International Journal of Cardiology 221 (2016) 1087–1094

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Review

Safety and efficacy of everolimus-eluting bioresorbable vascular scaffolds versus durable polymer everolimus-eluting metallic stents assessed at 1-year follow-up: A systematic review and meta-analysis of studies☆

Bertrand N. Mukete [a,1], Liefke C. van der Heijden [b,1], Kenneth Tandjung [b], Hassan Baydoun [a], Kapil Yadav [a], Qusai A. Saleh [a], Carine J.M. Doggen [c], Nidal Abi Rafeh [a], Thierry H. Le Jemtel [a], Clemens von Birgelen [b,c,*]

[a] Division of Cardiology, Department of Medicine, Tulane University School of Medicine, Heart and Vascular Institute, New Orleans, LA, USA
[b] Thoraxcentrum Twente, Medisch Spectrum Twente, Enschede, The Netherlands
[c] Health Technology and Services Research, MIRA Institute for Biomedical Technology and Technical Medicine, University of Twente, Enschede, The Netherlands

ARTICLE INFO

Article history:
Received 25 March 2016
Received in revised form 6 July 2016
Accepted 7 July 2016
Available online 9 July 2016

Keywords:
Bioresorbable vascular scaffold
Biodegradable device
Everolimus-eluting stent
Scaffold thrombosis
Stent thrombosis
Percutaneous coronary intervention

ABSTRACT

Background: The Absorb bioresorbable vascular scaffold (BVS) was developed to address long-term safety issues of metallic drug-eluting stents. However, it may be associated with an increased event risk during the first year.
Methods: A systematic literature search was performed (in MEDLINE/PubMed, Cochrane CENTRAL, EMBASE, and scientific meeting abstracts) to identify studies that compared BVS and cobalt-chromium durable polymer everolimus-eluting stents (EES). For randomized clinical trials and non-randomized propensity score matched studies that reported 1-year outcome data, fixed/random-effects models were used to generate pooled estimates of outcomes, presented as odds ratios (OR) with 95%-confidence intervals (CI).
Results: The 1-year follow-up data of 6 trials with 5588 patients were analyzed. A device-oriented composite endpoint (DOCE – cardiac death, target vessel myocardial infarction (MI), or target lesion revascularization (TLR)) was reached by 308 BVS or EES patients (195/3253 vs. 113/2315). Meta-analysis showed that patients who received BVS had an increased risk of MI (4.3% vs. 2.3%; OR:1.63, 95%-CI: 1.18–2.25, $p < 0.01$) and definite-or-probable scaffold thrombosis (1.3% vs. 0.6%; OR:2.10, 95%-CI: 1.13–3.87, $p = 0.02$). However, there was no significant between-group difference in risk of DOCE (6.0% vs. 4.9%; OR:1.19, 95%-CI: 0.94–1.52, $p = 0.16$), cardiac death (0.8% vs. 0.7%; OR:1.14, 95%-CI: 0.54–2.39, $p = 0.73$), or TLR (2.5% vs. 2.5%; OR: 0.98, 95%-CI:0.69–1.40, $p = 0.92$).
Conclusions: During the first year of follow-up, patients treated with BVS had a higher incidence of MI and scaffold thrombosis. The risk of DOCE was not significantly different. As BVS may pay off later, future robust data on long-term clinical outcome will be of paramount importance.

1. Introduction

Advancement in coronary device technology aims at reducing and ultimately eliminating late and very late stent thrombosis (ST), continued neointimal tissue growth with formation of neo-atherosclerosis, and long-term caging of the coronary vessel – issues that are still relevant to the latest generation of durable polymer drug-eluting stents (DES) [1]. The durable polymer coating of DES may account for impaired arterial healing and incomplete endothelial covering of the metallic struts with an increased risk of late ST.

The latest technical development is the bioresorbable vascular scaffold (BVS) that aims at providing a finite period of vascular support after stent implantation [2,3]. The potential advantages of BVS include the preservation of vessel geometry, adaptive vascular remodeling, and restoration of physiologic vasomotion, which offer the prospect of late luminal expansion [2,4,5]. The Absorb BVS (Abbott Vascular, Santa Clara, CA), a device that elutes the same drug as the widely used cobalt chromium everolimus-eluting stent (EES) [6], is the first BVS that received the Conformite European (CE) mark of approval for clinical use. In registries, the BVS showed clinical event rates that were overall comparable to durable polymer DES [7–11]. Nevertheless, safety and efficacy of the BVS has not yet been fully established, and there are concerns for a greater risk of scaffold thrombosis before the human body has resorbed the device [12].

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

* Corresponding author at: Thoraxcentrum Twente, Medisch Spectrum Twente, Koningsplein 1, 7512 KZ Enschede, The Netherlands.
E-mail address: c.vonbirgelen@mst.nl (C. von Birgelen).

[1] Both authors contributed equally to this manuscript.

http://dx.doi.org/10.1016/j.ijcard.2016.07.101

Recently multiple randomized clinical trials evaluating the Absorb BVS were published; however, by themselves they do not have sufficient power to detect differences in important but relative infrequent safety endpoints, such as cardiac death, myocardial infarction, and stent thrombosis. Therefore, in order to gain more insight into the safety and efficacy of the BVS versus EES during the first year from implantation, we performed a meta-analysis of studies that compared both devices and reported 1-year clinical outcome data.

2. Methods

2.1. Search strategy and selection criteria

A systematic search of randomized controlled clinical trials (and non-randomized) comparing Absorb BVS versus new-generation durable polymer cobalt-chromium EES using Medline, the Cochrane Central Register of Controlled Trials (CENTRAL), Embase, scientific sessions abstracts, and relevant websites (www.heart.org, www.cardiosource.com, www.tctmd.com, www.clinicaltrialresults.org, www.escardio.org) was performed according to the PRISMA guidelines [13]. Independent major search terms used included "bioresorbable vascular scaffold" and "Absorb stents". Minor search terms used in combination with the major terms included "everolimus-eluting stents", "clinical trials, and "randomized trials" was performed to retrieve peer reviewed published articles and presentations between January 2006 and October 2015.

2.2. Inclusion and exclusion criteria

We included studies that had a randomized or a propensity score matching design, and compared the Absorb BVS versus durable polymer cobalt-chromium EES. We included only studies that reported clinical outcome data at 12-month follow-up. Included studies provided numeric data on clinical endpoint of interest: target vessel myocardial infarction (MI); target lesion revascularization (TLR); cardiac death; definite-or-probable scaffold/stent thrombosis (ST). The ST criteria was based on the definition of the Academic Research Consortium (ARC) [14].

