Drug-eluting stents (DES) represent a revolutionary technology in their unique ability to provide both mechanical and biological solutions simultaneously to the target lesion. As a result of biological effects from the pharmacological agents and interaction of DES components with the arterial wall, considerable differences exist between DES and conventional bare metal stents (BMS), yet some of the old lessons learned in the BMS era remain clinically significant. In this context, contrast angiography provides very little information about in vivo device properties and their biomechanical effects on the arterial wall. In contrast, current catheter-based imaging tools, such as intravascular ultrasound, optical coherence tomography, and intracoronary angioscopy can offer unique insights into DES through direct assessment of the device and treated vessel in the clinical setting. This article reviews these insights from current DES with particular focus on performance and safety characteristics as well as discussing an optimal deployment technique, based upon findings obtained through the use of the invasive imaging technologies. (Circ J 2009; 73: 1371–1380)

Key Words: Coronary artery disease; Drug-eluting stent (DES); Intravascular ultrasound; Restenosis; Thrombosis

In the history of percutaneous coronary intervention, drug-eluting stents (DES) are recognized as revolutionary technologies with their unique ability to provide both mechanical and biological solutions simultaneously to the target lesion. While the clinical success of DES depends on these 2 properties, the ability of the operator to properly deploy the device is also of utmost importance. Although contrast angiography remains the clinical standard for coronary imaging, this conventional method provides very little information about in vivo device properties and their effects on the arterial wall. In contrast, catheter-based imaging tools, such as intravascular ultrasound (IVUS), optical coherence tomography (OCT), and intracoronary angioscopy can offer unique insights into novel interventional technologies through direct assessment of the device and the treated vessel. This article will review our multimodality insights into current DES, focusing on performance, safety, and an optimal deployment technique.

Performance Characteristics

Neointimal Hyperplasia

Spatial Distribution

IVUS observations from clinical experience with antiproliferative DES have shown a striking inhibition of in-stent neointimal hyperplasia. In addition to the absolute amount of neointimal hyperplasia, significant differences can be observed in its spatial distribution within conventional bare metal stents (BMS) vs current DES. In BMS, several IVUS studies reported an association between the native plaque burden and subsequent neointimal hyperplasia in terms of both circumferential and longitudinal distributions within the stent. On average, across most patients, a wide individual variation in native disease along the target segment generally results in a relatively even neointimal distribution throughout the stent. In

Figure 1. Focality assessment of neointima by intravascular ultrasound. If the data points spread near the line of identity (y=x), the drug-eluting stent (DES) has a diffuse nature of neointimal growth. On the contrary, if the data points are mostly located near the y-axis, the DES generally develops focal neointimal hyperplasia. This particular example demonstrates more diffuse neointimal growth of the Endeavor stents compared to the Cypher stents, indicating that volumetric data alone can significantly underestimate recurrence of ischemia in Cypher.
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Lesion-to-Lesion Variability In a statistical analysis of a given population, neointimal volume within BMS generally follows a near-Gaussian or normal frequency distribution around a mean value of 30 to 35%. On the histogram, the mean value represents the overall biological response to the stent, whereas the width of the distribution curve indicates the degree of individual variation in vascular response. Restenosis corresponds to the right tail end of the curve above a threshold of tolerable neointima. Biological effects of a drug-eluting stent (DES) can result in a markedly skewed or deformed frequency distribution (Right). A larger acute lumen gain would continue to help reduce the restenosis rate, if the DES shows a wide variation with a relatively long right tail end (DES-B) (even if the mean value looks small).

In DES, however, significant biological modification properties often result in a non-Gaussian frequency distribution with variable shapes of the tail ends. With a markedly skewed or deformed frequency distribution, the mean value of neointimal volume might no longer correlate well with the area of the right tail end (restenosis rate) (Figure 2), which in part explains the discrepancy between the reported IVUS results and clinical restenosis often seen in recent DES trials. Thus, it is essential to understand that our conventional approach to report and analyze IVUS data, such as data expression as mean ± SD or parametric analyses, might no longer be appropriate in the DES era. From a clinical perspective, while an aggressive bigger-is-better strategy does not theoretically provide further benefit for DES with a short right tail end, a larger acute lumen gain would continue to help reduce the restenosis rate of DES with a relatively long tail-end distribution, regardless of the mean values (Figure 2).

