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REVIEW

# Evolution of Coronary Stents: From Bare-Metal Stents to Fully Biodegradable, Drug-Eluting Stents

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## ABSTRACT

Coronary stenting represents the standard of care for percutaneous revascularization of symptomatic coronary artery disease. However, despite progress in the evolution of intravascular stents, clinical adverse events such as restenosis and stent thrombosis still represent the "achilles heel" of this ground-breaking technology. Of particular note was the association of these adverse events with the material, the polymer coating, and the active drug of currently approved drug eluting stents. Consequently, modifications were made to the design, coating, and the choice of drugs, eventually, resulting in (fully) biodegradable drug-eluting stents. Such stents offer the appealing concept of a temporary vascular scaffold and are currently under extensive preclinical and clinical investigation. However, biodegradable stents must demonstrate efficacy and safety in larger randomized clinical trials in real-world scenarios, which are currently on the horizon.

**Keywords:** Biodegradable polymer; Cardiology; Combination products; Drug-eluting stent; Pathology; Restenosis; Thrombosis

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## INTRODUCTION

The introduction of vascular stenting was a milestone in the field of interventional

cardiology [1]. The vascular scaffolding provided by coronary stents significantly reduced the incidence of acute vessel occlusions after dissection and restenosis by vascular recoil as compared with plain old balloon angioplasty (POBA) [2, 3]. This dramatic improvement in the percutaneous treatment of coronary artery disease resulted in their widespread use in daily practice [4, 5]. Unfortunately, similar to POBA, bare-metal stents (BMS) were associated with excessive neointimal formation as a response to procedure-related wound healing in upto 30–40% of cases [6–8]. Findings from autopsy studies showed that vascular healing after stent implantation is similar to wound healing, including platelet adhesion, fibrin deposition, and a focal inflammatory cellular infiltrate. This early process of vascular healing is followed by re-endothelialization and smooth muscle cell (SMC) migration and then by proliferation and matrix formation that can lead to excessive intimal hyperplasia and clinical restenosis typically within 3–6 months after stent implantation [9, 10], or even later.

Drug-eluting stents (DESs) were introduced as a means of reducing excessive SMC proliferation. These devices release anti-proliferative drugs, thus leading to a significant reduction of neointimal formation and consequently adverse clinical events like target lesion revascularization (TLR) and angiographic restenosis. Enthusiasm for DES grew quickly following the positive results of initial large randomized controlled trials comparing both sirolimus and paclitaxel DES with their BMS counterparts [11, 12]. However, early enthusiasm was tempered following clinical reports of late DES thrombosis [13, 14]. Pathology findings of delayed arterial healing, hypersensitivity reactions, and malapposition by vascular remodeling in DES raised concerns about the impact of the anti-proliferative drugs and the polymer that is critical for the modulation of local drug delivery [15, 16]. Given these safety concerns, second-generation DESs were introduced using cobalt chromium platforms and modified cell-cycle inhibitors (everolimus and zotarolimus) combined with more biocompatible polymers. When compared with first-generation DES, these stents proved to be more deliverable while clinically non-inferior with improved rates of stent thrombosis [17–24].

Despite the dramatic improvement from POBA to second-generation DES, there is still room for further reduction in adverse clinical events. The majority of adverse events (e.g., acute recoil, subacute closure, and dissection) occur early following POBA with very stable long-term lumen areas beyond a few months [25]. Therefore, perhaps the future of vascular scaffolding may be stents that can prevent the early complications of POBA and bioabsorb over time to allow the vessel to regain its natural shape and function while eventually improving rates of stent thrombosis and restenosis by minimizing late vascular inflammation, hyperproliferation, and induction of neoatherosclerosis.

## Bare-Metal Stents

BMS were designed as a vascular scaffold to treat POBA-related dissections and acute vessel occlusions, and to reduce vascular recoil. Early BMS were made of 316 L stainless steel, nitinol wire coils, or nitinol coils with various designs and were self- or balloon expandable [7]. Lessons from autopsies showed that vascular healing following intravascular BMS implantation is very similar to the response after wound healing [10]. The initial stage (<30 days) includes platelet adhesion, mild luminal thrombus formation, fibrin

deposition, and a focal inflammatory cellular infiltrate consisting of polymorphonuclear leukocytes and macrophages. T-lymphocyte infiltration starts around 2 weeks and persists for several months. The early process of vascular healing (2–4 weeks) is followed by SMC migration, proliferation, and matrix formation (proteoglycans/collagen type III). Completion of vascular repair in humans is usually achieved by re-endothelialization 3–4 months after BMS implantation. Neointimal formation peaks at 6–12 months, with a neointimal volume decrease by replacement of collagen III with collagen I [10]. In about 30–40% of cases the SMC activation leads to an untoward excessive intimal hyperplasia, which may result in clinically relevant restenosis and need for repeat revascularization [26].

