

Review Article

Stent Restenosis, Pathophysiology and Treatment Options: A 2010 Update

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Percutaneous coronary intervention (PCI) has seen a tremendous increase and tends to be the most frequently used method for myocardial revascularization.¹ An impressive array of stent improvements, newer drug regimens and technological advances have emerged and broadened the therapeutic spectrum for interventional cardiologists worldwide. The recurrence of luminal narrowing due to recoil, arterial vessel remodeling and intimal hyperplasia induced by artery injury and disease progression, has compromised the results of balloon angioplasty. The use of stents during PCI achieved both a significant decrease in the incidence of acute complications and an improvement in patients' outcomes.² The initial idea was for the implanted stent to serve as a scaffold that would maintain the artery's patency permanently. In reality, in-stent restenosis (ISR) compromises the long-term results.³⁻⁶ The introduction of drug-eluting stents (DES) aimed to reduce restenosis, the major drawback of bare-metal stent (BMS) implantation. Undoubtedly, a drastic improvement was observed but much to physicians' disappointment, restenosis remains the Achilles' heel of PCI, even in the DES era.

Mechanism and factors contributing to stent restenosis

BMS implantation bears a restenosis rate

of around 25%.^{2,7} A great number of randomized trials comparing DES with BMS have shown that the former significantly reduce the incidence, not only of angiographic, but also of clinical restenosis to a uniquely low, one-digit range (<10%).^{8,9} However, its prevalence will be greater in view of the fact that, in the real world, DES are being increasingly used in complex lesions such as those in the left main artery, bifurcations, small vessels, vein grafts, chronic total occlusions, acute coronary syndromes and diabetic patients. In these patient populations, "off-label" use has led to an ISR rate exceeding 10%.^{10,11} Another unsettling issue is that DES restenosis does not always present benignly, with myocardial infarction being the initial clinical manifestation in up to 10% of patients.¹²

A number of predisposing factors have been associated with restenosis and can be divided into lesion-related, procedure-related and patient-related. Vessel and lesion characteristics that could predict a high probability for ISR are vessel size, tortuosity, calcification, total occlusion and lesions located in the left anterior descending coronary artery (LAD). Technical failures of the implantation, such as small post-procedural minimum lumen diameter, higher residual percent diameter stenosis, underexpansion, overexpansion, stent fracture, non-uniform distribution of stent struts and malapposition have been

associated with DES restenosis.¹³⁻¹⁷ Many clinical factors have been linked with this phenomenon, such as the presence of diabetes mellitus.¹⁸ Genetic factors, such as the PIA polymorphism of glycoprotein IIIa,¹⁹ the insertion/deletion polymorphism and the plasma activity of angiotensin I-converting enzyme,²⁰ have been reported to be important patient-related risk factors of ISR.

Current evidence suggests that inadequate and predominantly focal delivery of the antiproliferative agent (mainly sirolimus or paclitaxel) into the vessel wall, localized hypersensitivity, polymer disruption and drug resistance are likely to be involved in DES restenosis.^{21,22} An earlier classification of lesions into either diffuse (lesion length >10 mm) or focal (<10 mm) has proved inadequate to predict the rate of target vessel revascularization (TVR). Nowadays, the angiographic pattern of restenosis based on Mehran's classification for ISR seems to have important prognostic value and may be used for further clinical assessment.²³ Recurrent ISR was more frequent with increasing grades of classification, as with diabetes. Target lesion revascularization (TLR) increased according to ISR class, ranging from 19% to 83% for classes I to IV, respectively ($p<0.001$).

Corbett et al²⁴ characterized 150 and 149 restenotic lesions in sirolimus-eluting (SES) and paclitaxel-eluting stent (PES) groups, respectively, and concluded that focal restenosis remains the most common pattern with SES. In contrast, just under half of restenoses in PES have the more severe non-focal pattern. Recently, Rathore et al,²⁵ studying 838 patients with ISR, reported 47% and 19.3% rates of focal ISR for SES and BMS treated patients, respectively. The majority of ISR is focal, but a considerable part presents as non-focal. It is the latter type of ISR that is associated with a higher need for revascularization. Therefore the type of ISR plays an undoubtedly prominent role in the clinical outcome.

