Metallic Stents Coated With Bioabsorbable Polymers

An overview of polymer technology as a drug-carrier mechanism.

BY WEI FAN; DAVE M. JOHNSON, PHD; AND MARC D. FELDMAN, MD, FACC

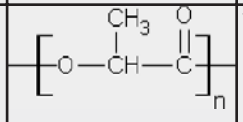
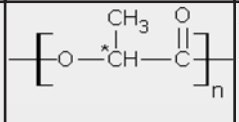
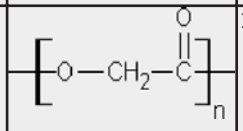
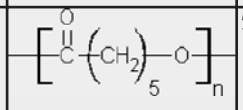
Drug-eluting stents (DES) are an important treatment option for patients with coronary artery disease and have been successful at suppressing the arterial neointimal hyperplasia response to stenting. Although the improved efficacy of DES in reducing in-stent restenosis rates compared to bare-metal stents (BMS) has been proven,[1,2] there remain long-term safety issues related to the use of DES, including localized and systemic hypersensitivity reactions[3,4] and late stent thrombosis.[5-7] Although the mechanism of these complications is not yet clear,[8,9] the infiltration of inflammatory cells at the site of polymer and impaired re-endothelialization[8,10] (possibly due to the presence of permanent polymer coating[3,4] and/or potent antirestenosis agents) could play a major role.[11] The next generation of DES will focus on the elimination of the polymer and the development of new drug carriers,[12,13] new platform materials,[14] and bioactive agent combinations.[15-17] The focus of this article is on stent-based drug carriers with better biocompatibility, which will replace the current generation of nondegradable polymers; specifically, systems that use biodegradable polymers in conjunction with the metal stent as a scaffolding are reviewed.

BIOABSORBABLE POLYMER

A typical DES is composed of three parts: a stent platform, a drug carrier, and a therapeutic agent.[18] Bioabsorbable polymers (BP) can be the drug carrier, as well as the stent platform to provide temporary radial support. Using BP as a coating material on a metallic stent has several advantages over current nondegradable polymer coatings. First, BP can be engineered to completely degrade in several months, therefore minimizing the late stent complications due to the persistence of the polymer and reducing the duration of dual-antiplatelet therapy. Second, the rate and profile of drug release can be fine-tuned by polymer degradation.

BP can be obtained from either natural sources or synthetic organic processes.[19] Natural polymers, such as collagen and fibrin, have good biocompatibility, but the risk of viral infection and batch-to-batch variation in properties hinders their use in mass production. Synthetic polymers, in contrast, allow engineers to fine-tune properties by changing the synthetic process, conditions, and thermal history to achieve the ideal materials.[20] Theoretically, the ideal BP should (1) have good biocompatibility to minimize inflammatory response, (2) form safe degradation products, (3) have good coating integrity upon deployment, (4) be compatible with therapeutic agents, (5) exhibit homogeneous distribution of drug in polymer matrix, (6) exhibit controlled release kinetics that synchronize with healing cascade and cell proliferation, and (7) have a stable shelf life. Synthetic polyesters, especially aliphatic polyesters such as poly(L-lactic acid) (PLLA), poly(D, L-lactic acid) (PDLLA), poly(glycolic acid) (PGA), and poly(lactic-co-glycolic acid) (PLGA), are the most widely used materials (Table 1). In

TABLE 1. PROPERTIES OF COMMON SYNTHETIC BP[a]

Polymer	Structure	Melting Point[b] (°C)	Glass Transition Temperature[c] (°C)	Modulus[d] (GPa)	Degradation Time (Mo)
Poly(L-lactic acid)		173–178	60–65	2.7	> 24
Poly(D, L-lactic acid)		Amorphous	55–60	1.9	12–16
Poly(glycolic acid)		225–230	34–40	7	6–12
Poly(ε-caprolactone)		58–63	-65– -60	0.4	> 24

[a]Data adapted from Eberhart RC, et al. J Biomater Sci Polym Ed. 2003;14:299-312.[21]

[b]Melting point is the temperature at which polymer is between (semi)crystalline phase and amorphous phase.

[c]Glass transition temperature is the temperature range at which the polymer is between glassy state and rubbery state.

