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Bioresorbable Scaffolds for Atheroregression: Understanding of Transient Scaffolding

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Abstract: This review focuses on the clinical and biological features of the bioresorbable scaffolds in interventional cardiology highlighting scientific achievements and challenges of the transient scaffolding with Absorb BVS. Special attention is granted to the vascular biology pathways which, involved in the resorption of scaffold, artery remodeling and mechanisms of Glagovian atheroregression setting the stage for subsequent clinical applications. Twenty five years ago Glagov described the phenomenon of limited external elastic membrane enlargement in response to an increase in plaque burden. We believe this threshold becomes the target for development of strategies that reverse atherosclerosis, and particularly transient scaffolding has a potential to be a tool to ultimately conquer atherosclerosis.

Keywords: Artery remodeling, atheroregression, bioresorption, bioresorbable scaffold, glagov phenomenon, stenting.

TRANSIENT SCAFFOLDING THROUGH THE PRISM OF THE GLAGOV REMODELING – A KEY MECHANISM TO MAINTAIN LUMEN PATENCY

Prevention of atherosclerosis and treatment of its complications remain a clinical challenge [1]. The lipid-lowering drugs have an outstanding track record of lowering cholesterol and improving outcomes. Clinical trials such as MIRACLE (2001), REVERSAL (2004), NORMALIZE (2004), PROVE IT (2004), ESTABLISH (2004), ASTEROID (2006), JUPITER (2008), JAPAN-ACS (2009), SATURN (2011), ZEUS (2014), and IBIS-4 (2015) have demonstrated that lowering LDL levels through intensive statin therapy can slow progression, or even partially reduce the total atheroma volume (TAV) up to a 13.14 mm^3 in IBIS-4 trial or a 6.3% per cent atheroma volume (PAV) in JAPAN ACS trial (vs up to 8.2 mm^3 TAV and 12.5% PAV in ZEUS trial with a combination of ezetimibe and atorvastatin) [1-3]. Of note, plaque regression was associated with only a 30% relative reduction in events. These findings also suggest that necrotic core and mineral deposits may resist risk factor modification or systemic drug therapy. Moreover, these trials documented [3] reduction of fibrous tissue and certain amount of intramural lipids with very slight effect on necrotic core accelerating calcium deposition in the coronary lesions whereas the fact that numerous studies of cholesterol lowering have failed to document a mortality benefit, and, so, the benefits of statins may have been overstated [4].

Current percutaneous coronary intervention (PCI) using drug-eluting stents (DES) is associated with a small, though sizeable risk of delayed healing, late stent thrombosis [5], abnormal vasomotion [6] and neoatherosclerosis [7] (Fig. **1**). New devices such as bioresorbable scaffolds (BRS) have been tested in more than 100,000 humans in the past six years (Absorb BVS – bioresorbable vascular scaffold, Abbott Vascular, Santa Clara, CA) [5, 8]. These devices scaffold the diseased coronary artery and elute an antiproliferative drug that counteracts constrictive remodeling [9], and excessive neointimal hyperplasia [7, 10]. Until now, the BRS platform has been used in both real-world and complex lesions due to the nature of patient selection in these clinical trials [8, 11-13]. BRS may represent a new era in cardiovascular medicine, since interventions will address not only the obstructive component of atherosclerotic disease, but also the biologic and functional properties of the vessel. BRS may thus be viewed as platforms upon which bioactive compounds are added to act as the disease-modifying agents.

New generations of devices may help us to fulfill our ultimate goal of atheroregression below the *Glagov threshold* by reversing atherogenesis, slowing the ageing process and triggering repair of diseased arteries. Glagov's observation [14] in 1987 suggests that vascular remodeling maintains the artery lumen dimensions [15] as long as the plaque burden threshold of 40% is not trespassed; a stage where the growth of the plaque can no longer be accommodated by external elastic membrane (EEM) enlargement (see Fig. **2**). This process or a window of the EEM enlargement (between a 20% and 55% PAV) [3] in accommodating the plaque and maintaining the lumen dimensions is referred to as the *Glagov phenomenon*, which is a cornerstone issue in the modern-day atheroprotective strategies [16]. Moreover, it was documented in PROSPECT trial [3] that PB>70% is an independent predictor of non-culprit major adverse cardiac events (MACE). Therefore, plaque reduction below the *Glagov threshold* would imply some kind of atherosclerosis reversal setting back a lesion.

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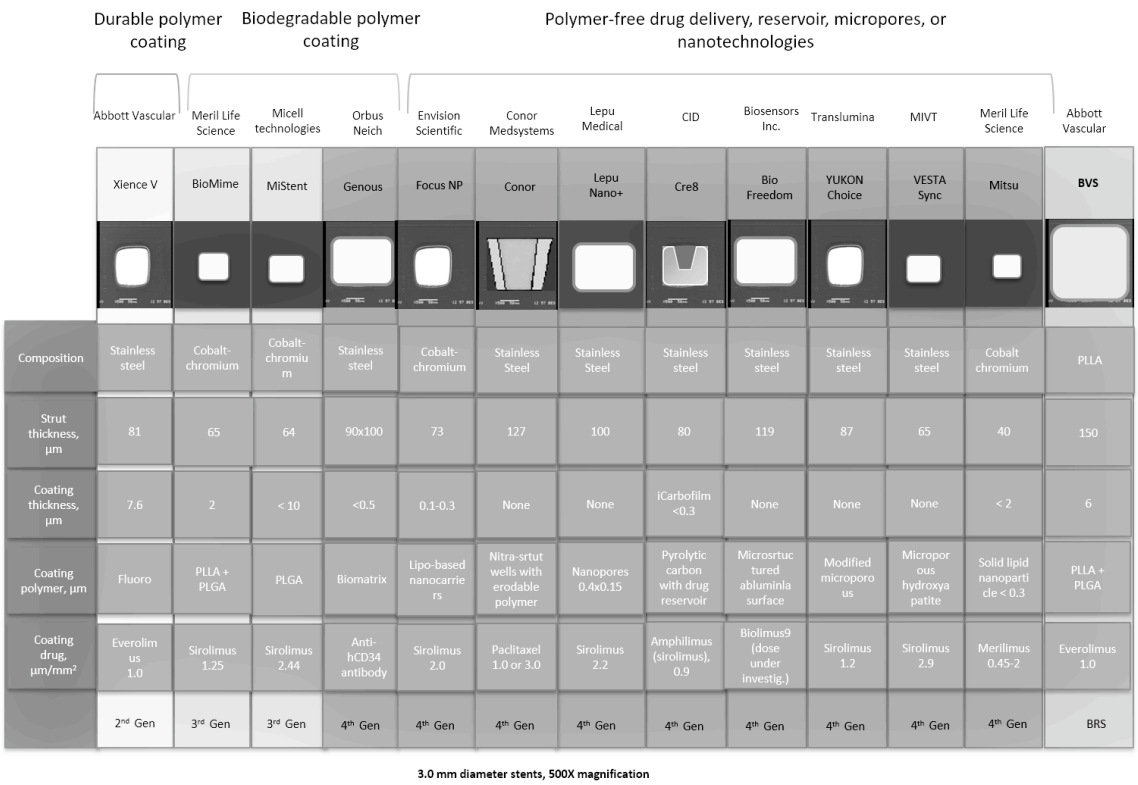

Fig. (1). Characteristics of the new generation metallic stents and BRS developed with nanotechnologies.
Panel demonstrates different generations of stents and BRS. In addition, some representatives of the new fourth generation are shown, utilizing polymer-free technologies with drug-loading in micro- and nanopores (LepuNano+), micro-reservoirs (Cre8), stents coated with $CD34^+$ cells-catching system (Genous), stents with lipid-based nanocarriers (Focus NP) and ultra-thin nanoplatforms (Mitsu).

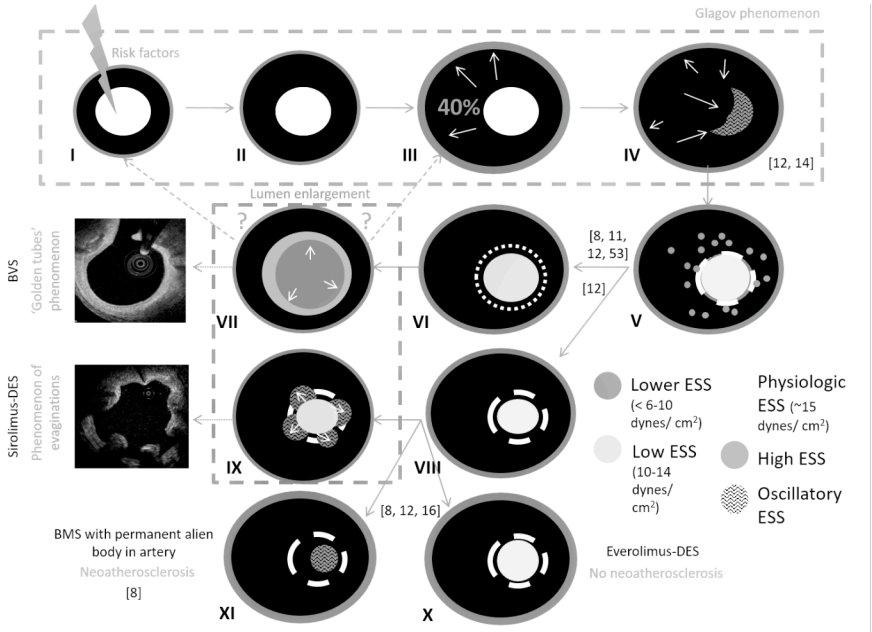

Fig. (2). Glagov phenomenon as target for reversal of atherosclerosis.
Panel shows the general concept of the Glagov phenomenon (frames I-IV), and of the BRS-mediated reversal (frames V-VII). After BRS implantation, an artery undergoes the remodeling process with lumen enlargement, vessel wall thinning (plaque-media reduction) and pseudo-atheroregression (with OCT-visible 'golden tube'), which can be regarded as a kind of vascular reparative therapy. At 24 months, most struts of BVS 1.0 ABSORB are no longer detectable. In contrast to BRS, a metal cage (usually sirolimus-DES or BMS; see frames V, VIII, XI) provokes chronic irritation of tissue with progressive neoatherosclerosis, or can prevent neoatherosclerosis (DES; see frames V, VIII, IX, X) with OCT-detectable coronary evaginations – defined as outward bulges in the luminal contour between struts (sirolimus-DES; see frame IX) fixed to the struts, limiting further artery wall expansion. Endothelial shear stress (ESS) adjusts to artery remodeling and transient scaffolding.

