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Impact of calcium on procedural and clinical outcomes in lesions treated with bioresorbable vascular scaffolds - A prospective BRS registry study

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ABSTRACT

Background: There is limited data on the impact of calcium (Ca) on acute procedural and clinical outcomes in patients with lesions treated with bioresorbable vascular scaffolds (BRS). We sought to evaluate the effect of calcium on procedural and clinical outcomes in a 'real world' population.
Methods: Clinical outcomes were compared between patients with at least 1 moderately or heavily calcified lesion (Ca) and patients with no/mild calcified lesions (non-Ca) enrolled in our institutional BRS registry.
Results: 455 patients (N) with 548 lesions (L) treated with 735 BRS were studied. Patients in the Ca group (N = 160, L = 200) had more complex (AHA B2/C lesion: 69.0% in Ca vs 14.9% in non-Ca, $p < 0.001$) and significantly longer lesions (27.80 ± 15.27 vs 19.48 ± 9.92 mm, $p < 0.001$). Overall device success rate was 99.1% with no significant differences between the groups. Despite more aggressive lesion preparation and postdilation compared to non Ca, acute lumen gain was significantly less in Ca lesions (1.50 ± 0.66 vs 1.62 ± 0.69 mm, $p = 0.040$) with lower final MLD (2.28 ± 0.41 vs 2.36 ± 0.43, $p = 0.046$). There were no significant differences in all-cause mortality, total definite scaffold thrombosis (ST), target lesion revascularization and myocardial infarction between the 2 groups. Late ST was more frequent in the Ca group compared to non Ca group (late ST: 2.1 vs 0%, $p = 0.02$).
Conclusions: Clinical outcomes after BRS implantation in calcified and non-calcified lesions were similar. A remarkable difference in timing of thrombosis was observed, with an increased rate of late thrombosis in calcified lesions.

1. Introduction

Bioresorbable scaffolds (BRS) have been developed as an alternative to metallic stents as the need for mechanical support for the treated vessel is temporary, and beyond the first few months there are potential disadvantages of a permanent metallic prosthesis. In earlier studies to demonstrate Absorb BRS feasibility and safety, severe calcification was an exclusion criterium [1–6]. Calcified lesions may be challenging and encountered in up to 35% of patients who undergo percutaneous coronary intervention (PCI) [7–8]. Lesion calcification has been associated with increased PCI complexity with worse procedural outcomes compared to non-calcified lesions [9]. Wire crossing, delivery of equipment during pre and post dilation and stent delivery may be more cumbersome. In calcific lesions, the effect of acute plaque recoil may affect stent expansion and is associated with adverse clinical and angiographic outcomes [10–11]. Currently there is still limited data on the impact of calcium (Ca) on acute procedural and clinical outcomes in patients with lesions treated with BRS. We sought to determine the impact of calcification on acute angiographic and 2 year clinical outcomes of a large cohort of patients treated solely with the Absorb Bioresorbable Vascular Scaffold (BVS) system (Abbott Vascular, Santa Clara, CA, USA).

2. Methods

This is an investigator-initiated, prospective, single-center, single-arm study evaluating performance of the Absorb BVS in lesions representative of daily clinical practice, including calcified lesions, total occlusions, long lesions and small vessels [12–13]. The study inclusion period was from September 2012 till January 2015. Inclusion criteria were patients presenting with STEMI [12], NSTEMI, stable/unstable angina, or silent ischemia caused by a de novo stenotic lesion in a native previously untreated coronary artery [13]. Procedural and long-term clinical outcomes were assessed. The primary endpoint was major adverse cardiac events, defined as a composite of cardiac death, myocardial infarction and target lesion revascularization.

Abbreviations: BRS, bioresorbable vascular scaffolds; Ca, calcium; DOCE, device oriented composite endpoints; MACE, major adverse cardiovascular events; MI, myocardial infarct; MLD, minimal lumen diameter; PCI, percutaneous coronary intervention; POCE, patient oriented composite endpoints; QCA, Quantitative Coronary Analysis; RVD, reference vessel diameter; ST, scaffold thrombosis; TLR, target lesion revascularization; TVR, target vessel revascularization.

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2.1. Ethics

This is an observational study, performed according to the privacy policy of the Erasmus MC, and to the Erasmus MC regulations for the appropriate use of data in patient-oriented research, which are based on international regulations, including the declaration of Helsinki. Approval of the ethical board of the Erasmus MC was obtained. All patients undergoing clinical follow-up provided written informed consent for the PCI and to be contacted regularly during the follow-up period of the study.

2.2. Quantitative Coronary Analysis (QCA)

The angiographic analysis was performed by three independent investigators. Coronary angiograms were analyzed with the CAAS 5.10 QCA software (Pie Medical BV, Maastricht, the Netherlands). The QCA (Quantitative Coronary Analysis) measurements provided reference vessel diameter (RVD), percentage diameter stenosis and minimal lumen diameter (MLD). Acute gain was defined as post-procedural MLD minus pre-procedural MLD (in an occluded vessel MLD value was zero by default).

2.3. Angiographic assessment of lesion calcification

Lesion calcification was recognized as radio-opacities within the vessel wall at the treated lesion. Calcification was categorized as either none/mild or moderate if the radio-opacities were noted only during the cardiac cycle before contrast injection and further classified as either none/mild or moderate based on visual assessment. Severe calcification was defined as having multiple persisting (that are noted even without cardiac motion) opacifications of the coronary wall and visible in more than one projection, surrounding the complete lumen of the coronary artery at the site of the lesion as per SYNTAX definition (www.syntaxscore.com). Angiographic assessment of calcification was conducted independently by 2 cardiologists. In cases of disagreement, a third independent cardiologist reviewed the films and provided a final diagnosis.

2.4. Follow-up

Clinical demographic data of all patients were obtained from municipal civil registries. Follow-up information specific for hospitalization and cardiovascular events was obtained through questionnaires. If needed, medical records or discharge letters from other hospitals were requested. Events were adjudicated by an independent clinical events committee (CEC). All information concerning baseline characteristics and follow-up was gathered in a clinical data management system. Only patients who had given written consent for follow up were included in the clinical outcome assessments.

2.5. Definitions

The primary endpoint was major adverse cardiovascular events (MACE), defined as the composite endpoint of cardiac death, myocardial infarction (MI) and target lesion revascularization (TLR). The secondary endpoints were device oriented composite endpoints (DOCE: composite of cardiac death, target vessel myocardial infarct and clinically indicated target lesion revascularization) and patient oriented composite endpoints (POCE: composite of all-cause mortality, all-cause myocardial infarct and any revascularization). Deaths were considered cardiac unless a non-cardiac cause was definitely identified. TLR was described as any repeated revascularization of the target lesion. Target vessel revascularization (TVR) was defined as any repeat percutaneous intervention or surgical bypass of any segment of the target vessel. Non-target vessel revascularization was described as any revascularization in a vessel other than the target lesion. Scaffold thrombosis (ST) and MI were classified according to the Academic Research Consortium (ARC) [14]. Clinical device success was defined as successful delivery and deployment of the first study scaffold/stent at the intended target lesion and successful withdrawal of the delivery system with attainment of final in-scaffold/stent residual stenosis of <30% as evaluated by QCA. Clinical procedure success was described as device success without major peri-procedural complications or in-hospital MACE (maximum of 7 days).

2.6. Statistical analysis

Categorical variables are reported as counts and percentages, continuous variables as mean ± standard deviation. The cumulative incidence of adverse events was estimated according to the Kaplan-Meier method. Patients lost to follow-up were considered at risk until the date of last contact, at which point they were censored. A cox regression was performed to investigate clinical outcomes at two years, with the binary variable calcification (yes/no). Adjusted cox regression were performed using fourteen patient and lesion factors (see Online Supplement Table 1) to account for baseline differences between patients with at least 1 moderately or heavily calcified lesion (Ca) and patients with no/mild calcified lesions (non-Ca). Statistical analyses were performed using SPSS, version 21 (IL, US). All statistical tests were two-sided and the p value of <0.05 was considered statistically significant.

