

Stent Pipeline

An update on absorbable polymers and stents.

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The unquestionable benefits brought by drug-eluting stents (DES) in reducing restenosis and target lesion revascularization (TLR) have triggered some drawbacks regarding their long-term safety.

Several studies in the preclinical and clinical scenarios have documented local inflammatory reactions (delayed healing^{1,2} and hypersensitivity³) after first-generation DES deployment, which have been considered one of the possible mechanisms of late and very late stent thrombosis. Because the drugs are the first to disappear usually no longer than 3 months after stent deployment, durable polymers are speculated to be the main DES components to instigate this untoward local reaction.

Following this biological hypothesis, a novel trend in the interventional cardiology scientific arena has emerged, with studies focusing on erodible polymers and stents.

BIOABSORBABLE POLYMERS

In theory, biodegradable polymers, being biocompatible and lasting long enough to release the antiproliferative drug, would avoid the previously mentioned possible inflammatory reactions. Table 1 contains the main studies with these polymers.

We will briefly discuss the results of a few preliminary studies with this novel technology, initially focusing on those using a limus family drug and eventually presenting the results of the studies with paclitaxel.

LIMUS FAMILY STUDIES

In the FUTURE I study,⁴ the everolimus-eluting stainless steel stent with a polyhydroxyacid bioabsorbable polymer (polylactic acid [PLA]) matrix was compared

to its metallic counterpart, the S-Stent (Biosensors International, Singapore). This polymer breaks down initially into low-molecular-weight PLA and later into carbon dioxide and water as it releases the drug. The everolimus-eluting stent was shown to significantly reduce neointimal formation (0.11 vs 0.85 mm; $P<.0001$), although the trial was unable to show clinical differences.

Using the Biolimus A9 drug-eluting stent (Biosensors International), combined with a PLA polymer in the stainless steel S-Stent platform (BioMatrix stent, Biosensors International), the STEALTH study⁵ also found a significant late loss (LL) reduction when compared to the bare-metal stent (BMS) S-Stent, with no differences regarding clinical endpoints (Table 1).

The just-published LEADERS⁶ trial enrolled more than 1,700 patients randomized (1:1) to receive a durable-polymer sirolimus-eluting stent (Cypher, Cordis Corporation, Warren, NJ) or the biodegradable-polymer biolimus-eluting stent (BioMatrix). The primary endpoint of clinical noninferiority at 9 months was achieved by the BioMatrix stent (9% vs 11%, rate ratio 0.88; 95% confidence interval [CI], 0.64–1.19; P for noninferiority=.003, P for superiority=.39). In the subset of patients who underwent angiographic follow-up, the novel DES showed similar reduction in LL and percentage of stenosis at 9 months.

After the success of this novel technology in noncomplex lesions, the Biolimus A9 degradable polymer was licensed to the Devax Company (Lake Forest, CA) and tested in a more complex lesion subset—the bifurcations (the AXXESS PLUS trial⁷). At 6-month follow-up, this dedicated stent showed marked neointimal hyperplasia suppression ($2.3\pm2.2\%$) and preserved main vessel and side branch minimum lumen areas at the ostium

