

Management of In-Stent Restenosis After DES Use

Insights on current mechanisms and strategies for treatment.

BY VINEET BHATIA, MD, DM, DNB, MNAMS,

AND UPENDRA KAUL, MD, DM, FCSI, FSCAI, FACC, FAMS

Percutaneous coronary interventional techniques have dramatically matured during the past several decades. The need of urgent coronary artery bypass surgery (CABG) was largely laid to rest after the introduction of bare-metal stents (BMS) in the 1990s. Technical refinements helped to vastly expand the indications for use of these stents, benefiting millions of patients. However, the one feature that frustratingly failed to change was the rate of in-stent restenosis (ISR), which is often considered the Achilles' heel of angioplasty. At this time, rates of ISR were as high as 30% with BMS, especially in diabetic patients or in those who had small vessels and/or long lesions. Attempts were made to conquer ISR using different stent platforms, coatings, debulking devices, and brachytherapy, but nothing seemed to work.

The menace of restenosis seemed to have been largely tamed once drug-eluting stents (DES) were introduced in early 2000. Data from the randomized trials of DES revealed the rate of angiographic ISR to be in the single digits.¹ These encouraging data led to widespread use of DES in coronary interventions. As more complex cases were included, it became apparent that the rate of ISR with DES was much higher than initial trials had revealed—varying into the double digits, with rates as high as 20%.^{2,3}

However, by this time, the concept of “DES for all” seemed to be gaining popularity.

By early 2006, DES were used in approximately 90% of interventions in developed nations.⁴ Similar trends have been noted in developing nations. Data showed that of the total stents implanted in India in 2005, 53.75% were DES, and in 2006, this had reached a phenomenal figure of 72%.⁵ Thus, although restenosis rates with DES were lower as compared to BMS, their rampant usage led to a considerable and unique population subset that present-

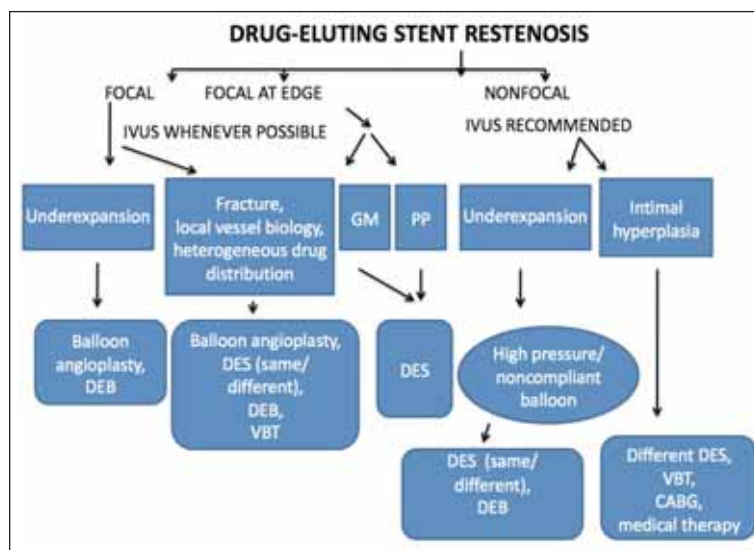


Figure 1. Algorithm depicting treatment of DES ISR (GM = geographical miss; PP = plaque progression; VBT = vascular brachytherapy).

ed with a complex problem of DES ISR. By this time, another problem unique to DES (late stent thrombosis) was highlighted. This led the US Food and Drug Administration Advisory Panel to urge interventional cardiologists to restrict DES usage to on-label situations in 2007.⁴ Since then, the situation has somewhat stabilized. In developed nations, DES use decreased to 60% and is presently approximately 70%.⁴ DES in India use was 59% in 2007.⁶

In this article, we will highlight the mechanisms involved in DES ISR and the various modalities available for its treatment. All references made to sirolimus-eluting stents (SES) and paclitaxel-eluting stents (PES) pertain to the Cypher (Cordis Corporation, Bridgewater, NJ) and Taxus (Boston Scientific Corporation, Natick, MA) stents, respectively.