3. Results

Baseline clinical characteristics are shown in Table 1A. A total of 548 lesions in 455 patients were studied of which 200 (36.5%) lesions in 160 patients (35.2%) were moderately or heavily calcified (Ca group) (Table 1A). Patients in the Ca group were older, with more hypertension, and kidney disease. In the calcified cohort, there were 1.24 lesions per patient. Lesion and QCA characteristics are as shown in Table 1B. The left anterior descending artery (n = 254, 46.4%) was the most commonly treated vessel in the study population. Lesions in the Ca group were more complex (AHA B2/C lesion: 69.0% in Ca vs 14.9% in non-Ca, p < 0.001) and significantly longer. Compared to non-Ca group, lesions in the Ca groups had smaller RVD and lower percentage diameter stenosis.

Procedural characteristics are as shown in Table 1C. Ca lesions were treated with more aggressive lesion preparation compared to non Ca as evidenced by the more significant use of predilation, rotational atherectomy and scoring balloon. The use of buddy wires was higher in Ca lesions compared to non Ca lesions. Fig. 1A illustrates the satisfactory expansion with minimal eccentricity on OCT of a calcified LAD treated with a BRS. Fig. 1B and C illustrates the acute and 2 year angiographic and IVUS result respectively after rotational atherectomy and lesion preparation followed by BRS implantation in a calcified coronary artery. A total of 735 scaffolds were implanted in the study population with more scaffolds per lesion for Ca lesions (1.58 vs 1.21). Scaffold diameter was similar in the two groups however scaffold length implanted was longer in the Ca group. Postdilation was more frequently used in the Ca group (Ca vs non Ca: 64.8% vs 42.1%, p < 0.001).

Procedural outcomes are shown in Table 2A. Post procedure, acute lumen gain was significantly less in Ca compared to non-Ca lesions (1.50 ± 0.66 vs 1.62 ± 0.69 mm, p = 0.040) with lower final MLD (2.28 ± 0.41 vs 2.36 ± 0.43, p = 0.046). RVD and percentage diameter stenosis were smaller in the Ca group compared to the non Ca group though the differences did not reach statistical significance. Procedural success was high for both patient groups (98.7 and 99.7%, p = 0.25). Overall device success rate and final TIMI 3 flow result were similar in the two groups.

We were able to obtain written consent for the follow up program in 395 patients (86.8%). Clinical outcomes were available in all (100%) of these patients (Table 2B). These patient had similar baseline and procedural characteristics as the total population. Kaplan-Meier curves for

Table 1A
Demographic characteristics of the study population.

	BRS (N = 455; L = 548)		
	Patients with at least 1 calcified lesion (N = 160/35.2%; L = 200/36.5%)	Patients with no calcified lesions (N = 295/64.8%; L = 348/63.5%)	
Age	62.12 ± 10.64	56.54 ± 10.25	<0.001
Male	122/160 (76.3)	220/295 (74.6)	0.734
Ex/active smoker	81/160 (50.7)	181/294(61.6)	0.064
Diabetes mellitus	31/160 (19.4)	40/295 (13.6)	0.107
Dyslipidemia	75/158 (47.5)	109/288 (37.8)	0.056
Hypertension	93/159 (58.5)	139/290 (47.9)	0.038
Family history	55/160 (34.4)	127/295 (43.1)	0.206
CVA/TIA	13/160(8.1)	16/295 (5.4)	0.260
Prior MI	26/160 (16.3)	27/295 (9.2)	0.032
Prior PCI	10/160 (6.3)	20/295 (6.8)	1.000
Prior CABG	1/160 (0.6)	0	0.352
Kidney disease	11/160 (6.9)	8/295 (2.7)	0.048
Heart failure	7/160 (4.4)	7/295 (2.4)	0.262
Clinical presentation			0.002
Stable angina	53/160 (33.1)	63/295 (21.4)	
Unstable angina	14/160 (8.8)	32/295 (10.8)	
STEMI	40/160 (25.0)	118/295 (40.0)	
NSTEMI	51/160 (31.9)	82/295 (27.8)	
CCF/others	2/160 (1.3)	0	
Disease involvement			0.060
SVD	97/160 (60.6)	210/295 (71.2)	
DVD	42/160 (26.3)	63/295 (21.4)	
LM/TVD	21/160 (13.1)	22/295 (7.4)	

Values are expressed in numbers (percentages) or mean ± standard deviation when appropriate.

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MACE were parallel throughout the follow-up to two year (Fig. 2A). Crude cumulative event rates at two years for the secondary endpoints, described as Kaplan-Meier estimates are as shown in Table 2B. There was a slight trend for higher events on cardiac death and all-cause mortality for patients with calcified lesions. No difference was observed in POCE and DOCE. Though definite ST rates were similar between the two groups (Fig. 2B), there was a remarkable variation in acute and late definite ST. For acute definite ST, the incidence was higher in the non-Ca lesions; for late definite ST there was a significant increase in Ca group compared to non-Ca group (late ST: 2.1% vs 0, p = 0.02) but not for very late ST (Table 2B). After adjusting for difference in baseline characteristics, Ca lesions was not found to be a significant predictor of any clinical events (Table 2C).

4. Discussion

In our study, the key finding was that despite Ca lesions were more complex, required more lesion preparation, and encountered more deliverability issues with lower acute luminal gain and smaller final MLD, acute procedural and 24 month clinical outcomes were similar regardless of the calcification group with the exception of a higher rate of late ST at 2 years in the Ca group compared to non-Ca group. While there have been earlier studies evaluating the use of BRS in calcified lesions. [15–17], this is the first large clinical prospective registry study involving BRS scaffolds that look at the impact of lesion calcification on long term clinical outcomes at 2 years.

Our findings, which showed that Ca lesions were more complex and required more careful and elaborate lesion preparation including rotational atherectomy (in 5.5% of the lesions), were consistent with similar findings published elsewhere [9,18]. The use of intracoronary imaging like IVUS was also increased in Ca lesions compared to non Ca lesions. The more frequent use of buddy wires in the Ca group suggested that difficult deliverability issues may be encountered more commonly in Ca lesions thus potentially prolonging procedure times. Despite the advances in interventional techniques, calcific lesions still pose a challenge for the procedurist. Due to their inherent polymeric structural composition and increased strut thickness, BRS have been shown to have less favorable mechanical characteristics including less deliverability and radial strength compared to current second generation DES [18,19]. There have been concerns as to whether such mechanical characteristics may result in less optimal stent performance which may be more pronounced in calcified lesions where focal areas of calcification limit expansion of the BRS more compared to DES [18]. This may have practical clinical implications since suboptimal stent expansions has been known to contribute to metallic stent failure [20] and there have been reports of inadequate scaffold expansion in BRS failure [21,22].