ATHEROPROTECTIVE AND CLINICAL ACHIEVEMENTS OF ABSORB BVS IN CLINICAL TRIALS

BRS technologies have been tested in some clinical studies (Fig. **3**). In the 1990s, the biocompatibility of poly-l-lactic acid (PLLA) was controversial [17, 18]. Among the first polymeric devices to be studied was the PLLA bioabsorbable stent designed and tested by *Stack et al.*, reported to hold up to 1,000 mmHg crush pressure and maintain its radial strength for 1 month [19]. This stent was almost completely degraded by 9 months with minimal thrombosis, moderate neointimal growth and a limited inflammatory response in porcine coronary arteries. *Dr. Igaki*, an engineer, and *Dr. Tamai*, an interventional cardiologist who passed away in 2009, invented the first-in-man fully biodegradable stent (Igaki-Tamai stent) made of PLLA [17]. At that time, 50 patients were treated with Igaki-Tamai stents in Japan. The pioneering experimental studies using a non-biodegradable polyethylene-terephthalate braided mesh stents in porcine animal models were published by the group of *Prof. Patrick Serruys* (Erasmus MC, Rotterdam, the Netherlands) in 1992 [12, 18, 19].

To date, Absorb BVS is the first device which has shown phenomena such as late lumen enlargement (without pathological remodeling) and wall thinning with reduction of plaque burden. Reversing atherosclerosis following transient scaffolding of a dilated stenotic lesion now provides the opportunity to further explore the general understanding of device therapy and local drug delivery in vascular biology.

In general, preclinical studies of BRS eluting mTOR (mammalian target of rapamycin) inhibitor everolimus in the porcine coronary model have shown that polymeric struts completely disappeared and remnants were fully incorporated into the vessel wall within 4 years (Fig. **4**), becoming indiscernible by histology, OCT and VH-IVUS [2, 5, 8, 18, 20, 21]. Moreover, a circumferential evaluation of the healing process by OCT after BRS implantation showed a minimal amount of neointima forming a neocap of 170 μm, which potentially contributes to plaque stability[5]. As in the porcine model, late lumen enlargement, and plaque-media reduction with wall thinning were also observed in humans using IVUS (a 12.7% PAV reduction in ABSORB A trial between 6 and 24 months, and a 7.9% plaque area decline in

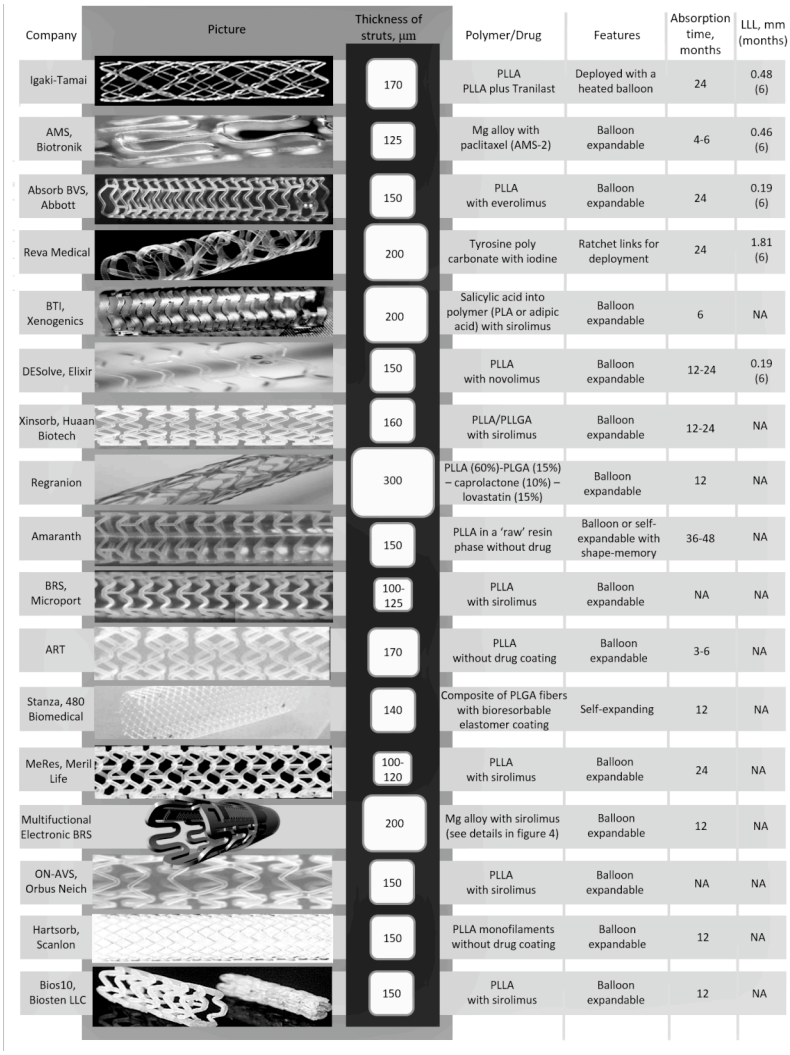

Fig. (3). Comparative analysis of BRS platforms currently available. This figure presents the main characteristics of 17 bioresorbable scaffolds (BRS), which are currently in clinical trials. NA – information is non-applicable or not available. FIGURE ADAPTED FROM REFERENCES 2, 7, 9. THE FIGURE OF ELECTRONIC STENT PROVIDED BY 57.

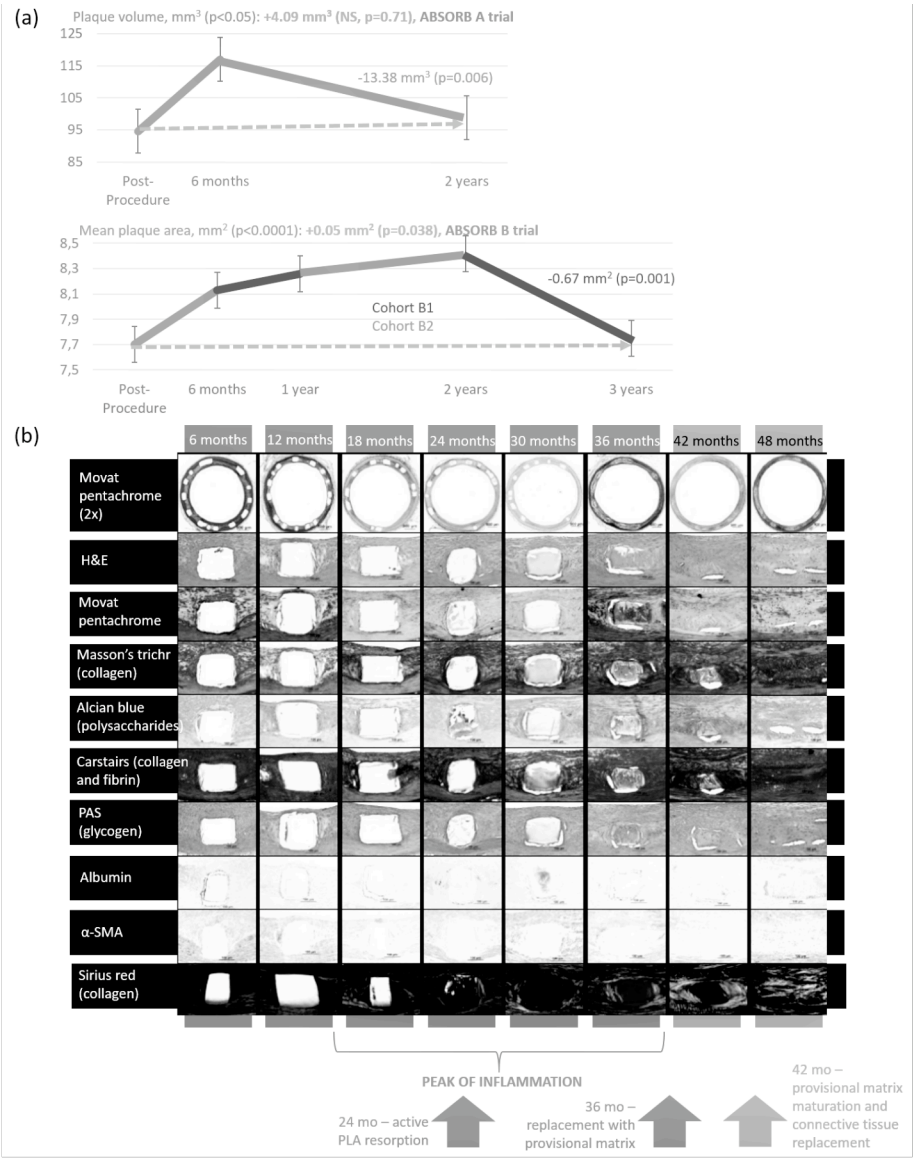

Fig. (4). Morphologic characterization of the atheroregression and strut composition in a porcine model and patients within 48 months after implantation of Absorb BVS. Panel (***a***) shows results of the multi-modality imaging clinical study of both ABSORB A and B trials documented the dynamics of vessel wall changes after implantation of a BRS, resulting at three years in stable luminal dimensions, a low restenosis rate and a low clinical major adverse cardiac events rate. In ABSORB B trial between two and three years there was a substantial plaque reduction (results of the IVUS longitudinal repeated measurement analysis with a mixed effect model) following the stepwise increase at six months, one year and two years. The result is a small non-significant increase between post-procedure and three years (Δ+0.27 mm^2, p=0.08; IVUS without imputations). The expansive remodeling in vessel area documented at two years regressed considerably at three years in parallel with the reduction in plaque behind the struts. ADAPTED FROM REFERENCES 5 AND 22. Panel (***b***) demonstrates that struts are of stable morphology through 18 months, being unstained and easily identified under polarized light. Thereafter, there is a rapid decline in birefringence of strut sites and color changes marked by increased proteoglycan staining by Movat pentachrome (MP) and Alcian blue (AB) (blue-green, ≥24 months) and increasing eosinophilia by H&E (≥30 months). AB and MP are first stains to show positivity in struts as their Cu cations bind to anionic end groups of the residual oligomers. These changes correspond to the absorption and inspissation of proteins (presence of albumin). At 24 months, there is sufficient density of oligomers to result in AB/MP+ staining. Because oligomer is still present, under polarized light there still appears to be polymer remaining. At 30 to 36 months, increasing loss of oligomers results in near to complete loss of birefringence within the resorption sites (at least >95% by 36 months). At the same time, as oligomers are resorbed, because cells cannot infiltrate that quickly into the region, there is absorption of tissue proteins = eosinophilic with H&E, tinctorial change with MP, decreasing positivity with AB. Strut sites are eventually composed of a provisional matrix that matures from collagen Type III integration (36 months) to eventual replacement by smooth muscle cells and collagen Type I at 42 to 48 months, demonstrating an increasing integration of scaffold into the arterial tissue. At 36, 42, and 48 months, sites are composed of increasing amounts of dense (glyco-)proteins resulting in intense deep pink staining by PAS. Because the dense regions are composed of collagen admixed with glycoproteins, the smooth muscle cells infiltrate slowly but lay down extracellular matrix. In this model, the artery ultimately shows intact media with mild neointimal thickening, which may allow normal physiological response of the artery. ADAPTED COURTESY OF FUMIYUKI OTSUKA, M.D., PH.D., ET AL (TEAM OF PROF. RENU VIRMANI, M.D., CVPATH INSTITUTE, GAITHERSBURG, MD, USA IN COLLABORATION WITH ABBOTT VASCULAR, SANTA CLARA, CA, USA; DOI: 10.1016/J.JACC.2014.07.680).

