

## Novel devices

# Bioresorbable scaffolds: rationale, current status, challenges, and future

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Current generation of drug-eluting stents has significantly improved the outcomes of percutaneous coronary intervention by substantially reducing in-stent restenosis and stent thrombosis. However, a potential limitation of these stents is the permanent presence of a metallic foreign body within the artery, which may cause vascular inflammation, restenosis, thrombosis, and neoatherosclerosis. The permanent stents also indefinitely impair the physiological vasomotor function of the vessel and future potential of grafting the stented segment. Bioresorbable scaffolds (BRSs) have the potential to overcome these limitations as they provide temporary scaffolding and then disappear, liberating the treated vessel from its cage and restoring pulsatility, cyclical strain, physiological shear stress, and mechanotransduction. While a number of BRSs are under development, two devices with substantial clinical data have already received a Conformité Européenne marking. This review article presents the current status of these devices and evaluates the challenges that need to be overcome before BRSs can become the workhorse device in coronary intervention.

## Keywords

Bioresorbable scaffolds • Drug-eluting stents • Coronary angioplasty

## Introduction

Coronary angioplasty, first performed by Gruntzig<sup>1</sup> in 1977, a technique that is now referred as plain old balloon angioplasty (POBA), revolutionized the treatment of coronary artery disease. However, the outcomes of POBA were compromised by re-narrowing of the coronary arteries due to elastic recoil, acute closure secondary to dissection, constrictive remodelling, and neointimal proliferation.<sup>2–4</sup> Coronary stents were developed to overcome these issues, by scaffolding the balloon-dilated artery, sealing the dissection flaps, and preventing acute recoil and late constrictive remodelling.<sup>4–7</sup> The two landmark trials, BENESTENT and STRESS, demonstrated superiority of the bare metal stents (BMS) over POBA and established BMS as 2nd revolution in coronary intervention.<sup>8,9</sup> The medium- and longer-term results of BMS were, however, compromised by high incidence of in-stent restenosis.<sup>10,11</sup> Drug-eluting stents (DESs) were developed by coating BMS with anti-proliferative drugs, sirolimus or paclitaxel, to overcome intra-stent neointimal proliferation. Drug-eluting stents have significantly reduced in-stent restenosis and target lesion revascularization (TLR) compared with BMS,<sup>12,13</sup> and hence considered as 3rd revolution in coronary intervention. The first-generation DESs

were associated with an increased risk of stent thrombosis,<sup>14,15</sup> but newer-generation DESs, with thinner struts and biocompatible or biodegradable polymers, have considerably improved safety profile.<sup>16–18</sup> However, these stents still leave a permanent metal implant inside the vessel with potential future problems. Bioresorbable stents (commonly referred as scaffolds) can provide support to the vessel wall (similar to a stent) for a defined period after angioplasty, but are subsequently resorbed, i.e. they ‘do their job and disappear’.<sup>19</sup> Although bioresorbable scaffolds (BRSs) have not yet overtaken the conventional stents, they are considered as 4th revolution in coronary intervention due to their promising potential. A list of abbreviations and acronyms used in this paper are provided in (Table 1).<sup>20</sup>

## Rationale for bioresorbable scaffolds

Bioresorbable scaffolds may offer potential advantages over other technologies (Table 2). Their superior conformability and flexibility compared with conventional stents reduce altered distribution of the tissue biomechanics and preserve vessel geometry.<sup>21</sup> The

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**Table 1** Abbreviations and acronyms

Abbreviation/acronym	Details
BMS	Bare metal stents
BRSs	Bioresorbable scaffolds
BVS	Biovascular scaffold
DAPT	Dual antiplatelet therapy
DESS	Drug-eluting stents
ISR	In-stent restenosis
IVUS	Intravascular ultrasound
MACE	Major adverse cardiac events
OCT	Optical coherence tomography
POBA	Plain old balloon angioplasty
PLLA	Poly-L-lactic acid
PDLLA	Poly-DL-lactic acid
ST	Stent thrombosis
TLR	Target lesion revascularization
TVR	Target vessel revascularization
VH	Virtual histology

**Table 2** Comparison of BRS with other angioplasty techniques/devices<sup>a</sup>

	POBA	BMS	DES	BRS
Acute occlusion	–	+	+	+
Acute recoil	–	+	+	+
Acute thrombosis	–	–	–	–
Sub-acute thrombosis	±	–	–	–
Late thrombosis	+	–	–	±
Very late thrombosis	+	±	–/±	+/?
Neointimal hyperplasia	–	–	+	+
Constrictive remodelling	–	+	+	+
Adaptive (expansive) remodelling	+	–	–	+
Restoration of vasomotion	+	–	–	+
Late luminal enlargement	+	–	–	+

<sup>a</sup>‘+’ indicates positive/beneficial effect; ‘–’ indicates negative/no effect; ‘±’ indicates neutral or uncertain effect; ‘?’ indicates the lack of definitive evidence.

POBA, plain old balloon angioplasty; BMS, bare metal stents; DESs, drug-eluting stents; BRSs, bioresorbable scaffolds.

<sup>a</sup>There are no direct comparative studies between these four techniques/devices and this table is, therefore, based on non-comparative data.

‘liberation of vessel from a metallic cage’ can help in restoration of physiological vasomotion, mechanotransduction, adaptive shear stress, late luminal gain (as opposed to late luminal loss with permanent stents), and late expansive remodelling.<sup>22</sup> The absence of any residual foreign material and restoration of functional endothelial coverage can also reduce the risk of stent thrombosis and need for long-term dual antiplatelet therapy (DAPT). Additionally, BRS can overcome some other problems associated with use of the permanent metallic stents such as ‘jailing’ of the side branches, overhang at ostial lesions, and inability to graft the stented segment.<sup>23</sup>

## Current status of the bioresorbable scaffolds technology

The historical development of bioresorbable polymers and scaffolds has been described elsewhere.<sup>24</sup> The efforts to make polymeric stents started nearly two decades ago; however, the technology failed to develop due to the lack of an ideal polymer at that stage (low-molecular-weight polylactides were associated with an intense inflammatory neointimal response) and the advent of metallic DES. IGAKI-TAMAI®, a fully bioresorbable scaffold made of poly-L-lactic acid (PLLA) without any drug coating, was the first device of its kind to be evaluated in man. This system was self-expanding, but also required contrast heated at 70–80°C and 30-s balloon inflation. First-in-man (FIM) trial ( $n = 15$ ) was reported in 2000, showing no stent thrombosis or major adverse cardiac events (MACEs) at 30 days, and one case of TLR at 6-month follow-up.<sup>25</sup> Despite these promising results and the possibility to reduce TLR by adding an anti-proliferative drug, this device failed to become a mainstream player due to concerns about use of the heated contrast in coronary arteries, although the device has a Conformité Européenne (CE) mark for use in peripheral arteries.

The current generation BRSs are composed of either a polymer or a metallic alloy (Table 3). Metallic BRSs are intuitively attractive, because they have potential to perform similar to the conventional metallic stents with respect to profile, deliverability, radial strength etc. in the initial phase, and the advantage of bioresorption subsequently. Iron- and magnesium-based alloys have been investigated as the candidates for BRS.<sup>26</sup> Polymeric BRSs are frequently made of PLLA and poly-DL-lactic acid (PDLLA), but there are also other polymers, each with a different biochemical characteristics and resorption time.<sup>24</sup>

## Bioresorbable scaffolds with a CE mark

The ABSORB biovascular scaffold (BVS; Abbott Vascular, CA, USA) and DESolve (Elixir Medical, CA, USA) devices have achieved a CE mark.

