



Review article

Bioresorbable Scaffolds: The Revolution in Coronary Stenting?

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Abstract: Bioresorbable scaffolds (BRS) represent the latest revolution in interventional cardiology. Thanks to their reabsorptive properties, they provide temporary scaffolding that helps stabilizing the plaque and promotes healing, and then disappear, thus restoring a functional endothelium and vasomotion. Several devices have been tested at the preclinical and clinical stage. Here we review the rationale, development, design and clinical data of the BRS platforms, providing a comprehensive review of the literature.

Keywords: bioresorbable vascular scaffold; bioabsorbable scaffold; percutaneous coronary intervention; coronary stenting

1. A Historical Perspective

In September 1977, Andreas Grüntzig, an ambitious young cardiologist from Zurich, performed the first coronary angioplasty on a severe stenosis of the left anterior descending artery in a conscious patient. The underlying concept was that the dilatation of the coronary stenosis using an inflatable balloon would allow redistribution of the atheroma (like “crushed snow”), and hence decrease in the degree of stenosis. The procedure was a complete success, and the patient—now asymptomatic—was soon discharged [1].

However, this technique was plagued by several problems, including the non-negligible risk of acute vessel closure (4–8%, due to occlusive dissection, and often requiring coronary artery bypass surgery, (CABG) [1,2] and high incidence of restenosis on mid-to-long term (\approx 30–60%, due to elastic recoil and constrictive remodeling) [3–5]. These *mechanical* problems required a *mechanical* solution. In the late 1980's, different groups in both the U.S. and Europe independently developed metal “sleeves” that could be crimped onto balloon catheters, carried across the lesion and delivered by means of balloon expansion, in order to support vessel wall and prevent the collapse of the artery. These “stents”—such as the Gianturco-Roubin [6] and the Palmaz-Schatz [7] devices—represented an elegant solution to both vessel dissection and, to some extent, restenosis. However, these novel devices introduced new problems and complications, such as embolization from the balloon catheter and subacute stent thrombosis (ST) [8,9]. Technical improvements in the stents [10–12], the implantation technique (high-pressure post-dilatation) and adjuvant medical therapy (aspirin and ticlopidine) [13] allowed improved outcomes. However, with the widespread adoption of coronary stenting, including challenging clinical settings, the rates of subacute ST (1%) and restenosis (16–44%) were still a concern [14,15].

Since the development of the platform of these “bare-metal” stents (BMS) was approaching technical limits, the answer to these problems would come from a pharmacological approach, in the form of a surface coating and a drug delivery system. In particular, the addition of an antiproliferative compound, which would be released over the course of several months, would minimize the exuberant smooth muscle tissue growth within the stent. Indeed, the first-generation drug-eluting stents (DES)—sirolimus-eluting Cordis CypherTM and paclitaxel-eluting Boston Scientific TaxusTM—showed very low rates of restenosis (\approx 10%). These promising results led to a widespread adoption of DES and an increase in clinical indications of percutaneous coronary intervention (PCI). The introduction of the novel drug-eluting concept uncovered a new type of complication: late and very late ST. In fact, the uncontrolled antiproliferative effect of first-generation DES was associated with delayed endothelialization and persistent inflammation, which in turn triggered ST at medium-to-long-term follow-up. All-comer registries showed a steady incidence of ST of 0.5% per year, which reached 3% at 4 years [16,17]. Improvements in drug choice, release and concentration, as well as in the polymer delivering the drug and in strut thickness, led to a marked mitigation of this complication, with reassuring ST rates of 1% at 3 years [15]. Additionally, these second-generation DES (e.g., Abbott Vascular Xience VTM and Boston Scientific Promus ElementTM) were also associated with even lower rates of restenosis (4% at 2 years) [18].

Despite these improved results, the concept of metallic stenting has several intrinsic drawbacks. Firstly, with the widespread increase in the volume of PCIs, together with the increasing life expectancy of the population, we have been witnessing an increase in the complexity of clinical scenarios where coronary stenting is now required. For example, it is not uncommon to encounter patients with a restenosed metallic stent, which had been in turn implanted to treat a first episode of restenosis. In this setting, the addition of a third layer of metallic stent does not look appealing.

Secondly, extensive stenting of distal vessels precludes further treatment with CABG (grafts cannot be anastomosed on metal-laden arteries). Thirdly, vasomotion tests have showed abnormal vasoconstriction in response to acetylcholine and exercise distally to the deployed metallic stent, suggesting that endothelium structure and function is abnormal following stent implantation [19,20]. Fourthly, metallic stenting of bifurcations has been associated with permanent jailing of side branches ostium. Finally, late lumen loss (LLL) and delayed endothelialization/persistent inflammation can still be improved beyond the limits reached with second-generation DES, thus reducing even further the risk of restenosis and ST [21].

