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Drug delivery via nano-, micro and macroporous coronary stent surfaces

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Drug-eluting stents (DESs) have revolutionized the treatment of occlusive coronary artery disease via marked reduction of in-stent restenosis. One critical feature for successful DESs is the sustained release of drugs, which is achieved using a polymer coating in the present generation of DESs. However, recent studies have raised a concern that polymers may trigger allergic reactions and/or prolonged inflammation in some patients. These untoward reactions may eventually lead to undesirable clinical events, including stent thrombosis and sudden cardiac death. A new drug delivery technology, using a porous stent surface, may offer desirable drug elution properties without the use of polymers, and may translate into an improved safety profile for the next-generation DESs.

Keywords: coronary intervention, coronary stent, porous surface, restenosis

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1. Introduction

Intracoronary stents are mesh-like metal prostheses placed in coronary arteries that have been diseased and narrowed by atherosclerotic plaques. Due to its high procedural success rate and safety [1,2], implantation of intracoronary stents has played a central role in percutaneous coronary interventions. However, the long-term clinical efficacy of bare-metal stenting has often been hampered by a renarrowing of the stented artery, known as in-stent restenosis, occurring in up to 30% of stent cases. In-stent restenosis develops as a result of the migration and proliferation of vascular smooth muscle cells in response to acute and/or chronic vessel wall injury by interventions. Systemic or catheter-based local delivery of antirestenotic drugs was attempted to inhibit this process [3-5], but it resulted in failure, presumably due to an insufficient local drug concentration. However, the recent advent of drug-eluting stents (DESs) has revolutionized the treatment of coronary artery disease, with a remarkable reduction of in-stent restenosis, demonstrated in a series of large-scale clinical trials [6-11]. As a result, DESs are employed in the majority of percutaneous interventions for occlusive coronary disease.

Present DES systems are comprised of three components: platform (stent), drug, and carrier matrix. The platform (stent) serves as a scaffold to prevent vessel recoil, and immunosuppressive or antiproliferative drugs are applied to the stent struts to prevent in-stent restenosis. Regarding the carrier matrix, a polymer coating is used in the majority of present DESs because it possesses a desirable drug-releasing property, thereby markedly inhibiting the restenotic process. In fact, a stent system with polymers has been shown to offer better clinical outcomes compared with another system without polymers, even though the same drug was applied to both systems [10-12].

However, the polymer coating is subject to mechanical damage or deformity at the time of stent implantation [13]. Bench tests and animal studies have demonstrated that stent implantation can cause significant deformities, including webbing and bonding, potentially resulting in inhomogeneous drug elution and increased

thrombogenicity. DES polymers have also raised concerns over provoking allergic reactions [14,15], prolonged inflammation and foreign body responses [16]. These biologic reactions may eventually precipitate catastropic clinical events, including stent thrombosis and sudden cardiac death [15,17].

Given these concerns, efforts to develop a new DES with reduced risks imposed by polymers are underway. Among such efforts is the use of porous stent surfaces as a new drug delivery technology, which may offer both desirable drug elution properties as well as favorable clinical outcomes [18,19]. This review article offers an overview of the basics and discusses recent advancements of porous DES systems.

2. Basics of porous drug-eluting stents

2.1 Definition

Porous DESs are defined as endovascular stents with a surface or internal porosity that functions as a reservoir for a continuous release of antirestenotic agents. Pore sizes range 1 – 100 nm in nanoporous stents, 1 – 100 µm in microporous stents and even larger in macroporous stents.

2.2 Surface processing

Surface processing on stents to provide porosity can be classified into two groups: i) manufacturing the stent surface or body itself, and ii) coating the stents with porous substances. Technologies to create surface porosity include mechanical surface treatment/modification [20,21], stent sculpturing [201] and laser-cut manufacturing [18]. Coating with porous substance methods include nanoporous ceramic coating [22], nanoporous metal coating and electroforming [202].

