Latest on the pathology of drug-eluting stents

The introduction of drug-eluting stents (DES) has significantly reduced restenosis when compared with bare-metal stents and are considered the standard of care in the treatment of symptomatic coronary artery disease. However, late stent thrombosis (LST), potentially resulting in a fatal occlusion of the vessel, emerged as a major concern in first-generation DES (polymer-based sirolimus- and paclitaxel-eluting stents). Pathologic studies of patients dying from late DES thrombosis showed that the underlying mechanism is delayed healing, characterized by poor endothelialization of stent struts and persistence of fibrin. Additional risk factors for LST include long lesions, left main coronary artery disease, bifurcation stenting, underlying ruptured plaques and hypersensitivity reactions. Most recently, correlation of intravascular ultrasound findings with histopathological analysis of thrombus aspirates in patients with very late DES thrombosis showed eosinophilic infiltrates were associated with intravascular ultrasound evidence of vessel remodeling leading to secondary stent malapposition. New DES technologies include biodegradable polymers and stents, polymer-free drug delivery and prohealing approaches. Further preclinical testing and evaluation through large clinical trials is needed to determine the safety and efficacy of future DES in clinical practice.

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Drug-eluting stents (DES) were designed with the primary purpose of inhibiting neointimal proliferation after percutaneous coronary intervention [1,2]. A better understanding of the mechanisms of neointimal growth (restenosis) within bare-metal stents (BMS) led to the development of first-generation DES (the polymer-based sirolimus-eluting stent [SES], Cypher™ [Cordis Corp., FL, USA]; and the polymer-based paclitaxel-eluting stent, Taxus™ [Boston Scientific, Natik, MA, USA]). Prior to approval of these stents they had been tested for safety and efficacy in animal models [3,4] followed by large clinical trials with subsequent approval by the US FDA for use in humans. Both used an already approved pre-existing BMS platform (Bx VELOCITY™ [Cordis Corp.] and Express™ stent [Boston Scientific]) coated with a polymer that allowed controlled release of antiproliferative drugs (sirolimus [Cordis Corp.] or paclitaxel [Boston Scientific]). While DES have significantly reduced the rates of restenosis compared with BMS, they have not completely eradicated it. Moreover, late stent thrombosis (LST) has emerged as a major safety concern, especially in patients with 'off-label' use such as bifurcation lesions, long lesions (>30 mm), acute myocardial infarction (AMI) [5–7], saphenous vein bypass grafts, left main disease, chronic total occlusion and renal failure.

Pathologic studies of patients dying from late DES thrombosis demonstrates delayed arterial healing, characterized by persistent fibrin deposition, mild smooth muscle growth and poor endothelialization as the primary substrate [8]. In this article we will consider the current status of DES in clinical practice and discuss the strengths and limitations of recent advances in this new technology of DES.

Pathology (first-generation DES)

