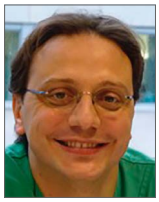
EuroIntervention 2020;16:e147-e154 published online May 2019 ■ published online e-edition June 2020

Special feature: Bioresorbable scaffolds

Procedural microvascular activation in long lesions treated with bioresorbable vascular scaffolds or everolimus-eluting stents: the PROACTIVE trial



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This paper also includes supplementary data published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-18-01138

KEYWORDS

- bioresorbable scaffolds
- drug-eluting stent
- fractional flow reserve
- other technique
- stable angina

Abstract

Aims: Significant platelet activation after long stented coronary segments has been associated with periprocedural microvascular impairment and myonecrosis. In long lesions treated either with an everolimus-eluting bioresorbable vascular scaffold (BVS) or an everolimus-eluting stent (EES), we aimed to investigate (a) procedure-related microvascular impairment, and (b) the relationship of platelet activation with microvascular function and related myonecrosis.

Methods and results: Patients (n=66) undergoing elective percutaneous coronary intervention (PCI) in long lesions were randomised 1:1 to either BVS or EES. The primary endpoint was the difference between groups in changes of pressure-derived corrected index of microvascular resistance (cIMR) after PCI. Periprocedural myonecrosis was assessed by high-sensitivity cardiac troponin T (hs-cTnT), platelet reactivity by high-sensitivity adenosine diphosphate (hs-ADP)-induced platelet reactivity with the Multiplate Analyzer. Post-dilatation was more frequent in the BVS group, with consequent longer procedure time. A significant difference was observed between the two groups in the primary endpoint of ΔcIMR (p=0.04). hs-ADP was not different between the groups at different time points. hs-cTnT significantly increased after PCI, without difference between the groups.

Conclusions: In long lesions, BVS implantation is associated with significant acute reduction in IMR as compared with EES, with no significant interaction with platelet reactivity or periprocedural myonecrosis.

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SUBMITTED ON 03/12/2018 - REVISION RECEIVED ON 05/04/2019 - ACCEPTED ON 10/05/2019

DOI: 10.4244/EIJ-D-18-01138

Abbreviations

BVS	bioresorbable vascular scaffold
CFR	coronary flow reserve
cIMR	corrected index of microvascular resistance
DAPT	dual antiplatelet therapy
DES	drug-eluting stent
EES	everolimus-eluting stent
FFR	fractional flow reserve
hs-ADP	high-sensitivity adenosine diphosphate
hs-cTnT	high-sensitivity cardiac troponin T
MBF	myocardial blood flow
PCI	percutaneous coronary intervention
PET	positron emission tomography
PMI	periprocedural myocardial infarction

Introduction

Platelet activation significantly increases during the implantation of long coronary stents despite dual antiplatelet therapy (DAPT)[1]. This is proportional to the extent of vascular damage induced by the coronary intervention and to the length of the stent, translating into periprocedural myocardial infarction (PMI)[2]. The stiffness of the metallic drug-eluting stent (DES) might in fact result in a distortion at the stented segment and an increased compliance at the contiguous segments (compliance mismatch)[3]. The latter has been associated with ring vortices at the inflow of the stent and rapid variations of wall shear stress that might potentially induce platelet activation and thrombus formation[4,5].

Bioresorbable vascular scaffolds (BVS) were developed to overcome the shortcomings of DES, providing transient scaffolding and local drug delivery, with potential restoration of vasomotion, cyclic strain, and shear stress[6-8]. In addition, BVS are less stiff than metallic stents[9], and are not associated with increased compliance at the inflow segment, but rather with a decreased compliance at the outflow segment, resulting in lower compliance mismatch[10]. However, the higher scaffold thrombosis rate has tempered the initial enthusiasm for BVS[11-13]. It is not yet clear what the impact of BVS on microvascular function might be, especially in relation to platelet inhibition during and after PCI. Given the inherent flexibility, we hypothesised that the Absorb™ BVS (Abbott Vascular, Santa Clara, CA, USA) might be associated with less platelet activation, thrombus formation and downstream microvascular impairment as compared with the XIENCE metallic EES (Abbott Vascular) in stable patients undergoing PCI of long coronary stenoses.

