

## Review Article

# Drug-eluting stents

Xiaodong Ma<sup>1,2</sup>, Tim Wu<sup>1,2</sup>, Michael P. Robich<sup>3</sup>, Xingwei Wang<sup>1</sup>, Hao Wu<sup>2</sup>, Bryan Buchholz<sup>1</sup>, Stephen McCarthy<sup>1</sup>

<sup>1</sup>Biomedical Engineering and Biotechnology Doctoral Program, University of Massachusetts, Lowell, MA 01854, USA; <sup>2</sup>VasoTech, Inc., Lowell, MA 01854, USA; <sup>3</sup>Department of Surgery, Division of Cardiothoracic Surgery, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA 02215, USA

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**Abstract:** Coronary artery disease (CAD) is currently a leading cause of death worldwide. Drug-eluting stents (DESs) have been dominant for the treatment of CAD in the interventional cardiology world owing to their efficacy in significantly reducing restenosis. However, late stage stent thrombosis has become a major concern. Stent platform, drug delivery vehicle and type of drug are three parts of DES and each part affects the performance of the DES. Aiming to provide a clue for the design of future DES, this review focuses on the development of the three major components of DES and their roles in restenosis and thrombosis.

**Keywords:** Drug-eluting stents, restenosis, thrombosis

### Introduction

Coronary artery disease (CAD) is the most common cause of morbidity and mortality in the world, for example, it is responsible for 1 out of 5 deaths in United States where approximately 13 million people are suffering this disease [1, 2] and over 4.5 million deaths in Europe [3]. Coronary artery bypass graft (CABG) surgery has been proven an effective approach to coronary heart disease. Nevertheless, patient demand has driven the development of less invasive therapies. The treatment for CAD has been changed significantly since the introduction of percutaneous coronary interventions (PCIs) including percutaneous transluminal coronary artery angioplasty (PTCA) and coronary artery stenting (CAS). PTCA was the first milestone of PCI performed by Andreas Gruentzig in the late 1970s [4]. However, its further development was retarded by one major limitation—restenosis, up to 30%-60% of patients had recurrence of their disease within the first 6 months [5-7]. Restenosis is the re-narrowing of the opened artery after a PTCA procedure involving vascular elastic recoil, neointimal prolif-

eration, and negative remodeling, which will lead to blockage of the blood and insufficient oxygenation of cardiac tissue, resulting in myocardial ischemia, infarction, cardiac arrhythmia, or cardiac arrest. The second milestone of PCI was development of the bare metal stent (BMS) in the late 1980s, a tiny metal scaffolding that functions to brace the vessel wall, which effectively reduced restenosis compared to PTCA alone [5, 6, 8] and significantly decreased the rates of the major adverse cardiac events (MACE), myocardial infarction (MI), and death [9, 10]. However, with the wide use of BMS, a new problem came forth: in-stent restenosis (ISR), which is defined as late lumen diameter loss greater than 50% within the stent [2]. Then, the PCI was moved toward to the third milestone, drug-eluting stents, in the early 2000s [11]. A drug-eluting stent (DES), namely, a stent combined with a drug, is designed to prevent ISR through inhibition of smooth muscle cell (SMC) proliferation. Generally, there are three components in DES: 1. stent platform; 2. drug delivery vehicle; 3. drug. Both of the first two FDA approved DESs in 2002-2003, Cypher (sirolimus-eluting stent, Cordis, Warren, NJ) and

Taxus (paclitaxel-eluting stent, Boston Scientific, Natick, MA), can significantly reduce the rate of restenosis compared to BMS [12-15]. However, an increase in the rate of myocardial infarction (MI) and cardiovascular mortality was reported in patients at 18 months to 3 years after the implantation of Cypher and Taxus [16-19]. These events were found to be due to late stent thrombosis (LST), which is often an acute thrombosis of the artery caused by the platelet aggregation and blood clotting. Furthermore, some studies have indicated that DESs have higher rates of major adverse cardiac events (MACE) compared with BMS [20-22]. Therefore, though DESs have made great progress on the treatment of CAD, it is still a long way from an ideal DES to reduce or even eliminate the ISR and the LST. This article reviewed the development of three components of currently commercial and investigational DESs, and their roles in restenosis and thrombosis, respectively, in order to provide a framework for the design of future DESs.