CLINICAL PRESENTATION

Although some patients with ISR may be clinically silent, the majority present with recurrence of symptoms. As with BMS, the most common presentation in cases of ISR with DES is unstable angina (26%–53% and 16%–66% with Cypher and Taxus, respectively).⁷ Depending on the definitions applied, the incidence of BMS and DES ISR presenting as myocardial infarction is 3.5% to 20% and 1% to 20%, respectively.⁷ These rates show that ISR is not a benign phenomenon and that a wide spectrum of the acuity of clinical presentation exists.

Another feature that deserves mention is the average time to presentation. In BMS and DES, the mean time to ISR is 5.5 months⁷ and 12 months,⁸ respectively. This is thought to represent the “late catch-up phenomenon” that is seen with several types of DES. The delay in biological response to injury in DES in the form of cellular proliferation is slower, and the critical narrowing that produces reduction in blood flow appears later. This may explain the later presentation of ISR in patients with DES.

MECHANISMS OF DES RESTENOSIS

The mechanisms of DES restenosis can be broadly classified into three factors: biological, mechanical, and technical.

Biological Factors

Drug resistance. Drugs used in DES work on different stages of the cell cycle. Genetic mutations may influence the sensitivity to these drugs, leading to a resistance to sirolimus, its analogs, or paclitaxel. Sirolimus resistance is thought to be caused by receptor mutations and down-regulation of transcription proteins.⁹ Although a wide variety of resistance mechanisms lead to paclitaxel resistance,¹⁰ the most important is overexpression of the mul-

tidrug resistance (MDR-1) gene. Problems related to the MDR-1 gene have been shown to be associated with increased late loss in paclitaxel-eluting stents.¹¹

Hypersensitivity. The stent platform in BMS and first-generation DES is 316L stainless steel, which releases nickel and molybdenum ions. Allergic reactions to these ions may play a role in initiating ISR.¹² Newer BMS and DES have largely shifted to cobalt chromium stent platforms due to technical advantages but have similar chemical compositions¹³ and ion release properties.

DES have been shown to lead to aneurysm formation at sites of implantation that are often complicated by thrombosis.⁷ Autopsy studies have shown predominantly eosinophilic infiltrates pointing toward localized hypersensitivity. This may be secondary to one of the various components of the DES, as shown in data from the RADAR (Research on Adverse Drug Events and Reports) project.¹⁴

Serum matrix metalloproteinase activity and genetics. Circulating serum matrix metalloproteinase (MMPs) (especially MMP-2 and 9) has been shown to be helpful in identifying the patients who are at risk of DES ISR.¹⁵ MMPs are released in response to injury and play a role in healing after mechanical injury. Low levels of these MMPs were associated with no significant intimal hyperplasia.¹⁶

Certain genetic polymorphisms (homozygosity of the 16/glycine variant in the beta 2-adrenergic receptor and two functional polymorphisms of interleukin-8) are linked to inflammatory responses that may lead to ISR.¹⁷ Currently, these polymorphisms are rare and have limited clinical application.

Mechanical Factors

Intravascular ultrasound (IVUS) has been fundamental in helping us to understand the various mechanical factors associated with DES ISR.

Stent underexpansion. Stent underexpansion is a condition in which the stent is not properly expanded during implantation. Such underexpansion is best detected using IVUS. On IVUS, the stent cross-sectional area at the site of underexpansion is much lower than the stent cross-sectional area at other sites within the same stent and is smaller than the reference lumen area. According to criteria by de Jaegere et al, excellent expansion is evident when the lumen area in the stent is $\geq 90\%$ of the average reference lumen area.¹⁸

A condition that needs to be differentiated from underexpansion is stent malapposition (due to use of

undersized stents in tortuous vessels or due to positive remodeling). Stent malapposition does not predispose to stent thrombosis.¹⁹

Stent overexpansion. Stent overexpansion may lead to stent strut fracture or polymer disruption, which may impair homogenous drug delivery and may, theoretically, promote restenosis.²⁰ This hypothesis, though attractive, currently has no data to support it. With the availability of a greater range of stent sizes, the problem of overdilation will be of critical importance.