Treatment of in-stent restenosis

In this update article, we provide an overview of the therapeutic options for restenosis treatment, which include balloon angioplasty, cutting balloon, debulking techniques, intravascular radiation therapy-brachytherapy, DES, and finally some newer thoughts concerning novel treatments based on molecular biology and genetic studies to identify patients at increased risk for restenosis, leading to individualized therapy.

Recurrent restenosis rates after balloon angioplasty for ISR treatment have been reported to be 22%, with TVR rates of 11-17%, particularly in cases of focal ISR.^{26,27} Furthermore, higher restenosis rates have been reported for the recurrence of the diffuse type of ISR lesions, with rates as high as 80%.²⁸ According to a study²⁹ in San Raffaele Hospital in Milan, Italy, at 6-month follow up the recurrence of angiographic restenosis was 20%, 35.9%, 41.1% and 45.2% for cutting balloon, rotational atherectomy, BMS stenting and PTCA, respectively ($p<0.001$). The same study showed a 15.8%, 31.9%, 35.5% and 37.8% TLR for the same methods, respectively. In the long WRIST study concerning brachytherapy for long lesions, restenosis was found in 32% of patients who underwent brachytherapy and a need for TLR in 30% of them, compared to 71% and 60% of patients who were treated by conventional PTCA, respectively.³⁰ In the SCRIPPS trial³¹ 26 patients were assigned to coronary stenting followed by 192Ir irradiation and 29 to coronary stenting followed by placebo. There was a 65% reduction of intimal hyperplasia, resulting in a restenosis rate of 16.7% for patients treated with 192Ir vs. 53.6% for placebo patients ($p=0.009$). These favorable results persisted even after a 2-year follow up, with the combined death, myocardial infarction and TVR rate being 23.1% in the gamma radiation patients vs. 51.7% in the placebo group ($p=0.03$).³²

Several studies compared the efficacy of DES in the treatment of ISR with other percutaneous treatment modalities, such as PTCA, cutting balloon angioplasty, and intracoronary radiation therapy. In the RIBS-II³³ trial, comparing the efficacy of SES and balloon angioplasty in patients with ISR, ISR and TVR rates were both favorable for SES (11% vs. 39%, $p<0.001$, and 11% vs. 30%, $p<0.003$, respectively). IRT and DES were considered equally effective in some studies,^{34,35} but the results need to be interpreted with caution. Torguson et al,³⁶ evaluating the outcome in DES ISR treated with IRT versus DES implantation, demonstrated a TLR rate of 10% versus 18%, respectively. However, it is highly possible that the advantageous IRT results are related to the highly experienced centers and may be difficult to reproduce in a widespread interventional setting. The ISAR-DESIRE study offered the first randomized controlled data on the efficacy of DES versus balloon angioplasty for ISR.³⁷ A strategy using DES was superior to conventional balloon angioplasty for the treatment of ISR. SES were compared with cut-

ting balloon angioplasty for ISR in a study of 55 patients treated with SES and a group of 214 patients with matched lesion characteristics from the cutting balloon arm of the Restenosis Cutting Balloon Evaluation Trail (RESCUT).³⁸ A 57% relative reduction in the incidence of recurrent restenosis with SES implantation was described, compared with that observed in the cutting balloon group ($p=0.038$). Ellis et al,³⁹ in their follow-up analysis through 2 years after randomization, reported the durability of PES for ISR after BMS and continued superiority over brachytherapy. The data suggest that the efficacy of a PES in preventing restenosis relative to brachytherapy is enhanced with continuing long-term follow up, due largely to mitigation of the restenosis 'catch-up phenomenon' described after radiation therapy.

