Bioresorbable Scaffold
The Emerging Reality and Future Directions

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Abstract: **In the era of drug-eluting stents, large-scale randomized trials and all-comer registries have shown excellent clinical results. However, even the latest-generation drug-eluting stent has not managed to address all the limitations of permanent metallic coronary stents, such as the risks of target lesion revascularization, neoatherosclerosis, preclusion of late lumen enlargement, and the lack of reactive vasomotion. Furthermore, the risk of very late stent, although substantially reduced with newer-generation drug-eluting stent, still remains. These problems were anticipated to be solved with the advent of fully biodegradable devices. Fully bioresorbable coronary scaffolds have been designed to function transiently to prevent acute recoil, but have retained the capability to inhibit neointimal proliferation by eluting immunosuppressive drugs. Nevertheless, long-term follow-up data of the leading bioresorbable scaffold (Absorb) are becoming available and have raised a concern about the relatively higher incidence of scaffold thrombosis. To reduce the rate of clinical events, improvements in the device, as well as implantation procedure, are being evaluated. This review will focus on the current CE-mark approved bioresorbable scaffolds, their basic characteristics, and clinical results. In addition, we summarize the current limitations of bioresorbable scaffold and their possible solutions. (*Circ Res*. 2017;120:1341-1352. DOI: 10.1161/CIRCRESAHA.117.310275.)**

Key Words: bioresorbable scaffold ■ magnesium ■ polymers ■ thrombosis

In the era of drug-eluting stents (DESs), large-scale randomized trials and all-comer registries have shown significant reductions in the need for repeat revascularization. The early enthusiasm has been tempered after widespread concern regarding the increased risk of late (defined as 30 days to 1 year) and very late (after 1 year) stent thrombosis.[1–8] However, second-generation DES solved some parts of these problems by introducing biocompatible or biodegradable polymers and thinner platforms. The frequency of stent thrombosis in the most popular second-generation DES (everolimus-eluting stent) has been reduced to <1% at a mean follow-up of 21.7 months.[9] The NORSTENT trial (Norwegian Coronary Stent Trial) recently reported the lowest 6-year rate of definite stent thrombosis in contemporary DES (0.8%) compared with bare metal stents (1.2%; P=0.0498).[10] Despite these improvements, newer-generation DESs have not managed to address all the limitations of permanent coronary stents, such as the persistent risks of target lesion revascularization and neoatherosclerosis, hindrance of late lumen enlargement, and the lack of reactive vasomotion in the stented vessel. Furthermore, the risk of very late stent thrombosis and its clinical sequelae, although substantially reduced with newer-generation DES, still remains.

These problems were anticipated to be solved with the advent of fully bioresorbable devices. As such, these devices are currently referred to as bioresorbable scaffolds (BRSs) rather than stents. Fully bioresorbable coronary scaffolds have been designed to function transiently to provide mechanical support against acute recoil, but have retained the capability to prevent neointimal proliferation by eluting immunosuppressive drugs. The potential and theoretical benefits of BRS over current metallic stent technology can be summarized as follows: (1) reduction in long-term adverse events from permanent materials; (2) restoration of the pulsatility, cyclic strain, physiological shear stress, and mechanotransduction of the treated vessel through bioresorption; (3) feasibility of noninvasive imaging, such as computed tomographic angiography or magnetic resonance imaging; (4) maintaining suitability for future possible treatment options (either percutaneous or surgical) in multivessel disease and long lesions; (5) implantation in ST-segment–elevation myocardial infarction patients (frequently young patients, less extensive disease); and (6) pediatric applications.[11–21] Although clinical data supporting these potential benefits are still sparse, this new era in interventional cardiology may be viewed as the era of vascular reparative therapy, with fully bioresorbable devices.

Long-term follow-up data of the leading BRS (Absorb) are becoming available and have raised concerns about the relatively higher incidence of scaffold thrombosis (ScT). To reduce the rate of clinical events, procedural and device

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Nonstandard Abbreviations and Acronyms	
BVS	bioresorbable vascular scaffold
DES	drug-eluting stent
OCT	optical coherence tomography
PLLA	poly-l-lactic acid
ScT	scaffold thrombosis
VLScT	very late scaffold thrombosis

improvement are being evaluated. This review will focus on the current CE-mark approved BRSs, their basic characteristics, and clinical results. In addition, we summarized the current limitations of BRS and their possible solution, namely optimized procedure and the next-generation BRSs.

Current CE-Mark Approved BRSs

As of January 2017, 4 products, Absorb, Desolve, ART Pure, and Magmaris scaffolds, acquired the CE mark in Europe. The Absorb scaffold was also approved by Food and Drug Administration in the United States and by Pharmaceuticals and Medical Devices Agency in Japan. An overview of the current status of BRSs is summarized in Online Table I. The most commonly used biodegradable material is poly-L-lactic acid (PLLA; 28 products), followed by magnesium (6 products). Other materials being explored are tyrosine polycarbonate, salicylic acid polymer, and iron. Details of the current CE-mark approved BRS are summarized in Table 1. Device images and appearance on optical coherence tomography (OCT) are presented in Figure 1.

Absorb BVS

The backbone of Absorb bioresorbable vascular scaffold (BVS; Abbott Vascular, Santa Clara, California) is made of a semicrystalline PLLA polymer.[22] The coating consists of the amorphous poly-D,L-lactide, which is a random copolymer of D- and L-lactic acid with lower crystallinity than the BVS backbone and fully bioresorbable. The coating contains and controls the release of everolimus, with a coating-to-drug ratio of 1:1.[23,24] The release kinetics of everolimus in the Absorb is purely diffusion-controlled.[25]

DESolve

The DESolve (Elixir Medical, Sunnyvale, CA) BRS, like the Absorb scaffold, also has a PLLA backbone but elutes the antiproliferative drug, novolimus, an active metabolite of sirolimus. The coating polymer is a biodegradable polylactide-based polymer. The drug–polymer matrix is applied to the surface of the stent, without a primer polymer coating underneath, using a proprietary spray resulting in a coating thickness of <3 μm. The important features of the DESolve distinguishing it from other BRSs are (1) intrinsic self-correcting deployment properties that become operative in the event of minor strut malapposition, and (2) relative elasticity/ductility that provides a wide range of expansion without risk of strut fracture.[26] In a bench test model, the 3.0-mm device did not fracture at diameters up to 5.0-mm postdilatation balloon.[26]