### ABSORB biovascular scaffold

ABSORB BVS is the first drug (everolimus)-eluting BRS composed of PLLA and PDLLA (Table 3). The first-generation device (BVS 1.0) was tested in the ABSORB Cohort A (Table 4), which showed late lumen enlargement, feasibility of non-invasive imaging with computed tomography (CT) scanning, and restoration of vasomotion and endothelial function at 2 years.<sup>27–29</sup> Five-year clinical follow-up showed no stent thrombosis, only one case of non-Q-wave myocardial infarction (MI), and an MACE rate of 3.4%.<sup>30,31</sup> The second-generation device (BVS 1.1), tested in the ABSORB Cohort B, demonstrated an MACE rate of 9.0% (three non-Q-wave MI, six ischaemia-driven TLR, and no cardiac death) during a 2-year follow-up (Table 4). The ABSORB Cohort B has completed 3-year follow-up, and there has been no case of a cardiac death or scaffold thrombosis, three cases of MI (all non-Q-wave), and seven ischaemia-driven TLR with an MACE rate of 10%.<sup>32</sup> A small head-to-head study comparing BVS ( $n = 31$  lesions) and XIENCE DES ( $n = 19$  lesions) has shown no significant differences in late lumen loss ( $0.18 \pm 0.20$  vs.  $0.29 \pm 0.36$  mm;  $P = 0.42$ ), percentage of uncovered struts (5.3 vs. 4.5%;

**Table 3** Summary of the design and structure of clinically tested bioresorbable scaffolds

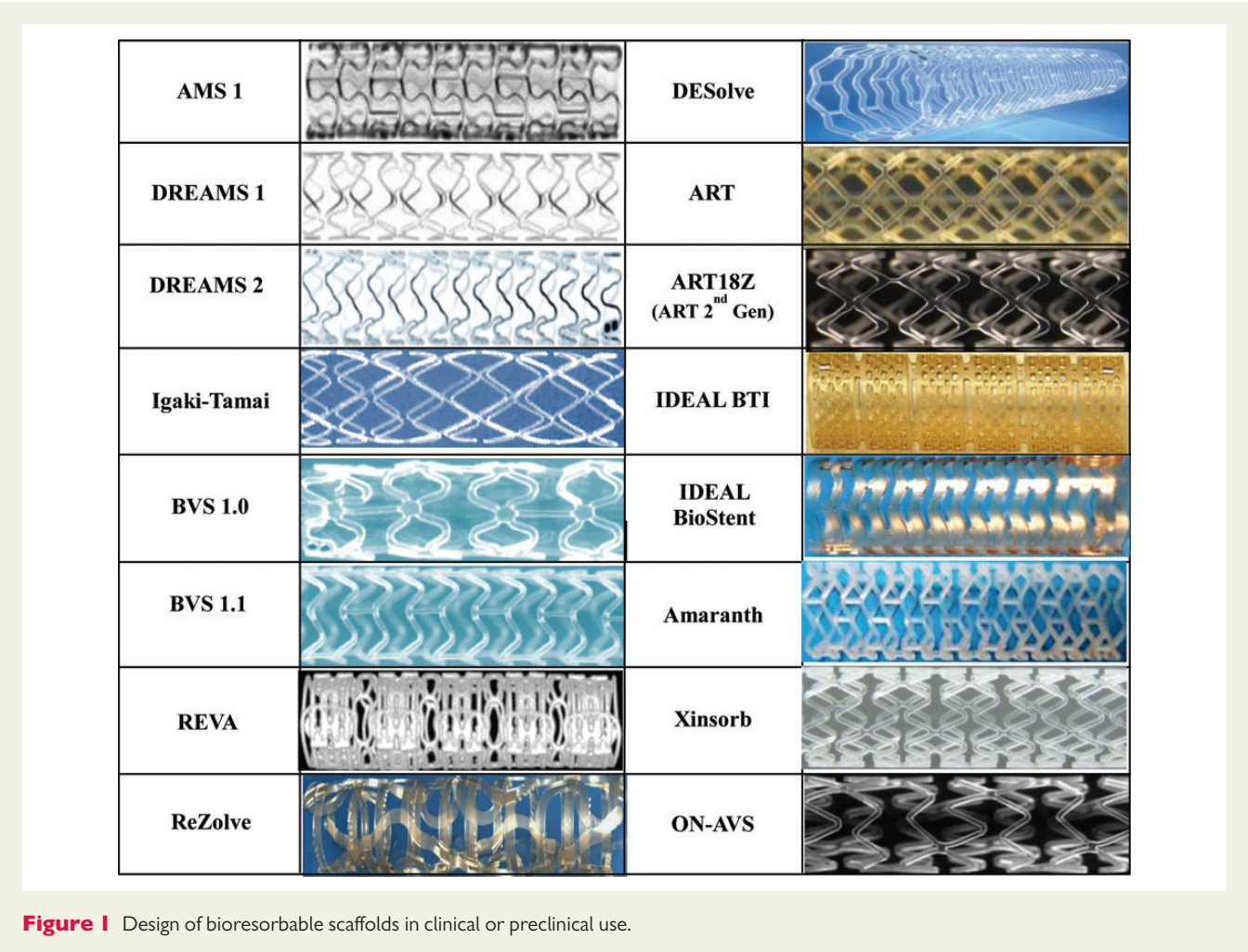
Scaffold (manufacturer)	Strut material	Coating material	Eluted drug	Strut thickness	Crossing profile	Radio-opacity	Radial support	Resorption (months)	Current status
<b>Metallic</b>									
AMS-1 (Biotronik)	Mg alloy	None	None	165	1.2 mm	None	Weeks	<4	Discontinued
DREAMS-1 (Biotronik)	Mg alloy with some rare metals	PLGA	Paclitaxel	125	N/A 6-Fr compatible	None	3–6 months	9	Clinical trials
DREAMS-2 (Biotronik)	Mg alloy with some rare metals	PLLA	Sirolimus	150	N/A 6-Fr compatible	Metallic markers	3–6 months	9	Clinical trial to be commenced
<b>Polymeric</b>									
Igaki-Tamai (Kyoto Medical)	PLLA	None	None	170	N/A	Gold markers	6 months	24–36	CE mark for peripheral use
BVS 1.0 (Abbott Vascular)	PLLA	PDLLA	Everolimus	156	1.4 mm	Platinum markers	Weeks	18–24	Discontinued
BVS 1.1 (Abbott Vascular)	PLLA	PDLLA	Everolimus	156	1.4 mm	Platinum markers	6 months	24–48	CE mark
DESolve (Elixir)	PLLA	None	Myolimus	150	1.5 mm	Metallic markers	N/A	12–24	CE mark
REVA (Reva Medical)	PTD-PC	None	None	200	1.8 mm	Radiopaque scaffold	3–6 months	24	Discontinued
ReZolve (Reva Medical)	PTD-PC	None	Sirolimus	115–230	1.8 mm	Radiopaque scaffold	4–6 months	4–6	Clinical trials
ReZolve2 (Reva Medical)		None	Sirolimus		1.5 mm	Radiopaque scaffold			
ART 18AZ (ART)	PDLLA	None	None	170	N/A 6-Fr compatible	None	3–6 months	3–6	Clinical trials
Fortitude (Amaranth)	PLLA	None	None	150–200	N/A 6-Fr compatible	None	3–6 months	3–6	Clinical trials
IDEAL BTI (Xenogenics)	Poly(lactide and salicylates)	SA/AA	Sirolimus	200	1.5–1.7 mm	None	3 months	6–9	Clinical trials

Mg, magnesium; PLLA, poly-L-lactic acid; PDLLA, poly-DL-lactic acid; BVS, bioresorbable vascular scaffold; SA/AA, salicylic acid/adipic acid; PTD-PC, poly-tyrosine-derived polycarbonate; CE, Conformité Européenne.