Our findings are also consistent with clinical [23,24] data addressing the feasibility of BRS in calcified lesions. In a recent study looking at specific procedural outcomes in 62 calcified lesions by Panoulas et al. [23], expansion of BRS as measured in terms of lumen gain on QCA and intravascular ultrasound (IVUS) was similar between calcified and non-calcified lesions. Acute luminal gain (1.83 ± 0.6 vs 1.86 ± 0.6 mm, p = 0.732) and angiographic success were similar (98% non-calcific vs 95.2% calcific, p = 0.369), whereas procedural success was reduced in patients with calcific lesions (94.1% vs 83.9%, p = 0.034) due to higher rates of periprocedural myocardial infarction (MI) (5% vs 13.1%, p = 0.067). MACE rates (10.9% non-calcific vs 12.9% calcific, p log-rank = 0.546) were similar in the median follow-up time of 14 months. However a greater degree of lesion preparation in calcified lesions was also required. OCT was not used and a comparison of the expansion of BRS compared with DES was not performed. In our study, we report 2 year clinical outcomes in a larger study population which showed MACE rates were similar between Ca and non-Ca groups. In another study conducted by Kawamoto et al. [24], though eccentric calcium distribution resulted in asymmetric expansion of BRS, the final MSA was still comparable irrespective of calcium distribution, and the use of IVUS for scaffold optimization led to favorable clinical outcomes even in calcified lesions. Earlier OCT findings published from our center [25] also suggest that regardless of the degree of angiographic calcification, BRS can achieve a similar expansion as DES, in the context of an imaging-guided strategy with adequate lesion preparation. Our findings were also consistent with recent published literature showing that the presence of moderate or severe lesion calcification does not negatively affect angiographic outcomes at both post-procedure and 13-month follow-up after BVS implantation [26]. However, in this study [26], heavily calcified lesions or those requiring extensive lesion preparation such as rotational atherectomy were excluded according to the study protocol whereas our study included “all comers” lesions with various degrees of calcification or that require rotational atherectomy.

However, BRS deployment requires more lesion preparation and decalcification strategy particularly for moderately or heavily calcified lesions. Further studies are needed to ascertain if in such lesions the use of such a strategy may impact on long term clinical outcomes such as increased TLR rates such as seen in DES deployment after lesion debulking or decalcification using rotational atherectomy [27,28]. In addition, the postdilation rate reported in our study (Table 1C) was comparable to other studies considering that systematic postdilation was implemented on average in <50% of previously published studies [29]. It is still debatable if pursuing a systematic postdilation strategy will have an impact on long term results particularly the risk of very late ST (VLST). Given the results of this study, an analysis of BRS specific implantation technique such as PSP (Prepare the lesion to be reengineered; Size the vessel appropriately; Postdilate to embed scaffold struts into the vessel wall) would be timely and of interest [30]. Though the lesions treated in the Ca group were more complex, requiring longer and more overlapping scaffolds and the post dilatation rate of 64.8% was considered relatively low for calcific lesions, the procedural and clinical results were still similar between the Ca and non Ca groups. This may be reassuring since the current practice suggest a large use of postdilation especially in stable patients with complex lesions.

BRS offers several unique potential advantages over DES. The future bioresorption of BRS permits potential future grafting of treated

Table 1B
Lesion characteristics of the study population.

	BRS (L = 548)		p value
	Calcified lesions (L = 200/36.5%)	Non calcified lesions (L = 348/63.5%)	
Target vessel			
LAD	126/200 (63.0)	128/348 (36.8)	<0.001
LCX	27/200 (13.5)	96/348 (27.6)	<0.001
RCA	42/200 (21.0)	111/348(31.9)	0.007
Diagonal	4/200 (2.0)	13/348(3.7)	0.314
Left main	1/200 (0.5)	0	0.365
SVG	0	0	–
Lesion AHA			<0.001
A	5/200 (2.5)	71/348 (20.4)	
B1	60/200 (30.0)	226/348 (64.9)	
B2	85/200 (42.5)	46/348 (13.2)	
C	53/200 (26.5)	6/348 (1.7)	
Bifurcation	61/199 (31.7)	58/347 (16.7)	<0.001
CTO	13/200 (6.5)	4/348 (1.1)	0.001
TIMI			
Pre-procedure			0.074
TIMI 0	35/200 (17.5)	87/344 (25.0)	
TIMI 1	6/200 (3.0)	17/344 (4.9)	
TIMI 2	50/200 (14.4)	50/344 (14.4)	
TIMI 3	125/200 (62.5)	190/344 (54.6)	
QCA analysis			
Pre-procedure			
Treatment length	27.80 ± 15.27	19.48 ± 9.92	<0.001
RVD (mm)	2.52 ± 0.57	2.62 ± 0.57	0.053
MLD (mm)	0.85 ± 0.47	0.75 ± 0.55	0.036
Diameter stenosis (%)	65.39 ± 18.68	70.78 ± 20.98	0.004

Values are expressed in numbers (percentages) or mean ± standard deviation when appropriate.

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Table 1C
Procedural characteristics of the study population.

	BRS (L = 548)		p value
	Calcified lesions (L = 200/36.5%)	Non calcified lesions (L = 348/63.5%)	
Number of treated lesions per procedure	1.24 ± 0.48	1.17 ± 0.48	0.133
Aspiration thrombectomy	34/200 (17.1)	106/348 (30.5)	0.001
Rotational atherectomy	11/200 (5.5)	0/348	0.002
Scoring balloon	9/200 (4.5)	1/348 (0.3)	0.001
Intracoronary imaging			
IVUS	30/199 (15.1)	30/348 (8.6)	0.023
OCT	62/200 (31.0)	95/348 (27.3)	0.378
Predilation performed	177/200 (88.5)	265/348 (76.1)	<0.001
Max predilation diameter	2.66 ± 0.36	2.53 ± 0.42	0.002
Predilation balloon: artery ratio	1.08 ± 0.25	1.01 ± 0.23	0.005
Maximum predilation inflation pressure, atm	14.25 ± 3.35	13.56 ± 3.01	0.067
Buddy wire	23/199 (11.6)	22/347 (6.3)	0.036
Additional daughter catheter	3/199 (1.5)	3/348 (0.9)	0.673
Mean number of scaffold	1.58 ± 0.823	1.21 ± 0.53	<0.001
Number of scaffolds (total 735)	315	420	<0.001
0	1/200 (0.5)	1/348 (0.3)	
1	117/200 (58.5)	289/348 (83.0)	
2	56/200 (28.0)	47/348 (13.5)	
3	18/200 (9.0)	7/348 (2.0)	
4	8/200 (4.0)	4/348 (1.1)	
Scaffold diameter, mm	3.11 ± 0.32	3.12 ± 0.38	0.615
Scaffold length implanted, mm	34.65 ± 19.94	23.84 ± 12.20	<0.001
Overlapping scaffolds	80/200 (40.0)	52/348 (15.0)	<0.001
Maximum scaffold implantation pressure, atm	14.99 ± 1.88	14.86 ± 1.97	0.510
Postdilation performed	129/199 (64.8)	146/347 (42.1)	<0.001
Postdilation balloon: mean scaffold diameter ratio	1.06 ± 0.15	1.07 ± 0.10	0.422
Max postdilation balloon, mm	3.31 ± 0.43	3.31 ± 0.44	0.906
Maximum postdilation inflation pressure, atm	16.27 ± 3.63	15.83 ± 3.97	0.496

Values are expressed as numbers (percentages) or mean ± standard deviation when appropriate.

segments, allows potential reopening of "jailed" side branches and potential recovery of vasomotor function and vessel remodeling. These benefits would be more pertinent in patients with calcific lesions, who often have widespread disease resulting in long stented segments. However whether these will translate into long term clinical benefits in more complex lesions such as those with significant calcifications would