ABSORB B trial between 24 and 36 months) [22]. However we must mind the fact that existing today intravascular approaches to assess vascular contours remain not properly optimized [23], and can be one of the misguiding options which not allow us to ultimately judge the patterns of the artery remodeling after deployment of the transient interventions with Absorb BVS. In contrast to BRS, a non-resorbable metal cage as used in the current generation of DES fixes the vessel boundaries, interferes with mechanotransduction, disturbs shear stress, and induces chronic irritation of the underlying tissue with a severe immune-inflammatory response, progressive neoatherosclerosis [7] and expansive remodeling [15, 16].

The first two publications on Absorb BVS eluting everolimus and then results of ABSORB A and B trials in patients have reported three seminal observations (see Table **1**) made respectively at 6-month and 24-month follow-up: a) complete resorption documented indirectly by optical coherence tomography (OCT), intravascular ultrasound (IVUS) grey scale and IVUS radiofrequency backscattering; b) physiologically or pharmacologically induced restoration of vasomotion in the scaffolded area; c) late luminal enlargement with plaque/media regression documented by IVUS and OCT between 6 and 24 months [1, 8, 11, 12, 18-20].

However, analysis of the first-generation Absorb BVS revealed unwanted late scaffold recoil which was fully remediated by a second-generation design and process that showed an unchanged scaffold area at 6 months follow-up. Further evaluation at 12 and 24 months follow-up as well as analysis by OCT and IVUS confirmed the persistence of an unchanged scaffold area without substantial loss in lumen area, while vasomotion became detectable. These observations brought the evidences of the ongoing yielding process [18] and mechanical integrity of the scaffold to the vessel [2, 5, 7, 18]. A 3-year follow-up of this second generation is currently under way to refine these observations and to confirm whether the first signs of late lumen enlargement are detectable.

Table 1. Pivotal bench and clinical studies of Absorb BVS with the main scientific achievements.

Study (year)	Results and main findings	Comments	Reference (doi), or link
Preclinical studies			
Pre-clinical BVS 1.0 Design: porcine coronary artery model	The lifecycle of a BRS is divided into three phases: (1) revascularisation; (2) restoration; and (3) resorption. In the revascularisation phase spanning the first three months after intervention, the BRS should perform comparably to metallic drug-eluting stents (DES) in terms of deliverability, radial strength, recoil, and neointimal thickening. The ensuing restoration phase is characterised by gradual erosion of radial strength and a loss of structural continuity, where the time scale at which each occurs is related to the hydrolytic degradation rate of the polymer. Natural vasomotion in response to external stimuli is theoretically possible at the end of this phase. Finally, in the resorption phase, the passive implant is systematically resorbed and processed by the body.	Limited clinical data have been speaking to the potential of BRS as a new therapy, and future studies proved critical to inspiring a fourth revolution in PCI.	Design principles and performance of scaffolds published in EuroIntervention 2009 (10.4244/EIJV5IFA3), the bioresorption process described in EuroIntervention 2009 (10.4244/EIJV5IFA5). Both revisions of BVS presented at Circ Cardiovasc Intervent 2009 (10.1161/CIRCINTERVENTIONS.109.859173).
Pre-clinical BVS 1.1 Design: porcine coronary artery model	At 28 days, by OCT, 82% of struts showed sharply defined, bright reflection borders, best described as a box-shaped appearance. Histologically, all struts appeared intact with no evidence of resorption. At 2 years, by OCT, 60±20 struts were discernible per BVS with 80.4% of the strut sites as a box-shaped appearance. Despite their defined appearance by OCT, by histology, these structures appeared to be composed of proteoglycan, with polymeric material being at such low level as to be no longer quantifiable by chromatography. At 3 years, by OCT, recognizable struts decreased to 28±9 struts per BVS: 43.7% showed dissolved black box; 34.8%, dissolved bright box; 16.1%, open box; and 5.4%, preserved box appearance. Histology shows that connective tissue cells within a proteoglycan-rich matrix replaced the areas previously occupied by the polymeric struts and coalesced into the arterial wall. At 4 years, by OCT, 10±6 struts were recognizable as either dissolved black or dissolved bright box. In histology, these struts are minimally discernible as foci of low-cellular-density connective tissue. Relative to the prediction of histological type by OCT appearance, the preserved box appearance of OCT corresponds well with 2-year histology (86.4%), whereas the dissolved bright and black box appearances correspond to 3-year histology (88.0% and 90.7%, respectively). Struts indiscernible by OCT correspond to the integrated strut footprints seen at 4 years (100%). Struts are of stable morphology through 18 mo, being unstained and easily identified under polarized light. Thereafter, there is rapid decline in birefringence of strut sites and color changes marked by increased proteoglycan staining by Movat and Alcian blue (blue-green, ≥24 mo) and increasing eosinophilia by H&E (≥30 mo). These changes correspond to the absorption and inspissation of proteins (presence of albumin). Strut sites are eventually composed of a provisional matrix that matures from collagen Type III integration (36 mo) to eventual replacement by smooth muscle cells and collagen Type I at 42 to 48 mo, demonstrating an increasing integration of scaffold into the arterial tissue.	Detailed histological characterization of the Absorb struts provides insight into the process of bioresorption and integration that may be correlated to changes observed by in vivo imaging modalities such as OCT.	The concept of the stent described in EuroIntervention 2009 (doi is not provided). The histology analyzed in Circulation 2010 (10.1161/CIRCULATIONAHA.109.921528). The comparative analysis of two revisions provided in EuroIntervention 2010 (10.4244/EIJV5I8A157), and then in Eur Heart J 2011 (10.1093/eurheartj/ehq458). Pathological analysis performed in EuroIntervention 2015 (10.4244/EIJV11SVA39). Detailed morphologic characterization of the strut composition following absorb scaffold placement in a porcine coronary artery model through 48 months published in JACC 2014 (10.1016/j.jacc.2014.07.680).

(Table 1) contd…

Study (year)	Results and main findings	Comments	Reference (doi), or link
Simple to moderately complex populations			
ABSORB cohort A Design: Allocated (non-randomized), N=30, 1st end-point: safety and performance ID-MACE	The first-in-human fully bioabsorbable drug-eluting stent (BVS poly-L-lactic acid everolimus-eluting coronary stent) implantation was performed at Auckland City Hospital, New Zealand as part of the ABSORB trial. There were no adverse events in-hospital or by 1 month. A stent that supports the vessel when needed, delivers an antiproliferative drug then disappears has theoretical advantages with regard to CT and MRI compatibility, restored vessel vasomotion, and facilitated future percutaneous intervention or surgical grafting to the treated site. Procedural success was 100% (30/30 patients), and device success 94% (29/31 attempts at implantation of the stent). At 1 year, the rate of major adverse cardiac events was 3.3%, with only one patient having a non-Q wave myocardial infarction and no target lesion revascularisations. No late stent thromboses were recorded. At 6-month follow-up, the angiographic in-stent late loss was 0.44 (0.35) mm and was mainly due to a mild reduction of the stent area (−11.8%) as measured by intravascular ultrasound. The neointimal area was small (0.30 [SD 0.44] mm^2), with a minimal area obstruction of 5.5%. At 2 years, the device was safe with no cardiac deaths, ischaemia-driven target lesion revascularisations, or stent thromboses recorded, and only one myocardial infarction (non-Q wave). 18-month multislice CT (assessed in 25 patients) showed a mean diameter stenosis of 19% (SD 9). At 2-year angiography, the in-stent late loss of 0·48 mm (SD 0.28) and the diameter stenosis of 27% (11) did not differ from the findings at 6 months. The luminal area enlargement on OCT and intravascular ultrasound between 6 months and 2 years was due to a decrease in plaque size without change in vessel size. At 2 years, 34.5% of strut locations presented no discernible features by OCT, confirming decreases in echogenicity and in radiofrequency backscattering; the remaining apparent struts were fully apposed. Additionally, vasomotion occurred at the stented site and adjacent coronary artery in response to vasoactive agents. At 3-year the hierarchical ID-MACE of 3.4% remained unchanged. Clinical follow-up at 4 years was available in 29 patients since one patient withdrew consent after the six month follow-up. At four years, the hierarchical ID-MACE of 3.4% remained unchanged. Clopidogrel therapy had been discontinued in all patients. At 5 years, the ischemia-driven major adverse cardiac event rate of 3.4% remained unchanged.	Proved the restoration of vessel physiology/ functionality, allowance of non-invasive imaging, local hemodynamic milieu. At 2 years after implantation the stent was bioabsorbed, had vasomotion restored and restenosis prevented, and was clinically safe, suggesting freedom from late thrombosis. Late luminal enlargement due to plaque reduction without vessel remodelling needs confirmation. Three-year clinical results have demonstrated a sustained low MACE rate (3.4%) without any late complication such as stent thrombosis. Four-year clinical results demonstrate a sustained low MACE rate (3.4%) without any late complications such as stent thrombosis. The low event rate at 5 years suggests sustained safety after the implantation.	FIM report published in Catheter Cardiovasc Interv 2007 (PMID: 17139655). First results published in The Lancet 2008 (10.1016/S0140-6736(08)60415-8). Two-year results published in The Lancet 2009 (10.1016/S0140-6736(09)60325-1). Three-year follow-up was published in EuroIntervention 2010 (doi not provided). Four-year clinical outcomes presented in EuroIntervention 2012 (10.4244/EIJV7I9A168). Five-year clinical and functional multislice computed tomography angiographic results announced in JACC Cardiovasc Interv 2013 (10.1016/j.jcin.2013.05.017).
ABSORB cohort B Design: Allocated (non-randomized), N=101 (cohort B1, 45 patients; cohort B2, 56 patients), 1st endpoint: safety and performance	The serial analysis of the second generation of the BRS confirmed, at medium term, the safety and efficacy of the new device. From 6 to 24 months, late luminal loss increased from 0.16±0.18 to 0.27±0.20 mm on quantitative coronary angiography, with an increase in neointima of 0.68±0.43 mm2 on optical coherence tomography and 0.17±0.26 mm2 on intravascular ultrasound. Struts still recognizable on optical coherence tomography at 2 years showed 99% of neointimal coverage with optical and ultrasonic signs of bioresorption accompanied by increase in mean scaffold area compared with baseline (0.54±1.09 mm2 on intravascular ultrasound, P=0.003 and 0.77±1.33 m2 on optical coherence tomography, P=0.016). Two-year major adverse cardiac event rate was 6.8% without any scaffold thrombosis. Between one and three years, late luminal loss remained unchanged (6 months: 0.19 mm, 1 year: 0.27 mm, 2 years: 0.27 mm, 3 years: 0.29 mm) and the in-segment angiographic restenosis rate for the entire cohort B (n=101) at three years was 6%. On IVUS, mean lumen, scaffold, plaque and vessel area showed enlargement up to two years. Mean lumen and scaffold area remained stable between two and three years whereas significant reduction in plaque behind the struts occurred with a trend toward adaptive restrictive remodelling of EEM. Hyperechogenicity of the vessel wall, a surrogate of the bioresorption process, decreased from 23.1% to 10.4% with a reduction of radiofrequency backscattering for dense calcium and necrotic core. At three years, the count of strut cores detected on OCT increased significantly, probably reflecting the dismantling of the scaffold; 98% of struts were covered. In the entire cohort B (n=101), the three-year major adverse cardiac event rate was 10.0% without any scaffold thrombosis. In Absorb BVS, neointima tissue continued to develop at midterm follow-up (2.17±0.48 mm^2 vs. 1.38±0.52 mm^2, p<0.0001) and covered the underlying tissues without compromising the luminal dimensions (5.93±1.49 mm^2 vs. 6.14±1.49 mm^2, p=0.571) as it was accommodated by the expanded scaffold (8.28±1.74 mm^2 vs. 7.67±1.28 mm^2, p<0.0001). Of 51 patients with OCT imaging post-procedure, acute scaffold disruption was observed in 2 patients (3.9%), which could be related to overexpansion of the scaffold at the time of implantation. One patient had a target lesion revascularization that was presumably related to the disruption. Of 49 patients without acute disruption, late discontinuities were observed in 21 patients. There were no major adverse cardiac events associated with this finding except for 1 patient who had a non-ischemia-driven target lesion revascularization.	Proved the restoration of the vessel analtomy, physiology/ functionality. The current investigation demonstrated the dynamics of vessel wall changes after implantation of a BRS, resulting at three years in stable luminal dimensions, a low restenosis rate and a low clinical major adverse cardiac events rate. Early and late restenosis after implantation of the Absorb bioresorbable scaffold could be related to anatomical or procedural factors. In this small cohort of patients late or very late restenosis seems to be attributed to pure intra-scaffold tissue growth without extrinsic encroachment of the scaffold. Neointimal tissue develops following either Absorb BVS or BMS implantation and shields lipid tissues. The neointimal response in the BMS causes a higher reduction of luminal dimensions compared to the Absorb BVS. Thus, Absorb BVS may have a value in the invasive re-capping of high-risk plaques. Acute scaffold disruption is a rare iatrogenic phenomenon that has been associated with anginal symptoms, whereas late strut discontinuity is observed in approximately 40% of patients and could be viewed as a serendipitous OCT finding of a normal bioresorption process without clinical implications.	First 6-month imaging (IVUS, IVUS-VH, OCT) results published in EuroIntervention 2010 (doi not provided), and then in Circulation 2010 (10.1161/CIRCULATIONAHA.110.970772). The preliminary results were documented in JACC Cardiovasc Interv 2011 (10.1016/j.jcin.2011.08.016), JACC 2011 (10.1016/j.jacc.2011.05.050), JACC Cardiovasc Interv 2012 (10.1016/j.jcin.2012.02.017). Results of multi-modality imaging study published first in Circ Cardiovasc Interv 2012 (10.1161/CIRCINTERVENTIONS.112.971549), and then in EuroIntervention 2014 (10.4244/EIJV9I11A217). A concern of restenosis analyzed in EuroIntervention 2015 (10.4244/EIJV10I11A218). An option of the formation of neointimal cap that seals the underlying plaque without compromising the luminal dimensions described comprehensively in EuroIntervention 2015 (10.4244/EIJY14M10_06). A concern of the BRS fracture/ discontinuity presented in JACC Cardiovasc Interv 2014 (10.1016/j.jcin.2014.06.016). The restoration of vasomotion was described in Eur Heart J 2012 (10.1093/eurheartj/ehr466).

