Next-Generation Fully Bioresorbable Polymer Stents

A summary of technology undergoing testing and a look at what is on the horizon.

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Since the first percutaneous balloon angioplasty was performed in 1977,[1] significant advances have been made in the percutaneous treatment of coronary artery disease. The development of bare-metal stents addressed the issue of acute vessel closure. Although bare-metal stents prevented elastic recoil and constrictive remodeling, high rates of in-stent restenosis remained due to significant neointimal hyperplasia.[2,3] This prompted the development of drug-eluting stents (DES), which were able to reduce the incidence of in-stent restenosis with the addition of antiproliferative drugs to the stent platform, thereby reducing the occurrence of neointimal hyperplasia.[4-6] However, safety issues were raised with the first generation of DES when a new entity of late stent thrombosis became a significant problem, with a risk of 0.6% per year.[7] Second-generation DES, with more biocompatible antiproliferative drugs and thinner struts/improved designs were able to significantly decrease the incidence of major adverse cardiac events and late stent thrombosis.[8-10] However, the presence of any permanent endoprosthesis has led to other consequences: decreased vasoreactivity/impaired physiology of the artery, prevention of positive remodeling, obstruction of the side branch by stent struts, impaired imaging of the lesion with CT or MRI, and inability to insert a coronary bypass graft at the site that a stent was implanted.[11] These limitations led to the development of bioresorbable scaffolds (BRS; Table 1), which would theoretically allow for the benefits of transient scaffold support by preventing acute vessel recoil/closure, but overcome the limitations of metallic stents such as impaired vasomotor response and late stent thrombosis, while facilitating repeat treatments of the lesion site.[11]

BIORESORBABLE POLYMER STENTS CURRENTLY UNDER EVALUATION

Igaki-Tamai Scaffold

The Igaki-Tamai scaffold (Kyoto Medical Planning Co., Ltd.) was the first BRS implanted in humans more than 15 years ago.[12] It is poly-L-lactic acid (PLLA) based, not a DES (Figure 1). It is a heat-treated, self-expandable device, which means that the contrast material has to be heated to 80°C and applied through the delivery balloon. The device has 170-mm-thick struts that resorb in 18 to 24 months. The initial clinical data were encouraging, with the pilot trial of 15 patients showing no major adverse cardiovascular events (MACEs) and only one repeat coronary intervention at 6-month follow-up. The second 50-patient study confirmed the long-term safety of the device, with survival free of all-cause death, cardiac death, and major adverse cardiac events at 10 years of 87%, 98%, and 50%, respectively.[13] Two definite scaffold thromboses occurred, one subacute and one very late, which was related to another sirolimus-eluting stent (not the Igaki-Tamai scaffold). Intravascular ultrasound data confirmed the disappearance of stent struts within 3 years, and the stent area remained stable over time.[13] Because of possible safety issues related to the use of heated contrast material (arterial wall necrosis, exaggerated neointimal proliferative response, and increased platelet adhesion) and the need for an 8-F guiding catheter for delivery, the device is no longer used for coronary intervention but did receive CE Mark approval for use in peripheral vascular disease.

DESolve: Myolimus-Eluting Poly-L-Lactic Acid Scaffold

The DESolve scaffold (Elixir Medical) is a PLLA, myolimus-eluting (3 mg/mm) scaffold that has a strut thickness of 150 mm (Figure 1). In animal studies, the

TABLE 1. SUMMARY OF THE DESIGN AND STRUCTURE OF CLINICALLY TESTED BIORESORBABLE SCAFFOLDS						
Scaffold	**Strut Material**	**Coating Material**	**Eluted Drug**	**Strut Thickness (mm)**	**Resorption (mo)**	**Current Status**
Igaki-Tamai	PLLA	None	None	170	24–36	CE Mark for peripheral use
DeSolve	PLLA	None	Myolimus	150	12–24	CE Mark
DeSolve 100	PLLA	PLLA	Novolimus	100	24	CE Mark
IDEAL biostent	Polymer salicylate	Salicylate	Sirolimus	175	> 12	Clinical trials
REVA	PTD-PC	None	None	200	24	Discontinued
ReZolve	PTD-PC	None	Sirolimus	115–230	4-6	Clinical trials
ReZolve 2	PTD-PC	None	Sirolimus	100	48	Clinical trials
Fantom	PTD-PC	—	Sirolimus	125	36	Clinical trials
Fortitude	Semicrystalline polylactide	—	None	150–200	3–6	Clinical trials
Mirage BRMS	PLLA	—	Sirolimus	125–150	14	Clinical trials
MeRes	PLLA	PDLLA	Sirolimus	100	24	Clinical trials
Xinsorb	PLLA	PDLLA	Sirolimus	160	24–36	Clinical trials
ART 18AZ	PDLLA	None	None	170	3–6	Clinical trials

Abbreviations: PDLLA, poly-DL-lactic acid; PLLA, poly-L-lactic acid; PTD-PC, poly-tyrosine-derived polycarbonate. (Adapted with permission from Tenekecioglu E, Farooq V, Bourantas CV, et al. Bioresorbable scaffolds: a new paradigm in percutaneous coronary intervention. BMC Cardiovasc Disorders. 2016;16:38.)