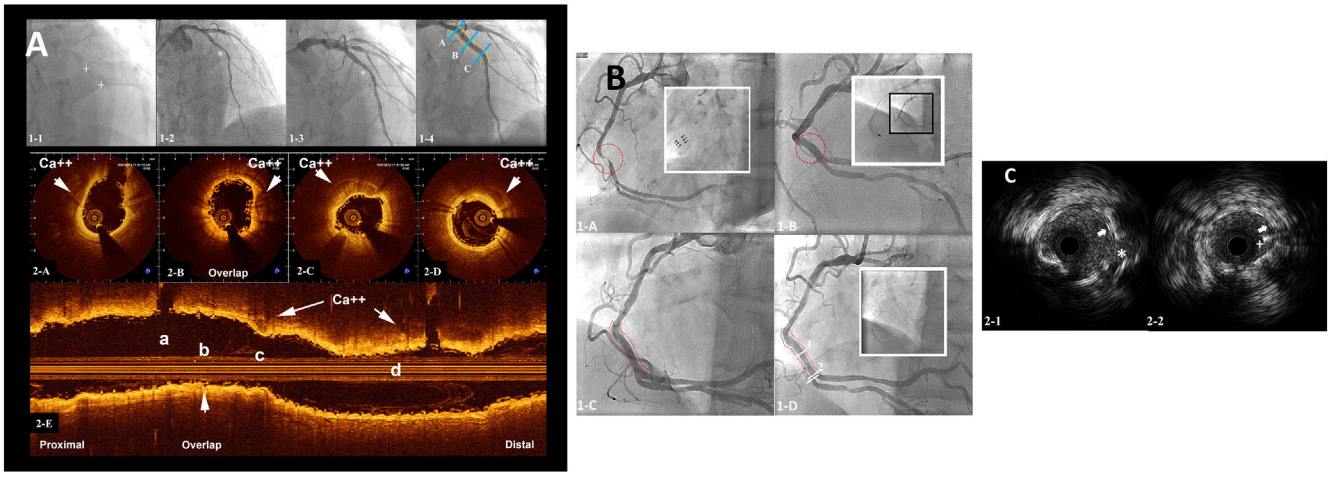

Fig. 1. A. Implantation of Bioresorbable vascular scaffold (BRS in calcified left anterior descending artery (LAD). Panel 1. Implantation of bioresorbable vascular scaffolds (two 3.0 × 28 mm Absorb™ BVS deployed in an overlapping manner-indicated in yellow) in a calcified left anterior descending artery (LAD). Calcification marked '+' in Panel 1-1. Target lesion marked '*' preprocedure (Panel 1-2), after predilation with a 2.5 mm balloon at (Panel 1-3) and after postdilation with a noncompliant 3.0 mm balloon at high pressure (Panel 1-4).Panel 2A–E: Final OCT performed showed that the scaffold was well expanded and apposed with no significant dissection seen. Proximal and distal reference areas were 7.21 mm^2 and 5.52 mm^2 respectively. The minimal lumen area (MLA) was 4.5 mm^2 (2.83 × 1.81 mm) with an eccentricity index (EI) of 0.63. Panel 2-A–C showed the corresponding segments of the treated vessel in Panel 1-4. Panel 2-D showed the BRS implanted in a calcified segment of the treated vessel with satisfactory expansion with minimal eccentricity. Panel 2-E showed the longitudinal pullback of the treated vessel. B. Angiogram and intravascular ultrasound (IVUS) of the right coronary artery (RCA). Angiogram and intravascular ultrasound (IVUS) of the right coronary artery (RCA). Panel 1-A shows the preprocedural angiogram at baseline with a severely tight lesion (circled) in the mid segment of the RCA which is heavily calcified (see insert). Panel 1-B shows the RCA post rotational artherectomy with 1.5 mm burr (see insert) and predilation with a Trek NC 3.25 mm balloon. Panel 1-C shows the RCA after deployment of a BRS (BVS Absorb 3.0 × 28 mm - outlined in red). The borderline lesions in the ostium and mid right posterior descending artery (RPDA) was managed conservatively (white arrow). Panel 1-D shows the RCA at 2 years follow up which demonstrates that the previously deployed scaffold in the mid RCA was still widely patent with no significant restenosis (outlined red). C. IVUS images of the RCA. The figure shows IVUS images of the corresponding segments of the RCA in Fig. 1B Panel 1-D at 2 years follow up demonstrating that the scaffold struts (white arrow) remained visible in the mid RCA with good apposition and expansion with side branch (*-RPDA) patency and confirmed the scaffolded vessel remained widely patent with no significant restenosis (Panels 2-1 and 2-2). + - Guidewire. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

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still require further evaluation. Previous studies have highlighted a higher rate of ST related to the use of BRS [4,31–33], but did not provide details on the effect of calcification. In our study, we see an observation pattern of higher early ST cases in the non-Ca group followed by a significantly higher rate of late ST in the Ca group. To the best of our knowledge, we believe the difference in timing on ST observed in the two groups is notable and interesting which warrant further studies. The observation of early ST in the non-Ca group (a group with a higher number of acute coronary syndromes; ACS) patients might be related to scaffold under sizing and to increased platelets activation. Predisposing factors of scaffold undersizing include the increased thrombus burden and vasoconstriction in the setting of acute STEMI leading to underestimation of the actual size of the infarct-related artery, thus increasing the risk of the implantation of undersized scaffolds which can be seen even in the setting of metallic drug eluting stents [34]. Implantation of a relatively small scaffold in a relatively larger vessel can result in incomplete apposition, predisposing to ST [35]. Higher rates of ST were also previously noted in patients with ACS which could be due to reduction of early neointimal growth and strut coverage [36,37]. Reasons for the increase in late ST in the Ca compared to the non Ca group include a role for technical factors such as suboptimal implantation with incomplete lesion coverage, underexpansion and malapposition [35,38] and possibly greater impact on the scaffold endothelization and resorption process from a reduced MLD in the Ca group. The additional risks of late ST in the Ca lesions may arise from either the loss of radial strength after scaffold resorption (which typically commences 6 months to >1 year after scaffold implantation) or the scaffold 'dismantling' around calcified lesions which will have forces localized at the edge of the calcified areas where expansion tends to be asymmetrical [24]. Scaffold 'dismantling' might result in rapid changes in vessel wall architecture and therefore exert localized forces on the neointimal coverage potentially resulting in microdissections, triggering the thrombosis.

In our current study, though the event rate is similar between the Ca and non Ca groups, this may also be partially attributed to a higher ACS population in the non Ca group which is known to have higher risk of clinical events at follow up. In an earlier study evaluating the one-year outcomes in patients presenting with ACS compared to stable angina patients after implantation of a BRS from our center, one-year clinical outcomes in ACS patients treated with BRS were similar to non-ACS patients. One-year definite ST rate was comparable: 2.0% for ACS population versus 2.1% for stable population ($p = 0.94$), however, early ST occurred only in ACS patients [39]. Comparatively, overall ST rates were similar between the two groups in this study and further analysis did not show that Ca lesions were a significant predictor of ST (Table 2C). Of note, there was no difference in VLST between the Ca and non-Ca groups.

Though recent guidelines have supported a shift towards a shorter duration of DAPT [40], our findings on an increased late ST rate in Ca lesions may suggest that a longer duration of DAPT may still be necessary if BRS is to be implanted before the patient is to derive the potential benefits of BRS resorption. In our study, data on the use of dual antiplatelets therapy (DAPT) were available in the 395 patients whose follow up were available. All patients were prescribed aspirin during the duration of the study. Second generation $P2Y_{12}$ antiplatelet medications were used; clopidogrel (n = 157, 39.7%), prasugrel (n = 187, 47.3%) and ticagrelor (n = 51, 12.9%). The median duration of DAPT was 365.00 (IQR 364.00–394.50) days and was similar between the 2 groups. In a study to evaluate the impact of DAPT termination on late and very late ST in patients treated with the Absorb BRS, the incidence of ST was low while on DAPT but potentially higher when DAPT was terminated before 18 months [41,42]. Further studies may be required to evaluate the effect of a prolonged duration of DAPT on the rate of late ST.

The findings showing a lesser acute lumen gain and similar 2 year MACE were consistent with previous research involving metallic DES in calcified versus non calcified lesions [8]. Moussa et al. reported in a subanalysis of the TAXUS IV trial [8] a significant reduction in late lumen loss in calcific lesions (n = 247) treated with PES vs BMS (0.26 ± 0.56 vs 0.51 ± 0.48 mm, $p = 0.015$). In a study from the SPIRIT II trial by Onuma et al. [43], the efficacy of EES in patients with at least one angiographically defined moderate calcific lesion (68 patients), was compared to those without any calcific lesion (144 patients). Late lumen loss was similar between the two groups at two years. No significant difference in two-year MACE rates was observed between the two groups (calcific vs non-calcific: 10.9% vs 4.4%, $p = 0.12$). The numerically increased MACE rate was attributed to an increased ischemia-driven TLR (7.8% vs 1.5%, $p = 0.03$). However TLR rates were similar between the Ca and non Ca groups in our study.