[d]Modulus indicates the elasticity of the polymer.

fact, the first BP stent[22] was made of polyesters. Poly(ortho esters), polyanhydrides, and polyphosphazenes are also being actively investigated.

DEGRADATION OF POLYMERS

Degradation of polymers generally refers to cleavage of covalent bonds between repeating units.[23] During this chemical process, long backbones break into smaller oligomers (or monomers) by hydrolysis, oxidation, and enzymatic mechanisms. The small oligomers are phagocytosed by macrophages and further metabolized to carbon dioxide and water by the human body. The polymerization byproducts (initiators, stabilizers, and catalysts) are also released into surrounding tissues, which may cause an adverse response.[23] Increased toxicity due to elevated local concentrations of acid has been reported.[24] The degradation rate is accelerated as water accessibility into the polymer matrix becomes feasible. Water accessibility depends on the chemical structure (hydrophobicity of the polymer, molecular weight), dimension, morphology (crystallinity and porosity), and the local tissue environment.[23] Knowledge of degradation behavior is important for predictable use of BP because it also affects release kinetics, mechanical properties, and biocompatibility.

Currently in clinical trials, PDLLA,[14,25] PLGA,[26,27] and PLA-co-PCL[28] are the most common coating materials. The ultimate degradation products are lactic acid for PDLLA, lactic acid and glycolic acid for PLGA, and lactic acid and w-hydroxyhexanoic acid for PLA-co-PCL. These degradation products are natural metabolites and finally degrade to carbon dioxide and water via the Krebs cycle. However, despite this theoretical advantage, van der Giessen et al[29] have shown that both nondegradable polymers and BP-coated stents showed extensive inflammatory responses and subsequent neointimal hyperplasia in the porcine artery. Drachman et al[28] demonstrated that 6 months after implantation of PLA-co-PCL stents,

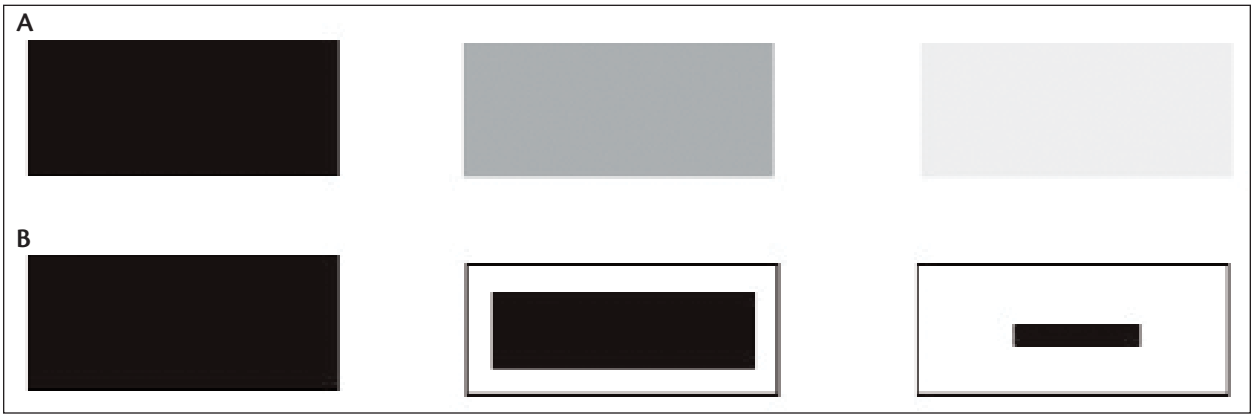


Figure 1. An illustration of bulk erosion (A) and surface erosion (B) (Adapted from Ha C, et al. Chem Rev. 2005;105:4205-4232).[32]

macrophages were still present in the surrounding tissue after the PLA-co-PCL fully degraded. Even with the incorporation of anti-inflammatory drugs, BP may still induce inflammation. Vogt et al[30] studied BMS, a fully absorbable PDLLA stent, and a fully absorbable paclitaxel-eluting stent in the porcine model. Three months after implantation, both PDLLA stents showed extensive inflammation compared to BMS during histologic analysis. In addition, the biocompatibility of BP is not solely dependent on degradation products. Lincoff et al[31] demonstrated that stents coated with high-molecular-weight (321 kDa) PLLA are associated with minimal inflammatory reaction, whereas an intense inflammatory reaction is observed in the susceptible low-molecular-weight (80 kDa) PLLA-coated stent, which is more susceptible to hydrolysis.