(Table 1) contd…

Study (year)	Results and main findings	Comments	Reference (doi), or link
Simple to moderately complex populations			
ABSORB EXTEND Design: prospective, single-arm, open-label clinical study, N=800, 1st endpoint: ID-MACE	The safety and performance of the Absorb BVS system has been previously established in 131 patients from cohort A and cohort B of the first-in-man ABSORB trial. Following this trial, ABSORB EXTEND was initiated as a global continued access study (outside of the USA) to expand experience with the Absorb BVS system to different geographies with broader inclusion criteria to include the treatment of longer lesions and multiple vessels. The composite endpoints of ischaemia-driven MACE and ischaemia-driven target vessel failure were 4.3% and 4.9%, respectively. The cumulative rate of ARC defined definite and probable scaffold thrombosis for this population was 0.8% at one year.	First 512 patients shows low rates of MACE and scaffold thrombosis at 12-month follow-up. Preliminary results from the first 250 patients enrolled in ABSORB EXTEND demonstrate that the low rates of MACE, repeat revascularization and scaffold thrombosis seen at 12 and 24 months are sustained through 36 months.	The pivotal review article regarding to the concept of the transient scaffolding with BRS was presented in Eur Heart J 2012 (10.1093/eurheartj/ehr384). Results presented in EuroIntervention 2015 (10.4244/EIJV10I12A243), see comments in EuroIntervention 2014 (10.4244/EIJV10I4A73)
ABSORB II Design: Randomized, 2 Absorb BVS: 1 Xience, N=501, 1st endpoint: vasomotion and lumen diameter after the index procedure and at 3 years	At 1 year, cumulative rates of first new or worsening angina from adverse event reporting were lower (72 patients [22%] in the BRS group vs 50 [30%] in the metallic stent group, p=0·04), whereas performance during maximum exercise and angina status by SAQ were similar. The 1-year composite device orientated endpoint was similar between the BRS and metallic stent groups (16 patients [5%] vs five patients [3%], p=0·35). Three patients in the BRS group had definite or probable scaffold thromboses (one definite acute, one definite sub-acute, and one probable late), compared with no patients in the metallic stent group. There were 17 (5%) major cardiac adverse events in the BRS group compared with five (3%) events in the metallic stent group, with the most common adverse events being myocardial infarction (15 cases [4%] vs two cases [1%], respectively) and clinically indicated target-lesion revascularisation (four cases [1%] vs three cases [2%], respectively).	The BRS showed similar 1-year composite secondary clinical outcomes to the everolimus-eluting metallic stent.	The Lancet 2015 (10.1016/S0140-6736(14)61455-0)
All-comers			
GABI-R Design: registry, N=5000	Although two randomized controlled trials and several registries have documented safety and efficacy as well as non-inferiority of the BRS compared with drug-eluting metal stents, the current knowledge regarding clinical application, treatment success, and long-term safety of using this BRS in daily routine is limited. Thus, the goal of GABI-R is to address this lack of information.	None	Design published in Cardiovasc Revasc Med 2015 (10.1016/j.carrev.2015.09.002), NCT02066623 (results expected in 2020).
ABSORB FIRST, Design: prospective, multi-center global registry, N=1,800, 1st endpoint: scaffold thrombosis, cardiac death, myocardial infarction, revascularization, MACE, TLF	The safety and performance of the Absorb BVS has been previously demonstrated with clinical data up to 5 years (Cohort A), 3 years (Cohort B), 2 years (EXTEND). ABSORB FIRST is designed for post-approval surveillance of Absorb BVS used in complex lesions and patients typically treated in real-world settings. The largest report of 30-day post-PCI clinical results in Absorb-treated patients from a single trial (ABSORB FIRST, N=1,200) presented. Compared to the Cohort A, B and EXTEND these patients are at greater risks of CAD, higher rates of dyslipidemia (65.8% %), hypertension (64.8%), diabetics (25.1%), family history of premature CAD (37.9%), multivessel disease (48.4%), and prior cardiac interventions (24.4%). There is also a high proportion of patients with Class B2/C lesions (48.3 %), moderate/severe calcified lesions (18.6%), bifurcations (12.1%), total occluded lesions (10.4%), ostial lesions (6.2%). The mean lesion length is 18.6 ± 9.2 mm. The device success and procedure success rates were 98.4 % and 97.9 %, respectively. Subgroup analyses by patient and lesion complexities, access site, and physician's treatment techniques and implantation experience with BVS will also be reported.	The interim results from this large, global registry demonstrate excellent acute and subacute performance of Absorb in complex, real-world patients.	The interim report published first in JACC 2014 (10.1016/j.jacc.2014.07.679), but the final results remain unpublished, NCT01759290.
GHOST EU, Design: registry, N=1,189, 1st endpoint: TVF	TLF was recorded in 67 of 1,189 patients at a median of 109 (interquartile range 8-227) days after implantation. The cumulative incidence of TLF was 2.2% at 30 days and 4.4% at six months. The annualized rate of TLF was 10.1%. At six months, the rate of cardiac death was 1.0%, target vessel myocardial infarction was 2.0%, TLR was 2.5%, and target vessel revascularization was 4.0%. Diabetes mellitus was the only independent predictor of TLF (hazard ratio 2.41, 95% confidence interval: 1.28-4.53; p=0.006). The cumulative incidence of definite/probable scaffold thrombosis was 1.5% at 30 days and 2.1% at six months, with 16 of 23 cases occurring within 30 days.	"Real-world" outcomes of BVS showed acceptable rates of TLF at six months, although the rates of early and midterm scaffold thrombosis, mostly clustered within 30 days, were not negligible.	Early and midterm outcomes published in EuroIntervention 2015 (10.4244/EIJY14M07_11).
FRANCE ABSORB, Design: feasibility study in de novo lesions, N=2,000, 1st endpoint: 1-year MACE	This study will prospectively evaluate all procedures for coronary angioplasty with implantation of at least one BVS with a clinical follow-up of all patients implanted with ABSORB BVS. This national observatory will collect all the events related to product and/ or to procedure.	None	Unpublished (results expected in 2021), NCT02238054.