## First-Generation DES

While BMS were a dramatic leap forward in the arsenal of interventional cardiologists, the 30–40% rate of clinically relevant restenosis prompted the development of DES to inhibit neointimal hyperplasia and SMC proliferation. Permanent polymer coatings were applied to control the release kinetics of the anti-proliferative drug that acts to minimize neointimal growth. The sirolimus-eluting stents (SES) used polyethylene-co-vinyl (PEVA) and poly *n*-butyl methacrylate (PBMA) as a non-erodible polymer releasing 80% of the drug sirolimus (140 mg/cm$^2$) from the BxVelocity$^{TM}$ (Cordis, Johnson & Johnson, Miami, FL, USA) BMS backbone within the first month. The various generations of paclitaxel-eluting stent (PES) (originally on NIR BMS backbone and subsequently Express and then Liberte backbones) had a slow release polymer with 8.8% drug to polymer ratio (1 μg/mm$^2$). The moderate release version with three times the local drug concentration was studied in the TAXUS II trial, with improved rates of target lesion revascularization, but was not released commercially [27].

Early DES versus BMS trials demonstrated DES superiority with significantly reduced rates of TLR and angiographic restenosis to <10% in the RAVEL trial [11], the SIRIUS trials [28–31], and the TAXUS trials [12, 32–34]. Consequently, both first-generation DES, the SES (Cypher®, Cordis, Johnson & Johnson, Miami, FL USA), and the PES (Taxus®, Boston Scientific, Natick, MA USA) were rapidly approved by the regulatory bodies in Europe and the USA in 2002/2003.

Following the success of initial clinical trials of first-generation DES, the indications rapidly expanded to complex lesions [35] like chronic total occlusion [36] and left main disease [37]. However, the initial enthusiasm was tempered by clinical case reports and preliminary data from the large Swedish Coronary Angiography and Angioplasty Register (SCAAR), and other groups [13, 14], showing a significant increase in late stent thrombosis (LST) in DES. Concomitantly, autopsy studies revealed that delayed arterial healing and impaired re-endothelialization were strongly associated with the frequently fatal LST [38]. Pathologic findings showed the development of unstable features like neoatherosclerosis within the neointima as a frequent finding in first-generation DES, which may partly contribute to events of lLST [15]. Of note, clinical cases of very LST were reported up to 4 years after the initial implantation of first-generation DES. These safety concerns led to a remarkable reduction of DES usage in 2007. Clinicians began to prescribe dual anti-platelet therapy for 1 year or longer to avoid LST. Around this time the US Food and Drug Administration

(FDA) demanded that all DES manufacturers support the ongoing DAPT trial [39] in an effort to determine the optimal duration of dual anti-platelet therapy for DES. Interestingly, the 5-year follow-up of the SCAAR results did not suggest a long-term significant increase of LST in DES as compared with BMS [40].

## Second-Generation DES

The first-generation DESs were another leap forward compared with BMS; however, there was still concern about LST and reduced deliverability with the 140 μm strut/polymer thickness. The second-generation DESs were designed to overcome these flaws using for example thinner cobalt chromium alloys, new cell-cycle inhibitors (everolimus/zotarolimus), and more biocompatible polymers (fluoropolymers/phosphorylcholine). Whereas the first-generation DES continued to release drug for a prolonged duration, the release kinetics of the second-generation DES was generally shorter.

The Xience V® (Abbott Vascular, CA, USA) everolimus-eluting stent (EES) is also marketed by Boston Scientific as PROMUS® (Everolimus-Eluting Platinum Chromium Coronary Stent System) and is composed of a poly-vinylidene fluoride and hexafluoropropylene (PVDF–HFP) polymer that is loaded with everolimus at a concentration of 1 μg/mm$^2$. EES release 80% of everolimus within 1 month and 100% release within 4 months after implantation. The clinical trial program included the SPIRIT I [17], SPIRIT II [19], SPIRIT III [18], and SPIRIT IV trials [20] the open-label SPIRIT V registry [41], and the all comer COMPARE trial [42]. These studies consistently exhibited low major adverse cardiac event (MACE) rates, target vessel failure, and definite or probable stent thrombosis with the EES as compared with first-generation DES (PES).

Biocompatibility is largely considered secondary to the hydrophilic nature of stent polymers, as measured by lower contact angles (the angle between liquid/blood versus solid/stent), in vitro. The contact angles of the various DES are as follows: PC (Endeavor®, Medtronic Vascular, Santa Rosa, CA, USA) 83°, BioLinx™ (Resolute, Medtronic, Santa Rosa, CA, USA) 94°, PBMA (Cypher) 115°, SIBS (Taxus) 118° and fluoropolymer (Xience) 129°. In vitro studies demonstrate that the more hydrophilic, the less macrocyte adhesion occur relative to other DES platforms [43]. Rabbit models confirmed these findings with the Endeavor stents demonstrating the lowest inflammation and fibrin scores at 30 days [44]. The Endeavor zotarolimus-eluting stent (ZES) was well studied in the ENDEAVOR [23], ENDEAVOR II [21], ENDEAVOR III [24], SORT OUT III [45], and ZEST [46] trials, and in the E-FIVE registry [47], which confirmed consistently low MACE rates and target vessel failure. Notably, LST was rare compared with the first-generation DES (PES, SES). The Resolute ZES has a novel biocompatible hydrophilic polymer, termed BioLinx, that combines the biocompatible nature of the Endeavor stent with a hydrophobic core to allow for prolonged drug elution and improved long-term reductions in neointimal hyperplasia. The Resolute stent has 50% and 85% drug release at 7 and 60 days after stent implantation, respectively, versus the Endeavor, with 75% drug release at 2 days. This effect is correlated clinically with TLR rates of 12% of the Resolute versus 16% in the Endeavor group at 2 years [48].