The answer to all these limitations could be represented by temporary scaffolding of the diseased coronary segment by means of so-called “bioresorbable scaffolds” (BRS). Specifically, BRS could provide the advantages of metallic stents (i.e., plaque modification and stabilization, sealing of dissection, etc.) for several months, thus promoting vessel healing; when this is achieved, they would start the reabsorption process, leaving no trace of their previous presence behind (therefore avoiding the aforementioned long-term shortcomings of metallic stents). For these reasons, BRS have been considered the fourth revolution in the history of interventional cardiology [21,22]. Table 1 compares balloon angioplasty, BMS, DES and BRS.

Table 1. Theoretical advantages of BRS over plain old balloon angioplasty (POBA), bare-metal stents (BMS) and drug-eluting stents (DES).

	POBA	BMS	DES	BRS
Acute occlusion	–	+	+	+
Acute recoil	–	+	+	+
Acute thrombosis	–	–	–	–
Sub-acute thrombosis	+/-?	–	–	–
Late/very late thrombosis	+	–	–	+/-?
Neointimal hyperplasia	–	–	+	+
Constrictive remodeling	–	+	+	+
Expansive remodeling	+	–	–	+
Restoration of vasomotion	+	–	–	+
Late luminal enlargement	+	–	–	+

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2. History of the Development of BRS

The idea of developing a bioresorbable scaffold was conceived \approx 25 years ago. The first efforts were devoted to identify and develop non-metallic compounds (e.g., polyester or other polymers) to build stents which would exhibit less inflammatory and prothrombotic behavior than conventional stainless steel stents [23]. These experiments showed promising results in a swine model: the extent of neointimal proliferation was similar to that observed after placement of metal stents, despite the

presence of a more pronounced inflammatory reaction [23]. Subsequently, several biodegradable polymers—mounted on conventional metallic stents—were tested by Dutch and American researchers, in order to assess their biocompatibility in porcine coronary arteries. Unfortunately, all resulted in marked inflammation, leading to neointimal hyperplasia and/or thrombus formation [24]. Additional experiences demonstrated that a metallic stent coated with high-molecular weight poly-L-lactic acid (PLLA) was well tolerated in a porcine coronary injury model, exhibiting little inflammation, and also showed interesting properties as effective means of providing sustained, site-specific drug delivery [25]. Furthermore, Japanese researchers showed that a fully bioabsorbable PLLA scaffold eluting a tyrosine kinase inhibitor was able to efficiently suppress neointima hyperplasia induced by balloon injury in a swine model [26]. The first device that was tested in humans was the Igaki-Tamai (Kyoto Medical), a fully bioresorbable scaffold made of poly-L-lactic acid (PLLA) without any drug coating. It required a 30-second inflation with a balloon filled with contrast heated at 70–80°C to be implanted [27]. The first-in-man trial (n = 15) was published in 2000, and showed no stent thrombosis or major adverse cardiac events (MACE) at 30 days, and one case of target lesion revascularization (TLR) at 6 months [28]. Notwithstanding these promising results, this device did not become popular due to concerns about use of the heated contrast in coronary arteries. Despite these fast-paced advances during the 1990's, the development of what will be later known as BRS stagnated for a large part of the following decade, due to a combination of inability to manufacture an ideal polymer that could limit inflammation and restenosis, and because of the growing interest in metallic DES [21].

3. Current Clinically Tested BRS

Current, mature BRS technology relies on a bioresorbable polymer or metal (the “scaffold”) that elutes an antiproliferative drug similar to metallic DES (most often, everolimus or sirolimus), although some devices lack any drug coating. Table 2 and Figure 1 show current BRS for which clinical data are available.

Table 2. Technical specifications of clinically tested bioresorbable scaffolds.

Scaffold (manufacturer)	Strut material	Coating material	Eluted drug	Strut thickness (μm)	Crossing profile (mm)	Radio-opacity	Radial support	Reabsorption (months)	Current status
<i>Metallic</i>									
AMS-1 (Biotronik)	Mg alloy	None	None	165	1.2	None	Weeks	< 4	Discontinued
DREAMS-1 (Biotronik)	Mg allow with some rare metals	PLGA	Paclitaxel	125	N/A—6F compatible	None	3-6 months	9	Discontinued
DREAMS-2 (Biotronilk)	Mg allow with some rare metals	PLLA	Sirolimus	150	N/A—6F compatible	Metallic markers	3-6 months	9	Clinical trial
<i>Polymeric</i>									
Igaki-Tamai (Kyoto Medical)	PLLA	None	None	170	N/A	Gold markers	6 months	24–36	CE mark for peripheral use
Absorb 1.0 (Abbott Vascular)	PLLA	PDLLA	Everolimus	156	1.4	Platinum markers	Weeks	18–24	Discontinued
Absorb 1.1 (Abbott Vascular)	PLLA	PDLLA	Everolimus	156	1.4	Platinum markers	6 months	24–48	CE mark

