Restenosis

Delineating the Numerous Causes of Drug-Eluting Stent Restenosis

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In the past decade, tremendous progress has been made in reducing the incidence of restenosis with the advent of the drug-eluting stent (DES). With "plain old balloon angioplasty," rates of acute and chronic vessel occlusion were unacceptably high at ≈30% to 60%, secondary to acute and chronic recoil and constrictive remodeling. The advent of bare-metal stents (BMS) appeared to eliminate the issue of acute and chronic recoil but introduced a new entity, neointimal hyperplasia (NIH), with classical papers unequivocally demonstrating a strong and linear relationship between NIH formation and late lumen loss (LLL). The restenosis rates with BMS were reported to be between 16% and 44%, with higher rates of stenosis attributable to several risk factors, in particular, long lesion length and small vessel caliber.[1]

DES were thus conceived as the next step in tackling this iatrogenic entity of NIH, with large-scale reductions in restenosis rates reported at 0% in highly selective lesions and up to 16% in a broader range of patients and lesions with first-generation DES.[1] In contrast to plain old balloon angioplasty and BMS, in which an almost classical gaussian distribution of LLL is seen postprocedurally, the LLL after DES implantation appears to follow a bimodal pattern of distribution (Figure 1).[2]

Despite the significant advances in the technology to reduce DES restenosis, conservative estimates still suggest that the incidence of in-stent restenosis (ISR) requiring target vessel revascularization (TVR), so-called DES failure, to be ≈5% to 10%, with one estimate suggesting ≈200 000 repeat revascularizations in the United States alone.[3]

Whereas the pattern of restenosis in BMS has been shown to be primarily diffuse, with DES it has been demonstrated to be usually focal (Figure 2) and most commonly located at the proximal DES edge, as demonstrated in >60% of ISR with either paclitaxel-eluting stent (PES) or sirolimus-eluting stent (SES) implantation. However, over one-fifth of ISR cases remain diffuse, and 10% to 20% are even occlusive.[4]

In 2004, the first report of risk factors associated with DES restenosis in patients with the unrestricted use of SES since approval of its CE mark was made by our group. Despite the apparent differences in the distribution of LLL between BMS and DES as previously described, the main message of these and subsequent findings was that the usual patient characteristics, lesion types, and procedural factors incriminated with restenosis in BMS were equally responsible with DES, with diabetes mellitus implicated as one of the strongest risk factors. It should however be emphasized that the "slope" of the distribution of restenosis with DES appears to be much flatter compared with BMS, especially in long lesions and small vessels, highlighting the importance of drug elution in potentially attenuating the NIH response.[3]

Histopathologic analyses of in-stent neointima taken by directional atherectomy at the time of reintervention also have been shown to be remarkably similar between BMS and DES. This is almost exclusively composed of proteoglycan-rich smooth muscle cells (SMCs) and fibrolipidic areas rich in collagen and reticular fibers. A more "immature" restenotic process, as evidenced by differences in SMC phenotypes, however, has been shown to potentially exist with certain types of DES compared with BMS.[5,6]

ISR traditionally has been suggested as being potentially less benign with the recurrence of anginal symptoms alone. However, emerging evidence now suggests that between 30% and 60% of ISR cases present with an acute coronary syndrome with unstable angina being the most common presentation and up to 5% of patients even reported to present with ST-elevation myocardial infarction (STEMI).[7,8] However, one series has suggested no differences in the incidence of acute coronary syndrome associated with either BMS or DES restenosis.[7]

The treatment of ISR and the determinant factors involved in the development of late stent thrombosis (LST) are well described elsewhere and are outside the scope of this review.[3,9] The underlying mechanisms of restenosis with DES can broadly be divided into 4 main causes (Table), namely, biological, arterial, stent, and implantation factors, accepting that this classification is somewhat arbitrary and that mechanisms of restenosis may be attributable to more than one factor. In this review we explore these 4 main mechanisms and identify the potentially controllable and noncontrollable factors from the perspective of the interventional cardiologist intending to implant a DES.

Biological Factors

Resistance to Antiproliferative Drugs

The underlying mechanisms of action and causes of resistance to paclitaxel or sirolimus are well documented in the
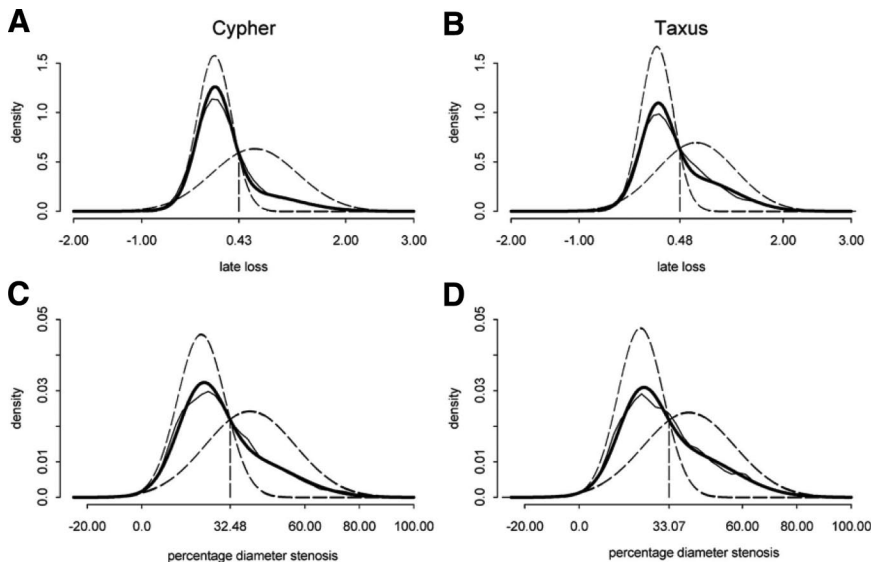
Figure 1. The bimodal distribution of LLL (A, B) and percentage diameter stenosis (C, D) after Cypher (left) and Taxus (right) implantation. LLL indicates late lumen loss. Reproduced with permission from Byrne et al.[2]

cancer literature and either can be present in genetically predetermined individuals or be acquired following cytotoxic exposure to the drug.[10,11]

The so-called drug resistance gene expression program, described for paclitaxel resistance, best exemplifies the complex pathways involved in the etiology of drug resistance.[10] Essentially, the cellular context determines the expression of the genes that contribute to drug resistance, either in genetically predetermined cells or primed for expression following the cytotoxic insult after drug exposure. These genes may operate in conventional pathways that are well known (drug delivery and metabolism, apoptosis regulation, DNA repair), but the temporal (ie, pro- and antiapoptotic gene activity) and spatial regulation (ie, cell survival signaling pathways) of these gene products after drug exposure also appears to be important.