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Methods

The PROcedure-related microvascular ACTIVation in long lEsions treated with bioresorbable vascular scaffold versus everolimus-eluting stent implantation (PROACTIVE) study was a prospective, randomised (1:1), open-label, superiority controlled trial **(Figure 1)** carried out at the Cardiovascular Research Center Aalst, OLV Hospital, Aalst, Belgium, between December 2013 and March 2017.

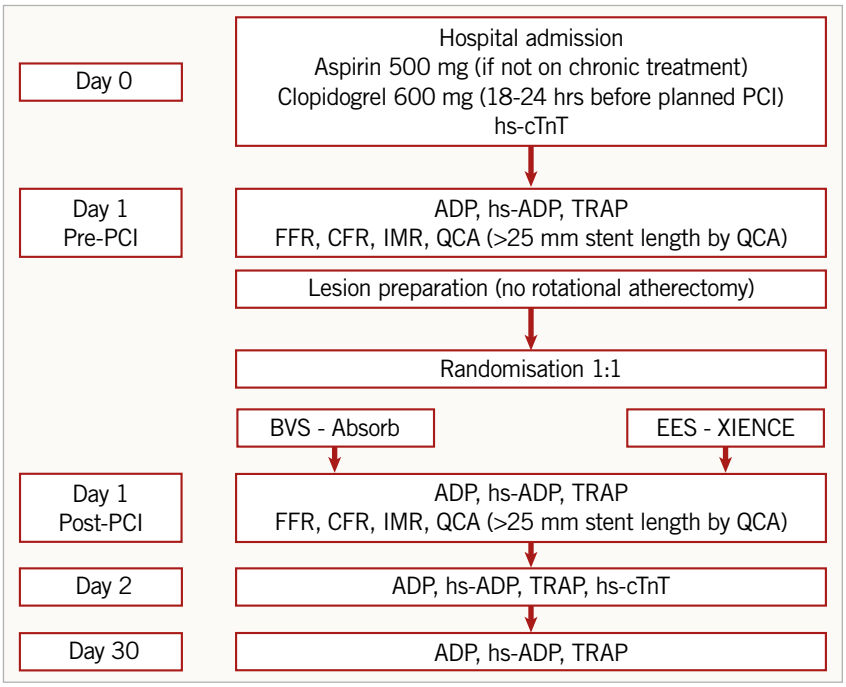

Figure 1. *Study design. ADP: adenosine diphosphate; BVS: bioresorbable vascular scaffold; CFR: coronary flow reserve; EES: everolimus-eluting stent; FFR: fractional flow reserve; hs-ADP: high-sensitivity adenosine diphosphate; hs-cTnT: high-sensitivity cardiac troponin T; IMR: index of microvascular resistance; PCI: percutaneous coronary intervention; QCA: quantitative coronary angiography; TRAP: thrombin receptor-activated peptide*

PATIENT POPULATION

We enrolled patients with stable coronary artery disease and long lesions (i.e., lesions to be treated with a stent ≥25 mm long) **(Figure 1)**. The study protocol **(Figure 1, Supplementary Appendix 1)** was approved by the Institutional Ethics Committee and all patients gave written informed consent for participation and data collection. Exclusion criteria are reported in **Supplementary Appendix 1**.

PLATELET FUNCTION ANALYSIS AND CORONARY PHYSIOLOGY INDICES

Details on platelet function analysis and coronary physiology indices can be found in **Supplementary Appendix 1**.

STUDY ENDPOINTS

The primary endpoint of the PROACTIVE trial was the difference in the Δ corrected index of microvascular resistance (cIMR post-PCI – pre-PCI) between the two groups. Secondary endpoints were: a) immediate periprocedural (post-PCI – pre-PCI) variations in platelet reactivity assessed by hs-ADP; b) periprocedural myonecrosis as assessed by hs-cTnT at 24 hours between the two groups; c) changes at 30-day follow-up in hs-ADP between the two groups.

