EuroIntervention 2020;16:645-653 published online May 2020

Bioresorbable vascular scaffold versus metallic drug-eluting stent in patients at high risk of restenosis: the COMPARE-ABSORB randomised clinical trial

Pieter C. Smits[1]*, MD, PhD; Chun Chin Chang[2,3], MD; Bernard Chevalier[4], MD; Nick E.J. West[5], MD; Tommaso Gori[6], MD, PhD; Emanuele Barbato[7,8], MD, PhD; Giuseppe Tarantini[9], MD, PhD; Victor Kocka[10], MD, PhD; Stephan Achenbach[11], MD, PhD; Dariusz Dudek[12], MD, PhD; Javier Escaned[13], MD, PhD; Adrian Włodarczak[14], MD; Mohamed Abdel-Wahab[15,16], MD; Giovanni Esposito[17], MD, PhD; Jan G.P. Tijssen[18], PhD; Marie-Claude Morice[19], MD; Yoshinobu Onuma[2,20], MD, PhD; Robert-Jan van Geuns[2,21], MD, PhD; on behalf of the COMPARE-ABSORB trial investigators

The authors' affiliations can be found in the Appendix paragraph.

This paper also includes supplementary data published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-19-01079

KEYWORDS

- bioresorbable scaffold
- drug-eluting stent
- stent thrombosis

Abstract

Aims: The aim of this study was to investigate clinical outcomes of patients at high risk of restenosis after implantation of a bioresorbable vascular scaffold (BVS).

Methods and results: The COMPARE-ABSORB trial was an investigator-initiated, prospective randomised study. Patients at high risk of restenosis were randomly assigned to receive either a BVS or an everolimus-eluting stent (EES). A dedicated implantation technique was recommended for BVS. The primary endpoint was target lesion failure (TLF), defined as the composite of cardiac death, target vessel myocardial infarction (TVMI) or clinically indicated target lesion revascularisation at one year. The enrolment was discontinued prematurely because of a high thrombosis and TVMI rate in the BVS arm. A total of 1,670 patients were recruited (BVS 848 patients and EES 822 patients). TLF occurred in 43 patients (5.1%) of the BVS group and 34 patients (4.2%) of the EES group (absolute difference 0.9%, 95% confidence interval [CI]: −1.2%-3.0%, p non-inferiority <0.001). Definite or probable device thrombosis (2.0% vs 0.6%, hazard ratio [HR] 3.32, 95% CI: 1.22-8.99, p=0.012) and TVMI (4.0% vs 2.1%, HR 1.96, 95% CI: 1.10-3.51, p=0.02) were significantly higher in the BVS group than in the EES group.

Conclusions: In patients at high risk of restenosis, non-inferiority of BVS compared with EES in terms of TLF was met at one year. BVS carried a higher risk of device thrombosis and TVMI than EES.

**Corresponding author: Department of Cardiology, Maasstad Ziekenhuis, Maasstadweg 21, 3079 DZ Rotterdam, the Netherlands. E-mail: SmitsP@maasstadziekenhuis.nl*

SUBMITTED ON 04/12/2019 - REVISION RECEIVED ON 1st 16/03/2020 / 2nd 29/04/2020 - ACCEPTED ON 20/05/2020

DOI: 10.4244/EIJ-D-19-01079

Abbreviations

BVS	bioresorbable vascular scaffold
EES	everolimus-eluting stent(s)
PCI	percutaneous coronary intervention
TLF	target lesion failure
TVMI	target vessel myocardial infarction

Introduction

The bioresorbable vascular scaffold (BVS) is designed for treatment of obstructive coronary artery disease providing temporary mechanical support and antiproliferative drug delivery, but without perceived disadvantages of permanent metallic implants[1]. In a series of randomised trials, BVS met the criteria of non-inferiority compared with metallic drug-eluting stents (DES) for composite endpoints in relatively low-risk coronary lesions and patients at one year[2,3]. However, BVS resulted in higher rates of target lesion failure (TLF) and device thrombosis compared with metallic DES at three-year follow-up[4]. These disappointing outcomes have been shown to be attributable, at least partially, to a suboptimal implantation technique of this thick-strut device[5].

In previous randomised trials, the "BVS-specific" implantation technique was neither fully developed nor employed as part of the study design; whether using optimal implantation techniques with BVS could reduce the risk of device thrombosis requires further examination. In the DES era, prevention of in-stent restenosis and neoatherosclerosis remains an unmet need, especially for patients at high risk of restenosis, such as those with long lesions and patients with diabetes mellitus[6]. We hypothesised that the use of BVS in a high-risk population might demonstrate better long-term outcomes compared with DES after full BVS resorption. Therefore, we conducted the COMPARE-ABSORB trial to investigate the concept of short-term equivalence and long-term benefit of BVS over metallic DES in patients at high risk of restenosis with complex lesion(s).