Magmaris

Three iterations of this magnesium device have been tested in the clinical arena[27–30]: The latest generation, Magmaris (BIOTRONIK AG, Buelach, Switzerland), is made of a refined, slower-degradable magnesium alloy and has a modified electropolished strut cross-sectional profile to slow down resorption and to prevent fracture.[27] As an inherent nature of metal, magnesium scaffolds offer good radial strength, low acute recoil, high compliance to the vessel geometry,[31] and can, therefore, be implanted via a single-step inflation. Electropolishing

Table 1. CE-Mark Approved Bioresorbable Scaffolds

Stent Name (Manufacturer)	Stent Platform	Strut Thickness	Coating Material	Coating Thickness	Drug	Reported Release Profile	Drug Dose
BVS 1.1 (Abbott)	PLLA	157 μm	PLLA	2–4 μm	Everolimus	75% of loaded everolimus within 30 days	100 μg/cm^2
DESolve (Elixir)	PLLA	150 μm	Bioresorbable polymer	<3 μm	Novolimus	More than 85% of the drug is released over 4 wk	5 μg/mm
ART Pure (ART)	PDLLA	170 μm	…	…	No drug	NA	NA
Magmaris (Biotronik)	93% Mg and 7% rare earth elements	150 μm	PLLA	1 μm	Sirolimus	Over 3 to 6 mo	1.4 μg/mm^2

BVS indicates bioresorbable vascular scaffold; NA, data not available; PDLLA, poly(L-lactide-co-D,L-lactide); and PLLA, poly-L-lactide.

Table 2. Mechanical Properties and Degradation Time for Different Polymers and Metals

Composition	Tensile Modulus of Elasticity, Gpa	Tensile Strength, Mpa	Elongation at Break, %	Degradation Time, mo	Products
Poly (L-lactide)	3.1–3.7	60–70	2–6	>24	Absorb (platform), DESolve (platform), Magmaris (coating)
Poly (D,L-lactide)	3.1–3.7	45–55	2–6	6–12	Absorb (coating)
Magnesium alloy	40–45	220–330	2–20	1–3	Magmaris (platform)
Cobalt chromium	210–235	1449	≈40	Biostable	Xience

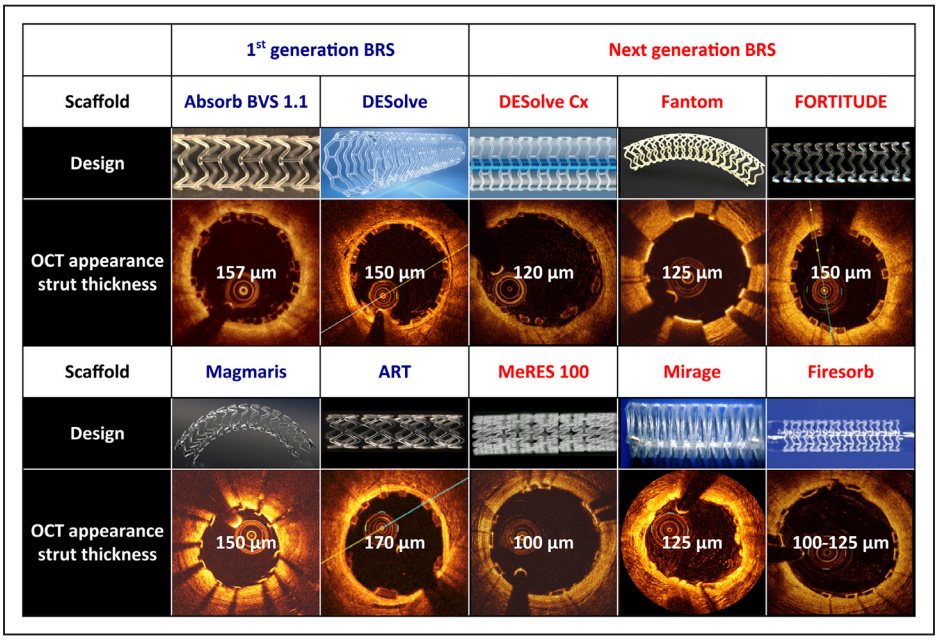

Figure 1. Design and optical coherence tomography (OCT) appearance of first and next generation bioresorbable scaffolds (BRSs).

of magnesium scaffolds produces soft, rounded edges for good trackability, deliverability, and flow dynamics.

Bioresorption Process

The current BRSs are composed of either a polymer or bioresorbable metal alloy. Numerous different polymers are available, each with different chemical compositions, mechanical properties, and subsequent bioresorption times.[32,33] The most frequently used material in the current generation of BRS is PLLA, followed by magnesium (Table 2). These polymer-based and metal-based alloys have inherently different behaviors in vitro and in vivo. Among the CE-marked