CONTROLLED DRUG RELEASE

In the current generation of DES, antiproliferation agents, such as sirolimus, are mixed in the nondegradable polymer matrix. The controlled drug release from the nondegradable polymer matrix is controlled by diffusion. For example, the Cypher stent (Cordis Corporation, Warren, NJ) has a barrier coating outside the drug layer to prevent burst release and allow proper diffusion of sirolimus. In the BP drug matrix, however, drug release can occur as the polymer degrades in addition to diffusion. Polymer degradation occurs via two mechanisms: bulk erosion and surface erosion (Figure 1).[32] Surface erosion occurs when diffusion of water into the polymer is slower than the degradation reaction, whereas bulk erosion occurs when diffusion is faster than degradation. Polyanhydrides and poly(ortho esters) are highly water-labile moieties and thus usually take the surface erosion route, whereas other polymers engage in bulk erosion. With surface erosion, release kinetics are typically zero-order.[32] On the other hand, with bulk erosion, release kinetics are controlled by both diffusion and degradation, rendering these release profiles as second-order, as is evident in polymers such as PDLLA and PCL.

Drug release can also be adjusted by means other than the erosion rate of the polymer. Hydrophobicity/hydrophilicity of the polymer, which can be adjusted by modification of side chains in the backbone, can affect the release kinetics. Additionally, homogeneous dispersion of drug in the polymer matrix can be influenced by polymer crystallinity. For example, PLGA is normally a semicrystalline polymer that results in a heterogeneous dispersion of drug in the matrix, whereas, in amorphous PDLLA, the drug can easily be dispersed evenly in the polymer.

STORAGE OF BP

Polymers are more responsive to the ambient environment than the metal stent platform. Thus, careful control of the environment, including temperature and moisture, during each step of production is of great importance. For instance, during the sterilization process, gamma irradiation and ethylene oxide gas treatment may affect polymer properties. In addition, polymer-coated metal stents may have special storage needs. For example, the BVS stent (a fully bioabsorbable PLA everolimus-eluting stent, Abbott Vascular, Santa Clara, CA) needs to be stored at -20ºC and is only good for 8 weeks.[14] This time constraint makes clinical use of these novel stents difficult.

NEW BP

Nakano and colleagues developed a PLGA nanoparticle-eluting stent. Fluorescein isothiocyanate (FITC, used as a less hydrophobic model drug) encapsulated nanoparticles were cationic electrodeposited on a metallic stent.[33] In the porcine model, the concentration of FITC in the arterial wall at the site of stent placement was more intense with the FITC-nanoparticle stent compared to a dip-coated FITC stent 2 weeks after implantation. This indicated that the nanoparticle technique can prolong the release of less

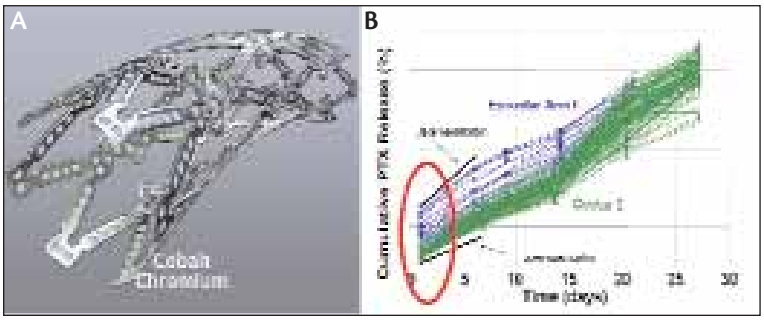


Figure 2. CoStar stent (A) (Reprinted with permission from Krucoff MW, et al. J Am Coll Cardiol. 2008;51:1543-1552).[27] Cumulative paclitaxel release from CoStar stent in COSTAR II study and EuroStar study (B) (Reprinted with permission from Krucoff MW, et al. Presented at the 2007 Transcatheter Cardiovascular Therapeutics annual meeting).[35]

hydrophobic drugs. Another potential application of this technique is targeting the nanoparticles to specific cell types by incorporating ligands on the nanoparticle surface.