Editorial, see page 623

Methods

The study design has been published previously[7]. In summary, the COMPARE-ABSORB trial is a prospective, randomised, controlled, single-blind, multicentre study across 45 centres in Europe **(Supplementary Table 1)**. Patients aged 18-75 years with symptomatic ischaemic heart disease and presence of high-risk features for restenosis due to clinical profile or coronary lesion complexity and who were scheduled to undergo elective or emergent percutaneous coronary intervention (PCI) were eligible. Subjects participating in the trial met at least one of the inclusion criteria: medically treated diabetes, or multivessel disease with more than one *de novo* target lesion and/or presence of at least one complex target lesion (long lesion, small vessel, total occlusion or bifurcation). Key exclusion criteria included target lesion not suitable for BVS implantation, patients with cardiogenic shock, severe renal failure, severe impaired ejection fraction, left main disease or being on oral anticoagulants. Detailed criteria are listed in **Supplementary Table 2**. Patients were 1:1 randomly assigned to receive either BVS (Absorb™; Abbott Vascular, Santa Clara, CA, USA) or EES (XIENCE; Abbott Vascular). Block randomisation was performed with randomly selected block sizes. A dedicated implantation technique was defined in the protocol: predilatation using non-compliant balloons of the same diameter as the reference vessel diameter (RVD) and post-scaffold high-pressure (≥16 atm) dilatation were mandatory in the BVS group. Scaffold to vessel sizing was based on the instructions for use. The primary endpoint was TLF (a composite of cardiac death, myocardial infarction in the target vessel territory and clinically indicated target lesion revascularisation) at one year. An extended Methods section is provided in **Supplementary Appendix 1**, including study organisations **(Supplementary Table 3)**, study procedures, hypotheses, endpoints **(Supplementary Table 4)**, five definitions of optimal implantation technique (OIT) **(Supplementary Table 5)**, and protocol revisions. Follow-up is planned for all patients up to seven years. Consideration will be given to extending follow-up to 10 years.

STATISTICAL ANALYSIS

All clinical data were analysed according to the intention-to-treat principle. For time-to-event endpoints, Kaplan-Meier plots were constructed and compared using the log-rank test. Binomial variables were evaluated with Fisher's exact probability test, continuous variables tested with a two-sample t-test or with the Mann-Whitney U test when data were not normally distributed, and a p-value for interaction was calculated for the subgroup analyses.

The device implantation was evaluated in a combination of different parameters of predilatation, central core lab quantitative coronary angiography (QCA) sizing and post-dilatation. A two-sided p-value of less than 0.05 was considered to indicate statistical significance. All statistical analyses were performed using SAS software, Version 9.3 (SAS Institute Inc., Cary, NC, USA). This trial was registered at ClinicalTrials.gov (NCT 02486068).

Results

BASELINE PATIENT CHARACTERISTICS AND FOLLOW-UP

Between September 2015 and August 2017, 1,670 of the intended 2,100 patients with 2,457 lesions were randomly assigned to receive either BVS (848 patients with 1,243 lesions) or EES (822 patients with 1,214 lesions). The trial was prematurely stopped on the recommendation of the Data and Safety Monitoring Board based on safety concerns seen in interim analyses. Follow-up at 12 months was complete in 824/848 patients treated with BVS versus 804/822 patients in the EES group (p=0.43). In the 24 BVS patients with incomplete follow-up, the median duration of follow-up was 74 days versus 160 days in the 18 EES patients (p=0.36) **(Figure 1)**. Baseline clinical characteristics are shown in **Table 1**. Of the 1,670 patients, 293 (34.6%) in the BVS group and 296 (36.1%) in the EES group had a history of diabetes, and 442 (52.1%) in the BVS group and 400 (48.7%) in the EES group presented with acute coronary syndrome.

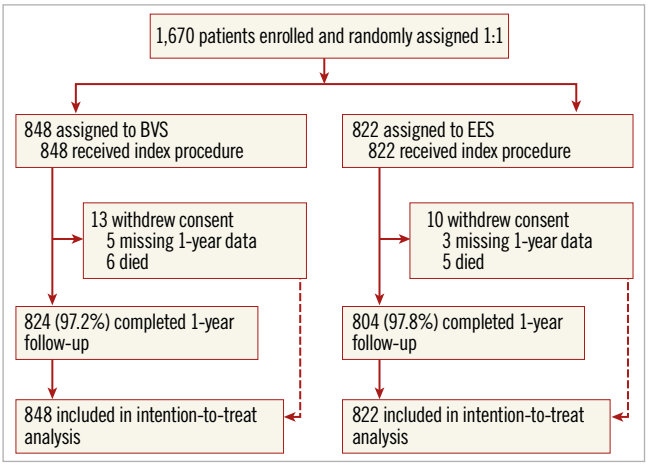


Figure 1. *Study flow chart. BVS: bioresorbable vascular scaffold; EES: everolimus-eluting stent*

Table 1. Baseline patient characteristics.

Characteristic	BVS (n=848)	EES (n=822)	*p*-value
Age, years	62 (56-69)	63 (56-69)	0.61
Male	674/848 (79.5%)	627/822 (76.3%)	0.13
Body mass index	27 (25-31)	27 (25-30)	0.43
Current smoker	241/837 (28.8%)	217/807 (26.9%)	0.41
Diabetes mellitus	293/846 (34.6%)	296/821 (36.1%)	0.57
Hypertension	601/839 (71.6%)	567/819 (69.2%)	0.31
Hypercholesterolaemia	546/824 (66.3%)	531/801 (66.3%)	0.88
Family history of coronary artery disease	278/767 (36.2%)	241/760 (31.7%)	0.07
Previous MI	154/847 (18.2%)	166/820 (20.2%)	0.29
Established peripheral vascular disease	59/842 (7.0%)	56/819 (6.8%)	0.92
Previous PCI	229/847 (27.0%)	238/822 (29.0%)	0.38
Previous CABG	16/848 (1.9%)	21/822 (2.6%)	0.41
Previous stroke	29/845 (3.4%)	39/820 (4.8%)	0.18
Renal insufficiency*	33/845 (3.9%)	49/817 (6.0%)	0.054
Left ventricular ejection fraction			
Good (>60%)	492/661 (74.4%)	486/647 (75.1%)	0.84
Reduced (30 to 60%)	155/661 (23.4%)	143/647 (22.1%)	
Poor (<30%)	14/661 (2.1%)	18/647 (2.8%)	
Clinical presentation			
Stable coronary artery disease	406/848 (47.9%)	422/822 (51.3%)	0.17
Silent ischaemia	63/848 (7.4%)	73/822 (8.9%)	
Stable angina	343/848 (40.4%)	349/822 (42.5%)	
ACS	442/848 (52.1%)	400/822 (48.7%)	0.17
Unstable angina	149/848 (17.6%)	141/822 (17.2%)	
Non-ST-elevation MI	183/848 (21.6%)	156/822 (19.0%)	
ST-elevation MI	110/848 (12.9%)	103/822 (12.5%)	