The so-called 'third-generation' Promus Element (Boston Scientific, Natick, MA, USA) DES has the same polymer and drug elution properties as the Promus/Xience EES, with a

new platinum alloy to improve fluoroscopic visibility. The stent backbone is designed for improved deliverability by removing some of the interconnectors, though this may be related to reports of longitudinal compression both clinically and in bench-top models relative to other DES [49, 50]. The clinical outcomes of the Promus Element versus the Xience V stents were comparable up to 3 years in the PLATINUM studies [51]. Due to concerns about longitudinal compression, the stent has since been altered to allow for more support on the proximal and distal crowns.

While being generally considered biocompatible, the polymer coating of the first- and second-generation DES prevents them from truly behaving like BMS, after time, even after all of the drug is eluted. Reports of hypersensitivity reactions and positive vascular remodeling resulting in stent strut malapposition in those DES have raised concerns that the permanent polymer implants may be linked to late DES thrombosis [15]. Other pathologic studies of BMS and DES have implicated alloyed stents themselves in chronic inflammation, angiogenesis, neoatherosclerosis [52], restenosis, obstruction of side branches, and LST via stent fracture [15]. Therefore, the concept of a biodegradable polymer coating or fully biodegradable vascular scaffolds remains appealing as a means of mitigating these late stent/polymer-vessel interactions.

## Biodegradable Polymer Implementation in the Vascular Scaffold Stent

Various biodegradable polymers have been used since the 1960s for orthopedic, dental, and wound closure applications. The ideal bioabsorbable polymer should demonstrate no toxic or inflammatory responses, should be readily metabolized, easy to produce, and have a good shelf life as well as homogenous application properties [53]. Polymer biodegradation is generally a hydrolytic process starting with the penetration of water into the polymer. The hydrolysis of ester bonds between repeating lactide units fragments the long polymer chain into multiple products including lactic acid, glycolic acid, and finally water and carbon dioxide [54]. Polyacidic acid copolymers such as polylactic acid (PLA, 6 months degradation time) or polyglycolic acid (PGA, 2–3 months degradation time) are commonly used in current biodegradable vascular stents [55]. The time course of degradation itself depends on various factors including the chemical bond, the pH, the presence of catalysts, and the co-polymer composition. Stent polymer coatings are prone to mechanical damage during the fabrication process as well as the deployment procedure. The clinical impact of uneven polymer distribution, flaking or webbing remains poorly understood [56] (Fig. 1).

## Clinical Impact of Biodegradable Polymer Coated Stents

DESs with completely biodegradable polymer coatings were designed with the goal of early neointimal hyperplasia inhibition, followed by polymer absorption, with the hope of minimal long-term inflammatory responses similar to the BMS vascular interaction. Preclinical histopathologic analysis of porcine implanted biodegradable polymer (PLA and PGA) SES demonstrated a reduction of neointimal formation and a reduced cellular inflammatory response when compared with permanent polymer SES and BMS at 28, 90, and 180 days post-implantation [57]. Similar results were seen