**Table 4** Summary of clinical trials with bioresorbable scaffolds

Scaffold	Clinical study	Number of patients	Major endpoints	Late loss (mm)	TLR	MACE
Metallic						
AMS-1	PROGRESS-AMS	63	MACE at 4 months	1.08 at 4 months	24% at 4 months	24% at 4 months
DREAMS-1	BIOSOLVE-I	46	Target lesion failure at 6 and 12 months	0.64 at 6 months 0.52 at 12 months	4.3% at 6 months 6.5% at 12 months	4.3% at 6 months 6.5% at 12 months
Polymeric						
Igaki-Tamai	Igaki-Tamai study	15	Acute recoil, late loss, and MACE at 6 months	0.48 at 6 months	6.7% at 6 months	6.7% at 6 months
BVS 1.0	ABSORB Cohort A	30	Acute success, MACE up to 5 years	0.44 at 6 months 0.19 at 6 months	0% at 6 months, 0% at 5 years	3.3% at 6 months, 3.4% at 5 years 9% at 2 years
BVS 1.1	ABSORB Cohort B	101	LLL, TLR, and MACE at 6 months, 1, 2, and 3 years	0.27 at 12 months	3.6% at 12 months	10% at 3 years
DESolve	DESolve 1	15	LLL at 6 months	0.19 at 6 months	6.7% at 12 months	20% at 12 months
	DESolve NX	120	Procedural success, LLL at 6 months, and MACE up to 5 years	0.21 at 6 months	1.6% at 6 months	3.25% at 6 months
REVA	RESORB	27	MACE	1.81 at 6 months	66.7% at 6 months	
ReZolve	RESTORE	50	TLR at 6 months, LLL at 12 months	0.20 at 12 months for $n = 8$	2 of 12 at 6 months	2 of 12 at 6 months

LLL, late lumen loss; MACE, major adverse cardiac events; TLR, target lesion revascularization.



$P = 0.11$ ), mean neointimal thickness ( $120.6 \pm 46.0$  vs.  $136.1 \pm 71.4 \mu\text{m}$ ;  $P = 0.82$ ), and in-stent/scaffold area obstruction ( $12.5 \pm 7.1$  vs.  $13.6 \pm 9.7\%$ ;  $P = 0.91$ ) at 12 months.<sup>33</sup>

**DESolve bioresorbable scaffolds**

DESolve<sup>®</sup>, a novolimus-eluting BRS, was tested in the DESolve FIM trial, which showed an effective suppression of neointimal hyperplasia at 6 months (Table 4), no significant change in vessel volume ( $148.0 \pm 37.0 \text{ mm}^3$  at baseline and  $150.03 \pm 35.38 \text{ mm}^3$  at 6 months) and, instead of ‘chronic recoil’, a scaffold enlargement (scaffold area  $5.35 \pm 0.78 \text{ mm}^2$  at baseline and  $5.61 \pm 0.81 \text{ mm}^2$  at 6 months).<sup>34</sup>

The DESolve Nx trial ( $n = 126$ ) presented at EuroPCR 2013 has shown that the primary endpoint of in-stent late lumen loss was  $0.21 \pm 0.34 \text{ mm}$  at 6 months. Intravascular ultrasound (IVUS) assessment of the scaffolds and vessels at 6 month in a subset of 40 patients has demonstrated a significant ( $P < 0.001$ ) increase in vessel area (17%), mean scaffold area (16%), and mean lumen area (9%). Serial optical coherence tomography (OCT) analysis in 38 patients also demonstrated a 17% increase in mean scaffold area ( $P < 0.001$ ) at 6 months. Nearly 99% of struts were covered by 6 months. An MACE rate was 3.35%, including one cardiac death, one non-Q-wave MI, and two cases of TLR (Table 4).<sup>35</sup> DESolve<sup>®</sup> has rather rapid drug

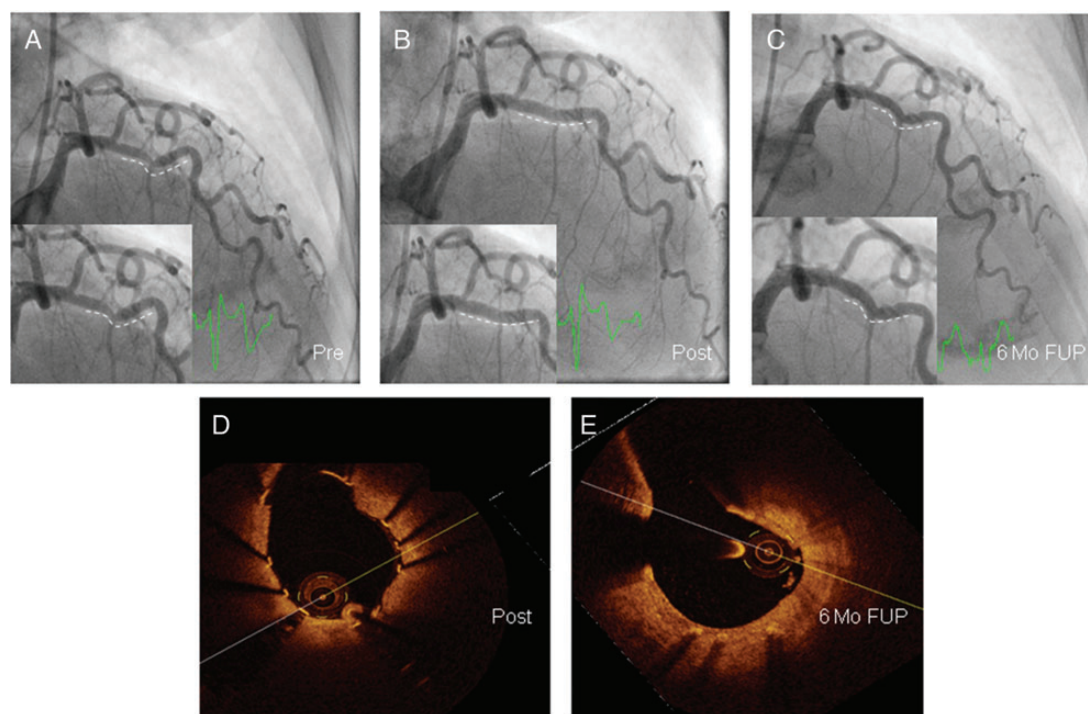
release (85% over 4 weeks). Therefore, there are some concerns about the long-term efficacy of device. A subset of patients will undergo multi-slice CT assessment at 12 months and angiographic, IVUS, and also OCT assessment at 24 months to provide longer-term assessment of the scaffold.

**Bioresorbable scaffolds in clinical trials**

**Magnesium-based metallic bioresorbable scaffolds**

AMS-1<sup>®</sup> (Biotronik AG, Bülach, Switzerland) was the first magnesium-based BRS evaluated in man in the PROGRESS-AMS study (Table 4). The immediate angiographic results were similar to metallic stents. However, the radial support was lost within a few weeks after implantation, resulting in a high rate of recoil and constrictive remodelling.<sup>36</sup> In addition to the mechanical insufficiency, the device was not eluting any anti-proliferative drug and hence associated with a high incidence of late loss and TLR (Table 4). However, no death, MI, or stent thrombosis occurred. Long-term follow-up data from angiographic and IVUS examination performed in eight patients who did not require repeat revascularization at 4 months have demonstrated no evidence of either late recoil or late neointimal growth.<sup>37</sup> These findings suggest that the magnesium scaffold was safe but lacked efficacy due to loss of scaffold support and uncontrolled neointima proliferation. Therefore, a drug-eluting version





**Figure 2** Angiographic and optical coherence tomography illustrations of a case with DREAMS<sup>®</sup> bioresorbable scaffold. Angiographic appearance of the scaffolded vessel segment before implantation (A), after implantation (B), and at 6 months' follow-up (C); and representative optical coherence tomographic images after implantation of drug-eluting absorbable metal scaffold (D) and at 6 months (E). Figures kindly provided by Hironori Kitabata and Ron Waksman.

called DREAMS<sup>®</sup> was developed by modifying scaffold design (Figure 1) and structure (Table 3). The drug-eluting absorbable metal scaffold (DREAMS)-1 which eluted paclitaxel ( $0.07 \mu\text{g}/\text{mm}^2$ ) for the first 3 months was tested in the BIOSOLVE-1 study (Table 4), showing good safety (one case of MI, no death, and no stent thrombosis) and efficacy at 12 months.<sup>38</sup> The 2-year clinical outcomes presented at EuroPCR 2013 showed 6.8% target lesion failure, including two cases of clinically driven TLR and one target vessel MI. No cardiac death or stent thrombosis was observed.<sup>39</sup> The device has been further optimized. DREAMS-2 has a six-crown, two-link design,  $150 \mu\text{m}$  strut thickness, radiopaque marker at both ends, and a thin PLLA-based carrier to deliver a more potent anti-proliferative drug (sirolimus). DREAMS-2 is currently being tested in the BIOSOLVE-II study ( $n = 120$ ) to get the data needed to apply for CE mark. An illustrative case of DREAMS BRS with OCT images is shown in Figure 2.