Figure 2. The patterns of restenosis in SES and PES. The predominant pattern of ISR is focal, although diffuse and proliferative restenosis is still seen with DES. SES indicates sirolimus-eluting stent; PES, paclitaxel-eluting stent; DES, drug-eluting stent. Reproduced with permission from Corbett et al.[4]

As examples, polymorphisms in the genes that encode mTOR or proteins involved in paclitaxel or sirolimus metabolism have been shown to confer drug resistance both in vitro and in vivo[10,11]; decreased binding of sirolimus to mTOR because of mutations in FK-B12 and mTOR and mutations of downstream effector molecules of mTOR may all cause resistance to sirolimus.[11]

The OSIRIS study investigated the administration of higher doses of oral sirolimus to patients with refractory ISR in the theoretical attempt of overcoming drug resistance and delivering increased amounts of drug to the implantation site.[12] A significant correlation was demonstrated between the level of sirolimus concentration in the bloodstream and rates of further LLL (Figure 3). However, given that the patients received a short duration of oral sirolimus (7 days), it was unclear whether these findings would be maintained at longer-term follow-up.
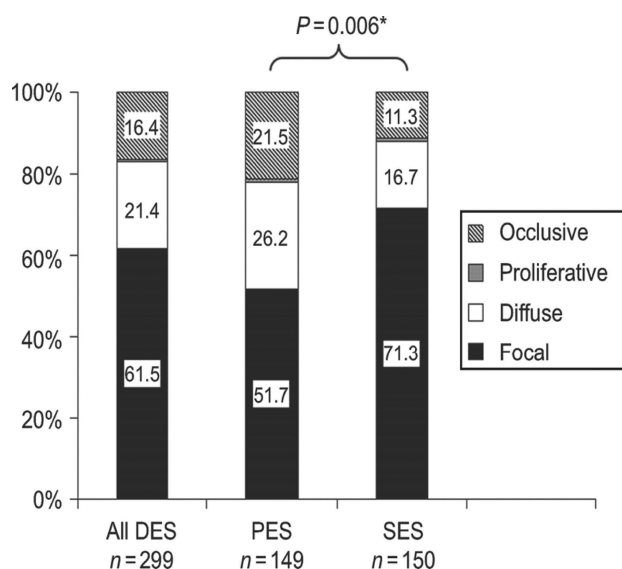
Hypersensitivity Reactions (the Polymer)

The inflammatory reaction that occurs after arterial injury is a critical factor that influences the extent of neointimal response, with the persistence of this inflammatory response beyond 90 days being strongly associated with delayed healing and implicated in an increased risk of LST and restenosis long term.[13,14]

PES and SES have each been demonstrated to provoke distinctive inflammatory responses in animal models beyond 90 days: SES triggering giant cell infiltrations and PES eosinophilic reactions around stent struts. The inflammatory responses associated with SES have been shown to persist beyond 180 days and up to 2 years (Figure 4); this phenomenon may also be further exacerbated at sites of overlapping DES. This is in contrast to BMS and the second-generation everolimus-eluting stent (EES-Xience V) with a more biocompatible polymer, in which the inflammatory responses have been demonstrated to be limited to a period of 90 days and 12 months, respectively (Figure 4).[13,14]

Evidence of persistent inflammatory responses in humans also has been reported in both autopsy cases, with one case

Table.   The Underlying Mechanisms of Restenosis With Drug-Eluting Stent

Biological Factors	Arterial Factors	Stent Factors	Implantation Factors
Resistance to antiproliferative drugs	Wall shear stress	Polymer drug release kinetics	Incomplete stent expansion
Hypersensitivity reaction (polymer)	Progression of atherosclerosis within a stented segment	Type of DES? Type of drug?	Geographical miss
Hypersensitivity reaction (metallic stent platform)	"Thromborestenosis"	Stent gap, nonuniform strut distribution, and drug deposition	Barotrauma to unstented segments
Serum matrix metalloproteinases	Vessel remodeling	Stent strut thickness	Deployment of DES in a clot-laden arterial segment
Genetics	Small vessels	"On- and off-label" use of DES	
		Polymer disruption, peeling, and cracking	
		Stent fractures	

involving up to one third of struts in first-generation DES at 3 months,[1,14] and from thrombus aspirates taken at the time of emergency percutaneous coronary intervention in patients presenting with very LST.[15]

The timing of restenosis associated with DES implantation, therefore, appears complex and may potentially be related to this persistent inflammatory response not usually associated with BMS, with some evidence to suggest a "catch-up" in LLL with SES as discussed in Stent Factors.

Hypersensitivity Reactions (Metallic Stent Platform)

Despite retrospective studies suggesting an association between nickel hypersensitivity and ISR, to date, no prospective studies have confirmed such an association. A few small prospective studies, however, have suggested a possible association between nickel hypersensitivity and recurrent ISR with BMS that previously had been treated with plain old balloon angioplasty; this, however, was found not to be associated with the initial BMS implantation.[16] Whether the issue of nickel hypersensitivity is a potential issue with DES is both speculative and theoretical. Only one small study (Nakazawa et al[17]) has examined this issue and found no association with SES implantation.