Time Course In event-free patients, both previously published data and our core laboratory database suggest that neointimal proliferation within BMS generally reaches its peak around 6 months after the implantation and, thereafter, a certain degree of neointimal regression occurs, presumably reflecting a reduction in proteoglycan content as a natural healing response to initial vascular injury. However, earlier clinical experience with intracoronary brachytherapy raised a concern of a possible late catch-up phenomenon following antiproliferative treatment of BMS.
A preclinical study with sirolimus-eluting stents has also suggested that DES might delay, rather than permanently suppress, neointimal proliferation. Although serial IVUS data beyond the primary follow-up period (6–9 months) are limited in most DES trials, a few clinical studies have addressed this potential issue. In an IVUS study of the TAXUS-II trial, the slow-release and moderate-release Taxus stents both exhibited a small but significant increase in neointimal area between 6 months and 2 years.8 Similar results were also reported in our recent IVUS substudy of the DDD (Double Dose Diabetes) trial, in which serial volumetric analyses at baseline, 6 months and 2 years were evaluated in diabetic patients treated with double-dose or conventional single-dose sirolimus-eluting stents.10 Furthermore, the First-In-Man registry of sirolimus-eluting stents has reported a continued increase of neointimal volume over the 4-year period, although the rate of neointimal growth slowed down after 2 years.11 In this study, a continued increase in neointimal echogenicity was also observed, suggesting that a fibrotic process of neointima might still be ongoing up to 4 years after the implantation. Despite the well-maintained neointimal suppression as compared to BMS, the exact duration of arterial healing following DES implantation remains to be investigated.

Vessel Scaffolding
Acute Expansion and Recoil Combined with the pharmacological neointimal suppression discussed above, mechanical vessel scaffolding represents the primary mechanism of action of DES. To date, the majority of clinically available DES have been developed based on conventional BMS platforms. Because current polymer coatings do not significantly affect mechanical stent properties, the expandability and radial strength of current DES are equivalent to those reported in the BMS era. In an in vivo porcine study of normal coronary arteries, real-time IVUS assessment using a 0.018-in imaging core revealed significant acute stent recoil from the maximum balloon inflation to deflation: 10% in diameter and 16–17% in cross-sectional area for 316L stainless-steel, slotted-tube, balloon-expandable stents (MultiLink and NIR).12 In a recent case report utilizing an OCT imaging wire in a patient treated for a significant lesion in the left circumflex artery, the real-time in vivo assessment of a commercially available DES (Cypher) demonstrated acute stent recoil of 16% in diameter immediately after post-dilatation.13 Another clinical study has systematically compared IVUS-measured final DES dimensions vs the values expected from manufacturer-supplied compliance charts.14 In this study, Cypher and Taxus achieved only 75% of predicted stent diameter and 66% of predicted stent area in clinical settings. Thus, careful attention to appropriate post-dilatation techniques is mandatory, because initial stent expansion remains an important determinant of both restenosis and stent thrombosis in the DES era.

Chronic Recoil and Expansion In a serial IVUS study of various BMS, chronic stent recoil was observed in some stent designs thereby contributing to late lumen loss. More recently, the incidence and degree of chronic stent recoil of current DES were reported from our core laboratory IVUS database (Figure 3).15 In this retrospective study, diffuse stent recoil was defined as >10% decrease in stent volume during follow-up, whereas focal stent recoil was defined as >20% stent area decrease in 3 consecutive 1-mm sub-segments. Although both diffuse and focal stent recoil at 6 months were observed slightly more often in cobalt-chromium modular DES (Endeavor: 5–7%) than in the first-generation stainless-steel DES (Cypher and Taxus Express: 0–2%), neither finding reached statistical significance. Considering that the Endeavor stents were used in more complex lesions in this study population, the incidence of chronic stent recoil appears to be low with no clinically meaningful difference among current generation DES. Nevertheless, both acute and chronic stent recoil might be design and/or material specific. The detailed mechanical scaffolding properties have yet to be investigated in vivo for newer generation DES utilizing a different stent material,