Our understanding of the pathophysiology of late DES thrombosis is derived from human autopsy pathologic samples from patients who received these devices and died from stent-related causes. Since 2004, when the first autopsy case report (FIGURE 1) appeared describing the pathologic findings in a patient with late DES thrombosis [9], our laboratory has acquired over 150 cases in our stent registry and therefore our understanding of the pathology underlying LST has evolved. Most recently, we have expanded our studies to include living patients, in whom we reported correlative pathologic findings in thrombectomy specimens aspirated from living patients with late DES thrombosis who had undergone intravascular ultrasound (IVUS) (FIGURE 2) and optical coherence tomography (OCT) at the time of clinical presentation of LST [10–13].
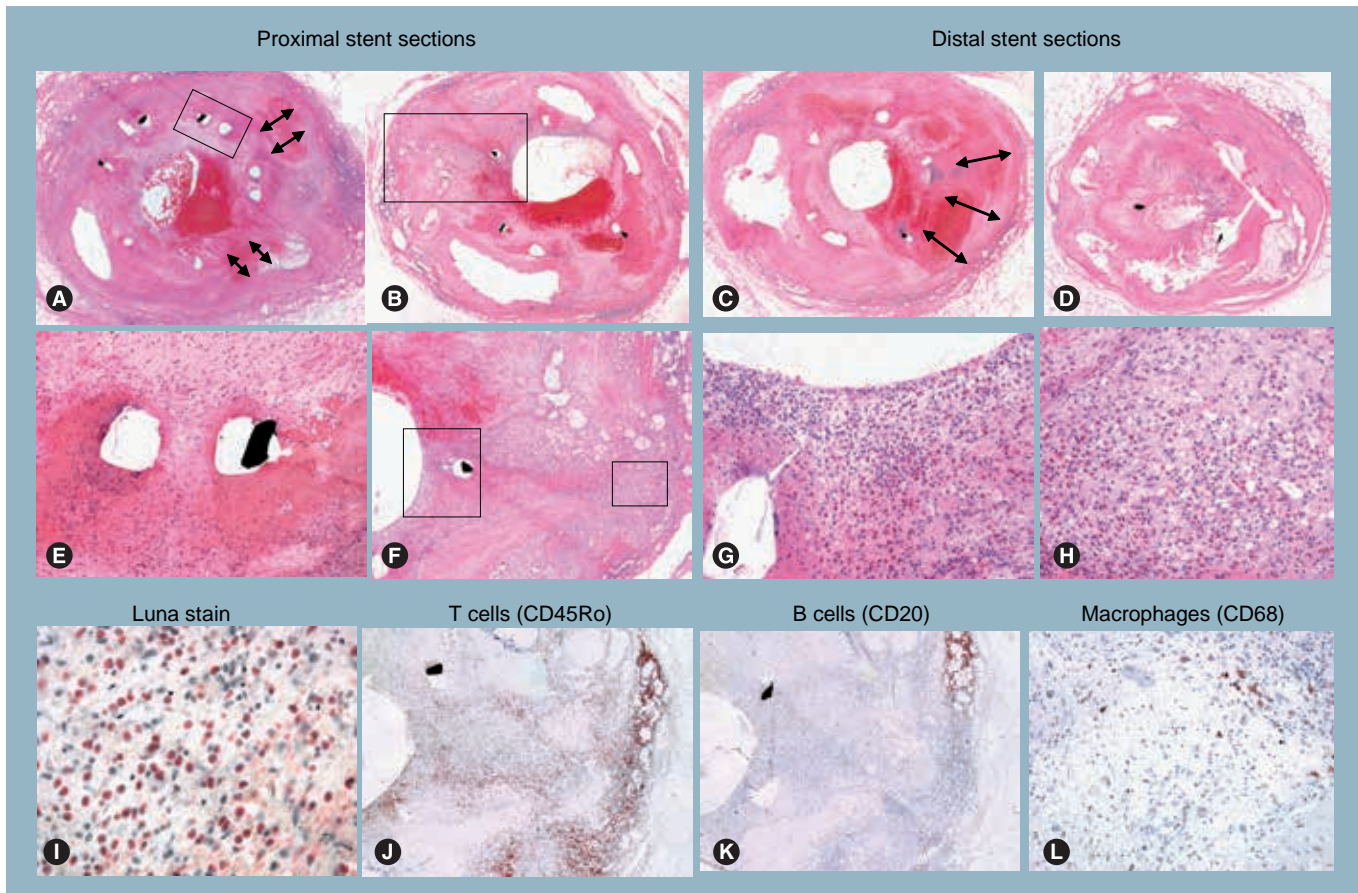
Figure 1. Pathologic findings in a patient with late drug-eluting stent thrombosis. A 58-year-old male died of late stent thrombosis. Two Cypher™ stents had been placed in the left circumflex coronary artery 18-months antemortem. Representative cross-sections of proximal **(A & B)** and distal **(C & D)** Cypher stents: focal strut malapposition with aneurismal dilatation (double arrows in **A & C**) and occlusive luminal thrombosis **(A)** are present. **(E–H)** High-power views of stented artery from proximal **(A & B)**. There is diffuse inflammation within intima and media **(F–H)**. **(E & I)** Extensive inflammation consisting primarily of eosinophils and lymphocytes, with a focal giant cell reaction around stent strut and surrounding polymer. Marked inflammation is similarly present in intima, media and adventitia. **(I)** Luna stains show numerous eosinophils within arterial wall. **(J–L)** Immunohistochemical identification of T cells (CD45Ro), B cells (CD20) and macrophages (CD68), respectively; T lymphocytes are the predominant inflammatory cell type. Adapted from [9].