DESolve (Elixir Medical)	PLLA	None	Novolimus	150	1.5	Metallic markers	N/A	12–24	CE mark
ReZolve (REVA Medical)	PTD-PC	None	Sirolimus	115–230	1.8	Radiopaque scaffold	4–6 months	4–6	Discontinued
ReZolve2 (REVA Medical)	PTD-PC	None	Sirolimus	N/A	N/A	Radiopaque scaffold	N/A	N/A	Clinical trial
Fantom (REVA Medical)	PTD-PC	None	Sirolimus	~120	1.27	Radiopaque scaffold	N/A	N/A	Clinical trial
ART 18AZ (ART)	PDLLA	None	None	170	N/A—6F compatible	None	3–6 months	3–6	Clinical trial
Fortitude (Amaranth)	PLLA	None	None	150–200	N/A—6F compatible	None	3–6 months	3–6	Clinical trial
IDEAL BT1 (Xenogenics)	Poly lactide and salicylates	SA/AA	Sirolimus	200	1.5–1.7	None	3 months	6–9	Clinical trial
MeRes100 (Meril Life Sciences)	PLLA	PDLLA	Sirolimus	100	N/A—6F compatible	Metallic markers	N/A	24–36	Clinical trial

Abbreviations: CE, Conformité Européenne; PDLLA, poly-DL-lactic acid; PLGA, poly-lactic-co-glycolic acid; PLLA, poly-L-lactic acid; PTD-PC, poly-tyrosine-derived polycarbonate; SA/AA, salicylic acid/adipic acid. Reproduced with permission from [27].

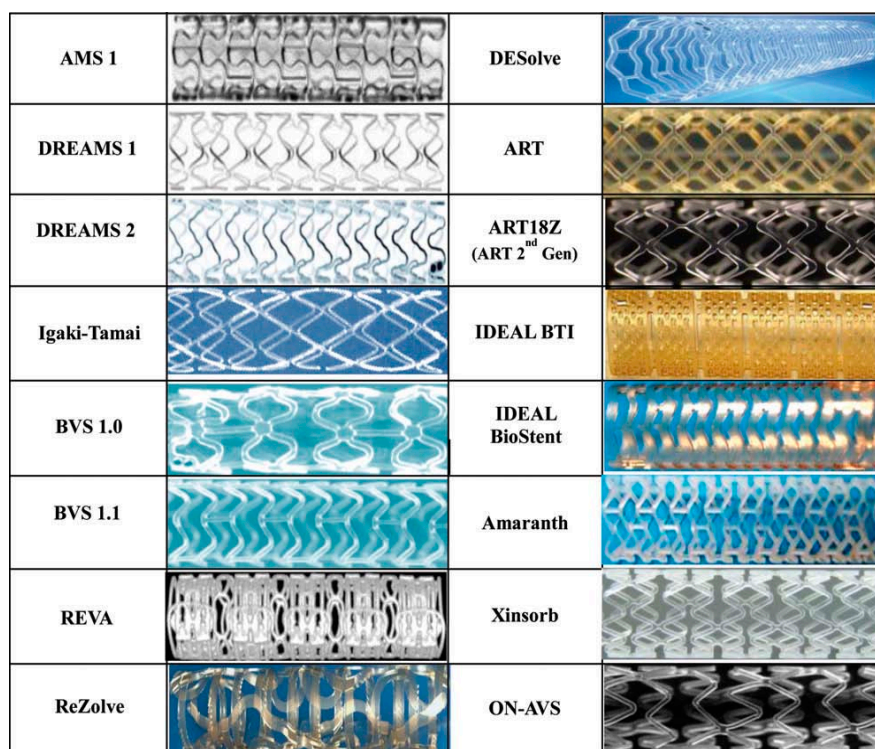


Figure 1. Bioresorbable scaffolds in clinical or preclinical use. Reproduced with permission from [27].