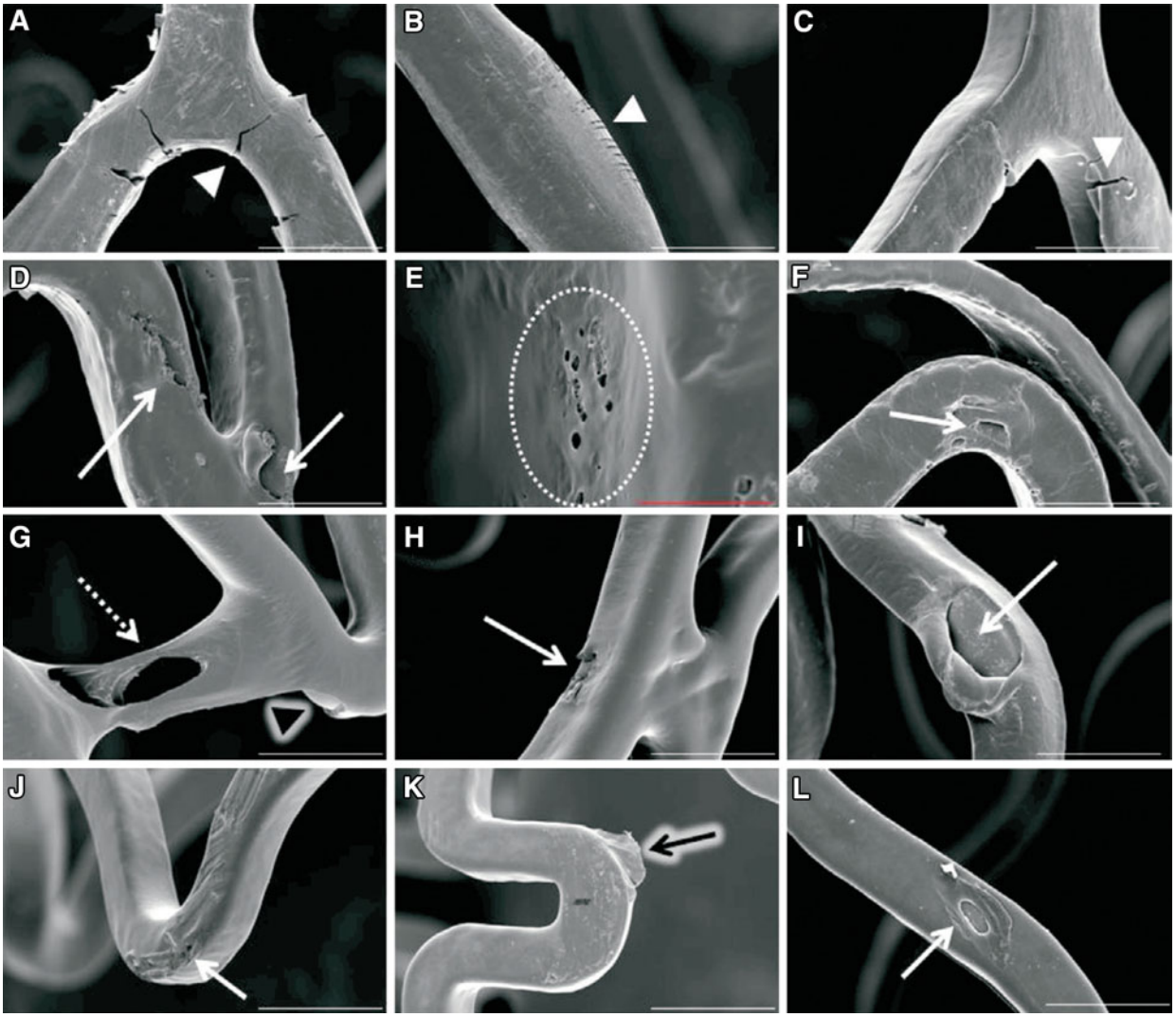


**Fig. 1** Representative SEM images from the enzymatic digested stents deployed into the coronary arteries of pigs for 7 days. **a–c** The polymer coating of the BioMatrix stent displayed polymer cracking within the inner curvature and linker bards (*white arrow head*); **d–f** the polymer coating of the Cypher SELECT displayed uneven coating (*white arrows*) with small-round defects (*dashed circle*); **g–i** the TAXUS Liberté polymer coating displayed webbing (*dashed arrow*), uneven coating (*white arrow*), and focal regions of bare metal exposure (*black arrow head*); **j–l** the XIENCE V polymer coating displayed regions of uneven coating (*white arrow*) and polymer flaking (*black arrow*). (*white bar* 200 μm; *red bar* 30 μm). Reproduced with permission from [56]

in the Nobori™ biolimus-eluting stent (Terumo, Tokyo, Japan) as compared WITH a permanent polymer SES [58] and the stainless steel sirolimus releasing Combo® stent (OrbusNeich, Wanchai, Hong Kong) with a biodegradable SimBioSYS coating and anti-CD34 antibody coating in a porcine model [59] (Fig.2).

Following the non-inferiority 1-year results of the EVOLVE trial, the SYNERGY® (Boston Scientific, Natick, USA) stent with an abluminal everolimus releasing PLGA polymer coating was

