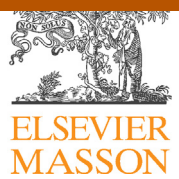
Archives of Cardiovascular Disease (2015) 108, 385—397



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REVIEW

Fully bioresorbable drug-eluting coronary scaffolds: A review

Stents coronaires actifs entièrement résorbables : revue générale

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Received 8 January 2015; received in revised form 7 March 2015; accepted 12 March 2015
Available online 22 June 2015

KEYWORDS
Bioresorbable scaffolds;
Percutaneous coronary angioplasty;
Randomized controlled trials

Summary Following the development of stents, then drug-eluting stents (DES), bioresorbable scaffolds are proposed as a third evolution in coronary angioplasty, aiming to reduce the incidence of restenosis and stent thrombosis and to restore vascular physiology. At least 16 such devices are currently under development, but published clinical data were available for only three of them in September 2014. The first device is Abbott's BVS®, a poly-L-lactic acid (PLLA)-based everolimus-eluting device, which has been tested in a registry and two non-randomized trials. Clinical results seem close to what is expected from a modern DES, but possibly with more post-procedural side-effects. Two randomized trials versus DES are underway. This device is already marketed in many European countries. The second device is Elixir's DESolve®, a PLLA-based novolimus-eluting device, which has been evaluated in two single-arm trials. Results are not widely different from those expected from a DES. The third device is Biotronik's DREAMS®, a metallic magnesium-based paclitaxel-eluting device, which has been assessed in an encouraging single-arm trial; its second version is currently undergoing evaluation in a single-arm trial. The available results suggest that the technological and clinical development of bioresorbable scaffolds is not yet complete: their possible clinical benefits are still unclear compared with third-generation DES; the impact of arterial physiology restoration has to be

Abbreviations: BMS, bare-metal stent; BVS, Bioresorbable Vascular Scaffold; DES, drug-eluting stent; DREAMS, Drug Eluting Absorbable Metal Scaffold; MACE, major adverse cardiac events; OCT, optical coherence tomography; PLLA, poly-L-lactic acid; SBO, side-branch occlusion STEMI, ST-segment elevation myocardial infarction.

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http://dx.doi.org/10.1016/j.acvd.2015.03.009

assessed over the long term; and their cost-effectiveness has to be established. From the perspective of a health technology assessment, there is no compelling reason to hasten the clinical use of these devices before the results of ongoing randomized controlled trials become available.

MOTS CLÉS
Stents coronaires bioresorbables ;
Angioplastie coronaire percutanée ;
Études contrôlées

Résumé Après le développement des stents, puis des stents actifs, les stents actifs entièrement résorbables constituent la troisième évolution de l'angioplastie coronaire. Ces dispositifs visent à réduire l'incidence des resténoses et des thromboses et à restaurer la physiologie vasculaire. Au moins seize dispositifs sont en développement mais seulement trois ont fait l'objet de publications jusqu'en septembre 2014. Le premier (ABBOTT—BVS®) est en polymère d'acide L-lactique (PLLA) délivrant de l'évérolimus. Il a été évalué par un registre et deux essais non comparatifs. Les résultats cliniques semblent proches de ceux d'un stent actif mais avec peut-être plus d'événements indésirables. Deux essais comparatifs randomisés versus stents actifs sont en cours. Ce stent est commercialisé dans la plupart des pays européens. Le deuxième (Elixir—DESolve®), (PLLA, novolimus), a été étudié par deux suivis de cohorte. Les résultats ne semblent pas différents de ceux obtenus avec les stents actifs. Le troisième (Biotronik—DREAMS®), (alliage magnésium-terres rares, paclitaxel), a fait l'objet d'un suivi de cohorte encourageant ; l'industriel étudie une deuxième version dans le cadre d'une cohorte. Les résultats disponibles suggèrent que le développement technique et clinique des stents actifs entièrement résorbables n'est pas finalisé. Les bénéfices cliniques semblent comparables à ceux des stents actifs de dernière génération et ceux imputables à la récupération de la vasomotricité artérielle ne sont pas encore démontrés à long terme. Leur rapport coût-efficacité n'est pas encore connu. En termes d'évaluation des technologies de santé, il n'existe pas d'argument convainquant pour en recommander l'utilisation en pratique clinique avant le résultat des études contrôlées en cours.

Background

Restenosis is an important limitation of myocardial revascularization after routine balloon coronary angioplasty [1,2]. An 'elastic recoil' phenomenon was mainly involved in the mechanism of restenosis (along with constrictive remodelling and neointimal proliferation), leading to the development of bare-metal stents (BMS) [3].

While the widespread use of BMS enabled a reduction in early restenosis and in the incidence of arterial wall dissection, an increase in the incidence of late restenosis was noted and attributed primarily to neointimal proliferation. These observations led to the development of drug-eluting stents (DES) [4], whose diffusion of antiproliferative agents was accompanied by a reduction in post-stenting reintervention rates [5,6]. However, their impact on clinical events occurring after revascularization remains poorly evaluated.