Studies of DES restenosis treatment have been published over the years and showed a subsequent restenosis rate ranging from 17% to 42.9%^{40,41} and a TLR rate of 15%. A prospective, randomized, multicenter comparison of the Cypher SES (Cypher™ sirolimus-eluting stent, Cordis Corp., Miami FL, USA) and balloon re-angioplasty for treatment of patients with intra-DES restenosis (CRISTAL study), which is currently in progress, hypothesizes that DES re-stenting shows similar results in both DES and BMS ISR. The Focal In-Stent Restenosis After Drug Eluting Stent (FOCUS) study, whose main aim is to evaluate optimal treatment of focal DES ISR, and the Diffuse Types In-Stent Restenosis After Drug Eluting Stent (DES-ISR) for diffuse DES ISR are important ongoing trials.

Many interventional cardiologists commonly use the stent-in-stent technique (sandwich technique) to treat DES ISR, despite the lack of supporting clinical evidence. While repeat DES implantation seems preferable, the optimal stent type is not known. There is great interest in the literature concerning the use of different DES ("hetero-DES") or same DES ("homo-DES"). Anecdotal evidence would suggest that using a different class of antiproliferative agent would be efficacious, but this strategy has not yet been tested. In a non-randomized study, Cosgrave et al included 174 patients presenting with 201 DES restenoses.⁴¹ They implanted the same DES in 107 lesions and another DES in 94 lesions. There were no differences in outcome when implanting the same or a different DES for DES restenosis, with TLR rates of 15.9% and 16%, respectively ($p=1.0$), and angiographic restenosis rates of 26.4% and 25.8% ($p=1.0$). Moreover, the recently presented results of the ISAR-DESIRE 2 trial,⁴² a prospective randomized trial of PES

vs. SES for the treatment of coronary restenosis of SES, confirmed that repeat DES implantation is safe for DES restenosis up to 1 year, and that using either SES or PES for SES restenosis has similar anti-restenotic efficacy. In the GISE-CROSS study, currently run by the Italian society of cardiology, patients presenting with ISR after PES or SES will be randomly assigned to repeat intervention using the same or a different DES.⁴³

Therefore, no clinical studies to date have been able to demonstrate a clear clinical benefit of deploying a different DES rather than the same DES, and the initial hypothesis about drug-resistance has not been confirmed. However, this strategy raises several concerns, the most important being the potential increase of stent thrombosis risk. Possible mechanisms include exposure to a higher drug dose, if the same DES is used, or a synergistic effect if a different one is implanted. Moreover, it is already known that the kinetic release of a specific drug varies between different DES.⁴⁴ Therefore the time of implantation of DES may influence the remaining drug dose. Stent strut overlap has also been incriminated as a stimulus for neointimal hyperplasia and correlates with late angiographic restenosis.⁴⁵ Additionally, a double layer of non-resorbable polymer may contribute to stent thrombosis.

Newer thoughts for novel treatment

Recently evaluated methods for the prevention of ISR and its recurrence consist of improved implantation techniques, such as better stent design, improvements in reservoir design, development of bioabsorbable polymers, polymer-free drug delivery, fully biodegradable stents, stents eluting new pharmaceutical agents, and finally, gene therapy. Thus, besides techniques that aim at improving the interventional procedure and its immediate result, new approaches focus on inhibition of induced tissue proliferation. Researchers, seemingly inspired by Einstein's apothegm, according to which "we cannot solve problems by using the same kind of thinking we have used when we created them", started to move towards ISR treatment even at the molecular level. Zotarolimus, ABT-578, tacrolimus, everolimus and biolimus A9 were introduced into our armamentarium of new pharmaceutical agents to prevent and decrease ISR. Novelities in stent skeleton construction are also available with the introduction of bioabsorbable stents aiming to decrease TLR rates.