TABLE 1. BIOABSORBABLE POLYMER TRIALS

Study	Type	Stent Type (Polymer+ Platform)	No. of Patients	Drug	Primary Endpoint	LL (In Stent)	BAR
FUTURE 1	Rand 2:1	PLA+SS vs SS	27 vs 15	Everolimus	MACE at 30 d	0.11 vs 0.85 mm*	0% vs 9.1%†
STEALTH	Rand 2:1	PLA+SS vs SS	80 vs 40	Biolimus A9	LL at 6 mo	0.26 vs 0.74 mm*	3.9% vs 7.7%†
SERIES I	Registry	PLA/PLGA/PVP+SS	126	Sirolimus	BAR at 6 mo	0.09 mm	1.70%
EXCEL	Registry	PLA+SS	31	Sirolimus	LL at 6 mo	0.07 mm	0
Liu H et al	Registry	PLA+SS vs NEP+SS	93 vs 97	Sirolimus	Not specified	0.19 vs 0.14 mm†	0 for both
ISAR-Test-3	Rand	BDP/NEP/PF	625	Sirolimus	LL at 6–8 mo	0.17 mm/0.23 mm/0.47 mm	Data not available
CURAMI ²⁵	Registry	PLA/PLGA	49	Sirolimus	6-month LL	0.74±0.89 mm	22%
SIMPLE II	Registry	PLC/PVP + SS	103	Paclitaxel	MACEs at 30 d	0.38 mm	8.30%
Buszman et al	Registry	LA/GA+SS	116	Paclitaxel	9-mo BAR/ 12-mo TLR	0.46 mm	11.90%
Wessely et al ²⁶	Rand	BDP+SS vs BDP+SS	45 vs 46	Paclitaxel vs Sirolimus	LL at 6–8 mo	0.96 vs 0.33 mm*	39% vs 12.2% P=.005
COSTAR II	Rand	PLGA+CC vs PP+SS	989 vs 686	Paclitaxel	8 mo MACE	0.64 vs 0.26 mm*	17.9% vs 4.1%*

BAR, binary angiographic restenosis; Rand, randomized; LL, late loss; SS, stainless steel; CC, cobalt chromium; PLA, polylactic acid; NEP, nonerodible polymer; BDP, biodegradable polymer; PF, polymer free; PLGA, poly-lactide-co-glycolide; PVP, polyvinyl pyrrolidone; PLC, poly-L-lactide-co-caprolactone; LA, lactic acid; GA, glycolic acid; TLR, target lesion revascularization; d, days; mo, month; MACE, major adverse cardiac events.

When comparisons are made, the results are depicted respecting the order of the stents described above.

*P<.001

†P=NS.

TABLE 2. BIOABSORBABLE STENTS

Study	Type	No. of Patients	Stent Type	Drug	LL	BAR	TLR	MACE
Igaki-Tamai	Registry	15	Polymeric	No	0.67 mm	6.7%	6.7%	6.7%
ABSORB	Registry	30	Polymeric	Everolimus	0.44 mm	12%	0	3.3%
Progress AMS	Registry	63	Metallic absorbable stent	No	1.08 mm	47.5%	26.7%*	26.7%

Abbreviations are explained in the footnote to Table 1.

*Ischemia-driven BAR.

(7.9 ± 2.6 mm² and 4 ± 1.4 mm², respectively).

Using the same biodegradable polymer (ie, PLA) in a different platform (ie, stainless steel) combined with sirolimus, the Excel stent (JW Medical Systems, China) showed enthusiastic preliminary results with a significant reduction in LL.⁸ This stent then was compared to the Firebird stent (MicroPort Medical Co. Ltd., Shanghai, China),⁹ a sirolimus durable polymer stent. Clinical and angiographic 6-month follow-up showed no differences regarding major adverse cardiac events (MACE), binary angiographic restenosis (BAR), and LL.

A differently designed, biodegradable polymer matrix consisting of poly-L-lactic acid, 50/50 poly-DL-lactide-co-glycolide acid, and polyvinyl pyrrolidone (PVP), with a sirolimus-eluting stainless steel stent, was recently tested by Dani et al in the SERIES I Trial.¹⁰ In this formulation, the outer layer containing only PVP prevents premature drug release and is completely removed within 2 hours after implantation, after which an early burst phase releases 50% of the drug within the first 7 days, and the remaining 50% is released within 41 days (average, 48 days). Angiographic results showed sustained LL reduction with relevant clinical benefits (cumulative MACE of 9% at 9 months, and an event-free survival at 30 months of 93%).

In the only randomized trial so far, the ISAR-TEST-3 trial,¹¹ when comparing different polymers in stents with the same platform and drug (sirolimus), the bioerodible polymer stent group met the angiographic pre-specified criteria for noninferiority ($P < .001$) against the durable polymer group, whereas the polymer-free group stent did not ($P = .94$) (Table 1). There were no differences in safety outcomes among the cohorts.

