Prognostic factors in primary and elective percutaneous coronary intervention
Claessen, B.E.P.M.

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Chapter 23

In-Stent Restenosis in the Drug-Eluting Stent Era

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Dangas GD, Claessen BE, Caixeta A, Sanidas EA, Mintz GS, Mehran R
ABSTRACT

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 (PCI). However, the rapid implementation of DES in standard practice and expansion of the indications for PCI to high risk patients and complex lesions also introduced a new problem: DES in-stent restenosis (ISR), which occurs in 3-20% 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 an 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 mechanisms and in selecting treatment modalities. Based upon the current available evidence, an algorithm for the treatment approaches to DES restenosis is proposed.
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 since 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 pathophysiological mechanisms, clinical presentation, morphological patterns and management options of DES ISR.

**DEFINITION**

Restenosis, or reduction in lumen diameter after percutaneous coronary intervention, 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 (ARC). 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 paper, it is important to distinguish it from ISR. Stent thrombosis frequently presents as myocardial infarction, while ISR can present as myocardial infarction in a small minority of cases.\(^8\) The ARC 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 less than 6% of patients.\(^9,\,10\) After these promising initial 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 above 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) aiming to minimize the incidence of DES ISR and improve 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, myocardial infarction, and stent thrombosis.\(^16,\,17\)
Clinical Presentation

While 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 (26-53%). Moreover, depending on the definitions applied, BMS ISR presented as myocardial infarction (MI) in 3.5-20% of patients.

The presentation of DES ISR is similar to that of BMS ISR with approximately 16%-66% of patients presenting with unstable angina and 1-20% with MI.

The mechanism of late MI associated with ISR is multifactorial. First, a silent occlusive restenosis can be difficult to differentiate from a thrombotic event. In addition, a highly stenotic ISR lesion may also promote local non-occlusive thrombosis and lead to a clinical presentation of non-ST-elevation MI.
or a troponin positive unstable coronary syndrome. Based upon the wide variety in definitions and reported incidence of unstable angina and MI, it is impossible definitively to confirm or reject that ISR is indeed a benign phenomenon; a spectrum of the acuity of clinical presentation exists.\textsuperscript{20-23} Certain studies reported biomarker positive acute coronary syndrome (ACS) as presentation of ISR to be a predictor for further adverse events after treatment of ISR.\textsuperscript{23, 24} In contrast, an observational study by Steinberg et al. showed no differences in the occurrence of subsequent adverse events after treatment of ISR in patients presenting with ACS versus patients presenting with recurrent exertional angina.\textsuperscript{25}

Of note, in the BMS era ISR has been reported to occur at an average of 5.5 months after the stent implantation, with a shorter interval for patients presenting with MI than those presenting with recurrent angina.\textsuperscript{26} Furthermore, diffuse ISR was also more frequent in MI patients and correlated with early ISR presentation.\textsuperscript{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 showed that the mean time from PCI to ISR detection was approximately 12 months.\textsuperscript{27} The time frame to restenosis after DES may indeed be longer than after BMS because antiproliferative drugs can delay the biological response to injury.

### Pathophysiologic Mechanisms

The clinical effect of a DES is highly dependent on its components: the stent platform, the active pharmacologic compound, and the drug carrier. DES technology enables anti-inflammatory, immuno-modulatory, and/or anti-proliferative 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).

#### Biological Factors

**Drug resistance.** Sirolimus and its analogues have a cytostatic effect. They inhibit the function of the mammalian target of rapamycin (mTOR) and suppress smooth muscle cell migration and proliferation by arresting the cell cycle in the G1 phase.\textsuperscript{28} Paclitaxel has a cytotoxic effect, binding specifically to the β-tubulin subunit of microtubules, and its principle action is to interfere with microtubule dynamics, preventing their depolymerization.\textsuperscript{28} Recent data indicate that genetic mutations can influence the sensitivity to these drugs, conferring resistance to sirolimus, its analogs, or paclitaxel.\textsuperscript{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 a potential triggering mechanisms for in-stent restenosis. The platform material used in many novel DES (but not in the widely used paclitaxel-eluting stent [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, as DES consist of 3 components (the stent platform, the anti-restenotic drug, and the polymer carrying the drug) the hypersensitivity reactions can be caused by any one of these components. In the Research on Adverse Drug/Device events And Reports (RADAR) project, 5,783 reports of adverse events after DES placement collected by the FDA were analyzed, and 261 reports described hypersensitivity reactions. Subsequently, 17 patients were identified in which the DES themselves appeared to be a probable cause of hypersensitivity. 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. This 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 (Figure 1). Stent underexpansion may be undetectable angiographically in many cases; a suspicion may be raised in an area of fluoroscopically underexpanded stent struts (compared to 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 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. excellent expansion is evident when the minimum lumen area in the stent ≥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. a 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. However, a recent study by Steinberg et al. found no association between early or late incomplete stent apposition and stent thrombosis in 1,580 patients enrolled in IVUS substudies of various TAXUS clinical trials. Since both malapposition and underexpansion are affecting selected regions of a stent, it is entirely possible that they coexist in two separate sites of the same stent (e.g. proximal struts can be malapposed due to large and tortuous proximal reference site, while the mid-stent area at the original lesion site can be underexpanded).

