5%, BMS 82%, VBT 4.5%
Lee et al. (67)	2006	140	SES	7.2 ± 1.8 months	14.0%	N/A	PES 100%
Torguson et al. (71)	2006	111	PES 22%, SES 78%	8 months	13.5%	N/A	PES 11%, SES 34%, VBT 55%
Kim et al. (66)	2006	58	PES 47%, SES 53%	12 months	5.2%	16.7%	BA 19%, SES 57%, VBT 24%
Cosgrave et al. (64)	2006	250	PES 34%, SES 66%	9 months	14.4%	28.4%	BA 38%, DES 62%
Mishkel et al. (69)	2007	108	SES, PES	15 ± 6 months	28.2%	N/A	BA 1%, BMS 18%, DES 80%, VBT 1%
Garg et al. (65)	2007	116	SES, PES	12 months	15.7%	N/A	SES, PES
Solinas et al. (20)	2008	152	PES 22%, SES 78%	12 months	8.3%	N/A	BA 16%, DES 84%
Bonello et al. (72)	2008	122	N/A	12 months	10.0%	N/A	VBT
Chatani et al. (73)	2009	140	SES	2 yrs	33.7%	32.5%	OTHER 35%, PES 22%, SES 43%
Steinberg et al. (22)	2009	119	N/A	12 months	22.2%*	N/A	DES
Rathore et al. (23)	2010	351	SES	9 months	37.0%*	41.1%	BA 67%, BMS 1%, PES 5%, SES 17%
Tagliareni et al. (75)	2010	252	PES 39%, SES 57%, ZES 4%	23 ± 10 months	11.8%	N/A	BA 53%, DES 47%
Singh et al. (74)	2010	319	N/A	3.2 yrs	15.0%	N/A	N/A

*These rates are for target *vessel* revascularization.

BA = balloon angioplasty; DES = drug-eluting stent(s); TLR = target lesion revascularization; VBT = vascular brachytherapy; ZES = zotarolimus-eluting stent(s); other abbreviations as in Table 5.

new stent implantation in cases of excess neointimal proliferation as the dominant cause of ISR.

DES or cutting/scoring balloon angioplasty for DES restenosis. Clinical and angiographic results with DES for BMS restenosis were superior to those from conventional therapy (balloon angioplasty or VBT) in several randomized trials (76–78). DES are also currently the most popular retreatment modality for DES restenosis, particularly of the focal type, because of immediate feasibility and safety. Several observational studies compared the clinical or angiographic effect of repeat-DES placement with that of other therapies (66,69,71). Kim et al. (66) (n = 58) reported significantly lower 6-month restenosis rates after new SES treatment (4%) compared with 35% with conventional treatment (cutting balloon angioplasty or VBT). Mishkel et al. (69) reported similar results in 108 DES failure lesions. The 1-year TLR rate was 29% in patients given the same DES, 19% with a different DES, and 37% with conventional (cutting balloon angioplasty, BMS, or VBT) treatments. A recent observational study (n = 211) reported no differences in TLR rates at a mean follow-up period of 2 years between repeat DES and balloon angioplasty (75). However, patients in the repeat DES group more often had a diffuse pattern of restenosis at baseline. A well-targeted, small, randomized study was recently conducted on 197 DES patients with ISR (79). The investigators assigned the patients (original DES were 55% SES and 45% PES) to treatment with either SES or balloon angioplasty alone, and reported a trend toward lower target lesion revascularization with SES (5.9% vs. 13.1%, p = 0.097); switching the type of DES implanted (relative to the original one) did not appear to confer any significant benefit or risk. However, these initial results are subject to the limitations of the predominantly focal type ISR and the small sample size of this study. Notably, no randomized studies to date have compared DES retreatment with bypass surgery or cutting/scoring balloon angioplasty.

Same DES or different DES. One of the etiologies of DES restenosis is drug resistance. Therefore, the placement of a DES eluting a different drug might more effectively treat DES restenosis than an identical DES. Few studies have investigated same or different DES implantation for DES restenosis; in general, these studies have compared SES versus PES. To date, there have been no reports on the use of ZES, EES, or biolimus A9–eluting stents. The ISAR-DESIRE (Intracoronary Stenting and Angiographic Results: Drug Eluting Stents for In-Stent Restenosis) trial randomized 450 patients with SES restenosis to treatment with a same DES (homo-DES) or a different DES (hetero-DES [i.e., PES]) (80). The mean lesion lengths were 12.7 and 12.5 mm, respectively, and the majority of patients had a focal pattern of restenosis (65% and 61%, respectively). No significant differences were observed in terms of in-stent late lumen loss at 6 to 8 months' follow-up (0.40 ± 0.65 mm vs. 0.38 ± 0.59 mm) or in 1-year clinical end points of TLR (17% vs. 15%), death/MI (6.1% vs. 5.8%), and stent thrombosis (0.4% in both groups).

These results may reflect that focal ISR might not be due to drug resistance but rather to a gap, injury zone mismatch, fracture, localized imperfect drug elution, polymer disruption during device delivery, or their combinations. Diffuse ISR has a greater chance to be due to drug resistance, and perhaps future studies with alternate DES treatment should focus solely on the diffuse ISR pattern.