PACLITAXEL STUDIES

In parallel, a few studies assessed the safety and effica-

cy of paclitaxel delivered by bioerodible polymers.

The SIMPLE II trial¹² evaluated the Infinium stent (Sahajanand Medical Technologies Pvt. Ltd., Surat, India) designed with paclitaxel 1.4 µg/mm², stainless steel, and two polymers—poly-L-lactide-co-caprolactone and PVP—displayed in three layers, which coat the drug with different combinations of drug and polymer, each one having a different release profile and a cumulative release within 48 days. The angiographic endpoints showed similar LL as identified in most paclitaxel-eluting stent trials, with an acceptable 9-month TLR rate.

Buszman et al¹³ documented the results of a novel paclitaxel-eluting biodegradable polymer stent—Luc-Chopin stent (Balton, Warszawa, Poland)—which is coated with a multilayer structure containing a copolymer of lactic and glycolic acid, degrading entirely in 8 weeks. The trial results were in accordance with other paclitaxel-eluting stent studies, with an LL of 0.46 mm and binary restenosis of 11%.

In the COSTAR II trial,¹⁴ a novel cobalt-chromium, poly-DL-lactide-co-glycolide acid polymer, paclitaxel-eluted stent (Conor MedSystems, Menlo Park, CA) was compared to the Taxus stent (Boston Scientific Corporation, Natick, MA). Carrying out specifically designed laser-cut drug reservoirs, this device could not reach the primary endpoint of angiographic noninferiority at the 9-month invasive follow-up.

Most of the previously mentioned trials demonstrated a successful use of biodegradable polymers with low rates of adverse events. Their main limitations are the small number of patients associated with a relatively short duration of follow-up in selected populations, precluding conclusions about delayed inflammatory reactions.

The currently ongoing multicentric e-Series Registry is aimed to include 2,000 patients (“all comers”) in Brazil and India. These patients are receiving the Supralimus

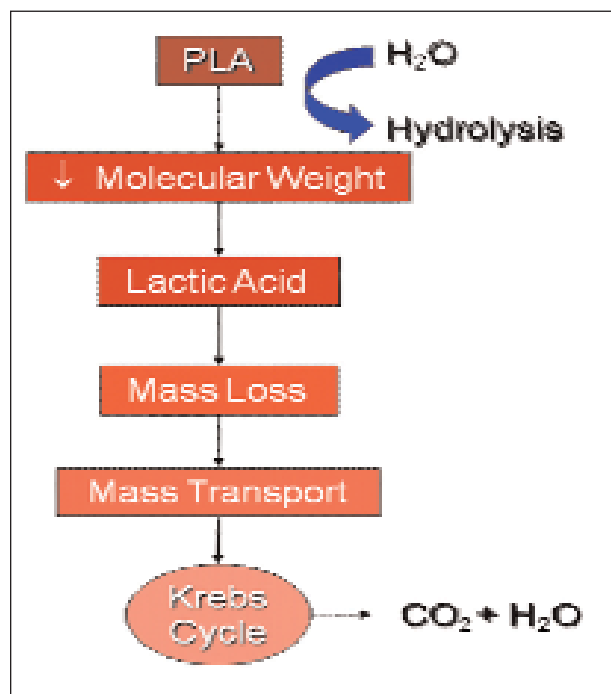


Figure 1. Metabolic pathway of PLA polymer degradation.

stent (Sahajanand Medical Technologies Pvt. Ltd.) and will be followed by a minimum 2-year period. Preliminary results are expected to be presented at the 2008 TCT meeting.

BIOABSORBABLE STENTS

In the same direction of the erodible polymers, but a step further, is the research on completely bioabsorbable stents.