Figure 3. A case with focal chronic stent recoil detected by intravascular ultrasound (IVUS). Dashed lines represent stent contours on the longitudinal IVUS images (Left). At 9 months, minimal neointima is observed, and thus, the late lumen loss primarily resulted from the decrease in vessel (VA) and stent areas (SA) at the tightest, calcified segment.
such as cobalt-based alloy, with a thinner strut design.

At the other end of the spectrum, some newer DES with nitinol-based self-expanding configurations have demonstrated significant chronic stent expansion as assessed by serial IVUS examination. The CARE 1 trial was a single-arm feasibility study of a novel ultra-low profile, guidewire-mounted self-expanding stent system (Sparrow, CardioMind, Inc). The bare-metal configuration used in this First-in-Man study resulted in a similar degree of neointimal response (34±9%) as seen with conventional BMS.25 However, stent volume increased by 13% during the first 6 months thereby negating lumen loss as a result of neointimal hyperplasia by 33%. No additional changes in any IVUS parameters were observed between 6 and 12 months. Another new DES project with self-expanding technology includes a dedicated bifurcation stent comprised of a nitinol, flared-shaped stent platform and bioabsorbable polymer coating with Biolimus A9 (Axxess, Devax Inc). A series of early clinical trials demonstrated significant neointimal suppression (2.3% volume obstruction in left main, and 4.3% in non left main bifurcation lesions) comparable to current generation balloon-expandable DES.17-19 Consequently, chronic stent expansion of this DES (12% stent volume increase in left main, and 30% in non left main lesions) led to a considerable late lumen gain at 6–9 months after the implantation (1.0 mm³/mm in left main, and 1.9 mm³/mm in non left main lesions). Importantly, in these types of DES, angiographic assessment alone would significantly underestimate the amount of neointimal hyperplasia inside the stent.

**Impact of Non-Uniform Vessel Scaffolding** DES technology utilizes the stent platform not only for mechanical prevention of vessel recoil, but for drug delivery to the vessel wall as well. Therefore, strut distribution can impact the neointimal suppression effect of DES, as a result of the non-uniformity of drug concentration within the vessel wall. This theoretical concern was first highlighted by an experimental study of paclitaxel-eluting stents and was subsequently demonstrated in clinical settings by an IVUS study of closed-cell sirolimus-eluting stents (Cypher).20,21 In the initial clinical report, the maximal neointimal area correlated with fewer stent struts and with a larger angle between adjacent stent struts. These observations were also replicated in our IVUS substudy of the ENDEAVOR-II trial in which an open-cell stent (Driver, Medtronic Vascular, Inc) was used as the platform of zotarolimus-eluting PC coating stents (Endeavor).22 When defined as >90° of inter-strut angle at >1-mm stent length, non-uniform strut distribution was detected in 36% of the enrolled patients, and the average length of the non-uniform strut segment was 2.1 mm. In addition to the correlation with increased neointimal hyperplasia, the non-uniform strut segments showed a larger stent area than the uniform strut segments, suggesting that stent overdilatation, possibly with target segment angulation, might be associated with this observation.