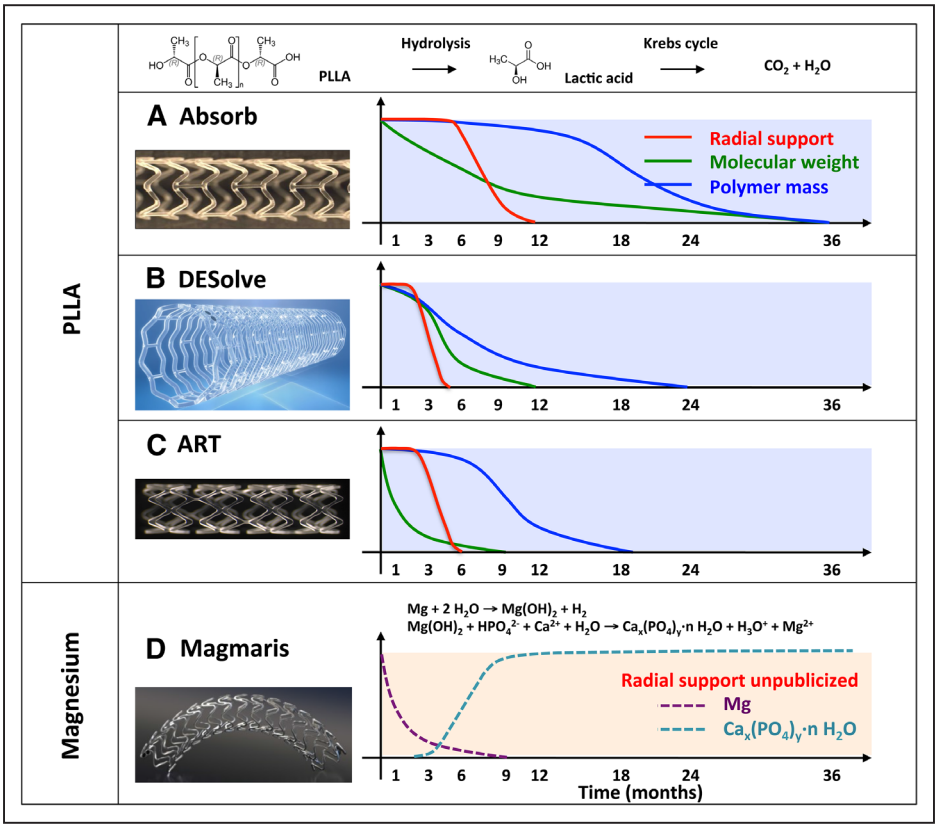

Figure 2. Biodegradation process of CE-mark approved bioresorbable scaffolds. References: (**A**) Absorb,[37,38] (**B**) DESolve,[39,40] (**C**) ART,[41] and (**D**) Magmaris.[42,43] PLLA indicates poly-L-lactide.

BRSs, Absorb, Desolve, and ART Pure are made of PLLA, whereas Magmaris uses magnesium.

Poly-L-Lactic Acid

PLLA is a semicrystalline polymer: –[–O–CH(CH3)–CO–]n–. The ordered polymer chains constitute the crystalline component of the semicrystalline polymer, whereas the random polymer chains form the amorphous segment.[34] In other words, the semicrystalline PLLA polymer is made of crystal lamella (regions with high concentrations of polymer with crystalline structure) interconnected by amorphous tie chains binding the crystallites. Because of the properties of semicrystalline polymers, they are used predominantly for mechanical support (ie, the scaffold backbone), whereas amorphous polymers allow a more uniform dispersion of the drug and are therefore preferred for usage in controlled drug release systems (eg, coating). PLLA is converted to lactate through hydrolysis. Lactate is in turn converted to pyruvate, which eventually enters the Krebs cycle and is further converted into carbon dioxide and water. These final products are excreted from the body through kidney (H_2O) or lung (CO_2), which results in complete bioresorption of the implant.[35] Remaining particles smaller than 2 µm are phagocytosed by macrophages. Thus, the final products of the biodegradation are removed by cells, which would normally be involved in inflammation (activation of macrophage).[36,37] The bioresorption process of the 3 PLLA products is summarized in Figure 2A through 2C.

Magnesium

Several elements, such as aluminum, calcium, manganese, rare earth elements, yttrium, zinc, and zirconium, can be combined with magnesium to modify the mechanical properties (eg, radial strength, hardness) and physical characteristics (eg, degradation speed) of the magnesium-based alloy.[44–46] The magnesium alloy used in the BIOTRONIK scaffold (Magmaris) offers higher deformation resistance and lighter weight compared with pure magnesium.[44,47]

Two phases have been described in the degradation.[45] The first phase is the anodic reaction of the magnesium alloy in water, resulting in magnesium hydroxide. The second phase is the conversion of magnesium hydroxide to a calcium phosphate phase via a magnesium (hydrogen) phosphate phase. The final phase consists mainly of amorphous calcium phosphate with high water content. Only a small portion of the original strut areas is converted to magnesium oxide/hydroxide after 90 days, and the complete conversion of the implanted material to an amorphous calcium phosphate with high water content requires up to 360 days (Figure 2D).

Summary of Clinical Outcomes of BRSs

After the approval of BRS by the European Commission, several randomized clinical trials and observational registries have been performed. Most of the data available on clinical outcomes stem from the first CE-marked BRS, the Absorb BVS. There is limited clinical evidence beyond 1 year with DESolve, ART Pure, and Magmaris.

Absorb

Six randomized clinical trials (n=3738) comparing the Absorb BVS with everolimus-eluting metallic stent (EES) have been conducted. Five of these trials (ie, ABSORB II, ABSORB III, ABSORB China, ABSORB Japan, and EVERBIO II [Everolimus- Versus Biolimus-Eluting Stents in All-Comers])[48–51] included patients presenting with stable ischemic heart disease, whereas one study (ie, TROFI II)[52,53] included patients with ST-segment–elevation myocardial infarction . At 1-year follow-up, the results of each study suggested that there were no differences in the rates of the composite patient-oriented and device-oriented adverse events between devices. Nevertheless, a meta-analysis found an increase in the risk of target-vessel myocardial infarction with Absorb BVS compared with EES (relative risk, 1.45 [95% confidence interval {CI}, 1.02–2.07]; *P*=0.04), mainly because of periprocedural myocardial infarction (relative risk, 1.29 [0.82–2.03]; *P*=0.27) and device thrombosis (relative risk, 2.09 [0.92–4.75]; *P*=0.08).[54] Plausible mechanisms of the early thrombotic hazard observed with Absorb BVS included rheological alterations caused by the thick struts of the scaffold, as well as technical factors during implantation.[55]