Figure 3. The association of sirolimus blood concentrations at the time of repeat intervention and LLL at 6-month angiographic follow-up from the OSIRIS study. LLL indicates late lumen loss. Reproduced with permission from Hausleiter et al.[12]

Serum Matrix Metalloproteinase (MMP) Activity and Genetics

Circulating MMPs recently have been demonstrated to be potentially useful in identifying patients at greater risk of developing ISR following DES implantation.[18] MMP-2 and MMP-9 are well known to play fundamental roles in the migration of vascular SMCs and matrix remodeling during wound healing and are produced by vascular SMCs, endothelial cells, macrophages, lymphocytes, and mast cells in response to mechanical injury. Significant elevations in MMP-9 levels at baseline and MMP-2 and MMP-9 levels 24 hours post-percutaneous coronary intervention have proven to be strongly associated with the development of ISR following DES implantation. Conversely low and near-normal MMP-2 and MMP-9 levels were associated with a lack of a significant restenotic response.[18]

Gene polymorphisms linked with the inflammatory response have been found to be associated with ISR.[19] As examples, homozygosity of the 16/glycine variant in the β_2-adrenergic receptor (a mediator of nitrous oxide synthetase) has been associated with β_2-adrenergic receptor down-regulation and an increased risk of restenosis[19]; Vogiatzi et al[20] described a 15-fold increase in the risk of restenosis associated with 2 functional polymorphisms of interleukin-8 (a strong mediator of inflammation). However, the reported gene polymorphisms are relatively rare, thus limiting any clinical applicability.

Arterial Factors

Wall Shear Stress

Wall shear stress refers to the principle that fluid dynamics and vessel geometry may play a potential role in the cause of focal plaque or neointimal formation. The concept of wall shear stress is that blood does not move at the same velocity at every point within the vessel, with blood flowing fastest in the vessel center or, for example, at the carina of a bifurcation (ie, a high-shear stress area) and slowest when closest to the vessel wall or, using the same example, at the ostium of a bifurcation (ie, a low-shear stress area), because of frictional forces exerted by the vessel endothelium. Low shear stress consequently may lead to the accumulation of growth factors, mitogenic cytokines, and platelets, which may promote atherosclerosis or neointimal formation after vessel injury.
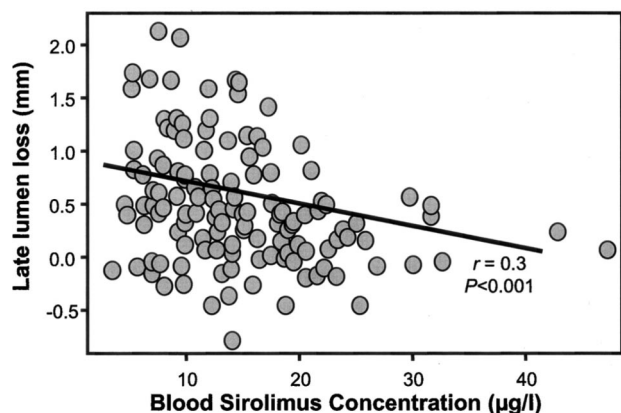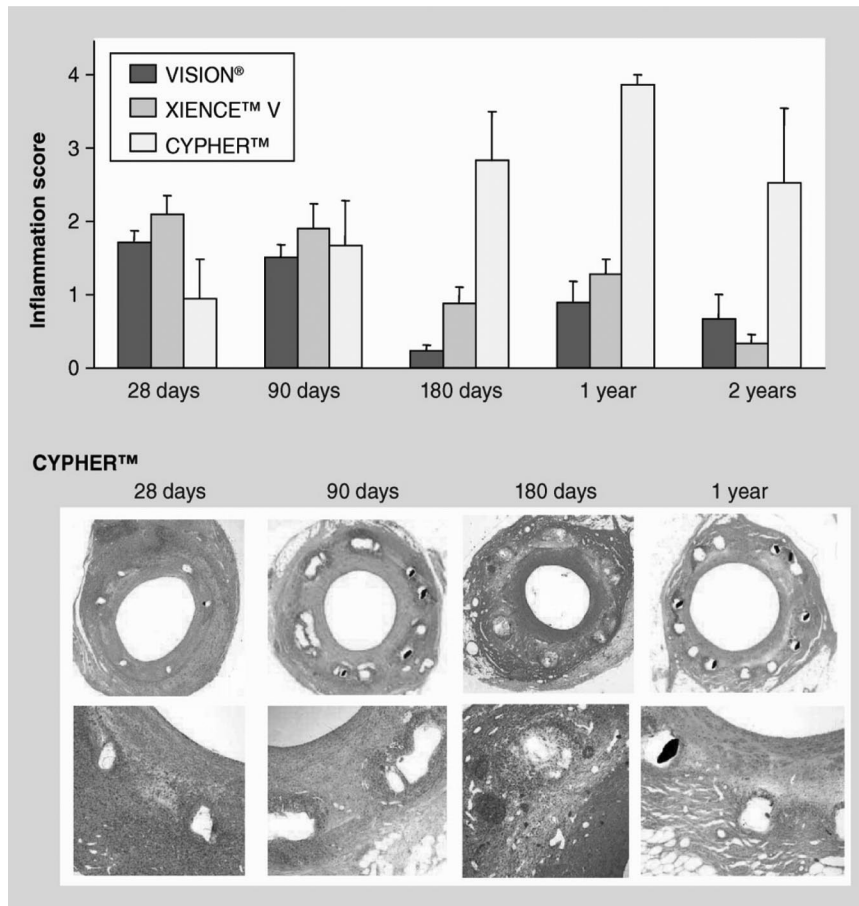
Figure 4. The persistent granulomatous inflammatory response to Cypher stents for a period of up to 2 years in a porcine model. Reproduced from *Expert Rev Cardiovasc Ther.* 2008;6:1379–1391, with permission of Expert Reviews Ltd.[13]

Conversely, high shear stress can potentially directly inhibit SMC proliferation and therefore limit atherosclerosis or restenosis unless it progresses from a low-shear stress area.[1,21,22]

In a novel experiment in an animal model, Carlier et al[23] demonstrated that through the implantation of a "flow divider" into the center of a stent implanted in the iliac arteries, they were able to modulate and increase the local wall shear stress with a consequential reduction in local inflammation and neointima formation.

The most similar human model of this example has been with so-called "shotgun stenting," in which simultaneous V-stenting is performed with the formation of a "new" carina in the left main stem or other suitably sized vessels.[24–26] Kim et al[24] showed that in 36 consecutive patients (29 with left main stem interventions) using SES, a 14% (5 patients) restenosis rate occurred over an average follow-up period of >2 years. Interestingly, a "membranous diaphragm" at the carina was identified in nearly half the patients, with restenosis occurring in just one of these patients.