The pathologic mechanisms underlying LST were first reported by our laboratory and served to underscore the importance of stent design. In 2003, we reported incomplete endothelial coverage with persistent fibrin within the necrotic core at 16 months following Cypher stent implantation [14] in the absence of luminal thrombosis. At 1 year later, we reported a new pathologic entity, localized hypersensitivity reaction, associated with late DES thrombosis in a patient with a Cypher stent that was characterized histologically by an intense peristrut and diffuse inflammatory cell infiltrate rich in eosinophils and T lymphocytes [9]. In 2006, we demonstrated delayed healing in both Cypher and Taxus DES compared with BMS at autopsy. Pathologically, there was persistence of fibrin around the stent struts, incomplete endothelialization and sparse smooth muscle coverage compared with BMS implanted for similar durations [15]. Subsequently, it was shown that a lack of endothelial strut coverage was the single best correlate of LST, using data from a larger number of autopsy cases [16]. Joner *et al.* found other pathologic features associated with LST, including stent malapposition, stent struts penetrating the necrotic core, local hypersensitivity, restenosis and bifurcations. The arterial healing in DES lesions was heterogeneous, especially in thrombosed cases, suggesting that the underlying lesion morphologies also contribute to delayed healing and LST. For example, bifurcation is one of the more susceptible sites for stent thrombosis. The incidence of stent thrombosis at bifurcation with DES is significantly greater than BMS at autopsy. Flow disturbances at bifurcations have been well described, but with the use of DES, there is delayed arterial healing from

drug effects and a continued risk of thrombosis. Another underlying plaque morphology associated with a greater incidence of LST is observed in patients presenting with AMI from plaque ruptures. We have observed a significantly higher incidence of LST in patients treated with DES for plaque rupture compared with those with stable lesions (fibrous cap >250 μm) [17]. Furthermore, we have observed heterogeneity of healing in AMI patients at culprit sites (site of plaque rupture) with greater delayed healing compared with nonculprit sites within the same section, emphasizing the importance of underlying plaque pathology.

In addition, there have been recent improvements in imaging modalities such as OCT and angioscopy that have allowed for *in vivo* assessment of neointimal strut coverage following stent implantation. Greater stent tissue coverage was confirmed in BMS compared with DES, using both angioscopy and OCT [18]. These observations of focal coverage are significantly less in Cypher at 6 months versus BMS, and have also been observed to occur in the Taxus.

As mentioned above, localized hypersensitivity is one of the complications that we have reported following DES implantation [9]. Clinical manifestations of hypersensitivity include rash, itching, hives or dyspnea; however, these are not always present when there is localized hypersensitivity at the site of stent placement. The most important complication of hypersensitivity reaction is thrombosis, as most cases with this reaction have had LST documented at autopsy. The inflammatory infiltrate is characterized by a diffuse eosinophilic and lymphocytic infiltrate, with
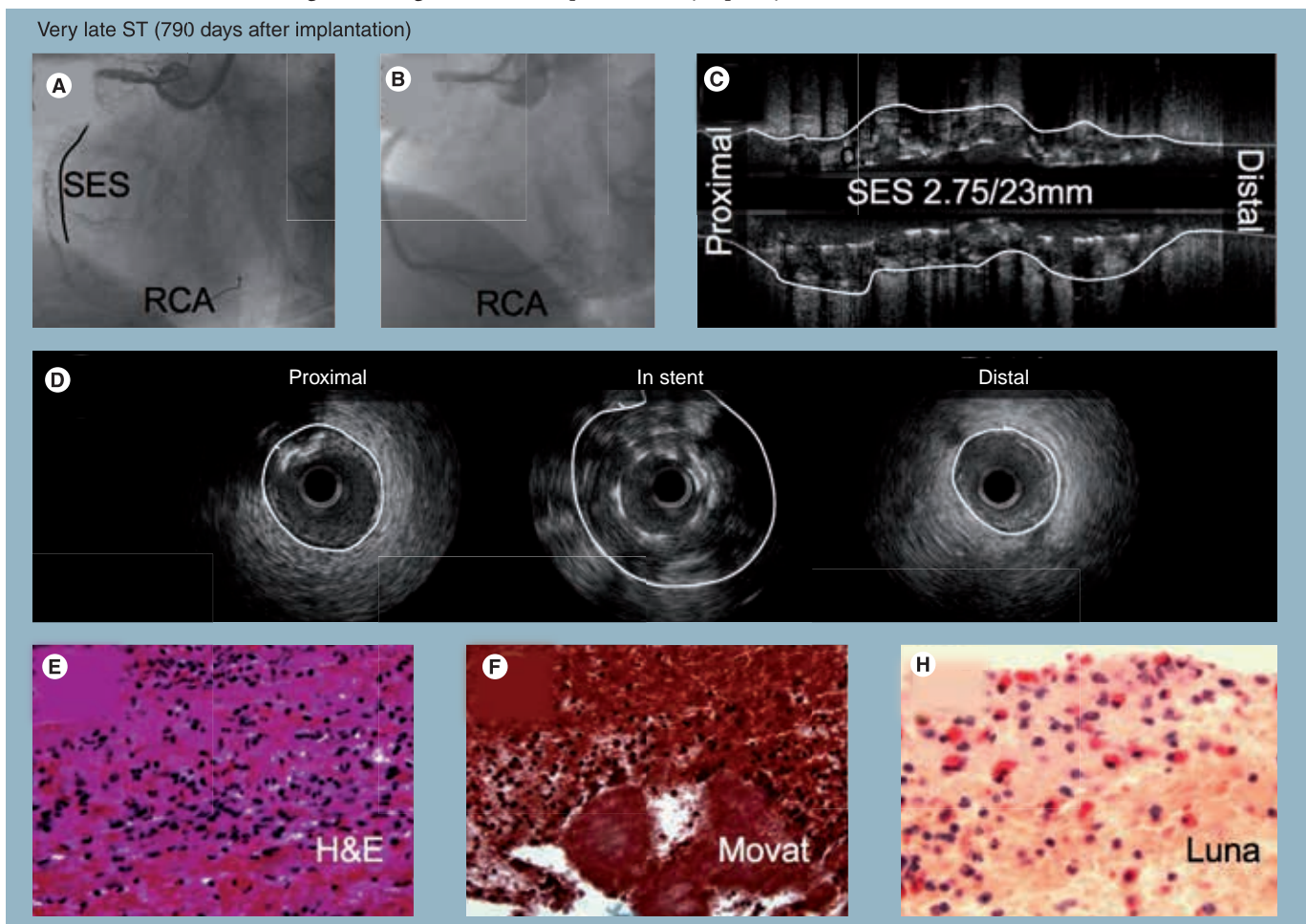