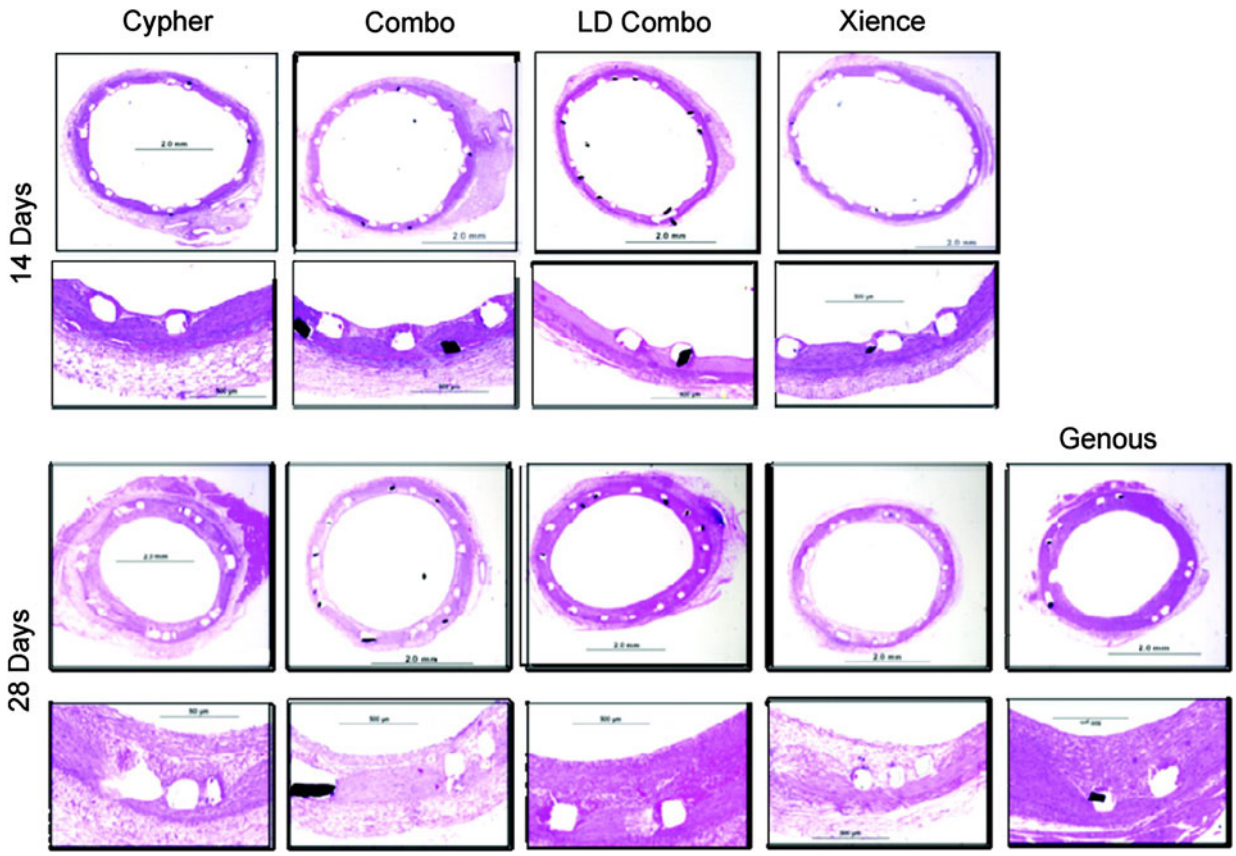


**Fig. 2** Representative histomorphometric images at 14 and 28 days in Cypher, Combo, LD-Combo and Genous stent. Reproduced with permission from [59]

CE marked in October, 2012. The EVOLVE II trial was designed with the goal of approval within the US and Japanese markets and enrolled the first patient in November 2012. The trial compared the SYNERGY stent with the Promus Element Plus platinum chromium stent with a primary endpoint of 12-month target lesion failure defined as any ischemia-driven revascularization of the target lesion, myocardial infarction (MI; Q-wave and non-Q-wave) related to the target vessel, or cardiac death.

The EXCELLA BD randomized clinical trial with the DESyne™ BD Novolimus-Eluting Coronary Stent System, Elixir Medical Corporate, Sunnyvale, CA, USA, with resorbable polymer demonstrated superior results compared to the Endeavor stent for the primary endpoint of in-stent late lumen loss [60]. The LEADERS trial demonstrated that a biodegradable polymer-based biolimus eluting stent (BioMatrix Flex™, Biosensors, Biosensors International, Tokyo, Japan) was non-inferior to permanent polymer SES at 1 year. Another biolimus-eluting degradable PLA polymer stent (Nobori, Terumo; 6–9 month degradation time) was evaluated in the COMPARE II and NOBORI trials, demonstrating clinical non-inferiority versus EES at 1 year [61]. Contrarily, the large (1,229 patient) SORT OUT V trial compared the biodegradable polymer lated biolimus-eluting stent (Nobori) with permanent polymer SES and found that at 9 months the rate of cardiac death, MI and definite stent thrombosis or

target vessel revascularization (TVR) was 4.1% for the Nobori versus 3.1% ($P = 0.22$) for the permanent polymer SES [62]. Interestingly, the difference was largely driven by the stent thrombosis endpoint of 0.7% for the biolimus-eluting stent versus 0.2% for the SES ($P = 0.034$). Likewise, the PLGA PES in the CoSTAR II trial demonstrated an unexpected clinical inferiority compared with the PES control stent [63]. Long-term data derived from the ISAR-TEST 4 trial found similar 3-year rates of TLR, target vessel re-infarction and cardiac death while numerically (though not statistically significant) less definite stent thrombosis with a custom-made biodegradable polymer SES versus permanent polymer SES/EES [64].

Numerous other iterations of biodegradable polymer-coated stents are currently on the clinical trial horizon, including the sirolimus-eluting Biolute stent with a PLA or PLGA polymer Orsiro® stent (Biotronik, Berlin, Germany [65]), the Excel® stent (JW Medical Systems, Shandong, China [66]), and the Coracto stent (Alvimedica, Istanbul, Turkey [67]).