Conversely, Stinis et al[26] showed that in 74 consecutive patients with predominantly left anterior descending-diagonal lesions, that the target lesion revascularization rate was more than twice as high in the simultaneous V-stenting group (14 patients, 40%), compared with the crush group (5 patients, 12.8%) at a follow-up of >3 years. Whether lesion location played a role in the disparity of these results remains unclear.

Robust, well-designed trials are required to evaluate the feasibility of this technique further.

The issue as to whether the actual presence of the stent in the vessel wall negatively alters the wall shear stress sufficiently to promote restenosis has proven to be controversial, with conflicting evidence existing in the literature. In a recent, larger, well-designed trial, Papafaklis et al[27] demonstrated the presence of significant numbers of "pockets" of low shear stress within stented segments, secondary to local geometric factors such as angulation or curvature, and that these pockets were significantly associated with NIH formation at 6-month follow-up with BMS and PES. Interestingly, this was not seen with SES, suggesting that sirolimus significantly attenuated the neointimal response to low shear stress. Paclitaxel was unable to do this, perhaps because of its differing pharmacological mode of action or even its shorter drug-release kinetics, which will be discussed later.[1,3,27]

Progression of Atherosclerosis Within a Stented Segment

Plaque progression and rupture leading to myocardial infarction (MI) have been reported in rare case reports involving BMS[28,29] and more recently DES.[30] The underlying pathological mechanisms are one of necrotic core plaque progression and rupture either within the stent with BMS or at the stent edge in incompletely covered lipid-core plaque with DES (see Implantation Factors).[30]
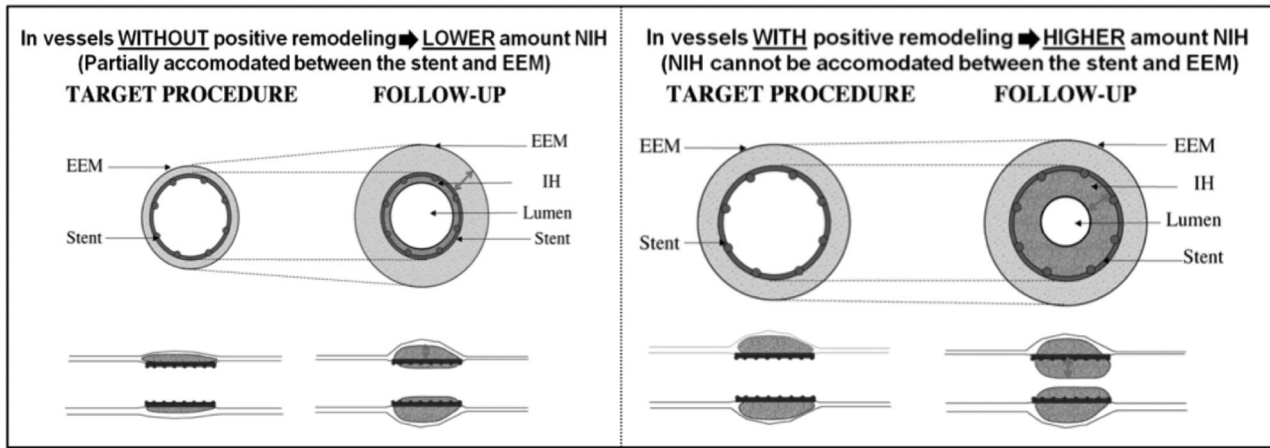
Figure 5. The phenomenon of the increased likelihood of restenosis occurring in positively remodeled vessels. Red arrow indicates position where NIH can potentially grow in nonremodeled (between the stent and EEM) (left image) and remodeled vessels (right image). Because the NIH cannot be accommodated between the stent and the EEM in remodeled vessels, this results in luminal compromise. NIH indicates neo-intimal hyperplasia; EEM, external elastic membrane. Adapted and reproduced with permission from Spanos et al.[37]

In the Moderate Vein Graft Lesion Stenting With the Taxus Stent and Intravascular Ultrasound (VELETI) pilot trial,[31] it was potentially shown that PES implantation to cover moderately diseased, flow-limiting lesions in old saphenous vein grafts lead to apparent "plaque sealing." A reduced rate of saphenous vein graft disease progression, as evidenced by a lower 12-month minimum lumen area on intravascular ultrasound (IVUS) assessment and a trend toward a lower incidence of major adverse cardiovascular events at 1-year follow-up was found, compared with medical treatment alone. Conversely, Jensen et al[32] showed in a serial IVUS study of 74 patients with diabetes post-DES implantation that, at 8-month follow-up, PES led to a significant, but mild, increase in the rate of plaque progression compared with SES.

"Thromborestenosis" Phenomenon

"Thromborestenosis" is a term first described by Oikawa et al[33] to describe an intriguing theory in which chronic thrombus formation may play an integral part in the development of ISR. Within their study, the incidences of thrombus and fibrin deposition were more frequently observed with ISR lesions associated with SES implantation (12 of 13 cases) compared with BMS (2 of 8 cases). In support of this theory is the fact that plaque rupture with nonocclusive thrombus is a well-recognized mechanism of progression of disease in de novo atherosclerotic lesions.[34] Furthermore in a study of patients who died of LST, 2 of 14 autopsy cases revealed evidence of ISR with superimposed thrombus.[35]

Conversely, Rittersma et al[36] also showed evidence of chronic thrombi that were days to weeks old in at least 50% of 211 consecutive STEMI patients with de novo lesions who had thrombus aspirates taken within 6 hours of the onset of their symptoms. Hypothetically the presence of older thrombi was speculated to be related to clinically silent nonocclusive athero-thrombotic events in the preceding days to weeks before the clinical presentation of occlusive thrombosis. Whether this latter theory is also an explanation for the presence of thrombi seen with ISR is presently unclear.

Vessel Remodeling

The implantation of DES in vessels that previously have undergone positive remodeling secondary to a large plaque burden, the "Glagov" phenomenon, also has been shown to be a significant predictor of restenosis (Figure 5).[37]

Small Vessels

This is discussed in Stent Factors with strut thickness.

