ABSTRACT

Coronary artery disease (CAD) is the leading cause of morbidity and mortality worldwide. The pathogenesis of CAD relates to the presence of atherosclerotic plaques in coronary arteries, which are today most frequently treated by percutaneous coronary intervention. Initially, plain old balloon angioplasty demonstrated feasibility of dilating atherosclerotic coronary lesions; however, the high rate of acute-vessel recoil, restenosis, and dissection resulted in high acute closure rates and restenosis, which lead to the introduction of coronary stents, improving clinical outcome. However, in-stent restenosis (ISR) became the Achilles heel of bare metal stents owing to sustained neointimal (NI) growth. Drug-eluting stents (DES) were developed to reduce ISR, improving clinical outcomes and reducing the need for target vessel revascularisation. However, late and very late stent thrombosis emerged as a new problem compromising long-term results of DES, along with late catch-up of NI growth. Better materials, especially more biocompatible polymers, contributed to the refinement of DES technology, which substantially reduced stent thrombosis rates in second-generation DES. The idea of eliminating the foreign material after temporary scaffolding using fully bioresorbable scaffolds may hold great potential to revisit the interventional approach of treating CAD. This article will review the evolution of coronary artery intervention from clinical application to pathology, and will discuss current status and potential future directions of the newer therapeutic approaches.

Keywords: Plain old balloon angioplasty (POBA), bare metal stent, drug-eluting stent, bioresorbable stent, late stent thrombosis, very late stent thrombosis.

INTRODUCTION

Coronary balloon angioplasty, described by Dotter and Judkins (1964), was primarily performed by Andreas Gruntzig in 1977, which led to the initial revolution in the treatment of coronary artery disease (CAD). Plain old balloon angioplasty (POBA) often resulted in acute vessel recoil owing to the inherent elasticity of coronary arteries, and along with the occurrence of dissection resulted in the frequent need of urgent revascularisation, which was solved by the implantation of metal scaffolds called stents. While stents helped to avoid acute vessel closure, persistent vascular injury of a metallic foreign body led to a new disease termed in-stent restenosis (ISR), which is the result of an exaggerated proliferation and migration of smooth muscle cells (SMCs) from the media into the nascent neointimal (NI) tissue. Consequently, the idea to disrupt NI growth by the use of anti-proliferative drugs delivered via coating the metal surface with non-erodible polymers was born.

To this end, drug-eluting stents (DES) are composed of a metallic platform with polymers releasing anti-proliferative compounds for days to weeks, which resulted in a significant reduction of NI growth in major clinical trials. However, this undoubted clinical success was acquired at the expense of a substantial delay in vascular healing, which manifested in an increased risk of late thrombotic events. With these major drawbacks...
in mind, newer alloys, thinner struts, better radial strength, and conformability were implemented in second-generation DES. Owing to the permanent irritation of metallic stents in the coronary arteries with all its consequences on vascular biology, bioresorbable scaffolds (BRS) have recently been introduced as a novel therapeutic option to temporarily scaffold dilated atherosclerotic plaques with eventual resorption of the scaffold that leads to the restoration of vascular function in the long-term. This review article discusses the clinical evidence of the different interventional coronary approaches and provides important pathological insights into the underlying vascular reactions of the different endovascular therapies, with a focus on coronary stents.

**BARE METAL STENT (BMS)**

**Clinical Data**

Sigwart et al. implanted the first WALLSTENT® (Schneider AG, Bülach, Switzerland), a self-expanding Nitinol stent in 1986. The Palmaz-Schatz® (Johnson & Johnson, New Brunswick, NJ, USA) stent was developed thereafter (1987); it was the first balloon-expandable stainless steel stent. In the 1990s, concerns were first raised referring to high metallic density, frequent deployment failure, embolisation, complete occlusion, and significant risk of ISR. However, at later stages of developmental efforts, two studies related to BMS changed the existing treatment paradigm, the BENESTENT and STRESS clinical trials; both established the superiority of BMS over POBA, making implantation of BMS a standard for the treatment of CAD.

**Pathology Findings**

A systematic examination of BMS pathology was performed by Farb et al., who evaluated data from 35 coronary arteries (55 BMS). Fibrin, platelets, and acute inflammatory cells were predominantly observed ≤11 days after stenting, chronic inflammatory cells surrounded the struts after 12 days, and granulation tissue with SMC infiltration appeared after 14 days, which was only complete after 6 months. Based on the recognition of restenosis as a clinical problem, Farb et al. determined that media injury induced greater arterial inflammation, and penetration of stent struts into a necrotic core was associated with increased NIH growth (Figure 1).