Table 2A
Procedural outcomes of the study population.

	BRS (L = 548)		p value
	Calcified lesions (L = 200/36.5%)	Non-calcified lesions (L = 348/63.5%)	
TIMI postprocedure			0.850
TIMI 0	0	0	
TIMI 1	1/200 (0.5)	2/348 (0.6)	
TIMI 2	12/200 (6.0)	17/348 (4.9)	
TIMI 3	187/200 (93.5)	329/348 (94.5)	
QCA analysis post-procedure			
RVD (mm)	2.75 ± 0.48	2.78 ± 0.45	0.401
MLD (mm)	2.28 ± 0.41	2.36 ± 0.43	0.046
Diameter stenosis (%)	16.71 ± 8.89	15.30 ± 8.61	0.069
Acute lumen gain	1.50 ± 0.66	1.62 ± 0.69	0.040
Procedural outcomes			
Device success	197/200 (98.5)	346/348 (99.4)	0.208
Bailout by scaffold	6/200 (3.0)	5/348 (1.4)	0.439
Bailout by metallic stent	4/200 (2.0)	5/348 (1.4)	0.547
Intraprocedural thrombosis	1/200 (0.5)	1/348 (0.3)	1.000
Significant dissection	14/200 (7.0)	16/348 (4.6)	0.444
Significant no reflow/slow flow	9/200 (4.5)	9/348 (2.6)	0.272

MLD: minimal lumen diameter; QCA: Quantitative Coronary Analysis; RVD: reference vessel diameter. Values are expressed as numbers (percentages) or mean ± standard deviation when appropriate.

In summary, clinical outcomes of calcified and non-calcified lesions treated with BRS are in general similar except for late ST. Overall two-year MACE rates appear acceptable in patients with and without calcific lesions treated with BRS. Further larger randomized controlled trials comparing clinical outcomes of DES to BRS in calcified lesions may be required to evaluate the full impact of calcium on BRS outcomes compared to DES.

4.1. Study limitations

This is a single-center, single-arm registry with no direct comparison with metallic DES. The total number of patients in this study was still limited. In addition, calcification assessment was based on angiographic classification alone rather than characterization of coronary calcification using alternative imaging modality such as intravascular ultrasound. Thus, these findings warrant further confirmation in a large-scale trial. Furthermore, deciding which patient or lesion was suitable for treatment with BRS could have resulted in selection bias. The event rate is unknown in the patients (n = 60, 13.2%) who did not agree to participate in further follow up and hence excluded from clinical outcome analysis. We further evaluated the population who did not agree to further follow up and compared the baseline demographic, lesion and procedural characteristics between the cases with calcified lesions and non-calcified lesions. There were significant differences in terms of age and use of predilation between the 2 groups which were similarly observed in the main population. Overall, the results are similar which provide support to our inference that the clinical outcomes reported in our study may be extrapolated to the patients whose clinical outcomes were not available. In addition, as our study was not powered to study clinical outcomes in relation to DAPT, we believe that further

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Table 2B
Clinical endpoints at two years, described as Kaplan-Meier estimates.

	Ca (n = 143)	Non-Ca (n = 252)	p value
MACE (%)	11.7 (17)	8.0 (19)	0.351
DOCE (%)	9.0 (12)	7.3 (17)	0.564
Cardiac death (%)	3.8 (5)	0.8 (2)	0.052
Target vessel MI	5.3 (7)	5.1 (12)	0.945
Clinically indicated TLR (%)	4.7 (6)	5.9 (14)	0.544
Definite ST (%)	2.1 (3)	2.4 (6)	0.856
Acute	0.0	1.2 (3)	0.191
Subacute	0.0	0.4 (1)	0.450
Late	2.1 (3)	0.0	0.020
Very late	0.0	0.8 (2)	0.287
Probable ST (%)	0.7 (1)	0.4 (1)	0.682
Acute	0.0	0.0	
Subacute	0.0	0.0	
Late	0.7 (1)	0.4 (1)	0.682
Very late	0.0	0.0	
Definite/probable ST (%)	2.9 (4)	2.8 (7)	0.993
Acute	0.0	1.2 (3)	0.191
Subacute	0.0	0.4 (1)	0.450
Late	2.9 (4)	0.4 (1)	0.039
Very late	0.0	0.8 (2)	0.287
POCE (%)	12.2 (23)	17.2 (29)	0.211
All-cause mortality (%)	3.8 (6)	0.8 (3)	0.052
Any revascularization	12.2 (16)	10.3 (25)	0.714
TVR (%)	5.3 (7)	6.5 (16)	0.544
Non-TVR (%)	7.7 (10)	4.7 (11)	0.260
All cause MI (%)	8.3 (11)	6.5 (15)	0.509

DOCE: device oriented composite endpoints (composite of cardiac death, target vessel myocardial infarct and clinically indicated target lesion revascularization); POCE: patient oriented composite endpoints (composite of all - cause mortality, all cause myocardial infarct and any revascularization). (Number of composite endpoints does not add up as any patient may have multiple events.) Ca - calcified lesions; non-Ca - non calcified lesions.

Table 2C
Predictors for clinical outcomes at two years follow-up (using Cox regression), calcified vs non-calcified lesions.

	Unadjusted HR (95% CI)	p-Value	Adjusted[a] HR (95% CI)	p value
All-cause death				
Ca vs non-Ca	4.428 (0.859–22.822)	0.075	1.7 (0.263–10.994)	0.578
Cardiac death				
Ca vs non-Ca	4.428 (0.859–22.822)	0.075	1.7 (0.263–10.994)	0.578
MACE				
Ca vs non-Ca	1.378 (0.700–2.712)	0.353	0.850 (0.382–1.895)	0.692
MI				
Ca vs non-Ca	1.393 (0.632–3.068)	0.411	0.944 (0.366–2.433)	0.905
TLR				
Ca vs non-Ca	0.754 (0.290–1.963)	0.564	0.644 (0.225–1.845)	0.644
TVR				
Ca vs non-Ca	0.762 (0.314–1.853)	0.549	0.629 (0.236–1.674)	0.353
Non-TVR				
Ca vs non-Ca	1.627 (0.691–3.831)	0.265	0.950 (0.342–2.634)	0.921
Definite ST				
Ca vs non-Ca	0.880 (0.220–3.518)	0.856	0.930 (0.206–4.234)	0.930
Probable ST				
Ca vs non-Ca	1.771 (0.111–28.307)	0.686	0.917 (0.039–21.720)	0.957
Def/prob ST				
Ca vs non-Ca	1.005 (0.294–3.434)	0.993	0.935(0.242–3.610)	0.922
DOCE				
Ca vs non-Ca	1.242 (0.593–2.600)	0.566	0.961 (0.416–2.218)	0.926
POCE				
Ca vs non-Ca	1.416 (0.819–2.448)	0.213	1.045 (0.556–1.963)	0.891

To account for baseline differences between patients with at least 1 moderately or heavily calcified lesion (Ca) and patients with no/mild calcified lesions (non-Ca), covariate adjustment using fourteen patient and lesion factors were used (see Online Supplement).
[a] Adjusted for gender, age, presentation with ACS, multivessel disease, diabetes mellitus, dyslipidemia, smoking, hypertension, peripheral artery disease, small vessel, bifurcation, average scaffold diameter per patient, total scaffold length per patient. DOCE: device oriented composite endpoints (composite of cardiac death, target vessel myocardial infarct and clinically indicated target lesion revascularization); POCE: patient oriented composite endpoints (composite of all - cause mortality, all cause myocardial infarct and any revascularization). (Number of composite endpoints does not add up as any patient may have multiple events.) Ca - calcified lesions; non-Ca - non calcified lesions; MACE - major adverse cardiovascular events; MI - myocardial infarct; TLR - target lesion revascularization; TVR - target vessel revascularization; ST - scaffold thrombosis.

studies may be required to evaluate if a prolonged duration of DAPT may reduce late onset ST in calcified lesions.