Nonuniform drug distribution. Drug delivery at the site of interest depends on a complex interplay of several factors. Local blood flow alterations, nonuniform distribution of stent struts, and polymer damage may jeopardize the uniformity of drug delivery. Delivering stents into difficult lesions may lead to underexpansion, stripping off the polymeric material with resultant compromised local drug elution. Nonuniform circumferential stent strut distribution may also affect local drug concentrations. Drug delivery into the arterial wall is also affected by the presence of local mural thrombi at the site where the stent is to be deployed. Also, clot geometry and composition have an impact on drug delivery.²¹ All of these factors have the potential to lead to nonuniform drug delivery and subsequent ISR.

Polymers in first-generation DES. The durable polymers used in both Cypher and Taxus stents have been reported to induce inflammation at different stages and could be a factor in producing fibrosis leading to ISR.

The second-generation DES, Xience V (Abbott Vascular, Santa Clara, CA), Promus (Boston Scientific Corporation), and Endeavor (Medtronic, Inc., Minneapolis, MN), are possibly safer in this regard. Thus, evolving data from bioabsorbable polymer stents seem to be encouraging.

Stent fracture. Stent fracture is defined as the presence of an angiographically visible interrupted connection of stent struts, or fewer visible stent struts, at the suspected site than a normal-looking stented area on IVUS and may be associated with ISR, which instead is most commonly a focal pattern. Various studies have reported the rates of DES fracture to be between 0.84% and 3.2%. In a recent study from Korea,²² the incidence of stent fracture was 0.89% for SES and 0.09% for PES. Chronic kidney disease, SES, higher maximal inflation pressure, and implantation in the right coronary artery were independent predictors of stent fracture. Also, stent fracture was associated with a higher rate of binary restenosis (11.4% vs 41.7%; $P < .001$)

and an increased risk of target lesion revascularization (TLR) (8.1% vs 33.3%; $P = .001$). When stent fracture was not associated with significant restenosis, the prognosis was good with medical follow-up.

The SES has a closed-cell design that helps to even drug distribution at the cost of the stent being more rigid and less deformable, thereby increasing shear stress and stent breakage. The PES has an open-cell design, as do the newer-generation stents (the zotarolimus-eluting Endeavor stent and the everolimus-eluting Xience V stent), and fewer reports of stent fracture are found with this stent design.

Technical Factors

Barotrauma outside stented segment/geographical miss. Geographical miss (GM) is essentially a failure to appropriately cover an injured vessel, as occurs after balloon-associated vessel barotrauma or incomplete coverage of atherosclerotic plaque. GM associated with SES implantation was investigated in the prospective evaluation of the impact of the STLLR study.²³ At 1-year follow-up, there was more than a twofold increase in target vessel revascularization (5.1% vs 2.5%; $P = .025$) and a threefold increase in myocardial infarction (2.4% vs 0.8%; $P = .04$) in patients with GM.

These findings were almost exclusively related to longitudinal GM (6.1% vs 2.6%; $P = .001$), with two-thirds of cases being secondary to balloon injury outside the stent margins. The lack of effect of axial GM (4.2% vs 4.3%; $P =$ nonsignificant) has recently been corroborated, showing that the balloon-to-artery ratio or the occurrence of edge dissections (potentially associated with axial GM) did not have a significant impact on the risk of restenosis and does perhaps argue against the IVUS optimization of DES deployment.^{24,25}

Stent gap. Stent gap causes discontinuous coverage with DES. A short gap between two DES typically occurs in a zone of balloon injury that is due to either predilation or postdilation. 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 previously described, short stent gaps should be avoided.²⁶

Predictors of ISR and TLR. Factors that are predictors of restenosis and TLR can be classified into patient-related, lesion-related, and procedure-related factors. Patient-related factors include patient age, female sex, diabetes, and multivessel coronary artery disease. Lesion-related factors are bypass grafts, chronic total occlusions, small vessels, calcified lesions, ostial lesions, and left anterior

descending artery lesions. Procedural characteristics predicting ISR are treatment of multiple lesions, type of DES, and final diameter stenosis.