We excluded studies if they met any of the following criteria: duplicate publication; outcomes of interest not clearly reported or impossible to extract or calculate from the published results; follow-up duration <12-months; single-arm studies; and studies that compared BVS to a non-permanent polymer DES (i.e., bioabsorbable or bioresorbable polymer DES). Fig. 1 depicts a flow diagram for the selection of trials included in this review, using the PRISMA guidelines [13].

2.3. Inclusion and exclusion criteria of selected studies

In general, patients aged 18 years and older, presenting with stable angina, unstable angina or silent ischemia, who underwent percutaneous coronary intervention for one or two de novo native coronary artery lesions in separate epicardial coronary vessels, were eligible for enrollment in the ABSORB II, ABSORB Japan, ABSORB III, ABSORB China, and ABSORB Extend trial [15–19]. Patients with acute myocardial infarction were excluded in all ABSORB trials. In addition, left ventricular ejection fraction <30%, PCI of the target vessel during the last 12 months, and patients with a high bleeding risk were excluded.

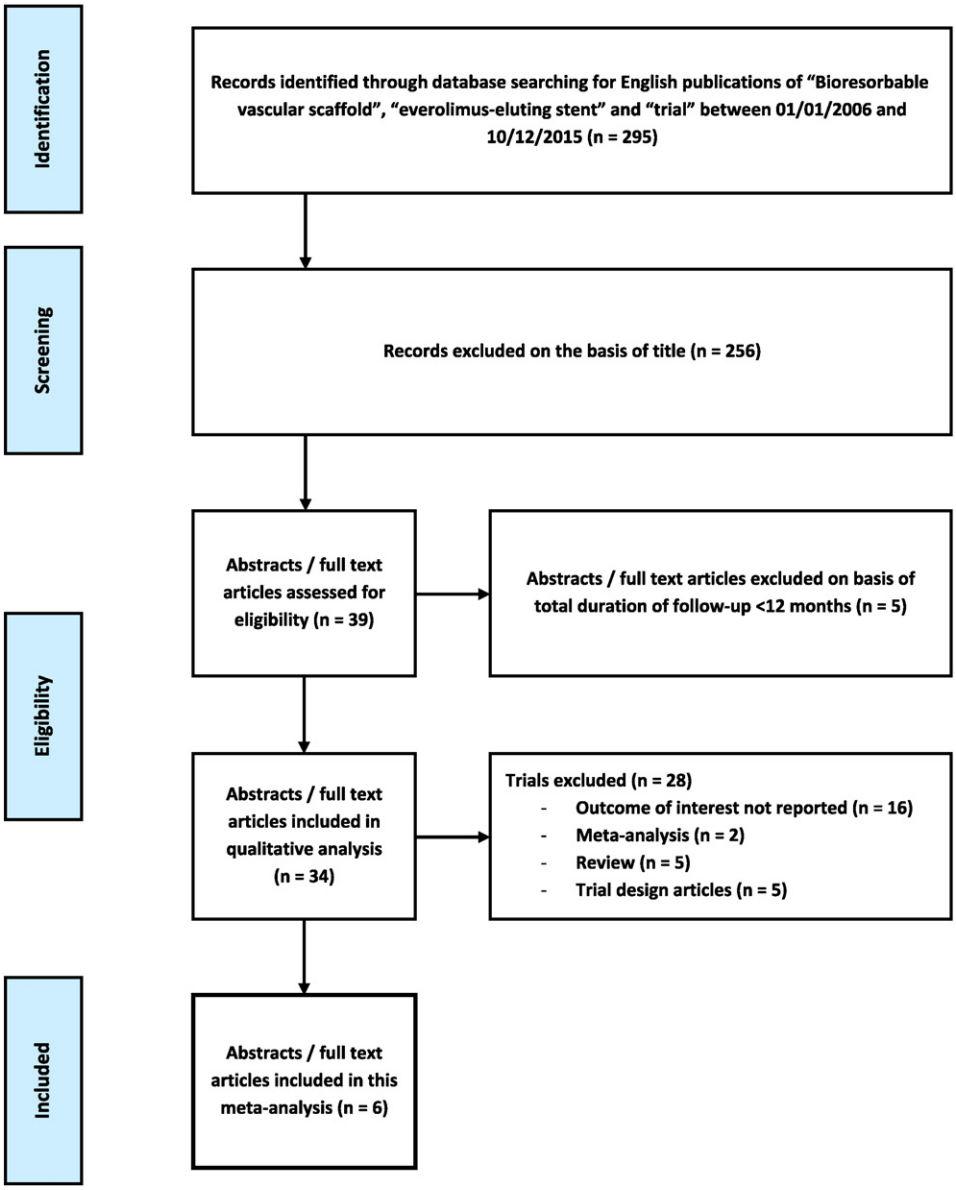

Fig. 1. Flow diagram of literature search and study selection.

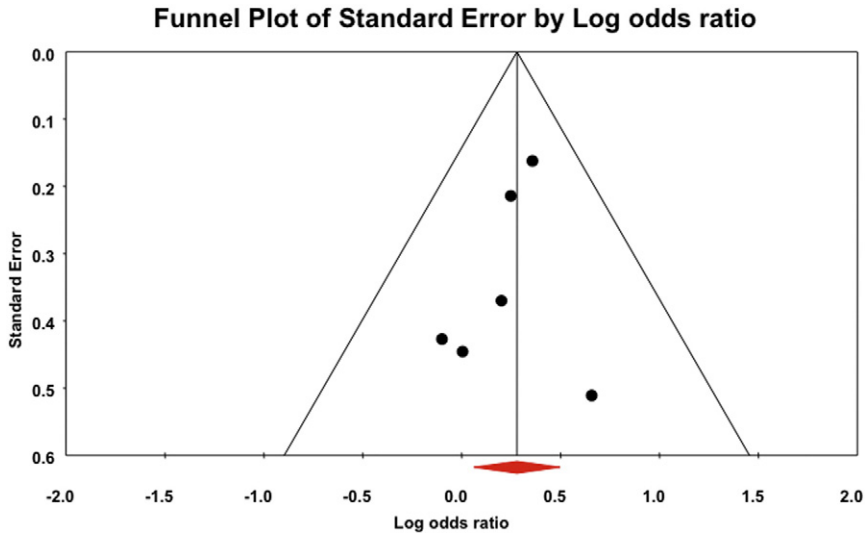

Fig. 2. Funnel plot of standard error by log odds ratio A total of 6 studies was analyzed for effect size. Abbreviations: BVS: bioresorbable vascular scaffold; EES: everolimus-eluting stent.