5. Conclusion

Careful more elaborate lesion preparation and the use of dedicated devices, such as scoring balloons and rotational atherectomy and intracoronary imaging were more likely encountered in Ca lesions. Even after more lesion preparation, acute gain and resulting final MLD by BRS implantation was less compared to non-calcified lesion. Clinical outcomes of calcified and non-calcified lesions treated with BRS were otherwise similar. However this is accomplished in the setting of appropriate case selection, adequate lesion preparation and scaffold optimization with attention to an adequate duration of dual antiplatelet in line with guideline recommendations. Interestingly, a different pattern of timing of ST was observed with no early ST but an increased late ST rate when implanted in calcified lesions.

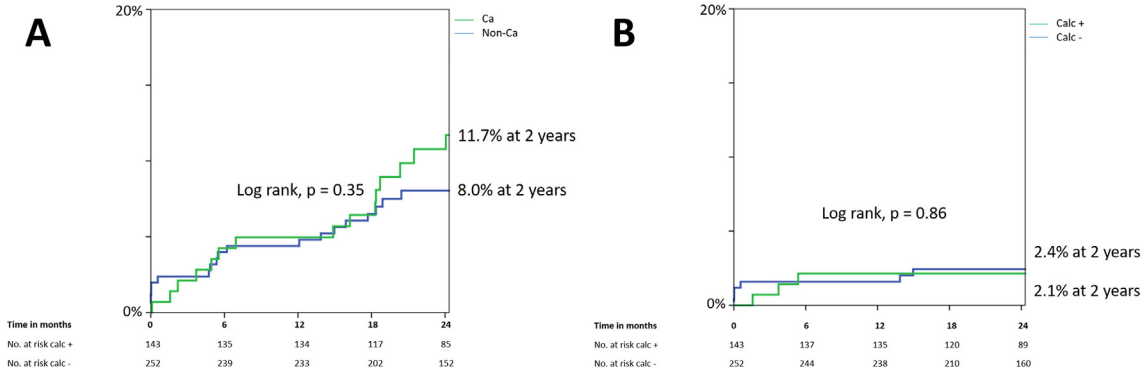

Fig. 2. Kaplan-Meier curve showing no significant difference in A) MACE and B) definite ST at 2 years in patients with calcified (Ca) and non-calcified (non-Ca) lesions treated with bioresorbable vascular scaffolds (BRS). The primary endpoint was major adverse cardiovascular events (MACE), defined as the composite endpoint of cardiac death, myocardial infarction (MI) and target lesion revascularization (TLR). Of note while the incidence of acute ST was higher in the non-Ca group compared to Ca group, there was a significant increase in late ST in calcified lesions compared to non-Ca lesions. ST - scaffold thrombosis.

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5.1. Clinical perspectives

Data on the impact of calcium (Ca) on outcomes in patients with lesions treated with bioresorbable vascular scaffolds (BRS) is limited, particularly in a "real world" study population. Careful more elaborate lesion preparation and the use of dedicated devices, such as scoring balloons and rotational atherectomy and intracoronary imaging were more likely encountered in Ca lesions. Late ST was more frequent in the Ca group compared to non-Ca group and no difference for VLST was observed. The findings merit further evaluation of clinical outcomes of BRS and the impact of implantation techniques in complex calcified lesions.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2017.08.046.

Conflict of interest

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References

[1] C. Simsek, A. Karanasos, M. Magro, H.M. Garcia-Garcia, Y. Onuma, E. Regar, E. Boersma, P.W. Serruys, R.J. van Geuns, Long-term invasive follow-up of the everolimus-eluting bioresorbable vascular scaffold: five-year results of multiple invasive imaging modalities, EuroIntervention (Oct 28 2014) https://doi.org/10.4244/EIJY14M10_12 (Epub ahead of print).

[2] A. Karanasos, C. Simsek, M. Gnanadesigan, N.S. van Ditzhuijzen, R. Freire, J. Dijkstra, S. Tu, N. Van Mieghem, G. van Soest, P. de Jaegere, P.W. Serruys, F. Zijlstra, R.J. van Geuns, E. Regar, OCT assessment of the long-term vascular healing response 5 years after everolimus-eluting bioresorbable vascular scaffold, J. Am. Coll. Cardiol. 64 (22) (Dec 9 2014) 2343–2356.

[3] P.W. Serruys, J.A. Ormiston, Y. Onuma, E. Regar, N. Gonzalo, H.M. Garcia-Garcia, K. Nieman, N. Bruining, C. Dorange, K. Miquel-Hébert, S. Veldhof, M. Webster, L. Thuesen, D. Dudek, A bioabsorbable everolimus-eluting coronary stent system (ABSORB): 2-year outcomes and results from multiple imaging methods, Lancet 373 (2009) 897–910.

[4] S.G. Ellis, D.J. Kereiakes, D.C. Metzger, R.P. Caputo, D.G. Rizik, P.S. Teirstein, M.R. Litt, A. Kini, A. Kabour, S.O. Marx, J.J. Popma, R. McGreevy, Z. Zhang, C. Simonton, G.W. Stone, ABSORB III Investigators, Everolimus-eluting bioresorbable scaffolds for coronary artery disease, N. Engl. J. Med. 373 (20) (Nov 12 2015) 1905–1915, https://doi.org/10.1056/NEJMoa1509038 (Epub 2015 Oct 12).

[5] R. Gao, Y. Yang, Y. Han, Y. Huo, J. Chen, B. Yu, X. Su, L. Li, H.C. Kuo, S.W. Ying, W.F. Cheong, Y. Zhang, X. Su, B. Xu, J.J. Popma, G.W. Stone, ABSORB China Investigators, Bioresorbable vascular scaffolds versus metallic stents in patients with coronary artery disease: ABSORB China Trial, J. Am. Coll. Cardiol. 66 (21) (Dec 1 2015) 2298–2309, https://doi.org/10.1016/j.jacc.2015.09.054 (Epub 2015 Oct 12).

[6] T. Kimura, K. Kozuma, K. Tanabe, S. Nakamura, M. Yamane, T. Muramatsu, S. Saito, J. Yajima, N. Hagiwara, K. Mitsudo, J.J. Popma, P.W. Serruys, Y. Onuma, S. Ying, S. Cao, P. Staehr, W.F. Cheong, H. Kusano, G.W. Stone, ABSORB Japan Investigators, 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 (47) (Dec 14 2015) 3332–3342, https://doi.org/10.1093/eurheartj/ehv435 (Epub 2015 Sep 1).

[7] R. Kawaguchi, H. Tsurugaya, H. Hoshizaki, T. Toyama, S. Oshima, K. Taniguchi, Impact of lesion calcification on clinical and angiographic outcome after sirolimus-eluting stent implantation in real-world patients, Cardiovasc. Revasc. Med. 9 (2008) 2–8.

[8] I. Moussa, S.G. Ellis, M. Jones, D.J. Kereiakes, D. McMartin, B. Rutherford, R. Mehran, M. Collins, M.B. Leon, J.J. Popma, M.E. Russell, G.W. Stone, Impact of coronary culprit lesion calcium in patients undergoing paclitaxel-eluting stent implantation (a TAXUS-IV sub study), Am. J. Cardiol. 96 (2005) 1242–1247.