Figure 2. Correlation of angiographic and intravascular ultrasound findings with histopathological analysis of thrombus aspirates harvested from very late ST segments (A) with and (B) without incomplete stent apposition. (A & B) Angiographic findings; **(C & D)** Intravascular ultrasound (IVUS) findings; **(E–G)** Histopathological analysis. **(A)** Very late ST occurred 790 days after implantation of SES in the RCA of a 76-year-old woman treated for a non-ST-segment elevation myocardial infarction. IVUS demonstrates incomplete stent apposition with evidence of positive arterial remodeling. Histopathology shows fresh thrombus with an intense inflammatory infiltrate of white blood cells and numerous eosinophils.
H&E: Hematoxylin–eosin; RCA: Right coronary artery; SES: Sirolimus-eluting stent.
Adapted from [10].

focal areas of granulomatous reaction consisting of macrophages and multinucleated giant cells localized in areas of the polymer resulting in a positive remodeling of the vessel, malapposition and subsequent LST. Furthermore, our observations revealed that this phenomenon is limited to the Cypher stent, and that most of our cases of hypersensitivity reactions are observed beyond 4 months. Therefore, it has been proposed that persistence of the nonerodable polymer contributes to the hypersensitivity reaction, since the drug should be completely eluted by this time, as documented in animal release kinetic studies. Cypher nonerodable polymers consists of poly(etheylene-co-vinyl acetate [PEVA]) and poly(n-butyl methacryalte [PBMA]), and both have been associated with hypersensitivity reactions in humans and animals when used in nonvascular locations [19,20].

Recently, Cook and colleagues performed an *in vivo* IVUS study in which thrombi were aspirated from patients with very late DES thrombosis and correlated with IVUS findings and histopathology of the thrombus [10]. The study concluded that very late DES thrombosis is associated with histopathological and serological signs of inflammation. In particular, eosinophilic infiltrates were associated with IVUS evidence of vessel remodeling leading presumably to secondary stent malapposition. The findings suggested eosinophilic coronary arteritis due to delayed-type hypersensitivity reaction as one of the causes of very late DES thrombosis. Compared with other causes of myocardial infarction, eosinophilic infiltrates were more common in thrombi harvested from very late DES thrombosis, particularly in Cypher stents, and correlated with the extent of stent malapposition. As previous autopsy studies of patients with very LST showed hypersensitivity as one of the pathologic substrates of underlying DES LST, the current data in living patients presenting with LST – and if the thrombus aspirate showed a large number of inflammatory cells – there was an association with incomplete stent apposition and vessel enlargement in 70% of cases. However, if the aspirate had a high eosinophilic count, it was mostly associated with the SES [10].

Recently, we showed that the incidence of stent fractures in the first generation of DES is a common phenomenon and is observed in 29% of stented lesions at autopsy, which is much higher than clinically reported (FIGURE 3). A high rate of adverse pathologic findings was observed in lesions with grade V stent fractures (i.e., lesion with multiple strut fractures with acquired transection with gap in the stent body), while grade I–IV fractures (I: involving single strut fracture; II: two or more strut fractures without deformation; III: two or more strut fractures with deformation; and IV: multiple strut fractures with acquired transection but without gap) did not have a significant impact on the pathological outcome. Stent length, duration of implant and usage of SES were independent predictors of stent fracture [21].

