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Advances in stent drug delivery: the future is in bioabsorbable stents

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This expert opinion review offers a perspective on the future developments in drug-eluting stent design. Initial efforts were focused on reduction of in-stent restenosis, which the drug-eluting stents addressed effectively. Current concerns are predominantly with regard to risk of stent thrombosis and delayed endothelialization. All three components of the stent have been modified to achieve the goal of endothelialization and vessel healing: drug, polymer and the platform. We review different approaches to reduce this risk from design of different drug combinations, through less traumatic metallic stent platforms, via biodegradable polymers and, finally, fully biodegradable stents. It seems at this time that fully biodegradable solutions to stenting hold the greatest promise, but larger long-term studies are needed to evaluate fully their safety and efficacy in 'all-comer' patient populations. At the time of this review, design of a safe drug-eluting stent still remains a challenge.

Keywords: bioabsorbable, biocompatible, drug-eluting stents, endothelialization, in-stent restenosis

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1. Introduction

Drug-eluting stents (DES) have been quickly embraced by interventional cardiologists owing to their lower restenosis rate compared with bare metal stents. As the use of DES expanded to patient populations with more complex disease than the preselected populations in the initial trials, the risk of late stent thrombosis, previously seen with brachytherapy, resurfaced. While analysis from the initial SIRIUS trial of first-generation stents quoted a risk of stent thrombosis of 0.6% at 1 year, in registries stent thrombosis rates as high as 2% at 1 year have been seen [1,2]. At present, new stent registries in Europe that use 'all-comers' rather than preselected patient populations also confirm higher stent thrombosis rates [3]. New pharmacologic strategies are therefore needed that would allow for rapid re-endothelialization of the stent as well as modulation of the neointimal hyperplasia [4-6]. Drug-eluting stents are composed of three elements: the stent platform, a drug carrier (usually a polymer) and the active drug itself [7].

1.1 Metalic stent platforms

Balloon-expandable coronary stents used today are made from stainless steel, cobalt chromium or other metal alloys and composites that allow for adequate radial strength, low recoil and uniform scaffolding, are radio-opaque and do not undergo foreshortening [8]. Stents can be of open and closed cell design and have various cell sizes, which in part affects uniformity of drug delivery [9,10].

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1.2 Drugs and their pharmacokinetics, and the mechanism of controlled release

Drug-eluting stents are the first successful application of the controlled drug delivery (CDD) system in interventional cardiology for local treatment of coronary artery disease. Several CDD mechanisms have been designed: diffusion-controlled systems (that rely on diffusion through the polymer matrix) or degradation of the polymer matrix, osmotic pressure or ion exchange [11]. Various methods of drug delivery from a stent have been proposed: non-polymeric drug coatings [12], covalent drug attachment via linkers, drug-infused polymer sleeves [13], nonabsorbable or bioabsorbable polymer carriers. Regardless of the drug-release mechanism, using polymers as a drug delivery vehicle usually enables best controlled and sustained release of the drug.

1.3 Polymers

Kinetics of the drug release in the drug-eluting stent should parallel the kinetics of the restenosis process and, thus, controlled-release drug delivery systems such as polymers are required [14]. The ideal polymer should have good coating integrity throughout the manufacturing and deployment process, should be compatible with drug and vessel, provide uniform drug distribution along the stent and retain the drug during stent deployment, provide controlled drug release and have stable shelf-life [15]. The various polymer formulations investigated over the last decade included: polyurethanes, silicone, polyorganophosphazenes and fibrin [16,17]. These polymers have all been discovered to cause inflammatory changes in porcine coronary arteries [18]. Cypher stents use two nonerodable polymers: polyethylene-co-vinyl acetate (PEVA) and poly-n-butyl methacrylate (PBMA). The combination of these two polymers and sirolimus is coated with a drug-free PBMA layer, which provides the mechanism of controlled release. Taxus stents use the Translute polymer, which is a matrix-controlled system made of soft elastomeric triblock co-polymer called poly(styrene-b-isobutylene-b-styrene) (SIBS). Paclitaxel sits on the surface of the SIBS matrix as particles. As the drug-to-polymer ratio increases, so does the speed of release kinetics. Low ratios provide slower sustained release and do not cause fibrin deposition on the stent struts, and thus are used in Taxus SR [15]. Phosphorylcholine (PC) is another biostable nonerodible polymer that is biomimetic and was used in Endeavor and ZoMaxx zotarolimus eluting stents. Bioabsorbable polymers such as polylactides and polylactide-co-glycolides polymer matrices degrade gradually into carbon dioxide and water with rates based upon their molecular weights, and the ratio of monomer to polymer, and are described later.

2. Current stent designs and their challenges

Initial percutaneous treatment of coronary artery disease was done with balloon angioplasty and resulted in frequent recoil and abrupt vessel closure, often necessitating surgical intervention [19,20]. While metallic stents introduced in 1986 reduced these complications as well as restenosis rate, acute stent thrombosis and significant rate of restenosis still remained a concern [21-24]. Stent thrombosis rate was significantly reduced with the introduction of dual antiplatelet therapy administered until the injured endothelium healed, and prothrombogenic metallic stent struts were covered with endothelial cell [25,26]. Neointimal hyperplasia at 3 – 6 months after stent implantation was still occurring in 20 – 30% of patients and was even more prevalent in diabetics, necessitating multiple procedures. After failure of brachytherapy, which gave a late stent thrombosis rate of 6% [27,28], drug-eluting stents were introduced in 2002/2003.