Furthermore, the presence of neovascularisation as a consequence of persistent inflammation was another source for growth factor release, and this process turns into a vicious circle of sustained NIH growth. Also, arterial medial fracture was associated with a 29% increase in NIH thickness compared to an intact media wall (p<0.01).

There have been significant changes in the material and design of BMS over the past decade. New alloys such as cobalt chromium and platinum chromium have outdated stainless steel as the material of choice for stents. The newer materials permit manufacture of stents with lower profile, pushability and trackability, higher radiopacity, and thinner struts without compromising radial strength.

**FIRST-GENERATION DES**

**Clinical Data**

The need for repeat revascularisation secondary to restenosis was the main limitation of BMS implantation. The introduction of DES has resulted in a dramatic reduction of restenosis with a decrease in revascularisation procedures in a wide variety of patient and lesion subsets in large randomised clinical trials (RCTs).

Landmark studies such as RAVEL, SIRUS, and TAXUS IV clearly demonstrated a reduction of angiographic restenosis and the need for target lesion revascularisation (TLR) or target vessel revascularisation (TVR), angiographic restenosis, and NIH proliferation. Subsequently, the efficacy of DES in reducing ISR was confirmed in a number of larger clinical studies for different indications.

However, the undoubted efficacy of first-generation DES came at the expense of substantially delayed arterial healing, and McFadden et al. were the first to publish four confirmed cases of late stent thrombosis/very late stent thrombosis (LST/ VLST) with sirolimus-eluting stent (SES) and paclitaxel-eluting stent (PES). After that, various meta-analyses were published reporting an LST/ VLST incidence ranging from 0.2-0.7% and from 0.15-0.5%, respectively. The risk of VLST was reported to increase at 0.5% per year for up to 4
27-29 Higher rates of LST and VLST were related to ‘off-label’ indication and anatomic factors such as: long lesions, calcification, vessel diameter (<3.0 mm), renal disease, or prior brachytherapy.30,31

Pathology Findings

Delayed arterial healing

Fundamental histopathologic insights of human DES implants were derived from a number of pathology studies that reported differences between DES and BMS cases. Joner et al.2 evaluated 32 DES and 36 BMS to determine the long-term effects of DES on arterial healing, and identified pathologic mechanisms underlying LST. In ≥30 days duration, stent thrombosis (ST) was observed in 61% of DES versus 8% in BMS (p=0.0001). DES had significantly less in-stent NI growth compared with BMS (NI 2.9±1.1 mm² versus 4.9±3.0 mm², p=0.005). Regardless of implant duration, the percentage of covered (endothelialised) stent struts was significantly higher in BMS compared to DES.2 At 60 days, the SES showed greater inflammatory reaction including eosinophils and giant cells, whereas PES predominantly showed

![Photomicrographs (A and B) and bar graph (C) showing the association of arterial injury (medial fracture, arrow in A) with increased neointimal (ni) thickness versus stents in which the arterial media was intact (B). Medial fracture length as a percentage of the circumference of the internal elastic lamina was greater in restenotic stents compared with stents without restenosis (D). A and B have a Movat pentachrome stain. Scale bars 0.23 mm in A and 0.30 mm in B. Reproduced from Farb et al.]({"id":522821,"dimension":1})
greater fibrin deposition. At 120 days, there was focal fibrin deposition and giant cell reaction around SES, whereas PES showed increased inflammation. At 60 days, BMS did not show fibrin deposition, but relatively greater NI coverage of stent struts was observed, which was complete at 120 days.

In another study, Finn et al. demonstrated that the pathologic determinant of LST/VLST following DES implantation was the presence of uncovered struts. A total of 46 human autopsy cases (62 coronary lesions) with DES implanted for >30 days were investigated. 28 ST lesions were compared with 34 lesions without ST of similar implant duration. The ratio of uncovered to total stent struts per section (RUTTSS) was greater in thrombosed compared to the patent lesions (0.50±0.23 versus 0.19±0.25, p<0.0001). Moreover, while some struts showed NI growth (healing), other struts remained bare and served as a nidus for thrombus (Thr) formation. RUTTSS was best correlated with endothelialisation among other morphometric parameters.