The bioerodible stent concept has emerged from the inherent limitations of the contemporary metallic stents, which are based on the assumption that the need of artery scaffolding is temporary until the healing process takes place. Beyond that period, the metallic struts have no other role than acting as a foreign body inciting local inflammatory responses. Thus, the theoretical benefits of these novel devices are:

- Prevention of delayed healing and inflammation
- Diminishing of the impact on endothelial dysfunction and vessel remodeling over time
- Shortening of the dual-antiplatelet therapy
- Limit side branch jailing
- Allow later noninvasive studies, such as multislice computerized tomography and magnetic resonance imaging
- Allow new revascularization techniques when required in the follow-up, such as bypass graft surgery (limited by full-metal jacketed arteries)

Basically, two different materials—polymer and metal—have been tested in this scenario.

POLYMER-BASED STENT SYSTEMS

Poly lactide polymers and copolymers have been approved for use in various medical scenarios, from orthopedics to the cosmetic fields. The repeating units of the PLA/poly-DL-lactic acid polymers are absorbed through hydrolysis, leading to lactic acid that is metabolized via the Krebs cycle and small particles (<2 μm in diameter) further being phagocytosed by macrophages (Figure 1). The time for complete absorption of the polymer backbone is estimated to be approximately 2 to 3 years, whereas the polymer coating is much more rapidly absorbed. Important inflammatory reactions were initially shown in animal studies,^{15,16} which were significantly decreased with the advent of novel technologies.^{17,18}

The first biodegradable polymeric stent shown to be feasible and safe for coronary use was the Igaki-Tamai stent (Igaki Medical Planning Co. Ltd., Kyoto, Japan), with results initially presented in 2000.¹⁹ The Igaki-Tamai is a self-expanding coil stent made of PLA monofilament (molecular mass, 183 kDa), with a zigzag helical design and a 0.17-mm strut thickness. It has two radiopaque gold markers in its borders. The stent continues to expand gradually to its original size after in vivo deployment, depending on the size of the artery. Twenty-five stents were implanted in 15 patients, with angiographic and intravascular ultrasound (IVUS) follow-up at 1 day, 3 months, and 6 months. All procedures were successfully performed, with a $22 \pm 7\%$ acute recoil measured by quantitative coronary angiography (QCA). The 3-month stenosis rate was 33%, with an LL comparable to conventional BMS and very reasonable BAR and TLR (Table 2). IVUS analysis demonstrated an increase in the stent cross-sectional area from postprocedure to the 3-month follow-up ($7.4 \pm 1.51 \text{ mm}^2$ vs $8.18 \pm 2.42 \text{ mm}^2$; $P < .01$), which was sustained at 6 months ($8.13 \pm 2.52 \text{ mm}^2$). Furthermore, at 6 months, stent struts could still be visualized by IVUS. No major clinical events were noted. However, the high profile of the stent restricted its use to peripheral interventions only.

DRUG-ELUTED POLYMER-BASED SYSTEMS

The first bioabsorbable DES system to show enthusiastic results was the everolimus-eluting stent system (Bioabsorbable Vascular Solutions, Abbott Vascular, Santa Clara, CA), evaluated by Ormiston et al²⁰ in a single-arm, first-in-man (FIM) study (the ABSORB Trial).

The stent is made of a bioabsorbable PLA backbone coated with a more rapidly absorbed poly-D-lactic acid