In light of possible adverse effects caused by coating substances, manufacturing the stent itself, where no extra materials are added, provides a theoretical advantage. On the other hand, pre-established techniques can be readily applied when a porous substance is used to provide porosity.

2.3 Stent composition

Both 316L stainless steel and cobalt chromium are primarily used for porous DESs due to their high biocompatibility, radial strength and radioopacity. These two alloys are also widely used in polymer-based DESs as well. The specific properties of materials (e.g., electroformability) are additionally required for some porous DESs [202].

2.4 Drug application

A variety of techniques are used to apply the drugs onto the stents. For example, the drug may be applied by on-site spraying using a specific instrument, such as the Yukon® DES (Translumina) [21]. For the nanoporous ceramic coated stents, a simple process of dip-and-dry step is used [22]. In contrast, precise manufacturing processes are required to accurately inlay the drugs into the holes or slits in macroporous stents [18,201].

When compared with polymer-based DESs, the drug application process of porous DESs is more varied, which is reflective of the different surface geometries and characteristics. However, only limited information is available due to the proprietary aspects of porous stent systems technology.

So far, many of the antiproliferative or immunosuppressive agents used in the available polymeric DESs have been examined in porous DESs, including sirolimus [19], paclitaxel [18], pimecrolimus and tacrolimus.

2.5 Pharmacokinetics

In most porous DESs, desirable drug-releasing kinetics are achieved without using a carrier matrix (polymers). In the Setagon stent, a pharmacokinetic study demonstrated that the release curve of sirolimus is similar to that of the CYPHER® stent (Cordis Corporation), a polymer-based DES available for clinical use [7-9]. The Yukon DES, with its slow drug-releasing property, also allows sustained sirolimus release for > 21 days, with more than two-thirds of the total dose released in the first 6 days [20]. In the Janus stent, direct adhesion of the drug to the stent reservoir slit achieves longer drug-releasing kinetics.

In contrast, biodegradable polymers are used in the Conor/CoStar® (Conor Medsystems) macroporous stents to modify the drug-releasing profiles. The Conor macroporous DES enabled six different drug-release formulations that varied in dose, elution kinetics, direction (abluminal or adluminal), and duration [18]. These different formulations were produced by changing the ratio of the drug and the biodegradable polymers loaded in the holes within the stent struts.

However, with other porous DESs, drug-releasing properties have not been fully documented. As suitable drug elution is one of the key elements for safe and efficacious DESs, this will need to be verified in these stents before their approval for clinical application.

2.6 Clinical trials/registries

So far, only a limited number of clinical studies evaluating porous DESs have been published. However, among them, a randomized trial comparing the Yukon sirolimus-eluting stent with polymer-based paclitaxel-eluting stents (TAXUS® stent; Boston Scientific Corporation), showed similar inhibition of in-stent restenosis at 8 months follow-up in both groups [19], demonstrating the favorable efficacy of Yukon DESs. In another prospective trial, follow-up at 6 months with an intravascular ultrasound assessment of Conor paclitaxel-eluting stents showed significantly less neointimal proliferation compared with bare metal stents (BMSs) [18]. Clinical studies evaluating Janus stents have also demonstrated favorable efficacy and safety profiles, although results have not yet been published. As a result, these three porous DESs are available in the European Union with Conformité Européene approval.

3. Porous drug-eluting stents

A summary of individual porous drug-eluting stents is shown in Table 1.

Table 1. Porous drug-eluting stents.