STATISTICAL ANALYSIS

Continuous variables are expressed as mean±SD or as median (interquartile range), as appropriate. Categorical variables are reported as frequencies and percentages. Normal distribution was evaluated with the Shapiro-Wilk test. Comparisons between continuous variables were performed using the Student's t-test or Mann-Whitney test. Repeated measurements on a single sample for platelet reactivity assessment were performed with the Wilcoxon signed-rank test. Repeated measures two-way analysis of variance (ANOVA) was used to assess the effect interaction between treatment and time on continuous variables. Comparisons between categorical variables were evaluated using Fisher's exact test or the Pearson chi-square test, as appropriate. Correlations between continuous variables were assessed using the Pearson correlation test. A sample size of 33 patients randomised per group was calculated to demonstrate the statistically significant superiority of the Absorb BVS versus the XIENCE EES in terms of post-PCI versus pre-PCI changes in cIMR. A power of 90% was estimated in order to detect a difference in means of 8.280 assuming a common standard deviation of 10.000, using a two-group t-test with a 0.025 one-sided significance level. Statistical analysis was performed using GraphPad Prism 6.0 (GraphPad Software Inc., San Diego, CA, USA) and SPSS, Version 23.0 (IBM Corp., Armonk, NY, USA) and p-values <0.05 (two-tailed) were considered significant.

Results

CLINICAL AND ANGIOGRAPHIC CHARACTERISTICS

A total of 66 patients were enrolled in this trial, 33 randomised to the Absorb BVS, and 33 to the XIENCE Xpedition® or XIENCE Alpine™ EES (both Abbott Vascular). Baseline clinical characteristics were not different between the groups **(Table 1)**. No in-hospital major adverse events occurred. No differences between the two groups in number of diseased vessels, vessels and SYNTAX segments treated as well as complexity of the lesions defined according to the ACC/AHA classification were observed **(Table 2)**. Only one vessel per patient was treated and procedural success was reached in 100% of the patients.

Table 1. Baseline clinical characteristics of the population.

	EES group (33 patients)	BVS group (33 patients)	*p*-value
Age, years	64.2±8	62.1±9.4	0.33
Male gender	23/33 (70%)	26/33 (79%)	0.14
BMI, kg/m²	27.4±4.1	28.1±4.5	0.49
Hypertension, %	16/33 (48%)	20/33 (61%)	0.32
Hypercholesterolaemia, %	31/33 (94%)	26/33 (77%)	0.73
Diabetes, %	8/33 (24%)	6/33 (18%)	0.54
Smoking habit, %	5/33 (15%)	7/33 (21%)	0.52
Former smoking habit, %	8/33 (24%)	10/33 (30%)	0.58
Family history of CAD, %	9/33 (27%)	11/33 (33%)	0.59
Previous MI, %	2/33 (6%)	2/33 (6%)	1
Previous PCI, %	3/33 (9%)	5/33 (15%)	0.45
Previous CABG, %	2/33 (6%)	1/33 (3%)	0.55
LVEF, %	65.3±9.07	66.5±9.8	0.26
Baseline hs-cTnT	11.4±13.4	10.7±16	0.25

BMI: body mass index; CABG: coronary artery bypass graft; CAD: coronary artery disease; hs-cTnT: high-sensitivity cardiac troponin T; LVEF: left ventricular ejection fraction; MI: myocardial infarction; PCI: percutaneous coronary intervention

PROCEDURAL CHARACTERISTICS

Procedural characteristics are shown in **Table 3**. Semi-compliant balloons were more frequent in patients treated with EES, although there were no differences between the groups in terms of lesion preparation, maximum and minimum stent/scaffold diameter, number of stents/scaffolds implanted per patient and total stent/scaffold length. As per protocol, post-dilatation was more frequent in patients treated with BVS, with longer procedure time. However, no differences between the two groups were observed regarding the use of semi-compliant and non-compliant balloons, maximal diameter balloons, maximal pressure and total balloon inflation times. Occlusion of small side branches (<2 mm) was evenly distributed in the two groups (7/33 in the BVS group versus 7/33 in the XIENCE EES group, p=1).

HAEMODYNAMIC CHARACTERISTICS AND CORONARY PHYSIOLOGY ASSESSMENTS

A significant difference in heart rate was observed between the two groups both pre and post PCI. No significant between-group differences were observed in fractional flow reserve (FFR), coronary flow reserve (CFR) and cIMR both before and after PCI **(Table 4)**.

Table 2. Angiographic characteristics.