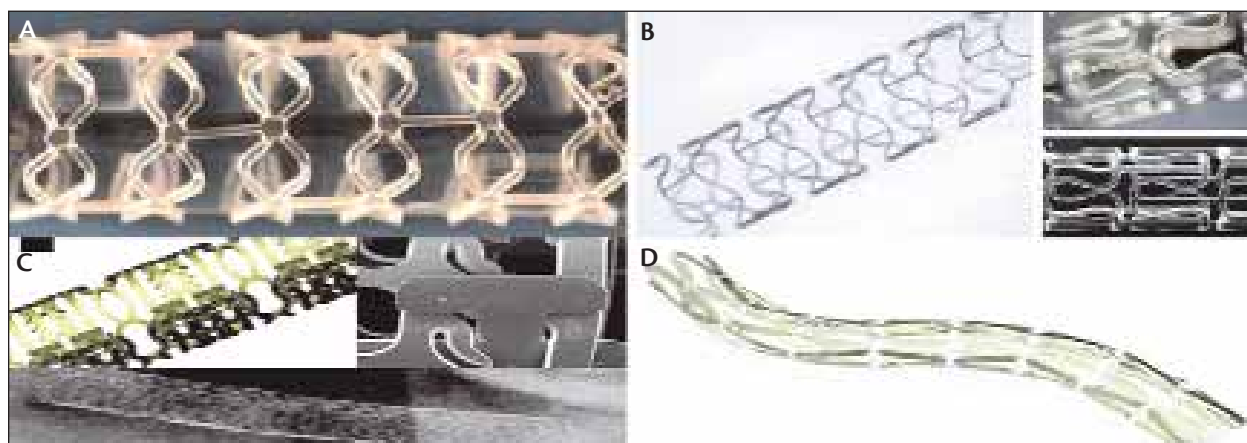


Figure 2. Bioabsorbable stents: Bioabsorbable Vascular Solutions stent (A); Biotronik Magnesium stent (Biotronik GmbH & Co. KG, Berlin, Germany) (B); Reva stent (Reva Medical Inc., San Diego, CA) (C); and the BTI stent (Bioabsorbable Therapeutics, Inc., Menlo Park, CA) (D). Please refer to the text for details about the stent systems.