The sirolimus-eluting Cypher stent (Cordis, NJ) is composed of a stainless steel platform (140 micron struts) coated with a permanent polymer (polyethelyne co-vinyl acetate and poly-n-butyl methacrylate) with sirolimus concentration of 140 μg/cm^2, 80% of which is released in 30 days [29]. Sirolimus (rapamycin) binds to FK506-binding protein 12 and targets mTOR, thereby blocking the cell cycle transition from G1 to S phase (**Figure 1**). By this mechanism, sirolimus blocks proliferation and migration of smooth muscle cells and prevents neointimal hyperplasia. At the same time, however, it also affects endothelial progenitor cells and inhibits endothelialization. The SIRIUS trial showed reduction of in-stent restenosis from 35% to 3.2% with Cypher DES and late loss of only 0.17 mm [30]. Target vessel failure was reduced from 21% to 8.6% and stent thrombosis rates were 0.4% and 0.8% at 1 year. This trial, however, excluded patients with complex lesions such as lesions > 30 mm, bifurcations, ostial lesions, left main disease or ejection fraction (EF) of 25%. E-Cypher registry with more than 18,000 lesions including bifurcation and left main stenting as well as small vessels and long lesions also confirmed the good safety profile of the stent [31], as did the RESEARCH registry [32]. However, RESEARCH and T-SEARCH combined analysis at 3 years showed rate of stent thrombosis of 0.6% per year approaching 2% at 3 years in both patients treated with Cypher and Taxus stents (**Figure 2**) [1,33,34]. Histopathological assessment [35] in autopsy cases showed delayed healing and endothelialization, as well as evidence of hypersensitivity reaction in patients with stent thrombosis who had received drug-eluting stents. Hypersensitivity reaction was ascribed to the nonerodable polymer. Lack of endothelialization and presence of thrombus was also demonstrated on angioscopy with uncovered struts being present in 20% of patients at 2 years postimplantation and thrombus present in 40% of cases [36].

The Taxus (Boston Scientific, MA) paclitaxel-eluting stent also has a stainless steel platform with a permanent polymer coating (polystyrene-b-isobutyle-b-styrene; SIBS), which contains 1 μg/mm^2 of paclitaxel with biphasic elution profile. The drug is eluted within the first 48 h

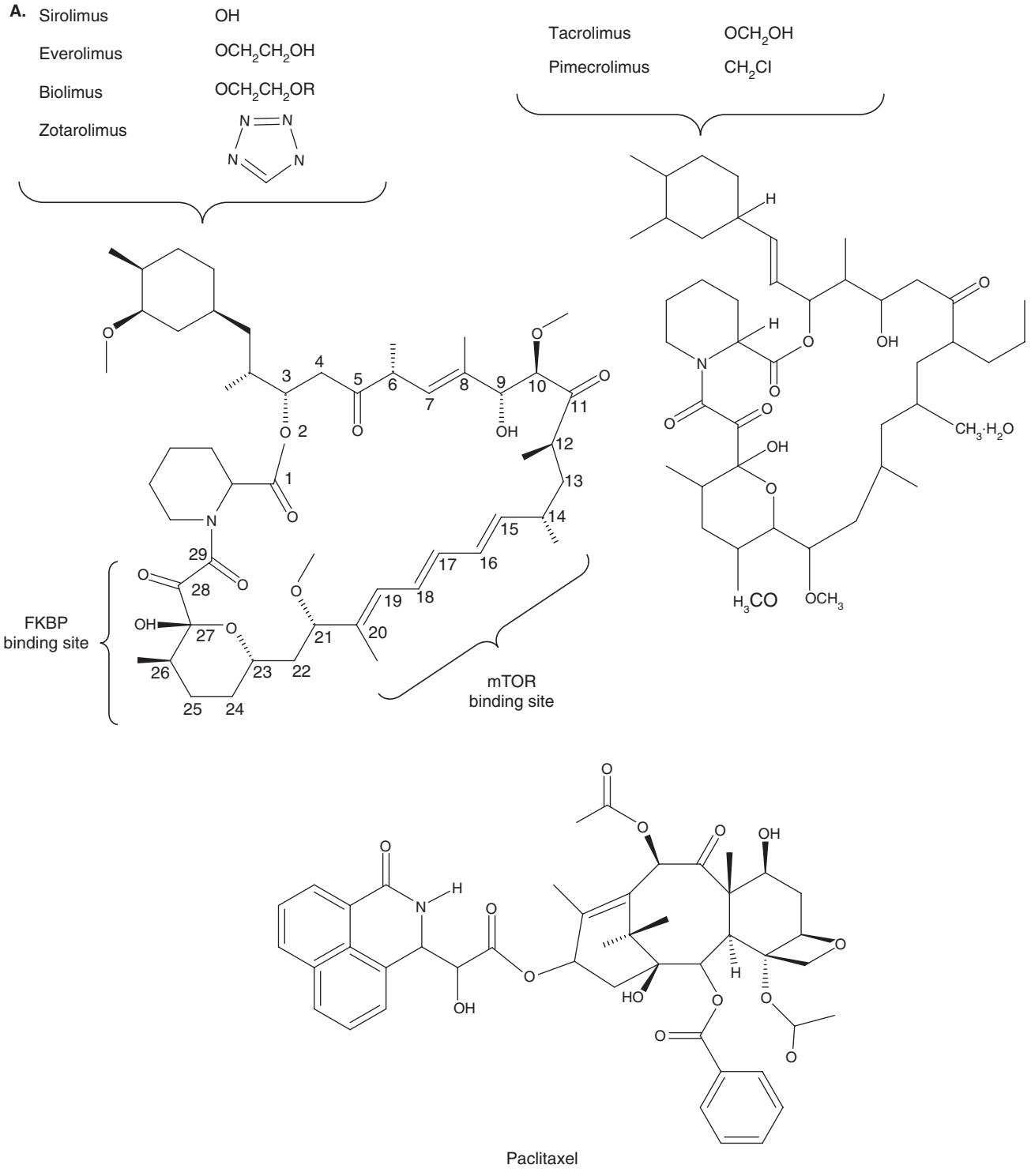


Figure 1. Chemical structures of sirolimus analogues, calcineurin inhibitors and paclitaxel (**A**).