Patterns of restenosis. In DES, the pattern of restenosis is most commonly focal. Proliferative and diffuse patterns are rare with SES but are seen more often with PES and zotarolimus-eluting stents. Cosgrove et al²⁷ recently analyzed the effect of the pattern of restenosis on therapeutic outcomes. When intervened upon, the rates of angiographic restenosis were 17.8% in the focal group and 51.1% in the nonfocal group ($P = .00001$). The incidence of TLR also increased with the type of restenosis treated (9.8% and 23%, respectively; $P = .007$). Also, diabetes mellitus emerged as the only clinical variable associated with the pattern of restenosis (28.8% for focal as compared with 52.9% for diffuse; $P = .0001$).

TREATMENT OF RESTENOSIS

Perhaps the greatest dilemma for an interventional cardiologist is how to treat a patient with DES ISR in the absence of any clear-cut guidelines. A treatment algorithm summarizing treatment of DES ISR is shown in Figure 1. The modalities available are the same as for BMS ISR (conventional balloon angioplasty, cutting or scoring balloons, drug-eluting balloons [DEB], BMS, same DES, different DES, vascular brachytherapy, or bypass surgery). Although many observational studies have been published, no definitive conclusions can be drawn due to small sample sizes and the diverse treatment modalities used. Only one randomized trial (ISAR-DESIRE 2) has been performed in patients with SES ISR.²⁸

Balloon Angioplasty

Limited success has been achieved using plain balloon angioplasty (PBA) and cutting balloon angioplasty (CBA) in DES ISR. Cutting balloons could only offer the advantage of nonslippage over conventional balloons. A recent Japanese study²⁹ compared the efficacy of PBA and CBA in treating DES ISR versus BMS ISR. The 252 ISR lesions in 224 consecutive patients treated by CBA ($n = 167$) or PBA ($n = 85$) were analyzed. At 6-month angiographic and 12-month clinical follow-up, CBA and PBA showed similar efficacies: repeat ISR (37% vs 37.8%; $P = .90$), late loss (0.62 ± 0.6 mm vs 0.61 ± 0.47 mm; $P = .92$), and TLR (18.3% vs 22.4%; $P = .50$).

This comparable efficacy was maintained for treatment in the DES ISR and BMS ISR subgroups. However, target lesion-related myocardial infarction ($n = 9$) occurred more frequently in the CBA arm than in the PBA arm (6.2% vs 0%; $P = .03$), most of which developed early after ISR treatment ($n = 7$; 54 ± 26 days).

Independent predictors of repeat ISR were diffuse ISR and smaller pretreatment minimal lumen diameter, both of which might imply heavier plaque burden in the ISR group.

The authors concluded that PBA and CBA for ISR seemed to be comparable because the angiographic or clinical endpoints were not affected by initial stent type but rather by parameters related to the plaque burden of the ISR lesion. However, CBA might be associated with a higher risk of myocardial infarction than PBA, suggesting more attention to dual-antiplatelet therapy after its use for ISR.

Several studies have compared balloon angioplasty versus repeat DES implantation for DES ISR. Kim et al³⁰ reported significantly lower 6-month restenosis rates after new SES (4%) as compared to conventional treatment (CBA or vascular brachytherapy). Mishkel et al³¹ also reported similar results in 108 DES failure lesions. The 1-year TLR rate was 29% in patients who were given the same DES, 19% in patients receiving a different DES, and 37% in patients undergoing conventional treatments.