[9] C.V. Bourantas, Y.J. Zhang, S. Garg, J. Iqbal, M. Valgimigli, S. Windecker, F.W. Mohr, S. Silber, Vries Td, Y. Onuma, H.M. Garcia-Garcia, M.A. Morel, P.W. Serruys, Prognostic implications of coronary calcification in patients with obstructive coronary artery disease treated by percutaneous coronary intervention: a patient-level pooled analysis of 7 contemporary stent trials, Heart 100 (15) (Aug 2014) 1158–1164.

[10] P. de Jaegere, H. Mudra, H. Figulla, Y. Almagor, S. Doucet, I. Penn, A. Colombo, C. Hamm, A. Bartorelli, M. Rothman, M. Nobuyoshi, T. Yamaguchi, V. Voudris, C. DiMario, S. Makovski, D. Hausmann, S. Rowe, S. Rabinovich, M. Sunamura, G.A. van Es, Intravascular ultrasound-guided optimized stent deployment. Immediate and 6 months clinical and angiographic results from the multicenter ultrasound stenting in coronaries study (MUSIC Study), Eur. Heart J. 19 (1998) 1214–1223.

[11] H. Otake, J. Shite, J. Ako, T. Shinke, Y. Tanino, D. Ogasawara, T. Sawada, N. Miyoshi, H. Kato, B.K. Koo, Y. Honda, P.J. Fitzgerald, K. Hirata, Local determinants of thrombus formation following sirolimus-eluting stent implantation assessed by optical coherence tomography, J. Am. Coll. Cardiol. Intv. 2 (2009) 459–466.

[12] R. Diletti, A. Karanasos, T. Muramatsu, S. Nakatani, N.M. Van Mieghem, Y. Onuma, S.T. Nauta, Y. Ishibashi, M.J. Lenzen, J. Ligthart, C. Schultz, E. Regar, P.P. de Jaegere, P.W. Serruys, F. Zijlstra, R.J. van Geuns, Everolimus-eluting bioresorbable vascular scaffolds for treatment of patients presenting with ST-segment elevation myocardial infarction: BVS STEMI first study, Eur. Heart J. 35 (12) (Mar 2014) 777–786, https://doi.org/10.1093/eurheartj/eht546 (Epub 2014 Jan 6).

[13] C.M. Felix, J.M. Fam, R. Diletti, Y. Ishibashi, A. Karanasos, B.R. Everaert, N.M. van Mieghem, J. Daemen, P.P. de Jaegere, F. Zijlstra, E.S. Regar, Y. Onuma, R. van Geuns, Mid- to long-term clinical outcomes of patients treated with the everolimus-eluting bioresorbable vascular scaffold: the BVS expand registry, JACC Cardiovasc. Interv. 9 (16) (Aug 22 2016) 1652–1663, https://doi.org/10.1016/j.jcin.2016.04.035 (Epub 2016 Jul 27).

[14] D.E. Cutlip, S. Windecker, R. Mehran, A. Boam, D.J. Cohen, G.A. van Es, et al., Clinical end points in coronary stent trials: a case for standardized definitions, Circulation 115 (2007) 2344–2351.

[15] S. Basavarajaiah, T. Naganuma, A. Latib, A. Colombo, Can bioabsorbable scaffolds be used in calcified lesions? Catheter. Cardiovasc. Interv. 84 (1) (Jul 1 2014) 48–52, https://doi.org/10.1002/ccd.24939 (Epub 2013 Aug 31).

[16] A. Seth, V. Ravisekar, U. Kaul, Use of 'Guideliner' catheter to overcome failure of delivery of Absorb™ Bioresorbable Vascular Scaffold in calcified tortuous coronary lesions: technical considerations in 'Real World Patients', Indian Heart J. 66 (4) (Jul–Aug 2014) 453–458, https://doi.org/10.1016/j.ihj.2014.05.019.

[17] T. Miyazaki, V.F. Panoulas, K. Sato, A. Latib, Colombo A[1]. Bioresorbable vascular scaffolds for heavily calcified lesions: how to tackle the rugged passage? J. Invasive Cardiol. 27 (8) (Aug 2015) E167–8.

[18] S. Tanimoto, P.W. Serruys, L. Thuesen, D. Dudek, B. de Bruyne, B. Chevalier, J.A. Ormiston, Comparison of in vivo acute stent recoil between the bioabsorbable everolimus-eluting coronary stent and the everolimus-eluting cobalt chromium coronary stent: insights from the ABSORB and SPIRIT trials, Catheter. Cardiovasc. Interv. 70 (2007) 515–523.

[19] J.A. Ormiston, B. Webber, B. Ubod, M.W. Webster, J. White, Absorb everolimus-eluting bioresorbable scaffolds in coronary bifurcations: a bench study of deployment, side branch dilatation and post-dilatation strategies, EuroIntervention 10 (2015) 1169–1177.

[20] S.Y. Choi, B. Witzenbichler, A. Maehara, A.J. Lansky, G. Guagliumi, B. Brodie, M.A. Kellett Jr., O. Dressler, H. Parise, R. Mehran, G.D. Dangas, G.S. Mintz, G.W. Stone, Intravascular ultrasound findings of early stent thrombosis after primary percutaneous intervention in acute myocardial infarction: a harmonizing outcomes with revascularization and stents in acute myocardial infarction (HORIZONS-AMI) substudy, Circ. Cardiovasc. Interv. 4 (3) (Jun 2011) 239–247.

[21] Antonios Karanasos, Nicolas M. Van Mieghem, Nienke van Ditzhuijzen, Cordula Felix, Joost Daemen, Anouchska Autar, Yoshinobu Onuma, Mie Kurata, Roberto Diletti, Marco Valgimigli, Floris Kauer, Heleen van Beusekom, Peter de Jaegere, Felix Zijlstra, Robert-Jan van Geuns, Evelyn Regar, Angiographic and optical coherence tomography insights into bioresorbable scaffold thrombosis. A single-center experience, Circ. Cardiovasc. Interv. 8 (5) (May 2015) https://doi.org/10.1161/CIRCINTERVENTIONS.114.002369 (pii: e002369).

[22] G. Longo, F. Granata, D. Capodanno, Y. Ohno, C.I. Tamburino, P. Capranzano, A. La Manna, B. Francaviglia, G. Gargiulo, C. Tamburino, Anatomical features and management of bioresorbable vascular scaffolds failure: a case series from the GHOST registry, Catheter. Cardiovasc. Interv. (Jan 8 2015) https://doi.org/10.1002/ccd.25819 (Epub ahead of print).

[23] V.F. Panoulas, T. Miyazaki, K. Sato, T. Naganuma, A. Sticchi, H. Kawamoto, F. Figini, A. Chieffo, M. Carlino, M. Montorfano, A. Latib, A. Colombo, Procedural outcomes of patients with calcified lesions treated with bioresorbable vascular scaffolds, EuroIntervention 11 (12) (Mar 2016) 1355–1362, https://doi.org/10.4244/EIJY15M03_11.

[24] H. Kawamoto, N. Ruparelia, A. Latib, T. Miyazaki, K. Sato, A. Tanaka, T. Naganuma, A. Sticchi, A. Chieffo, M. Carlino, M. Montorfano, A. Colombo, Expansion in calcific lesions and overall clinical outcomes following bioresorbable scaffold implantation optimized with intravascular ultrasound, Catheter. Cardiovasc. Interv. (Aug 22 2016) https://doi.org/10.1002/ccd.26725 (Epub ahead of print).

[25] Ming Jiang Fam, J.N. van Der Sijde, A. Karanasos, C. Felix, R. Diletti, N. van Mieghem, P. de Jaegere, F. Zijlstra, R. Jan van Geuns, E. Regar, Comparison of acute expansion of bioresorbable vascular scaffolds versus metallic drug-eluting stents in different degrees of calcification: an optical coherence tomography study, Catheter. Cardiovasc. Interv. (Oct 7 2016) https://doi.org/10.1002/ccd.26676.