Second-generation DES (clinical findings)

The second generation of DES with zotarolimus- (Endeavor® [Medtronic Vascular, CA, USA]) and everolimus- (Xience™ V [Abbott Vascular, CA, USA]) eluting stents were approved by the US FDA in 2008. These DES have shown significant reduction of target vessel revascularization compared with the respective BMS in each of the initial small, randomized studies [22,23]. However, a larger randomized clinical trial, SPIRIT III, demonstrated that Xience V stents had a significantly reduced angiographic late loss, without an increase of stent thrombosis over the Taxus stents [24]. On the other hand, the ENDEAVOR III trial showed that Endeavor stents were associated with a higher late loss compared with Cypher stents [25]. Nevertheless, a later trial comparing Endeavor (ENDEAVOR IV) with Taxus stents showed an equivalent target lesion revascularization rate. Furthermore, no cases of very LST over 4 years from earlier ENDEAVOR trials have been reported, thus indicating that the long-term safety of the Endeavor stent may be superior to the first generation of DES [26].

Components of DES

Drug-eluting stents consist of three major components: the stent platform to scaffold the vessel; the polymer to deliver the drug; and drugs to inhibit neointimal growth [27]. A number of strategies are being employed to improve stent design including novel stent platforms, biodegradable polymers as well as polymer-free drug delivery and pharmacological agents that not only inhibit neointimal proliferation, but also promote endothelialization.

■ Stent platform

The first generation of DES (Taxus and Cypher) had thick struts made from stainless steel (316 L stainless steel) mounted on a balloon-expandable system (Express and Bx VELOCITY) and the strut thickness ranged from 130 to 140 μm. The radial strength of 316 L stainless steel is dependent upon the thickness of the stent strut
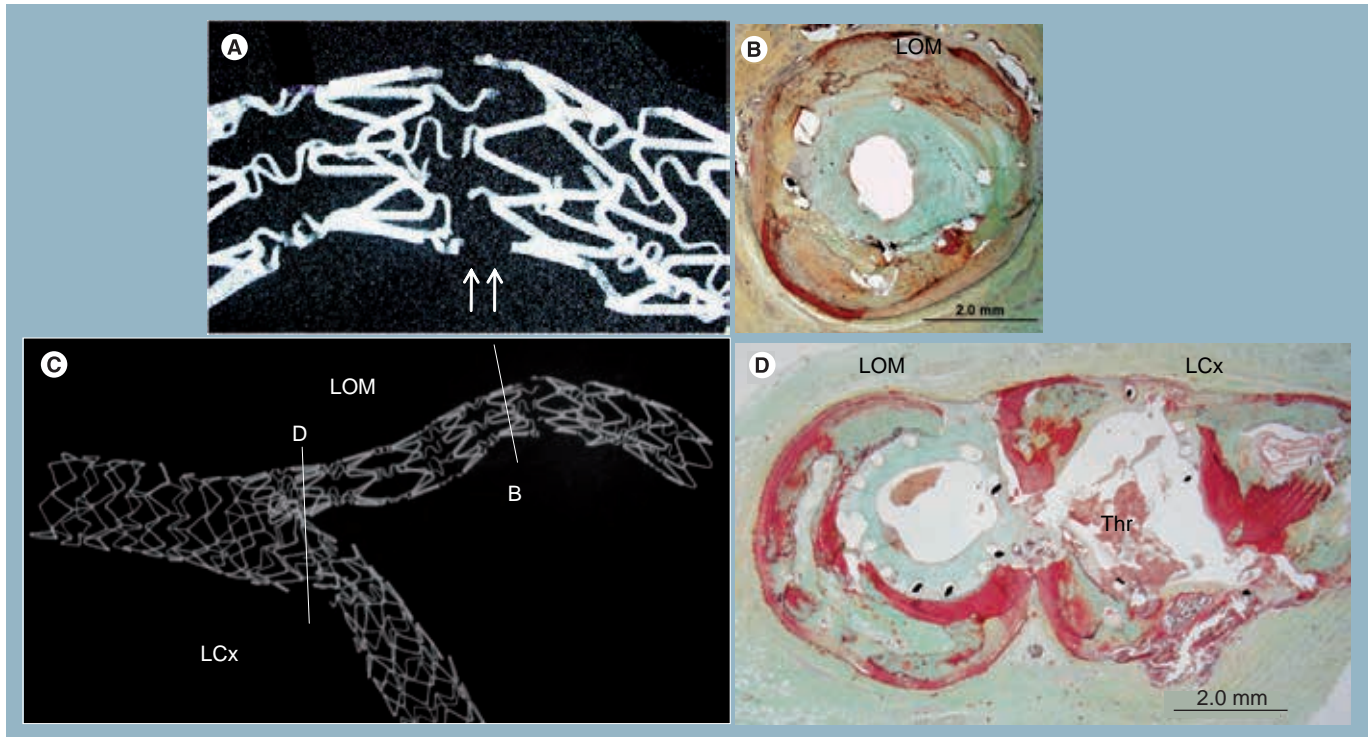
Figure 3. Mechanism of late stent thrombosis in bifurcation stenting. (C) Low- and **(A)** high-power radiographs and histologic sections (Movat pentachrome B and D) from a 68-year-old black woman with a history of stenting of the LCx and LOM using the crush technique (Taxus™ to LCx and Cypher™ to LOM) 172 days before death. She presented 2 days before her death with acute myocardial infarction and was taken to the catheterization laboratory, where 90% occlusion of the LCx near the LOM take-off was found. The LCx artery was opened with balloon angioplasty, but the patient died of complications shortly thereafter. **(A)** High power of the Cypher struts fracture site within LOM. **(B)** Note the extensive neointimal formation close to the fracture site. **(D)** The histologic section taken at the LCx/LOM bifurcation show Thr in the LCx (Taxus), whereas the Cypher stent in the LOM is covered by neointimal growth.
LCx: Left circumflex coronary artery; LOM: Left obtuse marginal; Thr: Thrombus.
Adapted from [15].