	Nanoporous DES		Microporous DES			Macroporous DES		
	Ceramic-coated tacrolimus-eluting stent	***Nanoporous metal coating stent (Setagon stents)***	***Yukon DES***	***ESI microporous DES***	***Electrochemical porous DES***	***Janus Flex***	***Conor stent***	**CoStar stent**
Company	Jomed International (aquired by Abbott)	Setagon, Inc.	Translumina	Electroformed Stents, Inc.	Medlogics Device Corporation	Sorin group	Conor Medsystems (aquired by Johnson & Johnson)	Conor Medsystems (aquired by Johnson & Johnson)
Materials								
Stent body	316L stainelss steel	Stainless steel, cobalt chromium, for example	316L stainless steel	Gold	Stainless steel, cobalt chromium, for example	NA	316L stainelss steel	Cobalt chromium
Coating	Aluminum oxide (Al_2O_3)	Same material as that of stent struts	No (No additional material)	Gold (platinum or silver, technically possible)	NA	Carbofilm™ coating	No‡	No‡
Surface processing	Electrochemical conversion of alminum layer	Sputter coating techniques	Mechanical treatment/ modification (Sand blasting)	Electroforming	Electrochemical deposition	External surface sculpturing	Laser cut holes	Laser cut holes
Pore size	5 – 15 nm	5 – 20 nm	1.96 ± 0.21 µ*	1 – 5 µ	< 10 mm	NA	NA	NA
Drug	Tacrolimus	Sirolimus	Sirolimus	Sirolimus	NA	Tacrolimus	Paclitaxel	Paclitaxel
Application process	Dipping	NA	On-site spray coating	Drug in solvent dip/evaporate		Melting, coagulating and adhering	Automated micro-jet system	Automated micro-jet system
Release	75% over 2 – 3 days	Compatible to Cypher stent	Sustained release > 21 days	NA		50% release at 1 month	5 – 30 days	30 days
Clinical trial(s)	PRESENT I, PRESENT II	NA	ISAR-TEST	NA	NA	Jupiter I, Jupiter II e-Janus registry	DepoStent, PISCES, SCEPTER	COSTAR I, COSTAR II, EuroSTAR
Regions of availability	No	No	European Union	No	No	European Union	No	European Union

* The roughness determined by a perthometer, ‡ No coating, but biodegradable polymers are inlayed in the laser cut holes.

COSTAR: Cobalt Chromium Stent with Antiproliferative for Restenosis; DES: Drug-eluting stent; EuroSTAR: The European Cobalt Chromium Stent with Antiproliferative for Restenosis Trial; ISAR-TEST: Intracoronary Stenting and Angiographic Restenosis–Test Equivalence Between 2 Drug-Eluting Stents; Jupiter: Treatment of Restenosis of Coronary Lesions with Janus Carbostent in Direct Stenting; NA: Not applicable; PISCES: The Paclitaxel In-Stent Controlled Elution Study; PRESENT: Preliminary Safety Evaluation of Nanoporous Tacrolimus Eluting Stents; SCEPTER: Study of Controlled Elution of Paclitaxel for the Elimination of Restenosis.

3.1 Nanoporous drug-eluting stents

3.1.1 Ceramic (aluminum oxide)-coated tacrolimus-eluting stent

Jomed International, recently acquired by Abbott Vascular, developed one of the initial porous stents. Exploiting the porous features of ceramics, a compound of aluminum and oxygen (Al_2O_3) was utilized to provide a nanoporous stent surface. In the process of surface manufacturing, a 316L stainless steel stent was first coated with aluminum and the metallic layer was then electrochemically converted into a nanoporous ceramic. The antirestenotic drug was then applied, simply by dipping the stents into a defined solution of tacrolimus, with subsequent drying steps [22].

However, the clinical performance of this system in PRESENT (Preliminary Safety Evaluation of Nanoporous Tacrolimus Eluting Stents) trials was not satisfactory [23]. Subsequent development of this technology has been abandoned, despite the pioneering endeavors.

3.1.2 Setagon stents

The Setagon DES (Setagon, Inc.) utilizes a thin, nanoporous, metal coating (Figure 1A). The nanoporous layer is produced through sputter coating techniques, which allow deposition of a precursor material, the same metal as the stent, along with a sacrificial metal that is then selectively removed to produce porosity. This technology can be applied to a variety of materials, including cobalt chromium, nitinol, platinum, and stainless steel. Importantly, the coating process does not affect stent performance or drug/coating interactions [203]. Figure 2 shows that the release curve of sirolimus is nearly identical to that of the CYPHER stent (Figure 2). So far, no clinical study using this stent has been reported.