Table 1
Trial design and characteristics.

Trial name	Publication year	Sample size	Stent comparator		Primary endpoint	Trial design	Clinical setting	Follow-up duration (months)
			BVS	EES				
ABSORB II [15]	2015	501	Absorb everolimus-eluting bioresorbable vascular scaffold	Xience cobalt–chromium stent (Abbott Vascular)	Mean lumen diameter change before and after nitrate administration at 3 years	Prospective, randomized, active-controlled, single-blind, parallel two-group, multicenter clinical trial	Myocardial ischemia	12
ABSORB Japan [16]	2015	400	Absorb everolimus-eluting bioresorbable vascular scaffold	XIENCE Prime/Xpedition cobalt–chromium stent (Abbott Vascular)	Target-lesion failure (cardiac death, target-vessel myocardial infarction, or ischemia-driven target-lesion revascularization)	Prospective, multicentre, randomized, single-blind, active-controlled clinical trial	Myocardial ischemia (stable angina, unstable angina, or silent ischemia)	12
BVS-EXAMINATION [20]	2015	290	Absorb everolimus-eluting bioresorbable vascular scaffold	Xience V cobalt–chromium stent (Abbott Vascular)	Combined DOCE, including cardiac death, target vessel myocardial reinfarction, and target lesion revascularization	Prospective study with propensity-matched data from Xience V	STEMI	12
ABSORB III [17]	2015	2008	Absorb everolimus-eluting bioresorbable vascular scaffold	Xience V cobalt–chromium stent (Abbott Vascular)	Target-lesion failure (cardiac death, target-vessel myocardial infarction, or ischemia-driven target-lesion revascularization)	Prospective, multicentre, randomized, single-blind, active-controlled clinical trial	Myocardial ischemia (stable angina, unstable angina, or silent ischemia)	12
ABSORB China [18]	2015	480	Absorb everolimus-eluting bioresorbable vascular scaffold	Xience V cobalt–chromium stent (Abbott Vascular)	In-segment Lumen loss	Prospective, randomized, active-controlled, open-label, multicenter trial	Stable angina, unstable angina, post-infarct angina or silent ischemia	12
ABSORB Extend [19]	2015	1624	Absorb everolimus-eluting bioresorbable vascular scaffold	Xience V cobalt–chromium stent (Abbott Vascular)	Stent thrombosis, cardiac death, MI (target and non-target vessel), and revascularisation rates (TLR/TVR/all revascularizations)	Prospective registry with propensity matched data from Xience V	All-comers with moderately complex lesion in up to 2 de novo lesions in separate epicardial vessels	12

Abbreviations: BVS: bioresorbable vascular scaffold; EES: everolimus-eluting stent; DOCE: device-oriented composite endpoint; MI: myocardial infarction; STEMI: ST-elevation myocardial infarction; TLR: target lesion revascularization; TVR: target vessel revascularization.

Table 2
Patient and lesion characteristics of included studies.

	ABSORB II		ABSORB Japan		BVS EXAMINATION		ABSORB III		ABSORB China		ABSORB Extend		Total*			
	BVS	EES	BVS	EES	BVS	EES	BVS	EES	BVS	EES	BVS	EES	BVS	EES	difference (95%-CI)	p
Age	61.5 ± 10.0	60.9 ± 010.0	67.1 ± 9.4	67.3 ± 9.6	56.01 ± 12.75	57.57 ± 12.01	63.5 ± 10.6	63.6 ± 10.3	57.2 ± 11.4	57.6 ± 9.6	61	NR	62.1 ± 10.7	61.5 ± 10.5	0.60 (−0.09 to 1.29)	0.09
Diabetes	80/332 (24%)	40/166 (24%)	96/266 (36%)	48/134 (36%)	37/290 (13%)	37/290 (13%)	416/1320 (32%)	224/686 (33%)	60/238 (25%)	55/237 (23%)	219/812 (27%)	NR	689 (28%)	404 (27%)	0.01 (−0.01 to 0.04)	0.32
Active smoking	79/335 (24%)	36/166 (22%)	53/266 (20%)	29/134 (22%)	177/290 (61%)	220/290 (76%)	281/1322 (21%)	142/686 (21%)	78/238 (33%)	84/237 (35%)	187/812 (23%)	NR	668 (27%)	511 (34%)	−0.07 (−0.09 to −0.04)	<0.01
Previous MI	93/335 (28%)	48/166 (29%)	42/262 (16%)	32/134 (24%)	10/290 (4%)	10/290 (4%)	282/1311 (22%)	150/681 (22%)	40/238 (17%)	38/237 (16%)	235/812 (29%)	NR	467 (19%)	278 (18%)	0.01 (−0.02 to 0.03)	0.57
Previous PCI	14/120 (12%)	5/56 (9%)	9/266 (3%)	7/134 (5%)	10/290 (3%)	11/290 (4%)	96/1249 (8%)	38/651 (6%)	23/238 (10%)	19/237 (8%)	NR	NR	152 (7%)	80 (6%)	0.01 (−0.01 to 0.03)	0.17
Unstable angina	68/335 (20%)	37/166 (22%)	26/266 (10%)	22/134 (16%)	NA	NA	355/1321 (27%)	168/686 (25%)	154/238 (65%)	152/237 (64%)	219/812 (27%)	NR	603 (28%)	379 (31%)	−0.03 (−0.06 to 0.001)	0.06
Multivessel disease	57/335 (17%)	25/166 (15%)	NR	NR	24/290 (8%)	28/290 (10%)	NR	NR	42/238 (18%)	51/237 (22%)	NR	NR				
LAD	163/364 (45%)	84/182 (46%)	127/275 (46%)	58/137 (42%)	145/290 (50%)	117/290 (40%)	617/1385 (45%)	301/713 (42%)	139/251 (55%)	132/252 (52%)	NR (45%)	NR	1191 (46%)	692 (44%)	0.02 (−0.01 to 0.06)	0.12
LCX	106/364 (29%)	42/182 (23%)	63/275 (23%)	36/137(26%)	29/290 (10%)	45/290 (16%)	363/1385 (26%)	218/713 (31%)	49/251 (20%)	61/252 (24%)	NR (26%)	NR	610 (24%)	402 (26%)	−0.02 (−0.04 to 0.01)	0.20
RCA	95/364 (26%)	56/182 (31%)	85/275 (31%)	43/137 (31%)	114/290 (39%)	126/290 (43%)	404/1385 (29%)	194/713 (27%)	63/251 (25%)	59/252 (23%)	NR (28%)	NR	761 (30%)	478 (30%)	−0.01 (−0.04 to 0.02)	0.63
ACC/AHA lesion class																
B1	193/363 (53%)	90/180 (50%)	55/275 (20%)	28/137 (20%)	NR	NR	NR	NR	53/251 (21%)	56/252 (22%)	NR (53%)	NR				
B2	159/363 (44%)	87/180 (48%)	154/275 (56%)	68/137 (50%)					120/251 (48%)	126/252 (50%)	NR (42%)					
C	6/363 (2%)	2/180 (1%)	55/275 (20%)	36/137 (26%)					68/251 (27%)	55/252 (22%)	NR (3%)					
Type B2/C lesion class	165/363 (45%)	89/180 (49%)	209/275 (76%)	104/137 (76%)	NR	NR	949/1381 (69%)	513/708 (73%)	241/251 (96%)	236/251 (94%)	NR (98%)	NR	1564 (69%)	942 (74%)	−0.04 (−0.08 to −0.02)	0.002