B. How do current DES stack up

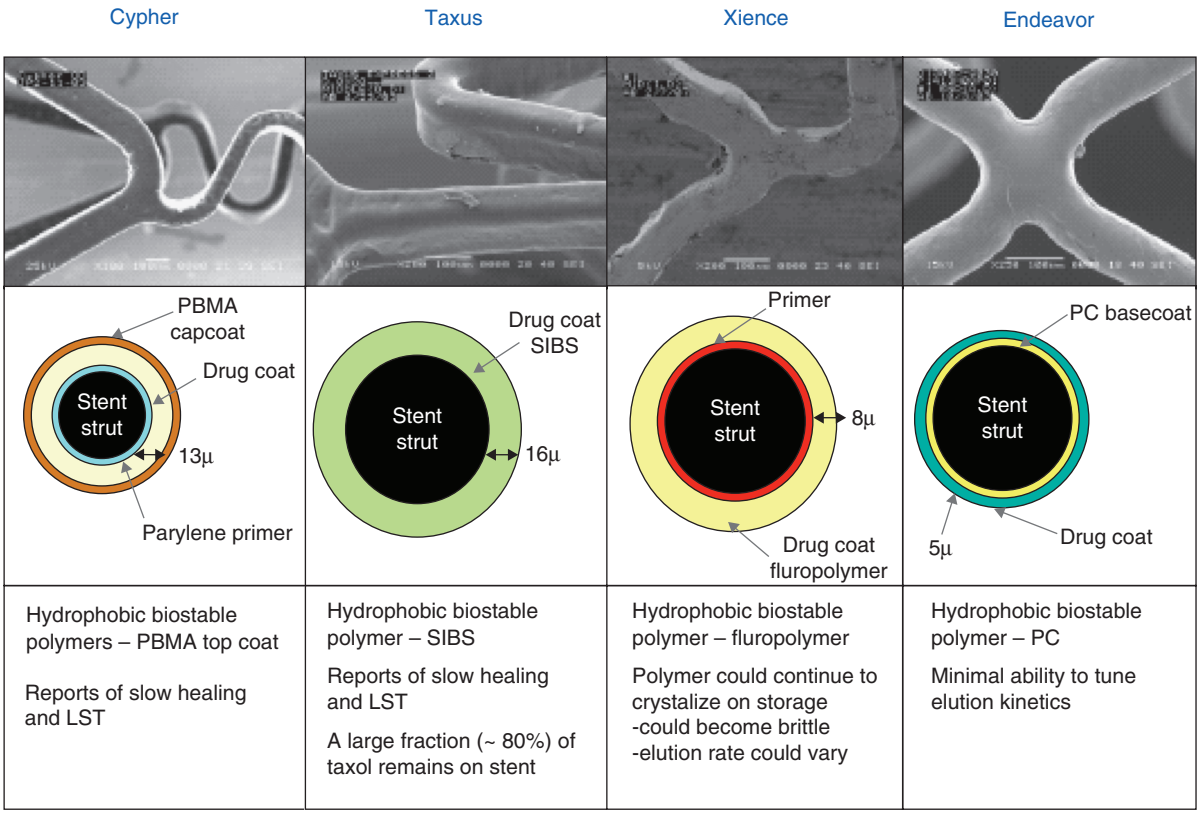


Figure 1. Comparison of currently available stents (**B**).

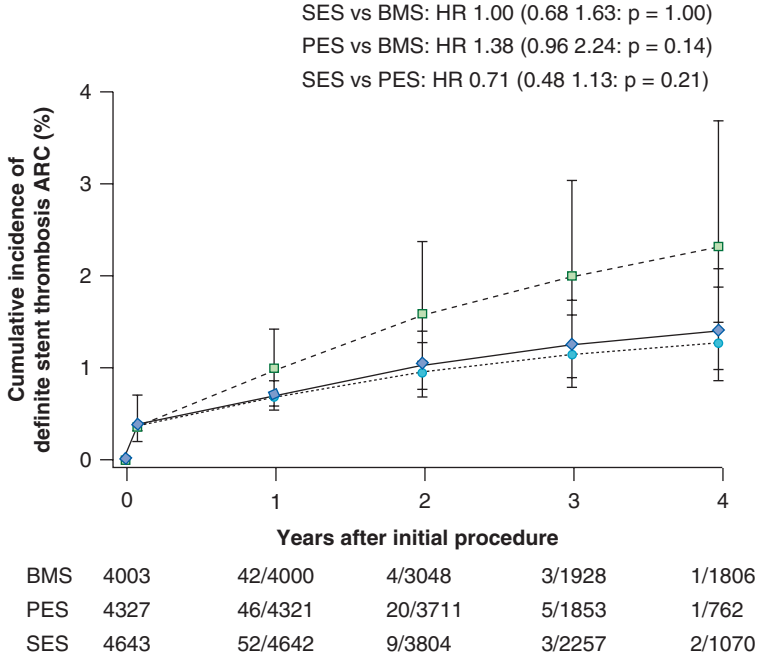


Figure 2. Incidence of stent thrombosis in the Rotterdam-Bern registry approaches 2.5% at 3 years ([34], used with permission).

and subsequently over 2 weeks with 90% of the drug remaining bound to the polymer. Paclitaxel is also an antiproliferative agent and microtubule inhibitor that arrests cell cycle in G0/G1 and G2/M phases and inhibits smooth muscle cell proliferation (**Figure 1**). The Taxus II trial of more than 500 patients saw reduction in angiographic in-stent restenosis rates from 17.9% to 2.3% in the Taxus stent groups, with both slow and moderate release of the drug [37]. Subsequent T-SEARCH registry of paclitaxel stent implantation in unselected population showed equivalent outcomes to patients treated with rapamycin-eluting stents in the RESEARCH registry [38].