### **Stent platforms**

The physical properties of the stent platform play an important role in the deliverability and limiting of restenosis. A series of physical stent parameters, such as the mode of expansion, material, surface smoothness, strut thickness, and shape, as summarized by Allison C. Morton, et al. have been considered the main contributors to restenosis [23]. Therefore, it is necessary to optimize these parameters and hence to improve stent deliverability and decrease the rate of restenosis.

The first generation of DESs, Cypher and Taxus, consists of 316L stainless steel with balloon-expandable systems and the strut thickness ranged from 130 to 140 $\mu$ m, providing a radiopaque property and adequate radial strength, however, compared to thinner struts, stents with thicker struts have a higher rate of restenosis [24, 25]. In addition, 316L stainless steel is a non-MRI compatible and is a poorly visible fluoroscopic material due to its ferromagnetic nature (60-65 wt% pure Fe) and low density. The cobalt chromium (CoCr) with thinner struts (80-90 $\mu$ m) was used in the second generation of DESs, Xience V (everolimus-eluting stent, Abbott Vascular, Santa Clara, CA) and Endeavor (zotarolimus-eluting stent, Medtronic Vascular, Santa Rosa, CA), resulting in de-

creased neointimal response and more rapid re-endothelialization [26]. These latter two DES platforms were approved by US FDA in 2008.

Some other new stents with different platforms are still under evaluation. The Xtent custom NX stent (Xtent, Menlo Park, CA) is a CoCr (cobalt chromium) platform coated with polylactic acid (PLA) and biolimus A9, which can be deployed either in combination or separately due to its novel multiple 6mm interdigitating segments. The system allows for in situ customization of stent length instead of relying on fixed-length stents. It has been applied in human studies and further trials are ongoing [27]. The CoCr platform with multiple intra-strut cells was utilized in the Conor DES (Conor Medsystems, Menlo Park, CA) instead of initial stainless steel. These wells functioned as drug carrier which will not deform or separate from the stent during expansion [28, 29], but further investigation on the effect of a rough surface after the drug is eluted completely is needed. Besides stainless steel and CoCr, nitinol is also a common material for both peripheral and coronary stents. Nitinol is an alloy of nickel and titanium with good biocompatibility and radial force, but it may lead to mild inflammation when in contact with monocyte [30]. However, several stents made of nitinol have promising preliminary data. The Cardiobond self-expanding nitinol stent incorporated with a 0.014-in. guidewire has a far lower crossing profile than balloon-expandable stents. Promising results have been reported by a bare Cardiobond stent and further evaluation of a biodegradable polymer-coated stent is in progress [31]. The Axxess Plus stent (Devax, Irvine, CA) is also a nitinol self-expanding thin strut stent coated with abluminal PLA and biolimus A9 designed for treatment of coronary bifurcation narrowings [32].

Another concept is the fully biodegradable polymeric stent. The first fully biodegradable polymeric stent made of knitted poly-L-lactic acid (PLLA) was manufactured by Stack and colleagues [33], and then it was redesigned by Igaki and Tamai to PLLA monofilaments (molecular mass, 183 kDa) in a zigzag helical coil configuration with 0.17mm thick struts and 12mm length [34]. The Igaki Tamai stent (Igaki Medical Planning Co, Ltd, Kyoto, Japan) has already been tested in humans, where 25 stents were implanted in 15 patients at 19 lesion sites. It was reported that the percentage

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of acute recoil of the stent was  $22\pm 7\%$  as measured by quantitative coronary angiography (QCA), and both the restenosis rate and the target lesion revascularization rate were 10.5% at 6 months in this small group clinical study [34]. However, it was only a pilot study as the number of patients was small and the follow up period was short. Additionally, the deployment procedure of the Igaki Tamai stent is more technically complicated compared to the typical balloon-expandable metal stent. The deployment of Igaki Tamai stent employs a balloon catheter and a hot liquid [34], which may result in thermal injury that has been considered as a potent stimulus for smooth muscle cell proliferation and therefore may increase the percentage of restenosis [35]. After the pilot clinical study of the early Igaki Tamai stent, Abbott Vascular (Chicago, IL) has recently launched another clinical evaluation (30 patients) with an everolimus-eluting PLLA stent (BVS) and promising results have been published [36, 37]. Although the feasibility and safety of the BVS stent was demonstrated in the study, it was still a small patient group.