**Safety Characteristics**

**Tissue Coverage Over DES Struts**

Delayed arterial healing and incomplete tissue coverage over stent struts have been suggested as pathological risk factors of late DES thrombosis. Despite its limited spatial resolutions, several IVUS studies have demonstrated that IVUS-detectable neointimal coverage over the stent surface can vary significantly among different types of DES, nearly in parallel with stent surface endothelialization reported in animal studies.25 The recent advent of OCT technology has also enabled microscopic-level evaluation of thin tissue coverage over stent struts in clinical patients (Figure 4). In sirolimus-eluting stents, tissue coverage has been reported to occur in >85% of stent struts by 6 months, although complete strut coverage was seen in only 24–42% of the stents even at 12 months.26-29 Several investigators have also suggested that the degree of arterial healing might be affected by underlying plaque pathology, demonstrating higher rates of uncovered struts in unstable patients.30-34 Accordingly, OCT assessment of strut coverage has been incorporated as a primary endpoint of multicenter DES trials, including ORCA-1 and ODESSA.31 One technical limitation, however, is accurate discrimination of the thin tissue covering the stent struts (ie, neointima or thrombus/fibrin), and whether this can be used as a surrogate safety endpoint of DES thrombosis awaits future investigations.

Intracoronary angioscopy is another optical diagnostic modality to provide unique insights into tissue inside DES. Particularly, the high sensitivity of angioscopy to detect...
mural thrombus has allowed showing sustained subclinical thrombus formation associated with delayed neointimal coverage over DES struts even 2 years after implantation. Several groups have also demonstrated a significant association of this finding with underlying yellow plaque that is generally sealed by white smooth neointima by 1 year in BMS but often continues to be exposed in DES. The sustained exposure of yellow plaque because of significant neointimal suppression might in part account for late occurrence of stent thrombosis, independent of possible thrombogenicity of the DES itself. Furthermore, a recent angiographic study reported that yellow color grade of neointima within DES increased significantly from baseline to 10-month follow-up. Even in lesions with no yellow plaque at baseline, yellow color was newly developed in 94% of lesions at follow-up, suggesting that DES might indeed promote formation of atherosclerotic yellow neointima in the stented lesion. This in vivo finding is compatible with an autopsy study wherein atherosclerotic change within the neointima was seen in >40% of DES by 9 months, whereas it occurred only beyond 2 years in BMS and remained a rare finding until 4 years. A possible mechanism for this might be endothelial dysfunction or its incomplete lining within DES allowing accelerated infiltration of lipid as well as monocyte adherence and migration through the impaired endothelial barrier. An unknown percentage of very late stent thrombosis might also be explained by this accelerated atherosclerosis of the tissue within DES.

Endothelial Function

As discussed previously, ideal re-endothelialization as a safety profile of DES includes not only anatomical restoration of a complete endothelial layer, but effective functional recovery as well. Although direct assessment of endothelial function within the stented segment is technically difficult in vivo, the functional recovery at the adjacent non-stented segment has been investigated by measuring acetylcholine-, atrial pacing- or exercise-induced coronary vasomotor changes. To date, multiple physiological studies of DES have consistently shown persistent (>6 months) endothelial dysfunction of the stented artery particularly in the first-generation DES (sirolimus- and paclitaxel-eluting stents). Interestingly, these paradoxical vasoconstrictor responses appeared to be more prominent in distal rather than in proximal vessel segments. A study of reperfusion therapy for acute myocardial infarction also demonstrated aggravated endothelium-dependent vasomotor function both in resistance and epicardial coronary arteries 2 weeks after sirolimus-eluting stent implantation. This was associated with reduced myocardial vascular endothelial growth factor secretion, suggesting that diffusion of sirolimus into coronary blood flowing through the stent might impair the recovery of reperfusion-induced endothelial injury in the infarct-related coronary artery. Interestingly, sustained endothelial dysfunction appears to be less pronounced in newer-generation DES (zotarolimus-eluting stents with PC coating and biolimus A9-eluting stents with a bioresorbable polymer). The clinical relevance of these observations, however, needs to be clarified in large-population studies.