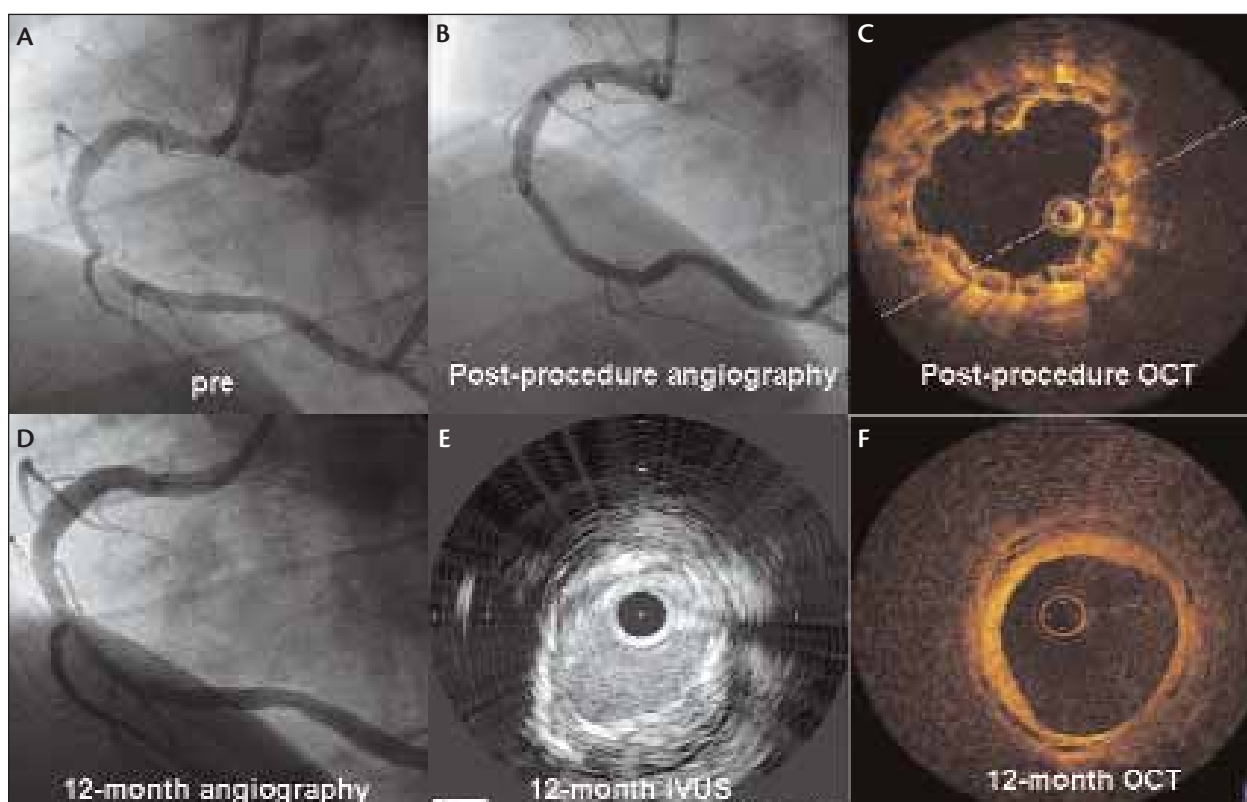


Figure 3. Example of a patient from our FIM series treated with the Reva bioabsorbable stent system. Twelve-month OCT (F) documented the presence of neointimal tissue covering the entire treated segment. Furthermore, signs of stent absorption could be noticed along the treated segment.

layer that contains and releases the antiproliferative drug (Everolimus, Novartis International AG, Basel, Switzerland). The bioabsorption process has been previously described. The struts are 150 μ m thick with radiopaque markers at both ends (Figure 2). The dose

of everolimus tested was 98 μ g for the 12-mm stents, and 153 μ g for the 18-mm stents, with a release rate of 80% by 30 days.

The angiographic, IVUS/virtual histology, and clinical follow-up were performed at 6 months and 1 year,

respectively, with rates of LL and TLR aligned with other “conventional” DES systems (Table 2). The IVUS analysis demonstrated a reduced neointimal area (0.3 mm^2), a constant vessel area (13.55 mm^2 postprocedure vs 13.49 mm^2 at follow-up; $P=.98$), and an 11.8% stent recoil (6.08 mm postprocedure vs 5.37 mm at follow-up; $P<.0001$), which was the main mechanism responsible for the 24.3% decrease in the minimum lumen area (5.11 vs 3.85 mm^2 ; $P<.0001$). The in-stent area obstruction was modest (5.54%). Incomplete stent strut apposition at baseline was reported in six patients (24%)—it resolved in two and persisted in four by 180 days. There were seven cases of late acquired incomplete stent apposition with a malapposition volume of 3.2 mm^3 , which represents $<10\%$ of the theoretical volume of the stent (85 mm^3). IVUS/virtual histology analysis suggested the first signs of the expected bioabsorption of struts at 6 months. Furthermore, according to this image-modality assessment, the tissue growth documented inside and outside the stent struts at follow-up consisted of fibrous and fibrofatty tissues with no signs of inflammatory (necrotic core) activity.

An optical coherence tomography (OCT) subgroup (13 patients) was evaluated at baseline and 6 months. Five percent of the struts were incompletely apposed at baseline and, in the follow up, 5% had persistent incomplete stent apposition. Additionally, there was a 1% rate of late acquired incomplete strut apposition. Tissue coverage was present in 99% of the struts at 6 months.

METALLIC-BASED SYSTEMS

Polymeric biodegradable stents still have several challenges to be pursued: (1) lower radial strength, responsible for postimplantation early recoil; (2) slow bioabsorption rate (2–3 years), precluding earlier dual-antiplatelet discontinuation; (3) radiolucency; and (4) high profile.

Metallic bioabsorbable stents have been developed in order to surpass some of these limitations. Like the stainless-steel BMS, these novel stents are supposed to have greater radial strength in comparison to the polymeric biodegradable stents. Additionally, they are expected to have a faster absorption.