Recently, long-term data concerning long-term outcomes have started to emerge from randomized clinical trials. Toyota et al[56] conducted a meta-analysis of 24 studies (BVS: n=2567 and EES: n=19 806) reporting the 2-year outcomes. This meta-analysis demonstrated that BVS compared with EES was associated with higher risk for ScT through 2 years (odds ratio, 2.08 [95% CI, 1.02–4.26]) and for very late scaffold thrombosis (VLScT) between 1 and 2 years (odds ratio, 2.03 [95% CI, 0.62–6.71]). Moreover, the long-term outcomes (>2 years) of 1730 patients included in the randomized controlled trials (ABSORB II, ABSORB China, ABSORB Japan, TROFI II, and EVERBIO II) have confirmed an extended risk of adverse events with Absorb BVS. The risk of the composite end point of device-oriented adverse events was higher in patients treated with Absorb BVS compared with EES (Peto odds ratio, 1.47 [95% CI, 1.00–2.17]; *P*=0.05). Furthermore, a higher risk of target vessel myocardial infarction, ischemia-driven target lesion revascularization, and ScT was observed in patients treated with Absorb BVS (Figure 3). No difference was observed in the risk of cardiac death. Notably, VLScT occurred in 12 of 996 (1.4%) patients treated with Absorb BVS compared with 1 of 701 (0.5%) patient treated with EES (Peto odds ratio, 3.89 [95% CI, 1.30–11.62]; *P*=0.02). The unexpected relatively high rate of VLScT seen with Absorb BVS represents a drawback for this technology. Although large-scale randomized trials are still ongoing, the debate surrounding the mechanism underlying VLScT centers around the possible influence of the implantation technique on very late outcomes as opposed to the impact of late scaffold discontinuities observed during the biodegradation process.[49,57]

DESolve

The first iteration of the DESolve myolimus-eluting scaffold was tested in a small first-in-man trial (n=16). The late lumen loss at 6 months was 0.19±0.19 mm, which is similar to that seen with contemporary DES.[39] The second iteration of the DESolve scaffold was assessed in the DESolve Nx trial. Late lumen loss at 6 months was 0.20±0.32 mm; MACE rate at 24 months was 7.4%. No definite scaffold thromboses were observed.[58]

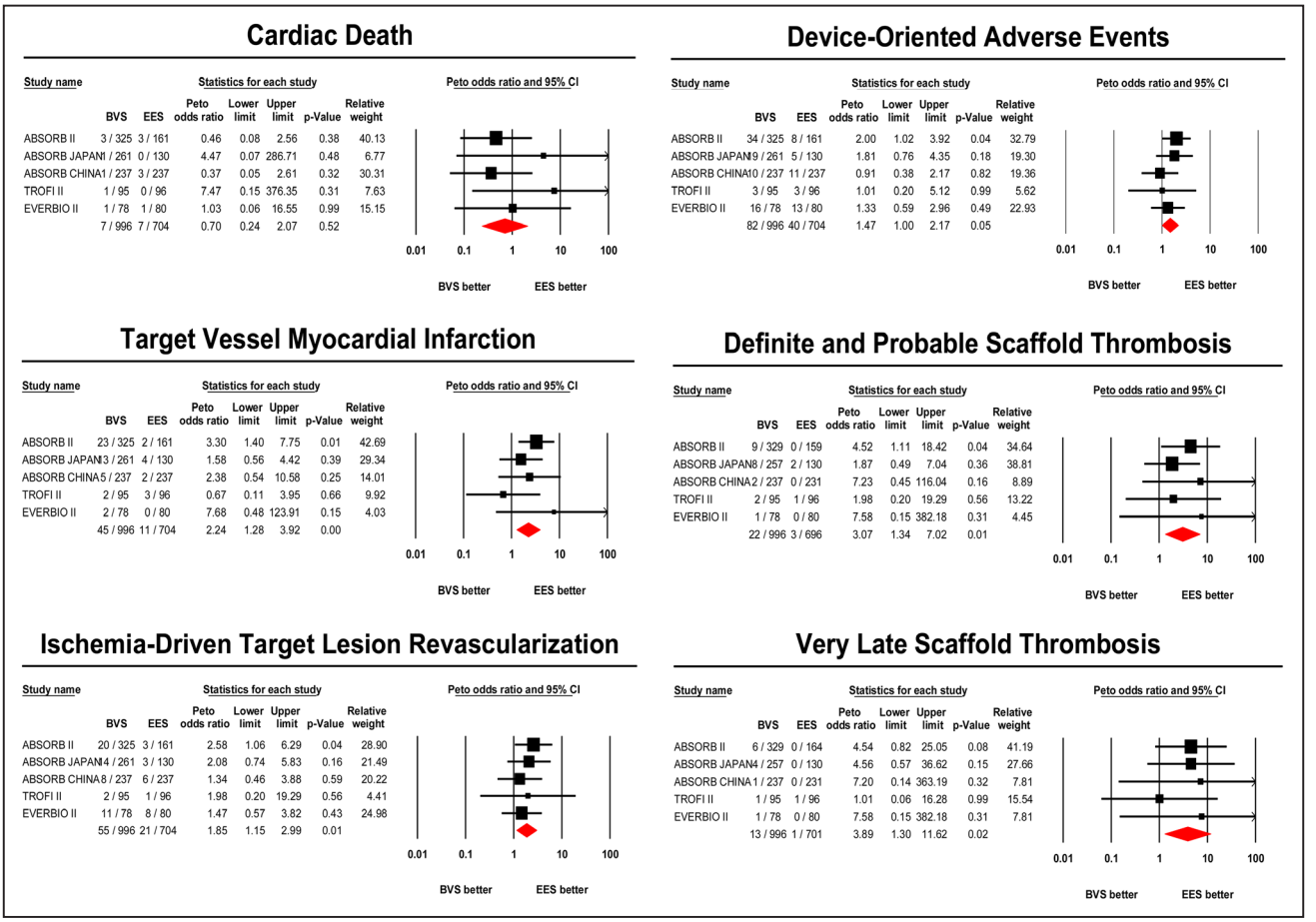

Figure 3. Meta-analysis of recent Absorb trials. Including randomized clinical trials comparing the Absorb and the Xience metallic stent with at least 24 months of follow-up, a study level meta-analysis showed an increased risk of the composite end point of device-oriented adverse events in patients treated with Absorb (Peto odds ratio, 1.47 [95% confidence interval, 1.00–2.17]; *P*=0.05). Also, a higher risk of target vessel myocardial infarction, ischemia-driven target lesion revascularization, and scaffold thrombosis was observed in patients treated with Absorb. No difference was found in the risk of cardiac death. BVS indicates bioresorbable vascular scaffold; CI, confidence interval; and EES, everolimus-eluting metallic stent.