(Table 1) contd…

Study (year)	Results and main findings	Comments	Reference (doi), or link
All-comers			
AIDA Design: RCT vs XIENCE, N=2,690, 1st endpoint: 2-year TVF	The objective of the AIDA trial is to evaluate the efficacy and performance in an contemporary all-comer population of the Absorb BVS strategy vs the XIENCE family everolimus-eluting metallic coronary stent system in the treatment of coronary lesions. The study population includes both simple and complex lesions, in patients with stable and acute coronary syndrome. The follow-up continues for 5 years. The primary end-point of the trial is target vessel failure, defined as the composite of cardiac death, myocardial infarction, and target vessel revascularization, at 2 years.	None	Design published in Am Heart J 2014 (10.1016/j.ahj.2013.09.017), NCT01858077 (first results expected in 2017)
REPARA Design: registry, N=1,500, 1st endpoint: 1-year MACE	A multicentre, observational, prospective device registry, with no control group, de-signed to evaluate the efficacy and safety of the bioresorbable coronary device, used according to the indications of use, in daily clinical practice in a consecutive number of patients undergoing PCI in de novo coronary artery lesions.	None	Unpublished (results expected in 2016), NCT02256449
EVERBIO II Design: non-inferiority RCT EES vs BES vs BVS, N=240, 1st endpoint: late lumen loss at 9 months	The purpose of this study is to compare the efficacy and safety of everolimus- and biolimus-bluting stents with everolimus-eluting BRS. The null hypothesis to be re-jected is that there is no significant difference with regard to lumen late loss at 9 months and a clinical end point of death, myocardial infarction and TVR at 12 months between everolimus-eluting and biolimus-eluting stents and everolimus-eluting BRS.	None	Study protocol published in Trials 2014 (10.1186/1745-6215-15-9), NCT01711931.
ASSURE Design: registry, N=180, 1st end-point: safety and efficacy	A surveillance registry aims to evaluate the safety, performance and efficacy of the BVS system in patients with de novo native coronary artery lesions in all-day clinical practice.	None	Partly published in JACC Cardiovasc Interv 2011 (10.1016/j.jcin.2011.04.009), JACC 2011 (10.1016/j.jacc.2011.02.052), JACC 2011 (10.1016/j.jacc.2011.05.050), and EuroIntervention 2012 (10.4244/EIJV7I9 A168), and then in EuroIntervention 2015 (10.4244/EIJY14M12_10). The final results expected in 2016 (NCT 01583608).
BVS-RAI Design: registry, N=1,000, 1st endpoint: TLF at 1 year and device-oriented major adverse cardiac events within 5years	The Registry will contribute observational knowledge on the long-term safety and efficacy of the Absorb BVS as used in a number of Italian interventional centres in a broad spectrum of settings. Unrewarded and undirected consecutive patient enrol-ments are key-features of this observation, which is therefore likely to reflect common clinical practice in those centres.	None	Design published in Cardiovasc Revasc Med 2015 (10.1016/j.carrev.2015.05.010), NCT02298413.
Complex populations			
POLAR-ACS Design: ACS registry, N=100, 1st endpoint: safety, clinical evidence, proce-dure, success and in-hospital MACE	Predilation was performed in 93% of the patients. The final Thrombolysis In Myocar-dial Infarction (TIMI) 3 flow was achieved in 99% of the patients. In all patients, BVS was successfully implanted. In 81% of the patients, postdilation was performed with a balloon catheter with the same diameter as BVS; in 11%, with a balloon catheter with a diameter of 0.25 mm larger than BVS; and in 7%, with a balloon catheter with a diameter of 0.5 mm larger than BVS. We observed no no-reflow phenomenon, 1 distal embolization, and 2 slow-flow phenomena. Two major adverse cardiac events were reported, namely, periprocedural myocardial infarction in 2 patients. During 1-year follow-up, we observed only 1 additional myocardial infarction caused by stent thrombosis as well as 1 target lesion revascularization.	Study in acute coronary syn-drome population showed to be a safe and effective procedure.	Pol Arch Med Wewn 2014 (PMID: 25563622).
ABSORB Expand trial (N=300) & BVS STEMI registry (N=49) Design: 1st end-point: clinical outcomes	In ABSORB Expand trial the scaffold used in patients with complex lesions including a long lesion (>32mm in length), a calcified lesion, a bifurcation lesion and a large vessel with up to 4 mm in diameter. Patients presenting with stable angina, unstable angina and non-ST elevation myocardial infarction were included. In total 248 scaf-folds were implanted, with a procedural success rate of 95%, in the lesions including 40 bifurcations and 11 chronic total occlusions. In 52 patients (53 lesions), more than one scaffold was implanted with overlap. An interim analysis of the population at one month revealed no MACE event except for one myocardial infarction. In BVS STEMI study optical coherence tomography analysis performed in 31 patients showed that the post-procedure mean lumen area was 8.02 ± 1.92 mm(2), minimum lumen area 5.95 ± 1.61 mm(2), mean incomplete scaffold apposition area 0.118 ± 0.162 mm(2), mean intraluminal defect area 0.013 ± 0.017 mm(2), and mean percent-age malapposed struts per patient 2.80 ± 3.90%. Scaffolds with >5% malapposed struts were 7. At the 30-day follow-up, target-lesion failure rate was 0%. Non-target-vessel revascularization and target-vessel myocardial infarction (MI) were reported. A non-target-vessel non-Q-wave MI occurred. No cases of cardiac death or scaffold thrombosis were observed.	The BVS implantation in patients presenting with acute MI appeared feasible, with high rate of final TIMI-flow III and good scaffold apposition. The concern of the BRS thrombosis was explored exten-sively with a single-center experi-ence. The study of 14 patients demonstrated that suboptimal implantation with incomplete lesion coverage, underexpansion, and malapposition comprises the main pathomechanism for both early and late BVS thrombosis, similar to metallic stent thrombosis. Dual antiplatelet therapy discontinuation seems to also be a secondary contributor in several late events.	ABSORB Expand trial presented first in JACC 2013 (10.1016/j.jacc.2013.08.1170), and BVS STEMI in Eur Heart J 2014 (10.1093/eurheartj/eht546). A concern of the BRS thrombosis explored in Circ Cardiovasc Interv 2015 (10.1161%2FCIRCINTERVEN-TIONS.114.002369).

(Table 1) contd…

Study (year)	Results and main findings	Comments	Reference (doi), or link
Complex populations			
ISAR ABSORB MI Design: non-inferiority vs EES, N=260, 1st endpoint: per cent diameter stenosis at 6-8 months	The aim of the study is to test the clinical performance of the everolimus-eluting BRS compared with that of the durable polymer everolimus-eluting stent (EES) in patients undergoing PCI in the setting of acute MI.	Study in MI population.	Unpublished, NCT 01942070 (completed).
PRAGUE 19 Design: STEMI (STEMI Killip I/II), N=142, 1st endpoint: Clinical outcomes	The BRS device success was 98%, thrombolysis in myocardial infarction 3 flow was restored in 95% of patients, and acute scaffold recoil was 9.7%. An optical coherence tomography (OCT) substudy (21 patients) demonstrated excellent procedural results with only a 1.1% rate of scaffold strut malapposition. Edge dissections were present in a 38% of patients, but were small and clinically silent. Reference vessel diameter measured by quantitative coronary angiography was significantly lower than that measured by OCT by 0.29 (±0.56) mm, P = 0.028. Clinical outcomes were compared between BVS group and Control group; the latter was formed by patients who had implanted metallic stent and were in Killip Class I or II. Combined clinical endpoint was defined as death, myocardial infarction, or target vessel revascularization. Event-free survival was the same in both groups; 95% for BVS and 93% for Control group, P = 0.674.	Study in MI population'	Eur Heart J 2014 (10.1093/eurheartj/eht545).
ABSORB STEMI - TROFI II Design: STEMI vs XIENCE, N=190, 1st endpoint: 6-month, neointimal healing score	At 6 months, HS was lower in the Absorb arm when compared with EES arm [1.74 (2.39) vs. 2.80 (4.44); difference (90% CI) −1.06 (−1.96, −0.16); Pnon-inferiority <0.001]. Device-oriented composite endpoint was also comparably low between groups (1.1% Absorb vs. 0% EES). One case of definite subacute stent thrombosis occurred in the Absorb arm (1.1% vs. 0% EES; P = ns).	Stenting of culprit lesions with Absorb in the setting of STEMI resulted in a nearly complete arterial healing which was comparable with that of metallic EES at 6 months.	Eur Heart J 2015 (10.1093/eurheartj/ehv500). The final results expected in 2017 (NCT01986803).
BVS STEMI STRATEGY-IT Design: registry, N=500, 1st endpoint: device oriented composite end-point	This is a registry on consecutive STEMI patients eligible to undergo primary percutaneous coronary intervention (PPCI) with BRS implantation on the basis of the pre-specified inclusion and exclusion criteria. This registry has the objective to assess the immediate (peri-procedural and 30 days), mid (6 months and 1 year) and long-term (3 and 5 years) results following BVS implantation using a pre-specified implantation strategy during PPCI in STEMI subjects.	None	Unpublished (first results expected in 2016), NCT02601781
ABSORB CTO Design: CTO, N=35, 1st endpoint: safety and performance	According to the Japanese-CTO (J-CTO) complexity score, most lesions were classified as intermediate (49%) or difficult-very difficult (26%); 34% were moderate-severely calcified. Most cases (86%) were treated with an anterograde strategy, 60% by radial or biradial approach. In 71% a cutting balloon was used. The total scaffold length implanted per lesion was 52.5±22.9 mm. All scaffolds were successfully delivered and deployed. Post-dilatation was undertaken in 63%. By OCT, final minimum scaffold area and lumen stenosis were 7.1±1.5 mm2 and 11.7±6.6%, without areas of significant strut malapposition. At complete six-month follow-up, no major adverse events were observed. MSCT identified two cases of scaffold reocclusion.	BRS for CTO recanalisation demonstrates excellent feasibility and safety as well as mid-term efficacy. Appropriate lesion preparation is key to aiding adequate expansion of these scaffolds in this setting.	EuroIntervention 2015 (10.4244/EIJY14M12_07).
PABLOS Design: bifurcations, N=30, 1st endpoint: device, procedural main and side branches	The prospective observational registry evaluating the use of Absorb BVS specifically in patients with bifurcation lesions. Details are not available.	Study in population with bifurcation lesions.	Details are not available.
IT-DISAPPEARS Design: MVD and long lesion registry, N=1,000, 1st endpoint: safety and efficacy	A growing body of evidence worldwide is supporting BRS implementation into daily practice as being associated with comparable results as the second-generation everolimus-eluting stent. However, these pieces of evidence come from 'studies in which the majority of the patients had low-risk stenoses', whereas patients with more complex coronary artery disease could benefit the most from the Absorb BVS technology. Primary endpoint will be the cumulative hierarchical incidence of major adverse cardiac events at 1 year, defined as: cardiac death, nonfatal target vessel myocardial infarction, or clinically driven target lesion revascularization. The efficacy as well as safety parameters will be evaluated along with a detailed evaluation of the dual antiplatelet therapy duration/interruption.	Study in patients with multivessel disease, diffuse and long lesions.	Design published in J Cardiovasc Med (Hagerstown) 2015 (10.2459/JCM.0000000000000219), NCT02004730 (completed).