Stent Factors

Polymer Release Kinetics

Polymer release kinetics plays a key and fundamental role in the prevention of restenosis. The Paclitaxel In-Stent Controlled Elution Study (PISCES) trial[38] was the first human study to demonstrate this principle involving the use of the Conor stent with 6 different polymer-drug release formulations. The main finding of this trial was that the duration of the drug release had a far greater impact on the inhibition of NIH than the dose of drug delivered. For example, 10 μg of paclitaxel released over 10 days following DES implantation appeared to have little effect on NIH formation, whereas the same dosage of drug released over a 30-day period led to a profound reduction in NIH, with a more than halving (57% reduction) of the LLL. Interestingly, 30 μg of the same drug released over a 10-day period also was less effective.

The polymer-free biolimus A9-eluting stent, with two different doses of biolimus, demonstrated noninferiority compared to PES in the first-in-human BIOFREEDOM study.[39] An in-stent LLL of 0.17 mm (standard-dose biolimus group: 15.6 μg/mm stent length), 0.22 mm (low-dose biolimus group: 7.8 μg/mm stent length) and 0.35 mm (PES) were reported, with no significant differences in major adverse cardiovascular events or cases of stent thrombosis observed.

Molecular biology studies have suggested that the genes responsible for the proliferative response potentially remain active for a period of up to 21 days after vessel injury.[40] These clinical findings therefore support the concept of a certain threshold of drug, delivered over a sustained prolonged

period of time, being required to "dampen" down the inflammatory and subsequent NIH response.

Type of DES? Type of Drug?

Schomig et al,[41] in a meta-analysis of 16 trials comparing SES with PES, suggested the benefit of SES over PES over a median 2-year follow-up, with a significant reduction in TVR (hazard ratio 0.74, 95% [confidence interval] CI 0.63 to 0.87, $P<0.001$) and stent thrombosis (hazard ratio 0.66, 95% CI 0.46 to 0.94, $P=0.02$) without a mortality benefit. The reasons for this apparent benefit are complex but have been suggested to be related to the slower polymer release kinetics of SES compared with PES. However, data from the Sirolimus-Eluting Stent Compared with Paclitaxel-Eluting Stent for Coronary Revascularization (SIRTAX) trial have suggested a possible "catch-up" in LLL with SES over a 5-year follow-up, with no significant differences in LLL observed between the 2 groups.[3]

Data from the Swedish Coronary Angiography and Angioplasty Registry (SCAAR), registry involving >35 000 patients implanted with 4 different types of DES (Endeavor, SES, Taxus Express, and Liberte) in real-world practice at 2-year follow-up showed that the rates of restenosis with DES implantation were significantly higher in patients with diabetes mellitus and that important differences in the efficacy of differing types of DES existed.[42] In particular, the restenosis rates with Endeavor were twice as high in diabetic patients compared with other DES types. Higher restenosis rates were also evident in diabetic patients with Endeavor (relative risk 1.77, 95% CI 1.29 to 2.43) and SES (relative risk 1.25, 95% CI 1.04 to 1.51) when compared with nondiabetic patients. Five-year unpublished follow-up data from the SCAAR registry[43] continued to demonstrate differences in the efficacy of the first- and second-generation DES in reducing the rates of restenosis, with a trend toward better outcomes seen after nearly 2 years of EES use.

The EES releases 80% of the drug within 30 days and nearly all the drug within 4 months. In the Spirit I, II, and III trials, a LLL of 0.10, 0.16, and 0.33 mm and TVR rates of 3.8%, 3.4%, and 4.6% were observed at 6, 12, and 24 months, respectively.[3]

Conversely, the Endeavor reported a LLL of 0.60 mm and 0.67 mm and TVR of 6.3% and 4.5%, respectively, in the Endeavor III and IV trials at 12 months. The Endeavor, however, elutes 95% of its drug very rapidly (within 14 days); this is highly likely to be the main reason for the poorer results seen. The next-generation Endeavor Resolute stent, consisting of the same cobalt chromium metallic platform (Driver BMS) and the drug (zotarolimus) as the Endeavor stent, but with substantially longer polymer drug release kinetics (180 days), reported an in-stent LLL of 0.12, 0.22, and 0.27 mm at 4, 9, and 13 months respectively, with angiographic equivalency (LLL 0.19 mm) in terms of meeting the criteria for noninferiority ($P=0.08$), being met when compared with EES. Equivalency in the 12-month primary end point of target lesion failure (a composite of cardiac death, target vessel MI, and clinically driven target lesion revascularization (8.2% versus 8.3%) and a slight increase in

the rate of definite stent thrombosis (1.2% versus 0.3%, $P=0.01$) were also seen.[44]

Stent Gap, Nonuniform Strut Distribution and Drug Deposition

Takebayashi et al[45] classically described the number and distribution of DES struts, as indentified by IVUS, as being independent significant risk factors (fewer struts and nonuniform stent strut distribution) for NIH formation and the subsequent risk of restenosis. Nonuniform DES strut distribution has been suggested to be attributable to features such as stent design (eg, open versus closed cell), stent gap, vessel curvature, coronary bifurcations, ostial lesions, stent under or overexpansion, polymer peeling, and stent fracture.

Small Vessels and Strut Thickness

Small-vessel disease is a recognized challenging lesion subset with significant risks of restenosis seen with plain old balloon angioplasty and BMS.[1] A recent meta-analysis of the use of DES in small-vessel disease demonstrated that both LLL and binary restenosis were largely dependent on the type of DES implanted.[46] In particular, Xience and Cypher led to restenosis rates of 10% to 15% (5% to 10% and 0% to 5% in medium and large vessels, respectively), compared with 20% to 25% with Taxus (10% to 20% and 2.5% to 7.5% in medium and large vessels, respectively) and 30% to 35% with Endeavor (20% to 30% and 5 to 12.5% in medium and large vessels, respectively).