(316 L is a Society of Automotive Engineers steel grade. The 316 L stainless steel has high molybdenum and extra-low carbon content leading to a high resistance to corrosion). It was reported that stents with thicker struts have higher rates of restenosis, probably associated with greater vessel wall injuries [28]. In the second generation of DES (e.g., Endeavor and Xience V) the stent platform is constructed from cobalt chromium with thin struts (80–90 µm), which result in decreased neointimal response. Preclinical data demonstrated that stents with thinner struts have greater endothelialization compared with those with thicker struts [29]. Despite thinner struts, cobalt–chromium alloys maintain radiopacity, allowing both flexibility and trackability.

■ **Polymer**
In the first-generation DES, nonerodable polymers were used on both Cypher and Taxus stents (in Cypher: PEVA and PBMA; and in Taxus: poly[styrene-b-isobutylene-b-styrene]). These polymer-based coatings were selected based on durability, release kinetics and drug miscibility. However, doubts have been raised about the long-term safety of durable polymers, particularly in relation to the risk of persistent inflammation and LST. The inflammatory reaction may result from poor integrity of the polymer, uneven application, webbing of the polymers or surface debris [30]. In preclinical studies, we showed that the luminal inflammation was high in both Cypher and Taxus at 28 days and that it persisted at 90 days in the rabbit model. Whereas in the pig model a granulomatous inflammation has been observed in 30–60% of Cypher stents at 90 and 180 days, the inflammation may persist for longer periods, even up to 1 year [31,32].

Biodegradable polymer
There is general consensus that the continued presence of polymer is a key factor in LST. Therefore, in the development of the second-generation stents, there is a drive to utilize biodegradable polymers for drug delivery. There are many different types of biodegradable

polymers; the earliest and most commonly used type of biodegradable polymers in the medical industry belongs to the polyester family, which includes poly(lactide), poly(glycolide) and poly(glycolic-co-lactic acid).

In our preclinical studies using the porcine coronary artery model, some biodegradable polymers have shown promising results, with minimal inflammation and sustained efficacy over time [Virami R, Unpublished Data]. The degradation speed is controlled by many factors and may be accelerated by low or high pH, reactive hydrolytic groups in the backbone, less crystallinity and smaller polymer size [33]. In a vessel with inflammation, the pH is expected to be low, which will accelerate polymer degradation.