Endeavor (Medtronic, CA, USA) is a zotarolimus-eluting stent with a CoCr platform and a phosphorylcholine polymer. Zotarolimus is eluted in 70% over 30 days (**Figure 1**). Endeavor I, II and III trials have all shown that Endeavor stent compares favorably in the rate of restenosis and TVR to the bare metal stents (7.3% vs 15.1%, p = 0.0001) [39,40]; however, comparison with sirolimus- and paclitaxel-eluting stents revealed much less effective inhibition of intimal hyperplasia and greater rate of late loss [41,42]. The Endeavor Resolute multicenter study that randomized 'all-comer' patients to the Endeavor Resolute stent with a new platform and Xience V stent is now underway. The new Biolinx polymer in the Resolute stent [43] with extended elution kinetics has a hydrophilic outer layer of vinyl pyrrolidinone groups and promises to be more biocompatible with less inflammation and less neointimal proliferation.

Xience V (Abbot Vascular, CA, USA) is an everolimus-eluting (EES) stent with a nonerodible fluoropolymer and also a flexible CoCr platform (**Figure 1**). The Spirit III trial has shown it to be superior to paclitaxel drug-eluting stents (PES) in late loss and resultant MACE rate (cardiac death, any MI, or ischemia-driven target lesion revascularization (TLR), which were 6% vs 10% at 1 year, p = 0.02) [44,45]. At 2 years, treatment with EES compared with PES resulted in a significant 32% reduction in TVF (11.0% vs 15.7%, HR [95% CI] = 0.68 [0.48, 0.98], p = 0.038), and a 45% reduction in MACE (cardiac death, MI, or target lesion revascularization; 12.8 vs 7.3%, HR [95% CI] = 0.55 [0.36, 0.83], p = 0.004). X-SEARCH registry is now underway to confirm this superior efficacy in 'all-comers' unselected population.

3. Need for further improvement – 'It's the endothelium, stupid'

Although drug-eluting stents, particularly the latter generation Xience V, have had a dramatic effect on the reduction of in-stent restenosis, the concern about stent thrombosis due to delayed endothelialization or endothelial dysfunction remains [46-48]. Animal studies and scanning electron microscopy evaluation reveal that, at 28 days postimplantation in an animal model where stent strut coverage might be better than in patients with coronary disease, sirolimus stents have 3 mm^2, paclitaxel stents 3.8 mm^2, zotarolimus 2.54 mm^2 and everolimus stents 1.33 mm^2 of uncovered struts compared with 0.12 mm^2 of bare metal stents [49]. To allow for drug release, the first-generation stents used permanent polymers, which may cause hypersensitivity reaction [18,35]. Thus, one potential solution to the problem of delayed healing/endothelialization may be to use biodegradable or biocompatible polymers. Reduction in the strut thickness of the stent may also allow for less vessel wall injury and better endothelial coverage. Another possibility is elution of the drug that would improve endothelial function, such as probucol, or a means of recruiting of endothelial progenitor cells to enhance endothelial healing. Lastly, a stent that can prevent acute recoil but then be fully bioabsorbable without leaving any struts behind would be an ideal solution to the stent thrombosis risk in the long term [50,51].

4. New metallic platforms: search for a more deliverable stent

Cobalt chromium platforms used in Endeavor and Xience V stents are more deliverable, flexible and have better radial strength allowing for thinner strut design than first-generation stainless steel 316L Cypher and Taxus stents. One of the novel stent designs is the Conor stent (**Figure 3A**), which is also on the cobalt chromium platform but has multiple intrastrut wells that allow for drug delivery. The struts are linked with flexible bridges (ductile hinges). This design is distinct in that the polymer and drug are not bonded to the stent structure through coating, but rather multiple holes are drilled through the stent structure and are filled with bioabsorbable polymer/drug mixture, thereby serving as local drug depots.

Several novel stents use the self-expanding design and are composed of nitinol. One such stent from Prescient 'Shield', which has good radial strength but causes minimal outward chronic force on the plaque (high radial resistive force to chronic outward force ratio), is dedicated to 'high-risk plaque' or Thin-Capped FibroAtheroma stenting and is specifically designed to cause minimal plaque rupture and embolization (Serruys, personal communication; Ramcharitar *et al.*, 2008, in press) (**Figure 3B**).

Xtent (**Figure 3C**) has a cobalt chromium platform coated with biolimus on a PLA erodable polymer (**Figure 3D**). The unique feature of the metallic platform is that it consists of multiple 6-mm interdigitating elements, which can be deployed in combination or separately. This allows for customization of the stent length. The CUSTOM II trial [52] was a single-arm 100-patient study with complex and long-lesions (average length 28.7 mm). TVR rate was 4% at 1 year with no cases of stent thrombosis, which compares favorably to other DES stents. CUSTOM III (90-patient study with long and complex lesions) results were recently presented at EuroPCR2008 and showed 6 months' MACE rate of 7.8% (5.6% TVR). There was one early stent