**Non-uniform Drug Distribution.** The effectiveness of local drug delivery requires transmural and circumferential distribution across and within the vessel walls. Physiological and computational models have shown that local blood flow alterations, strut overlap, and polymer damage may hamper the uniformity of drug elution. Treating lesions in noncompliant vessels not only increases the odds of stent underexpansion, but difficult device delivery may also 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 non-uniform/circular stent expansion) may produce focal areas within the stented segment with less than optimal drug distribution and contribute to increased ISR risk.\textsuperscript{40-42} Achieving drug-elution not only from the metallic stent, but also 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.\textsuperscript{43} Not only does it eliminate the metal scaffolding support at the specific site, but it also 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 non-uniform stent expansion in a highly mobile and hard arterial area that ultimately separated the stent (Figure 2). By IVUS, partial stent fracture is defined by the absence of at least one third or 120 degrees of stent struts for at least one frame; complete stent fracture is defined by the complete absence of stent struts within the stented segment for at least one frame.\textsuperscript{43} Furthermore, a number of classification systems for the severity of stent fracture have been proposed (Table 3).\textsuperscript{44-46} The incidence of DES fracture has been reported to range from 1-8\%.\textsuperscript{47-49} The need for subsequent revascularization in fractured stents has been reported to range from 15-60% in these relatively small studies.\textsuperscript{47-49} Right coronary artery lesions, excessive tortuosity, angulation and torsion of the vessel, overlapping stents, longer stents, and SES due to its rigid closed-cell structure have been associated with an increased risk of stent fracture.\textsuperscript{47-49}

**Figure 1** Stent underexpansion

The white arrow in panel A shows a mid left anterior descending coronary artery lesion after stent implantation. Panel B shows the IVUS imaging of the distal reference lumen diameter, which measured 6.8mm\textsuperscript{2}. Panel C shows the intravascular ultrasound imaging of the underexpanded stent in the treated lesion, which shows well-apposed stent struts but a small stent cross sectional area of only 3.1mm\textsuperscript{2}; the vessel diameter is almost double the stent diameter.
Technical factors

**Barotrauma outside the 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. 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 two DES typically occurs in a zone of balloon injury due to either pre- or post-dilatation. 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 above, short stent gaps should be avoided.

**Residual uncovered atherosclerotic plaques**

The prospective evaluation of the impact of Stent deployment Techniques on clinical outcomes...
of patients treated with the cypheR stent (STLLR trial) evaluated the frequency of suboptimal PCI and its impact on the long-term outcomes of 1,557 patients treated with SES. 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 TVR and MI at 1 year. Therefore, the risk and cost of implanting additional DES in such cases should be weighted 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). Considering that post-procedural minimal lumen diameter is a major factor in restenosis, obtaining optimal acute angiographic results after DES implantation remains important.

**The issue of 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. Whereas a modest late decrease of 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. reported serial IVUS neointimal volume measurements at 2 and 4 years in 23 patients receiving a SES. A modest, non-significant increase in neointimal volume occurred between 2 and 4 years. Furthermore, the 2 year angiographic and IVUS results of the SPIRIT II trial, comparing the EES with the PES in de novo coronary artery lesions, suggested a limited late neointimal ‘catch-up’ in the EES group. 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 6-8 months between the SES (12.0%) and the 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).

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

| Table 3 Stent Fracture Classification Methods |
|-------------------------------|-----------------|------------------|
| **Type** | Popma et al. | Allie et al. | Scheinert et al. |
| 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 the stent Complete transverse stent fracture | Multiple single stent fractures occurring at different sites Multiple single stent fractures resulting in complete transverse linear fracture but without stent displacement Complete transverse linear type 3 fracture with stent displacement | Moderate: fracture >1 strut Severe: complete separation of stent segments |
| 3 | Complete transverse stent fracture with abundant movement and displacement of fractured fragments of more than 1 mm during the cardiac cycle | | |
| 4 | Complete transverse stent fracture | | |
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.