VBT. A small number of observational studies have investigated the use of VBT as a treatment option for DES ISR (71,72). Torguson et al. (71) reported a significantly lower rate of a composite end point of death, MI, or target vessel revascularization at 8 months in patients treated with VBT relative to patients treated with DES for DES ISR. However, the investigators did not use a multivariate model to adjust for possible confounders in this retrospective study. Moreover, because of high rates of late restenosis and logistic issues, the use of VBT has declined in recent years, and most hospitals no longer possess the necessary set-up (81).

Coronary artery bypass graft surgery. The variability of the results of interventional treatment of DES ISR necessitates the consideration of coronary artery bypass graft surgery as a treatment option in complex cases (e.g., multivessel DES with multivessel ISR, especially diffuse or even single-vessel ISR at a very critical lesion location).

Although not specifically outlined in any guideline document, a patient treated with a new DES for ISR should be considered high risk and should continue on dual antiplatelet therapy unless a complication emerges. Therefore, the track record of dual antiplatelet adherence until ISR development is also important because any complication or noncompliance issues may preclude further interventional treatment options and favor coronary artery bypass graft selection.

Future Directions

Several randomized trials investigating treatment strategies for DES ISR are currently ongoing. The randomized GISE-CROSS (DES Crossover for In-Stent Restenosis) trial is evaluating same versus different DES as alternate therapies for DES restenosis. Moreover, 2 Korean multicenter trials are currently enrolling patients. The DES-ISR trial is evaluating the relative efficacy of PES and SES for diffuse DES ISR, and the FOCUS (Focal In-Stent Restenosis After Drug-Eluting Stent) trial compares cutting balloon angioplasty with SES for focal DES ISR.

The drug-eluting balloon is another novel promising modality to treat DES ISR. The theoretic advantage of a drug-eluting balloon over DES could be that it allows for delivery of an antirestenotic agent without adding a second layer of metal. The drug-eluting balloon has been shown to be effective in the treatment of BMS ISR (82,83). The PEPCAD-DES (Treatment of DES In-Stent Restenosis With SeQuent Please Paclitaxel Eluting PTCA Catheter)

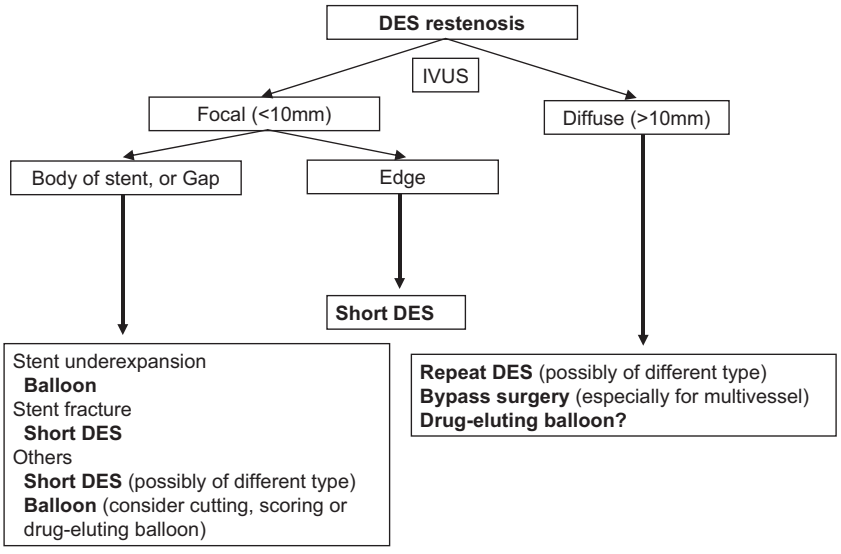

Figure 3 Algorithm for the Treatment of DES Restenosis

DES = drug-eluting stent(s); IVUS = intravascular ultrasound.

trial is currently recruiting patients to investigate the efficacy of a paclitaxel-eluting balloon for the treatment of DES ISR.

Proposed Clinical Approach Algorithm

It is important to consider that therapeutic options for DES restenosis are somewhat controversial because there are few data comparing interventional modalities (balloon, cutting balloon, scoring balloon, drug-eluting balloon, BMS, same DES, different DES, or VBT) with surgery. Therefore, we recommend that treatment of DES restenosis be "individualized" using IVUS analysis to clarify the etiologic mechanism. Figure 3 depicts a proposed algorithm for the current approach to DES restenosis.

Conclusions

DES result in reduced rates of restenosis compared with BMS across all lesion and patient subsets. Angiographic coronary restenosis rates after DES implantation have fallen below 10% in several randomized trials. However, this rate increases when complex lesions are treated. Although predictors of restenosis after BMS deployment—such as diabetes mellitus, small vessels, and stenting long lesions—are still significant in the era of DES, the morphologic pattern of restenosis is different following BMS versus DES implantation. The predominant pattern of angiographic restenosis is focal, and this pattern is related to better prognosis. However, a diffuse pattern type still exists and is associated with a high incidence of restenosis recurrence. In addition, the issues of delayed restenosis and the mechanisms of restenosis with DES have not been fully investigated with these devices. Further detailed studies are warranted to understand the development of restenosis in DES and its precise treatment. We anticipate that these studies will become more complex with the emergence of new types of DES.

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Key Words: drug-eluting stent(s) ■ in-stent restenosis ■ target lesion revascularization.