Values are n (%) or mean ± SD. *ABSORB Extend was not included in "total" because no baseline data was available for the EES group. Abbreviations: ACC: American College of Cardiology; AHA: American Heart Association; BVS: bioresorbable vascular scaffold; EES: everolimus-eluting stent; LAD: left anterior descending artery; LCX: left circumflex artery; MI: myocardial infarction; NA: not available; NR: not reported; PCI: percutaneous coronary intervention; RCA: right coronary artery.

Table 3
Procedural characteristics of included studies.

	ABSORB II		ABSORB Japan		BVS- examination		ABSORB III		ABSORB China		ABSORB extend		Weighted Mean ± SD*		
	BVS	EES	BVS	EES	BVS	EES	BVS	EES	BVS	EES	BVS	EES	BVS	EES	p-value
Number of lesions treated	364	182	275	137	NR	NR	1385	713	251	252	874	NR	570	321	
Scaffold/stent diameter	3.01 ± 0.31	3.05 ± 0.28	3.09 ± 0.37	3.13 ± 0.38	3.22 ± 0.33	3.19 ± 0.40	3.18 ± 0.43	3.12 ± 0.45	3.1 ± 0.4	3.1 ± 0.4	NR	NR	3.14 ± 0.40	3.12 ± 0.41	0.12
Scaffold/stent length	21.1 ± 8.8	20.9 ± 7.4	20.2 ± 5.8	19.5 ± 5.8	22.5 ± 8.8	21.8 ± 9.2	20.5 ± 7.2	20.7 ± 9.0	22.8 ± 6.7	22.3 ± 5.8	NR	NR	21.0 ± 7.5	21.1 ± 8.2	0.79
Reference vessel diameter	2.59 ± 0.38	2.63 ± 0.40	2.72 ± 0.44	2.79 ± 0.46	NR	NR	2.67 ± 0.45	2.65 ± 0.46	2.81 ± 0.03	2.82 ± 0.03	2.65 ± 0.39	NR	2.68 ± 0.41	2.70 ± 0.40	0.16
Lesion length	13·8 ± 6.5	13.8 ± 6.6	13.5 ± 5.28	13.3 ± 5.52	NR	NR	12.6 ± 5.4	13.1 ± 5.8	14.1 ± 0.3	13.9 ± 0.3	12.3 ± 5.3	NR	13.1 ± 5.3	13.4 ± 5.3	0.11
MLD before intervention	1.07 ± 0.32	1.05 ± 0.32	0.96 ± 0.33	0.99 ± 0.36	NR	NR	0.92 ± 0.37	0.90 ± 0.34	0.98 ± 0.03	1.01 ± 0.03	1.11 ± 0.32	NR	0.96 ± 0.34	0.95 ± 0.30	0.38
MLD finally after intervention	2.22 ± 0.33	2.50 ± 0.33	2.42 ± 0.38	2.64 ± 0.40	NR	NR	2.37 ± 0.40	2.49 ± 0.40	2.48 ± 0.02	2.59 ± 0.03	NR	NR	2.36 ± 0.36	2.53 ± 0.35	<0.01
In-scaffold/in-stent gain	1.15 ± 0.38	1.46 ± 0.38	1.46 ± 0.40	1.65 ± 0.40	NR	NR	1.45 ± 0.45	1.59 ± 0.44	1.51 ± 0.03	1.59 ± 0.03	NR	NR	1.41 ± 0.41	1.58 ± 0.38	<0.01

Values are mean ± SD unless otherwise stated. *The weighted mean ± SD was calculated based on available data from the included studies, except data from ABSORB Extend. Abbreviations: BVS: bioresorbable scaffold; EES: everolimus-eluting stent; MLD: minimum lumen diameter; NR: not reported.

Main angiographic exclusion criteria were left main or ostial location of the lesion, excessive vessel tortuosity, heavy calcification proximal to or within the target lesion, and bifurcation lesions with side branch ≥2.0 mm requiring guidewire or dilation [15–19]. The BVS-EXAMINATION Study is an observational study, in which all consecutive STEMI patients treated with BVS were enrolled [20].

2.4. Data extraction and assessment of bias

All publications were independently assessed for eligibility at the title or abstract level by 3 independent investigators (BNM, LCvdH, KT). We collected information about the study design, clinical and procedural characteristics, and clinical and safety outcomes. The Cochrane Collaboration's tool was used to assess the risk of bias based on the quality of each eligible trial [21]. In addition, we visually assessed for publication bias with a funnel plot (Fig. 2) while the Begg and Mazumdar test [22] was used to quantify the amount of publication bias.

2.5. Study endpoints

We assessed a device-oriented composite endpoint (DOCE–cardiac death, target vessel myocardial infarction, or target lesion revascularization), reflecting efficacy and safety. Individual endpoints of efficacy were TVR and TLR. Individual safety endpoints were cardiac death, target vessel MI, and definite-or-probable ST, as defined by the ARC [14].