Vascular Responses Outside DES

Edge Effects

The discovery of ‘edge effects’ associated with intracoronary brachytherapy raised the concern of lumen narrowing in adjacent reference segments as a potential limitation of DES as well. In brachytherapy, edge effects are mostly related to inadequate coverage of injured edge segments, also known as geographic miss. In terms of the spatial relationship between the balloon-injured zone and an effective drug delivery zone, DES can theoretically show a similar phenomenon, unless the pharmacological agent can sufficiently diffuse several millimeters beyond both stent edges into the adjacent segments. Current DES, however, have not shown accelerated edge restenosis overall when compared to conventional BMS. Serial IVUS analyses in multiple clinical trials indeed demonstrated a beneficial edge effect of DES that primarily resulted from the lack of vessel shrinkage, despite similar amounts of plaque proliferation compared to BMS. This phenomenon is often more distinct in distal rather than in proximal edge segments, possibly suggesting the effect of a loaded drug on the downstream vessel segment. However, a series of our IVUS analyses from the core laboratory database indicates that in-stent lumen patency might be the primary determinant of distal vessel responses at follow-up. Preserved lumen dimensions within DES might better maintain proximal laminar flow than BMS, leading to favorable flow dynamics and shear stress profiles at the distal adjacent segment.

Peri-Stent Vessel Remodeling

IVUS studies of DES trials utilizing paclitaxel have consistently demonstrated increased vessel and peri-stent plaque volumes during follow-up; whereas sirolimus- and zotarolimus-eluting stents have shown no significant changes in overall vessel volume in the stented segment. The characteristic positive vessel remodeling, or peri-stent plaque increase, of paclitaxel-eluting stents appears to be dose-dependent. In TAXUS-II, serial IVUS analyses revealed progressive peri-stent plaque increases from BMS, slow-release to moderate-release paclitaxel-eluting stents during the first 6 months, which subsequently regressed completely in the slow-release group but only partially in the moderate-release group at 2 years. In contrast, the First-in-Man registry of sirolimus-eluting stents showed no change in peri-stent plaque volume up to 2 years, followed by significant plaque shrinkage with an increase in plaque echogenicity between 2 and 4 years. Similarly, a recent IVUS report from ENDEAVOR-IV showed no significant change in plaque volume surrounding zotarolimus-eluting stents at 8 months. Interestingly, however, more detailed mm-by-mm analyses applied to this IVUS study found focal vessel remodeling (defined as >20% vessel area increase in >3 consecutive 1-mm sub-segments) in 5% of zotarolimus-eluting stents (vs 25% of paclitaxel-eluting stent), which was not well appreciated with conventional volume comparisons. At present, the mechanism underlying positive vessel remodeling after DES implantation is poorly understood, and further investigation is required to clarify if the presence and degree of this phenomenon represent abnormal pathological processes within the arterial wall (such as fibrin deposition, chronic inflammation, or medial necrosis) and thus, could serve as one of the safety measures of DES.

Incomplete Stent Apposition (ISA)

Definitions

ISA is characterized by IVUS as 1 or more struts clearly separated from the vessel wall with evidence of blood speckle behind the strut in a segment not associated with any side branches. With serial IVUS performed both at post-procedure and follow-up, ISA can be classified as baseline or late acquired (Figure 5). Baseline ISA can either be resolved or persist at follow-up, and therefore,
ISA observed at follow-up is due to either persistence of baseline ISA (persistent ISA) or newly developed ISA in the segment where struts were completely apposed to the vessel wall at post-procedure (late-acquired ISA). In OCT imaging, strut apposition to the vessel wall is often determined based upon the measured distance from the strut to the vessel wall as compared to the nominal strut thickness including the metal and polymer (Figure 4). Unlike IVUS, the optical interferometer can cause a blooming effect of metal struts, and hence, it is recommended to use the highest intensity point within the strut image as the strut surface, rather than the endoluminal leading edge of the strut image. At follow-up, the higher spatial resolution of OCT can offer further detailed classifications of individual stent strut in relation to the vessel wall and tissue/neointima, such as embedded, apposed without tissue coverage, or incompletely apposed (malapposed) with/without tissue coverage over the strut (Figure 4).