3.1. Polymer-based BRS

3.1.1. Abbott Vascular AbsorbTM

The device with more abundant and solid clinical data available is by far AbsorbTM by Abbott Vascular. The current version is made of a PLLA platform, with 156- μ m struts, coated with poly-DL-lactic acid (PDLA) and eluting everolimus. Platinum markers facilitate scaffold identification once implanted. Radial support is provided for the first 6 months, and reabsorption is completed between 24 and 48 months (Figure 2 and 3), although the now discontinued first version of the device (used in the ABSORB A trial [29]) featured a faster reabsorption kinetics (18–24 months). It is available in 2.5, 3.0 and 3.5 mm diameters, and in 8, 12, 18, 23 and 28 mm lengths. AbsorbTM has obtained CE mark. Clinical data on AbsorbTM will be reviewed in the next section.

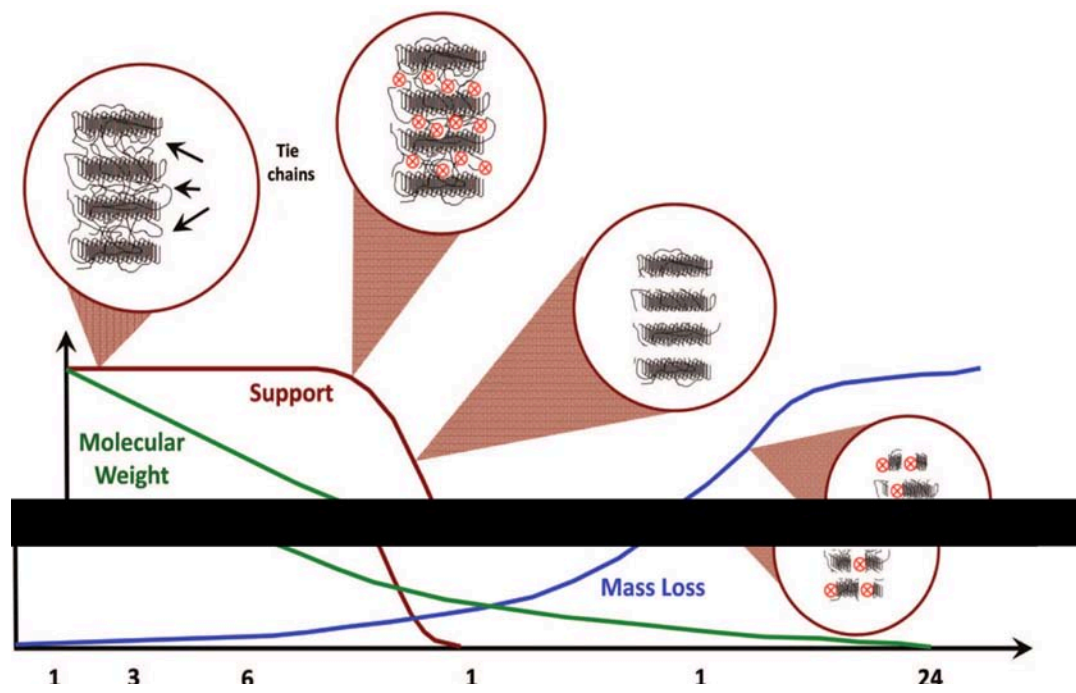


Figure 2. Reabsorption process of a polymeric bioresorbable scaffold. The encircled cartoons describe the progressive change in amorphous tie chains of poly-L-lactic acid (PLLA) and the progressive fragmentation of the crystal lamella. Reproduced with permission from [21].

3.1.2. Elixir Medical DESolve™

This device is made of an uncoated PLLA platform and elutes novolimus. Strut thickness is 150 μm . Metallic markers facilitate scaffold identification. It undergoes a faster degradation process than Absorb, since reabsorption is completed between 12 and 24 months. It is available in 2.5, 3.0, 3.25 and 3.5 mm diameters, and in 14, 18 and 28 mm lengths. Both the first-in-man experience ($n = 16$) and the larger DESolve NX trial ($n = 126$) showed effective suppression of neointimal hyperplasia at 6 months, no significant change in vessel volume and a LLL of 0.20 ± 0.32 mm at 6 months. Intravascular ultrasound data at 6 months demonstrated a significant ($p < 0.001$) increase in vessel area (17%), mean scaffold area (16%), and mean lumen area (9%). Moreover, only 1.2% of struts were left uncovered at 6 months (as opposed to 3.2% for Absorb™). Clinical outcomes were also promising, with an incidence of MACE of 3.3% at 6 months and 7.4% at 24 months, including a TLR rate of 1.6% and 4.1%, respectively, with no cases of definite ST [30,31]. DESolve™ has obtained CE mark.