Another novel polymer-based biodegradable stent is the tyrosine-derived polycarbonate REVA stent (REVA Medical, San Diego, CA) which incorporates iodine for radiopacity and utilizes a "slide and lock" design rather than the usual material deformation for deployment, with 150 $\mu$ m thick struts and a 3mm diameter. The stent is currently undergoing clinical evaluation [38, 39]. Though it may be promising to use a fully biodegradable polymeric stent, many issues still need to be addressed such as mechanical properties (e.g. radial strength), polymer degradation, stent geometry, and deployment [40].

To solve the problem of insufficient radial strength in the polymeric stent, Biotronik (Bulach, Switzerland) has developed a biodegradable magnesium metal stent—Lekton Magic stent (93% magnesium + 7% rare earth metals), which is safe and can provide sufficient support to the stenotic arteries within its degradation time (2-3 months) [41, 42]. The preliminary clinical data showed promising results that one-month after implantation of Magic stents, 18 out of 20 patients had normal flow while 30%-40% restenosis occurred in other 2 patients [43]. However, the drawback for the biodegradable magnesium stent is that it does not have drug releasing capability by itself, and early clinical

results have demonstrated that the bare magnesium stent has high rates of repeat revascularization [44]. Thus, a promising direction would be to combine the biodegradable magnesium metal stent with the biodegradable coating loaded with the drug.

### **Drug delivery vehicles**

Most DESs currently are using polymer as a drug carrier including non-degradable and biodegradable polymer. Non-degradable polymers were employed in the first generation of DES (Cypher: polyethylene-co-vinyl acetate [PEVA]/poly-n-butyl methacrylate [PBMA], Taxus: polystyrene-b-isobutylene-b-styrene [SIBS]) to control drug release. There are three layers on the Cypher stent (US Food and Drug Administration; Center for Devices and Radiological Health, "CYPHER™ Sirolimus-eluting coronary stent—P020026". Available from <http://www.fda.gov/cdrh/mda/docs/p020026.html> updated 10 June 2003.): 1. parylene C, an inert, hydrophobic and biocompatible polymer coated on the 316L stainless steel stent platform firstly; 2. a mixture of PEVA/PBMA in ratio of 67/33 with sirolimus coated on parylene C layer; 3. pure PEVA/PBMA to prevent burst release. Compared with Cypher stent, Taxus stent (TAXUS™ Express2™ Coronary Stent System (P030025); Summary of safety and effectiveness data. <http://wwwfdagov/cdrh/pdf3/P030025bpdf>, <http://wwwfdagov/ohrms/dockets/dailys/04/sep04/090904/04m-0403-aav0001-03-SSED-vol1pdf> 2003.) used another biocompatible polymer, SIBS, without additional drug release barrier coating to delivery drug locally, which leads to drug elution profiles of 30 days periods while Cypher stent is a 60 days period. However, these polymers provoke inflammatory responses [45, 46].

The second generation of DESs also uses non-degradable but more complex biocompatible polymers as drug carriers (Endeavor: phosphorylcholine, Xience V: fluoropolymer). Both Endeavor and Xience V stents reduced the target vessel revascularization (TVR) significantly compared with the respective BMS [47, 48]. In the SPIRIT study, Xience V stents reduced angiographic late loss without an increase of stent thrombosis compared with Taxus stents [49], whereas Endeavor stents showed a higher incidence of restenosis compared with Cypher stents in the ENDEAVOR trial [50]. However, an

equivalent target lesion revascularization rate was found while comparing Endeavor with Taxus stents in a later trial [51]. Moreover, there were no cases of very late stent thrombosis in the earlier ENDEAVOR trials indicating that the Endeavor stent is likely safe in the long-term [52]. Although the precise mechanism of drug-eluting stent thrombosis is still unknown, it is generally believed that there are three main reasons: the persistence of non-degradable polymer, delayed endothelialization caused by anti-proliferative therapy, and residual active drug that may not be eluted. Virmani, *et al.* predicted this even before the introduction of first generation of DESs, noting that the potential problems in DESs may arise due to “non-erodable thick polymer sleeve, very high concentration of the active drug, extended release kinetics, loose architecture, and inhomogeneous drug delivery” [53, 54]. Therefore, biodegradable polymers are going to be preferential for the next generation of DESs.