The attention of interventional cardiologists has now turned to very late restenosis and thrombosis. These events may be induced by a long-term effect of the polymer bonding the stent itself to the drug to be delivered into the arterial wall. The first proposed solution to this issue involved bioresorbable polymer stents (the metal frame of which stays in the artery), which remain in development [7,8]. Moreover, persistent late acquired malapposition with durable metal stents may be associated with chronic inflammation, neoatherosclerosis, very late lumen loss and stent thrombosis [9], contrasting with the fact that a stent has no mechanical function after a few months. It has also been argued that the presence of the stent suppresses arterial wall motility and vasodilation ability. This line of reasoning has led some manufacturers to start developing fully bioresorbable devices (usually called 'scaffolds' rather than 'stents') for coronary artery stenting. Some feasibility studies are available, but large-scale trials are yet to be published.

The present paper reviews the available evidence on fully bioresorbable coronary scaffolds, with a heath technology assessment perspective, setting aside the development of resorbable polymer stents.

Methods

The Comité d'Évaluation et de Diffusion des Innovations Technologiques (CEDIT) undertook an early assessment of this emerging health technology for the Assistance Publique—Hôpitaux de Paris (AP—HP). A systematic search for relevant literature, using subsets of the set ('coronary', 'scaffold', 'resorbable' 'stent'), up to September 2014, was conducted using the MEDLINE and EMBASE databases, completed by a manual search of the references of retrieved

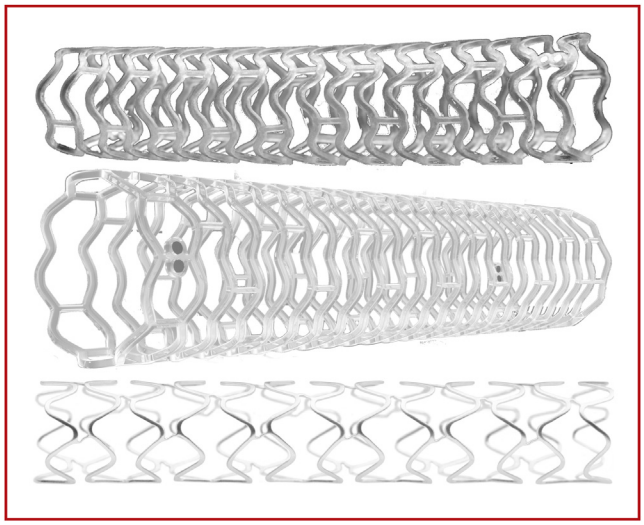

Figure 1. Fully bioresorbable scaffolds with published human assessment. From top to bottom: Abbott's BVS (version 1.1); Elixir's DESolve; Biotronik's DREAMS (first generation). Images courtesy of the respective manufacturers.

papers. References pertaining to 'resorbable polymer stents' only were rejected.

This search aimed for the exhaustive retrieval of formally published clinical and economic results relating to fully bioresorbable scaffolds currently on the market or under development in humans, while giving enough technical and organizational information to allow for decision making at a hospital management level. We limited our review to devices for which we retrieved at least one formally published human clinical use and that are still available or under further development.

As is customary for CEDIT assessment reports, the information was organized under four headings: technical, clinical, economic and organizational. The scarcity of available information precluded formal aggregation (meta-analysis) of the results and led us to quote some indirect information, such as press releases.

Results

The available background papers [10—12] summarize a large quantity of information on the current development of these devices. According to these papers, various manufacturers have started the development of at least 16 different devices to date.

Technical aspects

The technical characteristics of fully resorbable scaffolds with published human use and currently under development are listed in Table 1; these devices are pictured in Fig. 1.

A fully bioresorbable device for coronary artery stenting was attempted early in the 1990s [13]; however, the initial success of DES targeting the same clinical problem caused these initial efforts to be discarded.

All currently developed fully bioresorbable scaffolds but one are drug-eluting devices; therefore, current research concerning the associated drugs (sirolimus or paclitaxel families) is relevant to these devices. In contrast, their mechanical properties strongly depend on their base material and are, by definition, unstable, as the device is bound to disappear eventually. The question to be answered is whether the mechanical function of a scaffold is sufficient for its clinical purposes, in terms of strength of the acute stent recoil and duration.

The devices for which we retrieved results regarding human clinical use are based on two classes of biomaterials: poly-L-latic acid (PLLA) polymers and magnesium rare-earth alloys.

PLLA polymers

At least four manufacturers have attempted to create a bioresorbable scaffold based on this material.

In 2000, Kyoto Medical Planning (Kyoto, Japan) published the results of the first clinical trial [13] assessing their Igaki-Tamai® biodegradable coronary stent. This first-generation device was thermoplastic, its deployment needing the injection of contrast medium heated to 80 °C; furthermore, this deployment used a large-calibre guide. These drawbacks and the initial results did not lead the manufacturer to undertake further development at the time of the publication of the first DES clinical results. One should note, however, the recent publication of the 10-year follow-up of this cohort [11]. A second iteration of this device is said to be in development.

Abbott (Chicago, IL, USA) has also developed a PLLA device (the ABSORB Bioresorbable Vascular Scaffold [BVS®]). This device is the oldest of those presently aimed at the market and, therefore, the best documented. Some information is available about its pharmacological and resorption dynamics [8]: the everolimus elution is maximal during the first weeks and null after 3 months; the scaffold provides mechanical support for 3 months, but its strength is then lost rapidly; the structure is lost 6 months after implantation, but scaffold elements are visible up to 2 years after implantation.