**Baseline ISA** Despite optimal angiographic results with high-pressure balloon dilatation, baseline ISA can be observed in 8% to 30% of DES cases by IVUS. This morphological abnormality primarily results from under-sized stent selection, stent underexpansion, or insufficient stent conformability in calcified or complex-shaped lesions (so-called mechanical ISA). A recent OCT study of current DES suggested that stent designs, including material, cell design and strut thickness, might have a strong impact on the occurrence of this suboptimal result. Despite its theoretical concern, however, there are no data directly linking this finding with unfavorable clinical events at long-term, especially for minor baseline ISA (only detectable by OCT) under dual antiplatelet regimens. However, initial optimization might still be important in patients at particularly high risk for thrombosis (eg, slow flow, renal failure) or in whom the consequences of thrombosis would be severe (eg, left main coronary artery or equivalent). There is also the practical concern that a ‘permanent’ gap between stents and vessel wall might be problematic when operators need to rewire the vessel at future interventions.

**Late-Acquired ISA** The incidence of late-acquired ISA appears to be dependent on the treatment modality. This phenomenon was first brought into the spotlight in intracoronary brachytherapy trials (9.3% average incidence by IVUS). However, subsequent IVUS studies revealed that this can also occur in up to 5–6% of balloon-expandable BMS cases. In contrast, its incidence in DES significantly varies among different DES types and patient populations. In elective stenting, PC-coating zotarolimus-eluting stents have consistently shown extremely low incidences of late-acquired ISA (0.4% in ENDEAVOR-I to IV) compared to reports of 8–13% in patients treated with sirolimus- or paclitaxel-eluting stents. Even higher incidences are often observed in complex studies enrolling acute myocardial infarction, chronic total occlusions, or patients treated with antherectomy before stenting. Overall, a recent meta-analysis of 7 randomized trials reported that the risk of late-acquired ISA in patients with DES was 4 times higher compared to those with BMS (odds ratio 4.36, 95%CI 1.74–10.94, P=0.002).

In contrast to baseline ISA as a mechanical problem, late-acquired ISA primarily results from structural vessel wall changes that occur during the follow-up period (so-called biological ISA). The most commonly reported mechanisms are (1) dissolution of thrombus present at baseline, and (2) chronic, pathological dilatation in the vessel wall (Table 1). While thrombus dissolution can be seen in any type of stents in the treatment of thrombus-containing lesions, abnormal positive vessel remodeling is observed more frequently in DES and brachytherapy. In cases with vessel remodeling, incompletely apposed struts are seen primarily in eccentric plaques, and the gaps develop mainly on the disease-free side of the vessel wall. The combination of mechanical injury at stent implantation and biological injury by DES components might predispose the vessel wall to chronic, pathological dilatation in the setting of little underlying plaque.

At present, the clinical significance of late-acquired ISA remains controversial. The majority of clinical trials failed to show a direct association of this finding with late thrombotic events with the prospective follow-up of late-acquired ISA cases. However, IVUS examination of late DES thrombosis often shows significant ISA at the time of the event. This discrepancy might be partly because of the numbers of late-acquired ISA in each study being too small to be powered to detect a causal relationship with rare thrombotic events. To circumvent this issue, a literature-based meta-analysis was recently performed, suggesting a significantly higher risk of late/very late DES thrombosis in patients with
late ISA (persistent or late-acquired) compared to those without late ISA (odds ratio 6.51, 95% CI 1.34–34.91, \(P=0.02\))\(^5\) However, careful interpretation is still required, considering the inherent limitations of literature-based analysis of heterogeneous studies.