ART Pure

There are few clinical data concerning the ART Pure scaffold. The ARTDIVA trial (Arterial Remodeling Transient Dismantling Vascular Angioplasty), a first-in-man trial enrolling 30 patients, demonstrated 1 case of ischemic-driven target lesion revascularization at 6 months.[41] No other clinical result is available to date.

Magmaris

The first iteration of this paclitaxel-eluting scaffold (DREAMS-I [drug-eluting absorbable metal scaffold]) was assessed in the BIOSOLVE-I trial that enrolled 46 patients with 47 lesions at 5 European centers.[30] At 3-year follow-up, 3 target lesion failures occurred (6.6%), consisting of 2 clinically driven target lesion revascularizations that were performed at scheduled 6-month angiography (4.3%) and 1 myocardial infarction after drug-eluting balloon treatment in a nontarget lesion in a nontarget vessel that occurred at 12-month angiography (2.2%). No cardiac death or ScT occurred.[29]

The latest iteration of this sirolimus-eluting magnesium scaffold (DREAMS 2G, marketed as Magmaris) was assessed in the prospective, international, multicenter, first-in-man BIOSOLVE II trial (N=123).[28] In-scaffold late lumen loss was 0.39±0.27 mm at 12-month follow-up. Target lesion failure occurred in 4 patients (3.4%), consisting of 1 death of unknown cause, 1 target-vessel myocardial infarction, and 2 clinically driven target lesion revascularizations. During the entire 12-month follow-up, none of the patients experienced a definite or probable ScT.[27] The long-term clinical outcome is still to be demonstrated.

Current Limitations

Mechanical Integrity

The mechanical properties of bioresorbable materials are inherently different from those of such metal alloys as cobalt chromium or stainless steel that are used for permanent implants. Presently, BRS materials have 3 primary limitations.

- Insufficient ductility, which impacts scaffold retention on balloon catheter and limits the range of scaffold expansion during deployment;
- Low tensile strength and stiffness, which require that struts be thick to prevent recoil during vessel remodeling[2,3,7,8];
- Limited elongation-to-break, which defines the expansion range of scaffold.

Material properties of PLLA and magnesium in comparison with cobalt chromium are summarized in Table 2. Because of

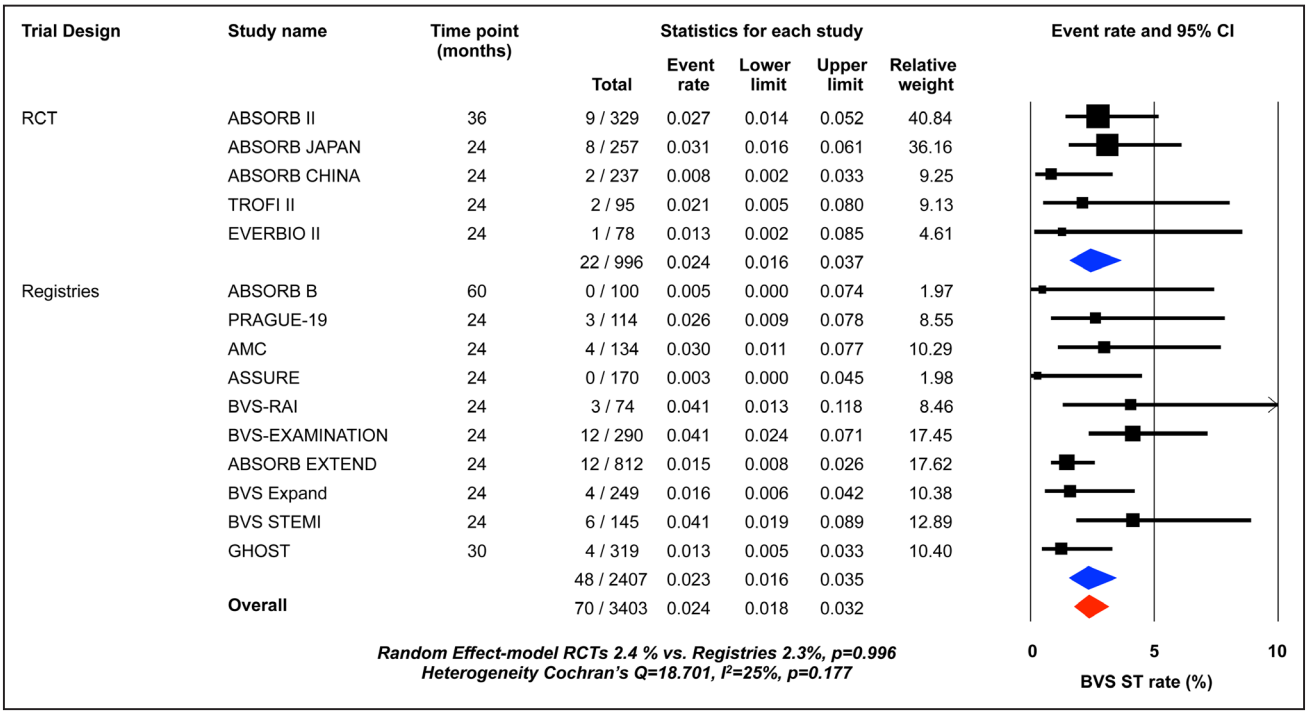

Figure 4. Rate of scaffold thrombosis in randomized controlled trials (RCTs) and registries with at least 24-month follow-up. A pooled analysis of randomized and observational studies showed a rate of scaffold thrombosis of 2.4% (95% confidence interval [CI], 1.8–3.2), with no difference between randomized and observational registries. BVS indicates bioresorbable vascular scaffold.

these inherent limitations, the implantation technique for BRS is different from the metallic stent. Specifically, it necessitates more precise preprocedural sizing of the vessel and potentially postprocedural optimization using intravascular imaging as discussed in the following paragraph. Larger strut thickness leads to a larger profile of the device, resulting in difficulty delivering the device through tortuous and noncompliant arteries. Consequently, the crossing profiles (diameters of BRS when they are crimped on the delivery balloon) are inferior to those of their slimmer and more flexible metallic comparators. To enhance the mechanical integrity of polymeric materials, several processing techniques are applied to the material. Annealing, extrusion, spinning, microbraiding, etc are being intensively investigated as potential solutions.