		EES group (33 patients)	BVS group (33 patients)	*p*-value
No. of diseased vessels		1.54±0.66	1.24±0.43	
1 VD		18/33 (55%)	25/33 (76%)	0.07
2 VD		12/33 (36%)	8/33 (24%)	0.28
3 VD		3/33 (9%)	0 (0%)	0.24
Vessels treated	LAD/diagonal branch	30/33 (91%)	28/33 (85%)	0.16
	LCX/OM	0/33 (0%)	2/33 (6%)	0.49
	RCA	3/33 (9%)	3/33 (9%)	1
SYNTAX coronary segments treated	2	3 (9%)	2 (6%)	0.32
	3	0 (0%)	1 (3%)	
	6	9 (27%)	6 (18%)	
	7	13 (39%)	11 (33%)	
	8	1 (3%)	0 (0%)	
	9	1 (3%)	0 (0%)	
	13	0 (0%)	2 (6%)	
	6+7	5 (15%)	11 (33%)	
	6+7+8	1 (3%)	0 (0%)	
One treated vessel		33/33 (100%)	33/33 (100%)	1
Procedural success		33/33 (100%)	33/33 (100%)	1
Lesion type	A	0 (0%)	0 (0%)	0.96
	B1	8 (24%)	8 (24%)	
	B2	15 (46%)	14 (42%)	
	C	10 (30%)	11 (33%)	
Visual estimation % stenosis		70.4±9.5	68.9±7	0.49

LAD: left anterior descending artery; LCX: left circumflex artery; OM: obtuse marginal branch; RCA: right coronary artery; VD: vessel disease

Table 3. Procedural characteristics.

		EES group (33 patients)	BVS group (33 patients)	*p*-value
Lesion preparation	Use of SC balloon, n (%)	32/33 (97%)	27/33 (82%)	0.04
	Use of NC balloon, n (%)	5/33 (15%)	8/33 (24%)	0.35
	Max balloon diameter, mm	2.9±1	2.9±0.9	0.9
	Max inflation pressure, atm	16±7	15±6	0.8
	Total balloon inflation time, sec	40±26	41±28	0.9
	No. of predilations	2.3±1.6	2.3±1.2	0.9
Max stent/scaffold diameter, mm		3.1±0.3	3.2±0.3	0.1
Minimum stent/scaffold diameter, mm		2.9±0.4	2.8±0.3	0.5
No. of stents/scaffolds used		1.3±0.5	1.5±0.6	0.1
Total stent/scaffold length, mm		32±9	36±10	0.12
Stent/ scaffold optimisation	Post-dilations	25/33 (75%)	31/33 (94%)	0.04
	Use of SC balloon, n (%)	1/33 (3%)	3/33 (9%)	0.6
	Use of NC balloon, n (%)	24/33 (73%)	29/33 (88%)	0.12
	Max balloon diameter, mm	3.4±0.4	3.4±0.6	0.7
	Max inflation pressure, atm	17±3	17±4	0.9
	Total balloon inflation time, sec	39±23	51±28	0.1
	No. of post-dilations	2.3±1.3	2.7±1.8	0.3
Procedure time, min		84±23	96±21	0.03
hs-ADP pre-PCI (AU)		18.4±9.3	21.6±11	0.25
hs-ADP post-PCI (AU)		15.9±9.7	13.8±7.2	0.37
hs-ADP 30-day follow-up (AU)		16.4±8.1	17.5±8.1	0.61

AU: aggregation units; hs-ADP: high-sensitivity adenosine diphosphate; NC: non-compliant; SC: semi-compliant

However, a significant difference in cIMR was observed within the BVS group after PCI versus baseline (19±8 vs 24±12, p=0.04), but not in the EES group (21±9 vs 21±13, p=0.84) **(Figure 2)**. A significant difference in the primary endpoint of ΔcIMR was observed between the two groups (EES group -0.3±13.6 vs BVS group –4.7±13.2; p=0.04) **(Figure 3)**.

PLATELET FUNCTION ANALYSIS AND PERIPROCEDURAL MYONECROSIS

Platelet function metrics were not different between the two groups at the different time points **(Table 3, Supplementary Appendix 2)**. Likewise, myocardial biomarkers and periprocedural myonecrosis were not different between the two groups **(Table 1, Figure 4, Supplementary Appendix 2)**.

Discussion

In the PROACTIVE trial we found a significant reduction of cIMR after PCI in the BVS group but not in the EES group (p=0,04), therefore meeting the primary endpoint of significant between-group difference in ΔcIMR, in favour of the BVS group. In addition, we observed a significant platelet reactivity reduction after PCI with both EES and BVS implantation, without differences between the two groups at baseline, post PCI and at 30-day follow-up. Also, no difference in platelet reactivity over time up to 30-day follow-up was detected. Last, periprocedural myonecrosis after PCI of long coronary lesions was important with both BVS and EES, without significant variations in terms of Δhs-cTnT between the two groups.