Another methodological issue in the investigation of clinical relevance is lack of appropriate grading or classification of late-acquired ISA. Apparently, currently reported late-acquired ISA is a spectrum ranging from tiny incomplete apposition to extensive aneurysm formation, whereas late ISA associated with thrombosis is often at the extreme end of this spectrum. In addition, the mechanisms by which ISA might contribute to DES thrombosis appear to be multifactorial. Long persistence of incompletely apposed DES struts (persistent baseline ISA or late-acquired ISA) might be associated with delayed re-endothelialization allowing fibrin and platelet deposition. A significant gap or aneurysm formation might reduce local blood flow that promotes platelet adhesion and the coagulation cascade. Or, the late development of ISA might simply represent a pathological process within the arterial wall, such as chronic inflammation with endothelial dysfunction weakening the vessel structure, rather than serving as a direct cause of thrombosis. To more accurately identify late-acquired ISA at risk of future events across the spectrum, a better understanding of this phenomenon is essential.

**Strut Fracture**

Stent strut fracture is not a rare phenomenon in peripheral artery stenting and can also occur following DES implantation in coronary lesions. By angiography, strut fracture is diagnosed as complete or partial separation of the strut at follow-up that had been contiguous at post-deployment. In contrast, intravascular imaging can directly visualize strut struts, offering more detailed morphological assessment and classifications. By IVUS, strut fracture is defined as longitudinal strut discontinuity and can be categorized based upon its morphological characteristics: (1) strut separation, (2) strut subluxation, or (3) strut intussusception (Figure 6). Another recently proposed classification focuses on potential mechanisms of the strut fracture, categorizing them based upon the presence and absence of aneurysm at the fracture site (Type I and II, respectively)\(^5\)

Angiographic or IVUS studies have reported the incidence of DES fracture as 0.8–7.7%, among which in-stent restenosis or stent thrombosis occurred at 22–88%\(^5\) Theoretically, strut fracture of DES can reduce the local drug dose delivered to the arterial wall, as well as affecting the mechanical scaffolding of the affected lesion segment. In addition, the irregular edge of the fractured struts might give chronic stimuli to the vessel wall under cardiac movement. On the other hand, the deployment of long and rigid stents in angulated lesions with hinge motion can lead to significant alteration of local physiology, and therefore, the strut fracture might help restore the original dynamic state in at least some cases. The exact incidence and clinical implications of strut fractures remain to be further investigated in large clinical studies.

**Insights Into Optimal Deployment Technique**

There is compelling clinical evidence that procedure-related factors are important contributors to the development of both restenosis and thrombosis after DES implantation. In particular, the most consistent risk factor is stent underexpansion, the incidence of which has been reported as 60–80% of DES failures. In a study of native coronary lesions treated with sirolimus-eluting stents, the only independent predictors of angiographic restenosis were post-procedural final minimum stent area (MSA) >5.5 mm\(^2\) and IVUS-measured stent length >40 mm (odds ratio 0.586 and 1.029, respectively)\(^5\) In a series of restenotic BMS lesions treated with sirolimus-eluting stents, 82% of recurrent lesions had an MSA <5.0 mm\(^2\) vs 26% of non-recurrent lesions (\(P=0.003\))\(^7\) As previously discussed, the drugs on current DES dramatically reduce the variability of the biological response (neointimal proliferation), and therefore, magnify the prognostic value of the MSA as a powerful predictor for instant restenosis, compared to that in the BMS era\(^5\)

Although published data on DES thrombosis are still limited, several small IVUS studies have suggested stent underexpansion and significant residual reference disease as risk factors of acute, subacute, late DES thrombosis (Figure 7)\(^5\) Some investigator groups have also suggested baseline or late ISA as another possible risk factor however, there is significant overlap in each risk factor between thrombosis and non-thrombosis cases, undoubtedly representing a multifactorial process of this phenomenon. Nevertheless, the importance of procedural optimization cannot be overemphasized because these risk factors are the only variables that operators could alter in the cardiac catheterization laboratory.