The results of the SPIRIT-III⁴⁶ and SPIRIT IV (TCT 2009, Gregg Stone, San Francisco) trials showed that second generation DES, such as everolimus-eluting stents (EES), result in lower ISR and TLR rates compared to PES (2.3% vs. 5.7%, $p=0.07$, and 2.6% vs. 5%, respectively, in the SPIRIT-III trial). On the other hand, zotarolimus eluting stents (ZES), in the ENDEAVOR IV⁴⁷ and SORT OUT IV⁴⁸ trials, were not inferior to PES but did not achieve better results when compared to SES. The COMPARE⁴⁹ investigators randomized 1800 patients to either the Xience (XIENCE V[®] Everolimus Eluting Coronary Stent System) or the Taxus Liberté (TAXUS[®] Liberté[™] Paclitaxel-Eluting Coronary Stent System) stent and followed them for 1 year, looking at a primary composite endpoint of all deaths, nonfatal myocardial infarction (MI), and TVR. The trial included a more complex patient population than SPIRIT IV, including 23% STEMI patients, and relatively high proportions of patients with calcified lesions, bifurcations, multivessel disease, and diabetes. Real-world implantation of the Xience V stent significantly reduced major adverse cardiac events compared with the Taxus Liberté stent. The significant difference in MI was directly related to the increased rate of stent thrombosis in the Taxus group. A possible explanation was linked with the differences in the Xience stent design elements that affect its deliverability and interactions within the vessel. A second generation DES (biolimus A9 eluting stent) performs quite similarly to SES with regard to major adverse cardiac events in the “real world” according to the LEADERS trial,⁵⁰ which included a high proportion of previous MI patients or revascularisation procedures, lower left ventricular systolic function, and more patients with acute myocardial infarction; results were better when the SYNTAX score was higher than 16 (higher angiographic risk).

After exhausting drug delivery, the remaining DES skeletons pose a thrombogenic risk as the stent itself induces impaired endothelial function. Temporary scaffolding with bioresorbable stents seems to be the next field to focus on the prevention of stent failure. The ABSORB trial⁵¹ assessed the safety of the bioabsorbable everolimus-eluting stent (BVS) and concluded that 2 years after implantation the stent was bioabsorbed, had vasomotion restored and restenosis prevented, with an in-stent late loss of 0.48 mm (SD 0.28) and diameter stenosis of 27%, and was clinically safe, suggesting freedom from late thrombosis.

Finally, patients with and without diabetes who

underwent coronary artery bypass surgery (CABG) for treatment of ISR (mainly because of the presence of multivessel disease) had a significantly better outcome than those who underwent percutaneous interventions, mostly in the form of lower TVR rates. Besides, a revolutionary new advance, such as the robotic technology that has been developed to facilitate a less invasive approach for CABG,⁵² seems promising.

Intravascular imaging modalities

The need for more sophisticated visualization, not only of arterial lumen, but of the vessel wall as well, has attracted great interest in imaging technologies such as intravascular ultrasound (IVUS).⁵³ In the CRUISE (Can Routine Ultrasound Influence Stent Expansion) trial, a randomized trial with 499 lesions subject to either angiographic or intravascular ultrasound guided stent expansion, the final lumen cross-sectional area within the stent was found to be the only multivariate predictor of subsequent TLR.⁵⁴ Furthermore, intravascular ultrasound analysis showed that the lesion plaque burden before stent placement was an important independent predictor for ISR.⁵⁵ It has been suggested that aggressive implantation techniques, resulting in a minimal stent cross-sectional area of 90% of the reference areas, lead to low restenosis rates.⁵⁶ So the utilization of IVUS guidance to optimize stent dimensions is necessary.⁵⁷ Although IVUS-guided PCI is still far from being characterized as routine practice, IVUS is currently the best way to recognize the causes of stent failure.⁵⁸

A more sophisticated technique, virtual histology intravascular ultrasound (VH-IVUS) offers an opportunity to assess lesion morphology, composition and plaque characteristics *in vivo*. Kubo et al⁵⁹ showed that there is a difference in native artery vascular responses after implantation of DES compared with BMS, concerning the protective neointimal hyperplasia layer coupled with a lack of vulnerable plaque resolution at reference segments, mostly in DES.