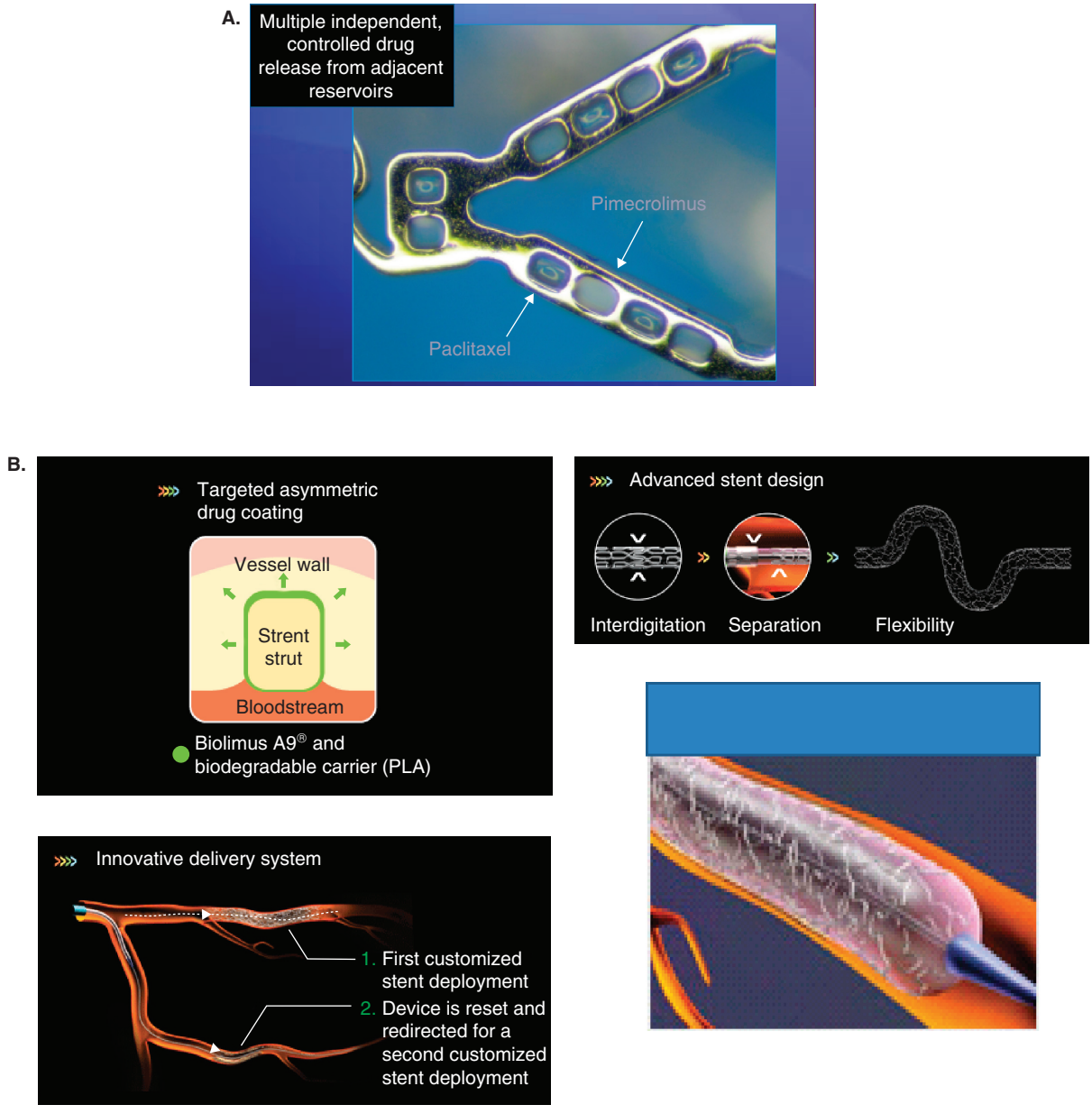


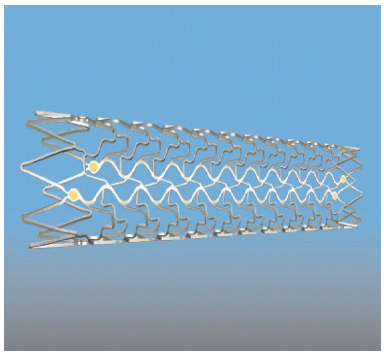
Figure 3. Conor paclitaxel erodable polymer stent (**A**), X-stent (**B**).

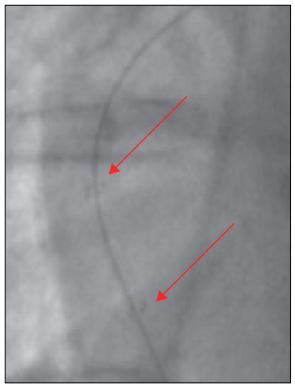
thrombosis, and late loss was only 0.17 mm with a 4.4% rate of binary in-stent restenosis.

Finally, the titanium-nitride-oxide stent has been shown to have excellent biocompatibility and low thrombogenicity in animal models [53]. It has been tested in a randomized trial against stainless steel bare metal stents. It has lower late loss (0.55 vs 0.9 mm; p = 0.03) and percentage diameter stenosis rates (26% vs 36%; p = 0.04) compared with stainless steel bare metal stents [54]. Intravascular ultrasound examination showed lower neointimal volume (18 vs 48 mm^3, p < 0.001). MACE rate (TVR-driven) was 7% in the titanium-nitride-oxide stent group versus 27% in the stainless steel bare metal stent group (p = 0.02). Larger-scale clinical trials are awaited.

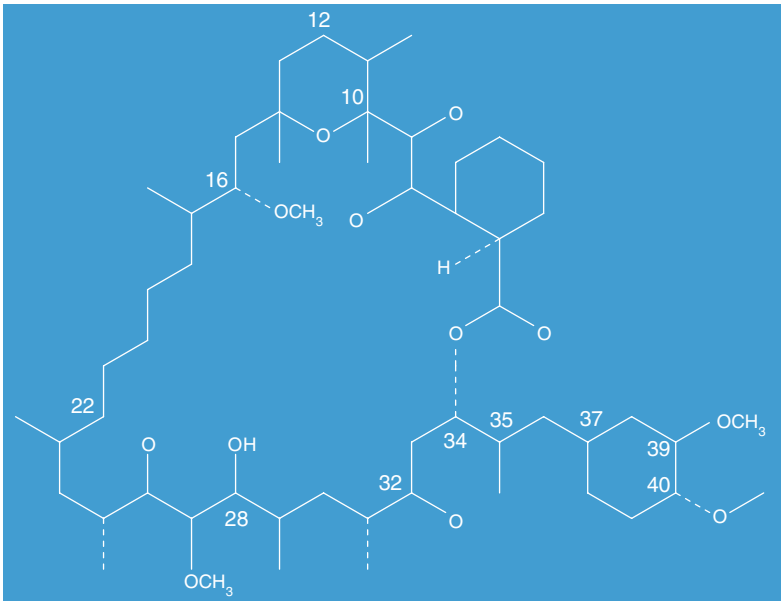
Under evaluation are also several novel stent designs dedicated specifically to bifurcation stenting to provide better coverage for the side-branch ostium. Axxess Plus (Devax, CA, USA) is a self-expanding nitinol bifurcation stent that also elutes biolimus (**Figure 3D**). The majority of other bifurcation stents such as Tryton, Capella, Nile Croco, Frontier or Stentys are nondrug-eluting in their present first-generation versions, but many, such as Tryton and Capella, allow for DES placement in the main branch [43,55].