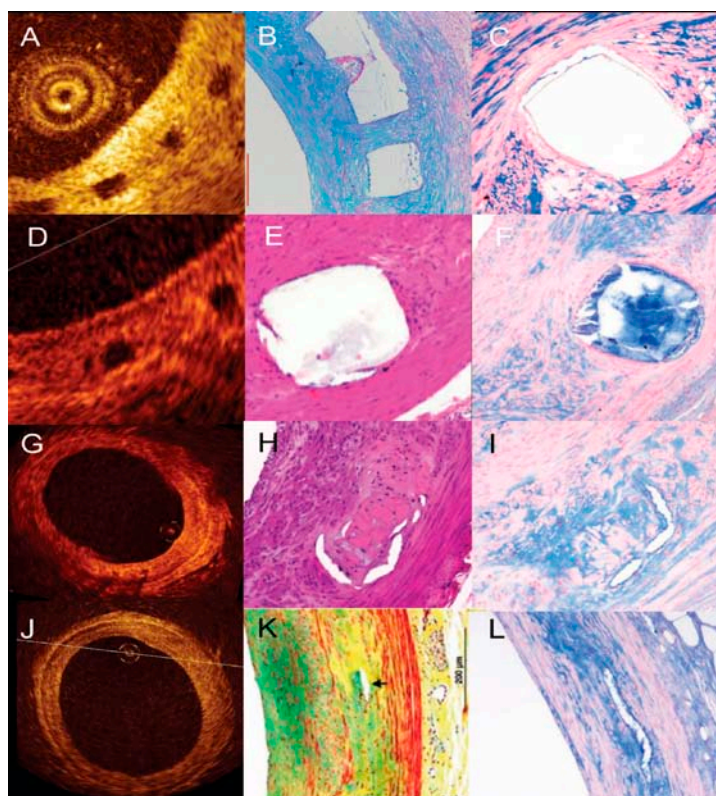


Figure 3. Optical coherence tomography (OCT) and histology at 28 days and 2, 3, and 4 years after BRS implantation. At 28 days, OCT shows preserved “box” appearance (A), corresponding to the voids not stained by Alcian Blue (B and C). At 2 years, OCT still shows struts as preserved box (D), but the persistent voids (E) are now replaced by proteoglycan, which stained positively with Alcian Blue (F). At 3 years, only 2 struts at 6 o’clock remained detectable (G). Otherwise, connective tissue cells are now infiltrated in the strut footprints (H, hematoxylin and eosin staining; I, Alcian Blue). At 4 years, struts are no longer discernible by OCT (J); the strut footprints are hardly detectable in Movat staining (K) and Alcian Blue (L) and are characterized by paucity of connective tissue cells and a small amount of calcification. Reproduced with permission from [21].

3.1.3. REVA ReZolve2™

After the promising preliminary experience with ReZolve™ in the RESTORE trial [32], REVA introduced a new iteration of its BRS, the ReZolve2™, which features an improved delivery system and crossing profile. It is an uncoated sirolimus-eluting BRS based on REVA’s proprietary desaminotyrosine-derived polycarbonate platform. This interesting polymer is radiopaque, and thus enables complete visualization of the BRS, helping the operator minimizing geographic miss at

implantation. It allows traditional one-step implantation (as opposed with AbsorbTM stepped inflation, meant to avoid disrupting the delicate PLLA architecture). It features an 85% degradation by 12 months and thick struts ($\approx 200 \mu\text{m}$) that confer high radial force. The ReZolve2 clinical program tested this scaffold in $n = 112$ patients with low-to-intermediate complexity lesions. Preliminary data reported a 4.5% MACE rate at 6 months (3.0% TLR) [33]. However, issues linked to the “slide and lock” delivery mechanism (which allowed the operator to ratchet open the device to a desired diameter during implantation) hampered the deliverability of this BRS, so that the new iteration of this scaffold will feature a conventional balloon expandable system. The ReZolve2 experience has contributed building data and knowledge for the development of the next generation device (Phantom), which is currently being tested in humans. Of note, to date no article publication on any of these BRS iterations has been released.