The most important property, at least from a pathologist's point of view, is that they should not evoke an inflammatory/toxic response and should metabolize in the body once it has fulfilled its purpose. Of course, it should have a long shelf life and be sterilizable. The biodegradable polymer-coated polylactic acid biolimus A9 Nabori™ (Terumo, Belgium) and BioMatrix® (Biosensors International, Singapore) have been recently approved in Europe and demonstrated a significant reduction of angiographic restenosis in the first-in-man STEALTH trial [34] and an all-comers LEADERS trial [35]. The animal studies in pigs and rabbits also showed significant reduction in neointimal growth and better endothelialization than the nonerodable Cypher and Taxus stents. Similarly, significantly less inflammation was observed for the Nabori stent in the rabbit model and better neointimal coverage than historic first-generation DES. Cypher and Taxus have been associated with impaired local endothelium-dependent vasomotion at adjacent stent segments [36]. Similarly, Hamilos *et al.* recently showed preservation of endothelial function of adjacent biolimus A9-eluting Nabori stents in humans [37], thus suggesting that it is likely the characteristic of bioerodable polymer that is different in the two stents and not the drug, since sirolimus and biolimus A9 bind to the FK binding protein 12 and subsequently inhibit the mTOR. This prevents the degradation of p27^{kip1}, a cyclin-dependent kinase inhibitor that plays an important role in regulating vascular smooth muscle cell migration and proliferation. In conclusion, we believe that biodegradable polymers are safer than nonerodable polymers because polymer degradation and the resulting inflammatory response is a transient phenomenon if it does occur and thereafter leaves a BMS behind.

Drug

In the first-generation DES, the use of antiproliferative agents such as sirolimus and paclitaxel showed a dramatic reduction of restenosis rates over BMS [7,38]. This led to the generalized use of DES in patients with coronary artery disease. While the two drugs operate through different mechanisms of action, they both inhibit proliferation of smooth muscle cells and impair re-endothelialization. The drug is completely eluted by 90 days in normal healthy animal models but in atherosclerotic arteries it is possible that the drugs are released over a longer period and therefore remain effective in suppressing neointimal formation long term. Yet there is some doubt that DES can be effective permanently, as long-term follow-up for 5 years in clinical trials have demonstrated a gradual but significant increase of target revascularization rates from 1 to 5 years, especially in the first generation of DES [39,40].

It is likely that newer analogs of rapamycin such as zotarolimus and everolimus, used in second-generation DES (Endeavor and Xience V) have similar biological effects. The Xience V stent uses a lower concentration of everolimus than first-generation DES, with similar release kinetics as Cypher. Although Endeavor has a higher drug dose (zotarolimus) than the other first- and second-generation DES, it has the fastest release kinetics among the currently available DES; therefore, the tissue concentration in the arterial wall is likely to be less at 30 days, and the late loss is also greater than the other DES.

Other drugs being tested in DES include biolimus A9, tacrolimus and pimecrolimus. Biolimus A9, as stated above, is also a rapamycin analog with high lipophilicity but similar suppression of smooth muscle cells to sirolimus and its other analogues. Pimecrolimus and tacrolimus act through the Ca/calmodulin-dependent protein phosphatase calcineurin pathway. Both the drugs failed to show clinical efficacy; in fact, pimecrolimus has been associated with greater late loss as compared with BMS with the use of permanent and bioerodable polymers, suggesting that calcineurin blockage may even induce greater smooth muscle cell proliferation when locally delivered on the stent platform [41].

Next-generation DES

Next-generation DES are being developed to further refine current device technology and respond to clinical needs within the

cardiovascular stent arena. The optimal drug–polymer–device iteration continues to be sought, with novel designs focused on platform (biodegradable stents), polymer (polymer-free delivery) and drug (prohealing technology), and are briefly discussed below.

■ Polymer-free technology

In the first-generation stents, polymeric coatings were incriminated as a potential cause of localized hypersensitivity reaction and LST; therefore, the second-generation designs focused on biocompatible and bioerodable polymers to reduce hypersensitivity and late thrombosis. An alternative approach, referred to as polymer-free technology, avoids the use of any polymer at all, utilizing the stent structure itself as a drug carrier. The Janus™ stent (Sorin Biomedica Cardio., Italy) has grooves on the abluminal side of stent struts that serve as 'reservoirs' for the drugs loaded onto the stent. However, the Janus stent with tacrolimus failed to significantly reduce late loss as compared with bare stent in clinical studies [42]. The Yukon® stent (Translumina, Germany) is another stent specifically designed for drug elution. It uses 'microporous' technology consisting of pores with a diameter of less than 2 nm, which therefore allows the drugs to be eluted slowly. Recently, the Yukon stent with sirolimus on a microporous structure has shown noninferiority in restenosis rates compared with the Taxus stent in preclinical and clinical studies [43]. A third design, the BioMatrix® Freedom™ stent (Biosensors International) has microporous structures on the abluminal surface, enabling the loading of 225 µm of biolimus A9. The BioMatrix Freedom stent with biolimus A9 delivered abluminally has been tested and showed sustained efficacy in preclinical studies in the porcine coronary artery model without the induction of significant inflammation and is currently undergoing clinical trials.