In designing the PROACTIVE trial, the assumption was made that metallic DES are associated with an increased compliance at the two contiguous segments of the stent implanted, generating a compliance mismatch. This translates into important ring vortices at the inflow of the stent and rapid variations of wall shear stress that might potentially induce platelet activation and thrombus formation[10]. The significant reduction of cIMR after BVS implantation, while it confirms previous findings[14], might seem at odds with the available data in the literature suggesting increased thrombogenicity. To achieve a similar radial strength to that of an 80 µm metallic stent, the PLLA backbone of the 150 µm everolimus-eluting

Table 4. Haemodynamic characteristics.

	EES group (33 patients)	BVS group (33 patients)	*p*-value
Pre-PCI			
Heart rate, bpm	69.9±11.3	76.3±11.2	0.02
Systolic blood pressure, mmHg	127.7±22.5	124.5±18.7	0.53
Diastolic blood pressure, mmHg	70.3±11.1	66±7.7	0.09
Pd, mmHg	56.2±16.4	56.7±14.5	0.88
Pa, mmHg	84±7.6	79.7±15.8	0.3
FFR	0.66±0.13	0.71±0.10	0.14
CFR	2.4±1.6	2.1±0.95	0.42
Wedge pressure, mmHg	11.6±9.4	12.2±8	0.79
Hyperaemic mean transit time, sec	0.46±0.22	0.47±0.21	0.79
cIMR	21.4±12.8	24±12.1	0.39
Post-PCI			
Heart rate, bpm	72.3±8.5	77.8±9.1	0.01
Systolic blood pressure, mmHg	128.4±20.2	122.4±17	0.19
Diastolic blood pressure, mmHg	68.3±10.8	66.9±6.8	0.54
Pd, mmHg	72.3±15.4	67.2±11.1	0.12
Pa, mmHg	84.6±15.9	78.4±12	0.08
FFR	0.85±0.05	0.85±0.05	0.79
CFR	2.6±1.2	2.6±1.3	0.98
Wedge pressure, mmHg	11.6±9.4	12.2±8	0.79
Hyperaemic mean transit time, sec	0.30±0.13	0.30±0.14	0.95
cIMR	20.9±9.5	19.2±7.7	0.45

CFR: coronary flow reserve; cIMR: corrected index of microvascular resistance; FFR: fractional flow reserve

BVS is designed to have both thicker and wider struts[7,9]. On the one hand this translates into a significantly increased surface of contact between the BVS and vessel wall compared to second- and third-generation DES[15-17], but on the other hand the increased strut thickness and width have been associated with more thrombogenicity in animal models[18], also explaining the increased thrombogenicity of BVS in comparison with EES[12,19].

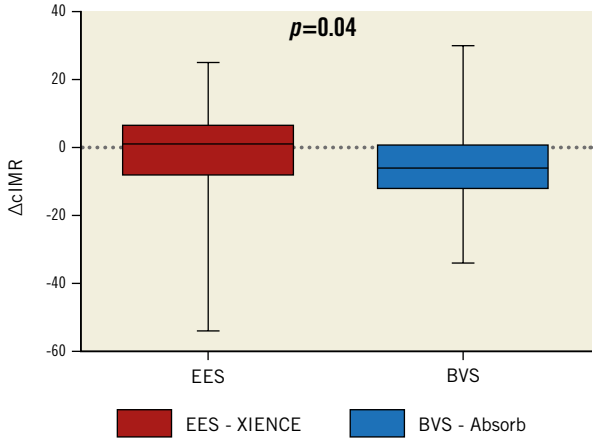

Figure 3. *Difference between the two groups in ΔcIMR. Significant difference between the two groups in the primary endpoint, in favour of the BVS group. ΔcIMR: delta corrected index of microvascular resistance*

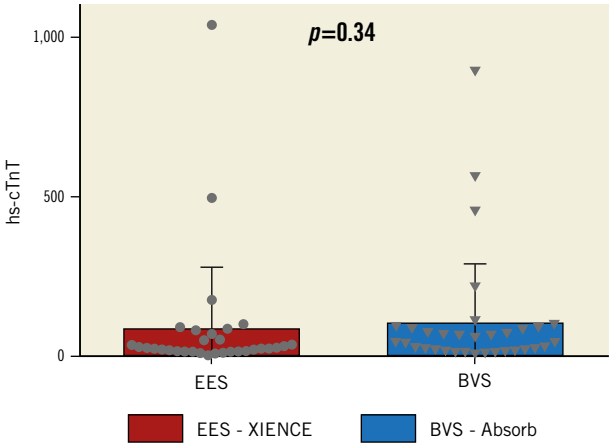

Figure 4. *Difference in hs-cTnT post PCI between the two groups. Significant increase of hs-cTnT after PCI, without difference between the two groups. hs-cTnT: high-sensitivity cardiac troponin T*