### ReZolve bioresorbable scaffolds

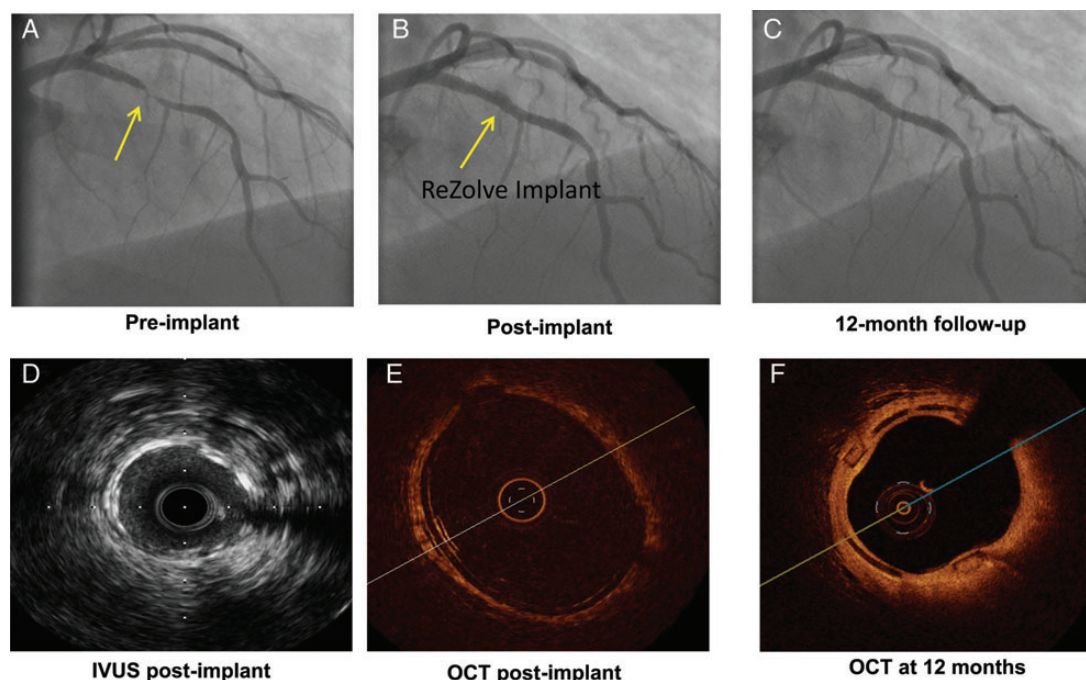
The ReZolve devices (REVA Medical, CA, USA) are made of desaminotyrosine polycarbonate, which is bioresorbable and radio-opaque polymer (Table 3). REVA's 'slide & lock' mechanism is based on a ratchet system where, as the stent is deployed in an artery by use of a balloon catheter, each 'tooth' on the sliding part passes through a bracket in the stent and gets locked to preventing it from going back (Figure 1).

The first-generation non-drug-eluting REVA BRS was evaluated in the RESORB FIM trial (Table 4). The data showed no vessel recoil

(vessel area  $15.5 \text{ mm}^2$  post-procedure and  $15.3 \text{ mm}^2$  at 6 months) but a disappointingly high in-stent late lumen loss and TLR.<sup>40</sup> To overcome these shortcomings, a sirolimus-eluting version, ReZolve BRS, was developed (Table 3) and is being evaluated in the RESTORE trial (Table 4). Preliminary data (26 patients with 6-month follow-up) have suggested reasonably good safety and efficacy.<sup>41</sup> However, the technical success rate of ReZolve was only 85%, due to sheathed delivery system and high crossing profile.<sup>41</sup> Further improvements in design have resulted in REVA's current product ReZolve2, which has a sheathless delivery system. ReZolve2 is being tested in the RESTORE-II study ( $n = 125$ ) to get the data needed to apply for CE mark. Angiographic, IVUS, and OCT illustrations of a case with ReZolve<sup>®</sup> BRS are shown in Figure 3.

### ART bioresorbable scaffolds

The ART BRS (Arterial Resorbable Therapies, Paris, France) is made from amorphous semi-crystalline PDLLA, so it resorbs relatively rapidly.<sup>42,43</sup> The design and structure are shown in Figure 1 and Table 3. In preclinical studies, positive remodelling (vessel enlargement) has been demonstrated to occur between 3 and 6 months. The device has no anti-proliferative drug, and it is hoped that outward vessel remodelling will accommodate intervention-induced intimal hyperplasia. The absence of anti-proliferative coating may also permit quicker restoration of endothelial coverage and function, which may limit neoatherosclerosis.<sup>44</sup> The ARTDIVA (Arterial Remodeling Transient Disrupting Vascular Angioplasty) FIM trial ( $n = 30$ ) is currently underway to assess an ART device in simple lesions.



**Figure 3** Angiographic, intravascular ultrasound (IVUS), and optical coherence tomography (OCT) illustrations of a case with ReZolve® bioresorbable scaffold. Angiogram revealed a 90% stenosis (A) which was treated with implantation of ReZolve bioresorbable scaffold (B) and showed good angiographic results at 12-month follow-up. Representative intravascular ultrasound (D) and optical coherence tomography sections post-implant (E) and at 12 months (F) are shown. Figures kindly provided by Alexandre Abizaid.

### Amaranth bioresorbable scaffolds

The Amaranth Fortitude™ (Amaranth Medical, CA, USA) is a non-drug-eluting PLLA device that has shown good performance in bench testing and animal models,<sup>45</sup> and an FIM study ( $n = 30$ ) has been started in 2013.<sup>46</sup> Considering the outcomes of previous non-drug-eluting BRS (AMS-1 and REVA), restenosis is a potential concern and therefore Amaranth has also developed a sirolimus-eluting version of BRS, which is currently undergoing preclinical testing.

### IDEAL bioresorbable scaffolds

The IDEAL BRS (Xenogenics Corporation, MA, USA) is a sirolimus-eluting device with the backbone of polylactide anhydride mixed with a polymer of salicylic acid and sebacic acid linker. The presence of salicylic acid provides anti-inflammatory properties to the device.<sup>47,48</sup> The IDEAL BRS was tested in the WHISPER FIM trial ( $n = 11$ ) in 2008. The first-generation device required an 8-Fr guide catheter and poorly suppressed neointimal proliferation due to inadequate drug dosing and rapid release of the sirolimus.<sup>49</sup> The second-generation IDEAL BioStent with a higher sirolimus dose, slower drug-release, and a 6-Fr compatible delivery system is currently undergoing preclinical evaluation.<sup>50</sup>

### Bioresorbable scaffolds at developmental stages

Biocorrosible iron<sup>51</sup> and nitriding iron<sup>52</sup> stents have been tested in swine models showing feasibility and safety. However, no long-term preclinical data or evaluation in man have been reported yet.

XINSORB BRS (Huaan Biotechnology, China) is a sirolimus-eluting, balloon-expandable polymeric device with a strut thickness of 160  $\mu\text{m}$  and has shown good acute performance in animal studies.<sup>53</sup> MeRes BRS (Meril Life Sciences, Gujarat, India) is a sirolimus-eluting BRS with a novel PLA formulation and a hybrid scaffold geometry, which provides high radial strength and avoids over expansion at edges. The ON-AVS (OrbusNeich, Fort Lauderdale, FL, USA) is a tube-shaped lockable and balloon-expandable polymeric device covered with sirolimus coating on abluminal surface and CD34+ antibodies (to capture endothelial progenitor cells) on luminal surface. Other polymeric devices in developmental stages include: FADES BRS (Zorion Medical, Indianapolis, IN, USA), Sahajanand BRS (Sahajanand Medical Technologies, India), Avatar BRS (S3V, India), Stanza BRS (480 Biomedical, MA, USA), and Arterius BRS (Arterius Ltd, Bradford, UK).

## Can bioresorbable scaffolds deliver what they promise?

### Initial scaffolding similar to metallic stents

Stents were developed to prevent and manage complications of POBA, namely acute vessel closure due to dissection or elastic recoil, late constrictive remodelling, and neointimal proliferation.<sup>7</sup> Ideally, the scaffolding provided by BRS in the first few months should be as good as provided by metal stents.