2.6. Statistical analysis

For each clinical and combined clinical endpoint, the independent odds ratio (OR) and weighted mean difference was calculated with the 95% confidence interval (CI). A summary OR was then derived for the comparison of BVS with EES. The summary effect size was determined using a fixed/random effect model based on the absence/presence of heterogeneity respectively. Heterogeneity was assessed using the I^2 statistic [23]. We assumed heterogeneity among the studies when the degree of inconsistency (using I^2 statistics) was >50% with an associated p-value ≤0.05. We used the Mantel–Haenszel [24] fixed-effect model and DerSimonian and Liard [25] random-effect model to calculate the summary effect size based on the absence or presence of heterogeneity among studies. A chi-square statistic was used to determine difference between baseline clinical and angiographic characteristics and Unpaired two-tailed student *t*-test was used to calculate difference in mean of the procedural characteristics between the two groups. We used the Comprehensive Meta-Analysis (CMA) version 2.0 program for outcomes statistical analysis [26].

3. Results

A total of 6 studies met the inclusion criteria with a sample size of 5588 patients (3263 in the BVS arm versus 2325 in the EES arm). The patients of the EES arm received cobalt-chromium-based stents (Xience V, Xience Prime, or Xience Xpedition, Abbott Vascular, Santa Clara, CA, USA) and those of the BVS group were treated with Absorb BVS. Five (ABSORB II [15], ABSORB Japan [16], ABSORB III [17], ABSORB China [18], and ABSORB Extend [19] out of 6 studies enrolled patients with stable angina or silent ischemia and one study (BVS-EXAMINATION [20]) enrolled only patients with ST-elevation MI. The BVS-EXAMINATION study included a third treatment arm that received a bare metal stent (Multilink Vision, Abbott Vascular) but was excluded from our analysis.

Patients were on average 62.1 ± 10.7 vs. 61.5 ± 10.5 years old ($p = 0.09$) and 28% vs. 27% ($p = 0.32$) diabetics for BVS vs. EES group. More than 70% of all patients were treated for ACC/AHH class B2 or C lesions. The follow-up period was 1 year in all studies. Tables 1, 2, and 3 shows the design of the individual studies, baseline clinical and angiographic characteristics, and the procedural characteristics. Between the BVS and EES groups there was no significant difference in the proportion of patients with diabetes, previous MI, previous PCI, presentation with unstable angina, or in the proportion of multivessel treatment. However, there were significantly more active smokers ($p < 0.01$) and type B/C lesions ($p < 0.01$) in the BVS group (Table 2). Between BVS and EES, there was no difference in mean reference vessel diameter (2.68 ± 0.41 mm vs. 2.70 ± 0.40 mm); $p = 0.16$, mean lesion length (13.1 ± 5.3 mm vs. 13.4 ± 5.3 mm); $p = 0.11$, mean scaffold/stent length (21.0 ± 7.5 mm vs. 21.1 ± 8.2 mm); $p = 0.79$ and mean scaffold/stent diameter (3.14 ± 0.40 mm vs. 3.12 ± 0.41 mm); $p = 0.12$. Between groups there was no significant difference in pre-dilatation minimum lumen diameter (0.96 ± 0.34 mm vs. 0.95 ± 0.30 mm; $p = 0.38$). However, the final minimum lumen diameter was lower (2.36 ±

0.36 mm vs. 2.53 ± 0.35 mm; $p < 0.01$) and the acute gain was higher (1.41 ± 0.41 mm vs. 1.58 ± 0.38 mm; $p < 0.01$) in patients with BVS.

3.1. Efficacy outcomes

Study-level outcomes after 12 months follow-up for DOCE, the individual components of DOCE, TVR, and ST were shown in Table 4 and Fig. 3. Follow-up was available in 3253 patients treated with BVS and in 2315 patients treated with EES. Slightly more than 80% of patients were on dual antiplatelet therapy at 12-month follow-up.

DOCE occurred in 6.0% of the patients treated with BVS and in 4.9% of the patients treated with EES (OR 1.19, 95%-CI: 0.94–1.52, $p = 0.16$; heterogeneity: $I^2 = 0$, $Q = 1.49$, $df = 5$; $p = 0.91$). The rate of cardiac death and TLR were similar for both patients treated with BVS and EES (OR 1.14, 95%-CI 0.54–2.39, $p = 0.73$ and OR 0.98, 95%-CI 0.69–1.40, $p = 0.92$, respectively).

3.2. Safety outcomes

During 1-year follow-up, definite-or-probable stent thrombosis occurred more often in the BVS-group (1.3% vs. 0.6%; OR 2.10, 95%-CI: 1.13–3.87, $p = 0.02$; heterogeneity: $I^2 = 0$, $Q = 1.63$, $df = 5$, $p = 0.90$). In addition, more patients treated with BVS developed target vessel MI as compared to patients treated with EES (4.3% vs. 2.3%; OR 1.63, 95%-CI: 1.18–2.25, $p < 0.01$; heterogeneity: $I^2 = 0$, $Q = 3.16$, $df = 5$, $p = 0.68$).

4. Discussion

The present meta-analysis shows that treatment of in patients with obstructive coronary artery disease with the Absorb BVS was similarly efficacious as implantation of durable polymer cobalt-chromium EES with regard to the risk of repeat revascularization (i.e. both TLR and TVR). In addition, there was no between-group difference in cardiovascular mortality. Patients who received BVS had an increased risk of MI and definite-or-probable scaffold thrombosis. The composite endpoint DOCE showed no significant difference between both device groups.

The present meta-analysis differs from previous meta-analyses in that we (1) included only trials with a minimum follow-up duration of 12-months and (2) compared the BVS only to cobalt-chromium-based EES. Cassese and colleagues [27] published a meta-analysis that compared the efficacy and safety outcomes in patients treated with Absorb BVS versus EES but included two studies with 6-month follow-up duration (TROFI II and EVERBIO II).

Despite the overall relatively small number of definite-or-probable stent thromboses in both groups, treatment with BVS showed a significantly increased risk of ST ($p = 0.02$) as compared to cobalt-chromium EES. The two-fold higher rate of ST with BVS, noted in our study, was similar to previous findings by Cassese et al. [27] and Lipinski et al. [28]. Our study also confirmed a significantly higher rate of MI associated with BVS implantation versus DES [28]. Similar to Cassese and colleagues [27], our study confirmed the known favorable safety profile of the EES. In addition, at 1-year follow-up, patients with predominantly ACC/AHA lesion types B or C treated with BVS showed no significant difference in mortality, revascularization rate, or DOCE.