Optical coherence tomography (OCT), with a spectacular resolution of 10 μm , is emerging as a new imaging modality that could assist optimal stent deployment, while elucidating restenotic mechanisms, vessel wall reaction and stent failures.⁶⁰ Large randomized trials are needed to categorize OCT's large array of findings into comprehensible and clinically relevant patterns.

All of the above could lead to a new trial focus on

the type and composition of the ISR tissue, revising the way we deal with this phenomenon.

Medical treatment

Undoubtedly, preventing ISR is better than curing it, and could spare physicians and patients from many re-interventions and life-threatening risks. Triple antiplatelet therapy after DES implantation decreased angiographic restenosis and extent of late loss, resulting in a reduced risk of 9-month TLR compared with dual antiplatelet therapy in diabetic patients.⁶¹ This randomized, multicenter, prospective study compared triple antiplatelet therapy (aspirin, clopidogrel, and cilostazol, triple group, n=200) and dual antiplatelet therapy (aspirin and clopidogrel, standard group, n=200) for 6 months in patients with diabetes mellitus receiving DES. The primary endpoint was in-stent late loss at 6 months. Triple antiplatelet therapy after DES implantation decreased angiographic restenosis and the extent of late loss, resulting in a reduced risk of 9-month TLR compared with dual antiplatelet therapy in diabetic patients.

On the other hand, in the Oral Sirolimus to Inhibit Recurrent In-Stent Restenosis (OSIRIS)⁶² trial 300 patients were randomly assigned to receive a cumulative loading dose of either placebo (0 mg), usual-dose (8 mg) oral sirolimus, or high-dose (24 mg) oral sirolimus 2 days before and on the day of repeat PCI, followed by maintenance therapy of 2 mg per day for 7 days. Restenosis was significantly reduced from 42.2% to 36.8% and 22.1% in the placebo, usual-dose, and high-dose groups, respectively (p=0.005). The need for TVR was reduced from 25.5% to 24.2% and 15.2%, respectively, although this was not statistically significant (p=0.08). The blood concentration of oral sirolimus was significantly correlated with late lumen loss at follow up (p<0.001). The investigators concluded that oral adjunctive sirolimus treatment for ISR resulted in a significant improvement in the angiographic parameters of restenosis. Further elucidation is needed concerning optimal dosing, need for pretreatment, and duration of oral sirolimus, over a long-term follow up.

Drug coated balloons

The acute neointimal and vascular injury from the procedure is prolonged by continued exposure to the drug-carrier platform, which may generate a persistent inflammatory and immunologic reaction. The

paclitaxel coated balloon is a new attempt to administer the drug to the vessel wall without the use of a stent coated with a biostable polymer as a platform for delivery. Late luminal loss was 0.74 ± 0.86 mm in the group treated by simple angioplasty, as compared with 0.03 ± 0.48 mm in the group treated with the paclitaxel-coated balloon (p=0.002). In absolute numbers, this mean value for late luminal loss is one order of magnitude smaller than values obtained with the use of either intracoronary radiation (0.35 ± 0.68 mm) or first-generation drug-eluting stents (0.32 mm; 0.03-0.74 mm) to inhibit neointimal growth.⁶³ The rationale for using a drug coated balloon over a stent polymer based drug delivery comes from cell culture experiments indicating that even brief contact between vascular smooth muscle cells and lipophilic taxane compounds can inhibit proliferation of such cells for a long period.^{64,65} PES (paclitaxel-eluting balloon) and balloon angioplasty will be compared for treating limus-DES restenosis in ISAR-DESIRE 3.