Magnesium-based BRSs have good radial strength and low recoil. In a simulated bench testing, AMS matched the recoil characteristics and

radial strength of permanent metal stents, but larger strut dimensions were required to achieve this.<sup>54</sup> However, there are concerns about the acute stent recoil and radial strength of polymeric BRS devices. IGAKI-TAMAI exhibited no early stent recoil in 19 treated lesions analysed by quantitative coronary angiography and IVUS performed immediately and 1 day after stenting.<sup>25</sup> REVA's slide & lock design has been reported to have no loss in material strength during expansion and enables the scaffold to have minimal recoil. A DESolve scaffold has also been shown to maintain radial strength and vessel support for the first 3–4 months. For ABSORB BVS, a comparison of BVS 1.0 ( $n = 27$ ) with XIENCE-V ( $n = 27$ ) demonstrated no statistical difference in absolute acute recoil (BVS  $0.20 \pm 0.21$  mm vs. XIENCE-V  $0.13 \pm 0.21$  mm,  $P = 0.32$ ) or percentage acute recoil (BVS  $6.9 \pm 7.0\%$  vs. XIENCE-V  $4.3 \pm 7.1\%$ ,  $P = 0.25$ ).<sup>55</sup> The newer-generation BVS 1.1 has acute recoil similar to BVS 1.0.<sup>56</sup> Although these data have shown no statistical difference in the acute recoil of polymeric and metallic stents, there is a numerical difference and concerns about acute performance of polymeric devices persist. With a number of new devices being developed, it is important that these are tested for acute recoil *in vivo*.<sup>53</sup>

### Gradual and predictable bioresorption

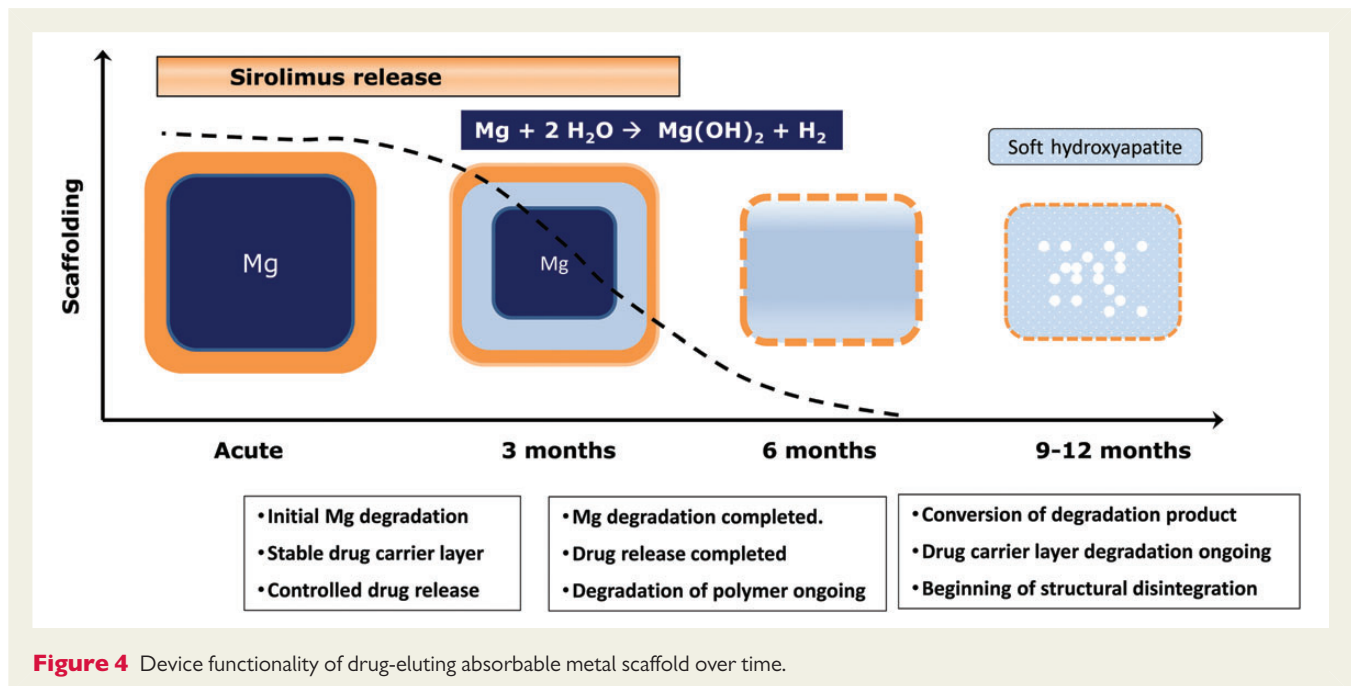
Poly-L-lactic acid is a biodegradable, thermoplastic, and aliphatic polyester that undergoes self-catalysed hydrolytic degradation to lactic acid, which finally metabolizes to carbon dioxide and water. Poly-L-lactic acid-based BRS usually have a combination of semi-crystalline polymers (to provide mechanical strength) and amorphous polymers (to allow uniform dispersion of the drug and loss of integrity at desired time).<sup>24</sup> The duration of the degradation process depends on the crystallization of the polymer and varies from 2 to 4 years.<sup>24</sup>

In the ABSORB trial, multiple imaging modalities were used to assess the bioresorption of BVS. IVUS-VH misinterprets polymeric struts as pseudo-dense calcium, so there was an increase in the

mean pseudo-dense calcium (9.8 vs. 25.4%,  $P < 0.001$ ) immediately after implantation, which was reduced by 30% at the 6 month and remained stable between 6 months and 2 years.<sup>28,57</sup> On echogenicity analysis, both calcified plaques and polymeric struts appear as hyper-echogenic tissue. There was a significant reduction in echogenicity from post-procedure to the 6 month ( $18.5 \pm 9.1$  vs.  $10.3 \pm 7.6\%$ ,  $P < 0.001$ ) and further reduction between 6 months and 2 years ( $10.3 \pm 7.6$  vs.  $7.7 \pm 6.5\%$ ,  $P = 0.005$ ). By 2 years, echogenicity returned to the pre-procedural level.<sup>57</sup> On serial OCT analysis, there was a 35% reduction in the number of visible struts from baseline to 2-year follow-up.<sup>57</sup> For REVA devices, it has been shown that, by 4 years, only tiny particles of the original polymer remain.

Magnesium bioresorption occurs via corrosion which varies from 2 to 12 months and can be modified by pH of the medium or addition of other rare metals.<sup>36,58</sup> The magnesium scaffolds are metabolized to its chloride, oxide, sulphate, or phosphate salts. The by-product in the vessel is hydroxyapatite, which is eventually digested by macrophages (Figure 4). For DREAMS®, OCT demonstrated that, at 6 months, 86% of the scaffold struts were discernible which reduced to 61% at 12 months, reflecting continuing resorption. Furthermore, serial IVUS-VH analysis done in nine patients showed a significant decrease in dense calcium at 6 (15.4% reduction) and 12 (12.9% reduction) months compared with post-procedure, without significant changes in necrotic core area over time. The decrease in dense calcium was therefore interpreted as a surrogate marker for the bioabsorption of the scaffold.<sup>38</sup>

The ability to control bioresorption to a predictable and desirable level is important in the success of BRS technology. The degradation of PLLA devices can be optimized by combining crystalline and amorphous polymers.<sup>24</sup> Lu et al.<sup>59</sup> have reported a novel approach to control the degradation of the magnesium-based alloys, allowing drug release by fabrication of a composite two layer coating film, one for control of the bio-corrosion rate of the magnesium alloy and another for the controlling rate of drug release.





## Preservation of vascular geometry

The metallic stents can alter vessel geometry and biomechanics, and resultant chronic irritation and flow disturbances may contribute to neointimal proliferation and adverse events.<sup>60,61</sup> Bioresorbable scaffolds offer the potential to preserve vascular geometry. ABSORB BVS is more conformable than metallic stents and produces less alteration in vessel angulation and curvature.<sup>21</sup> It has also been shown that, at 6- to 12-month follow-up, ABSORB BVS tends to restore the coronary configuration to pre-implant level, whereas coronary geometry remains permanently altered after implantation of permanent metallic stents.<sup>62</sup> It has not been demonstrated whether similar phenomenon occurs with other BRS, but it is plausible that vessel geometry will return to original status as bioresorption occurs.