Data are median (interquartile range) or count (percentage). * Renal insufficiency is defined as MDRD estimated glomerular filtration rate less than 60 ml/min or serum creatinine above 130 micromol/l. ACS: acute coronary syndrome; BVS: bioresorbable vascular scaffold; CABG: coronary artery bypass graft; CAD: coronary artery disease; EES: everolimus-eluting stent; MDRD: Modification of Diet in Renal Disease; MI: myocardial infarction; PCI: percutaneous coronary intervention

LESION AND PROCEDURAL CHARACTERISTICS

A total of 1,650 BVS and 1,554 EES were implanted in the two groups. **Table 2** shows a significantly higher performance of optical coherence tomography (OCT) in the BVS group, as well as higher incidences of both long lesions (>28 mm) and small-vessel lesions (between 2.25 and 2.75 mm) in the EES group. In the BVS group, predilatation was performed in 96.8% of the lesions and post-dilatation in 92.8% of the lesions. The percentages of predilatation and post-dilatation were significantly higher in the BVS group than in the EES group. According to angiographic analysis performed by the core lab, 21.9% (255/1,166) of lesions in the BVS group had a post-procedural in-scaffold RVD of less than 2.25 mm and 40.9% (477/1,166) less than 2.5 mm. The main failures with respect to the sizing recommendation were related to differences between the visually estimated diameters and QCA, followed by mismatch between the proximal and distal reference diameters. The proportions of lesions in the BVS group meeting the definition of OIT-0 to OIT-4 were as follows: OIT-0: 33.7% (383/1,137), OIT-1: 24.1% (274/1,137), OIT-2: 17.1% (194/1,137), OIT-3: 16.3% (185/1,137), and OIT-4: 11.1% (126/1,137). In addition, the device success rate was significantly lower in the BVS group than in the EES group (BVS 92.4% vs EES 96.8%, p<0.001), driven by a lower rate of successful device delivery.

CLINICAL OUTCOMES

The primary endpoint of TLF at one year occurred in 43 patients (5.1%) in the BVS group and in 34 patients (4.2%) in the EES group **(Table 3, Figure 2)**. The primary hypothesis, non-inferiority of BVS compared to EES, was met with an absolute difference of 0.9% and two-sided 95% confidence interval (CI) of −1.2% demonstrated (difference 0.9% [two-sided 95% CI: −1.2-3.0%], p non-inferiority <0.001). For individual components of TLF, the frequencies of cardiac death (5 [0.6%] vs 1 [0.1%]; hazard ratio [HR] 4.87, 95% CI: 0.57-41.7; p=0.11) and clinically indicated target lesion revascularisation (20 [2.4%] vs 22 [2.7%]; HR 0.89, 95% CI: 0.48-1.62; p=0.69) did not differ significantly between the groups. However, at 30 days, target vessel myocardial infarction (TVMI) was significantly higher in the BVS group than in the EES group (27 [3.2%] vs 10 [1.2%]; HR 2.64, 95% CI: 1.28-5.45; p=0.006), while no significant difference between groups beyond 30 days to one year (7 [0.9%] vs 7 [0.9%]; HR 0.99, 95% CI: 0.35-2.83; p=0.99) was observed **(Table 3, Figure 3)**. Similarly, definite or probable device thrombosis was significantly higher in the BVS group than in the EES group (13 [1.5%] vs 4 [0.5%]; HR 3.16, 95% CI: 1.03-9.69; p=0.033) at 30 days and was not significantly different between 30 days and one year (4 [0.5%] vs 1 [0.1%]; HR 3.94, 95% CI: 0.44-35.2; p=0.18). The majority of the BVS thromboses (13/17, 76%) occurred within 30 days of the index procedure and only one event was related to the cessation of antiplatelet agents.

At one-year follow-up, 80.0% of patients in the BVS group and 70.8% of patients in the EES group remained on dual antiplatelet treatment **(Supplementary Table 6)**. The one-year TLF rates were comparable across all pre-specified subgroups **(Figure 4)**.

Table 2. Angiographic and procedural characteristics.