C.

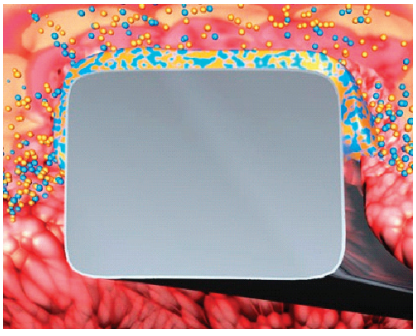




D.



Biolimus is a semi-synthetic sirolimus analogue with 10× higher lipophilicity and similar potency as sirolimus.
Biolimus is immersed at a concentration of 15.6 μg/mm into a biodegradable polymer, polylactic acid, and applied solely to the abluminal stent surface by a fully automated process.
Polylactic acid is co-released with biolimus and completely desolves into carbon dioxide and water during a 6 – 9 months period.
The stainless steel stent platform has a strut thickness of 112 μm with a quadrature link design.



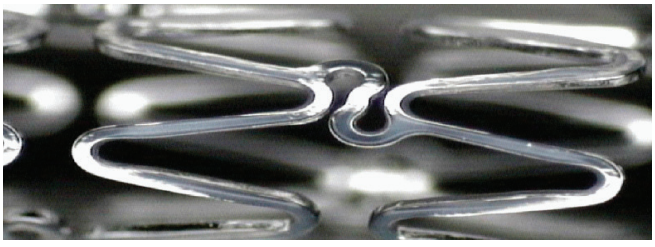


Figure 3. vShield (**C**; arrows showing radioopaque proximal and distal stent markers), and Biolimus erodable polymer stent (**D**).

5. Bioabsorbable polymers

The realization that DES polymers, while allowing for controlled drug release, may be the main culprit in inducing the pro-inflammatory reaction, lead to the search for more biocompatible or biodegradable materials. Fully biodegradable polymers include polylactic acid (PLA) and polylactic-co-glycolic acid (PGLA), which are both metabolized to water and carbon dioxide. They release the drug via degradation of the polymer matrix. Initial drug release is caused by drug elution from the surface, and subsequent release requires water diffusion into the matrix and its degradation.

Preliminary data are available on the Excel stent, which elutes sirolimus from PLA [56] and shows a lower restenosis rate in complex lesions than in other DES nonerodable stents. Results of COSTAR II, a 1700-patient study, where the Conor stent, which elutes paclitaxel from PGLA, was compared with the Taxus stent, showed higher MACE/TVR rates and a higher late loss at 9-month angiographic follow-up in the Costar arm [57]. Most recently, biolimus eluted from PLA polymer was compared with nonerodable polymer Cypher stent in an 'all-comers' randomized LEADERS trial of 1700 patients. The biolimus bioabsorbable polymer stent was noninferior in MACE rate at 9 months and provided a 21% relative risk reduction in clinically indicated TVR [3].

An alternative to bioabsorbable polymer stents are stents that elute drugs from nanopourous materials such hydroxy-apetite (biocompatible crystalline derivative of calcium phosphate) [5]. Finally, titanium-nitric-oxide applied to the stainless steel backbone also seems to reduce platelet adhesion and neointimal hyperplasia in preliminary studies and has less restenosis than bare metal stainless steel stents [54].

6. New drugs and drug combinations

Another way of reducing the risk of stent thrombosis, improving endothelialization, reducing inflammation and at the same time more selectively inhibiting neointimal hyperplasia is to choose more selective drugs or drug combinations. Tacrolimus is a macrolide that binds to FKBP12 and inhibits calcineurin, but unlike mTOR inhibitors has a preferential effect on smooth muscle cells rather than endothelial cells *in vitro* and in animal models. However, a preliminary clinical trial (JUPITER II) of the Janus stainless steel stent coated with tacrolimus failed to show any benefit on restenosis compared with bare metal stents [58]. Similarly, a tacrolimus-eluting cobalt chromium Mahoroba stent also failed to prevent neo-intimal hyperplasia [59].

The synchronnium stent, which consists of a stainless steel coated with biodegradable polymer that elutes both heparin and sirolimus, was safely used in 40 patients with a binary restenosis rate of 2% and late loss index of 0.18. There were no cases of stent thrombosis at 6 months (Abizaid, EuroPCR2008). The Genistein-Sirolimus-eluting stent is composed of five layers with varying degrees of elution of the two drugs. Genistein is a natural isoflavanoid phytoestrogen, which has anti-inflammatory and anti-thrombotic properties [7]. Another SymBio stent combining anti-inflammatory pimecrolimus and antiproliferative paclitaxel (Conor technology) was recently tested in the Genesis trial, but the trial was suspended owing to high TLR rates.