Mechanisms suggested to explain the poorer outcomes associated with small vessels include: (1) a high degree of vessel stretch and injury, (2) a smaller postprocedural lumen area, and (3) a higher metal density.[47] The overstretch theory, however, is controversial with evidence suggesting a possible adverse effect with increased NIH,[47] no significant effect,[48] or even potential benefit.[49] The latter beneficial effects have been proposed to be related to a higher balloon-to-artery ratio, the so-called bigger is better paradigm (see Implantation Factors) leading to appropriate apposition of the stent to the vessel wall.

Thicker stent struts have been linked to an increased risk of restenosis with BMS and small vessels.[47] The underlying rationale is that a thinner stent strut would have less of a "footprint" on the vessel wall with a consequential reduced inflammatory response. With DES, however, a complex relationship exists between the strut material and characteristics, stent design, polymer type, and drug release kinetics, with Cypher and Xience appearing to have the lowest risk of binary restenosis in small vessels, despite a large disparity in stent strut thicknesses ($\approx$150 μm versus 90 μm). A fairer comparison perhaps would be between the Taxus Liberte and Express because both are identical except the Taxus Liberte contains thinner struts, more flexible cell geometry, and uniform cell distribution. In the SCAAR registry,[42] the Taxus Express was shown to have a mild but significantly higher adjusted risk of restenosis compared to Taxus Liberte.

"On- and Off-Label" Use of DES

The Strategic Transcatheter Evaluation of New Therapies (STENT) Group, is the largest, multicenter, prospective
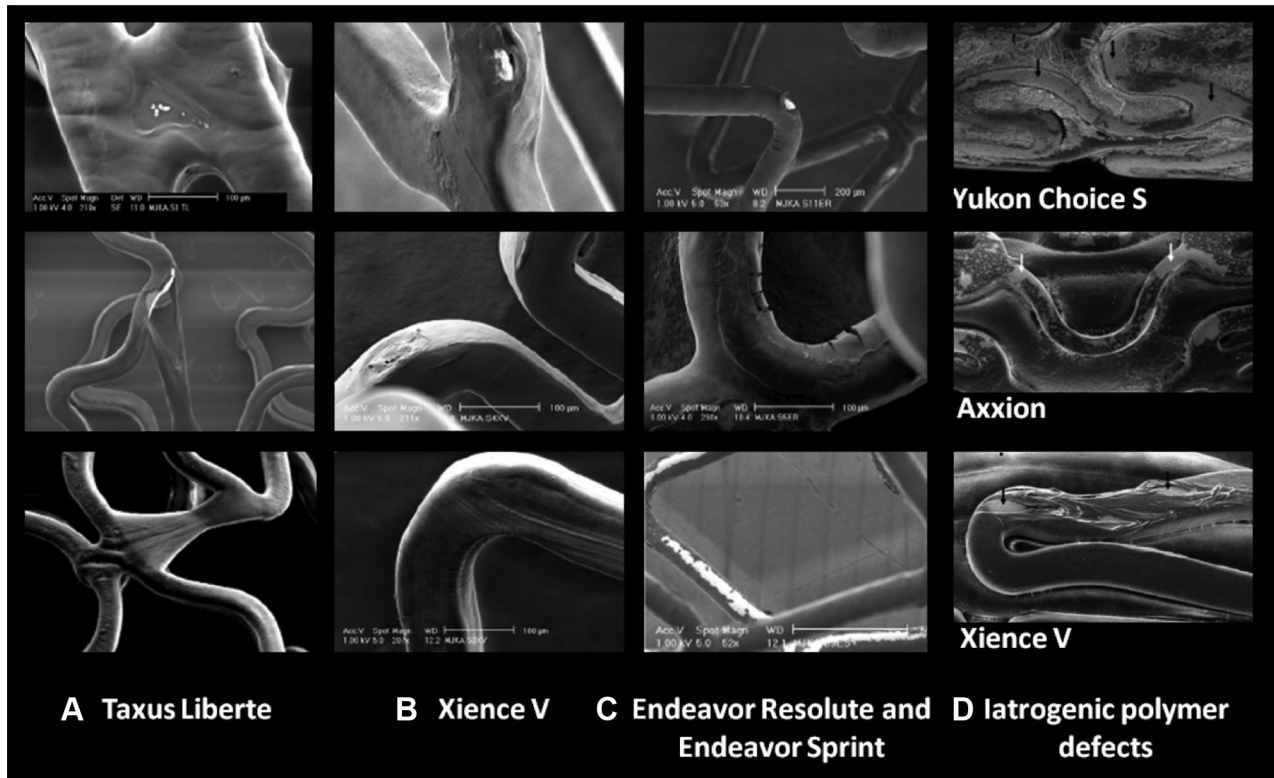
Figure 6. Polymer defects seen in second-generation DES. DES indicates drug-eluting stent. **A,** Taxus Liberte: thinning (top), webbing with (middle), and without (bottom) bare-metal exposure of the polymer coating. **B,** Xience V: apparent bare-metal area (top), crater-shaped irregularity without bare-metal exposure (middle), and "wrinkles" in the polymer coating (bottom). **C,** Endeavor Resolute: crater irregularity with an apparent central bare-metal area (top), cracks in the polymer coating (middle); **C,** Endeavor Sprint: polymer peeling with exposure of significant bare-metal areas (bottom). Iatrogenic polymer defects: **D,** No drug coverage was seen in up to 40% of the surface area of the unexpanded Yukon Choice S (black arrows) and Axxion (white arrows); **D,** Xience V: wrinkling and cracking of polymer with bare metal exposure (black arrows). **A–C,** Adapted and reproduced from Basalus et al, *EuroIntervention.* 2009;5:160, Copyright (2009), with permission from Europa Edition.[53] **D,** Adapted and reproduced with permission from Wiemer et al.[54]

registry involving >15 000 patients, evaluated the late outcomes associated with DES implantation in the United States.[50] This compared on-label (short de novo lesions in coronary arteries measuring >2.5 mm and <3.5 mm for SES or <3.75 mm PES) and off-label (ostial, left main stem, chronic total occlusion, saphenous vein graft, small or large vessels/multivessel, STEMI, ISR lesions) indications for DES implantation. An almost doubling in the TVR rate was seen in the off-label group at 9 months (5.7% versus 3.2%, $P<0.0001$) and 2 years (11.8% versus 6.5%, $P<0.0001$).