Gene therapy

More modern aspects focus on several approaches using gene therapy that are under evaluation to prevent intimal hyperplasia. Adenoviruses have been used as vectors for gene delivery to areas of vascular injury.^{66,67} The delivered genes can encode for proteins that are either directly or indirectly cytotoxic or cell cycle-inhibitory. In addition, the inhibition of various mediators of the cell cycle with antisense oligonucleotides has been proposed.⁶⁸

Molecular biology

The arterial wall injury induced by balloon inflation and stent placement during PCI is followed by a cascade of events, including platelet and leukocyte activation and smooth muscle cell proliferation, leading to restenosis. Genetic factors may explain the excessive risk of restenosis, independently of clinical and procedural parameters. Consequently, a genetic test to identify patients at increased risk may lead to improved risk stratification and eventually to a patient-tailored therapy.^{4,69,70} Most of the studies dealing with the treatment of DES restenosis have shown variable results. This may reflect the heterogeneity of the patient's characteristics and the etiology behind the restenosis. Genetic factors may elucidate the excessive risk of restenosis independently of conventional clinical and procedural parameters. Additional

genetic tests could identify patients at increased risk of restenosis. Current investigation and genetic studies are designed to identify single nucleotide polymorphisms in genes associated with restenosis.⁷⁰ Van Tiel et al⁷¹ proposed that increased p27^{kip1} expression in patients with a -838AA genotype results in decreased smooth muscle cell proliferation and explains the decreased risk of ISR in that specific group. On the other hand p27^{kip1}-838C>A single nucleotide polymorphism is associated with clinical ISR.

Current therapy – current guidelines

Table 1 summarizes all major trials and series concerning mechanical treatment options for ISR. Considering the frequency of recurrence after current treatment of stent restenosis, avoidance of stent placement in lesions with a high rate of restenosis or even diffuse ISR seems to be wise. The recommendation from some authors for an aggressive strategy, which includes optimal balloon angioplasty and provisional stenting in case of an insufficient result after balloon angioplasty, guided by IVUS, does not lack a well established rationale.

At the 2007 ESC congress, an interesting algorithm (Figure 1) was introduced for ISR of DES. Plain old balloon angioplasty, scoring balloons or even another DES are suggested if the ISR is focal. For diffuse lesions another DES or, if available, brachytherapy could be used. As a last resort, CABG should be considered for diffuse ISR. The optimal treatment for DES ISR remains to be established through more prospective and randomized trials. The

2001 ACC/AHA guidelines for PCI were revised in 2005 and in summary suggest that repeat PCI can be performed with a DES or a new DES (SES or PES) for ISR if anatomic factors are applicable (recommendation Class IIa, level of evidence B) or brachytherapy if it is available (recommendation Class IIa, level of evidence A).

All the above improvements require the investment of a significant amount of human and financial resources to justify the high price of DES. Having in mind that a DES costs about 3 times more than a BMS, the cost effectiveness of DES treatment compared to medical, balloon angioplasty, BMS or CABG has been a hot issue for patients, doctors and health professionals worldwide.

Conclusions

Restenosis remains a common problem, independent of the type of angioplasty. Patients who develop ISR after implantation of BMS carry a high risk for recurrence. The use of SES and PES effectively reduces the risk of recurrence and is associated with superior results compared with plain balloon angioplasty and vascular brachytherapy. Therefore, SES and PES should be recommended as the treatment of choice for patients with restenosis of BMS or DES.

As with most novel therapies, the solution to one problem often leads to another. The DES, which markedly reduces ISR, has relegated all other therapeutic approaches to the background. However, it is gradually emerging that rates of late restenosis after

Table 1. Major trials and series concerning mechanical treatment of in-stent restenosis.