## Completely Biodegradable Stents

The ultimate evolution of coronary stents is complete bioabsorption following lesion treatment with return of normal endothelial function while maintaining long-term patency. Igaki and Tamai pioneered the development of a completely biodegradable polymeric stent (poly-L-lactic acid [PLLA] polymer) (Igaki–Tamai stent, Kyoto Medical Planning Co. Ltd, Kyoto, Japan) with 170 μm strut thickness and 24% stent strut surface/vessel coverage that is both self-expanding and balloon expandable. They reported the first in-man series in 2000 after 25 stents were implanted in 15 patients. Initial 6-month angiographic and intravascular ultrasound (IVUS) follow-up demonstrated acceptable rates of restenosis and TVR (6.7%: 1/15 patients) with no deaths or MI [68]. The long-term follow-up (>10 years) of 50 patients reported lack of significant stent recoil and negative vessel remodeling, but with a 50% MACE rate and two cases of a definite stent scaffold thrombosis [69].

This concept was adopted and further developed into the drug-eluting bioresorbable vascular scaffold (BVS) program of Abbott Vascular (Abbott Vascular, Santa Clara, CA, USA). Their BVS PLLA back-bone provides radial force while a poly-D,L-lactic acid (PDLLA) coating controls the release of everolimus. Both the PLLA and PDLLA are fully biodegradable leaving only small platinum markers at the scaffold edges. In order to keep the mechanical strength of a conventional stent, strut thickness was almost doubled to 150 μm, which may negatively impact stent deliverability [70, 71]. Preclinical studies evaluated the fully biodegradable stents in porcine coronary arteries implanted for 1 month and up to 3 years demonstrating non-inferior rates of neointima formation and vascular inflammation in comparison with permanent polymer SES. The degradation of the polymer was evident within 2 years. Histopathology exhibits replacement of struts with a proteoglycan matrix [16, 72] (Fig. 3).

The first in-man ABSORB I (Cohort A) trial was a prospective, open-label study that enrolled 30 patients who had either stable, unstable, or silent ischemia and a single de-novo lesion (Type B1 and B2) that was suitable for treatment with a single 3.0 × 12 mm or 3.0 × 18 mm stent. At 5 years, there were no events of ischemia-driven TLR or cardiac death [73]. Two-year follow-up with optical coherence tomography (OCT) revealed fully bioabsorbed