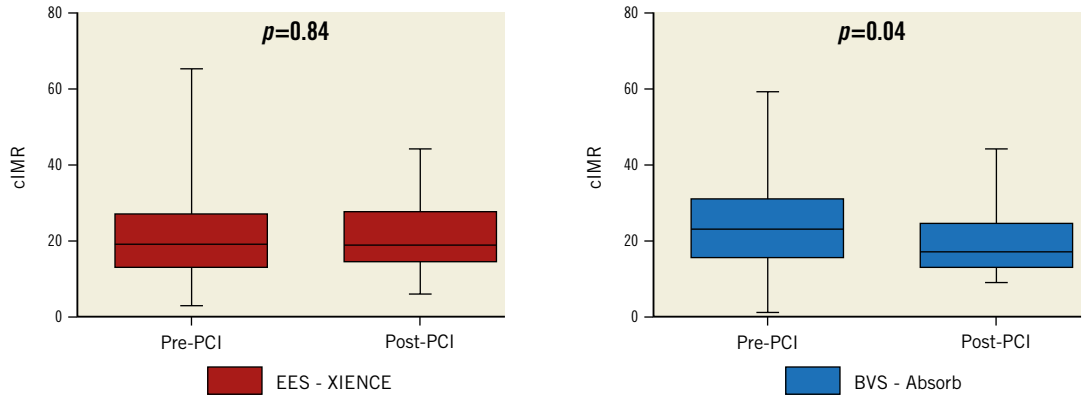

Figure 2. *Changes in cIMR after PCI in the two groups. Left panel: patients treated with the XIENCE EES; right panel: patients treated with the Absorb BVS. cIMR: corrected index of microvascular resistance*

How does one reconcile our findings with this evidence? We can speculate that the lower microvascular impairment after BVS implantation might be explained by the following. 1) As compared with EES implantation, the scaffold deployment is associated with a greater retention of atherothrombotic debris from the coronary plaques, preventing their embolisation distally in the microcirculation. 2) The potentially increased thrombogenicity of BVS is compensated for by a lower compliance mismatch, with a final neutral impact on the microvasculature. BVS implantation is not associated with an increase in compliance at the inflow segment, but conversely tended to decrease compliance at the outflow segment, therefore resulting in a potentially lower degree of compliance mismatch[10]. 3) The more accurate and prolonged vessel preparation and BVS optimisation with multiple balloon inflations might have resulted in a preconditioning of the microvasculature, possibly preventing an increase in resistance of the microcirculation[20].

Our results are corroborated by recent data obtained in 60 patients randomised to either Absorb BVS or XIENCE PRIME® DES implantation where myocardial blood flow (MBF) and CFR over three years were assessed non-invasively by positron emission tomography (PET) perfusion imaging. No differences in PET-derived absolute myocardial perfusion were observed between the BVS and DES groups at one-month follow-up[21], suggesting that BVS implantation is safe without major consequences in the short term with regard to myocardial perfusion. Similarly, in our trial the scaffold implantation did not affect the microcirculation. Although the initial one-year lower angina rates with BVS implantation of the ABSORB II trial[22] were not confirmed in the ABSORB III trial, we can hypothesise that our findings of missing microvascular resistance increase after PCI with BVS might contribute to an improvement of angina-related symptoms, as observed in the ABSORB IV trial[23]. The significant reduction in platelet reactivity with both BVS and EES is another interesting finding of the PROACTIVE trial. The significant reduction of hs-ADP in both groups, in fact, without differences at baseline, post PCI and 30-day follow-up, confirm the results of previous studies supporting the notion that, in patients with adequate response to DAPT, the thrombogenicity of the Absorb BVS is not affected by on-treatment platelet reactivity but is mainly due to a suboptimal vessel sizing and procedural technique at the time of its implantation[24,25].