Researchers also have examined new types of polymers, such as polyanhydrides and poly(ester-amides). Salix (Bioabsorbable Therapeutics, Inc., Menlo Park, CA) is a novel polyanhydride in which the repeat unit in the polymer backbone is two salicylic acid molecules joined by an adipic acid. As the polymer degrades, salicylic acid (the active ingredient in aspirin), as well as adipic acid and the drug embedded in the polymer, will be released to the surrounding arterial tissue. Jabara et al[34] compared the Cypher stent with a sirolimus-eluting stainless steel stent that was coated with this novel polymer. One month after implantation, similar intimal thickness was found between the two groups in the porcine model. In addition, a fully bioabsorbable sirolimus-eluting stent (BTI stent, Bioabsorbable Therapeutics, Inc.) made of this novel polymer has been tested in a clinical trial (WHISPER) (n = 40 patients) and was presented by Abizaid at the 2008 Transcatheter Cardiovascular Therapeutics meeting.[36] An alternative approach is the use of poly(ester-amide) developed by Tsuchikane et al, which is composed of L-leucine and L-lysine.[37] At day 28, a cilostazol-eluting, poly(ester-amide)-coated stent had significantly lower in-stent late loss compared to the BMS control group in a porcine model.

CLINICAL TRIALS WITH BIOABSORBABLE POLYMER-COATED METALLIC STENTS

S-Stent Platform

The BioMatrix (Biosensors International, Singapore) stent is a biolimus-A9–eluting stent comprised of a stainless steel stent platform (S-Stent, Biosensors International) coated with PLA drug matrix on the abluminal side of the stent. Biolimus-A9, a sirolimus analogue, is released from the BioMatrix stent at a nominal concentration of 15.6 µg per mm of stent length. In the first-in-man STEALTH (Stent Eluting A9 Biolimus Trial in Humans) study,[38] a significantly lower in-stent late loss was found in the BioMatrix than in the S-Stent without drug coating (0.26 vs 0.74 mm; $P < .001$), although no significant difference was observed in the binary restenosis rate at 6 months. In a recent randomized noninferiority study termed LEADERS (Limus Eluted from A Durable Versus Erodible Stent Coating) trial,[39] the BioMatrix stent was compared to the Cypher stent (nondegradable polymer coating) for major adverse cardiac events (MACE) at 9 months. A noninferior outcome was achieved by the BioMatrix stent at the primary endpoint (9% vs 11%) (Table 2). In addition, approximately 25% of the patients underwent angiographic follow-up at 9 months, and showed late loss and binary restenosis rates similar to those of the Cypher control group. Another interesting study by Hamilos and colleagues demonstrated better restoration of endothelium function with the Nobori biolimus-eluting stent (Terumo Interventional Systems, Somerset, NJ, a licensee of BioMatrix technology) compared to a sirolimus-eluting stent.[40]

The Excel (JW Medical systems, Weihai, China) sirolimus-eluting stent also used the S-Stent platform and an abluminal coating of PLA drug matrix. The recently published CREATE (Multicenter Registry of Excel Biodegradable Polymer Drug Eluting Stents) study[41] evaluated the safety and efficacy of the sirolimus-eluting stent with bioabsorbable coating. The MACE rate at 18 months was only 3.1% in 2,077 patients. Furthermore, only 0.87% of patients developed stent thrombosis, even though 80.5% of patients had discontinued clopidogrel therapy after 6 months. Additionally, angiographic follow-up showed that the binary in-stent and in-segment restenosis rates at 12 months were only 3.8% and 6.7%, respectively (Table 2). The authors ascribed the low incidence of MACE and stent thrombosis to the exclusion of patients with device failure and the inclusion of patients with less complicated clinical conditions than those enrolled in the e-CYPHER registry. To follow-up on these encouraging results, a more comprehensive EVOLUTION (A Randomized Study to Evaluate Safety and Efficacy of the Excel Sirolimus-Eluting Stent With a Biodegradable Polymer Versus Sirolimus-Eluting Stent With a Nonbiodegradable Polymer in the Treatment of Patients With De Novo Coronary Artery Lesions) study[42] is planned, which will compare the Excel and Cypher stents and will enroll 1,944 patients. The primary endpoints are ischemia-driven target vessel failure, myocardial infarction (MI), and target vessel revascularization (TVR) at 12 months.