Theoretically, one would expect a reduction in very late stent thrombosis with BVS after resorption of the polymeric scaffold after 2 to 3 years. Imaging studies have shown persistent presence of the BVS at 12 months and bioresorption at 24 to 26 months [2,3,29]. One of the anticipated benefits of BVS is minimization of very late stent thrombosis, which occurs after complete bioresorption of the vascular scaffold and return of normal vessel function [3]. In cohort A of the ABSORB trial, there was no reported stent thrombosis at 3-year follow-up although at 2 and 3 years only a single patient was on dual anti-platelet therapy (i.e. aspirin plus thienopyridine) [30]. After 2 years, optical coherence tomography (OCT) assessment of the BVS in the ABSORB cohort A showed that the polymeric struts were no longer recognizable, and on angiography there was very late lumen enlargement [30]. Similarly, the ABSORB trial cohort B showed at 2-year follow-up no scaffold thrombosis, a return of vasomotion, and very late lumen enlargement [7].

There are various factors that may have contributed to the higher incidence of device thrombosis up to 12-months in patients treated with BVS versus EES, as seen in the current meta-analysis: The thicker struts of the BVS may trigger platelet aggregation [31]. Moreover, the lower final in-device minimum lumen diameter achieved with BVS when compared to EES, may have contributed to the increased thrombotic risk. Suboptimal implantation may result in device malapposition and underexpansion, which are known to affect coronary flow pattern and may subsequently activate the thrombotic cascade [12,32,33]. Well-controlled post-dilatation and overexpansion of BVS is likely to prevent a substantial proportion of potential coronary thromboses by improving the apposition of the scaffold to the vessel wall; on the other hand, excessive overexpansion can lead to fractures of the polymeric BVS that may induce thrombus formation [34]. Late scaffold recoil, which may occur more frequently in the absence of adequate lesion preparation, has also been associated with BVS thrombosis [35].

Further potential mechanisms for very late BVS thrombosis include the presence of uncovered BVS struts after 12 months with discontinuation of dual antiplatelet therapy [32,36]. In our present analysis, slightly more than 80% of patients were on dual antiplatelet therapy at 12-month follow-up. Despite the relatively low rates of BVS thrombosis beyond 12 months, it may be considered to continue dual antiplatelet therapy until the polymeric scaffold is expected to

Table 4
Patient outcomes at 1-year follow-up.

	Stent type	Sample size (n)	DOCE	Cardiac death	MI (target vessel)	ID-TLR	ID-TVR	Scaffold/stent thrombosis*
ABSORB II	BVS	335	16 (4.8)	0 (0)	15 (4.5)	4 (1.2)	6 (1.8)	3 (0.9)
(2015)	EES	166	5 (3.0)	0 (0)	2 (1.2)	3 (1.8)	6 (3.6)	0 (0)
ABSORB Japan	BVS	265	11 (4.2)	0 (0)	9 (3.4)	7 (2.6)	13 (4.9)	4 (1.5)
(2015)	EES	133	5 (3.8)	0 (0)	3 (2.3)	3 (2.3)	5 (3.8)	2 (1.5)
BVS-EXAMINATION	BVS	290	17 (5.8)	6 (2.1)	6 (2.1)	5 (1.7)	NR	7 (2.4)
(2015)	EES	290	14 (4.8)	6 (2.1)	4 (1.4)	4 (1.4)	NR	4 (1.4)
ABSORB III	BVS	1313	102 (7.8)	8 (0.6)	79 (6.0)	40 (3.0)	66 (5.0)	20 (1.5)
(2015)	EES	677	41 (6.1)	1 (0.1)	31 (4.6)	17 (2.5)	25 (3.7)	5 (0.7)
ABSORB China	BVS	238	8 (3.4)	0 (0)	4 (1.7)	6 (2.5)	7 (2.9)	1 (0.4)
(2015)	EES	237	10 (4.2)	3 (1.3)	2 (0.8)	7 (3.0)	9 (3.8)	0 (0)
ABSORB Extend	BVS	812	41 (5.0)	6 (0.7)	27 (3.3)	19 (2.3)	NR	8 (1.0)
(2015)	EES	812	38 (4.7)	5 (0.6)	12 (1.5)	24 (3.0)	NR	2 (0.3)

Values are n (%). Abbreviation: BVS: bioresorbable vascular scaffold; DOCE: device-oriented composite endpoint; EES: everolimus-eluting stent; MI: myocardial infarction; NR: not reported; TLR: target lesion revascularization; TVR: target vessel revascularization.