Repeat DES Implantation Using the Same or Different Stents

One of the mechanisms of DES ISR is drug resistance; hence, the placement of a DES with a different drug seems to be a reasonable option. In the ISAR-DESIRE 2 trial,²⁸ 450 patients with clinically significant SES ISR were randomly assigned to either the same DES (SES) ($n = 225$) or a different DES (PES) ($n = 225$). The majority of cases had focal ISR (nearly 60%). The primary endpoint of the study (late lumen loss) was similar in both groups (mean, 0.4 ± 0.65 mm and 0.38 ± 0.59 mm, respectively; $P = .85$). Other surrogate angiographic parameters of antirestenotic efficacy, including minimal lumen diameter at follow-up (1.93 ± 0.73 mm vs 1.94 ± 0.70 mm), were also similar and translated into equivalent rates of target vessel revascularization (16.6% vs 14.6%). Safety data were also comparable, and rates of definite stent thrombosis (0.4%) were identical in the two arms.

These results indicate that focal ISR may not be due to drug resistance and that stent gap, strut fracture, localized imperfect drug elution, or polymer disruption seem to be the likely mechanisms. Switching over to a different DES may not prove beneficial. Diffuse DES ISR has a greater chance of being caused by drug resistance, and future studies with the same DES (ie, switch strategy) should focus on the diffuse ISR pattern.

The ISAR-DESIRE 2 trial is a landmark trial because it is the only well-planned and well-executed randomized controlled trial evaluating the switch concept. The study criteria helped recruitment of patients with complex dis-

ease patterns (occlusive and very diffuse disease requiring multiple DES), thus creating a population subset representing real-world patients. One of its few drawbacks is the failure to use IVUS while performing interventions. IVUS helps define the etiology of ISR, and thereby tailored therapies could be provided. Nowadays, IVUS is considered to be an integral part of planning and executing repeat intervention for DES ISR. Also, angiographic follow-up was carried out at 6 to 8 months.

After DES implantation, the possibility of ongoing erosion of luminal caliber beyond this time frame should be considered. However, the 1-year clinical follow-up did not suggest any late catch-up phenomena. In fact, after the scheduled late angiography, the event rate was very low, and curves tended to flatten and run parallel in both arms. Trials in which newer second-generation DES are used in the switch strategy are likely to give further answers to several unanswered questions.

Vascular Brachytherapy

Few observational studies have addressed this form of therapy for DES ISR. In the RESCUE registry,³² 61 patients who presented with ISR of a DES were assigned to vascular brachytherapy. Outcomes were compared with a group of 50 patients who were subject to repeat percutaneous coronary intervention using DES. At 8 months, there were fewer overall major adverse cardiac events (MACE) in the vascular brachytherapy group as compared to the repeat percutaneous coronary intervention group (9.8% vs 24%; $P = .044$). The need for target vessel and target lesion revascularization was similar in the two groups. There were no reports of subacute stent thrombosis in either group. However, the investigators did not use a multivariate model to adjust for possible confounders in this retrospective study. Because of high rates of late restenosis and logistic issues, this form of therapy has largely been abandoned.

DEB

DEB have emerged as a powerful tool to deal with BMS ISR. The drug used in DEB is paclitaxel, a lipophilic drug that elutes from the balloon surface upon inflation. The advantage of the DEB is that the antiproliferative properties of a DES are maintained but without the associated complications such as stent fracture, malapposition, and stent thrombosis. DEB offer a host of other benefits, such as the drug delivery being homogeneous, rapid, and in high concentrations. Furthermore, problems associated with the polymer have been eliminated, vessel anatomy is not altered (eg, jailing of side branches), and dual-antiplatelet therapy is needed for only 1 month.

Several trials (PACCOATH ISR 1 and 2 trials³³ and PEPCAD II³⁴) established the safety and efficacy of paclitaxel-eluting balloons in treating BMS ISR. The PACCOATH 1 trial compared the efficacy of DEB versus uncoated balloons. The 6-month binary restenosis and MACE rates were 5% and 4%, respectively, in the DEB group, whereas they were 43% and 31%, respectively, in the uncoated balloon group ($P = .002$ and $P = .2$, respectively).