(Table 1) contd…

Study (year)	Results and main findings	Comments	Reference (doi), or link
Complex populations			
PREVENT Design: allocated randomized, N=1,600, 1st endpoint: cardiovascular death, nonfatal myocardial infarction, unplanned hospitalization leading to unstable angina	The purpose of this study is to determine whether BRS implantation on functionally insignificant coronary stenosis with vulnerable plaque reduce the incidence of the composite of cardiovascular death, nonfatal myocardial infarction, or unplanned rehospitalization due to unstable angina compared with optimal medical therapy alone.	None	Unpublished (results expected in 2019), NCT02316886
Large randomized clinical trials			
ABSORB China Design: RCT, N=480, 1st endpoint: in-segment late loss at 1 year	The in-segment LL at 1 year was 0.19 ± 0.38 mm for BVS vs. 0.13 ± 0.37 mm for CoCr-EES; the one-side 97.5% upper confidence limit of the difference was 0.14 mm, achieving non-inferiority of BVS compared to CoCr-EES (Pnon-inferiority=0.01). BVS and CoCr-EES also had similar 1-year rates of TLF and definite/probable scaffold/stent thrombosis (0.4% vs. 0.0% respectively, p = 1.0).	BVS was non-inferior to CoCr-EES for the primary endpoint of in-segment LL at 1 year.	JACC 2015 (10.1016/j.jacc.2015.09.054)
ABSORB Japan Design: RCT, N=400, 1st endpoint: TLF at 1 year	TLF through 12 months was 4.2% with BVS and 3.8% with CoCr-EES [difference (upper one-sided 95% confidence limit) = 0.39% (3.95%); Pnon-inferiority < 0.0001]. Definite/probable stent/scaffold thrombosis at 12 months occurred in 1.5% of the patients with both devices (P = 1.0).	12-month clinical and 13-month angiographic outcomes of BVS were comparable to CoCr-EES.	Eur Heart J 2015 (10.1093/eurheartj/ehv435)
ABSORB III Design: RCT, N=2,250, 1st endpoint: TLF at 1 year	Target-lesion failure at 1 year occurred in 7.8% of patients in the Absorb group and in 6.1% of patients in the Xience group (difference, 1.7 percentage points; 95% confidence interval, −0.5 to 3.9; P=0.007 for noninferiority and P=0.16 for superiority). There was no significant difference between the Absorb group and the Xience group in rates of cardiac death (0.6% and 0.1%, respectively; P=0.29), target-vessel myocardial infarction (6.0% and 4.6%, respectively; P=0.18), or ischemia-driven target-lesion revascularization (3.0% and 2.5%, respectively; P=0.50). Device thrombosis within 1 year occurred in 1.5% of patients in the Absorb group and in 0.7% of patients in the Xience group (P=0.13).	The treatment of noncomplex obstructive coronary artery disease with a BVS, as compared with a CoCr-EES was within the prespecified margin for noninferiority with respect to target-lesion failure at 1 year.	New Engl J Med 2015 (10.1056/NEJMoa1509038)
Other running trials			
ABSORB PROSPECT & PROSPECT II Design: prospective observational study, N=900, 1st endpoint: NC-MACE	The study has two components, an overall prospective observational study using multimodality imaging (PROSPECT II) that will examine the natural history of patients with unstable atherosclerotic CAD with the specific goal to establish the utility of low risk intracoronary imaging modalities, IVUS and Near Infrared Spectroscopy (NIRS), to identify plaques prone to future rupture and clinical events. The randomized PROSPECT ABSORB substudy will examine whether treatment of vulnerable plaques (defined based on PROSPECT as lesions with plaque burden ≥70% which are expected to have a lesion specific event rate of 8.7% at 2 years) with the Absorb BVS plus Guideline Directed Medical Treatment (GDMT) safely increases the Minimal Lumen Diameter (MLA) at 2 years compared with GDMT alone.	None	Unpublished (expected in 2018), NCT02171065
ABSORB RESTORATION Design: subanalysis of ABSORB III trial	The imaging substudy of ABSORB III clinical trial which intends to address th issues following implantation of a fully resorbable scaffold vs. a metal stent.	Must prove the restoration of the vessel anatomy	Unpublished, NCT01751906 (ABSORB III)
ABSORB IV Design: RCT, N=3,000, 1st endpoint: angina within 1 year	ABSORB IV is a continuation of ABSORB III (NCT01751906) trial which are maintained under one protocol because both trial designs are related. The data from ABSORB III and ABSORB IV will be pooled to support the ABSORB IV primary endpoint. Both the trials will evaluate the safety and effectiveness of Absorb BVS.	None	Unpublished (first results expected in 2017), NCT02173379

(Table 1) contd…

Study (year)	Results and main findings	Comments	Reference (doi), or link
Other running trials			
ABSORB PHYSIOLOGY Design: Allocated, randomized, N=36, 1st endpoint: coronary artery endothelial responsiveness - change of vessel diameter by 1) pacing, 2) hand-grip and 3) acetylcholine injection	Study evaluates: the acute (post-implantation) effect of an implanted BVS or metallic drug eluting stent (mDES) on coronary blood flow and physiological responsiveness of the target coronary artery The long-term (2 years) effect of an implanted BVS or mDES on coronary blood flow and physiological responsiveness of the target coronary artery.	None	Unpublished, NCT01308346

Abbreviations: TLF – target lesion failure, ID-MACE - ischaemia-driven major adverse cardiac events, TVF – target vessel failure. MVD – multi-vessel disease, ACS – acute coronary syndrome, MI – myocardial infarction, NC-MACE – non-culprit MACE, BRS – bioresorbable scaffold, BVS – bioresorbable vascular scaffold.

The ABSORB II trial [24] had a 2:1 single-masked design matching Absorb BVS with everolimus-eluting metallic stent, and a small sample population of 501 patients, with sophisticated co-primary endpoints of nitrate-induced vasomotion and changes in minimum lumen diameter (in-stent late loss) at 3 years. The similar post implantation acute recoil (0.19 mm for both, p=0.85), and lower acute lumen gain were documented for BRS by both angiography (1.15 mm vs 1.46 mm, p<0.0001) and IVUS (2.85 mm^2 vs 3.60 mm^2, p<0.0001). The 1-year composite device orientated endpoint was similar between BRS and metallic stent groups (16 patients [5%] vs 5 patients [3%], p=0.35). Three patients in the BRS group had definite or probable scaffold thrombosis (one definite acute, one definite sub-acute, and one probable late), compared with no patients in the metallic stent group which is consistent with the previous studies [25, 26]. The ABSORB III trial confirmed non-inferiority of Absorb BVS if compare with XIENCE V stent [27]. In this large, multicenter, randomized trial, 2008 patients with stable or unstable angina were randomly assigned in a 2:1 ratio to receive an everolimus-eluting bioresorbable vascular (Absorb) scaffold (1322 patients) or an everolimus-eluting cobalt–chromium (Xience) stent (686 patients). Target-lesion failure at 1 year occurred in 7.8% of patients in the Absorb group and in 6.1% of patients in the Xience group (difference, 1.7 percentage points; 95% confidence interval, −0.5 to 3.9; P=0.007 for noninferiority and P=0.16 for superiority). Device thrombosis within 1 year occurred in 1.5% of patients in the Absorb group and in 0.7% of patients in the Xience group (P=0.13).

So, for today, the extensive experience (see Table **1**) demonstrates such advantages of BRS as reduction of late events (ABSORB EXTEND, 2014), restored vessel function (ABSORB cohort B trial, 2014), reduced revascularization rates (ABSORB II, 2014), plaque regression (two multi-imaging modality studies of ABSORB A and B trials documented a biphasic change of the total plaque area), and lumen gain (ABSORB cohort B trial, 2011, 2013) [3, 28]. Definitely, BRS performs well in STEMI patients covering the lesions if compare with DES, but thrombosis raises concerns. Running ABSORB IV trial aims to prove superiority of BRS. Meanwhile, BRS are generally more challenging to implant in comparison with metallic stents (especially in complex lesions), and careful patient and lesion selection is crucial to ensure the good results with this technology. Moreover, clinical experience with these devices remains rather limited (amid growing evidence of late clinical events attributed to late restenosis, late or very late stent thrombosis and in-stent neoatherosclerosis), and further comparative efficacy data are required before we can be sure of the place of these devices in the routine clinical practice [28].

Thus, Absorb BVS in combination with other state-of-the-art approaches could pave the way for a new era of atheroregression and vascular reparative therapy.

OPTIMIZING BRS – TARGETING KEY MOLECULAR AND CELLULAR PATHWAYS

mTOR inhibitors remain the key compound of BRS. mTOR is a key mediator of proliferation, growth, survival, motility, autophagy, protein synthesis, inflammation and metabolism [29]. mTOR is a part of two distinct multiprotein complexes, of which only mTOR complex 1 (mTORC1) is sensitive to cyclic macrolides, whereas mTOR complex 2 (mTORC2) is not. Preclinical systemic application of mTOR inhibitors decreases atherosclerotic plaque formation in both apolipoprotein E knockout ($ApoE^{-/-}$) and low-density lipoprotein-receptor knockout ($LDL\text{-}R^{-/-}$) mice [30]. Systemic mTOR inhibitors also increase plasma triglycerides and LDL cholesterol levels which may be mediated, at least in part by decreased levels of hepatic LDL-R and increased PCSK9 [30]. Very recent findings imply a novel role of mTOR in the ageing process [31]. Chronic rapamycin treatment prolongs life span in *C. elegans* [31], drosophila and mice [30, 31]. At the molecular level the following questions on mTORC1 inhibition remain unanswered: what are the effects of mTOR inhibitors on vascular healing, foam cell formation, autophagy, cholesterol metabolism and reverse cholesterol transport as well as their effects on vascular ageing.

The previous bench and bedside findings support the concept that BRS could set the stage for 'physiological reversal' of atherosclerosis (60 articles, 2006-2012, collected in the ABSORB Publication Compendium, Erasmus University Medical Center Library, Rotterdam, The Netherlands) [8, 12]. New treatment such as systemic mTORC1-inhibitor administration, advanced statins (such as rosuvastatin) [1, 2], Lp-PLA2 inhibitor darapladib [21], ApoA-I Milano, PCSK9 [30], other drug agents, and tailored physical exercises may improve clinical results after BRS implantation.