3.2. Metal-based BRS

3.2.1. Biotronik DREAMS 2TM

Biotronik adopted a radically different approach for the development of its BRS platform. Instead of a polymer, the company chose to use a bioabsorbable magnesium alloy. The first iteration of the device (AMS-1) was uncoated and did not elute any antiproliferative drug. Strut thickness was $165 \mu\text{m}$. The radial support was lost within a few weeks after implantation (reabsorption was complete in < 4 months), resulting in a high rate of recoil and constrictive remodeling [27]. AMS-1 was tested in the PROGRESS-AMS trial ($n = 63$), which showed marked LLL ($1.08 \pm 0.49 \text{ mm}$ at 4 months), which determined a 24% TLR rate at 4 months. There were no cases of death, myocardial infarction or ST [34]. The second iteration of this scaffold (DREAMS-1TM) featured thinner struts ($125 \mu\text{m}$), coating (poly-lactic-co-glycolic acid, PLGA) and drug elution (paclitaxel). The degradation process was longer (reabsorption was completed in 9 months). DREAMS-1TM was tested in the BIOSOLVE-I trial ($n = 46$), which showed a LLL of $0.65 \pm 0.50 \text{ mm}$ at 6 months and $0.52 \pm 0.39 \text{ mm}$ at 12 months. TLR rate was 4% at 6 months and 7% at 12 months. No deaths or ST were observed [35]. At 3-year follow-up, TLR rate was 4.5% and 2.3% of patients suffered a myocardial infarction. Again, no cases of death or ST were observed [36]. Further refinement to the device has been performed: DREAMS-2TM is a sirolimus-eluting scaffold that features PLLA coating. Strut thickness is $150 \mu\text{m}$. Improved radiopacity is provided by metallic markers. Reabsorption is completed by 9 months. DREAMS-2TM is being tested in the ongoing BIOSOLVE-II trial.

4. Clinical Data for Abbott Vascular AbsorbTM

As mentioned, the vast majority of clinical data available on BRS concerns Abbott Vascular AbsorbTM (Table 3).

Table 3. Main clinical data on Abbott Vascular Absorb™.

Study	Design	Sample size (n)	Primary endpoint	Main findings	Available follow-up	Comments
ABSORB A [37]	Single arm trial	30	Cardiac death, MI, ischemia-driven TLR	3.4%	5 years	Simple lesions and clinical scenarios, first iteration of the device
ABSORB B [38]	Single arm trial	101	Cardiac death, MI, ischemia driven-TLR	10%	3 years	Simple lesions and clinical scenarios, first iteration of the device
ABSORB II [39]	Randomized controlled trial (Absorb™ vs. Xience™)	501	Vasomotion and difference in MLD between implantation and 3 years	Cardiac death, target-vessel MI, TVR 5% vs. 3% ($p = 0.35$) at 1 year	1 year	Less self-reported angina with Absorb™, but similar exercise performance
ABSORB III [40]	Randomized controlled trial (Absorb™ vs. Xience™)	2008	Cardiac death, target-vessel MI, or ischemia-driven TLR	7.8% vs. 6.1% ($p = 0.007$ for non-inferiority)	1 year	Absorb™ clinically non-inferior to Xience™
ABSORB STEMI TROFI II [41]	Randomized controlled trial (Absorb™ vs. Xience™)	191	Healing score (OCT)	1.74 ± 2.39 vs. 2.80 ± 4.44 ($p < 0.001$)	6 months	Better healing (strut apposition and coverage) with Absorb™

ABSORB China [42]	Randomized controlled trial (Absorb vs. Xience)	480	In-segment late loss	0.19 ± 0.38 mm vs. 0.13 ± 0.37 mm ($p =$ 0.01 for non- inferiority)	1 year	Absorb TM angiographically non-inferior to Xience TM
GHOST-EU [43]	Registry	1189	Cardiac death, target- vessel MI, or ischemia- driven TLR	4.4%	6 months	2.1% of definite or probable scaffold thrombosis
ABSORB EXTEND [45]	Registry	512	Cardiac death, MI, ischemia driven-TLR	4.3%	1 year	0.8% of definite or probable scaffold thrombosis

Abbreviations: MI, myocardial infarction; MLD, minimal luminal diameter; OCT, optical coherence tomography; TLR, target lesion revascularization. TVR, target vessel revascularization.

The seminal ABSORB A trial ($n = 30$) tested the first version of the scaffold in a cohort of lesions of intermediate complexity. Two-year follow-up showed no cases of death or TLR, and a 3.6% of myocardial infarctions. No cases of ST were observed. LLL was 0.48 ± 0.28 mm at 2 years. At 2 years, 34.5% of strut locations presented no discernible features by optical coherence tomography (OCT). Additionally, vasomotion occurred at the stented site and adjacent coronary artery in response to vasoactive agents [29]. At five-year, MACE rate remained unchanged (3.4%), and again no cases of ST [37]. The second-generation device was tested in the ABSORB B trial ($n = 101$), showing a three-year MACE rate of 10.0% (3% of non-Q-wave MI, 7% of TLR, and no cardiac deaths), without any case of ST. LLL was 0.29 mm at 3 years [38].