Clinical Concerns

It was anticipated that ScT in the late and very late phases after DES implantation would be solved with the advent of fully BRSs. However, recent long-term follow-up data of Absorb from randomized trials and observational studies show the worrisome signal of a higher thrombotic risk.[48,49,59] A pooled analysis of randomized and observational studies with at least

Table 3. Next Generation BRSs With Thinner Struts (≤150 μm)

Device	Strut Thickness	Backbone	Coating	Antiproliferative Drug	Drug Dose	Complete Erosion of Polymer by
DESolve Cx	120 μm	PLLA	Biodegradable polymer	Novolimus	5 μm/mm	Uncages the vessel within 6 mo, degrades within 1 y, and resorbs within 2 y
Fantom	125 μm	Desaminotyrosine polycarbonate with iodine atoms	Same as backbone	Sirolimus	115 μg (for 3.0×18 mm scaffold)	>80% within 1 y; complete resorption within≈3 y
MeRes 100	100 μm	PLLA	PDLLA	Sirolimus	1.25 μg/mm²	50% at 4 to 6 mo; complete resorption by 2 y
FORTITUDE	150 μm	Ultra-high-molecular-weight PLLA	PDLLA	Sirolimus	101 to 160 μg (depending on scaffold size)	10 mo
Mirage	125 μm	PLLA: D(Dextro-rotary)-isomer is <5% of the total PLA	PLLA	Sirolimus	NA	Approximately 14 mo
Firesorb	100–125 μm	PLLA	PDLLA	Sirolimus	4 μg/mm	3 y

(*Continued*)

24-month follow-up reported a rate of ScT of 2.4% (95% CI, 1.8–3.2), with no difference between randomized and observational registries (Figure 4). The ongoing trials (ABSORB III [NCT01751906], ABSORB IV [NCT02173379], AIDA [NCT01858077], and COMPARE ABSORB [NCT02486068]) will further provide evidence on the late clinical outcomes.

To shed light on the apparent controversy, a systematic review of all reported ScT cases analyzed by intracoronary imaging was conducted.[60] In 17 early scaffold thromboses, malapposition (24%), incomplete lesion coverage (18%), and underdeployment (12%) are most frequent findings, whereas in 26 late/very late cases, malapposition (35%), late discontinuity (31%),[61] and peri-strut low-intensity areas (indicating the presence of neointima [19%])[62] were the predominant features.[37,60] To minimize the potential risk of ScT, it is important that operators try to avoid abnormalities, such as malapposition, incomplete lesion coverage, underdeployment, and acute disruption, at the time of implantation.[60,63] However, late discontinuity and peri-strut low-intensity areas may be less likely to be modified by an optimized implantation strategy.

Late discontinuity is theoretically a benign change during the bioresorption process and does not cause any problems if the scaffold struts are well covered by neointima.[57] However, whenever struts are not covered by neointima and late discontinuity allows protrusion of part of the struts into the lumen and brings thrombogenic proteoglycan (provisional matrix) into contact with blood, late discontinuity could be a malignant potential cause of VLScT.[60] Uncovered areas of late discontinuity could be critical, whereas late discontinuity itself would not be a culprit of ScT. Peri-strut low-intensity areas visualized by OCT might be related to biological responses that occur during polymer degradation, hypersensitivity reactions, and inflammatory responses against either the polymer components or the cytostatic agents during bioresorption.[37] However, the pathological correlates of peri-strut low-intensity area and its clinical significance still need to be investigated. Because long-term data are not yet available for the other BRS products, the above issues may be unique to the Absorb scaffold.

Future Directions

There are 2 aspects of BRS that lend themselves to improvement. One is to improve the device itself, and the other is to improve the implantation techniques, to improve management of patient comorbidities, and to optimize antithrombotic therapy.

Device Improvement

The design of newer generation devices is aimed at producing thinner struts and a smaller crossing profile compared with the currently available BRS. The next-generation BRSs with thinner struts are summarized in Figure 1 and Table 3. Several trials evaluating BRS with thinner struts (DESolve Cx [DESolve Cx novolimus-eluting BRS, Elixir; 120 μm],[64] FANTOM II [Fantom sirolimus-eluting BRS, Reva Medical; 125 μm],[65] MeRes-1 [MeRes100 sirolimus-eluting BRS, Meril Life Sciences; 100 μm],[66] FORTITUDE [Fortitude sirolimus-eluting BRS, Amaranth Medical; 150 μm],[67] and FUTURE-I [Firesorb sirolimus-eluting BRS, Shanghai MicroPort Medical; 100–125 μm])[68] are recently reported.[69]

- The DESolve Cx trial (n=25) demonstrated late lumen loss of 0.18±0.29 mm at 6 months' follow-up with no cardiac death, no target vessel myocardial infarction, no clinically indicated target lesion revascularization, and no stent thrombosis.[64]
- The FANTOM II trial (n=240) reported that over 6 months, there were 5 major adverse cardiac events, including 1 cardiac death.[65] On quantitative coronary angiography analysis, in-scaffold late lumen loss was 0.25±0.40 mm and in-segment late lumen loss was 0.17±0.34 mm. OCT showed 98.1% struts covered at 6 months.
- In the MeRes-1 trial (n=108), there were no major adverse cardiac events or scaffold thromboses within 6 months.[66] On quantitative coronary angiography analysis, in-scaffold reference vessel diameter was 3.06±0.39 mm and in-scaffold minimum lumen diameter was 2.67±0.40 mm. In-scaffold late lumen loss at 6 months was 0.15±0.23 mm. OCT analysis showed 99.3% of struts covered at 6 months.
- In the FORTITUDE trial (n=62), at 9 months, in-segment minimum lumen diameter was 2.4±0.5 mm and in-segment