The heterogeneity in vascular healing was especially pronounced in the clinical setting of acute myocardial infarction (AMI) and bifurcation stenting. Nakazawa et al. compared 25 AMI patients with 46 stable angina patients treated

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**Figure 2: Representative images of stent fracture and calcification.**

(A) Grade 1 fracture of paclitaxel-eluting stent (single-strut fracture), Grade 2 fracture of sirolimus-eluting stent (SES) (multiple breaks but alignment is preserved), Grade 3 fracture of SES (multiple breaks with deformation), Grade 4 fracture of SES (multiple breaks with transection but without gap), and Grade 5 fracture of SES (total separation). Arrows indicate fractured stents.

(B) Classification of calcification (mild: focal calcification; moderate: multiple sites of calcification; severe: >75% of stent length is associated with calcification). Arrows indicate areas of calcification.

Reproduced from Nakazawa et al.
by DES. In patients within 30 days after DES implantation, ST was similar in both groups (50%). However, in those implanted for >30 days, ST was more frequent (41%) in AMI compared to those with stable angina (11%). AMI culprit sites had significantly less NI thickness, greater fibrin deposition, higher inflammation, and greater incidence of uncovered struts compared with culprit sites from patients with stable angina.

A total 40 cases of bifurcation lesions with DES (n=19) and BMS (n=21) with implant duration >30 days were compared in a separate study. Plaque formation in native coronary bifurcations and NI growth after DES implantation was significantly less at the flow divider versus the lateral wall. A higher incidence of LST in DES compared with BMS was associated with greater uncovered struts at flow divider sites, which is likely due to flow disturbances.

### The impact of stent fractures

Clinical incidence of DES fracture is reported as 1-2%. Our group investigated the incidence of stent fracture by using high-contrast film-base radiography to determine the impact on histopathologic outcomes. Stent fracture and the amount of calcification were defined as shown in Figure 2. The prevalence of stent fracture was observed in 29% of cases of first-generation DES cases. In single-stented lesions, the majority of stent fractures were localised in the middle portion of the stent body. On the other hand, in overlapping stents, most fractures were observed within a 5 mm distance from the overlapping zone, with similar frequency in proximal and distal regions.

Lesions with stent fracture showed a higher rate of SES usage, longer stent length, greater number of stents, and a higher rate of overlapping stents. Six adverse pathologic findings (five thrombosis and one restenosis) were associated with Grade 5 fracture (67%).

### The pathology of restenosis

Nakano et al. evaluated the histomorphological predictors and NI characteristics of DES restenosis. From our autopsy registry, 65 patients with 82 stented lesions were analysed and categorised to four groups: (i) patent (<50% stenosis); (ii) intermediate (50-74% stenosis); (iii) restenosis (≥75% but with residual lumen); or (iv) total occlusion (in-stent area occupied by organised Thr, proteoglycan matrix with microcapillaries)

(Figure 3). The neointima of patent, intermediate, and restenotic DES stents consisted mainly of SMCs in a proteoglycan-collagen matrix, while the neointima of total occlusions consisted of an organised Thr showing a low smooth muscle cellularity within the proteoglycan matrix with micro-capillaries in the presence or absence of inflammation.

Medial disruption was more frequently observed in the occluded group (80%) when compared with the patent (25%), intermediate (52%), and restenosis groups (53%) (p=0.016). Medial tears were associated with a higher incidence of inflammation, angiogenesis, and haemorrhage around struts. Furthermore, NI thickness correlated with maximum inter-strut distance more robustly in the presence of medial disruption (r=0.678, p<0.001) than in the absence of medial disruption (r=0.332, p=0.11), suggesting that the combination of medial disruption and irregular strut distribution resulted in uneven drug distribution that may lead to greater NI growth. When NI composition was examined, DES showed significantly lower cellularity and collagen content than BMS. Conversely, the percentage of proteoglycan-rich extracellular matrix was greater in DES when compared to BMS.

### Pathology of malapposition

Malapposition or incomplete stent apposition (ISA) had been described as one of the risk factors for ST or restenosis. ISA, defined as the lack of contact between at least one stent strut and the vessel intimal surface, not overlying a side-branch, was evaluated by Attizziani et al. The author mentioned our group, which initially described the complex pro-inflammatory events after an ISA, with thick fibrin Thr between struts and vessels, also relating the ISA with ST due to healing delay. Another element to consider was the vessel positive remodelling, mentioning that Cook et al. found a correlation between positive remodelling and eosinophils infiltrate, suggesting a hypersensitivity reaction on patient with ISA.