## Restoration of vascular physiology

A number of studies using metallic DES have reported abnormal vasomotion in the segment distal to the DES, which may restrict the distal flow and predispose to late stent thrombosis. Bioresorbable scaffold technology has been described as vascular reparative therapy; after complete bioresorption, BRSs promise the return of dynamic vasomotion, pulsatility, distensibility, and mechanotransduction, i.e. the ability to translate mechanical forces into chemical signals (e.g. nitric oxide and prostacyclins).<sup>22</sup> In the ABSORB Cohort A, evaluation of the scaffolded segment following intraluminal administration of acetylcholine suggested that, at 2 years, the scaffolding function of the polymeric struts had completely disappeared and the scaffolded segment could exhibit vasomotion.<sup>63</sup> A positive acetylcholine test with vasodilatation of the scaffold also provided an indirect proof that the endothelial lining was intact and functional, so that the biochemical process of nitric oxide release was working efficiently. This observation corroborates with transmission electron microscopy findings in porcine model showing maturation of endothelial junctions between 1 and 36 months with dense intercellular desmosome at 3 years.<sup>57</sup> It has also been shown that implantation of ABSORB BVS leads to a significant decrease in vascular compliance, measured on palpography and described as Rotterdam Classification score/mm, at the scaffolded segment [from 0.37 (0.24–0.45) to 0.14 (0.09–0.23),  $P < 0.001$ ] with mismatch in compliance in a paired analysis between the scaffolded and adjacent segments [proximal: 0.23 (0.12–0.34), scaffold: 0.12 (0.07–0.19), distal: 0.15 (0.05–0.26),  $P = 0.042$ ]. This compliance mismatch disappears at short- and mid-term follow-up.<sup>64</sup> Magnesium BRSs have also demonstrated the recovery of the responsiveness of the treated vessel to vasoactive agents.<sup>65</sup>

## Prevention of very late thrombotic events

One of the major hopes with BRS is that, after bioresorption, the treated segment of the vessel will return to normal function and will be free of a permanent foreign body, thus minimizing the risk of very late thrombotic events and need for long-term DAPT. Bioresorbable scaffolds can potentially eliminate certain factors contributing to the late stent thrombosis including delayed endothelialization, chronic inflammatory response, and localized hypersensitivity reaction.<sup>66</sup> It has been shown that the incidence of very late stent thrombosis (ST) is significantly lower in DES with biodegradable polymer

compared with DES with durable polymer (0.4 vs. 1.8%,  $P = 0.004$ ).<sup>17</sup> It is noted that a recently reported study has shown that even balloon angioplasty has a risk of very late thrombosis, suggesting that BRS may not be able to eliminate this complication.<sup>67</sup> It may be argued that BRS implantation will lead to the formation of a homogenous neointimal layer and the prevention of neoatherosclerosis within the scaffolded segment and hence, potentially perform even better than POBA for the prevention of very late ST. However, there are no data yet to prove that BRSs have achieved this desired goal and further clinical studies are warranted.

## Passivation of vulnerable plaques

Metallic stents do not seem to fully protect the vessel from neoatherosclerosis or plaque progression. It is postulated that BRS implantation may provide a symmetrical uniform fibrous neointimal layer which along with late lumen enlargement and lack of any permanent vascular prosthesis may help to stabilize and passivate vulnerable plaques and thus prevent future cardiovascular events.<sup>64</sup>

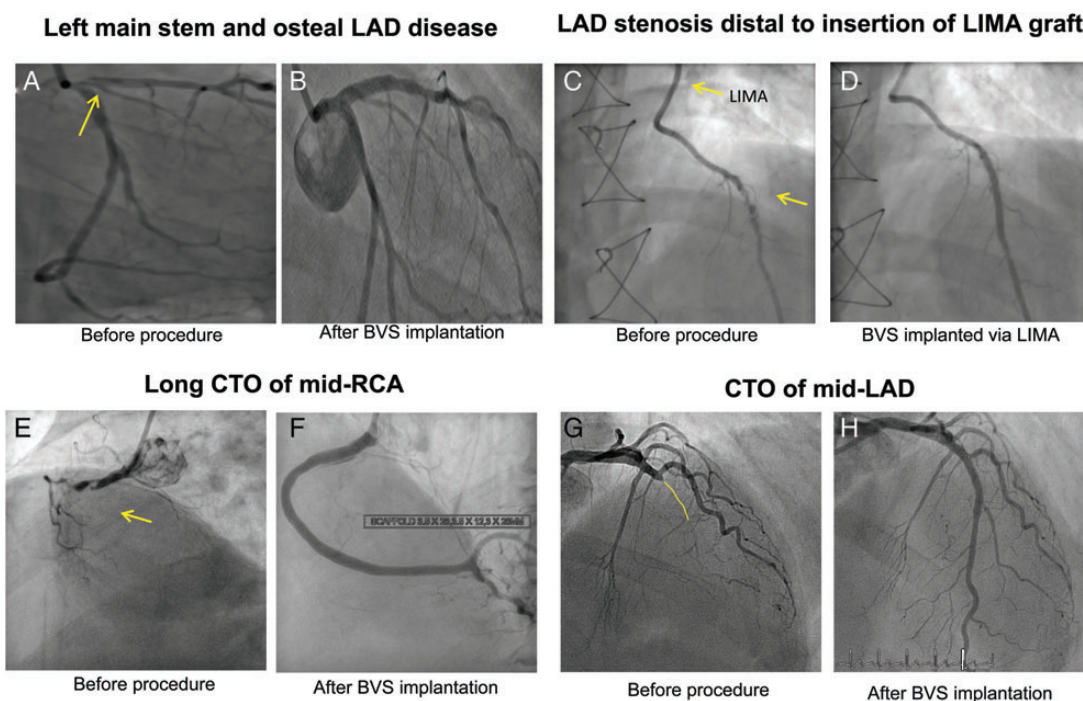
The idea is appealing and indirectly supported by studies on the concept of plaque passivation by stents<sup>68</sup> and BRS providing a symmetrical and circumferential thick fibrous cap with functional endothelium, late lumen enlargement, and normal shear stress distribution.<sup>64</sup> A total of 58 patients (59 lesions), who received ABSORB BVS 1.1 and a subsequent OCT investigation at 6 ( $n = 28$  patients/lesions) or 12 ( $n = 30$  patients with 31 lesions) months, showed that neointima area was not different between 6- and 12-month follow-up ( $1.57 \pm 0.42$  vs.  $1.64 \pm 0.77$  mm<sup>2</sup>;  $P = 0.691$ ). However, the symmetry of the neointima thickness was higher at 12 months than at 6 months follow-up ( $0.23$  [0.13–0.28] vs.  $0.16$  [0.08–0.21],  $P = 0.019$ ). These findings illustrate the formation of a neointimal layer that resembles a thick fibrous cap and may contribute to plaque stability.<sup>69</sup> This potential transformation of vulnerable lesions to stable plaques is an interesting hypothesis which needs further validation.

Intravascular ultrasound analysis of ABSORB BVS between 6 months and 2 years also revealed a significant plaque media reduction (12.7%), without a significant change in the vessel wall area.<sup>22,70</sup> However, further studies are needed to prove that this observation is indeed 'plaque media regression' due to changes in vessel wall and plaque, and not a pseudo-regression due to bioresorption of the polymeric struts.

## Challenges and future directions

### Deliverability and crossing profile

To provide sufficient hoop strength to oppose negative arterial remodelling and limit acute recoil, polymeric scaffolds have thicker struts (typically 150–200  $\mu$ m) than contemporary metallic stents ( $\sim 80$   $\mu$ m). This, along with challenges in the crimping process, results in larger crossing profile of polymeric scaffolds (1.4–1.8 mm) than the contemporary DES ( $\sim 1.0$  mm). The initial clinical studies have obviously restricted the use of BRS to simple Type-A lesions. The role of PCI extends to complex lesions<sup>71</sup> and whether BRS can be used for patients with complex lesions and tortuous or calcified vessels has largely remained unexplored. Hence, concerns exist over deliverability and trackability of these devices.