Finally, the periprocedural myonecrosis was notable in both groups, as expected by the complexity of PCI of long lesions, without significant difference in terms of Δhs-cTnT between the EES and BVS groups. As is known, the most common mechanisms of myocardial injury during PCI are distal embolisation and side branch occlusion[26]. In our trial, the discrepancy between the reduction of cIMR and the significant increase of hs-cTnT after BVS implantation could be explained by the fact that, although BVS implantation is associated with a high retention of atherothrombotic debris, because of thicker, wider struts as compared with DES, it is also related to an important rate of small side branch occlusion. Our results are in line with a *post hoc* analysis of the ABSORB II trial, where no differences in the incidence of cardiac biomarker rise and PMI were found between the two groups[27].

Limitations

First, enrolment in the PROACTIVE trial was restricted to patients with long lesions. Our findings may not be generalisable to patients with acute coronary syndrome (ACS) and more complex disease. Second, patients enrolled in the PROACTIVE trial were all treated with clopidogrel. Therefore, we cannot conclude that the same impact of Absorb BVS implantation on microcirculation, platelet reactivity and periprocedural myonecrosis can be obtained in patients treated with more potent $P2Y_{12}$ inhibitors. Third, our trial was not powered for clinical endpoints. Fourth, heart rate was significantly higher in patients randomised to BVS as compared with EES. Nevertheless, this latter finding has no impact on our results considering that one of the advantages of the IMR is that it is obtained by measuring the mean transit time and the distal coronary pressure during minimal and stable microvascular resistance (i.e., during stable hyperaemia with IV adenosine infusion). In this condition, IMR has previously been shown to be independent from heart rate. Fifth, in the BVS group, procedure time was significantly higher as compared with the DES group. Transient early dynamic changes possibly occurring during PCI in the microcirculation might therefore not have been detected. Sixth, plaque features of coronary stenosis (e.g., plaque burden and minimal lumen area) as assessed by intravascular imaging have been demonstrated to be independently associated with FFR[28]. In our patients, we did not perform intravascular imaging and are not able to provide any further insight on the possible association between plaque features and IMR findings.

Conclusions

In long lesions, BVS implantation is associated with a significant reduction in cIMR as compared with EES. The limited acute impact of BVS on the microcirculation effect is associated with an optimal periprocedural and short-term platelet inhibition, without significant difference in periprocedural myonecrosis as compared with patients treated with EES.

Impact on daily practice

The first generation of the Absorb BVS did not live up to its promise because of higher events due to greater scaffold thrombosis. However, we found a limited acute impact of BVS on the microcirculation, with lower periprocedural and short-term platelet inhibition. While refinements are warranted in the upcoming generations of the Absorb BVS in terms of reduction of the strut profile and vessel wall coverage area, our findings are reassuring on the acute impact of these devices on the microcirculation, suggesting that changes in the antiplatelet regimen of patients undergoing BVS are not needed.

Funding

The Cardiovascular Research Center Aalst received an unrestricted grant from Abbott Vascular.

Conflict of interest statement

M. Pellicano has been supported by a research grant provided by the CardioPath PhD program. The other authors have no conflicts of interest to declare.

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Supplementary data

Supplementary Appendix 1. Methods.

Supplementary Appendix 2. Results.

The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-18-01138

Supplementary data

Supplementary Appendix 1. Methods

Study protocol

Exclusion criteria were: a) acute coronary syndrome (ACS); b) contraindication to DAPT; c) bifurcations with a side branch >2.0 mm; d) need for rotational atherectomy; e) atrial fibrillation and treatment with oral anticoagulants; f) indication to PCI in more than one vessel (i.e., in the presence of angiographic multivessel disease, FFR was measured in the non-target vessels to exclude the need for multivessel PCI).

At day 0, all patients were loaded with 500 mg aspirin (if not on chronic aspirin treatment) and 600 mg clopidogrel 18-24 hours before planned PCI. Baseline laboratory tests, included hs-cTnT, were performed as per clinical routine.