(Courtesy of Cordis Corporation.)

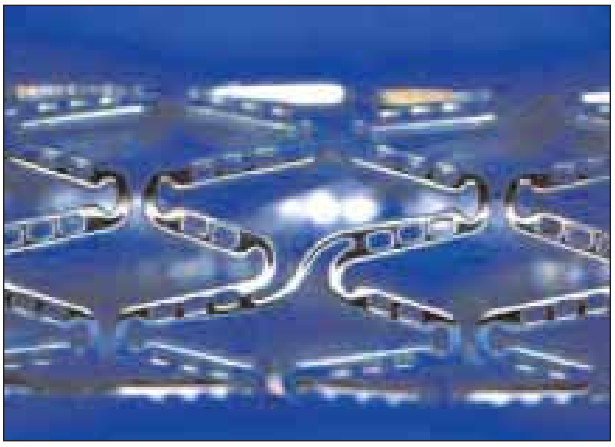


Figure 3. The Nevo stent (Cordis Corporation).

Reservoir-Based DES Platform

The CoStar (Cordis Corporation) stent includes several interesting features. The platform is made of a cobalt chromium alloy with laser-cut reservoirs within the stent struts (Figure 2A). Biodegradable PLGA polymers with drug fill the reservoirs. By modifying the number of drugs utilized, the drug-release kinetics, and the release direction (lumen, vessel, or both) of each individual reservoir, the drug distribution and release kinetics can be controlled for the entire stent. In the PISCES (The Paclitaxel In-Stent Controlled Elution Study) study,[43] the optimal drug-release kinetics (10 µg/30 days; abluminal direction) was determined with binary in-stent restenosis rates as the primary endpoint. In COSTAR I (Cobalt Chromium Stent With Antiproliferative for Restenosis trial in India)[44] and the EuroStar study,[45] the same drug release kinetics also showed favorable results. In the COSTAR II study,[27] however, the primary endpoint of MACE at 8 months was significantly higher in the CoStar group compared to the Taxus group (Boston Scientific Corporation, Natick, MA) (11% vs 6.9%; *P* = .005), where the high TVR rate (8.1% vs 4.3%; *P* = .002) played a major role in this poor outcome (Table 2). In-segment lumen loss and binary restenosis at 9 months were also significantly higher in the CoStar arm. Thus, noninferiority of the CoStar stent compared to the Taxus stent could not be concluded from this trial. Due to the favorable results in previous clinical trials, the result of COSTAR II was unexpected. The authors explained that this unexpected outcome was due to the small patient numbers in previous studies, variations in the device manufacturing process, and the learning curve for new device implantation by the investigators. Krucoff indicated another possible explanation:[35] in order to use the lowest effective amount of paclitaxel in an attempt to improve long-term safety, the amount of paclitaxel loading used in COSTAR II may have been too low (Figure 2B). Given that paclitaxel has a narrow therapeutic window, a given amount of paclitaxel will be less effective in patients with complicated lesions.

A newer version of a reservoir-based DES is the Nevo stent (Figure 3). Sirolimus is eluted from biodegradable matrix (completely degrades in 90 days) within the cobalt chromium strut. The RES-1 (NEVO RES-ELUTION) study compared in-stent late loss at 6 months in Nevo stents and Taxus Liberté stents (paclitaxel-eluting stents). The results showed that the Nevo stent had significantly lower in-stent late loss compared to the Taxus Liberté (0.13 vs 0.36 mm; *P* < .001) at 6 months, as well as lower in-segment late loss (0.06 vs 0.2 mm; *P* < .001). Moreover, Nevo performance was superior to Taxus Liberté at 6 months based on statistical analysis.[46,47] In two upcoming clinical trials, the Nevo stent will be compared to the Xience V (Abbott Vascular) and Cypher stents, respectively, with a primary endpoint of 12-month target lesion failure.[48]