	BVS (n=1,243 lesions)	EES (n=1,214 lesions)	*p*-value
Patient characteristics			
Number of target lesions attempted to be treated	1 (1-2) (n=848)	1 (1-2) (822)	0.64
Multivessel treatment	441/848 (52.0%)	433/822 (52.7%)	0.81
IVUS performed post procedure	126/848 (14.9%)	122/822 (14.8%)	1.00
OCT performed post procedure	84/848 (9.9%)	24/822 (2.9%)	<0.001
Target lesion characteristics			
LAD	569/1,243 (45.8%)	503/1,214 (41.4%)	0.031
LCX	281/1,243 (22.6%)	310/1,214 (25.5%)	0.10
RCA	392/1,243 (31.5%)	400/1,214 (32.9%)	0.46
Left main	1/1,243 (0.1%)	1/1,214 (0.1%)	1.00
Bifurcation lesions	254/1,243 (20.4%)	269/1,214 (22.2%)	0.30
Pre-existing total occlusions	181/1,243 (14.6%)	159/1,214 (13.1%)	0.32
Long lesions (>28 mm)	312/1,243 (25.1%)	382/1,214 (31.5%)	<0.001
Small vessel lesions (>2.25, ≤2.75 mm)	302/1,243 (24.3%)	404/1,214 (33.3%)	<0.001
SYNTAX score	11 (7-17)	11 (7-16)	0.88
Number of study devices implanted per lesion	1 (1-2)	1 (1-1)	0.06
Total device length per lesion, mm	28 (18-36)	28 (18-38)	0.29
Average device diameter per lesion, mm	3.0 (2.8-3.5)	3.0 (2.8-3.5)	<0.001
Overlapping devices implantation	194/1,243 (15.6%)	256/1,214 (21.1%)	<0.001
Bifurcation lesions	254/1,243 (20.4%)	269/1,214 (22.2%)	0.30
Two or more devices used	82/254 (32.3%)	68/269 (25.3%)	0.08
Lesions without study device	44/1,243 (3.5%)	9/1,214 (0.7%)	<0.001
Predilatation	1,199/1,243 (96.5%)	954/1,214 (78.6%)	<0.001
Largest balloon, mm	3.0 (2.5-3.0)	3.0 (2.5-3.0)	0.95
Non-compliant balloon used	815/1,199 (68.0%)	504/954 (52.8%)	<0.001
Maximum pressure used, atm	16 (12-18)	14 (12-16)	0.002
Cutting/scoring balloon used	72/1,243 (5.8%)	28/1,214 (2.3%)	<0.001
Post-dilatation	1,113/1,199 (92.8%)	699/1,205 (58.0%)	<0.001
Largest balloon, mm	3.5 (3.0-3.5)	3.5 (3.0-3.5)	0.53
Non-compliant balloon used	1,039/1,199 (86.7%)	616/1,205 (51.1%)	<0.001
Maximum pressure used, atm	18 (16-20)	18 (16-20)	0.80
Maximun pressure ≥16 atm	899/1,113 (80.8%)	561/699 (80.3%)	0.81
OIT-0	383/1,137 (33.7%)	226/1,139 (19.8%)	<0.001
Correct sizing by QCA	439/1,137 (38.6%)	527/1,139 (46.3%)	<0.001
Predilatation performed	1,161/1,199 (96.8%)	949/1,205 (78.8%)	<0.001
Any post-dilatation	1,071/1,199 (89.3%)	643/1,205 (53.4%)	<0.001
OIT-1	274/1,137 (24.1%)	161/1,139 (14.1%)	<0.001
Correct sizing by QCA	439/1,137 (38.6%)	527/1,139 (46.3%)	<0.001
Predilatation performed	1,161/1,199 (96.8%)	949/1,205 (78.8%)	<0.001
Post-dilatation with non-compliant balloon, maximum pressure ≥16 atm	785/1,199 (65.5%)	442/1,205 (36.7%)	<0.001
OIT-2	194/1,137 (17.1%)	111/1,139 (9.7%)	<0.001
Correct sizing by QCA	439/1,137 (38.6%)	527/1,139 (46.3%)	<0.001
RVD* ≥2.5 mm by QCA	689/1,166 (59.1%)	733/1,183 (62.0%)	0.1636
Predilatation performed	1,161/1,199 (96.8%)	949/1,205 (78.8%)	<0.001
Post-dilatation with non-compliant balloon, maximum pressure ≥16 atm	785/1,199 (65.5%)	442/1,205 (36.7%)	<0.001
OIT-3	185/1,137 (16.3%)	100/1,139 (8.8%)	<0.001
Correct sizing by QCA	439/1,137 (38.6%)	527/1,139 (46.3%)	<0.001
RVD* ≥2.5 mm by QCA	689/1,166 (59.1%)	733/1,183 (62.0%)	0.1636
Predilatation performed	1,161/1,199 (96.8%)	949/1,205 (78.8%)	<0.001
Post-dilatation with non-compliant balloon, pressure ≥16 atm, balloon diameter between device diameter and device diameter+0.5 mm	744/1,199 (62.1%)	399/1,205 (33.1%)	<0.001
OIT-4	126/1,137 (11.1%)	75/1,139 (6.6%)	<0.001
Correct sizing by QCA	439/1,137 (38.6%)	527/1,139 (46.3%)	<0.001
RVD* ≥2.5 mm by QCA	689/1,166 (59.1%)	733/1,183 (62.0%)	0.1636
Predilatation performed	1,161/1,199 (96.8%)	949/1,205 (78.8%)	<0.001
Post-dilatation with non-compliant balloon, maximum pressure ≥16 atm, balloon diameter ≥device diameter+0.25 mm	418/1,199 (34.9%)	270/1,205 (22.4%)	<0.001
Device success	1,149/1,243 (92.4%)	1,175/1,214 (96.8%)	<0.001
Successful delivery of device	1,181/1,243 (95.0%)	1,204/1,214 (99.2%)	<0.001
Residual stenosis <30%	1,204/1,243 (96.9%)	1,183/1,214 (97.4%)	0.40
Procedure success	749/848 (88.3%)	772/820 (94.1%)	<0.001
TIMI flow post procedure — Flow 0	2/1,243 (0.2%)	0/1,214 (0.0%)	0.80
TIMI flow post procedure — Flow 1	2/1,243 (0.2%)	1/1,214 (0.1%)	
TIMI flow post procedure — Flow 2	8/1,243 (0.6%)	12/1,214 (1.0%)	
TIMI flow post procedure — Flow 3	1,231/1,243 (99.0%)	1,201/1,214 (98.9%)	
Angiographic analysis (core laboratory)			
Pre-procedure			
Reference vessel diameter, mm	2.51 (0.50) (n=1,123)	2.49 (0.49) (n=1,109)	0.21
Minimum lumen diameter, mm	0.89 (0.49) (n=1,148)	0.89 (0.50) (n=1,129)	0.74
Diameter stenosis	64.3% (18.4) (n=1,148)	63.7% (18.7) (n=1,129)	0.41
Lesion length**, mm	12.46 (6.96) (n=986)	12.46 (6.96) (n=973)	0.23
Post-procedure			
In-device measurements			
Reference vessel diameter, mm	2.63 (0.45) (n=1,161)	2.66 (0.42) (n=1,159)	0.07
Minimum lumen diameter, mm	2.21 (0.41) (n=1,161)	2.32 (0.39) (n=1,159)	<0.001
Diameter stenosis	15.5% (8.6) (n=1,161)	12.10% (6.44) (n=1,159)	<0.001
Acute gain, mm	1.33 (0.57) (n=1,123)	1.42 (0.53) (n=1,111)	<0.001
In-segment measurements			
Reference vessel diameter, mm	2.55 (0.46) (n=1,161)	2.57 (0.44) (n=1,159)	0.38
Minimum lumen diameter, mm	2.01 (0.42) (n=1,161)	2.02 (0.44) (n=1,159)	0.61
Diameter stenosis	21.0% (9.7) (n=1,161)	21.3% (10.3) (n=1,159)	0.52
Acute gain, mm	1.13 (0.56) (n=1,123)	1.13 (0.55) (n=1,111)	0.98