### Pathology of neoatherosclerosis

Neoatherosclerosis has recently gained attention as a novel disease entity, representing a further manifestation of atherosclerotic lesion formation, which typically forms as an aftermath of stent implantation. Such atherosclerotic changes within the intra-stent NI tissue represent an accelerated...
manifestation of atherosclerotic disease and are likely to have a substantial impact on clinical outcomes. Nakazawa et al. evaluated 299 autopsy cases (142 BMS and 157 DES) with 406 lesions from our registry. The incidence of any neoatherosclerosis was greater in DES than BMS (31% versus 16%; p<0.001). Nearly one-half of the DES lesions with neoatherosclerosis (48%) contained peristrut foamy macrophage clusters, and the other half showed fibroatheromas. The implant duration was significantly shortened in DES with neoatherosclerotic change compared to BMS neoatherosclerotic change (DES 1.5±0.4 years compared to BMS 6.1±1.5 years). Neoatherosclerotic changes were greater in SES than in PES for implant durations of <2 years, while there was no significant difference for implant durations between 2 and 6 years.

SECOND-GENERATION DES

Clinical Data

Second-generation DES were designed to overcome the limitations of the first-generation DES, and consisted of thinner stent struts and more biocompatible polymeric coatings with reductions in drug load. Data from 13 RCTs demonstrated that cobalt-chromium everolimus-eluting stent (CoCr-EES) had significantly reduced ST, TVR, and myocardial infarction (MI) (p=0.001; p=0.004; p=0.02, respectively) compared to other stents.
In a network meta-analysis by Palmerini et al., CoCr-EES showed significantly lower rates of definite ST compared to BMS, as well as first and second-generation DES at 1 and 2-years.

In the RESOLUTE trial, Resolve-Zotarolimus-eluting stent (Re-ZES) was non-inferior to the CoCr-EES with respect to cardiac death, MI, or revascularisation. No differences in ST were observed between Re-ZES and EES at 13-months. These findings were also confirmed in the TWENTE trial, which demonstrated no differences in target vessel failure (TVF) between Re-ZES and CoCr-EES. Also, definite and probable ST were similar among groups (p=0.59).

Recently, in a further attempt to refine DES technology, biodegradable polymer-based DES and polymer-free DES were introduced. Koppara et al. compared the histopathology of biodegradable polyactic acid (PLLA) versus permanent polymer polyethylene-co-vinyl acetate/poly-n-butyl methacrylate (PEVA/PBMA) based DES with uncoated BMS, demonstrating significant reductions in inflammation and NI growth with biodegradable polymer PLLA among others groups. A recent meta-analysis by Stefanini et al. comparing biodegradable polymer-based DES to permanent polymer-based DES (ISAR-TEST, ISAR-TEST 4, and LEADERS) at 4-years showed a significant reduction in TLR and ST, driven by lower LST for biodegradable polymer-based DES group; also the incidence of MI was lower on the same group. Navarese et al. recently published a network meta-analysis comparing polymer-free versus durable polymer DES. From 8 studies and 6,178 patients, the polymer-free DES was as safe and as effective as durable polymer DES group; also the incidence of MI was lower on the same group.

The Pathology Findings

Recently, Otsuka et al. published a pathologic study comparing second-generation to first-generation DES (Figure 4). A total of 204 lesions (SES=73; PES=85; CoCr-EES=46) from 149 autopsy cases with duration of implantation >30 days and ≤3 years were pathologically analysed. The observed frequency of LST and VLST was lower in CoCr-EES (4%) compared with SES (21%; p=0.029) and PES (26%; p=0.008). The prevalence of restenosis for CoCr-EES (17%) did not differ significantly from that observed for SES (14%) and PES (12%). The frequency of uncovered struts was markedly lower in CoCr-EES (2.6%) compared to SES (18.0%; p<0.0005) and PES (18.7%; p<0.0005). The prevalence of DES lesions with >30% uncovered struts was also significantly lower in CoCr-EES (20%) than in SES (60%; p<0.0005) and PES (67%; p<0.0005) (Figure 4). Strut coverage was also evaluated in the setting of off-label clinical indications versus on-label indications. CoCr-EES compared with SES and PES showed greater strut coverage for both on and off-label indications. CoCr-EES showed significantly lower inflammation scores compared with SES. The overall prevalence of neoatherosclerosis after CoCr-EES implantation in native coronary arteries was 29%, which did not differ significantly from SES (35%, p=0.62) and PES (19%, p=0.47).