Morphological Patterns
Both the incidence and angiographic patterns of restenosis differ between DES and BMS ISR. Table 5 shows morphological patterns of ISR in SES, PES, and BMS. The predominant restenosis patterns in BMS are non-focal 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.\textsuperscript{9,21,23,58-63} Interestingly, DES ISR patterns in the randomized SIRIUS and TAXUS IV trials are relatively more often focal compared to 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.\textsuperscript{3} After DES implantation, the morphologic pattern of DES ISR remains an important predictor of clinical outcomes after ISR treatment.\textsuperscript{23,64} Cosgrave et al., reported the rate of ISR recurrence following previous successful DES ISR treatment to be 18% in the focal group and 51% in the non-focal group; the incidence of TLR at a median of 14 months was 10% and 23%, respectively.\textsuperscript{64} Rathore et al. reported that a focal pattern of SES ISR was an independent predictor of lower recurrent restenosis rate with a hazard ratio of 0.47 in a cohort of 351 patients treated for SES ISR.\textsuperscript{23}

Clinical Approach and Treatment Options
The optimal treatment for DES restenosis remains undefined. The variety of treatment options

**Table 5** Morphological pattern of SES PES and BMS in-stent restenosis

<table>
<thead>
<tr>
<th>Randomized trial</th>
<th>Year</th>
<th>N</th>
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<th>Non-Focal</th>
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<tr>
<td>SIRIUS</td>
<td>2004</td>
<td>31</td>
<td>83.9%</td>
<td>16.1%</td>
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<td>TAXUS IV</td>
<td>2004</td>
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<table>
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<tr>
<th>Observational studies</th>
<th>Year</th>
<th>N</th>
<th>Focal</th>
<th>Non-Focal</th>
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<tr>
<td>Lemos et al.</td>
<td>2003</td>
<td>20</td>
<td>75.0%</td>
<td>25.0%</td>
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<tr>
<td>Colombo et al.</td>
<td>2003</td>
<td>14</td>
<td>100.0%</td>
<td>0.0%</td>
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<tr>
<td>Iakovou et al.</td>
<td>2005</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Corbett et al.</td>
<td>2006</td>
<td>150</td>
<td>71.3%</td>
<td>28.7%</td>
</tr>
<tr>
<td>Park et al.</td>
<td>2006</td>
<td>97</td>
<td>76.3%</td>
<td>23.7%</td>
</tr>
<tr>
<td>Kitahara et al.</td>
<td>2009</td>
<td>124</td>
<td>79.0%</td>
<td>21.0%</td>
</tr>
<tr>
<td>Rathore et al.</td>
<td>2010</td>
<td>487</td>
<td>47.0%</td>
<td>53.0%</td>
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</table>

SES= Sirolimus-eluting stent, PES= Paclitaxel-eluting stent, BMS= Bare metal stent
(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 makes it difficult for interventional cardiologists to determine the optimal therapy for this condition except the almost uniform avoidance of VBT. Until now, only one 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 technical point of view, a larger high pressure balloon may be very useful in ISR cases due 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, which may in turn be somewhat more difficult to deliver in distal areas through stented segments. Drug-eluting balloons provide the theoretical advantage of avoiding a new stent implantation in case 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 re-treatment modality for DES restenosis, particularly of the focal type, due to immediate feasibility and safety. Several observational studies compared the clinical or angiographic effect of repeat-DES placement to other therapies.66, 69, 71 Kim et al. (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).66 Mishkel et al. reported similar results in 108 DES failure lesions.69 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. Notably, no randomized studies to date have compared DES re-treatment to 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

<table>
<thead>
<tr>
<th></th>
<th>PES</th>
<th>BMS</th>
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<tbody>
<tr>
<td>N</td>
<td>Focal</td>
<td>Non-Focal</td>
</tr>
<tr>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>16</td>
<td>62.5%</td>
<td>37.5%</td>
</tr>
<tr>
<td>N</td>
<td>Focal</td>
<td>Non-Focal</td>
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<td>-</td>
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<tr>
<td>98</td>
<td>50.0%</td>
<td>50.0%</td>
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<tr>
<td>149</td>
<td>51.7%</td>
<td>48.3%</td>
</tr>
<tr>
<td>80</td>
<td>51.3%</td>
<td>48.7%</td>
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In general, these studies have compared SES vs. PES; to date, there have been no reports on the use of ZES, EES, or BES. The “Intracoronary Stenting and Angiographic Results: Drug Eluting Stents for In-stent REstenosis” (ISAR-DESIRE) trial randomized 450 patients with SES restenosis to treatment with a same DES (homo-DES) or a different DES (hetero-DES, i.e. PES).