The manufacturer Elixir (Sunnyvale, CA, USA) has undertaken a cohort study of the DESolve® bioresorbable coronary scaffold system (16 patients); a larger single-arm trial (DESolve Nx) has been completed [14], but the first results, presented orally at EuroPCR 2013 [15], have not yet been published.

The French start-up company Arterial Remodeling Technologies (Noisy le Roi, France) has undertaken a first cohort study (ARTDIVA, 30 patients, five centres) assessing a PLLA-based non-drug-eluting resorbable scaffold; the first 30-day follow-up results were presented at TCT 2013 [16], but await formal publication.

Magnesium rare-earth alloys

The manufacturer Biotronik (Berlin, Germany) has undertaken trials evaluating such a device, called the Drug Eluting Absorbable Metal Scaffold (DREAMS®) [17], after a first iteration produced disappointing clinical results [18]. Detailed information about the mechanical and the pharmacological properties of this paclitaxel-eluting device does not seem

Table 1 Technical characteristics of available resorbable coronary scaffolds with published human use.

	BVS 1.1	DESolve 1.0	DREAMS 1G
Manufacturer	Abbott	Elixir	Biotronik
Availability	CE marked	CE marked	
Material	PLLA	PLLA	Magnesium rare-earth alloy
Eluted drug	Everolimus	Novolimus	Paclitaxel[a]
Design	In-phase hoops with straight links	In-phase hoops with straight links	6-Crown
Strut thickness (μm)	156	150	125
Radial support duration	6 months	—	3—6 months
Time to resorption	2—3 years	2—3 years	1 year

BVS: Bioresorbable Vascular Scaffold; CE: Conformité Européenne; DREAMS, Drug Eluting Absorbable Metal Scaffold; PLLA, poly-L-lactic acid.
[a] DREAMS 2G will use sirolimus.

to have been published; according to Patel and Banning [9], the mechanical strength of the metallic alloy would allow for less beam section inflation (150%) than for a PLLA-based device (240%), to achieve the same strength as a chrome-cobalt device.

Other devices

Other manufacturers have announced their intention to work on similar devices. Among them are Reva Medical (San Diego, CA, USA) (tyrosine polycarboxylate-based device), whose first clinical trial (RESTORE) results were presented at TCT 2012; a second pivotal trial (RESTORE II) has been initiated [12]. A first iteration of the IDEAL (modified PLLA-based) device led to disappointing clinical results; a second iteration was in the preclinical evaluation stage in 2013. Other devices have not yet reached the stage of human evaluation [12].

Clinical results

The main inclusion criteria of the published trials are listed in Table 2, the patient characteristics are described in Table 3 and the lesion characteristics in Table 4. Published clinical and angiographical results are summarized in Table 5.

Abbott's BVS®

ABSORB cohort studies

The first iteration of this device was evaluated in a single-arm cohort study (ABSORB A), which enrolled 30 patients [19] (Table 2). The protocol mandated a minimum 6-month duration of dual antiplatelet therapy, but 15 patients were still receiving this at 1 year. One non-Q-wave myocardial infarction was reported during the first 6 months of follow-up; this event was the only cardiac event reported over 5 years of follow-up (two non-cardiac deaths were reported, attributed to duodenal ulcer and Hodgkin's disease). The authors also reported evidence of arterial motility at 2 years. Incomplete strut apposition at baseline was reported in six patients (24%) and persisted in four patients at 180 days.

A new iteration of the BVS (version 1.1) was created, aiming at lowering late lumen loss. This device was assessed in the ABSORB B single-arm cohort study [20—22]. This cohort of 101 patients (102 lesions) was further split into cohort B1, whose members had invasive coronary imaging (quantitative coronary angiography, intravascular ultrasound imaging and optical coherence tomography [OCT] at 6 months and 2 years), and cohort B2, whose members had the same examinations at 1 and 3 years; all patients underwent computed tomographic angiography at 1 year. At 2 years, nine major cardiovascular events had been reported (three non-Q-wave myocardial infarctions and six ischaemia-driven target lesion revascularizations). An initial late lumen loss was observed in cohort B1 (going from 6.53 mm^2 immediately after stenting to 6.36 mm^2 at 6 months), followed by a late lumen gain (6.85 mm^2, i.e. +7.7%) at 2 years, with similar results using other imaging modalities; cohort B2 gave similar results (a detailed analysis showed no change in the scaffold area, whereas the lumen area decreased by 23.4%). Arterial motility was observed at 1 year and deemed augmented at 2 years.

ABSORB EXTEND international continuing accrual study (registry)

Partial results from the ABSORB EXTEND registry are available. An aggregation of the subgroups of patients in ABSORB A, ABSORB B and ABSORB EXTEND treated in Rotterdam [23] concluded on the efficacy and safety of the BVS at 1 month post procedure. A paper on the results obtained for the 450 first patients [24] reported (without details) ischaemia-driven major adverse cardiac events (MACE) in 4.2% of patients and target vessel failure in 4.7% of patients; it also discussed in detail three device dislodgements and four cases of late device thrombosis.

More importantly, a retrospective study [25] compared the rate of side-branch occlusion (SBO) in 435 patients from the ABSORB EXTEND registry and 250 patients from the Xience® (ABBOTT's everolimus-eluting stent) arm of the

Table 2 Main inclusion and exclusion criteria of published studies.