scaffold resorbed within 2 years and provided good radial support at 3 months.[14] The DESolve scaffold showed a "self-correction" capacity, which means that the scaffold will tend to expand to nominal pressure despite initial recoil after implantation.[15] The first-in-man trial, DESolve-1 FIM, showed that in 16 patients, the device was successfully deployed in 15 cases, with a late lumen loss of 0.19 ± 0.19 mm at 6 months.[16] Optical coherence tomography data showed that 98.7% of the struts were covered with a thin neointimal coverage (0.12 ± 0.04 mm) at 6 months. At 1 year, three MACEs occurred: one periprocedural myocardial infarction, one cardiac death (postoperative: nontarget coronary artery bypass graft and aortic valve replacement), and one target vessel revascularization (the DESolve stent was patent, the lesion was adjacent to the stent).[16] The multicenter prospective DESolve Nx trial enrolled 126 patients with single de novo coronary lesions to the newer DESolve scaffold, now coated with novolimus.[17] Recent 24-month follow-up data reported one subacute probable stent thrombosis and a MACE rate of 7.4%.[17] Six-month angiographic follow-up showed an in-scaffold late lumen loss of 0.20 ± 0.32 mm, and intravascular ultrasound analysis demonstrated an increase in vessel, lumen, and scaffold dimensions compared with postprocedure measurements.[17] Most stent struts (99% ± 1.7%) were also fully covered at 6 months.[17] Three newer versions of the scaffold are currently in development: the DESolve Cx (120 mm), which has already been implanted in humans; the DESolve Amity, which is designed for patients with STEMI, as it can self-correct its diameter by 0.6 mm over 3 days; and the DESolve 100, which is composed of thinner struts (100 mm) and is currently in clinical and preclinical investigations.[18,19]

REVA STENT: POLYCARBONATE SCAFFOLD

Reva (Reva Medical, Inc.) developed a poly (iodinated, desamino tyrosyl-tyrosine ethyl ester) carbonate device (Figure 1). An earlier version of this device had no antiproliferative drug coating and was composed of a side-locking design, which prevented deformation and weakening of the polymer during deployment. The initial RESORB study of 27 patients showed disappointing results, with a 6-month late lumen loss of 1.8 mm and a target lesion revascularization rate of 67%, which was driven by vessel recoil. In addition, neointimal hyperplasia response with the Reva device was similar to the bare-metal stent response.[20] Improvements to the stent design (ie, a spiral slide-and-lock mechanism and sirolimus coating) were tested in the RESTORE (n = 50) and RESTORE II (n = 125) trials (ReZolve and ReZolve 2 scaffolds, respectively).[21,22]

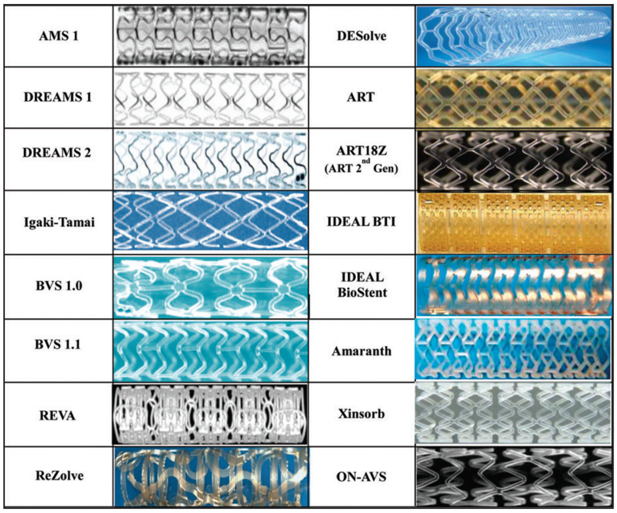

Figure 1. Bioresorbable scaffolds in clinical or preclinical use. (Reproduced with permission from Iqbal J, Onuma Y, Ormiston J, et al. Bioresorbable scaffolds: rationale, current status, challenges, and future. Euro Heart J. 2014;35:765-776.)

Its unique radiopaque polymer makes the ReZolve stents easy to deploy while minimizing the risk of geographical miss and allowing traditional one-step stent implantation (no need for a gradual inflation). Although the results of RESTORE II were encouraging with a 4.5% MACE rate at 6 months (3% target lesion revascularization), the slide-and-lock mechanism hampered the deliverability of the device and pushed the company to feature a conventional balloon-expandable system for its next iteration of the scaffold. The FANTOM study will test a newer version of the scaffold with 125-mm-thick struts and a sirolimus-coated, desaminotyrosine polycarbonate platform, in which 80% of the sirolimus is eluted within 90 days.[23] Preliminary results for the FANTOM II trial, which prospectively enrolled 240 patients, were recently presented at EuroPCR 2016. Acute technical success and clinical procedural success were observed in 96.6% and 99.1%, respectively. In the angiographic follow-up cohort, late lumen loss was 0.29 ± 0.38 mm at 6 months, while MACE occurred in two patients (1.7%).[24]