3.2 Microporous drug-eluting stents

3.2.1 Yukon drug-eluting stent

Yukon (Translumina, Hechingen, Germany) is a microporous, on-site coated, sirolimus-eluting stent. The porosity (roughened surface) of the 316L stainless steel stent is produced by mechanical treatment/modification [20,21] (Figure 1B). The roughness of the stent surface, determined by a perthometer, is 1.96 ± 0.21 µm, allowing drug deposition and prolonged drug release without an application of polymers.

The drug is applied by a spraying process using specific equipment. The equipment is composed of a drug reservoir, spraying system and a cartridge, where a mounted stent is positioned. This mobile machine can complete the entire drug application process in a cardiac catheterization laboratory within 10 min [20].

In a recent, randomized, controlled trial, Yukon DESs demonstrated comparable clinical performance with the Taxus stent (Figure 3) [19].

3.2.2 Electroformed microporous drug-eluting stents

The porous feature of the ESI microporous DES (Electroformed Stents, Inc., Stilwell, KS) is generated by utilizing electroforming – a metal part fabrication technology. Electroforming is a process that synthesizes a metal object using electrodeposition over a mandrel (stent struts in this case). The synthesized outer coating is porous because the deposited layer is made from small particles with abundant spaces between them. The prototype of this stent is composed of gold stent struts with an electroformed thin layer made from gold [202]. However, the stent struts and the porous layer can theoretically be made from different materials, thereby taking advantage of the wide applicability of electroforming. For example, a platinum or silver coating over stent struts composed of stainless steel or cobalt chromium represents a possible combination. There is no clinical experience with this stent.

3.2.3 Electrochemical porous drug-eluting stent

The surface porosity of the electrochemical porous drug-eluting stent (Medlogics Device Corporation) is provided by an electrochemically deposited material [201]. Information on this stent technology is limited, but the pore size (diameter) is reported to be ≤ 10 µm.

3.3 Macroporous drug-eluting stents

3.3.1 Janus™ tacrolimus-eluting Carbostent™ system

The Janus tacrolimus-eluting Carbostent system (Sorin Groups SPA) has multiple reservoir slits on the external surfaces [201]. Tacrolimus is loaded into the slits by a process where the drugs are melted, coagulated and adhered. Although no polymers are required in this process, the elution property of the loaded drug (tacrolimus) was shown to be sufficiently slow in an animal study (50% release in 1 month) [24].

One clinical registry and two randomized clinical trials are underway. In the e-Janus registry, clinical outcomes of Janus Tacrolimus-eluting Carbostent system were evaluated in 587 patients. The 6 months follow-up data showed a low rate for the requirement for repeat revascularization, which is comparable with the results of other DES systems (Joint Interventional Meeting Congress 2006, Rome). In a double-blind, randomized, clinical trial comparing this DES with BMSs, the Janus stent demonstrated equivalent safety and efficacy (Transcatheter Cardiovascular Therapeutics 2005, Washington, DC). Longer-term safety and efficacy of this stent system will be further evaluated.

3.3.2 Conor and CoStar stents

Conor stents (Conor Medsystems) are 316L stainless steel stents with laser-cut penetrating reservoir holes (Figure 1C). The concept of this DES is to provide programmable drug delivery with either uni- or bidirectional drug elution toward the vessel lumen and/or the vessel wall. The holes in this stent are inlaid with a combination of biodegradable polymers and a drug(s), and the loaded drug elutes through erosion of the polymers and diffusion of the drug itself. A predetermined drug-eluting pattern can be achieved by varying the process of drug loading in the holes [25].