The biodegradable polymers have been investigated in a number of new stents as the non-degradable polymers appear to lead to inflammation. The most commonly used polymers now are polylactic acid (PLA), polyglycolic acid (PGA), and their copolymer, polylactic-co-glycolic acid (PLGA) [55, 56]. These polymers are fully metabolized to water and carbon dioxide and excreted via respiratory system. Despite a series of promising preliminary data that were reported [28, 29, 57-59], the development of biodegradable polymers in DESs is still challenging. On the one hand, the degradation of polymers are affected by a variety of factors [60] such as the pH, the polymer's size, molecular weight, and crystallinity making the drug release difficult to control. On the other hand, the accumulated acidic products from polymer degradation may result in a significant inflammatory response of the vessel wall, and lead to restenosis. Therefore, PLGA blended with amorphous calcium phosphate (ACP) as a stent coating is under development by our group. ACP is a member of calcium phosphate family (CaP) [61], which has become increasingly significant in biomaterial tissue engineering due to its high solubility and better remineralization compared to other CaP members [62, 63]. Furthermore, the ions released from ACP are considered to play a role in neutralizing the acidity resulting from polymer biodegradation, retarding bioreabsorption rate and eliminating inflammation [64].

Other stents that do not use a polymer completely, are still under development. For example, a titanium-nitric oxide alloy has been applied to stainless steel stents with encouraging results, including decreased platelet adhesion and neointimal hyperplasia compared with BMS [65]. A microporous stainless steel stent (Yukon, Translumina, Germany) allows for dose-adjustable, multiple, and on-site coating [66]. The system is therapeutically effective with rapamycin [67]. A nanoporous hydroxyapatite (HA, a biocompatible crystalline derivative of calcium phosphate) coating, which can be impregnated with anti-restenotic drugs, is currently under development [68]. A stainless steel stent coated with nanoporous aluminium oxide and tacrolimus showed disappointing results however, with evidence of particle debris shed from the coating contributing to increased neointimal hyperplasia [69]. An interesting drug delivery system developed recently is composed of magnetic nanoparticles (MNPs) loaded with endothelial cells and a 304 grade stainless steel [70]. The endothelial cells were loaded on polylactide modified MNPs and then moved by a magnetic field gradient towards the stent surface after injection, which enables artificial endothelialization and repeated dosing, showing a promising future, however, further evaluation in animal studies and clinical trials is required as the idea is still in the experimental stage.

### Drugs

The common currently used drugs in the first and second generation of DESs are sirolimus, paclitaxel, and their analogues. Their chemical structures and mechanisms of inhibition of vascular smooth muscle cells (SMCs) migration and proliferation were reviewed elsewhere [54, 71].

Sirolimus (Rapamycin), a macrocyclic lactone, binds to FK-binding protein 12 and subsequently inhibits the mammalian target of rapamycin (mTOR). Inhibition of mTOR prevents the degradation of p27kip1, a cyclin-dependent kinase inhibitor, thereby inhibiting the migration and proliferation of SMCs [72, 73]. However, mTOR is also a downstream target of phosphatidylinositol-3 kinase pathway, which inhibits tissue factor in endothelial cells and monocytes in turn [74-76]. Therefore, the inhibition of mTOR by sirolimus leads to increasing expression and activity of tissue factor in endothelial cells [74]. Paclitaxel, a lipophilic diterpenoid, binds to the

$\beta$ -subunit of the tubulin heterodimer, promoting tubulin polymerization and cell cycle arrest, thus inhibiting the migration and proliferation of SMCs [77, 78]. Notwithstanding, an important regulator of endothelial and monocytic tissue factor induction [75, 76], c-Jun NH<sub>2</sub>-terminal kinase, is also activated by paclitaxel [79, 80], and, consequently, enhances and activity of tissue factor in endothelial cells [80]. Therefore, both sirolimus and paclitaxel not only reduce neointima formation by disrupting the migration and proliferation of SMCs, but also induce tissue factor, eventually, inhibit re-endothelialization and increase late thrombotic risk [81].