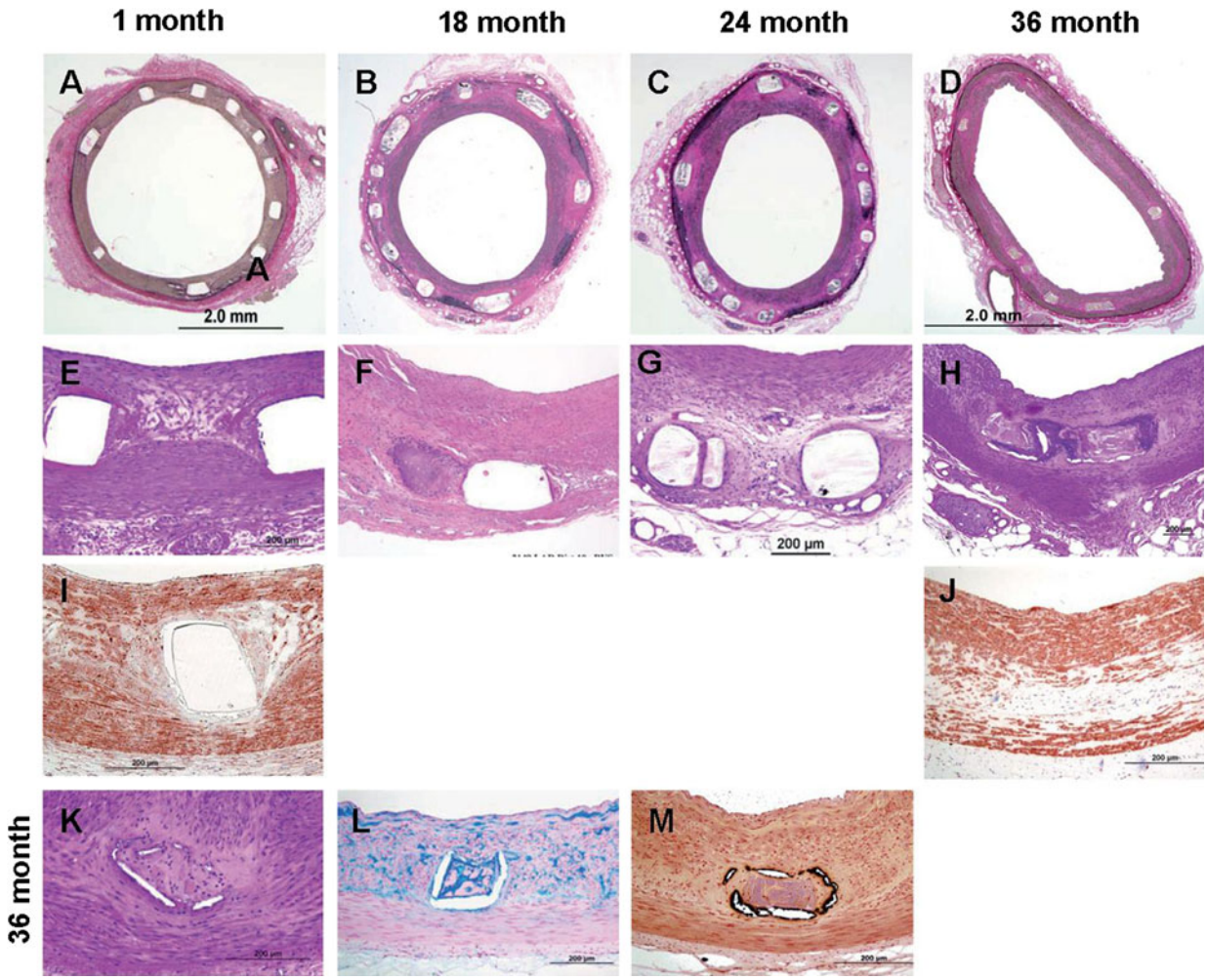


**Fig. 3** **a–d** Representative histological sections of a Bioabsorbable Vascular Solutions (BVS) stent in pig coronary arteries removed at 1, 18, 24, and 36 months (EVG staining); **e–h** High-power images of strut regions (H&E) showing presence of fibrin at 1 month and absence at all other time points. *Empty spaces* represent BVS struts up to 24 months; **i** and **j** Smooth muscle actin positive cells are observed in the neointima and media at 1 and 36 months, respectively; **k–m** Representative images of a 36-month BVS. Note the strut outline is barely visible. **k** Illustrates complete degradation of the polymer strut with surrounding basophilic deposition of calcium (H&E). **l** Alcian blue positive proteoglycan (*blue*) infiltrated the matrix of the BVS stent strut. **m** Calcification is seen around the degraded stent strut (von Kossa). Reproduced with permission from [72]

stents with late lumen loss of 10% and restored vasomotion [74]. Improvements of scaffold design and a modified manufacturing process of its polymer led to the second iteration of the trial (ABSORB I: Cohort B). Again, imaging studies with IVUS or OCT were performed at various intervals up to 36 months in 101 patients. There was 100% device deployment success with slightly more complex lesions than the Cohort A. Two-year results were comparable to the SPIRIT trial data with the original Xience V stent with no cardiac deaths, 3% non-Q-wave MI, and 6% ischemia-driving percutaneous coronary intervention with no scaffold thrombosis [75–77]. The ABSORB EXTEND trial is an ongoing non-randomized, single

**Table 1** Pros and cons of fully absorbable DES

| PRO | CON | Unanswered questions |
|---|---|---|
| Need orientated temporary scaffold | Cost | Optimal material/design |
| No indefinite foreign body | Limited radial force of the scaffold | Optimal time frame of degradation |
| No need for long-term DAPT | Bulky design limits application | Pathobiological long-term effects (inflammation, neoatherosclerosis, calcification) |
| Sufficient drug carrier | Lesion/implantation limitations | |
| | Potential for fracture | |

**Table 2** Biodegradable polymer-coated drug-eluting stents

| Stent | Company | Polymer | Drug |
|---|---|---|---|
| Orsiro™ | Biotronik | Biolute | Sirolimus |
| NOYA™ | Med favor | PDLLA | Sirolimus |
| Firehawk™ | MicroPort | PDLLA | Sirolimus |
| AXXess™ | Biosensors | PLA | Biolimus |
| Biomatrix™ | Biosensors | PLA | Biolimus |
| Combo™ | OrbusNeich | PLA | Sirolimus |
| Excel™ | JW Medical | PLA | Sirolimus |
| Elixir™ | Elixir Medical | PLA | Novolimus |
| JACTAX™ | Boston Scientific | PLA | Paclitaxel |
| Nobori™ | Terumo | PLA | Biolimus |
| BuMA™ | SinoMed | PLGA | Sirolimus |
| Coracto™ | Alvimedica | PLGA | Sirolimus |
| MiStent™ | Micell | PLGA | Sirolimus |
| SYNERGY™ | Boston Scientific | PLGA | Everolimus |
| Infinnium™ | Sahajanad | PLGA/PLLA/PCL/PVP | Paclitaxel |
| Supralimus™ | Sahajanad | PLGA/PLLA/PCL/PVP | Sirolimus |
| BioMime™ | Meril Life Science | PLLA/PLGA | Sirolimus |
| Inspiron™ | Sctech | PLLA/PLGA | Sirolimus |

arm, continued access trial allowing greater complexity of lesions with planned overlapping allowed in longer (22–28 mm) lesions and a greater variety of stent lengths and diameters. The ABSORB II trial is a European randomized trial against the Xience Prime looking at co-endpoints of vasomotion (change in minimal luminal diameter [MLD] before and after nitroglycerine and change in MLD at 2 years versus post-procedure). The ABSORB III trial started in early 2013 and is the first randomized trial in the US comparing the BVS against Xience DES with a primary endpoint of target lesion failure at 1 year. The duration of dual anti-platelet therapy in these trials remains 1 year and, given the increased strut thickness, may be more important than with current generation DES.