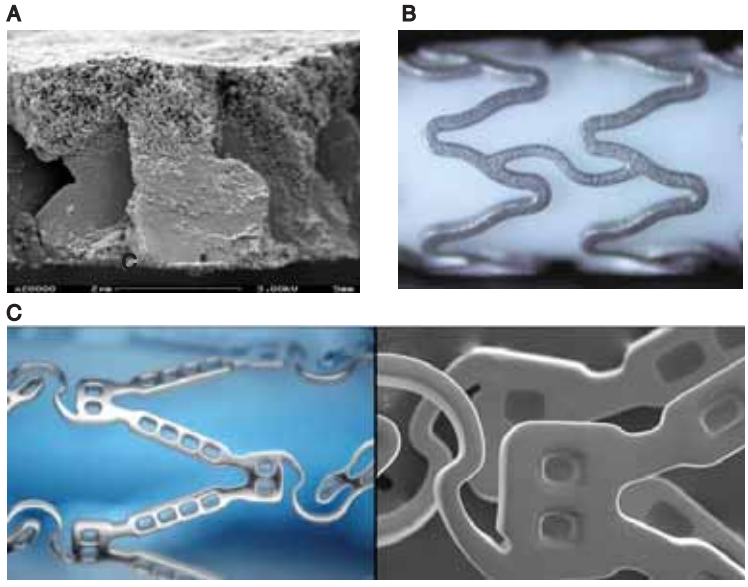

Figure 1. Porous stent surfaces. A. A nanoporous stent surface: a scanning electron microscopic view of a Setagon stent (x 20,000). Stent struts are gilded with this nanoporous layer (estimated porosity of 30%), which functions as a reservoir for prolonged release of antirestenotic drugs. **B.** A microporous stent surface (Yukon DES): the microporous structure of the stent surface is generated by mechanical treatment/modification. The roughness of the stent surface, as determined by perthometer, is 1.96 ± 0.21 µm. **C.** A macroporous stent surface (Conor stent): penetrating holes in the stent struts are generated by laser (left panel). The holes are inlaid with a mixture of biodegradable polymers and antirestenotic drug(s), which enable different eluting formulations of the loaded drugs. (Scanning electron microscopic image, right panel).

A. Reproduced with permission from Setagon, Inc.
B. Reproduced with permission from Translumina.
C. Reproduced with permission from Cordis Corporation and Dr John Ormiston.

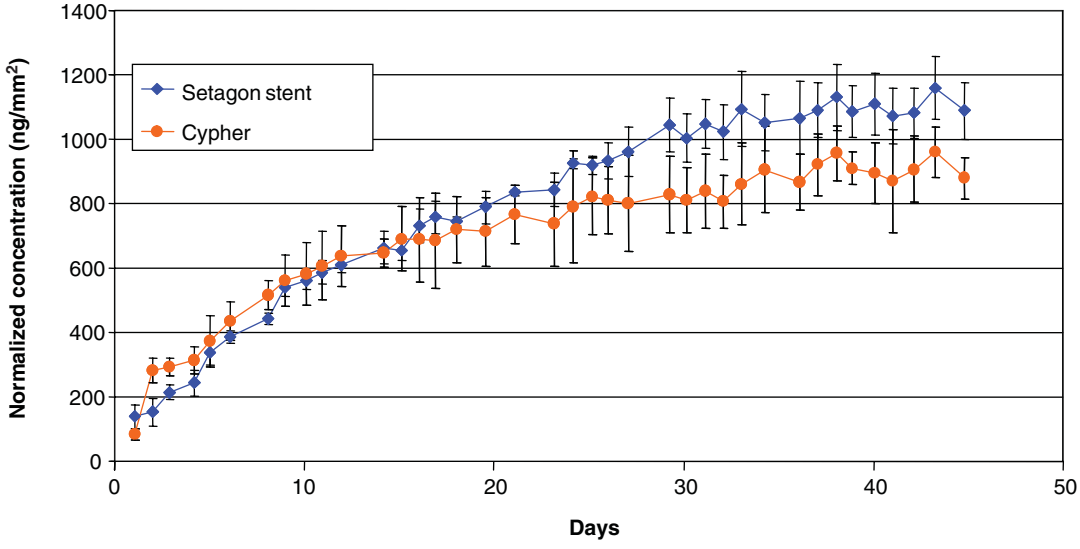

Figure 2. The pharmacokinetics of a nanoporous stent (Setagon stent) and a CYPHER stent. *In vitro* pharmacokinetic study of a Setagon stent, showing that the release curve of sirolimus is similar to that of the CYPHER stent.