BRS/mTOR-inhibitor-associated reversal of atherosclerosis (see Fig. **2**) is mediated by late wall thinning with putative atheroregression, and late lumen enlargement with unmodified or even expanded EEM, resulting in a dilated 'overcompensated' [15] vessel [16]. It has been hypothesized that the reversal of atherosclerosis is a result of reorganization of the extracellular matrix (ECM) by non-fibrillar collagen, elastin and entire connective tissue, with mobilization and reduction of the necrotic core, in conjunction with a change in macrophage (whereas existence of 6 subtypes: M1, M(Hb), Mhem, M2, Mox, M4), local immunity (including response of adventitia and adventitial tertiary lymphoid organs), myofibroblast (MF), vascular smooth muscle cell (VSMC) phenotypes and pools with the certain role of micro-RNAs in atherosclerotic plaque formation and rupture, through regulation of inflammation, microcalcification, angiogenesis and apoptosis, and interaction with biomechanical factors. It is unknown whether this 'plaque and media regression' on IVUS [20, 32] is a true atherosclerotic regression, with change in vessel wall composition and plaque morphology or a pseudo-regression due to resorption of the polymeric struts [32], remodeling of the provisional matrix left behind, or shrinking of new tissue [33, 34].

True atherosclerotic regression will be only confirmed and understood when the unresolved mechanistic questions are answered *in vitro* and *in vivo*, assuming that mTOR inhibitors durably affect central pathways in progression of atherosclerosis [12, 29], particularly halting vascular smooth muscle proliferation and migration. The restoration of vasomotion [35] and the recapping of lesions [6] in patients with Absorb BVS implantation open a new page in the history of the intravascular treatment already dubbed 'vascular reparative therapy' by some investigators [6, 11, 18].

BRS may potentially stimulate specific molecular pathways promoting vascular remodeling, innate [9, 36] and adaptive immunity, and trigger mechanisms including re-endothelialization, cellular reorganization, and resorption of calcium by osteoclast-like cells [37]. The rebuilding of the vessel wall via de- and transdifferentiation of the resident and other stem or progenitor cells is regulated by shear stress or mechanical tension and growth factors such as TGFβ, extra domain A fibronectin (ED-A FN) and other cytokines [38, 39]. Thus, BRS hypothetically triggers the physiological recovery of the vessel wall after the intervention, optimizing the biologic response to its implantation and enhancing atheroprotective mechanisms in the target lesion.

The mobilization and subsequent reduction of the necrotic core is a cornerstone target for BRS, halting macrophage-dependent pathways with impact on prolonged endoplasmic reticulum stress, phenotype and activity as well as primary and secondary necrosis [40]. The activity of the adventitia [41] as a niche for stem and progenitor cells, source of myofibroblasts, and a gate for inflammatory cells including B and T cells [41, 42] is a pivotal element of the vessel wall homeostasis, which might be also affected by BRS. Furthermore, the turnover of endothelium and optimal re-endothelialization with engraftment of circulating progenitors [42, 43] as well as neovascularization [10, 33, 44] and switch over VSMC or myofibroblasts [33, 34] are other factors determining the restoration of the vessel wall and optimal artery remodeling after Absorb BVS implantation.

BRS is also able to potentially modulate biologic effects of shear stress and mechano-transduction with a slow adaptive response of the vessel wall to the mechanical degradation of the BRS, facilitating restoration of cyclic strain by affecting the arterial stiffness as well as rearrangement of collagen/elastin density and the connective tissue frame [34]. The degradation of fibrillar and accumulation of non-fibrillar 'hyaline-like' [28] collagen maintains the balance of the fiber density between different sublayers, thereby probably changing the mechanics of the artery and ensuring the 'conservation' or 'cementation' of ECM particularly between necrotic core and lumen. This degradation, accompanied by continuous slow increase of production of elastic constituents with turnover of collagen, provokes overcompensated extension of the vessel wall.

The cellular mechanisms of the above-mentioned arterial remodeling remain unclear due to the limited interpretation of some histology studies [5, 6, 8]. The Russell-Movat pentachrome staining does not allow distinction between the synthetizing phenotype of VSMC and MF. Both types of cells synthesize smooth muscle alpha-actin and vimentin as well as collagen and proteoglycans, and have their distinction mostly in the transcriptional mechanism of protein expression [45]. The only difference between these cell types is expression of myosin (lacking in MF) and desmin (absent in VSMC) [45].

Accumulation of ECM, α-smooth muscle actin-expressing cells (Fig. **5**) such as VSMC, MF and macrophage subsets (along the M1 - M2 spectrum) may play a major role in the overcompensated remodeling and formation of the so called OCT (optical coherence tomography)-documented phenomenon of 'golden tubes' (novel optically-bright homogenous internal layer) observed after Absorb BVS implantation with fibro-elastic reconstruction [45-50].

The polylactate of BRS is highly biocompatible and promotes normal metabolism with degradation up to products of the Krebs cycle [51]. Metabolic turnover of lactate could be a key factor in the mitochondria- and ROS-mediated response to the exhaustion of energy and cell respiration. This approach is of significant value in designing new therapeutic strategies for alleviation of mitochondrial dysfunction and bioenergetics failure observed in atherosclerosis.

During the first 1-3 months after implantation local or systemic (long-term) mTORC1 inhibition using everolimus could modify parameters such as endothelial function (reduce eNOS expression at high shear stress); apoptosis/autophagy (stimulate innate immunity) [40]; matrix gen-

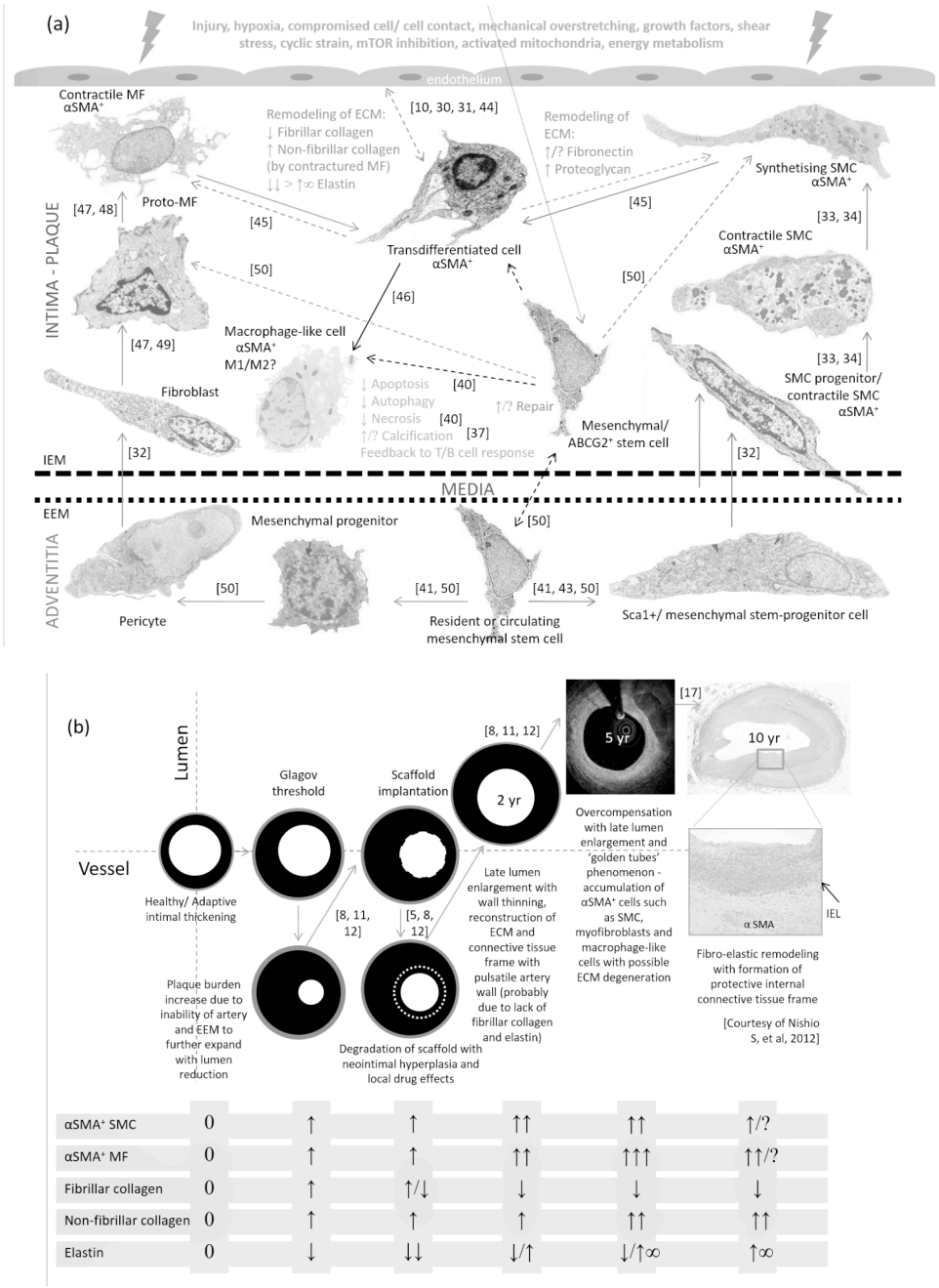

Fig. (5). Histological mechanisms of the artery remodeling after BRS implantation.
Panel (***a***) demonstrates the hypothetical cellular biology (animal data-based) of artery remodeling after the implantation of BVS/mTOR inhibitor platform. There are depicted: the role of phenotypic switch of smooth muscle cells (SMC) and fibroblasts/myofibroblasts (MF), migration (from the circulation, perivascular adipose tissue and resident sites – internal layers of adventitia) and action of different stem-progenitor cells (Sca1+, mesenchymal, circulating, bone marrow-derived) as well as activation of α-smooth muscle actin (+) (α-SMA) cells (MF, SMC, macrophages) with reconstruction of extracellular matrix (ECM) frame. IEM – internal elastic membrane, EEM – external elastic membrane. Pathways of α-SMA cell activation are considered as potential targets for the management of artery remodeling.
Panel (***b***) schematically represents the reorganization of the ECM and related artery remodeling after BVS implantation with analysis of the vessel/lumen ratio over time. Accumulation of α-SMA(+) cells with degradation of fibrillar collagen and deposition of elastin with non-fibrillar collagen play a major role in late lumen enlargement. IEL – internal elastic lamina. FIGURE ADAPTED FROM REFERENCE 2, 7, 9, 32.

eration (inhibit collagen synthesis) [52]; VSMC proliferation and migration [53]; cholesterol efflux (due to increased ABCA1) [53]; cholesterol uptake (suppression of scavenger receptors SR-A, SR-BII, CD68, CD36, LOX-1) [52, 53]; monocyte chemotaxis (decrease in MCP-1 and SDF-1) [52, 53], promoting a favorable immune and repair response with reduction of the necrotic core and atheroregression.

Taken together, BRS and mTORC1 inhibition may tip the balance in favor of scaffolding-mediated atheroprotection, and provide means to induce regression of atheroma below the *Glagov threshold*. This potential for atheroregression and vascular reparative therapy by BRS is also apparent in the development and application of bioactive nanostructured constructs for tissue regeneration and engineering.