There are, so far, two absorbable metal alloys used for this purpose—iron and magnesium, which already have been tested in humans. Their local toxicity is based on their elements’ local concentration. The tissue tolerance depends on the changes of the metal’s tissue concentrations during the resorption process, so the stent that most resembles its surrounding tissue might fit smoother in its place.²¹

The Progress AMS Multicentric Nonrandomized

Trial²² evaluated the feasibility (efficacy and safety) of implanting a bioabsorbable magnesium alloy stent (Biotronik GmbH & Co. KG) in humans. This novel device, in theory, performs similar to a stainless steel stent, with a low elastic recoil ($<8\%$) and minimum amount of shortening after balloon inflation ($<5\%$). It has two radiopaque markers (Figure 2). Animal studies have shown a complete reabsorption within 2 months with calcium, a phosphorous compound local replacement, and a corrosion limited to the vessel walls with rapid re-endothelialization and strut coverage.

In its FIM study, a cohort of 63 patients with reference vessel diameters between 3 and 3.5 mm and lesion lengths $<13 \text{ mm}$ were included. Study endpoints included 4-month QCA evaluation and 6-month clinical assessment. Device and procedure success were achieved in all cases, confirming the feasibility of the stent. There was good vessel scaffolding with a residual, postprocedure diameter stenosis of 12.6%. However, at 4 months, LL and BAR rates were disappointing (Table 2). Up to 6 months, there were no deaths, myocardial infarctions, or stent thrombosis.

IVUS analysis demonstrated a diminished strut echo reflectivity at 4 months, although their original position could still be identified. IVUS was also helpful to document the mechanisms of late luminal loss, which was the result of a decrease of the external elastic membrane volume (42% of LL), an increase of the volume outside the originally encircled stent (13% of LL), and neointima formation (45% of LL), with no substantial changes in the original atheroma volume.

Although the study showed the feasibility of using this stent in human coronaries, with a good acute gain and no signs of distal embolization, the expressive chronic recoil resembled the pre-stent era.

Waksman et al²³ recently documented the implant of biocorrosible iron stents in porcine coronary arteries. In a randomized comparison against cobalt-chromium stents, they found promising results concerning either efficacy and safety endpoints. Preliminary assessment of this novel device in humans is expected to be initiated soon.

FUTURE TRIALS AND DIRECTIONS

Many companies in the interventional cardiology field are currently focusing their research efforts in developing absorbable stents. We briefly present two next-generation bioerodible stent systems with FIM evaluations taking place in our institution.

REVA STENT

The Reva stent is a tyrosine-polycarbonate tunable resorption stent with a special slide-and-lock design

geometry (allowing thinner struts) and an inherently iodinated radiopaque material, with FIM experience (the RESORB trial) held in three centers (two in Germany and one in Brazil). The stent has a standard balloon deployment with a potential for dual (luminal/abulminal) drug delivery, maintaining its strength for approximately 6 months, being designed to resorb in 2 years. Primary endpoints include 30-day MACE and 6-month QCA and IVUS assessment (Figures 2 and 3).

BTI STENT

The BTI stent is characterized by a core of salicylic acid chemically incorporated into a polymer backbone, which is coated with a layer of salicylate eluted with sirolimus (BTI polymers) whose elution takes place over the first month after implantation.

The WHISPER Trial is a multicenter FIM study that aims to enroll 40 patients in three countries (Brazil, Belgium, and New Zealand). Primary endpoints include QCA, IVUS, and in a prespecified cohort, OCT assessment (Figure 3).

CONCLUSIONS

A well-balanced, timed arrangement between polymeric scaffolding and drug release remains the greatest challenge fostered by the bioabsorbable stent technology. The ideal polymer and/or metal capable of sustaining a sufficient radial force and, in the meantime, having an ideal degradation period not too long to meet unsafeness, is yet to be reached.

So far, the 2- to 3-year period necessary to complete resorption of the polymeric stents appears too long, as the extended need for dual-antiplatelet therapy obscures one important benefit of this technology.

Finally, inflammatory patterns and biocompatibility associated with these novel stents are yet to be confirmed by longer-term follow-up evaluations.^{20,24} ■

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