Other Platforms

The Mahoroba stent (Kaneka Corporation, Osaka, Japan) is a tacrolimus-eluting cobalt chromium stent coated with PLGA.[26] Tacrolimus binds to FKBP12 and suppresses smooth muscle and endothelial cell proliferation but is less potent than sirolimus. Unlike sirolimus though, tacrolimus does not affect tissue factor and endothelial nitric oxide synthase expression. In the first-in-man trial, however, the binary in-stent restenosis rate of the Mahoroba stent at 4 months was 26.7%, and it failed to prevent intimal hyperplasia.[26]

The Axxess stent (Devax, Inc., Lake Forest, CA) is a self-expandable, biolimus-eluting nitinol stent in a conical shape that is designed for bifurcation lesions, with four radiopaque markers on the ends. In the DIVERGE (Drug-Eluting Stent Intervention for Treating Side Branches Effectively) study,[49] 302 patients were enrolled, and 64.7% of the patients received additional stents in both the side branch and parent vessels. Nine-month follow-up showed that the MACE rate was 7.7% (the target lesion revascularization rate was 4.3%), and the in-segment restenosis rate was 6.4% (the side-branch restenosis rate was 4.3%).

The Custom NX stent (Xtent, Inc., Menlo Park, CA) is a biolimus-eluting stent formed from integrated cobalt chromium segments, which are each 6 mm in length. This unique design allows the cardiologist to adjust the length of the stent during the procedure (up to 60 mm). In the most recent CUSTOM III (n = 90) results, patients' lesions were challenging, with a 19.8-mm average lesion length and a 2.6-mm average reference vessel diameter. Six-month follow-up showed that the MACE

TABLE 2. BP CLINICAL TRIALS

Study	Study Design	Stent Groups	Drug and Polymer Coatings	Stent Platform	Primary Endpoints	Primary Endpoint Results (BP stent is always first)
LEADERS[38] (2008)	Multicenter, randomized, single-blind, noninferior	Biomatrix stents (n = 857); Cypher stent (n = 850)	PLA: biolimus-A9; abluminal 15-µm-thick polymer	SS (S-stent)	MACE (cardiac death, MI, and TVR) at 9 months	MACE: 9.2% versus 10.5 %
CREATE[40] (2009)	Single-arm, multicenter	Excel stent (n = 2,077)	PLA: sirolimus; abluminal 10- to 15-µm-thick polymer	SS (S-stent)	MACE (cardiac death, nonfatal MI, and TLR) at 12 months; secondary: in-stent LL and binary restenosis at 9 months; thrombosis at 18 months	MACE: 2.7%
COSTAR II[27] (2008)	Multicenter, randomized (3:2), single-blind, noninferior	CoStar stent (n = 989); Taxus stent (n = 686)	PLGA: paclitaxel; reservoir; PLGA completely degrades by 180 days in porcine model	CoCr	MACE (cardiac or unknown cause of death, Q-wave or non-Q-wave MI, and TVR) at 8 months	MACE: 11% versus 6.9%
RES-1[53] (2009)	Multicenter, randomized	Nevo stent (n = 202); Taxus Liberté (n = 192)	Biodegradable polymer: sirolimus; reservoir	CoCr	In-stent LL at 6 months	0.13 versus 0.36 mm; $P < .001$
DIVERGE[49] (2009)	Multicenter, single-arm	Axxess stent (n = 302)	PLA: biolimus-A9 (22 µg/mm)	Nitinol	MACE (cardiac or unknown cause of death, Q-wave or non-Q-wave MI, and TLR) at 9 months	MACE: 7.7%
SERIES I[54] (2008)	Single-center	Supralimus (n = 100)	Base layer: PLLA: sirolimus (PLGA and PVP): sirolimus; outer layers: PVP	SS	Binary in-stent restenosis at 6 months	Binary restenosis (in-stent): 0%
CURAMI[55,56] (2007)	Single-center first-in-man patients with acute ST-elevation MI	Cura (n = 49)	PLA/PLGA: sirolimus; abluminal	SS		Binary restenosis: 22%; late loss: 0.74 mm
FUTURE I[57] (2004)	Single-center, single-blind	Everolimus-eluting stent (n = 27); BMS (n = 25)	PLA: everolimus	SS	MACE (death, CABG to the target vessel, Q-wave and non-Q-wave MI, and TLR) at 30 days	MACE: 0% versus 0% (30 days); 7.7% versus 7.1% (6 months)