Data are median (interquartile range), mean (standard deviation) or count (percentage). * In-device reference vessel diameter. ** ST-elevation myocardial infarction and chronic total occlusion lesions were excluded. BVS: bioresorbable vascular scaffold; EES: everolimus-eluting stent; IVUS: intravascular ultrasound; LAD: left anterior descending artery; LCX: left circumflex artery; OCT: optical coherence tomography; OIT: optimal implantation technique; PCI: percutaneous coronary intervention; QCA: quantitative coronary analysis; RCA: right coronary artery; RVD: reference vessel diameter; SYNTAX: Synergy Between PCI With Taxus and Cardiac Surgery; TIMI: Thrombolysis In Myocardial Infarction

Table 3. Clinical outcomes at one year.

	BVS (n=848)	EES (n=822)	Hazard ratio (95% CI)	*p*-value
Primary outcome				
Target lesion failure*	5.1% (43)	4.2% (34)	1.24 (0.79-1.94)	0.35
Separate endpoints for the primary outcomes				
Cardiac death	0.6% (5)	0.1% (1)	4.87 (0.57-41.7)	0.11
Target vessel myocardial infarction	4.0% (34)	2.1% (17)	1.96 (1.10-3.51)	0.020
Clinically indicated target lesion revascularisation	2.4% (20)	2.7% (22)	0.89 (0.48-1.62)	0.69
Secondary outcomes				
Target vessel failure**	6.3% (53)	4.8% (39)	1.33 (0.88-2.02)	0.17
Any death	0.7% (6)	0.6% (5)	1.17 (0.36-3.83)	0.80
Any myocardial infarction	4.0% (34)	2.4% (20)	1.67 (0.96-2.90)	0.07
Target vessel myocardial infarction	4.0% (34)	2.1% (17)	1.96 (1.10-3.51)	0.020
Periprocedural	2.0% (17)	1.2% (10)	1.65 (0.76-3.61)	0.20
Spontaneous	2.0% (17)	0.9% (7)	2.38 (0.99-5.73)	0.046
Non-target vessel myocardial infarction	0.0% (0)	0.5% (4)	NA	0.043
Any revascularisation	7.0% (59)	7.4% (60)	0.96 (0.67-1.37)	0.82
Target lesion revascularisation	3.7% (31)	3.6% (29)	1.05 (0.63-1.73)	0.86
Clinically indicated	2.4% (20)	2.7% (22)	0.89 (0.48-1.62)	0.69
Non-clinically indicated	1.8% (15)	1.5% (12)	1.22 (0.57-2.60)	0.61
Target vessel revascularisation	4.8% (40)	4.5% (37)	1.06 (0.68-1.65)	0.81
Clinically indicated	3.6% (30)	3.7% (30)	0.97 (0.59-1.61)	0.91
Non-clinically indicated	2.1% (18)	1.6% (13)	1.35 (0.66-2.76)	0.41
Non-target vessel revascularisation	2.5% (21)	3.3% (27)	0.75 (0.43-1.34)	0.33
Thrombosis endpoints				
Definite device thrombosis	1.9% (16)	0.6% (5)	3.12 (1.14-8.51)	0.019
Probable device thrombosis	0.1% (1)	0.0% (0)	NA	0.32
Possible device thrombosis	0.2% (2)	0.1% (1)	1.95 (0.18-21.54)	0.58
Definite or probable device thrombosis	2.0% (17)	0.6% (5)	3.31 (1.22-8.98)	0.012
Acute (≤24 hours)	0.5% (4)	0.4% (3)	1.29 (0.29-5.77)	0.74
Subacute (>24 hours to 30 days)	1.3% (11)	0.1% (1)	10.71 (1.38-82.99)	0.004
Late (30 days to one year)	0.5% (4)	0.1% (1)	3.91 (0.44-34.98)	0.19

Data are Kaplan-Meier estimates. *Cardiac death, target vessel myocardial infarction, or clinically indicated target lesion revascularisation. ** Cardiac death, target vessel myocardial infarction, or clinically indicated target vessel revascularisation. BVS: bioresorbable vascular scaffold; CI: confidence interval; EES: everolimus-eluting stent; NA: not applicable