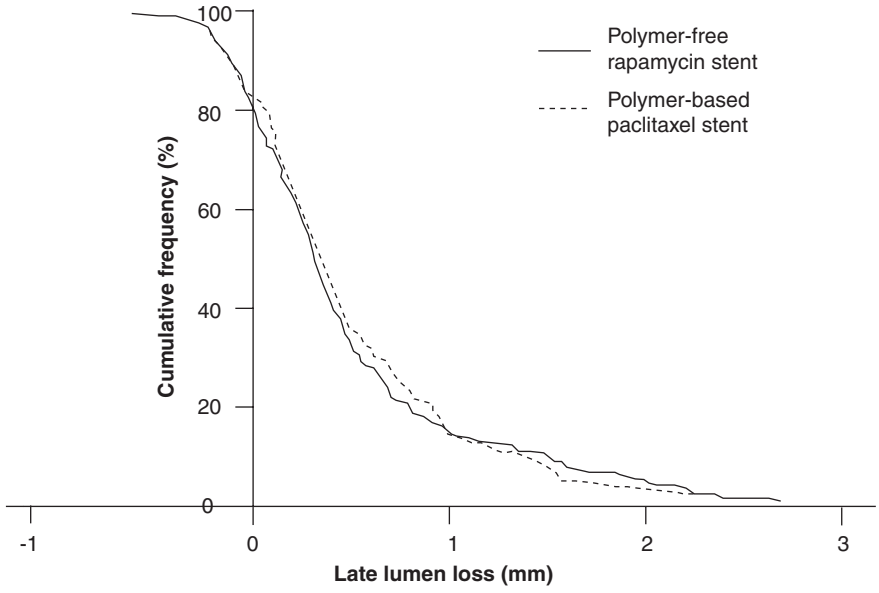

Figure 3. An angiographic comparison of in-stent restenosis (late loss) between the Yukon microporous stent and a polymer-based paclitaxel-eluting stent. Cumulative frequency curves of in-stent late lumen loss (difference between the minimum lumen diameter immediately after stent deployment and minimum lumen diameter at 6 – 8 months follow-up) are shown. Curves of the two stent systems exhibit superimposed patterns, suggesting comparable efficacy of Yukon microporous stent with the polymer-based paclitaxel-eluting stent in the inhibition of restenosis in humans.
Reproduced with permission from MEHILLI J, KASTRATI A, WESSELY R *et al.*: Randomized trial of a nonpolymer-based rapamycin-eluting stent versus a polymer-based paclitaxel-eluting stent for the reduction of late lumen loss. *Circulation* (2006) **113**(2):273-279.

Results of a prospective clinical trial testing the Conor stent have been published [18]. In this PISCES (Paclitaxel In-Stent Controlled Elution Study), 244 patients with single vessel disease were sequentially assigned to either a BMS or a paxlitaxel-eluting Conor stent with one of six different drug-releasing properties. During the first 4 months follow-up, patients treated with the slow-releasing Conor stent exhibited a trend toward less repeat revascularization compared with the BMS group. The extent of the restenotic process, evaluated by angiography and intravascular ultrasound, was also significantly lower in the Conor stent, compared with BMSs.

Recently, a modified stent system with the same basic design as Conor stents, but with thinner stent struts made from cobalt chromium has been developed (CoStar stents). In the EuroSTAR (European Cobalt Chromium Stent with Antiproliferative for Restenosis Trial), which included 176 lesions treated with the CoStar stents, 12-month clinical outcomes were equivalent to those of presently available DESs [26]. At present, this CoStar stent is being further evaluated in larger populations in the COSTAR II (Cobalt Chromium Stent with Antiproliferative for Restenosis) trial.