[26] M. Ohya, K. Kadota, Y. Sotomi, K. Kozuma, K. Tanabe, M. Uematsu, T. Kawasaki, Y. Morino, T. Tobaru, K. Nakao, K. Tachibana, K. Kishi, Y. Shibata, S. Ying, H. Kusano, G.W. Stone, J.J. Popma, Y. Onuma, P.W. Serruys, T. Kimura, Impact of lesion calcification on angiographic outcomes after Absorb everolimus-eluting bioresorbable vascular scaffold implantation: an observation from the ABSORB Japan trial, EuroIntervention (Nov 8 2016) https://doi.org/10.4244/EIJ-D-16-00359 (pii: EIJ-D-16-00359. Epub ahead of print).

[27] A. Colombo, V.F. Panoulas, After 3 decades, at long last, a new device to deal with calcific lesions, JACC Cardiovasc. Interv. 7 (2014) 519–520.

[28] S. Basavarajaiah, T. Naganuma, A. Latib, A. Colombo, Can bioabsorbable scaffolds be used in calcified lesions? Catheter. Cardiovasc. Interv. 84 (2014) 48–52.

[29] K. Yamaji, L. Räber, S. Windecker, What determines long-term outcomes using fully bioresorbable scaffolds - the device, the operator or the lesion? EuroIntervention (Jan 26 2017) https://doi.org/10.4244/EIJV12I14A277 (pii: EIJV12I14A277. Epub ahead of print).

[30] Patrick W. Serruys, Yoshinobu Onuma, Dmax for sizing, PSP-1, PSP-2, PSP-3 or OCT guidance: interventionalist's jargon or indispensable implantation techniques for short- and long-term outcomes of Absorb BRS? EuroIntervention (Mar 2 2017) https://doi.org/10.4244/EIJY17M02_01 (pii: EIJY17M02_01. Epub ahead of print).

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[31] S. Cassese, R.A. Byrne, G. Ndrepepa, S. Kufner, J. Wiebe, J. Repp, H. Schunkert, M. Fusaro, T. Kimura, A. Kastrati, Everolimus-eluting bioresorbable vascular scaffolds versus everolimus-eluting metallic stents: a meta-analysis of randomised controlled trials, Lancet 387 (10018) (Feb 6 2016) 537–544, https://doi.org/10.1016/S0140-6736(15)00979-4 (Epub 2015 Nov 17).

[32] G.W. Stone, R. Gao, T. Kimura, et al., 1-year outcomes with the Absorb bioresorbable scaffold in patients with coronary artery disease: a patient-level, pooled meta-analysis, Lancet 387 (2016) 1277–1289.

[33] Joanna J. Wykrzykowska, Robin P. Kraak, Sjoerd H. Hofma, Rene J. van der Schaaf, E. Karin Arkenbout, Alexander J. IJsselmuiden, Joëlle Elias, Ivo M. van Dongen, Ruben Y.G. Tijssen, Karel T. Koch, Jan Baan, Jr., M. Marije Vis, Robbert J. de Winter, Jan J. Piek, Jan G.P. Tijssen, and Jose P.S. Henriques, for the AIDA Investigators*. Bioresorbable scaffolds versus metallic stents in routine PCI. N. Engl. J. Med. https://doi.org/10.1056/NEJMoa1614954.

[34] R.J. van Geuns, C. Tamburino, J. Fajadet, et al., Self-expanding versus balloon-expandable stents in acute myocardial infarction: results from the APPOSITION II study: self-expanding stents in ST-segment elevation myocardial infarction, JACC Cardiovasc. Interv. 5 (12) (2012) 1209–1219, https://doi.org/10.1016/j.jcin.2012.08.016.

[35] S. Puricel, F. Cuculi, M. Weissner, A. Schmermund, P. Jamshidi, T. Nyffenegger, H. Binder, H. Eggebrecht, T. Münzel, S. Cook, T. Gori, Bioresorbable coronary scaffold thrombosis: multicenter comprehensive analysis of clinical presentation, mechanisms, and predictors, J. Am. Coll. Cardiol. 67 (8) (Mar 1 2016) 921–931, https://doi.org/10.1016/j.jacc.2015.12.019.

[36] J.P. Giblett, A.J. Brown, H. Keevil, C. Jaworski, S.P. Hoole, N.E. West, Implantation of bioresorbable vascular scaffolds following acute coronary syndrome is associated with reduced early neointimal growth and strut coverage, EuroIntervention 12 (6) (Aug 20 2016) 724–733, https://doi.org/10.4244/EIJV12I6A117.

[37] D. Capodanno, D.J. Angiolillo, Antiplatelet therapy after implantation of bioresorbable vascular scaffolds: a review of the published data, practical recommendations, and future directions, JACC Cardiovasc. Interv. 10 (5) (Mar 13 2017) 425–437, https://doi.org/10.1016/j.jcin.2016.12.279.

[38] A. Karanasos, N. Van Mieghem, N. van Ditzhuijzen, C. Felix, J. Daemen, A. Autar, Y. Onuma, M. Kurata, R. Diletti, M. Valgimigli, F. Kauer, H. van Beusekom, P. de Jaegere, F. Zijlstra, R.J. van Geuns, E. Regar, Angiographic and optical coherence tomography insights into bioresorbable scaffold thrombosis: single-center experience, Circ. Cardiovasc. Interv. 8 (5) (May 2015) https://doi.org/10.1161/CIRCINTERVENTIONS.114.002369 (pii: e002369).

[39] C.M. Felix, Y. Onuma, J.M. Fam, R. Diletti, Y. Ishibashi, A. Karanasos, B.R. Everaert, N.M. van Mieghem, J. Daemen, P.P. de Jaegere, F. Zijlstra, E.S. Regar, R.J. van Geuns, Are BVS suitable for ACS patients? Support from a large single center real live registry, Int. J. Cardiol. 218 (Sep 1 2016) 89–97, https://doi.org/10.1016/j.ijcard.2016.05.037 (Epub 2016 May 13).

[40] G.N. Levine, E.R. Bates, J.A. Bittl, R.G. Brindis, S.D. Fihn, L.A. Fleisher, C.B. Granger, R.A. Lange, M.J. Mack, L. Mauri, R. Mehran, D. Mukherjee, L.K. Newby, P.T. O'Gara, M.S. Sabatine, P.K. Smith, S.C. Smith Jr., ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines, J. Am. Coll. Cardiol. 68 (10) (2016) 1082–1115, https://doi.org/10.1016/j.jacc.2016.03.513 (2016 Sep 6. Epub 2016 Mar 29).

[41] C.M. Felix, G.J. Vlachojannis, A.J.J. IJsselmuiden, J.M. Fam, P.C. Smits, W. Lansink, R. Diletti, F. Zijlstra, E.S. Regar, E. Boersma, Y. Onuma, R.J.M. van Geuns, Potentially increased incidence of scaffold thrombosis in patients treated with Absorb BVS who terminated DAPT before 18 months, EuroIntervention 13 (2) (2017) e177–e184, https://doi.org/10.4244/EIJ-D-17-00119.

[42] C.M. Felix, G.J. Vlachojannis, A.J. IJsselmuiden, Y. Onuma, R.J. van Geuns, Very late scaffold thrombosis in Absorb BVS: association with DAPT termination? JACC. Cardiovasc. Interv. 10 (6) (Mar 27 2017) 625–626, https://doi.org/10.1016/j.jcin.2017.01.015.

[43] Y. Onuma, S. Tanimoto, P. Ruygrok, J. Neuzner, J.J. Piek, A. Seth, J.J. Schofer, G. Richardt, M. Wiemer, D. Carrie, L. Thuesen, C. Dorange, K. Miquel-Hebert, S. Veldhof, P.W. Serruys, Efficacy of everolimus eluting stent implantation in patients with calcified coronary culprit lesions: two-year angiographic and three-year clinical results from the SPIRIT II study, Catheter. Cardiovasc. Interv. 76 (2010) 634–642.

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