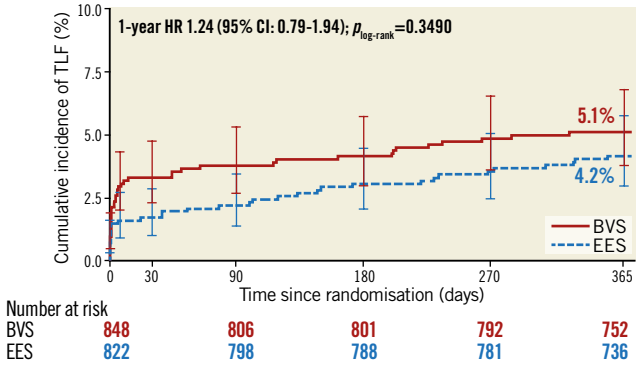


Figure 2. *Kaplan-Meier plot for the primary endpoint. Kaplan-Meier curves show the cumulative incidence of target lesion failure. BVS: bioresorbable vascular scaffold; CI: confidence interval; EES: everolimus-eluting stent; HR: hazard ratio; TLF: target lesion failure*

Additional *post hoc* analyses with respect to the TLF and definite and probable device thrombosis rates stratified by OIT did not show significant treatment-by-subgroup interactions **(Supplementary Figure 1A, Supplementary Figure 1B)**. The definite device thrombosis rates did not differ significantly between lesions with or without a correct vessel sizing, though a combined proximal and distal oversizing of the scaffold showed a high event rate **(Supplementary Figure 2)**. Results of quality of life reported at follow-up are shown in **Supplementary Table 7**.

Discussion

In the present large-scale, randomised trial, the BVS was non-inferior to the EES in terms of TLF at one year in a population at high risk of restenosis. Moreover, the treatment effect on TLF was similar across different subgroups, including risk groups defined according to lesion complexity or baseline

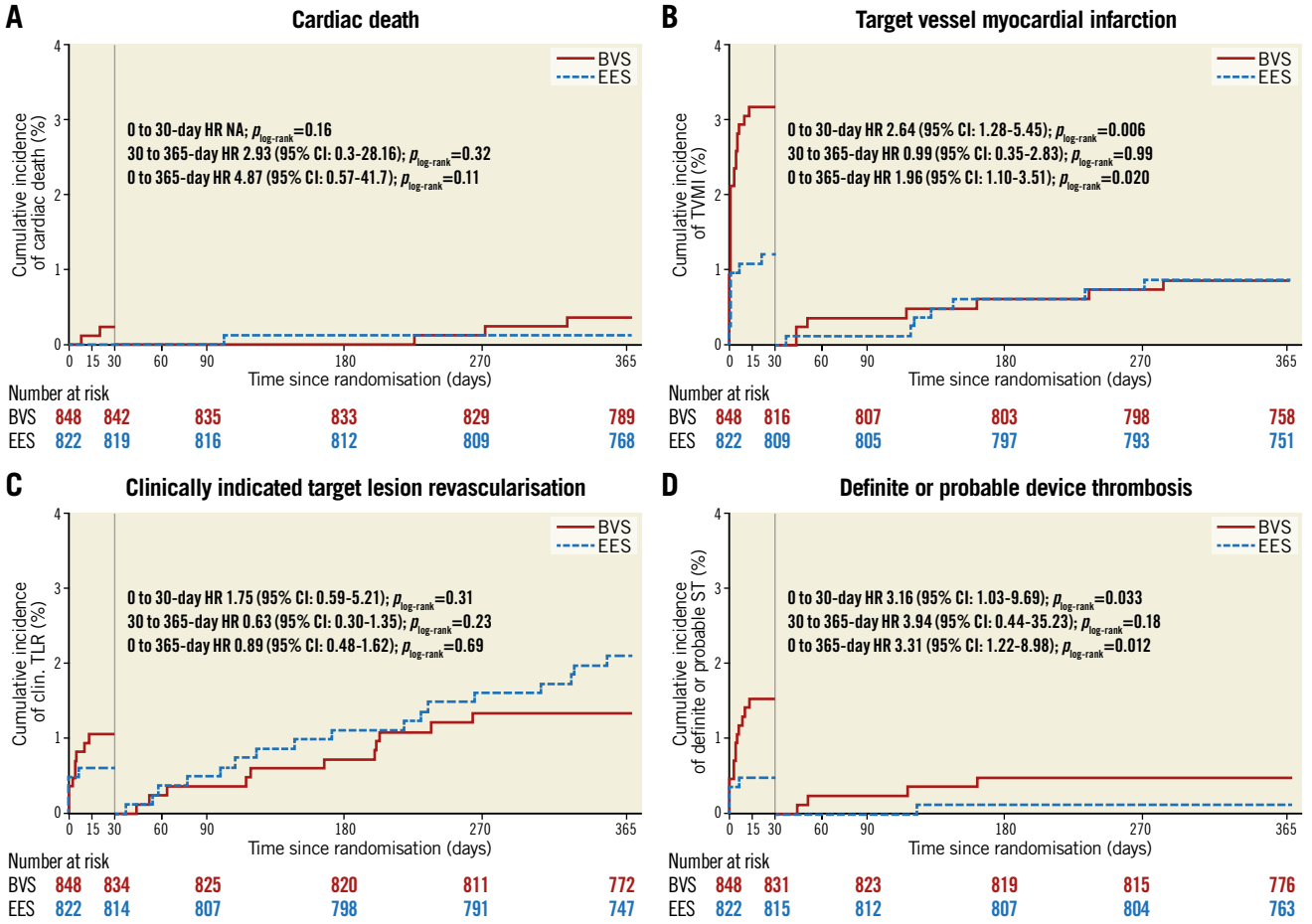


Figure 3. *Kaplan-Meier plots for the components of the primary endpoint and definite/probable device thrombosis. A) Cardiac death. B) Target vessel myocardial infarction. C) Clinically indicated target lesion revascularisation. D) Definite/probable device thrombosis. BVS: bioresorbable vascular scaffold; CI: confidence interval; EES: everolimus-eluting stent; HR: hazard ratio; NA: not applicable; ST: stent thrombosis; TLR: target lesion revascularisation; TVMI: target vessel myocardial infarction*

characteristics. Although non-inferiority of the primary endpoint was met, definite or probable device thrombosis and TVMI rates were significantly higher in the BVS group compared with the EES group, which resulted in premature cessation of recruitment to the study.