Table 3. Continued

Remarks	Latest Clinical Trial	Follow-Up	In-Scaffold LLL	Clinical Results	ScT	Reference
Self-correction/robust overexpansion capability	DESolve Cx (n=25)	6 mo	0.18±0.29 mm	No MACE/no ScT	No event	64
Complete scaffold visibility under x-ray	FANTOM II (n=240)	6 mo	0.25±0.40 mm	MACE 5 (2.1%)	NA	65
Crossing profile of 1.2 mm for 3.00 mm device	MeRes-1 (n=108)	6 mo	0.15±0.23 mm	No MACE	No event	66
Elongation at break >10× typical PLLA	FORTITUDE (n=62)	9 mo	0.17±0.49 mm	TVF 3 (4.8%)	NA	67
Tensile strength 210 Mpa; elongation at break >20%	MIRAGE RCT (Mirage n=31 vs Absorb n=29)	12 mo	0.48±0.49 mm	DOCE 16.9%	1 subacute ScT	70
Abluminal coating	FUTURE-I (n=45)	6 mo	0.15±0.11 mm	POCE 1 (2.2%)	No event	68

DOCE indicates device-oriented composite end point; MACE, major adverse cardiac event; NA, data not available; PLLA, poly-L-lactide; PDLLA, poly(L-lactide-co-D,L-lactide); POCE, patient-oriented composite end point; RCT, randomized controlled trial; ScT, scaffold thrombosis; and TVF, target vessel failure.

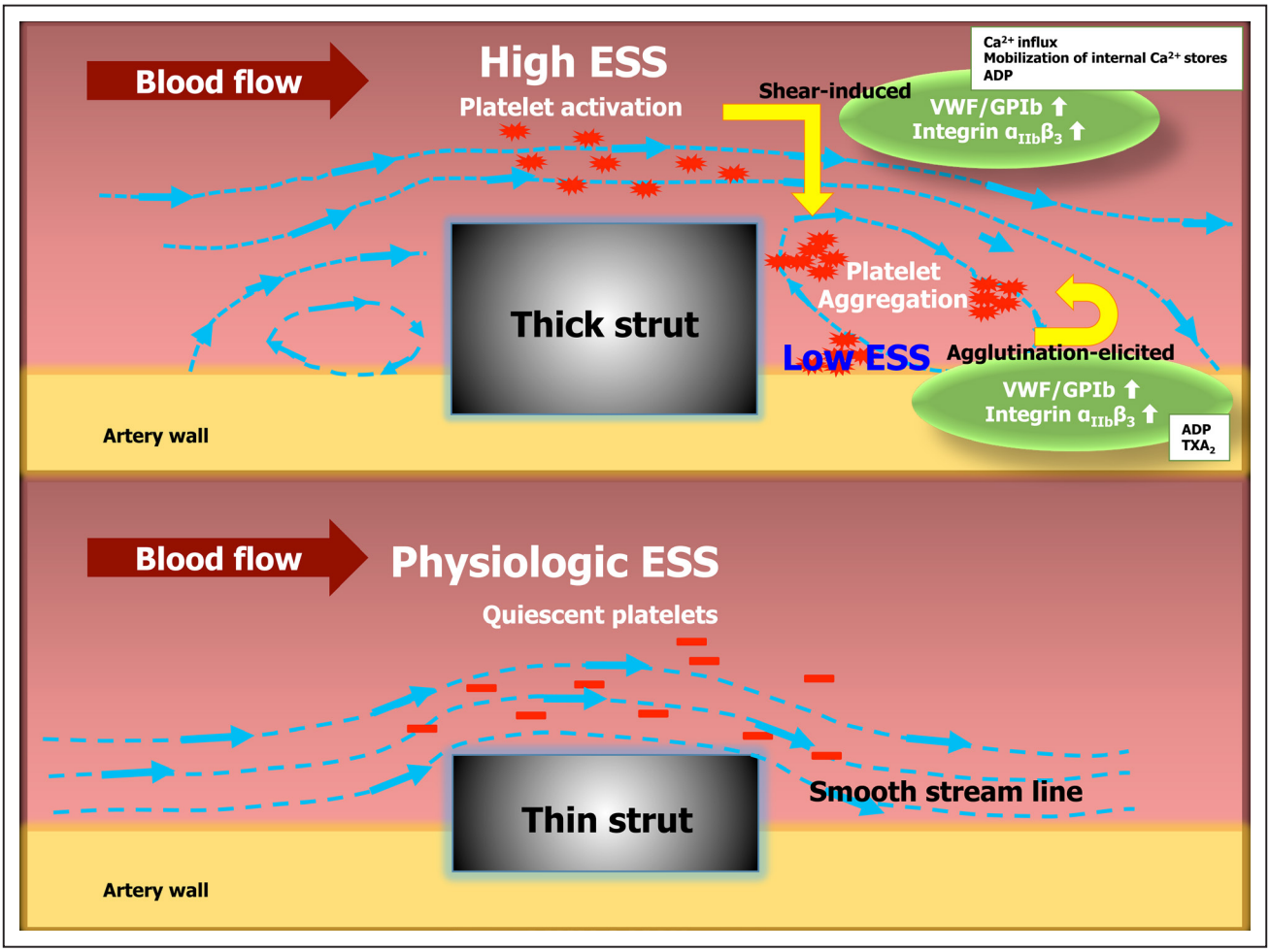

Figure 5. Strut thickness and platelet activation. The thick protruding strut disrupts the laminar flow and induces flow disturbances, and thereby endothelial shear stress (ESS) microgradients (**upper panel**). The shear microgradients can induce the formation of stabilized discoid platelet aggregates, the size of which is directly regulated by the magnitude and spatial distribution of the gradient.[72,73] Shear microgradient–dependent platelet aggregation requires 3 principal features: shear acceleration phase, peak shear phase, and shear deceleration phase. During shear acceleration, platelets in the central regions of blood flow exposed to laminar flow (constant physiological shear) are suddenly accelerated through the shear microgradient. During the peak shear phase, a proportion of the discoid platelets that are accelerated into the peak shear zone adhere to exposed thrombogenic surfaces through platelet membrane glycoprotein (GP) Ib/IX/V. Exposure of these platelets to elevated hemodynamic drag leads to the extrusion of thin filamentous membrane tethers. Membrane tether formation initiates discoid platelet adhesion with the thrombogenic surface and also facilitates the recruitment of discoid platelets into the downstream deceleration zone. During the shear deceleration phase, platelets transitioning into the flow deceleration zone experience decreasing hemodynamic drag forces. Reduced shear within this zone progressively favors the formation of integrin $\alpha_{IIb}\beta_3$ adhesion contacts. Integrin $\alpha_{IIb}\beta_3$ engagement is associated with low-frequency calcium spikes that trigger tether restructuring, leading to the stabilization of discoid platelet aggregates. Ongoing discoid platelet recruitment drives the propagation of the thrombus in the downstream deceleration zone, which may in turn amplify the shear microgradient and promote further platelet aggregation. Thus, the shear microgradients caused by the thick struts induce platelet aggregation, formation of microthrombi with potential embolization, and micromyocardial necrosis (so-called a nidus of thrombus). The magnitude of flow disturbance depends on the degree of protrusion of the strut into the lumen. Therefore, thin struts could be a potential solution for the less flow disturbance and thus less thrombogenic status (**lower panel**). There is another cascade of von Willebrand factor (VWF)/GPIb activation, namely agglutination-elicited GPIb signaling.[73] In contrast to shear stress–induced GPIb-elicited signaling, agglutination-elicited GPIb signaling that activates integrin $\alpha_{IIb}\beta_3$ requires thromboxane A_2 (TXA_2). Agglutination-elicited TXA_2 production is independent of Ca^{2+} influx and mobilization of internal Ca^{2+} stores.