4. Conclusions

Thanks to various technological advancements and their integration, diverse types of porous DES are now on the horizon. There have been only a limited number of clinical studies reported. However, preliminary data suggest a promising potential for porous DES technologies. Adequately powered clinical trials to examine long-term safety and efficacy profiles are mandatory before these unique DES systems are deemed to be clinically feasible, next-generation DESs.

5. Expert opinion

The essential goal of treating occlusive coronary artery disease is to reopen the lumen and maintain patency, thereby helping the patient to have a longer and better quality life. The available DESs are considered successful in achieving this goal within a short- or mid-term follow-up period. When compared with BMSs, DESs obviously elicit much less neointimal formation, with reduced chance of revascularization (either percutaneous or surgical), particularly within 1 year after stenting.

Although the present DESs undoubtedly offer superb efficacy, safety has become an issue, especially in the long term. For example, the rate of late-stent thrombosis

(occurring > 1 year after stenting) or death is reported to be higher in patients treated with DESs than those with BMSs [27,28]. Also, DESs were reported to cause more late cardiac events than BMSs after discontinuation of antiplatelet therapy, possibly related to late-stent thrombosis [29]. It is still controversial as to whether DESs are linked to increased late-thrombotic events. However, FDA issued a statement in 2006, representing their keen interest in the possible risk of stent thrombosis in patients with DES [204]. The long-term safety of DESs will be a matter of attention for both existing and future stents.

The polymers on the stent struts are suspected to trigger late-stent thrombosis, in view of the fact that stent struts or drug(s) alone are not likely to cause this late phenomenon. The stent struts of present DESs are usually made from the same materials used for BMSs, and the amount of the drug(s) on the struts is generally negligible ≥ 1 years after stenting. Thus, developing new drug-eluting systems with different polymers may help solve the problem of late-stent thrombosis.

Recent advancements in this regard include the development of biodegradable polymers, such as polylactide-co-glycolide, which theoretically disappears within 6 months. In addition, several prototypes of biodegradable stents have also been introduced. Biodegradable stent struts generally dissolve in ~ 6 months, avoiding the future risks of sustained allergic reaction, inflammatory vascular response and late thrombosis. The Igaki-Tamai stent [30] and Duke biodegradable stent [31] are early prototypes, with the absorbable magnesium alloy stent [32] and biodegradable, paclitaxel-eluting, coronary, polylactide stents [33] being introduced more recently. These biodegradable stents have the potential to be the 'ideal' device, particularly if the drug-elution properties and biodegradation process can be customized [34].

However, fully biodegradable stent technology does not guarantee short- or mid-term efficacy, despite its ideal potential. In fact, what we need is desirable drug-elution properties, and the use of any new material that may cause adverse events should be avoided.. In this context, porous stent surface technology is an attractive alternative, theoretically offering both the long-term safety of BMSs and the efficacy of DESs. Porous stents with a comparable efficacy to the latest DESs (e.g., Yukon DESs) may, therefore, be more promising than the polymer-based DESs, if late thrombotic events occur significantly less compared with polymeric DESs.

Another possible advantage of porous stents is the enhanced endothelialization promoted by porous surfaces. For example, Marois *et al.*, using an established *in vitro* model, demonstrated greater endothelial cell migration onto the porous surfaces than to the smooth surfaces of vascular prosthetic grafts [35]. Similarly, animal studies have also documented an improved endothelialization of implanted vascular grafts with porous flow surfaces [36,37]. However, these favorable effects of porous surfaces have not been directly shown in porous DESs so far.

Because of recent concerns of late clinical events accompanying DESs, new stent systems with higher long-term safety are eagerly awaited. However, all new stent technologies, including the new porous stent surface strategies, need to prove their efficacy and safety in comparison with approved stent systems in adequately powered trials. In fact, such a 'non-inferiority' trial is, so far, only available for the Yukon DES system.

Disclosure

P Fitzgerald is a consultant for Setagon, Inc., Medlogics Device Corporation and Cordis Corporation (Johnson & Johnson).

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