Two analogs of sirolimus—everolimus and zotarolimus, used in Xience V and Endeavor stents respectively, likely have the similar effects. However, better endothelialization was reported by comparing the second generation DESs with the first generation DESs [26]. Other sirolimus analogs including biolimus A9, tacrolimus and pimecrolimus are still under investigation. Biolimus A9 (Biomatrix; Biosensors International, Singapore and Nobori; Terumo, Japan) has a similar immunosuppressive effect as sirolimus, but can be absorbed by the vessel wall to more rapidly arrest SMCs cell cycle at the G<sub>0</sub> phase [82, 83]. In addition, the biolimus-eluting stent has been proved to be safe and effective in reducing neointimal proliferation when compared to Taxus in the Nobori 1 trial [84]. Tacrolimus, a hydrophobic macrolide immunosuppressant drug, is a T cell inhibitor which results in cell apoptosis by holding cells in the G<sub>0</sub> phase of the cell cycle, which has a different mechanism from that of sirolimus [85, 86]. Moreover, unlike the mTOR inhibitors and paclitaxel, tacrolimus does not increase expression of tissue factor since it has a preferential effect on SMCs as apposed to endothelial cells [74, 80, 87, 88]. Although some studies showed that tacrolimus-eluting stents can significantly reduce neointimal proliferation [69, 89], a study on Janus, a new design of tacrolimus-eluting stent (Sorin Biomedica Cardio, Italy), indicated the performance of Janus was no better than a BMS [90]. The long term outcomes of other tacrolimus-eluting stents are still under investigation [91]. Pimecrolimus is an analogue of tacrolimus, which has similar effects and mechanisms as tacrolimus [92]. Few paclitaxel analogs have been reported. Docetaxel, however, is one which is a semi-synthetic analog of paclitaxel, used for the treatment of ovarian, breast and

non-small cell lung cancer [93]. Compared to paclitaxel, docetaxel has better anti-proliferative properties [94]. However, it has dose-dependent cytotoxicity [95]. To improve the solubility of paclitaxel and reduce the non-drug related toxicities [96], a protein-engineered nanoparticle albumin bound paclitaxel (nab-paclitaxel) named Coroxane was developed by Abraxis Bioscience Inc. (Los Angeles, CA). The phase one study has been conducted showing 10-30mg/m<sup>2</sup> doses of the drug are safe for human [97]. The phase two study is undergoing.

Contrary to the usual goal of SMC inhibition, a novel prohealing technology is used in the Genous stent (Orbus Neich, Fort Lauderdale, FL), which is a stainless steel stent coated with murine monoclonal anti-human CD34 antibodies that attracts endothelial progenitor cell to enhance re-endothelialization. The reported results indicate that the Genous stent is effective and promising [98-101]. Another similar concept is the bevacizumab-eluting stent (Biocompatibles Ltd., London, UK) [102]. Bevacizumab, a specific antibody to vascular endothelial growth factor (VEGF), was coated on the surface of BiodivYsio stent to inhibit the development of vaso vasorum and thereby promote atheromatous plaque stability. Further investigation is under progress.

### Conclusion

As discussed above, every component of the DES plays a key role for treatment of CAD. The ideal drug-eluting stent should possess following properties: First, a stent “backbone” should provide adequate radial strength, deliverability and radiopacity but cause minimal injury to the vascular wall, minimal neointimal response and minimal restenosis. Second, the drug carrier should have ideal drug release that does not result in an inflammatory response. Biodegradable and biocompatible biomaterials should be the first option, as Waksman said “they do their job, and then disappear” [103]. Third, the drug, or the drug combination, should inhibit SMCs and inflammation effectively but not destroy re-endothelialization so as to prevent thrombosis.

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**Please address all correspondences to:** Tim Wu, M.D., VasoTech, Inc., 333 Aiken Street, Lowell, MA 01854. Tel: 617-686-2770; Fax: 617-446-1518; Email: [tiangenwu@yahoo.com](mailto:tiangenwu@yahoo.com).

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