late lumen loss was 0.17±0.49 mm on quantitative coronary angiography.[67] In-scaffold late lumen loss was 0.27±0.41 mm. There were 3 cases of target vessel failure, 1 noncardiac death, 2 target-vessel myocardial infarctions, 1 ischemia-driven target lesion revascularization, and no evidence of scaffold thrombosis over 9 months.

- The MIRAGE randomized controlled trial (n=31) with a comparator of Absorb (n=29) presented in-scaffold late lumen loss of 0.48±0.49 mm.[70] Device-oriented composite end point (Kaplan–Meier estimate at 12 months) was 16.9%. Clinical event rates were comparable between both arms.
- In the FUTURE-I trial (n=45), a postprocedural recoil of Firesorb was 0.13±0.10 mm.[68] Six-month follow-up observation demonstrated in-scaffold late lumen loss of 0.15±0.11 mm and no binary restenosis. On OCT, the proportion of covered struts was 93% in all patients and 100% in 7 patients.

Of note, these results are still limited to short-term follow-up and polymeric scaffolds. There is a lack of long-term data of magnesium scaffolds.

The first-generation BRSs have thick struts, which compromises the practical deliverability of the device and disrupts laminar flow. Disturbed endothelial shear because of dense and thick struts may serve as a stimulus for thrombus (Figure 5).[71] Thicker struts also take a longer time to be covered by neointima, resulting in the direct contact of products of polymer with blood. On the basis of the intracoronary imaging features observed in scaffold thrombosis cases, thinner struts and fast absorption characteristics could be a key to a solution of the issue. Refinement of device with thinner struts, while preserving strong radial force because of new postprocessing of the polymer seems promising and could reduce the risk of BRS-specific issues. Many companies and researchers are struggling to improve the products. Like the drawbacks of the first-generation DES that have been overcome in the past, it is likely that improvements of the second-generation BRS will represent an enormous technological leap.

Procedural Improvement

Because the clinical data concerning BRSs other than Absorb are sparse, the following issues are have resulted from observations confined to the Absorb BVS. Recent interest in the interventional community concerns whether the clinical outcomes can be improved by developing a BVS-specific implantation technique. To investigate the optimal implantation technique for implanting BRS, we have been investigating the influences of device sizing and implantation techniques on acute device performance indices, including acute gain, expansion index, asymmetry index, eccentricity index, and strut embedment.[74–78] Optimal predilatation and postdilatation are likely to improve the expansion index of the device.[77] A BVS-specific implantation strategy has shown to reduce the rate of scaffold thrombosis from 3.3% to 1.0%, an effect that remained significant after multivariate adjustment including propensity score (hazard ratio, 0.19 [95% CI, 0.05–0.70]; P=0.012).[55] The BVS-specific implantation strategy differs in several ways from that used for permanent metallic stents and can be summarized as follows:

1. Predilatation with a noncompliant balloon up to the same size as the reference vessel diameter.BVS implantation only in case of full expansion of the noncompliant angioplasty balloon as demonstrated by angiography in 2 orthogonal planes.
2. Implantation of a BVS of the same size as the reference vessel diameter at 10 to 12 atm.
3. Postdilatation with noncompliant balloons up to a maximum of 0.5 mm larger at 14 to 16 atm.

Although improvement in clinical results by BVS-specific implantation strategy was suggested by the observational studies,[55,79] it has not been proved by dedicated studies. To answer conclusively the question as to whether the BVS-specific implantation technique may overcome the increased risk of clinical events, a randomized controlled trial would be required with a metallic DES control group, as well as a BVS control arm without a dedicated implantation strategy. Such a study is, however, unlikely to be performed with current generation of BVS and, as a result, we need to analyze current and ongoing trials carefully.[80] Lack of the data of magnesium scaffold does not allow us to discuss this kind of issue yet.

Patient Management

Regarding the duration of dual antiplatelet therapy (DAPT), the latest American guideline recommends as follows[81]: In patients with stable ischemic heart disease treated with DES implantation, DAPT should be continued for at least 6 months, whereas in patients with acute coronary syndrome treated with DES implantation, DAPT should be continued for at least 12 months. For the time being, the optimal duration of DAPT for BRS should also follow the same recommendation. Nevertheless, the recent worrisome results of increased VLScT rate in BVS trials would favor the prolonged duration of DAPT for BVS. Optimal duration for BRS still needs to be investigated.

Cardiovascular risk factors (dyslipidemia, hypertension, and diabetes mellitus) must be strictly controlled in all patients, independently from BRS implantation.

Conclusions

Vascular reparative therapy has become a reality with BRSs. However, recent large trials evaluating clinical results of BRS raised concerns about the safety and efficacy of these devices. Intensive research in the field is being conducted, stimulating the development of the next-generation BRS and the improvement of implantation techniques. As we saw a huge leap from first- to second-generation drug-eluting metallic stents, the upcoming generation of BRS with thinner struts would be the most promising development to overcome the current limitations.

Disclosures

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