ABSORB II was the first trial comparing a BRS with a DES [39]. It randomized, in a 2:1 fashion, AbsorbTM and XienceTM $n = 501$ patients with evidence of myocardial ischemia and one or two de-novo native lesions in different epicardial vessels. Patient population was somehow less selected than in previous trials (24% diabetes, 14% moderately or severely calcified lesions, 9% two or more lesions treated), even though type-C lesions were observed in only 1.5% of cases, bifurcations and acute coronary syndrome patients were excluded, lesions were on average quite short (13.8 ± 6.5 mm) and very few (15%) overlapping scaffolds were implanted. At 1 year, rates of first new or worsening angina were lower in the BRS group (22% vs. 30%, $p = 0.04$)—a finding that is believed to be due to the restored vasomotion—whereas performance during maximum exercise and angina status by a standardized questionnaire were similar. At one-year follow-up, MACE rate was 5% in the BRS group and 3% in the DES group ($p = 0.35$), with the most common adverse events being non-Q-wave myocardial infarction (4% vs 1%, $p = 0.16$) and clinically-indicated TLR (1% vs 2%, $p = 0.69$). Three patients (0.9%) in the BRS group had definite or probable ST (two definite early and one probable late), compared with no patients in the DES group ($p = 0.55$).

The recently published ABSORB III [40] is to date the largest trial comparing a BRS to a metallic DES. It randomized $n = 2008$ patients to AbsorbTM ($n = 1322$) or to XienceTM ($n = 686$) with stable or unstable angina. Patient population risk profile was intermediate: 32% diabetes, 70% type B2 or C lesions, but ST-elevation myocardial infarction (STEMI) and non-STEMI were exclusion criteria, so that only stable and unstable angina patients with one or two lesions were included. Device success was 94% for AbsorbTM and 99% for XienceTM. At 1 year, Absorb was non-inferior to XienceTM in terms of MACE (7.8% vs. 6.1%, $p = 0.007$ for non-inferiority). Notably, there were no differences in stent thrombosis as well (1.5% vs. 0.7%, $p = 0.13$).

Additional randomized evidence on the safety and efficacy of AbsorbTM comes from the STEMI-TROFI II trial [41], which randomized $n = 191$ STEMI patients to either AbsorbTM or XienceTM. The primary endpoint was the 6-month OCT “healing score”. Healing was significantly improved in Absorb-treated patients, as compared with subjects randomized to XienceTM, thanks to better strut coverage and apposition. There were no differences in clinical endpoints.

Finally, ABSORB China, which again randomized $n = 480$ patients with stable coronary artery disease to either AbsorbTM or XienceTM, showed comparable outcomes in terms of angiographic in-segment late loss at one year [42].

Beside randomized data, a large body of evidence on BRS comes from observational registries. The largest of those is the GHOST-EU registry ($n = 1189$), which summarizes the European experience with BRS. Currently, 6-month follow-up is available [43]. A total of 1731 AbsorbTM scaffolds were implanted, with a technical success rate of 99.7%, despite a large proportion of type-C lesions (28%). Clinical scenarios included: bifurcations (27%), STEMI (16%), in-stent restenosis (3%), ostial lesions (6%) and chronic total occlusions (CTO) (8%). Target lesion failure was 2.2% at 30 days and 4.4% at 6 months. At 6 months, the rates of cardiac death, target vessel myocardial infarction and TLR were 1.0%, 2.0% and 2.5%, respectively. Diabetes mellitus was found to be the only independent predictor of target lesion failure. Alarming (but not surprisingly, given the broad spectrum of indications of BRS in this study), the cumulative incidence of definite/probable ST was 1.5% at 30 days and 2.1% at 6 months, with 70% of cases occurring within the first month (at a median of 5 days). Based on these data, the rates of ST with AbsorbTM resemble those of first-generation DES and do not compare favorably with the very low rates seen with second-generation DES [44].

Similar data comes from the ABSORB-EXTEND study, a registry that plans to enroll $n = 800$ patients from 100 sites worldwide. One of the strengths of this study is that an independent clinical events committee adjudicates all endpoint-related events. The one-year outcomes of $n = 512$ have recently been published [45]. Patient population was of intermediate complexity (26% of patients had diabetes, 41% had type B2/C lesions). Clinical device success was 98.5%. At one year, the composite endpoints of ischemia-driven MACE and ischemia-driven target vessel failure were 4.3% and 4.9%, respectively. The rate of definite and probable ST was 0.8%.

Finally, as the experience with the device builds up, several operators have become more comfortable to use it also in challenging clinical scenarios, including bifurcations [46–49], left main [50], calcified lesions [51], CTO [52], STEMI [53–56], saphenous vein grafts [57], mammary arteries [58], and in-stent restenosis [59]. In order to systematize the implantation technique and minimize the risk of adverse events both peri-procedurally and at follow-up, a group of European AbsorbTM experienced users redacted consensus criteria for patient and lesion selection, BRS implantation and optimization, as well as the role of intravascular imaging guidance, approach to multiple patient and lesion scenarios, and management of complications [60].