![Figure 6: Stanford classification of stent strut fracture. By intravascular ultrasound, strut fracture is defined as longitudinal strut discontinuity, and can be categorized based upon its morphological characteristics.](image-url)
Some early DES trials demonstrated a relatively high incidence of restenosis at the proximal edge segment compared to the distal edge, which led to an important clue for optimal deployment of DES. In our IVUS substudy of the SIRIUS trial, lesions with stent edge stenosis at 8 months had greater reference plaque burden (61% vs 49%, P=0.03) and a higher overexpansion index (maximum stent area/reference minimum lumen area: 1.8 vs 1.5, P=0.03) at baseline, compared to those without edge stenosis.62 More recently, the STLLR trial also demonstrated that geographic miss (defined as the length of injured or stenotic segment not fully covered by DES) had a significant negative impact on clinical outcomes. On-line IVUS guidance can facilitate both the determination of appropriate stent size and length as well as optimal procedural endpoint, achieving the goal of covering significant pathology with reasonable stent expansion, while anchoring the stent ends in relatively plaque-free vessel segments.

For DES treatment of restenosis, early clinical studies suggested a strategic hypothesis that full DES coverage of old BMS might be important for the prevention of recurrent restenosis.63 This aggressive optimization strategy, however, can be associated with several clinical issues, and thus, might not be feasible in every in-stent restenosis case. In a recent retrospective IVUS study of BMS restenosis treated with sirolimus-eluting stents, 77% of the uncovered BMS segments kept adequate lumen patency at follow-up (Figure 8).65 Therefore, as long as the original BMS is well expanded and has a segment with sufficient lumen area, conservative coverage with DES can be a clinical option. Another study from the TAXUS-IV, V, and VI trials evaluated 9-month IVUS results of patients who did not require revascularization at the time of 9-month angiography. At 3 years, revascularization was required in 4.9% of paclitaxel-eluting stents and 6.7% of BMS. Multivariate analysis identified minimum lumen area at 9 months as a significant predictor of late revascularization with the optimal thresholds to best predict subsequent revascularization-free survival of 4.2 mm² for paclitaxel-eluting stents and 4.0 mm² for BMS.

To date, there are several large studies that assessed the impact of IVUS guidance during DES implantation on clinical outcomes. In a single-center study of IVUS-guided DES implantation vs matched control population with angiographic guidance alone, a higher rate of definite stent thrombosis was seen in the angiography-guided group at both 30 days (0.5 vs 1.4%, P=0.046) and 12 months (0.7 vs 2.0%, P=0.014).66 In addition, there was a trend in favor of IVUS guidance in 12-month target lesion revascularization (5.1 vs 7.2%, P=0.07). Another registry enrolled patients with unprotected left main stenosis and demonstrated significantly lower 3-year mortality in the IVUS-guidance group as compared with the conventional angiography-guidance group (4.7% vs 16.0%, log-rank P=0.048; hazard ratio 0.39; 95%CI 0.15–1.02; Cox model P=0.055) in patients treated with DES.67

**Summary and Future Perspectives**

The last century was the period of basic technical develop-
ment and mechanical approaches in the history of percutaneous coronary interventions. In contrast, pioneered by coronary brachytherapy, the advent of DES has opened the new era of biological approaches in our daily clinical practice where our conventional standards established in the mechanical era might not always be applicable. In fact, some of the lessons we have learned from BMS remain clinically significant, yet considerable differences also exist between BMS and first-generation DES. Furthermore, a variety of newer DES with unique mechanical and/or biological properties, such as dedicated bifurcation DES and biodegradable DES, are continuously being added to the list of clinical evaluation. In this rapidly evolving field, it is crucial to properly evaluate the performance and safety characteristics of these novel treatment technologies.

Recent advancements in non-invasive cardiovascular imaging now allow rapid and detailed visualization of cardiovascular structures. At present, however, clinical demand for catheter-based imaging is growing, due to its greater spatial resolution and practical utility for precise procedural guidance and real-time assessment of treatment effects. Current technical efforts in invasive imaging are aimed not only at further improvement of anatomical information, but also at biological or physiological assessment of the target segment. These enhancements might allow a more comprehensive evaluation of the novel treatment device with both mechanical and biological effects, which could help achieve the ultimate goal to deliver the most effective treatment to our patients with truly low rates of complications.

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