Study	Age (years)	Number of lesions	Artery	Length (mm)	Diameter (mm)	TIMI	Stenosis (%)	AMI	LVEF (%)	Diff[a]	Other
ABSORB A	> 18	One de novo	Native	≤ 8	3	> 1	50 ≤ s < 100	No	> 30	No	
ABSORB B	> 18	One or two de novo (different vessels)	Native	≤ 4	≤ 3	> 1	50 < s < 100	No	> 30	No	
ABSORB Extend	> 18	One or two de novo (different vessels)	Native	≤ 28	2 ≤ d ≤ 3.8	≥ 1	< 100	No	—	No	In-stent restenosis or thrombus
ABSORB II	18 < a ≤ 85	One or two de novo (different vessels)	—	≤ 48	2.25 ≤ d ≤ 3.8	≥ 1	50 < s < 100	No	> 30	No	No recent PCI, bypass lesion
Prague 19	—	—	—	≤ 24	2.3 ≤ d ≤ 3.7	—	—	Yes[b]	—	—	In-stent restenosis or thrombus
BVS STEMI	18 < a ≤ 85	—	—	—	2.0 ≤ d ≤ 3.8	—	—	Yes[b]	—	—	Previous CABG, thrombus in stent
DESolve First-in-Man	—	One or two de novo	Native	≤ 10	≤ 10	—	≤ 80	No	> 30	—	Recent myocardial infarction, restenosis, calcifications
BIOSOLVE-1	—	One or two de novo (different vessels)	—	≤ 12	3.0 ≤ d ≤ 3.5	—	50 ≤ s ≤ 99	No	—	No	

a: age; AMI: acute myocardial infarction; BVS: Bioresorbable Vascular Scaffold; CABG: coronary artery bypass graft; d: diameter; Diff: difficult lesion (e.g. calcified, ostial or furcation lesions, angulations, thrombus); LVEF: left ventricular ejection fraction; s: stenosis; PCI: percutaneous coronary intervention; STEMI: ST-segment elevation myocardial infarction; TIMI: thrombolysis in myocardial infarction.

[a] Most studies excluded difficult lesions (calcified, ostial or furcation lesions, angulations, thrombus).

[b] Inclusion criterion.

Table 3 Compilation of the characteristics of patients treated with resorbable devices in published studies.

Study	ABSORB A ($n = 30$)	ASBORB B Small vessels[a] ($n = 41$)	ABSORB B Large vessels ($n = 60$)	ABSORB Extend (first 512 patients) ($n = 512$)	Prague 19 ($n = 40$)	BVS STEMI ($n = 49$)	ABSORB II (BVS group) ($n = 335$)	DESolve First-in-Man ($n = 16$)	BIOSOLVE-1 ($n = 46$)
Age (years)	62 ± 9	62.4 ± 9.4	62.2 ± 8.7	62 ± 11	58.9 ± 10.9	58.9 ± 10.5	61.5 ± 10.0	69.3 ± 8.4	65.3 ± 9.7
Male sex	18 (60)	26 (63)	47 (78)	74%	31 (78)	38 (78)	253 (76)	10 (63)	34 (74)
Smoker[b]	6 (20)	9 (22)	8 (14)	23%	25 (62)	27 (69)	79 (24)	11 (69)	17 (37)
Diabetes[b]	1 (3)	9 (22)	8 (13)	26%	1 (3)	4 (8)	80 (24)	1 (6)	7 (15)
Hypertension[b]	18 (60)	24 (58)	38 (64)	65%	—	19 (39)	231 (69)	10 (63)	40 (87)
Hyperlipidaemia[b]	19 (63)	35 (85)	44 (73)	67%	—	11 (22)	252 (75)	11 (69)	41 (89)
Previous target vessel intervention	3 (10)	—	—	5%	—	—	14/120 (12)	—	—
Previous PCTA	—	6 (15)	15 (25)	—	1 (3)	0 (0)	—	—	27 (59)
Previous CABG	—	1 (2)	2 (3)	—	0	0	—	—	
Previous myocardial infarction	1 (3)	7 (18)	18 (30)	16%	1 (3)	1 (2)	93 (28)	4 (25)	15 (33)
Functional status									
Silent ischaemia	1 (3)	—	—	5%	0	—	42 (13)	5 (31)	1 (2)
Stable angina	21 (70)	—	—	64%	0	—	214 (64)	11 (69)	43 (93)
Unstable angina	8 (27)	—	—	31%	0	—	68 (20)	0	2 (4)
Myocardial infarction	0	0	0	0	40 (100)	—	0	0	0

Data are expressed as mean ± standard deviation or number (%, unless otherwise indicated. BVS, Bioresorbable Vascular Scaffold; CABG: coronary artery bypass graft; PCTA: percutaneous transluminal coronary angioplasty; STEMI: ST-segment elevation myocardial infarction.

[a] The ABSORB B study investigators present most of their results separately for small (diameter < 2.5 mm) and large target vessels.

[b] Definition (present/history) varies among studies.

Table 4 Compilation of the characteristics of lesions treated with resorbable devices in published studies.