BRS as a scaffold is able to act as a temporary template, guiding cell organization, growth and differentiation and providing structuring stability and a 3D environment where cells can produce new tissue. Seeded with stem cells BRS could be used for reorganization of the vessel architecture. Current experience with the BRS implantation provides evidence of this effect [5, 6]. Dislocated struts and organized thrombus mediated by implantation of BRS in the lumen may cause rebuilding of the artery wall and formation of new tissue [6] with benign clinical prognosis.

OPTIMIZING BRS – IN SEARCH OF THE IDEAL PLATFORM

The optimal design of BRS (Fig. **6**) should confer excellent mechanical properties, timely release of appropriate drugs and defined duration of resorption. The currently available BRS platform (Absorb BVS, Abbott Vascular, Santa Clara, CA) is a balloon expandable open-cell design device consisting of a polymer backbone of poly-L-lactide (PLLA) coated with a thin layer of 1:1 mixture of an amorphous matrix of poly-D, L-lactide (PDLLA), and 1.0 μg/mm^2 of the antiproliferative drug everolimus [18].

A novel optimal BRS platform could have a hybrid-cell design (open cells in the middle and closed cells at the edges) with thinner struts (40-80 μm) and stronger mechanical properties (radial strength at least 900-990 mmHg) with extra benefits such as slow drug releasing system for:

(1) mTOR and mPTP (mitochondrial permeability transition pore) inhibitors which suppress cytochrome C and apoptosis as well as provide anti-proliferative effects

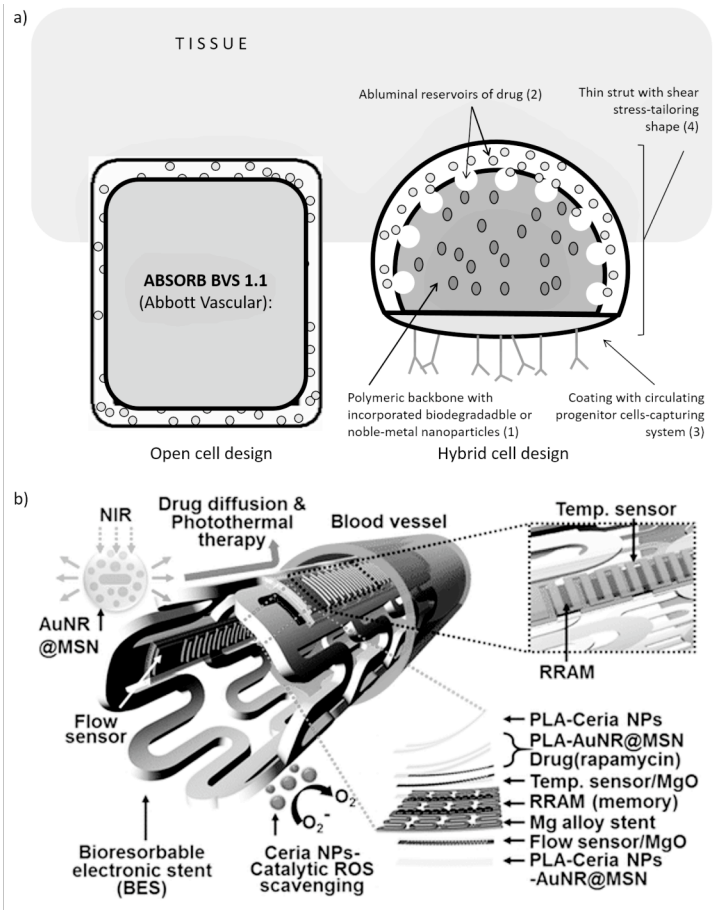

Fig. (6). The optimal implantable platform: BRS or nanotechnologies?
Panel (***a***) demonstrates a cross-sectional appearance of BRS (thick struts with weak mechanical properties, eluting mTOR inhibitor (one month release) and proposed optimal scaffold. The structure of the ultimate platform includes: (1) a polymeric backbone with incorporated biodegradable nanoparticles (for example, lipid and calcium-phosphate-based with better mechanical properties), carrying mTOR inhibitor/ drug (long-term drug-release and optimal local metabolism), (2) abluminal reservoir of mTOR inhibitor/ drug in lipid-based nanoparticles, acting acutely, (3) coating with antibodies to CD73$^+$, CD105$^+$ or CD133$^+$ in order to capture progenitor cells for optimal re-endothelialization and immune or repair responses.
Panel (***b***) depicts a scheme of the so-called multifunctional bioresorbable electronic stent (BRES) presented by the group of Dr. D. Son in 2015[49], which has a potential to become the ultimate concept of BRS. The conventional BRS technology was upgraded with the bioresorbable/bioinert nanomaterial attitudes, fitted with nanomembrane-based flexible flow/temperature sensors and memory storage devices, anti-inflammatory nanoparticles, and drug-loaded core/shell nanospheres that are activated by an external optical stimulus. Additionally, antenna characteristics of BRES for wireless power/data communication were performed. The ceria nanoparticles (NP) scavenge ROS generated in the perfusion by PEI and reduce inflammation that can cause in-stent thrombosis. The gold nanorod core/mesoporous silica NP shell (AuNR@MSN) design is able to control the drug loading and its release. The hyperthermia, which is regulated via feedback temperature sensing, controls localized drug delivery as well as provides thermal therapy.

via the peripheral benzodiazepine receptor, or other drugs, for example, regulators of immune-inflammatory response such as new generations of limus in stable formulation – micro-crystalline or in a lipid envelope; a preservation of the endothelial function is potentially possible with microRNA either [54], which is able to inhibit proliferative VSMC, thus preventing restenosis, while selectively promoting re-endothelialization and preserving endothelial function.

(2) Lipid metabolism modulators, for instance, rosuvastatin, lipoprotein-associated phospholipase A2 inhibitor, new substances such as PCSK9 inhibitors, ApoA1-Milano, monoclonal antibodies against oxLDL;

(3) Reparative therapy of vasomotion and artery remodeling;

(4) Agents against 'spontaneous' and necrotic-core-mediated calcification such as calcitriol and paricalcitol;

(5) Components of ECM, including components (powders) of adipose tissue, or recombinant with minimal concentration of platelet-reactive substances;

(6) Anti-platelet drugs with minimal local toxicity, atheroprotective and reparative potential.

The abluminal nanocoating (thickness no more than 100-150 nm) with bioresorbable polymer or nano-pores, and incorporation of nanoparticles, which are able to carry any drug could be helpful for the management of the vessel wall immediately after implantation and prevention of enhanced atherogenesis, atherothrombosis or detrimental and perverted biological feedback to the intervention. Local (drug-carrying nanoparticles within the backbone) or systemic administration (for example, low-dose chronic prescription of everolimus up to 2 mg each 2 days, or pulse therapy by 7.5 mg x 3 days, 5 mg x 2 days) [55, 56] of mTOR inhibitor enhances optimal re-endothelialization and the local cellular milieu's response and also provides general atheroprotective effects. Applying a drug-coated balloon [56] for pre-dilatation might be another solution for the local anti-proliferative therapy.

Calcium-phosphate [17, 56] or magnesium bioresorbable nanoparticles in the backbone and sophisticated management of the polymer structure ('raw' and rubber resin, shape memory technologies, solid freeform fabrication with microfilamentation) with alterations of carbon bonds are able to substantially alter mechanical properties of the scaffold (such as conformability, recoil, eccentricity or asymmetry) and allow reduction of strut thickness. Moreover, the PDLLA-luminal layer can be coated with antibodies to capture progenitor cells selectively, such as against CD73, CD105 (cells with pro-mesenchymal phenotype) or CD34 (bone marrow-derived cells) and CD133 (endothelial cells). Cell-capturing approaches involve different progenitor cell types with unpredictable local inflammatory and immune response and require sophisticated selection of capture antibodies.

The concept of the multifunctional bioresorbable electronic stent/ scaffold presented by the group of Dr. D. Son [57] from South Korea seems mostly revolutionary merely because it's comprising all the emerging technologies together including the most advanced achievements of the bio-inert nanomaterial with the flexible flow/temperature sensors and memory storage devices, anti-inflammatory and drug-loaded nanoparticles.

TRANSIENT SCAFFOLDING OPENS A NEW ERA OF VASCULAR REPARATIVE THERAPY

Transient scaffolding using BRS is foreseen as a potential platform upon which bioactive compounds will be added to act as disease-modifying agents [12]. The very recent results obtaining with BRS suggest that in the near future we might be able to treat coronary atherosclerotic plaques, prevents neoatherosclerosis, and partially restores the structure and function of the vessel wall. Furthermore, it is essential that BRS management attempts to promote partial anatomical and functional recovery of coronary artery and leads to some kind of repair with extracellular matrix-related 'conservation' of the arterial architecture [12].

In some recent studies on endoluminal long–term follow up of BRS-treated plaque, OCT (optical coherence tomography) has documented homogeneous layer of tissue, highly reflecting the incident light so that the appearance of the vessel has been dubbed 'golden tube' [11, 12]. The concept of plaque 'sealing' by coronary angioplasty was introduced two decades ago [12, 35]. After intervention, the healing mechanisms with intimal proliferation would provide a new, smooth, and elastic coat that is capable to cap the plaque prone to rupture. This new cap potentially prevents plaque rupture and protects against coronary thrombosis. But the histologic and biochemical nature of these so called 'golden tubes' still requires further investigations [11, 35]. Potentially, both late lumen enlargement with lesion recapping and plaque burden reduction after the BRS scaffolding underscore the clinical value of the transient scaffolding as a very promising approach for the reversal of atherogenesis below the Glagov threshold. In fact, design of the fully BRS pursues three aims: (1) revascularization with transient support of the lumen: the revascularization with BRS implies enough support to attain acute gain comparable to that of BMS, prevention of constrictive remodeling, maintenance of the artery dimensions during at least first six months after the intervention, and sufficient inhibition of biologic response by local drug delivery system to avoid restenosis; (2) restoration of a physiological response (shear stress, cyclic strain, vasomotion, immune-inflammatory response and morphology) of the transiently scaffolded vessel; and (3) benign scaffold resorption. Resorption of BRS is another major challenge and should correspond to certain conditions such as gradual degradation and elution of bio-products in order to minimize inflammation, while allowing restoration of vessel architecture.

Thus, if all the above parameters are carefully controlled, BRS may pave the way for atheroregression, optimal adaptive remodeling, tissue engineering, and partial vascular recovery.

CONCLUSION

The adoption of transient scaffolding using bioresorbable platforms and the progress of new technologies have created

an attractive field for device design in interventional cardiology and an important tool for treatment of atherosclerosis. This is largely due to the ability to guide artery remodeling, to generate multifunctional nanoagents bearing combinations of targeting, diagnostic, and therapeutic moieties. These approaches have the potential to achieve the goal of atheroregression below the *Glagov threshold*, thereby targeting restoration of vessel integrity.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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