Ideal BRS: Poly Salicylic Acid Stent

The Ideal BRS (Xenogenics Corporation) is made of polylactide anhydride mixed with a polymer of salicylic acid and sebacic acid (Figure 1). It is coated with sirolimus (8.3 mg/mm) and salicylate, which controls the release of sirolimus. The first-in-man study, WHISPER FIM trial (N = 11) reported suboptimal results secondary to neointimal hyperplasia.[25] It was hypothesized that a suboptimal timing/rapid release of sirolimus was responsible for the negligible suppression of neointimal proliferation. A new generation of the Ideal stent with a better profile and optimized sirolimus dose-release kinetics is in preclinical studies.

ART BRS

The ART BRS (Arterial Remodeling Technologies) is a poly-DL-lactide amorphous polymer without any antiproliferative drug coating that provides structural support for 5 to 7 months and fully resorbs within 18 months (Figure 1). The first-in-man ARTDIVA trial evaluated the safety and efficacy of the ART18Z BRS in 30 patients with single de novo lesions.[26] The 6-month follow-up showed in-stent stenosis diameter of 15 ± 5% and angiographic recoil of 4.3%. Three patients had a target lesion revascularization with no other MACE occurring during the study follow-up.[27]

Xinsorb BRS

The Xinsorb BRS (Huaan Biotechnology) is composed of PLLA polylactide-co-glycolide, and poly-L-lactide-co-ε-caprolactone (Figure 1). It has 160-mm-thick struts and is a fully bioresorbable sirolimus-eluting scaffold, with 80% of the sirolimus (8 mg/mm) released completely within 28 days ex vivo.[28] In the first-in-man trial (N = 30), single de novo coronary lesions were treated with the Xinsorb BRS.[29] The device was successfully implanted in 100% of patients, and the results demonstrated a late lumen loss of 0.17 ± 0.12 mm at 6 months. No change was observed in the percent diameter stenosis after implantation and at 6-month follow-up as assessed by intravascular ultrasound, but the in-scaffold minimal lumen diameter was smaller at 6 months compared to after implantation (2.62 ± 0.25 mm vs 2.44 ± 0.29 mm; *P* = .02).[29] No thrombus was detected at 6-month follow-up as assessed by optical coherence tomography, and 95.9% of the struts were covered by neointima. No MACE or stent thrombosis occurred during the study period.[29]

Mirage Microfiber Sirolimus-Eluting Bioresorbable Vascular Scaffold

The Mirage microfiber sirolimus-eluting bioresorbable vascular scaffold (MMSES) (Manli Cardiology Ltd.) is a PLA-based scaffold that has a unique helix coiled design mounted on three backbones and a biodegradable abluminal coating that releases sirolimus. The MMSES has a strut thickness of 125 mm (stents ≤ 3 mm in diameter) or 150 mm (stents > 3 mm in diameter), and its bioresorption time is nearly 14 months.[30] It possesses both high flexibility and radial strength, it does not require any waiting time for balloon inflation during deployment, and it can stay in the artery without any time limitation before deployment. The first-in-man MIRAGE trial was a prospective randomized trial enrolling 60 patients with single or up to two de novo coronary lesions to receive the MMSES versus the Absorb biovascular scaffold.[30] All of the MMSES devices were successfully implanted. The primary endpoint of 6-month late lumen loss evaluated by quantitative coronary angiography showed no difference between the Absorb and MMSES scaffolds.[30]

Amaranth Fortitude BRS

The Amaranth Fortitude BRS (Amaranth Medical) is a novel polymer resin PLLA scaffold, carrying crystalline and amorphous domain with a high molecular weight that allows for a higher radial strength and better overexpansion capability (Figure 1). The MEND I trial, which studied a 150-mm scaffold in 13 patients, showed a 1-year target lesion revascularization rate of 7.7% and no scaffold thrombosis. The 6-month angiographic follow-up showed a 0.90 ± 0.40 mm late lumen loss.[31] MEND II and RENASCENT are prospective trials in Columbia (MEND II) and Italy (RENASCENT) that enrolled 49 patients with symptomatic coronary artery disease; 9-month follow-up results are expected to be available in mid-2016. Finally, a new Aptitude (Amaranth Medical) 120-µm version is currently being tested in the RENASCENT-II clinical trial, with upcoming results in late 2016.

CONCLUSION

Numerous other bioresorbable vascular scaffolds are currently in development. We have presented only the platforms for which in-human results are available.[32] The quest for a temporary scaffold that could disappear and restore normal vascular function, as well as eliminate the risk of late stent thrombosis while providing deliverability and vessel support as good as the one provided with the current DES will continue for the next several years. If pending current and future investigations provide long-term safety and efficacy results, such devices could eventually contribute to moving interventional cardiology toward the field of preventive interventions, thereby addressing the important issue of vulnerable plaques before they manifest as an acute coronary syndrome. ■

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