The Genous stent uses antibodies to capture endothelial progenitor cells on its surface, which was hypothesized thereby to promote endothelial healing. Although initial results have been encouraging and accelerated endothelialization was demonstrated [60], Healing 2b results so far have been disappointing, showing significant rates of in stent restenosis and late loss. This may be due to intrinsic dysfunction of endothelial progenitors in patients with multiple coronary risk factors. Lastly, application of anti-angiogenic proteins may decrease vasa vasorum proliferation and promote plaque stability. The BiodivYsio bevacizumab (Avastatin) eluting stent is being investigated at present [61,62].

7. Fully bioabsorbale stents – the new and last frontier

Fully biodegradable stents carry a promise of reducing completely adverse reactions such as stent thrombosis. The premise is that drug elution and scaffolding will be provided by the stent only until such time that the vessel heals itself. Such stents would obviate the need for long-term antiplatelet therapy. Since no foreign material would be left behind, future surgical options will not be limited and follow-up with noninvasive imaging such as CT angiography would be possible.

The first metallic bioabsorbable stent, a magnesium Biotronik stent (AMS) was composed of 93% magnesium and 7% rare earth metals and is hypothrombogenic. Under normal conditions, it degrades over 2 months into inorganic salts. It has mechanical characteristics similar to stainless steel. After initial preclinical trials and successful deployment in critical limb ischemia, the PROGRESS AMS trial demonstrated good safety in the coronary arteries of 63 patients but ischemic TVR/MACE rates of 26.7% and overall TLR rate of 47.5% at 1 year [63,64].

The Igaki-Tamai stent is a nonmetallic biodegradable stent composed of poly-L-lactic acid (PLLA). It was safe, with late loss and TVR rates comparable to bare metal stents but an increased cross-sectional area by IVUS 3 and 6 months after implantation [65]. The deployment of the stent was rather complex, requiring thermal balloon expansion to actuate the device.

The next fully biodegradable stent in clinical trials was an everolimus-eluting PLLA stent from Abbot (BVS stent) (**Figure 4**). Acute recoil and radial strength after stent deployment was similar to the cobalt chromium stents now available on the market. Its stent strut thickness is 150 microns, and the struts are joined by thin and straight

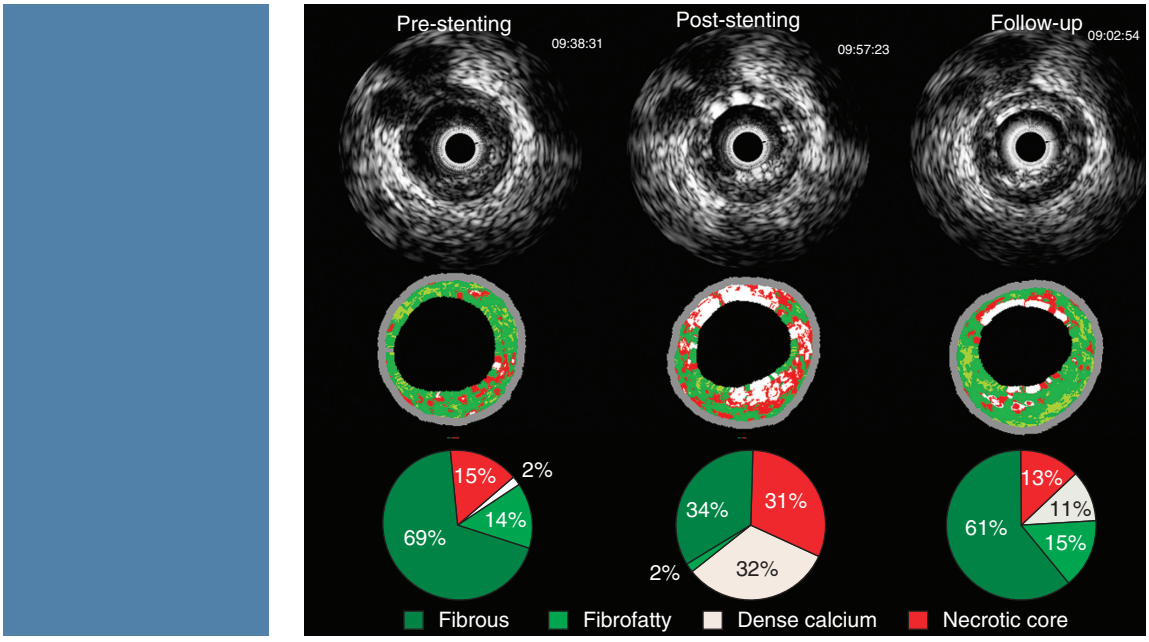
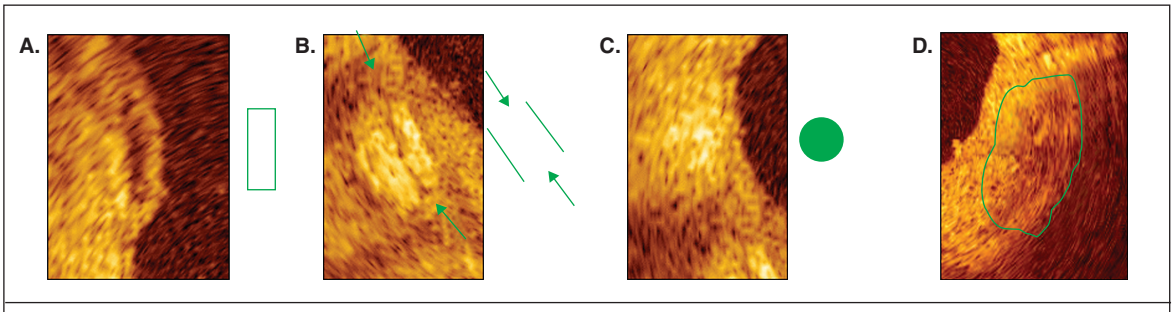


Figure 4. BVS stent and appearance of stent struts by IVUS and IVUS-VH at baseline, poststenting and at 6 months postimplantation. Plaque remodeling demonstrated with IVUS-VH ([50], used with permission).