■ Prohealing technology (proendothelial approaches)

Thus far, the primary role of drugs eluted from stent platforms has been one of inhibition (i.e., antiproliferative drugs aimed at reducing inflammation and smooth muscle cell proliferation). Unfortunately, these cell cycle-modifying agents exhibit concomitant endothelial toxicity, resulting in a precarious balancing act between adequate endothelialization (healing) while suppressing smooth muscle cell proliferation. Prohealing technology, designed to enhance re-endothelialization, is used in the Genous™ stent (OrbusNeich, FL, USA), which has an anti-CD34 antibody coating on the stent that attracts endothelial progenitor cells. In the first clinical study (Healthy Endothelial Accelerated Lining Inhibits Neoinitimal Growth – First-in-Man [HEALING]), no thrombotic events were observed with moderate late lumen loss of 0.66 ± 0.52 mm in Genous stents [44]. A preclinical study showed improved endothelialization of Cypher stents when it was coated with the anti-CD 34 antibody compared with Cypher noncoated stent [45]. These results suggest that the combination of endothelial progenitor cell-capture technology and antiproliferative drug could be modified for safety while maintaining efficacy.

■ Biodegradable stent

The permanently placed stent platform has a potential for adverse effects such as inflammatory reactions, restenosis, blockage of side branches and thrombotic risk. The idea of a completely biodegradable stent that remains *in situ* only as long as necessary and disappears once the job is done is very attractive. There are several polymeric degradable stents in development. One of the earliest was described by Tamai *et al.* (Igaki-Tamai® stent); the stent was made of poly(L-lactic acid) (PLLA) and did not have a drug coating [46]. A small trial showed satisfactory 6-month follow-up performance with hyperplasia comparable to BMS and complete degradation at 4 years. Recently, the bioabsorable everolimus-eluting coronary stent (Abbott Vascular, IL, USA), which also consists of a PLLA polymer with an everolimus coating, was tested in a first-in-man trial, and showed feasibility and safety with no restenosis, although mild stent recoil was observed [47]. In order to preserve the radial force, thick struts (150 µm) were applied, which increased the profile of the catheter and therefore led to reduced deliverability. *In vivo* imaging modalities, such as IVUS and OCT, were used to survey the degradation of this stent in humans. Although some stents appeared to be completely dissolved at the 2-year follow-up [48], the degradation rates may vary and may depend on lesion/patient characteristics. In preclinical studies, we have observed almost complete degradation of the polymers with no inflammation, with positive remodeling at 2 years following bioabsorabable everolimus-eluting coronary stent implantation in the porcine model [Virmani R, Unpublished Data].

Conclusion

The need for safer and more efficacious intravascular devices continues to drive advances in stent technology. The evolution from first- to second-generation DES has resulted in greater safety and less target-vessel revascularization. The third generation of DES with biodegradable polymers in preclinical trials and at least 2 years in randomized clinical trials show equivalent late loss, less LST, inflammation and better vascular response to exercise-induced vasoconstriction. However, regarding totally bioabsorbable DES stents, although showing promise in preclinical and small first-in-man clinical studies, we need to wait for the final verdict from larger all-comer trials to accurately assess their value.

Executive summary

Lessons from autopsy pathology studies of drug-eluting stents

- Autopsy studies have revealed delayed healing following implantation of drug-eluting stents (DES) as compared with bare-metal stents (BMS). The delayed healing consists of poor endothelialization, persistence of fibrin and a marked decrease in smooth muscle cell presence in the neointima. Although DES significantly reduce restenosis, they have been associated with late stent thrombosis (LST). LST is multifactorial, but the most important predictor is presence of uncovered stent struts (>30%), a marker for poor endothelialization. The frequency of LST is highest in patients receiving DES for 'off-label' indications. We have shown that the main causes of LST are placement of DES for acute myocardial infarction, bifurcation lesions, long and overlapped stenting, malapposition and hypersensitivity reactions.

Second-generation DES

- The second-generation DES reduced strut thickness, allowing for more rapid endothelialization. In addition, they used less polymer and utilized different polymer types, including more hydrophilic polymers, which resulted in less inflammation. Finally, either through the reduction of drug dose and/or faster release kinetics, the second-generation DES also demonstrated less fibrin with more rapid healing as compared with the first-generation DES.

Future perspective

- The first- and second-generation DES all use nonerodable polymers, which remain permanently in the body and with time, continue to induce inflammation. Biodegradable polymers should result in less toxicity to the vessel wall while reducing neointimal formation. In animal studies, some biodegradable polymers have shown promise with minimal inflammation observed during the degradation phases. Further improvements are emerging, such as polymer-free technology for drug delivery and prohealing technology to enhance re-endothelializiation. Finally, the use of permanent stent platforms may continue to induce inflammation and, therefore, the concept of a totally biodegradable stent is appealing.

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