Study	ABSORB A	ABSORB B Small vessels[a]	ABSORB B Large vessels	ABSORB Extend (first 512 patients)	Prague 19	BVS STEMI	ABSORB II (BVS group)	DESolve First-in-Man	BIOSOLVE-1
Device	BVS 1.0	BVS 1.1	BVS 1.1	BVS 1.1	BVS 1.1	BVS 1.1	BVS 1.1	DESolve	DREAMS
Number of lesions	30	41	61	93% single; 7% double	40	49	364	16	47
Localization									
Left anterior descending	14 (47)	19 (46)	25 (41)	45%	20 (50)	21 (43)	163 (45)	3 (21)[b]	16 (34)
Left circumflex	9 (30)	8 (20)	15 (25)	26%	11 (28)	6 (12)	106 (29)	5 (38)[b]	16 (34)
Right coronary artery	7 (23)	13 (32)	21 (34)	29%	9 (23)	22 (45)	95 (26)	6 (43)[b]	15 (32)
LMCA/ramus	0	0	0	1%	0	0	0	0	0
Saphenous graft	0	0	0	0	0	0	0	0	0
ACC/AHA lesion classification									
A	0	0	1 (2)	–	–	–	5 (1)	5 (38)[b]	12 (26)
B1	18 (60)	21 (53)	34 (57)	–	–	–	193 (53)	4 (29)[b]	31 (66)
B2	12 (40)	18 (45)	22 (37)	41%	–	–	159 (44)	5 (38)[b]	4 (9)
C	0	1 (3)	3 (5)		–	–	6 (2)	0b	0
Preintervention characteristics					–	–			
Lesion length (mm)	9.15 ± 3.99	–	–	–	–	–	–	2.65 ± 0.32[b]	2.73 ± 0.48
Mean reference vessel diameter (mm)	2.72 ± 0.47	2.27 ± 0.15	2.83 ± 0.29	2.62 ± 0.35	–	2.63 ± 0.53	2.59 ± 0.38	0.81 ± 0.29[b]	1.21 ± 0.52
Minimum luminal diameter (mm)	1.06 ± 0.26	0.97 ± 0.20	1.12 ± 0.30	1.08 ± 0.31	–	1.21 ± 0.46	1.07 ± 0.32	70% ± 10.5%[b]	55.9 ± 16.7
Diameter stenosis (%)	60 ± 11	57.0 ± 9.3	60.3 ± 10.3	59 ± 10	–	53.2 ± 16.1	59 ± 11	8.95 ± 2.64[b]	10.99 ± 4.59

Data are expressed as mean ± standard deviation, number (%), unless otherwise indicated. ACC: American College of Cardiology; AHA: American Heart Association; BVS, Bioresorbable Vascular Scaffold; LMCA: left main coronary artery; STEMI: ST-segment elevation myocardial infarction.

[a] The ABSORB B study investigators present most of their results separately for small (diameter < 2.5 mm) and large target vessels.

[b] Reported on a modified intention-to-treat population (see text and original paper).

Table 5 Compilation of clinical and angiographical follow-up results of resorbable scaffolds.

Study	Lesion length (mm)	Reference vessel diameter (mm)	In-scaffold minimal diameter (mm)	Diameter stenosis (%)	Procedural success	MACE	Late scaffold thrombosis	In-scaffold late loss (mm)	Stent area reduction (%)
ABSORB A (BVS 1.0) [34]									
Preprocedure	9.15 ± 3.99	2.72 ± 0.47	0.06 ± 0.26	60 ± 11	–	–	–	–	–
Post-procedure	–	–	2.32 ± 0.31	16 ± 6	100	–	–	–	–
6 months (30 pts) [34]	–	–	–	–	–	3.3	0	0.44 ± 0.35	−11.8
1 year (29 pts) [34]	–	–	–	–	–	3.4	–	–	–
2 years (29 pts) [19]	–	–	–	–	–	3.4	0	0.48 ± 0.28	−27
3 years (29 pts) [35]	–	–	–	–	–	3.4	–	–	–
4 years(29 pts) [36]	–	–	–	–	–	3.4	–	–	–
5 years (29 pts) [37]	–	–	–	–	–	3.4	0	–	–
ABSORB B[a] (BVS 1.1) [21,38]									
Preprocedure, global	10.2 ± 3.9	2.65 ± 0.46	1.06 ± 0.32	60 ± 12	100	–	–	0.19 ± 0.18[b]	−5.4[b]
Small vessels (< 2.5 mm) (41 pts)	–	2.27 ± 0.15	2.83 ± 0.29	57 ± 9.3	–	–	–	–	–
Large vessels (≥ 2.5 mm) (60 pts)	–	0.97 ± 0.20	1.12 ± 0.30	60.3 ± 10.3	–	–	–	–	–
Post-procedure	–				–	–	–	–	–
Small vessels (< 2.5 mm) (41 pts)	–	–	2.17 ± 0.22	13.8 ± 4	–	–	–	–	–
Large vessels (≥ 2.5 mm) (60 pts)	–	–	2.37 ± 0.23	16.2 ± 6.7	–	–	–	–	–
Six months [21]	–	–			–				
Small vessels (20 pts)	–	–	–	18.1 ± 7.2	–	3/41 (7.3)	0	0.16 ± 0.18[b]	−18.1[b]
Large vessels (25 pts)	–	–	–	20.2 ± 8.0	–	2/60 (3.3)	0	0.21 ± 0.17[b]	−20.2[b]
One year [20]	–	–	–		–				
Small vessels (21 pts)	–	–	–	18.8 ± 10.5	–	3/41 (7.3)	0	0.27 ± 0.32[c]	–
Large vessels (35 pts)	–	–	–	22.5 ± 11.5	–	4/60 (6.7)	0	0.27 ± 0.32[c]	–
Two years [20]	–	–	–		–				–
Small vessels (20 pts)	–	–	–	20.72 ± 7.33	–	3/41 (7.3)	0	0.29 ± 0.16	–
Large vessels (25 pts)	–	–	–	21.17 ± 8.11	–	6/59 (10.2)	0	0.25 ± 0.22	–