Preserved box	Open box	Dissolved bright box	Dissolved black box
Sharp defined, bright reflection borders with preserved box shaped appearance strut body shows low reflection	Luminal and abluminal "long-axis" borders thickened bright reflection; "short axis" borders not visible	Partially visible bright spot, contours poorly defined no box shaped appearance	Black spot, contours poorly defined, often confluent no box shaped appearance

Figure 5. OCT imaging of BVS stent at baseline and follow-up showing resorption of the stent struts ([50], used with permission).

bridges. Although the stent was radiolucent, it had two platinum markers at each end, which allowed for easy identification on angiography and with other imaging modalities. Everolimus concentration and elution pattern is similar to that of the Xience stent. In animal studies, the stent was completely endothelialized within 28 days of implantation [66]. The BVS stent was recently tested in a 30-patient trial called ABSORB (a bioabsorbable everolimus-eluting coronary stent system for patients with single *de novo* coronary artery lesions) [50]. This was a prospective multicenter study with follow-up every 6, 12, 18 and 24 months. In addition, angiographic, IVUS, IVUS-virtual histology and OCT were done in 10 patients at 6 months and 2 years (**Figures** 4, 5). At 6-month follow-up, MACE rate was low at 3.3% and QCA showed late loss of 0.44 mm. Restenosis rate was 11.5%, which is lower than that seen with bare metal stents. Stent

Table 1. Summary of requirements for successful treatment of coronary disease by stents.

Stent property	Deliverability	Scaffolding/recoil prevention	Minimal vessel trauma	Low level of inflammation	Antirestenosis properties	Endothelialization	No need for long-term antiplatelet therapy	Positive vessel remodeling
Traditional DES Cypher Taxus	+	+++	+	-	++	-	-	-
New DES Endeavor Xience	++	+++	++	+	++	+	-	-
Self-expanding VShield (nitinol) X-tent	++	++	+++	++	++	++	++	?
Bioabsorbable polymer Biolimus erodible	++	++	++	+++	++	++	+	?
Fully bioabsorbable BVS IDEAL BIOTRONIK	++	++	++	+++	++	++	+++	+++

-: Poor; +: Acceptable; ++: Good; +++: Excellent.

struts by IVUS are seen gradually to collapse in a characteristic pattern (**Figure 5**). Patients examined with IVUS-VH so far have exhibited replacement of the stent struts by fibrotic tissue now isolating any areas of necrotic core away from the lumen, and thereby rendering the plaque more stable (**Figure 4**). We also noted positive vessel remodeling and restoration of vasomotion (Serruys, personal communication). Such vessel remodeling and change in plaque characteristics towards a more stable phenotype is rather unprecedented and carries a great deal of promise. There were no stent thrombosis nor TVR events at 24 months clinical follow-up of the ABSORB trial.

Other stents that are undergoing trials are the biodegradable endothelial progenitor capturing stent from OrbusNeich. The cobalt chromium backbone of the Genous stent has been replaced with a polymorphic lactide copolymer hybrid platform. It elutes a prohealing drug on the abluminal surface and has EPC capturing antibodies on the luminal surface.

The REVA tyrosine poly(desaminotyrosyl-tyrosine ethyl ester) carbonate stent is a resorbable stent that is radio-opaque due to incorporation of iodine molecules. The polymer degrades into water and carbon dioxide but also into ethanol. Preclinical data show complete endothelialization at 30 days, low inflammation and reduction in percentage area stenosis from 1 to 12 months follow-up [66]. In addition, the REVA stent shows increase in the luminal area of the stent. The paclitaxel REVA stent is under development and a 60-patient trial has been completed.

The IDEAL poly(anhydride ester) salicylic acid stent incorporates anti-inflammatory NF-kappa-B inhibitor salicylic acid into a poly(anhydride ester) polymeric stent and elutes sirolimus [66]. The stent is layered with two different polymeric formulations with different resorption rates. Preliminary data show significant reduction in in-stent restenosis rates compared with bare metal stents.

8. Conclusion and expert opinion

Drug-eluting stents have significantly reduced the rate of restenosis and have been shown to be cost-effective. Patients no longer have to come back for cardiac catheterizations due to in-stent restenosis. Their success and impact on the practice of interventional cardiology is marred, however, by the ever-looming risk of stent thrombosis that does not appear to level off at 4 years posttreatment and necessitates long-term or indefinite antiplatelet therapy with its inherent bleeding risks. These risks may be even higher as indications for stenting expand to encompass larger patient populations. Novel stent designs, which have entered clinical trials and are summarized in this review, promise a potential solution to these problems. To provide effective treatment for coronary artery disease, a stent has to be deliverable and flexible, cause minimal trauma to the vessel wall, be as biocompatible as possible, cause minimal inflammatory reaction, endothelialize well, provide scaffolding for the vessel and, finally, promote vessel healing and remodeling. **Table 1** summarizes the ability of various classes of stents to fulfill these requirements. In our opinion, some of the novel biodegradable stents in preliminary assessment appear to have the best chance of overcoming drug-eluting stent limitations. They have become more deliverable and cause very little trauma to the vessel wall at deployment. They provide scaffolding long enough before eroding to prevent recoil and elute drugs long enough to prevent restenosis. Since the polymer is biodegradable and biocompatible, the inflammatory reaction is minimal. Endothelialization appears not to be inhibited, especially with novel drug combinations. Most striking, however, is the vessel remodeling with vessel lumen enlargement and plaque remodeling, where necrotic core is now isolated from the lumen by a strip of stable fibrous cap. Whether this favorable remodeling seen with IVUS-VH imaging translates into more favorable clinical outcomes, such as dramatic reduction in in-stent restenosis and thrombosis, remains to be seen in larger clinical trials.

Declaration of interest

The authors state no conflicts of interest and have received no payment in the preparation of this manuscript.

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