Study/Trial	Patients/lesions	Follow up (m)	Treatment options	Restenosis rate	Target lesion revascularization
San Raffaele Hospital ²⁹	258	6	CB vs. RA vs. BMS vs. PTCA	20% vs. 35.9% vs. 41.1% vs. 45.2%, p<0.001	15.8% vs. 31.9% vs. 35.5% vs. 37.8%, p<0.001
WRIST ³⁰	130	6	IRT vs. placebo	27% vs. 56%, p=0.002	26% vs. 66%, p<0.001
SCRIPPS ³¹	54	6	IRT vs. placebo	16.7% vs. 53.6%, p=0.009	
RIBS-II ³³	150	9	SES vs. PTCA	11% vs. 39%, p<0.001	11% vs. 30%; p<0.003
Torguson et al ³⁶	111	8	IRT vs. DES		10% vs. 18%
ISAR-DESIRE ³⁷	300	6	SES vs. PES vs. PTCA	14.3% vs. 21.7% vs. 44.6%	8% vs. 19% vs. 33%
RESCUT ³⁸	428	7	CB vs. PTCA	29.8% vs. 31.4%, p=0.82	
ABSORB ⁵¹	30	24	Bioabsorbable EES	27% diameter stenosis	
COMPARE ⁴⁹	1800	12	EES vs. PES		5% vs. 8%, p=0.005
SPIRIT III ⁴⁶	1002	9	EES vs. PES	2.3% vs. 5.7%, p=0.07	2.6% vs. 5%
ENDEAVOR IV ⁴⁷	1548	9	ZES vs. PES	15.3% vs. 10.4%, p=0.284	4.5% vs. 3.2%, p=0.228
LEADERS ⁵⁰	328*	12	BES vs. SES	23.2% vs. 13.1%, p=0.042	12.4% vs. 6.0%, p=0.07

*Substudy concerning long lesions. BES – biolimus-eluting stent; BMS – bare metal stent; CB – cutting balloon; DES – drug-eluting stent; EES – everolimus-eluting stent; IRT – brachytherapy; PES – paclitaxel-eluting stent; PTCA – percutaneous transluminal coronary angioplasty; RA – rotational atherectomy; SES – sirolimus eluting stent; ZES – zotarolimus-eluting stent;

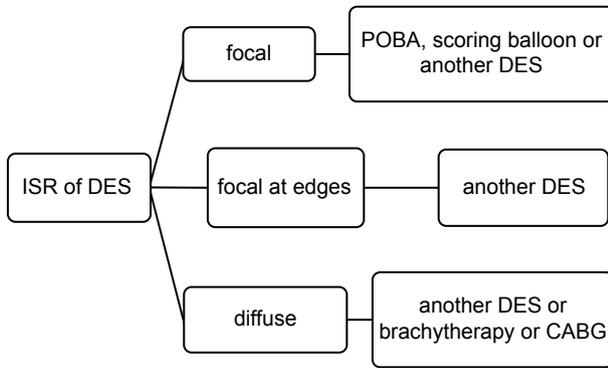


Figure 1. Recommendations for treating in-stent restenosis in drug-eluting stents. CABG – coronary artery bypass grafting; DES – drug-eluting stents; ISR – in-stent restenosis; POBA – plain old balloon angioplasty.

the use of DES are higher than initial experience suggested, particularly in patients who have complex lesions or are at high risk for complications (e.g. those with multivessel disease or diabetes).

The safety of DES has been an issue since the initial concerns about late stent thrombosis surfaced, back in 2006. Late and very late thrombosis has further dampened the initial enthusiasm and has reduced the indiscriminate use of first-generation DES.⁷² As a result, interventional cardiologists have tended to revert to more predictable devices (e.g. uncoated stents or ones that are coated with so-called inert compounds), designed to decrease acute surface thrombogenicity, or new pharmaceutical regimens, trying to modify this phenomenon. Thus, ISR is likely to remain an important clinical issue.⁷³ The challenge to treat ISR in the DES era is the next frontier of interventional cardiology, while gene therapy targeting the inhibition of the biological reaction of the vessel wall could be ideal to prevent the genesis of this phenomenon.

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