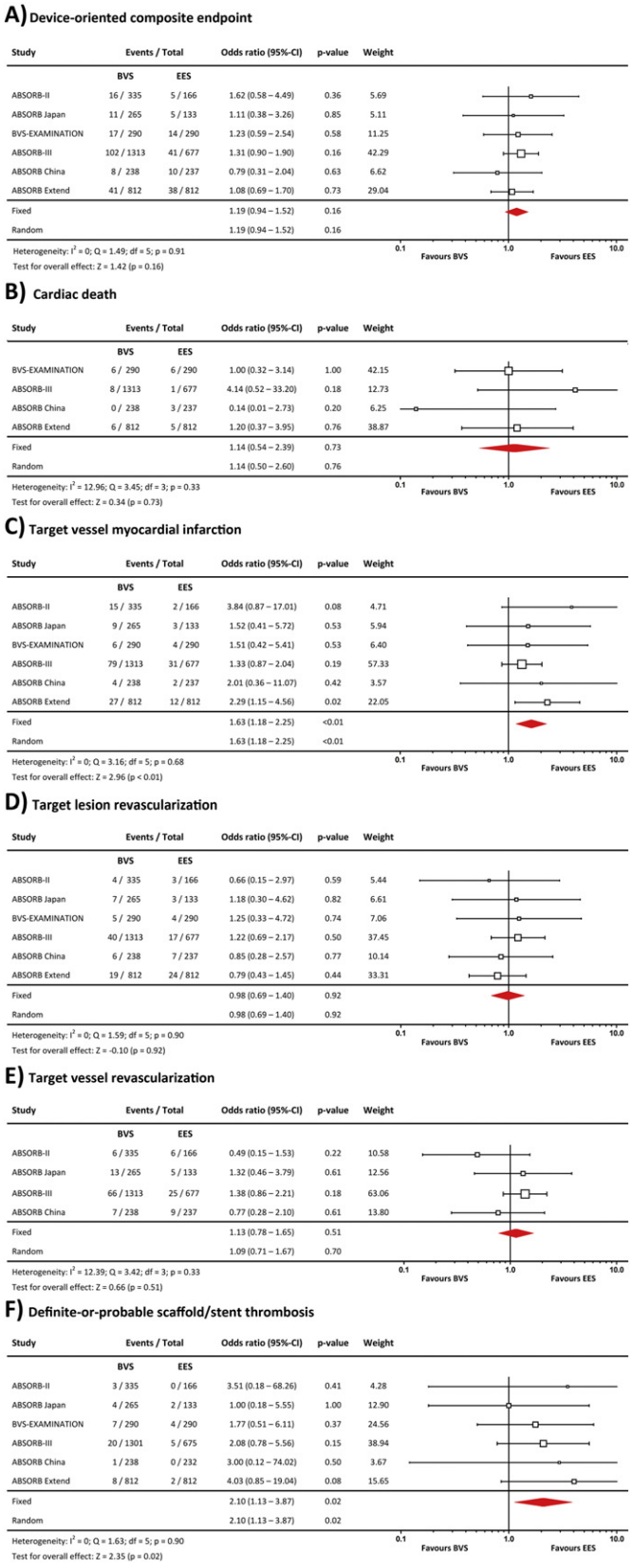

Fig. 3. Meta-analysis comparing 1-year clinical outcomes of patients treated with Absorb BVS vs. EES (panes A–F) A: device-oriented composite endpoint; B: cardiac death; C: target vessel myocardial infarction; D: target lesion revascularization; E: target vessel revascularization; F: definite-or-probable scaffold/stent thrombosis. Abbreviations: BVS: bioresorbable vascular scaffold; EES: durable-polymer everolimus-eluting stent.

be fully dissolved [37]. Prolongation of dual antiplatelet therapy might be particularly useful in patients or procedural results with increased thrombotic risk (e.g. diabetics, patients with renal failure, overlapping BVS). Finally, late scaffold discontinuity may cause dislocation of strut remnants into the coronary lumen, which may result in flow disturbance and shear stress to the vessel wall with subsequent platelet recruitment and thrombus formation [36].

5. Study limitations

In this meta-analysis, we used 4 randomized clinical trials in combination with 2 observational studies to detect differences between Absorb BVS and EES; nevertheless, both observation studies used propensity score matching, and as such meaningful comparisons could be made. While a respectable number of patients (n = 5588) were included in this meta-analysis, it may still be too few to assess true differences in the occurrence of rare adverse events such as stent thrombosis. The BVS technology is still relative new, and as such, from several randomized trials only 12-month outcome data is available. As a consequence, more data on a longer follow-up are required to assess the long-term safety and efficacy of BVS beyond the first year after treatment.

6. Conclusion

During the first year of follow-up, treatment with everolimus-eluting BVS was associated with a higher incidence of target vessel MI and scaffold thrombosis as compared to metallic EES, but the composite endpoint DOCE showed no significant difference between groups. As BVS may pay off beyond the follow-up period of 1-year, additional robust data on long-term clinical outcome will be of paramount importance.

Conflict of interest statements

Dr. von Birgelen has received moderate lecture fees from AstraZeneca and Biotronik, and his institution has received significant research grants from AstraZeneca, Biotronik, Boston Scientific, and Medtronic. The other authors reported no conflict of interest.

References

[1] J. Wiebe, H.M. Nef, C.W. Hamm, Current status of bioresorbable scaffolds in the treatment of coronary artery disease, J. Am. Coll. Cardiol. 64 (2014) 2541–2551.
[2] R. Waksman, Biodegradable stents: they do their job and disappear, J. Invasive Cardiol. 18 (2006) 70–74.
[3] J. Iqbal, Y. Onuma, J. Ormiston, A. Abizaid, R. Waksman, P. Serruys, Bioresorbable scaffolds: rationale, current status, challenges, and future, Eur. Heart J. 35 (2014) 765–776.
[4] J. Gomez-Lara, H.M. Garcia-Garcia, Y. Onuma, et al., A comparison of the conformability of everolimus-eluting bioresorbable vascular scaffolds to metal platform coronary stents, JACC Cardiovasc. Interv. 3 (2010) 1190–1198.
[5] P.W. Serruys, H.M. Garcia-Garcia, Y. Onuma, From metallic cages to transient bioresorbable scaffolds: change in paradigm of coronary revascularization in the upcoming decade? Eur. Heart J. 33 (2012) 16–25b.
[6] K. Tandjung, H. Sen, M.K. Lam, et al., Clinical outcome following stringent discontinuation of dual antiplatelet therapy after 12 months in real-world patients treated with second-generation zotarolimus-eluting resolute and everolimus-eluting Xience V stents: 2-year follow-up of the randomized TWENTE trial, J. Am. Coll. Cardiol. 61 (2013) 2406–2416.
[7] J.A. Ormiston, P.W. Serruys, Y. Onuma, et al., First serial assessment at 6 months and 2 years of the second generation of absorb everolimus-eluting bioresorbable vascular scaffold: a multi-imaging modality study, Circ. Cardiovasc. Interv. 5 (2012) 620–632.
[8] P.W. Serruys, Y. Onuma, D. Dudek, et al., Evaluation of the second generation of a bioresorbable everolimus-eluting vascular scaffold for the treatment of de novo coronary artery stenosis: 12-month clinical and imaging outcomes, J. Am. Coll. Cardiol. 58 (2011) 1578–1588.
[9] D. Capodanno, T. Gori, H. Nef, et al., Percutaneous coronary intervention with everolimus-eluting bioresorbable vascular scaffolds in routine clinical practice: early and midterm outcomes from the European multicentre GHOST-EU registry, EuroIntervention 10 (2015) 1144–1153.
[10] M. Jaguszewski, J.R. Ghadri, M. Zipponi, et al., Feasibility of second-generation bioresorbable vascular scaffold implantation in complex anatomical and clinical scenarios, Clin. Res. Cardiol. 104 (2015) 124–135.