5. Limitations of BRS

One of the Achilles' heels of BRS appears to be its thrombogenicity, which likely results from rheological disturbances (abnormally low shear stress) observed in the vicinity of its thick struts [61]. As previously mentioned, the rate of ST in early large real-world registries is high (2.1% at 6 months

in the GHOST-EU registry [43]). Additionally, the recent report of cases of very late BRS thrombosis [62,63] contributes debulking the belief that BRS were immune from this clinical entity, given the fact that reabsorption is at an advanced stage after one year since implantation, and is completed in most patients by 24 months. Suboptimal implantation (incomplete lesion coverage, underexpansion and malapposition) represents the main mechanism for both early and late BRS thrombosis, similar to metallic ST. Dual antiplatelet therapy discontinuation might also be a secondary contributor in several late events [64].

Similarly, BRS are also vulnerable to develop in-scaffold restenosis, as it has been highlighted by recent reports from the ABSORB B trial and the GHOST-EU registry [65,66]. In the ABSORB B trial, the incidence of BRS restenosis was 6% ($n = 6$) at a median time-to-restenosis of 399 ± 248 days. For half of these cases the main mechanism of restenosis was shown to be significant intra-scaffold tissue growth, whereas in the other half it was due to anatomical or procedural factors [65]. Similarly, in one of the centers participating in the GHOST-EU registry, the incidence of BRS restenosis was 3.6% ($n = 12$) at a median time-to-restenosis of 291 ± 101 days. In this case series, the most frequent mechanisms of restenosis were focal restenosis at the scaffold edge and underexpansion in BRS implanted in type-C lesions [66]. Of note, unlike for metallic stent restenosis, there is very little information on how to deal with BRS restenosis. Since at the time of presentation (> 9 –12 months) the scaffold has generally lost most of its mechanical properties, balloon angioplasty may disrupt the struts leading to adverse outcomes [66], so that additional stent/scaffold implantation may be unavoidable. A detailed dissertation on the risk factors and mechanisms of BRS failure, as well as possible strategies to deal with it, might be found elsewhere [67].

Another limitation of currently available BRS is their trackability and deliverability. To provide sufficient radial strength to oppose negative remodeling and minimize acute recoil, polymeric scaffolds have thicker struts (150–200 μm) than metallic stents (80 μm). This, together with challenges in the crimping process, results in worse crossing profile of BRS, which ranges between 1.4 mm (AbsorbTM) and 1.8 mm (first-generation ReZolveTM), which is markedly worse than current DES (1.0 mm) [27]. These technical limitations hamper the advancement of the BRS across tortuous segments of the coronary arteries and in calcified lesions, for example. Indeed, improvement in BRS crossing profile is one of the main goal of further upcoming iterations of these devices.

6. Conclusions and Future Perspectives

BRS have been hailed as the fourth revolution in the history of interventional cardiology [21,22], since they provide temporary scaffolding that helps stabilizing the plaque and promotes healing, and then disappear, leaving no trace behind. This has several advantages, as compared with metallic stents: e.g., the restoration of a functional endothelium and thus vasomotion, the ability to treat in-stent restenosis without delivering an additional layer of metal, the possibility of eventually performing a CABG anastomosis on the site of prior BRS implantation.

Even if several iterations of certain devices have been successfully developed and used in clinical practice, we are currently witnessing the introduction of the first-generation of BRS. As it had been for BMS first and DES later, this novel device is still immature to some extent, and further refinements should be performed before BRS can truly become a game-changer in the everyday practice in the cath lab. In particular, smaller strut thickness will improve BRS crossing profile and rheological properties (thus decreasing the risk of ST). Another limitation is the relatively weak radial strength than most current generation BRS exhibit, in comparison with metallic stents: this influences both lesion preparation and post-dilatation capabilities of these devices [22]. Indeed, aggressive lesion preparation has been advocated when BRS are to be implanted, and—although post-dilatation is recommended—over-dilatation has to be avoided, in order not to weaken BRS architecture, which might lead to strut fracture [60]. Finally, despite the first encouraging results on the performance of BRS in registries and small trials, convincing data on the superiority—and possibly also on the non-inferiority—of these devices, as compared with metallic DES, are still awaited. Indeed, a recent meta-analysis of randomized trials showed that AbsorbTM exhibits worse angiographic outcomes and a higher risk of ST, as compared with Xience, with comparable rates of MACE [68].

Conflict of Interests

The authors report no financial relationships or conflicts of interest regarding the content herein.

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