At day 1 in the pre-PCI setting, all patients received a weight-adjusted intravenous heparin bolus (100 IU/kg) in order to maintain an activated clotting time of between 250 and 300 seconds. A blood sample was collected for baseline platelet reactivity assessment. Quantitative coronary angiography (QCA) was performed to estimate vessel diameter and lesion length. Coronary flow reserve (CFR), fractional flow reserve (FFR) and index of microcirculatory resistance (IMR) were measured with intravenous infusion of adenosine (140 μg/kg/min) before and repeated after PCI. In the PCI setting, adequate lesion preparation was performed with non-compliant and semi-compliant balloons. During balloon inflation occlusion coronary wedge pressure was recorded. After lesion preparation, patients were randomised 1:1 to either the Absorb BVS or XIENCE Xpedition/XIENCE Alpine EES. Assignment to one of the two stents was determined by a computer-based randomisation system, and randomisation assignment for each patient was kept in a sealed envelope. Post-dilatation was allowed in both groups with non-compliant balloons not more than 0.5 mm bigger than the implanted scaffold/stent. After PCI, QCA was performed to estimate final scaffold/stent size. Before sheath removal, another blood sample was collected for platelet reactivity assessment.

At day 2, a blood sampling was carried out for hs-cTnT and platelet reactivity reassessment. A

clinical follow-up together with blood withdrawal for platelet reactivity evaluation was performed at 30-day follow-up.

The study protocol was approved by the Institutional Ethics Committee and all patients gave written informed consent for participation and data collection.

Platelet function analysis

Platelet reactivity was measured with the Multiplate™ Analyzer (Dynabyte medical, Munich, Germany), a whole blood platelet function test based on multiple electrode platelet aggregometry [18]. After 300 µL of whole blood had been diluted with 300 µL of 0.9% NaCl solution and stirred for 3 min in the test cuvettes at 37°C, 6.4 µmol L^{-1} adenosine diphosphate (ADP) was added, and the increase in electrical impedance was recorded over a period of 6 min. The mean values of two independent determinations are expressed as aggregation units (AU).

Coronary physiology indices

Coronary physiological indices (FFR, CFR, IMR) were measured as previously described [19-24]. An intracoronary pressure/temperature sensor-tipped guidewire (PressureWire™ Certus™; St. Jude Medical, St. Paul, MN, USA) was used to measure distal coronary pressure and to derive thermodilution curves. After intracoronary nitroglycerine administration (100–200 µg), pressure measurement from the wire was first equalised with that of the guiding catheter. The lesion was crossed, and the pressure sensor was positioned two thirds of the way down the artery, at least 3 cm beyond the lesion. At baseline, exact position of the pressure wire was filmed, possibly locating the tip close to angiographic landmarks (e.g., offshoots of side branches or calcification spots). After PCI, care was taken to ensure that the distal sensor was placed in the exact same position as it was at baseline to avoid errors in transit time acquisition. Hyperaemia was induced by adenosine infusion (140 µg/kg per minute). Coronary wedge pressure (P_w) was measured as the distal coronary pressure (from the distal pressure/temperature sensor) during first balloon occlusion of the vessel obtained during PCI. In order to account for the effect of microvascular collateral supply on microvascular resistance, the modified equation was used, herewith referred to as the corrected IMR (cIMR): $cIMR = P_a \times T_{mnH} [(P_d – P_w) / (P_a – P_w)]$, where P_a was the mean hyperaemic aortic pressure, T_{mnH} the mean hyperaemic transit time and P_w the coronary wedge

pressure, defined as the distal coronary pressure obtained during balloon occlusion of the culprit vessel and representing recruitable collateral vessels.

Supplementary Appendix 2. Results

Platelet function analysis and periprocedural myonecrosis

A significant reduction of hs-ADP was observed after PCI in both the EES (hs-ADP: pre-PCI 18.4±9.3 AU vs post-PCI 15.9±9.7 AU; p=0.04) and the BVS group (hs-ADP: pre-PCI 21.6±11.1 AU vs post-PCI 13.8±7.2 AU; p<0.0001) without any difference between the two groups at baseline, post PCI and 30-day follow-up **(Table 3)**. Also, no consistent trends of hs-ADP values across the three main times of measurement up to 30-day follow-up have been detected (ANOVA for trend, p=0.29).

Hs-cTnT significantly increased in both groups after PCI (EES: hs-cTnT pre-PCI 11.4±13.3 ng/L vs hs-cTnT post-PCI 84.9±195.2 ng/L; p<0.0001. BVS: hs-cTnT pre-PCI 10.7±16.1 ng/L vs hs-cTnT post-PCI 104.2±182 ng/L; p<0.0001), without difference at baseline **(Table 1)** and after PCI between the two groups **(Figure 4)**. Also, no significant difference in terms of Δhs-cTnT between the EES and BVS groups was observed (Δhs-cTnT EES group 73.4±195.1 vs Δhs-cTnT BVS group 93.4±185.3; p=0.38).