A different concept was initiated by Biotronik who introduced the first metallic bioabsorbable magnesium stent (AMS) with a strut thickness of 165 μm and 10% vessel coverage (comparable to current metallic stents) with no drug coating. The prospective, non-randomized, multicenter clinical trial, DREAMS (Drug Eluting Absorbable Metal Scaffold), demonstrated impressive angiographic results immediately after stent implantation [78]. However, accelerated absorption of the stent resulted in early loss of

**Table 3** Completely biodegradable stents

| Stent | Company | Polymer | Drug |
|---|---|---|---|
| BVS™ | Abbott | P(D)LLA | Everolimus |
| AMS-4.0™ | Biotronik | PLLA | Sirolimus |
| ReZolve™ | REVA Medical | Poly (DTE carbonate) | Paclitaxel |
| IDEAL™ | Xenogenics | PAE and salicylic acid | Sirolimus |
| On-ABS™ | OrbusNeich | PLLA/PCL/PDLLA | Sirolimus |
| BTI™ | Bioabsorbable therapeutics | Polymer/salicylate + linker | Sirolimus |
| DeSolve™ | Elixir Medical | PLLA | Novolimus/Myoli |
| ART | Arterial Remodeling Technologies | PLLA | n/a |
| Amaranth | Amaranth Med. | PLLA | n/a |
| Xinsorb | Huaan Biotech | PLLA | Sirolimus |
| Acute | Orbus Neich | Poly-L-lactic, poly-D-lactic, and poly-L-lactide-co-ε caprolactone | Sirolimus |

the structural integrity of the scaffold and radial force within weeks. Consequently, initial clinical trials in the periphery and coronary circulation suggested higher rates of restenosis when compared with traditional BMS [79, 80].

The REVA® stent (REVA Medical, Inc., San Diego, CA, USA) is made of a tyrosine-derived polycarbonate polymer (poly[deaminotyrosyl-tyrosine ethyl ester] carbonate) and is radio-opaque due to the incorporation of iodine molecules. The stent is balloon expandable, strut thickness is 200 μm, stent coverage 55% of the vessel and designed with a unique slide and lock (ratchet) mechanism. The first in-man RESTORE pilot study I (Pilot Study of the ReZolve® REVA Medical, Inc. San Diego, CA USA Sirolimus-Eluting Bioresorbable Coronary Scaffold) analyzed outcomes of 22 patients implanted between December, 2011 and July, 2012 and found a preliminary late lumen loss of 0.2 mm comparable to DES studies [81]. The ReZolve2 trial is underway with the next-generation REVA bioabsorbable stent with improved radial strength and deliverability.

Determination of the most efficient radial strength and optimal degradation time are still under extensive preclinical and clinical investigations (Table 1). Drug-eluting balloons that leave no scaffolding have demonstrated promising results for in-stent restenosis [82] and will need to be compared with bioabsorbable stent outcomes. A comprehensive list of investigational bioabsorbable polymer coated stents/fully bioabsorbable stents and current fully bioabsorbable stent trials is listed in Tables 2, 3 and 4.

## CONCLUSION

While the current generation DESs have dramatically improved the rates of adverse events in clinical practice, the ongoing quest to minimize late stent thrombotic events while maintaining maximal lumen diameters and retuning normal vessel physiology is ongoing. The biodegradable polymers and completely biodegradable stents represent the "cutting

**Table 4** Ongoing completely biodegradable stent trials

| Platform | Trial | Patient no. (pts) | Follow-up (years) |
|---|---|---|---|
| REVA | RESTORE II | 125 | 5 |
| ABSORB | Cohort B G1 | 45 | 5 |
| | Cohort B G2 | 56 | 5 |
| | EXTEND | 1,000 | 3 |
| | EURCT | 500 | 5 |
| | China RCT | 200 | 5 |
| | Japan RCT | 300 | 5 |
| | First | 10.000 | 4 |

edge" in the evolution of DES technology. As substantiated by early clinical trials, these stents achieve temporary vessel scaffolding to obtain optimal vessel calibers, prevent vessel recoil, and stabilize dissections until the vessel has healed. Through their bioabsorption, normal vessel physiology and vasomotion return over time. However, the clinical experience of currently available "bulky" and expensive biodegradable stents is limited to a total of <10,000 estimated implanted stents worldwide. Dual anti-platelet duration is not reduced and may be required for a longer time given the thicker stent struts with bioabsorbable stents.

Several important features such as optimal polymer composition, degradation, drug release kinetics, impact of neoatherosclerosis, and stent fracture are the focus of current investigations (Table 1). Likewise, ongoing "real world" clinical experience is needed to gain better evidence after promising initial results.

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***Compliance with ethics guidelines.*** The analysis in this article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.



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