**Figure 5** ABSORB biovascular scaffold (BVS) use in real-world complex cases. Left main stem and ostial left anterior descending (LAD) disease (A) treated with provisional strategy using biovascular scaffold (B). Patient with severe native coronary artery disease and previous coronary artery bypass graft developed a stenosis of LAD just distal to insertion of left internal mammary artery (LIMA) graft (C), which was successfully treated by placing a biovascular scaffold device from LIMA into LAD (D). Chronic total occlusion (CTO) of right coronary artery (RCA) (E) treated with implantation of three biovascular scaffold devices (F). CTO of LAD (G) treated with biovascular scaffold implantation (H) with good angiographic results. Figures kindly provided by Ribamar Costa, Talib Majwal, Manel Sabate, and Antonio Serra.

Bioresorbable scaffolds have recently been used for PCI of the left main stem,<sup>72</sup> small diameter ( $\leq 2.5$  mm) vessels,<sup>73</sup> calcific lesions, long lesion with overlapping stents, in-stent restenosis, bifurcations, and chronic total occlusions (Figures 5 and 6). However, further work is needed to improve deliverability, pushability, and crossing profile without compromising radial strength.

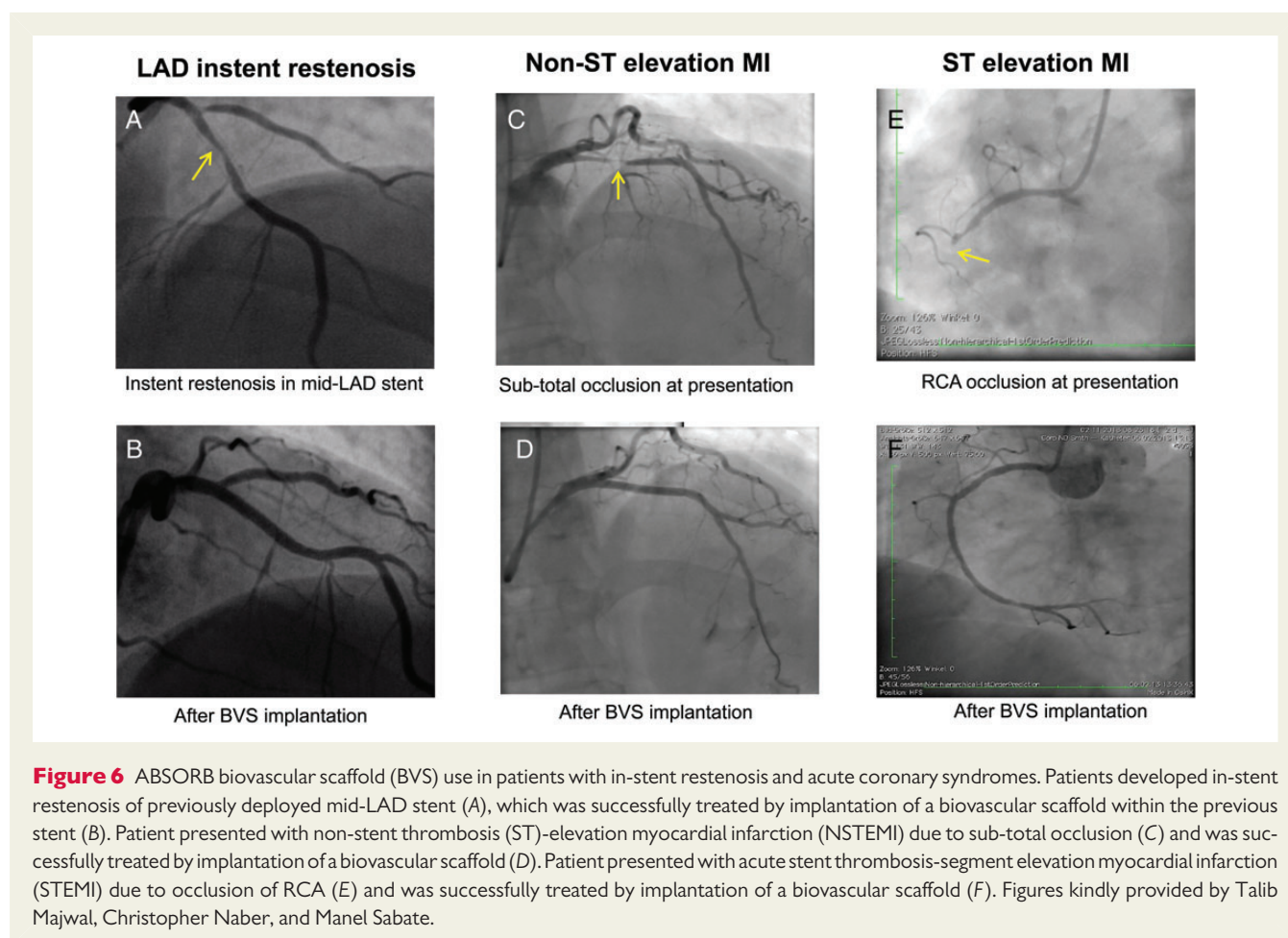
### Stretchability and strut fractures

Strut disruption with associated complications is a potential concern. Magnesium BRS has high tensile strength which can potentially offer good compliance of the scaffold without exposure to fractures during scaffold deployment.<sup>24</sup> However, the polymeric devices have inherent limit of expansion and can break as a result of over-dilatation. Although the radial strength of BVS has been reported to be comparable with metallic stents, this is true if the BVS is deployed within the limits of its size. If the BVS is over-stretched beyond its designed limits, it may lose some of its radial strength and may indeed fracture.<sup>74</sup> ReZolve devices with the slide & lock design do not rely on deformation for scaffold expansion, so mechanical strength is maintained during clinically relevant expansion range. DESolve scaffold has the ability to self-appose to the vessel wall in the cases of minor malapposition when expanded to the nominal diameter and a wide safety margin for expansion without strut fracture.

It is essential to further improve this technology to enhance stretchability of the devices while maintaining their radial strength. Currently, it is vital to appropriately size the reference vessel and to respect the nominal size of the scaffold. It is important to have an adequate lesion preparation before implantation of a BRS. Authors advocate a judicious use of pre-dilatation, cutting/scoring balloons, rotational atherectomy etc., as needed, to ensure that excessive post-dilatation is seldom required.

### Side-branch occlusion

Current BRSs have thicker struts and higher scaffold to artery ratio, hence the concern over side-branch occlusion. A post hoc angiographic assessment of 1209 side branches in 435 patients enrolled in the ABSORB-EXTEND, in comparison with 682 side branches in 237 patients treated with the everolimus-eluting Xience stent in the SPIRIT I and II trials, showed a trend towards more side-branch occlusions in BVS-treated patients (BVS 6.0% vs. XIENCE 4.1%,  $P = 0.09$ ). Patients with post-procedural side-branch occlusion had higher incidence of in-hospital MI (6.5 vs. 0.5%,  $P < 0.01$ ). Multivariable analysis revealed that BVS implantation was an independent predictor of post-procedural side-branch occlusion (odds ratio: 2.1; 95% confidence interval 1.2–3.7). By stratified analysis, BVS demonstrated a higher incidence of post-procedural side-branch occlusion compared with Xience only in small side branches with a reference



**Figure 6** ABSORB biovascular scaffold (BVS) use in patients with in-stent restenosis and acute coronary syndromes. Patients developed in-stent restenosis of previously deployed mid-LAD stent (A), which was successfully treated by implantation of a biovascular scaffold within the previous stent (B). Patient presented with non-ST elevation myocardial infarction (NSTEMI) due to sub-total occlusion (C) and was successfully treated by implantation of a biovascular scaffold (D). Patient presented with acute stent thrombosis-segment elevation myocardial infarction (STEMI) due to occlusion of RCA (E) and was successfully treated by implantation of a biovascular scaffold (F). Figures kindly provided by Talib Majwal, Christopher Naber, and Manel Sabate.

vessel diameter of  $\leq 0.5$  mm (10.5 vs. 3.9%,  $P = 0.03$  between the groups,  $p$  for interaction = 0.08).<sup>75</sup> The effect of implanting a BRS on future accessibility of side branch also remains unknown. As eluded earlier, future development of BRS with thinner struts and reduced surface area of struts, while maintaining mechanical strength, may potentially solve this issue.