Compared with the one-year results of the ABSORB III trial, the device thrombosis rate in the BVS group was slightly higher in the present study (2.0% vs 1.5%), whilst it was similar in the EES group (0.6% vs 0.7%). The observed higher device thrombosis rate in this trial is probably attributable to the complexity of patients and lesions included. Furthermore, device thrombosis events occurred predominantly during the early phase after implantation, implicating procedure-related causes. According to lessons learned from previous studies, a mismatch between vessel size and device size is a predictor of early and late scaffold thrombosis[8]. Furthermore, the meta-analysis on ABSORB trials incriminated BVS for vessels with a diameter of less than 2.5 mm[9]. Theoretically, these problems might be reduced by implementing an optimal implantation technique. The COMPARE-ABSORB study excluded vessels smaller than 2.25 mm in the original study design, then amended the exclusion criterion of minimal vessel size to 2.5 mm during enrolment because of these safety concerns. Investigators were also advised to estimate the vessel size by quantitative coronary analysis or intravascular imaging if the vessel size was less than 2.75 mm by visual assessment. Nevertheless, the *post hoc* angiographic analysis performed by the core lab showed that 40.9% of lesions in the BVS group had a post-procedural RVD smaller than 2.5 mm. These findings emphasise the importance of appropriate vessel sizing, which could not be truly achieved by visual assessment alone. Because underestimation of vessel size by QCA is a limitation of angiography[10], mandatory intravascular imaging guidance should be explored in future when implanting BVS in order to enhance safety. On the other hand, only a minority of lesions (33.7%) fit the OIT criteria due to sizing mismatch (the lesion segment not fitting any scaffold diameter due to incompatibility of proximal and distal reference requirements in sizing for a specific scaffold diameter). In the BVS group, 11.5% of lesions had both proximal and distal reference diameters within the range of correct sizing, which was defined as device size ± 0.25 mm, 27.1% had either

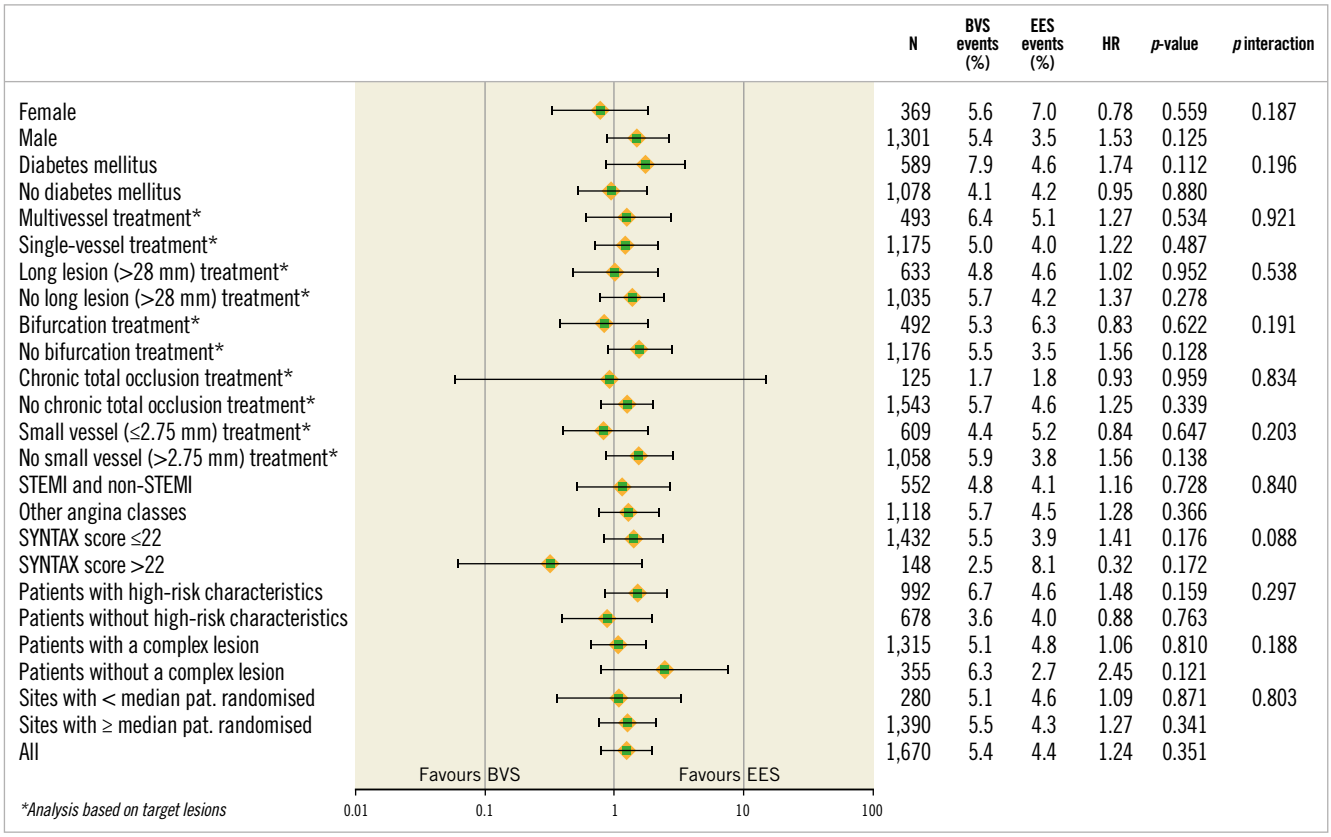


Figure 4. *Stratified analyses of the primary endpoint across subgroups. Hazard ratio with 95% CI and p-value results were from Cox proportional hazards analysis. BVS: bioresorbable vascular scaffold; EES: everolimus-eluting stent; HR: hazard ratio; N: number of patients; STEMI: ST-elevation myocardial infarction*