[11] R.P. Kraak, M.E. Hassell, M.J. Grundeken, et al., Initial experience and clinical evaluation of the absorb bioresorbable vascular scaffold (BVS) in real-world practice: the AMC Single Centre Real World PCI Registry, EuroIntervention 10 (2015) 1160–1168.
[12] L. Raber, S. Brugaletta, K. Yamaji, et al., Very late scaffold thrombosis: intracoronary imaging and histopathological and spectroscopic findings, J. Am. Coll. Cardiol. 66 (2015) 1901–1914.
[13] D. Moher, A. Liberati, J. Tetzlaff, D.G. Altman, P. Group, Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement, Ann. Intern. Med. 151 (2009) 264–269 (W64).
[14] Food and Drug Administration, Circulatory System Devices Panel Meeting, 2006.
[15] P.W. Serruys, B. Chevalier, D. Dudek, et al., A bioresorbable everolimus-eluting scaffold versus a metallic everolimus-eluting stent for ischaemic heart disease caused by de-novo native coronary artery lesions (ABSORB II): an interim 1-year analysis of clinical and procedural secondary outcomes from a randomised controlled trial, Lancet 385 (2015) 43–54.
[16] T. Kimura, K. Kozuma, K. Tanabe, et al., A randomized trial evaluating everolimus-eluting absorb bioresorbable scaffolds vs. everolimus-eluting metallic stents in patients with coronary artery disease: ABSORB Japan, Eur. Heart J. 36 (2015) 3332–3342.
[17] S.G. Ellis, D.J. Kereiakes, D.C. Metzger, et al., Everolimus-eluting bioresorbable scaffolds for coronary artery disease, N. Engl. J. Med. 373 (2015) 1905–1915.
[18] R. Gao, Y. Yang, Y. Han, et al., Bioresorbable vascular scaffolds versus metallic stents in patients with coronary artery disease: ABSORB China trial, J. Am. Coll. Cardiol. 66 (2015) 2298–2309.
[19] A. Abizaid, ABSORB EXTEND: One-Year Results in Moderately Complex Lesions (Abstr.). Presented at: EuroPCR. Paris, France, 2015.
[20] S. Brugaletta, T. Gori, A.F. Low, et al., Absorb bioresorbable vascular scaffold versus everolimus-eluting metallic stent in ST-segment elevation myocardial infarction: 1-year results of a propensity score matching comparison: the BVS-EXAMINATION study (bioresorbable vascular scaffold-a clinical evaluation of everolimus eluting coronary stents in the treatment of patients with ST-segment elevation myocardial infarction), JACC Cardiovasc. Interv. 8 (2015) 189–197.
[21] J.P. Higgins, D.G. Altman, P.C. Gotzsche, et al., The Cochrane Collaboration's tool for assessing risk of bias in randomised trials, BMJ 343 (2011) d5928.
[22] C.B. Begg, M. Mazumdar, Operating characteristics of a rank correlation test for publication bias, Biometrics 50 (1994) 1088–1101.
[23] J.P. Higgins, S.G. Thompson, Quantifying heterogeneity in a meta-analysis, Stat. Med. 21 (2002) 1539–1558.
[24] N. Mantel, W. Haenszel, Statistical aspects of the analysis of data from retrospective studies of disease, J. Natl. Cancer Inst. 22 (1959) 719–748.
[25] R. DerSimonian, N. Laird, Meta-analysis in clinical trials, Control. Clin. Trials 7 (1986) 177–188.
[26] M. Borenstein, Introduction to Meta-Analysis, Wiley, Chichester, 2009.
[27] S. Cassese, R.A. Byrne, G. Ndrepepa, et al., Everolimus-eluting bioresorbable vascular scaffolds versus everolimus-eluting metallic stents: a meta-analysis of randomised controlled trials, Lancet 387 (2015) 537–544.
[28] M.J. Lipinski, R.O. Escarcega, N.C. Baker, et al., Scaffold thrombosis after percutaneous coronary intervention with ABSORB bioresorbable vascular scaffold: a systematic review and meta-analysis, JACC Cardiovasc. Interv. 9 (2016) 12–24.
[29] Y. Onuma, P.W. Serruys, L.E. Perkins, et al., Intracoronary optical coherence tomography and histology at 1 month and 2, 3, and 4 years after implantation of everolimus-eluting bioresorbable vascular scaffolds in a porcine coronary artery model: an attempt to decipher the human optical coherence tomography images in the ABSORB trial, Circulation 122 (2010) 2288–2300.
[30] Y. Onuma, P.W. Serruys, J.A. Ormiston, et al., Three-year results of clinical follow-up after a bioresorbable everolimus-eluting scaffold in patients with de novo coronary artery disease: the ABSORB trial, EuroIntervention 6 (2010) 447–453.
[31] C.V. Bourantas, M.I. Papafaklis, H.M. Garcia-Garcia, et al., Short- and long-term implications of a bioresorbable vascular scaffold implantation on the local endothelial shear stress patterns, JACC Cardiovasc. Interv. 7 (2014) 100–101.
[32] A. Karanasos, N. Van Mieghem, N. van Ditzhuijzen, et al., Angiographic and optical coherence tomography insights into bioresorbable scaffold thrombosis: single-center experience, Circ. Cardiovasc. Interv. 8 (2015), http://dx.doi.org/10.1161/CIRCINTERVENTIONS.114.002369.
[33] S. Puricel, F. Cuculi, M. Weissner, et al., Bioresorbable coronary scaffold thrombosis: multicenter comprehensive analysis of clinical presentation, mechanisms, and predictors, J. Am. Coll. Cardiol. 67 (2016) 921–931.
[34] C. von Birgelen, M.W.Z. Basalus, Oversized post-dilatation of current bioresorbable vascular scaffolds: kill or cure? EuroIntervention 11 (2016) 1330–1333.
[35] B. Cortese, D. Piraino, A. Ielasi, G. Steffenino, P.S. Orrego, Very late bioresorbable vascular scaffold thrombosis due to late device recoil, Int. J. Cardiol. 189 (2015) 132–133.
[36] L. Timmers, P.R. Stella, P. Agostoni, Very late bioresorbable vascular scaffold thrombosis following discontinuation of antiplatelet therapy, Eur. Heart J. 36 (2015) 393.
[37] A. Karanasos, R.J. van Geuns, F. Zijlstra, E. Regar, Very late bioresorbable scaffold thrombosis after discontinuation of dual antiplatelet therapy, Eur. Heart J. 35 (2014) 1781.