Data from the Synergy between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery (SYNTAX) study, reflecting a population of patients with highly complex off-label use of DES in 3-vessel or left main stem disease, have reported even higher rates of TVR at 1, 2, and 3 years at 11.6%, 17.4%, and 19.7%, respectively.[51]

Polymer Disruption, Peeling, and Cracking

Polymer disruption, peeling, and cracking, and subsequent exposure of bare-metal areas have been demonstrated to occur in bench studies involving both first- and second-generation DES (Figure 6) using light or scanning electron microscopy.[52,53] Although there is no direct evidence to suggest that the integrity of the polymer coating is a direct cause of restenosis, there are sufficient theoretical concerns to

warrant concern through nonuniform local drug distribution or the disrupted polymer potentially acting as a nidus for an ongoing inflammatory response.[14]

Other concerns with regard to the potential for polymer disruption involve the percutaneous coronary intervention procedure itself. Wiemer et al[54] demonstrated that in DES that had failed to be delivered to the intended implantation site in tortuous calcified lesions, significant damage and cracking of the polymer had occurred to varying extents with multiple types of second-generation DES. Scanning electron microscopy revealed many cases of deep damage to the polymer with exposure of the bare metal, in particular, the Endeavor RX stents showed up to 20% damage to the surface area. With polymer-free DES, a large proportion of the surface area was shown to be without any layer of drug (Figure 6).

In bench work utilizing scanning electron microscopy of the polymer integrity of 5 different types of DES (Cypher, Cypher Select, Endeavor, Taxus Express, and Taxus Liberte) after undergoing kissing balloon postdilatation, Guerin et al[55] demonstrated significantly greater coating damage to the ostial struts, especially along the overstretched segments, with cracking of the polymer seen in all cases and even exposure of bare metal. Of note is that the Endeavor stent showed a subtotal destruction of its coating on the luminal surface in all segments, whereas the other DES demonstrated more focal localized abnormalities.
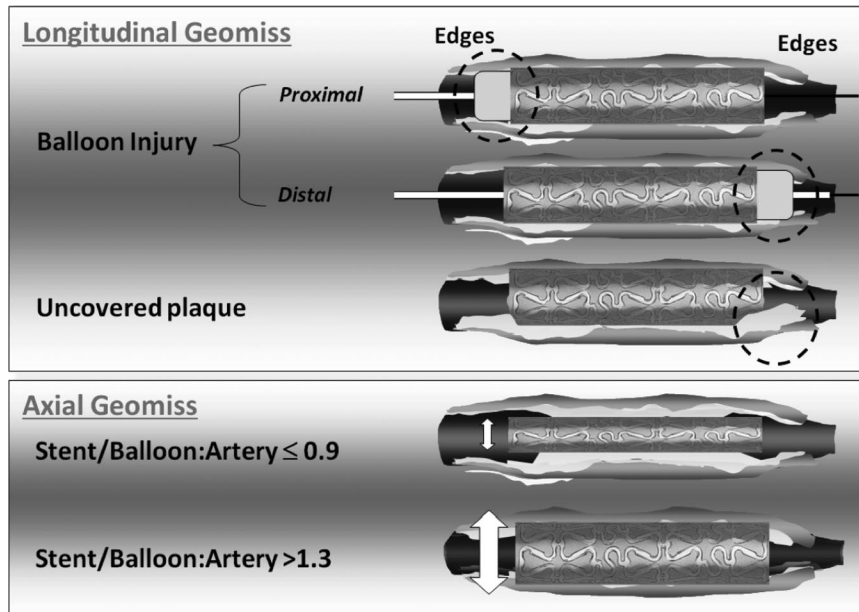
Figure 7. Illustration of the mechanisms of longitudinal (LGM) and axial geographical miss (AGM). Adapted and reproduced with permission from Costa et al.[64]

Stent Fractures

Stent fracture related to DES implantation in coronary arteries was first reported by our group in 2004. Subsequent retrospective and prospective registries have quoted restenosis rates ranging from 15% to 100% in patients identified to have stent fractures.[56] In the only randomized controlled trial reporting the incidence of stent fracture and outcomes after DES implantation and subsequent mandatory angiographic follow-up (LONG-DES-II study), a 14% incidence of restenosis was observed.[57]

The restenosis associated with DES fractures tends to occur fairly late and focally, reflecting the local trauma sustained by the vessel at the fracture site. Consequently, the subsequent healing response occurs without any drug to suppress the NIH response, which in itself may be further exacerbated by exposure of the vessel to the disrupted polymer.

The etiology of the DES fractures appears to be related to 2 principle factors. First, mechanical fatigue of the metallic stent can occur because of excessive movements during cardiac contraction, especially at a hinge-point where the potential for 2 opposing forces may occur at the same site. In particular, this may occur in the right coronary artery or a saphenous vein graft, because of their greater propensity for angulation and tortuosity. Second, a closed-cell design, such as occurs with SES, is less likely to be able to withstand the pressures related to excessive movements compared with the open-cell design of a PES. The incidence of stent fracture is reported at less than 0.1% with the PES and approximately 2.3% with SES.[56]

Long stents, overlapping stents, tight lesions that have been vigorously postdilated and expanded, myocardial bridge sites, and areas of significant curvature are all factors that may predispose patients to DES fracture.[56]

Implantation Factors

Incomplete Stent Expansion

A smaller postprocedural minimal lumen diameter and a greater residual stenosis have been shown to be significant predictors of long-term patency and clinical outcomes. Evidence of stent underexpansion, as assessed by IVUS and despite apparently successful angiographic results, has been reported to be as high as 24% and 28% with SES and PES, respectively.[58,59] However, what proportion of these cases is clinically relevant remains unclear.