TABLE 2. BP CLINICAL TRIALS (CONTINUED)

Study	Study Design	Stent Groups	Drug and Polymer Coatings	Stent Platform	Primary Endpoints	Primary Endpoint Results (BP stent is always first)
ISAT-TEST-3[58] (2008)	Randomized	BP stent (n = 202) polymer-free stent (n = 201) Cypher (n = 202)	Biodegradable polymer: sirolimus	SS	Late loss at 6–8 months	BP stent: 0.17 ± 0.45 mm; polymer-free stent: 0.47± 0.56 mm; Cypher: 0.23 ± 0.46 mm
SIMPLE II[59] (2006)	Multicenter	Infinnium (n = 103)	(PLLA, PLGA, PLA-co-PCL, and PVP): paclitaxel	SS	MACE at 30 days binary in-stent restenosis at 6 months	MACE: 2.9%; binary restenosis (in-stent): 7.3%
Onuma, et al[26] (2009)	First-in-man	Mahoroba (n = 47)	Tacrolimus PLGA	CoCr	Late loss at 4 months	LL: 0.99 ± 0.46 mm
CUSTOM III[50]	Multicenter	Custom NX (n = 90)	PLA: biolimus	CoCr	MACE at 30 days	MACE: 2.2%

Abbreviations: CABG, coronary artery bypass graft surgery; CoCr, cobalt chromium; LL, lumen loss; MI; myocardial infarction; PVP, polyvinyl pyrrolidone; SS, stainless steel; TLR, target lesion revascularization; TVR, target vessel revascularization.

rate was 7.8%, and the in-stent binary restenosis rate was 4.4%.[50] In addition, 2-year follow-up in the CUSTOM I trial (n = 30) found that no late stent thrombosis was observed.[51] In the CUSTOM II trial (n = 100), no late stent thrombosis rate was reported at 1-year follow-up.[52]

CONCLUSION

The ideal DES should (1) provide enough mechanical support to avoid acute recoil and negative remodeling, (2) release antirestenosis drugs to suppress intimal hyperplasia overgrowth at least for the first month, (3) promote (or at least not inhibit) re-endothelialization, and (4) have a drug delivery mechanism that is neither toxic nor inflammatory. Because the use of polymers is not ideal due to both local and systemic inflammation, if polymers must be used as a drug carrier mechanism, they should be biodegradable. All of the currently FDA-approved DES use nondegradable polymers. Thus, there is clearly a need to develop improved DES that employ biodegradable polymers. One approach has been the use of a fully bioabsorbable coating composed only of biodegradable polymers, coupled with a BMS platform. Long-term studies for these bioabsorbable stent coatings are in progress, and will define their future role in interventional cardiology. ■

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Wei Fan is with the Department of Biomedical Engineering, University of Texas at San Antonio; Briscoe Division of Cardiology, University of Texas Health Science Center in San Antonio, Texas. She has disclosed that she holds no financial interest in any product or manufacturer mentioned herein. Ms. Fan may be reached at (210) 458-6437; fanw@uthscsa.edu.

Dave M. Johnson, PhD, is with the Department of Biomedical Engineering, University of Texas at San Antonio in San Antonio, Texas. He has disclosed that he holds no financial interest in any product or manufacturer mentioned herein. Dr. Johnson may be reached at (210) 458-5444; dave.johnson@utsa.edu.

Marc D. Feldman, MD, FACC, is Professor, Briscoe Division of Cardiology; Director, Cardiac Catheterization Laboratory, University of Texas Health Science Center at San Antonio; Adjunct Professor of Biomedical Engineering, University of Texas at San Antonio; and he is with the South Texas Veterans Administration Health Care System in San Antonio, Texas. He has disclosed that he is the cofounder of Setagon, Inc., which was recently sold to Medtronic, Inc. Dr. Feldman may be reached at (210) 567-4600; feldmanm@uthscsa.edu.

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