Table 5 (*Continued*)

Study	Lesion length (mm)	Reference vessel diameter (mm)	In-scaffold minimal diameter (mm)	Diameter stenosis (%)	Procedural success	MACE	Late scaffold thrombosis	In-scaffold late loss (mm)	Stent area reduction (%)
Prague 19 (BVS 1.1) [27]									
1-year clinical follow-up	–	–	–	–	–	2/40 (5)	1 (2.5)	–	–
BVS STEMI (BVS 1.1) [28]									
1-month results	–	–	–	–	48/49 (97.9)	–	–	–	–
ABSORB EXTEND (BVS 1.1) (first 512 pts) [26]	–	–	–	–	540/548 (98.5) lesions	1/49 (2.6)	–	–	–
1 month	–	–	–	–	–	2.1	0.4	–	–
3 months	–	–	–	–	–	2.9	0.6	–	–
1 year	–	–	–	–	–	4.3	0.8	–	–
ABSORB II (BVS 1.1) [30]									
1-year interim analysis of BVS group (335 pts)	–	–	–	–	361/364 (99)	16/315 (5)	3/364 (0.9)	–	–
DESolve First-in-Man (16 pts) [33]	–	–	–	–	15/15 (100)[d]	–	–	–	–
1 month	–	–	–	–	–	1	0	–	–
6 months	–	–	–	–	–	2	0	0.19 ± 0.19	–
1 year	–	–	–	–	–	3	0	–	–
BIOSOLVE-1 (DREAMS) (46 pts) [17]	–	–	–	–	47/47 (100)	–	–	–	–
1 month	–	–	–	–	–	0/46	0	–	–
6 months	–	–	–	–	–	2/46 (4.3)	0	0.65 ± 0.50	–
1 year	–	–	–	–	–	3/43 (7)	0	0.52 ± 0.39	–

Data are expressed as mean ± standard deviation, number (%) or %. BVS, Bioresorbable Vascular Scaffold; MACE: major adverse cardiac events; pts: patients; STEMI: ST-segment elevation myocardial infarction.

[a] The ABSORB B study investigators present most of their results separately for small (diameter < 2.5 mm) and large target vessels.

[b] 6-month imaging subcohort (45 pts).

[c] 1-year imaging subcohort (56 pts, 57 lesions).

[d] Reported on a modified intention-to-treat population.

SPIRIT trial. SBO was observed in 73/1209 patients in the ABSORB EXTEND group versus 28/682 in the SPIRIT group (6% vs 4.1%; $p = 0.09$); these SBOs were associated with in-hospital non-Q-wave myocardial infarction (6.5% in the SBO group vs 0.5% in the non-SBO group; $p < 0.01$). Multivariable analysis confirmed the association of BVS with post-procedural SBO (Odds Ratio 2.09, 95% confidence interval 1.18—3.68); the results from a subgroup analysis suggest that this association may exist only for a side branch diameter < 0.5 mm ($p = 0.08$, not significant).

Recently, a preliminary report of the 12-month clinical outcomes in the first 512 patients enrolled [26] found that at 1 year, the frequencies of the composite endpoints of ischaemia-driven MACE and ischaemia-driven target vessel failure were 4.3% and 4.9%, respectively. The cumulative rate of Academic Research Consortium-defined definite and probable scaffold thrombosis for this population was 0.8% at 1 year.

Prague 19

A recent paper [27] reported the systematic use of Abbott's BVS 1.1 for the management of eligible patients presenting with acute ST-segment elevation myocardial infarction (STEMI) during a 7.5-month period, and compared their outcomes with those of ineligible patients during the same period. The authors reported a 98% procedural success rate, 95% of patients regaining arterial patency (Thrombolysis In Myocardial Infarction 3 flow); an OCT imaging substudy (21 patients) showed edge dissection in 38% and strut malapposition in 1.1%. These patients had clinical outcomes similar to those of ineligible patients treated with BMS (event-free survival of 95% in patients treated with the BVS and of 93% in patients treated with BMS). Leaving aside the comparison (which compared dissimilar populations), this continuous case series demonstrated the feasibility and, to some extent, the safety of the BVS in the setting of primary angioplasty for patients with STEMI.

BVS STEMI

This study [28], similar to Prague 19, included 49 patients among a cohort of 125 eligible (mostly in terms of lesion size and patient history) patients presenting with an acute STEMI; the criteria for treatment allocation were not reported. The authors reported no occurrence of MACE at 30-day follow-up and satisfactory angiographic results. Similar to Prague 19, this study demonstrated the feasibility of BVS implantation in patients presenting with acute STEMI, although with a very short follow-up.