In a classical meta-analysis (n=2972 patients) investigating IVUS versus angiographic-guided BMS implantation, Casella et al[60] demonstrated at 6-month follow-up a reduction in TVR (OR 0.62; 95% CI 0.49 to 0.78; $P=0.00003$), binary restenosis (OR 0.75; 95% CI 0.60 to 0.94; $P=0.01$), and major adverse cardiovascular events (OR 0.79; 95% CI 0.64 to 0.98; $P=0.03$). Of note is that only one small, single-center randomized controlled trial on IVUS-guided DES implantation has been published; this failed to show any differences in the clinical end points of major adverse cardiovascular events (death, MI, and reintervention) at 18 months.[61]

The initial results of the important Angiographic versus IVUS Optimization (AVIVO) randomized, multicenter trial, however, have recently been presented.[62] IVUS versus angiographic-guided DES implantation in complex lesions was investigated, with 142 patients in each study arm. At 30 days and 9 months, no significant differences were seen in the combined end point of MI, target lesion revascularization, TVR, or cardiac death (85.9% versus 83.1%, $P=0.47$). The primary end point of a higher minimal lumen diameter, however, was seen in the IVUS-guided DES implantation group (2.70 mm versus 2.51 mm, $P=0.0002$). Because only 39% of patients had quantitative coronary angiography at 9 months, no comments could be made regarding whether this approach would potentially lead to a reduction in restenosis rates.

The most plausible and strongest theory to explain the underlying mechanism relating stent underexpansion to restenosis is the so-called bigger-is-better paradigm. Effectively, if the minimum stent area is smaller at baseline, then the expected NIH formation post-DES implantation would be

more likely to be of significance, whereas if the minimum stent area was larger, then the same amount of NIH would be clinically less relevant in causing binary restenosis.[63] Other theories postulated have included possible asymmetrical stent expansion affecting the subsequent pattern of neointimal growth through uneven drug delivery.[1]

Geographical Miss/Barotrauma to Unstented Segments

Geographical miss (GM) is essentially a failure to appropriately cover an injured vessel, such 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 Stent deployment Techniques on cLinicaL outcomes of patients treated with the cypheR stent (STLLR) study.[64] GM was observed in nearly two-thirds (66.5%) of the study group with almost half (47.6%) of the patients experiencing longitudinal GM, over one-third (35.2%) axial GM, and 16.5% a combination of the two. Longitudinal GM was defined as injured or diseased stenotic segment not fully covered by DES, and axial GM was defined as potentially undersizing or oversizing the balloon (Figure 7).

At 1-year follow-up, there was more than a 2-fold increase in TVR (5.1% versus 2.5%; $P=0.025$) and a 3-fold increase in MI (2.4% versus 0.8%; $P=0.04$) in patients with GM. These findings were almost exclusively related to longitudinal GM (6.1% versus 2.6%; $P=0.001$) with two-thirds of cases being secondary to balloon injury outside the stent margins. The lack of effect of axial GM (4.2% versus 4.3%; p non significant) recently has been corroborated, in which it was shown 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[48,65] and does perhaps argue against the IVUS optimization of DES deployment.

Deployment of a DES in a Clot-Laden Arterial Segment

The deployment of a DES in a clot-laden arterial segment has been shown in an ex vivo model to lead to a 10-fold reduction in drug penetration into the vessel wall,[66] which may potentially affect clinical outcomes (Figure 8). Despite these theoretical concerns, a recent meta-analysis of 13 trials (n=7244) has shown the significant benefits of DES over BMS in primarily reducing TVR (5.11% versus 11.19%, $P<0.00001$) and recurrent MI (3.03% versus 3.70%, $P=0.02$) in patients with STEMI at up to 1 year.[67]

The widespread use of glycoprotein-IIb/IIIa inhibitors and aspiration thrombectomy devices may be the reasons why these concerns may have not materialized in clinical trials in the short term. Concerns over the long-term safety of DES in STEMI do persist, however, because of the potential risk of late-acquired stent malapposition and consequent LST.[3] The concerns about reduced absorption of the drug from DES should be borne in mind in a thrombus-laden vessel, especially when there has been inadequate resolution of thrombus and DES implantation is to be considered.
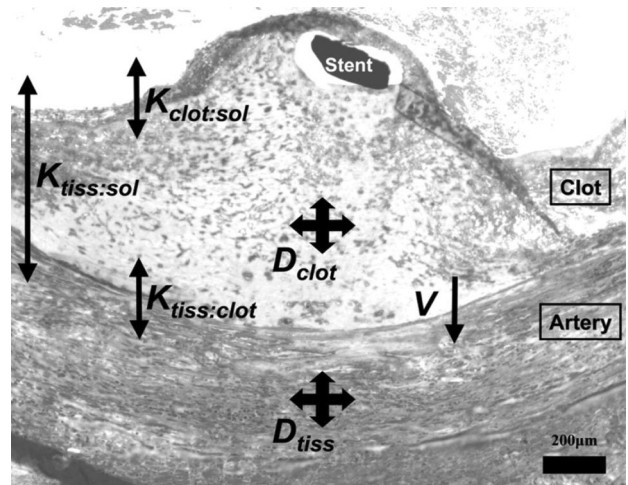

Figure 8. Deployment of a DES in a clot-laden arterial segment. The concepts of drug diffusivities in clot (Dclot) and tissue (Dtiss), drug capacity of clot relative to solution (Kclot:sol), drug capacity of arterial tissue relative to clot (Ktiss:clot), drug capacity of arterial tissue relative to solution (Ktiss:sol) and drug convective velocities (V) are illustrated and demonstrate the complexities of stenting in acute MI. DES indicates drug-eluting stent; MI, myocardial infarction. Reproduced with permission from Hwang et al.[66]

Conclusion

Despite the low incidence of DES restenosis, the burden of ISR in absolute numbers probably will continue to grow with the increasing uptake of second-generation DES in conventional percutaneous coronary intervention practice. Large-scale clinical trials and registries, therefore, are required to best translate these restenotic mechanisms into either enhanced DES design or further effective treatment options. For example, the pooled data of the RCTs investigating EES comprises almost 15 000 patients and, apart from mortality, would potentially be of sufficient power to detect rare events such as stent thrombosis.[68]

Apart from biological factors, there are potentially controllable factors within arterial and stent factors. However, it should be acknowledged that in the treatment of in-stent-restenosis, the evidence for using a DES with a different drug remains unproven.[9] Ultimately, the implantation factors are the most important controllable factors from the perspective of the interventional cardiologist.

Acknowledgments

Disclosures

None.

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