BRS

Clinical Data

The concept of BRS to support vascular integrity during the acute phase of percutaneous coronary intervention after dilatation procedures, followed by antiproliferative drug release and finally with a controlled scaffold degradation to restore vasoreactivity and function, has emerged as a potential solution to resolve the drawbacks of current metallic stents. Although results of large clinical trials are not available to date, several small clinical studies in selected populations have been published.

The ABSORB everolimus-eluting bioresorbable vascular scaffold (BVS) (Abbott Vascular, Santa Clara, CA, USA) was evaluated in the ABSORB cohort A study, a multicentre single-arm study that enrolled 30 patients. The ABSORB BVS was found to be safe and had a low ischaemia-driven major adverse cardiovascular events (id-MACE) rate at 4-year follow-up. There was only a single non-Q-wave MI, and no new id-MACE events were reported between 6 months and 4 years; also there was no occurrence of ST according to Academic Research Consortium (ARC) definitions. The second-
generation, Absorb BVS 1.1, has improved radial strength, mechanical integrity, and release kinetics. In the ABSORB Cohort B long-term follow-up trial, there were 6 cases of in-segment restenosis in a total of 101 patients. Of six restenosis cases, two occurred early (<6 months), one occurred late (6-12 months), and three occurred very late (>12 months) by angiography. More clinical studies are needed to determine the true safety and efficacy of BRS in complex lesion settings.

Figure 4: Late stent thrombosis in two cases with cobalt-chromium everolimus-eluting stent (CoCr-EES). A and B: Histological sections from a 55-year-old man with CoCr-EES implanted over an underlying paclitaxel-eluting stent (PES) in the proximal right coronary artery 6 months antemortem, who died suddenly of stent thrombosis (ST). A low-power image (A) shows occlusive luminal thrombus (Thr) within the stents with underlying calcified plaque; Ca indicates calcification. A few struts of CoCr-EES are covered with thin neointima, but the majority of the struts are uncovered, which is highlighted in a high-power image in B.

C and D: Histological sections from a 72-year-old woman with CoCr-EES implanted over an underlying PES in the proximal left anterior descending (LAD) coronary artery 7 months antemortem. The patient presented with acute myocardial infarction from ST and underwent balloon angioplasty, which resulted in rupture of the LAD coronary artery. A low-power image (C) shows in-stent restenosis with luminal Thr; the neointima is focally dissected because of the balloon angioplasty with overlying nonocclusive Thr. A high-power image (D) shows erosive neointima with overlying fibrin and platelet Thr. A and B are stained with Movat pentachrome, and C and D are stained with haematoxylin and eosin. Reproduced from Otsuka et al.52
Pathologic Finding

Preclinical experience

Preclinical studies are very important in the assessment of BRS since details of degradation and absorption can only be confirmed by histopathology. Onuma et al.\(^5\) correlated the histopathologic findings after implantation of the ABSORB BVS with optical coherence tomography (OCT). They described four degradation levels based on morphological appearance of stent struts: i) Perserved Box, an open acellular region with well-defined borders; ii) Open Box, a region of hyaline material (proteinaceous) separated by extracellular matrix (proteoglycans) and cells; iii) Dissolved Black Box, a region without hyaline material but with low to moderately cellular connective tissue; and iv) Dissolved Bright Box, a poorly circumscribed region of dense connective tissue with moderate-to-low cellularity in which cells were not regularly arranged.\(^5\) The chronological histopathology findings, found in the early phase as stent struts, are covered by NI tissue composed of SMCs and proteoglycans, while stent struts remain intact. In the intermediate phase, struts are partially substituted by proteoglycan matrix, followed by infiltration of connective tissue and cellular components. In the final phase, stent strut resorption sites become completely integrated into the arterial wall in the absence of polymer residues.\(^5\)

CONCLUSION

While DES contributed to the global success in improving outcomes of patients suffering from CAD, this benefit is partly counterbalanced by reports of delayed arterial healing associated with increased rates of ST in DES compared to BMS. While second-generation DES substantially improved upon the shortcomings of first-generation DES, there remain important issues such as increased inflammation, especially with the use of permanent polymers, which was clearly improved in second-generation DES as demonstrated by Otsuka et al.\(^5\) DES with biodegradable polymer technology will likely help to further improve outcomes. Complete BRS likely hold great value to eliminating some of the remaining hazards of current DES technology but this needs confirmation in large clinical trials. Histopathologic assessment of coronary stents provides valuable insights for the identification of relevant obstacles with contemporary endovascular approaches, and will likely play an important role for the improvement of future interventional strategies.

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