Ongoing and forthcoming studies

The investigators of two comparative trials have announced their protocols; one has also produced some intermediary results.

The ABSORB II trial (initiated by Abbott) is comparing [29] the BVS (335 patients) with the Xience everolimus-eluting metal stent (166 patients) in a wider population (see Table 2 for criteria). Clinical follow-up is planned at 30 and 180 days and at 1, 2 and 3 years. The primary endpoint is aimed at demonstrating the superiority of the BVS versus the XIENCE stent in terms of vasodilation properties of the treated segment at 2 years, defined (using quantitative coronary angiography) as the change in the mean lumen diameter before and after administration of nitrates, along with the non-inferiority (reflex to superiority) of the minimum lumen diameter at 2 years (same basis). In an interim 1-year analysis of clinical and procedural secondary outcomes [30], the authors found that there were 17 (5%) MACE in the bioresorbable scaffold group compared with five (3%) ($p = 0.35$) in the metallic stent group, with the most common event being myocardial infarction (15 cases [4%] vs 2 cases [1%], respectively).

The aim of the randomized AIDA trial [31] is to demonstrate the non-inferiority of the BVS stent (compared with two everolimus-eluting stents of similar design) in a wide range of coronary percutaneous intervention indications, intending to mimic its planned use in 'all comers' population. This study was initiated and is sponsored by the Academic Medical Center, University of Amsterdam, and is currently enrolling patients [32].

Elixir's DESolve®

The First-in-Man trial [33] of the DESolve myolimus-eluting scaffold included 16 patients with evidence of myocardial ischaemia due to a single de novo lesion (see Table 2 for details).

One lesion could not be reached within the protocol-allotted time and was excluded from further analysis; immediate success was achieved in the 15 remaining patients. One patient presented a spiral dissection distal to the stent; a non-Q-wave myocardial infarction followed the repair surgery. Between 30 days and 6 months, one target lesion revascularization using a DES was reported for a proximal left circumflex stenosis (85.9% diameter stenosis) located adjacent to the widely patent scaffold. Between 6 months and 12 months, one event was reported: a cardiac death following non-target vessel coronary artery bypass grafting and aortic valve replacement. There were no other MACE directly attributable to the scaffold nor cases of scaffold thrombosis as adjudicated by the clinical events committee throughout the 12-month time period.

Imaging studies at 6 months showed that the in-scaffold late lumen loss was 0.19 ± 0.19 mm (according to quantitative coronary angiography); neointimal volume (by intravascular ultrasound imaging) was $7.19 \pm 3.56\%$, with no evidence of scaffold recoil or late malapposition. Findings were confirmed with OCT and showed uniform thin neointimal coverage (0.12 ± 0.04 mm). At 12 months, multislice computed tomography demonstrated excellent vessel patency.

Elixir has completed enrolment in a second single-arm trial (DESolve NX) [14]; the 6-month results have been presented [15] at EuroPCR 2013, but no information about this trial has been formally published.

Biotronik's DREAMS®

Evaluation of the efficacy and safety of the first iteration of this device was the aim of the BIOSOLVE-I single-arm trial [17], which included 46 patients presenting with stable or unstable angina or documented silent ischaemia, with two de novo lesions at most (Table 2). The primary outcome was the occurrence of a composite endpoint of death, target vessel myocardial infarction or clinically driven target lesion revascularization; secondary outcomes were late lumen loss, restenosis (percentage and binary) at 6 and

12 months, device thrombosis and cumulative target lesion failure at 6, 12, 24 and 36 months.

Forty-six patients were included (47 lesions), all of whom were successfully treated. Two patients withdrew their consent to follow-up after the 6-month examination; one patient died of a non-cardiac cause at day 210 (the reported cause of death was 'haemolytic anaemia, which was probably drug induced')—the authors did not discuss the possible link between this event and the drugs prescribed by study protocol; two myocardial infarctions occurred during the 6-month coronary angiography itself (both successfully treated with a DES); a third patient presented a lesion in a side branch of the target vessel. The authors reported a late lumen loss of 0.52 mm and a statistically significant stenosis increase at 6 months, with no significant variation between 6 months and 1 year; six lesions (seven segments) presented a binary restenosis at 6 months and two more lesions (three segments) at 1 year. OCT imaging undertaken in seven patients showed some malapposed struts in three patients. The authors deemed these results to be similar to DES or Abbott's BVS in terms of target lesion failure; however, they deemed their late lumen loss results to be inferior to those of these comparators and concluded that another device iteration was required.

The BIOSOLVE-II trial, evaluating the second-generation DREAMS, is currently recruiting patients [32].

Economic aspects

Currently, the only Conformité Européenne-marked resorbable scaffolds are Abbott's BVS and Elixir's DESolve. The BVS is currently marketed in many European countries, including France, where the regulatory authorities do not oppose the use of this device, but so far have not taken the decision to reimburse it. Furthermore, the regulatory authorities require that centres using the device register all patients in the FRANCE-ABSORB registry, undertaken in collaboration with the French Society of Cardiology.