The PEPCAD II trial compared the efficacy of the SeQuent Please balloon (B. Braun Interventional Systems, Inc., Bethlehem, PA) with the Taxus stent in treating BMS restenosis. At 6 months, the in-segment late lumen loss was 0.38 ± 0.61 mm in the DES group versus 0.17 ± 0.42 mm in the DEB group ($P = .03$), resulting in binary restenosis rates of 12/59 (20%) versus 4/47 (7%) ($P = .06$). At 12 months, the MACE rates were 22% in the Taxus group and 9% in the DEB group ($P = .08$), while the TLR rates were 15% and 6%, respectively ($P = .15$).

Based on these pivotal trials, the 2010 European Society of Cardiology guidelines for percutaneous coronary intervention recommended that DEB should be considered for the treatment of ISR after previous BMS use. This was accorded a class 2 (IIa) indication with level B evidence.³⁵

With regard to the use of DEB in DES ISR, a few randomized trials have been completed, and a few more are underway. Some of the trials underway are:

- ISAR-DESIRE 3 will randomize 375 patients with limus DES restenosis to three treatment arms. Namely, 125 patients will receive Taxus stents, 125 will receive DEB, and 125 will receive uncoated balloon therapy.
- RIBS IV is a Spanish trial that plans to recruit 310 patients with DES restenosis and subsequently randomize 155 patients to SeQuent DEB and the other 155 patients to everolimus DES. Angiographic follow-up is planned at 6 and 9 months, and clinical follow-up for MACE is planned at 12 months.
- PEPCAD DES is a German trial that will recruit 120 patients. One-half of these patients will receive SeQuent DES, and the other half will receive uncoated balloon therapy.

Eight-month follow-up data from the randomized Valentines Trial 1 Global Registry were recently presented.³⁶ The Valentines trial was conducted with an objective to assess the efficacy of the paclitaxel-eluting balloon Dior II DEB (Eurocor GmbH, Bonn, Germany) at 6 and 9 months for treating ISR. Three hundred patients with ISR were enrolled by 96 investigators from 26 countries. The results convincingly showed that the Dior DEB is a very effective and safe treatment for cases of ISR, both for

BMS and DES. Treatment with the Dior DEB resulted in very low TLR rates of 7.4% on average (5.9% for BMS and 9.8% for DES). This compares to TLR rates of up to 20% for vascular brachytherapy. In diabetics, TLR was 11.5%. Data from other ongoing trials are eagerly awaited.

CABG

One may consider CABG in the absence of satisfactory results with interventional therapies in cases of multivessel DES with multivessel ISR, especially in diffuse or even single-vessel ISR at a very critical location.

CONCLUSION

DES ISR is a significant and worrisome problem of multifactorial origin. IVUS should be an integral part of the treatment strategy for DES ISR, as it may help expose issues such as underexpansion. Simple repeat dilatation with a larger balloon or a higher-pressure balloon may prove to be a simple treatment strategy rather than repeat DES implantation. Cutting balloon angioplasty and vascular brachytherapy have proved to be of no significant benefit. Repeat stenting with the same or different type of DES may be done when ISR is focal; however, a different DES should be used when ISR is diffuse.

Data available to date on the switch strategy are with the repeat use of first-generation DES. Trials with newer-generation DES as a part of a switch strategy are eagerly awaited. Another therapy that holds promise is drug-coated balloons. Several ongoing trials may help to reinforce the initial success seen in the Valentines trial. ■

Vineet Bhatia, MD, DM, DNB, MNAMS, is a consultant cardiologist at Fortis Hospital in Noida, India. He has disclosed that he has no financial interests related to this article. Dr. Bhatia may be reached at 91-9818168874; vinmonica@yahoo.co.in.

Upendra Kaul, MD, DM, FCSI, FSCAI, FACC, FAMS, is the Executive Director and Dean of Cardiology at Fortis Escorts Heart Institute and Fortis Vasant Kunj in New Delhi, India. He has disclosed that he has no financial interests related to this article. Prof. Kaul may be reached at 91-9811150518; ukaul@vsnl.com.

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