### Duration of dual antiplatelet therapy

The appropriate duration of DAPT for patients receiving BRS has not been investigated. It could be argued that the duration of DAPT should be similar to metallic DES; however, due to significant difference in strut thickness, concerns persist over early discontinuation of DAPT. Certainly, the median duration of DAPT was  $>1$  year in ABSORB Cohort B (97% patients on DAPT at 6 months, 81% at 12 months, and 25% at 24 months). Further studies defining the duration of DAPT are warranted.

### Use in acute coronary syndromes

The majority of PCI procedures are now carried out for acute coronary syndromes (ACS). First-in-man for BRS devices were carried out in stable patients. Safety and efficacy data for BRS use in ACS are not yet widely available. A recent small registry has suggested that BVS may be used safely and effectively in patients with ST-segment elevation myocardial infarction undergoing primary PCI.<sup>76</sup> There are

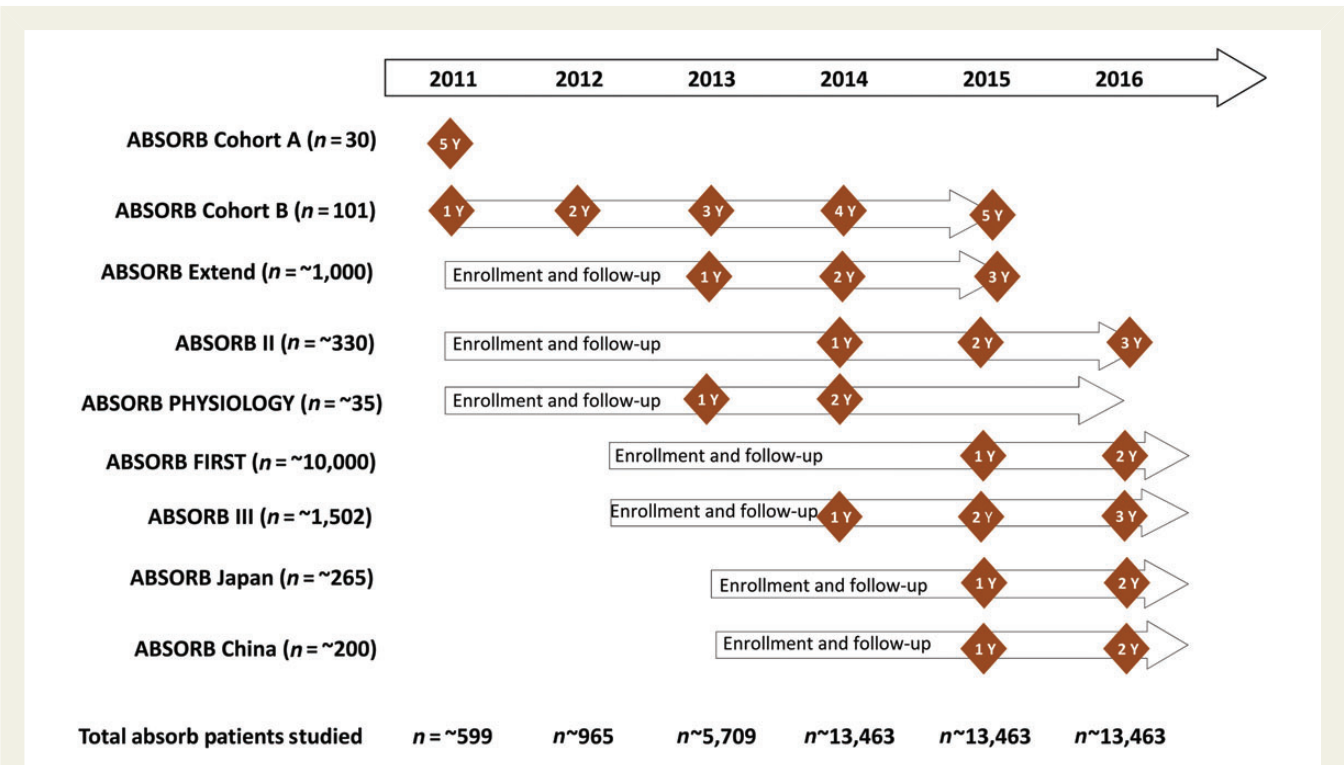
on-going studies (e.g. PRAGUE-19 trial and POLAR ACS registry) to further evaluate the use of BRS in ACS patients. Example cases of ABSORB BVS use in ACS patients are shown in Figure 6.

### Need for long-term safety and efficacy data

Limited data from very long-term follow-up of the IGAKI-TAMAI device have shown a reasonable safety profile.<sup>77,78</sup> Over 10-year follow-up of the first 50 patients (63 lesions) treated with 84 IGAKI-TAMAI scaffolds has shown that TLR rates were 16% at 1 year, 18% at 5 years, and 28% at 10 years. Only two cases of definite ST (one sub-acute and one very late which was probably related to a sirolimus-eluting stent implanted for a lesion proximal to an IGAKI-TAMAI scaffold) were recorded. Survival rates free of death and cardiac death at 10 years were 87 and 98%, respectively.<sup>78</sup> Furthermore, the data for 5-year follow-up of ABSORB Cohort A and 3-year follow-up of ABSORB Cohort B also look very promising. However, most of the data for BRS use are derived from small, non-randomized studies with short- or mid-term follow-up and further studies are warranted.

There are several clinical trials and registries currently running on planned for further evaluation of BRS. The second-generation DREAMS<sup>®</sup> is being tested in the BIOSOLVE-II study. The clinical trial with ReZolve2 has also started in March 2013. The ART device is currently undergoing FIM trial with the aim to complete





**Figure 7** Planned studies with sample size, time course, and follow-up using ABSORB biovascular scaffold.

recruitment of 30 patients in 2013. Amaranth has also just started a FIM study to evaluate the safety and efficacy of its non-drug-eluting Fortitude™ device in 30 patients.

ABSORB-EXTEND is an international prospective, single-arm study that will recruit over 800 patients with more complex coronary disease than previously studied in the ABSORB trial. The first patient was enrolled in January 2010. In this study, a 2.5 mm BRS is also introduced, thus allowing for the examining the feasibility of BRS use in small vessels. Additionally, patients with long lesions are not excluded, and hence it will be possible to evaluate the potential safety of overlapping devices. Interim results of first 450 patients enrolled in this trial have shown good safety and efficacy results at 12-month follow-up with 1 cardiac death (0.2%), 13 cases of MI (2.9%), 8 cases of ischaemia-driven TLR (1.8%), 4 cases of ST (0.9%), and a hierarchical MACE of 4.2%.<sup>79</sup> Another study, ABSORB Physiology, is planned to assess the acute and long-term effect of BVS compared with a conventional metallic DES, in terms of impact on vascular compliance, distensibility, endothelial responsiveness and changes in the shear stress distribution, after device/stent implantation, and at 2-year follow-up. The ABSORB-II is a prospective, randomized control trial that aims to compare the safety and efficacy of the BVS 1.1 vs. the Xience® stent in 501 patients with stable angina and 1–2 vessel disease randomized on a 2:1 basis.<sup>80</sup> Clinical follow-up is planned at 30 and 180 days and at 1, 2, and 3 years. All subjects will undergo coronary angiography and IVUS at baseline (pre- and post-device implantation) and at 2-year follow-up. The primary endpoints are the superiority of ABSORB BVS for vasomotion of the treated segment at 2 years and non-inferiority for

angiographic minimum lumen diameter at 2 years. An outline of ABSORB clinical programme is shown in Figure 7.

## Conclusion

Bioresorbable scaffolds have improved significantly over the last few years with multiple devices in clinical trials at the moment. Undoubtedly, further technological refinements to overcome current challenges and long-term safety and efficacy data from adequately powered clinical trials are required. However, the potential benefits of BRS and strong collaboration between device industry, academia, and clinicians are likely to make BRS a mainstream device for coronary intervention in a not very distant future.

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