To the best of our knowledge, no economic evaluation study is currently available. Because the current price of the device is said to be about € 1050, more than € 200 higher than the reimbursed price of a third-generation DES, the existence of this certain overcost and of a yet undetermined relative benefit make likely a high incremental cost-effectiveness ratio over third-generation DES.

Regulatory and ethical aspects

According to our information, these devices do not seem to present any specificities that differ from existing DES; therefore, their regulatory issues should not differ from those of DES. The available results do not seem to raise any specific ethical or organizational concerns.

Discussion

The availability of a fully bioresorbable coronary scaffold is conceptually very attractive for the interventional cardiologist, offering potential advantages over third-generation DES: preservation of vessel geometry, restoration of physiological vasomotion, late positive remodelling and eventual disappearance of any foreign material into the arterial wall on long-term follow-up. Have we reached the 'ideal' stent? Certainly not, because the history of these new devices showed that their engineering and technological development raised many issues, from bench to experimental evaluation in animals and finally to clinical studies in man. The available materials that are susceptible to resorption have mechanical characteristics weaker than those of the chrome-cobalt alloys used for BMS. A mechanical strength sufficient for the stent's expected function requires the manufacturing of a bulkier device (other design characteristics being equal). This problem hampered the development of the first scaffold (Igaki-Tamai) and might contribute to the excess of SBO reported for the BVS stent. However, the rates of restenosis were similar between the BVS and the everolimus-eluting stents suggesting that the radial force of the BVS is able, for a certain amount of time, to limit the elastic recoil and constrictive remodelling as well as the late-generation DES. In this respect, the magnesium rare-earth alloy used in the DREAMS device, which has better mechanical strength, might be of interest; however, the first iteration of this device had other problems.

Issues with strut fracture due to the inability of the polymeric device to achieve full expansion require some precaution with stent implantation. Predilatation is mandatory; primary stenting is not allowed with the BVS. Over-stretching is recommended quite routinely to avoid malapposition, but no more than 0.25 mm over the initial diameter of the stent. Thus, this over-stretching must be done very carefully with non-compliant balloons. Stent disruption may also have some serious secondary effects, such as coronary rupture.

A second problem is the dynamics of stent resorption. Too fast a resorption may have contributed to disputable results, leading to various device design iterations (BVS and DREAMS, among others). Resorption dynamics also have to be consistent with the dynamics of drug elution in drug-eluting devices.

Technological development is also needed if we want the widespread use of bioresorbable scaffolds in our daily angioplasty practice. Deliverability, pushability and crossing profile need to be improved in order to evaluate the efficacy of BVS in tortuous, calcified, ostial or bifurcation lesions, small vessels and also chronic total occlusion. In most randomized trials, patients with complex lesions such as these were excluded. The kissing technique, used and recommended in the treatment of bifurcation lesions, is not recommended with the BVS.

We have only limited data regarding some 'ideal' clinical situations for bioresorbable scaffolds, such as acute coronary syndromes. Even if we consider that the thicker struts and larger wall surface coverage with the BVS might entrap more thrombotic material, limiting distal embolization and, eventually, the no-reflow phenomenon, there was no clear clinical benefit [27]. Primary stenting without predilatation, contributing to some positive effects on the limitation of distal embolization, is not authorized with bioresorbable scaffolds. So, in this setting, even if the BVS may be used safely and effectively, one cannot recommend using it in all-comers with acute coronary syndromes.

Late resorption of the scaffold (up to 2—3 years) raises the issue of the optimal duration of dual antiplatelet

therapy, which is recommended for a minimal duration of 6 months after DES implantation in European guidelines. We have no evidence that this duration could be shortened and eventually reduce the risk of haemorrhagic complications without increasing the risk of in-stent thrombosis. Further studies dedicated to this specific issue are warranted and registries will be valuable for determining the rate of late stent thrombosis with bioresorbable scaffolds. Eventually, all manufacturers argue about the clinical value of restoring the vessel geometry and vasomotricity on long-term follow-up. Long-term clinical benefit (5—10 years) needs to be determined in large registries if we want to demonstrate any significant clinical differences (mainly on hard clinical endpoints, such as myocardial infarction and death) regarding the low rate of MACE.

From an economic point of view, any significant cost excess for the scaffolds over current DES will translate into an incremental cost-effectiveness ratio that is quite possibly unfavourable. Further development of these devices appears therefore as a wager to the manufacturers and their investors.

Given the current state of our information, there do not seem to be clinical reasons to choose one of these devices over current third-generation DES; further research is necessary—and possibly further development. The large-scale comparative randomized trials undertaken with the BVS device might give a better understanding of the possible late (and very late) clinical benefits of these innovative and attractive devices. Furthermore, the value of the design of the AIDA trial, which explicitly aims to assess results in 'everyday' use, should be underscored.

Conclusion

Clinical results published up to September 2014 are insufficient to allow a judgment to be made about the clinical performance of bioresorbable drug-eluting coronary scaffolds. However, a 'first impression' of clinical behaviour is close to that obtained after the first results with DES. Any clinical benefit of scaffolds over DES remains to be demonstrated, and the initial results do not lead to the expectation of large superiorities. Given the design of the bioresorbable scaffolds, potential clinical benefit might be expected in terms of late or very late outcomes. At this stage, one can say that the BVS is similar to the everolimus-eluting coronary stent in terms of safety and efficacy in selected patients with non-complex lesions.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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