The mean lesion length was 12.7mm and 12.5mm respectively, and the majority of patients had a focal pattern of restenosis (65%, 61%). No significant differences were observed in terms of in-stent late lumen loss at 6-8 months follow-up (0.40±0.65mm vs. 0.38±0.59mm), nor in 1-year clinical endpoints TLR (17% vs. 15%), death/myocardial infarction (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 greater chance to be due to drug resistance, and perhaps future studies with alternate DES treatment should focus solely on diffuse ISR pattern.

Vascular Brachytherapy.

A small number of observational studies investigated the use of VBT as a treatment option for DES ISR. Torguson et al. reported a significantly lower rate of a composite endpoint of death, myocardial infarction, or TVR 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, due to high rates of late restenosis and logistical issues, the use of VBT has declined in recent years and most hospitals no longer possess the necessary set-up.

Coronary Artery Bypass Graft Surgery

The variability of the results of interventional treatment of DES ISR necessitates the consideration of CABG 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
Table 6

<table>
<thead>
<tr>
<th>TLR</th>
<th>Angiographic restenosis</th>
<th>Treatment modalities used</th>
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<tr>
<td>16.7%</td>
<td>18.0%</td>
<td>PES 50%, SES 50%</td>
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<tr>
<td>20.8%</td>
<td>42.9%</td>
<td>BMS (4%), BA (11%), SES (44%), PES (41%)</td>
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<td>23.0%</td>
<td>n/a</td>
<td>BMS (82%), BA (13.5%), VBT (4.5%)</td>
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<td>14.0%</td>
<td>n/a</td>
<td>PES (100%)</td>
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<td>13.5%</td>
<td>n/a</td>
<td>VBT (55%), SES (34%), PES (11%)</td>
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<tr>
<td>5.2%</td>
<td>16.7%</td>
<td>SES (57%), VBT (24%), BA (19%)</td>
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<td>14.4%</td>
<td>28.4%</td>
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<td>DES (80%), BMS (18%), BA (1%), VBT (1%)</td>
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<td>15.7%</td>
<td>n/a</td>
<td>SES, PES</td>
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<td>8.3%</td>
<td>n/a</td>
<td>DES (84%), BA (16%)</td>
</tr>
<tr>
<td>10.0%</td>
<td>n/a</td>
<td>VBT</td>
</tr>
<tr>
<td>33.7%</td>
<td>32.5%</td>
<td>SES (43%), PES (22%), Other (35%)</td>
</tr>
<tr>
<td>22.2%*</td>
<td>n/a</td>
<td>DES</td>
</tr>
<tr>
<td>37.0%</td>
<td>41.1%</td>
<td>BA (67%), SES (17%), PES (5%), BMS (1%)</td>
</tr>
<tr>
<td>11.8%</td>
<td>n/a</td>
<td>DES (47%), BA (53%)</td>
</tr>
<tr>
<td>15.0%</td>
<td>n/a</td>
<td>n/a</td>
</tr>
</tbody>
</table>

brachytherapy, ZES= Zotarolimus-eluting stent
* these rates are target vessel revascularization

DES for ISR should be considered high risk and continued on dual antiplatelet therapy unless a complication emerges. Therefore, the track record of dual antiplatelet adherence until the ISR development is also important, since any complication or non-compliance issues may preclude further interventional treatment options and favor CABG selection.

**Future Directions**

Several randomized trials investigating treatment strategies for DES ISR are currently ongoing. The randomized GISE-CROSS trial is evaluating same vs. different DES as alternate therapies for DES restenosis. Moreover, two Korean multicenter trials are currently enrolling patients; The DES-ISR trial evaluates the relative efficacy of PES and SES for diffuse DES ISR, while the FOCUS trial compares cutting balloon angioplasty with SES for focal DES ISR. Finally, the CRISTAL trial compares SES and balloon angioplasty for the treatment of DES or BMS ISR.

The drug-eluting balloon is another novel promising modality to treat DES ISR. The theoretical 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. The PEPCAD-DES 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 as there are few data comparing interventional modalities (balloon, cutting balloon, scoring balloon, drug-eluting balloon, BMS, same DES, different DES, or VBT) to surgery. Therefore, we recommend that treatment of DES restenosis be “individualized” using IVUS analysis to clarify the etiological mechanism. Figure 3 depicts a proposed algorithm for the current approach to DES restenosis.
CONCLUSIONS

DES result in reduced rates of restenosis compared to 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 treating complex lesions. Whereas 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 vs. 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.

Reference List


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