proximal or distal reference diameter within the range but not both, and 61.4% had both reference diameters out of the range **(Supplementary Table 8)**. This demonstrates that correct sizing with BVS according to the OIT criteria is difficult to achieve in the majority of lesions with one BVS. Further improvements to the device such as thinner and smaller struts, better conformability and radial strength are therefore indispensable.

In the COMPARE-ABSORB trial, high-pressure post-dilatation with a non-compliant balloon was mandated by the protocol. Nevertheless, based on angiographic analysis, acute gain and established post-procedural minimal lumen diameter in the BVS arm did not match those of the EES arm, although the absolute differences between arms appeared to be smaller than or similar to the differences observed in previous trials **(Supplementary Table 9)**. This unclosed gap in acute performance between the devices could be a contributory factor for early scaffold thrombosis with BVS compared with EES.

Recently, the five-year results of the ABSORB II trial showed a significant difference in TLF in favour of EES compared to BVS (Serruys PW. The 5-year Clinical Outcomes of the ABSORB II Trial: First Randomized Comparison between the Absorb Everolimus Eluting Bioresorbable Vascular Scaffold and the XIENCE Everolimus Eluting Stent. Presented at Transcatheter Cardiovascular Therapeutics, San Diego, CA, USA, 22 September 2018). This significant difference in TLF was driven by events that had occurred within the first three years. No scaffold thrombosis was observed between three and five years. Therefore, extension of follow-up duration from five to seven years in this study is necessary to determine whether more normalised coronary function and physiology after complete scaffold bioresorption will provide a clinical advantage for BVS over metallic DES.

Limitations

First of all, despite the fact that optimal implantation technique was incorporated in the study design, on-line QCA or intravascular imaging was suggested, but not mandatory, for vessel sizing. Secondly, the one-year TLF rates for both devices were remarkably lower than anticipated and therefore the non-inferiority margin of 4.5% was relatively wide. However, the non-inferiority margin was in line with the ABSORB III study, in which the U.S. Food and Drug Administration was consulted. In the study design of ABSORB III[11], the assumed rate of the primary endpoint was 7.0%. The ratio of non-inferiority margin to assumed event rate was 64%. In our study, the assumed event rate was 8.5% and the ratio of non-inferiority margin to assumed event rate was 53%, which was slightly stricter than that in ABSORB III. Thirdly,

because of significant differences in predilatation and post-dilatation rates between the stent arms, we cannot exclude an influence on outcomes caused solely by differences in implantation technique. Fourthly, bleeding event was not a pre-specified endpoint and thus not reported in this paper. Lastly, the study results apply only to the BVS, which is no longer commercially available for use in clinical practice. Nevertheless, the COMPARE-ABSORB study was the first trial to investigate the performance of BVS in complex lesions and high-risk patients.

Conclusions

In the present large-scale randomised trial of patients at high risk of restenosis, BVS was non-inferior to EES for the primary endpoint, TLF at one year. BVS carried a higher risk for device thrombosis and TVMI, especially in the early stages after implantation.

Impact on daily practice

This trial showed that using an optimal implantation technique did not prevent an increase of device thrombosis with BVS at one year. Further exploration of the long-term benefit after BVS implantation and device modification is warranted.

Appendix. Authors' affiliations

1. Department of Cardiology, Maasstad Hospital, Rotterdam, the Netherlands; 2. Thoraxcenter, Erasmus University Medical Center, Rotterdam, the Netherlands; 3. Division of Cardiology, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan; 4. Ramsay Générale de Santé, ICPS, Hôpital Jacques Cartier, Massy, France; 5. Department of Interventional Cardiology, Royal Papworth Hospital, Cambridge, United Kingdom; 6. Center of Cardiology, Cardiology I, University Medical Center of the Johannes Gutenberg-University Mainz, and DZHK Standort Rhein-Main, Mainz, Germany; 7. Cardiovascular Research Center OLV Hospital, Aalst, Belgium; 8. Department of Advanced Biomedical Science, University Federico II, Naples, Italy; 9. Interventional Cardiology Unit, Department of Cardiac, Thoracic and Vascular Sciences, University of Padua, Padua, Italy; 10. Cardiocenter, Third Faculty of Medicine, University Hospital Kralovske Vinohrady, Charles University, Prague, Czech Republic; 11. Department of Cardiology, Universitätsklinikum Erlangen, Erlangen, Germany; 12. 2nd Department of Cardiology, Jagiellonian University Medical College, Krakow, Poland; 13. Hospital Clinico San Carlos IDISSC, Complutense University, Madrid, Spain; 14. Department of Cardiology, Miedziowe Centrum Zdrowia, Lubin, Poland; 15. Herzzentrum Segeberger Kliniken GmbH, Bad Segeberg, Germany; 16. Heart Center Leipzig at the University of Leipzig, Leipzig, Germany; 17. Facoltà di Medicina e Chirurgia, Università degli Studi di Napoli "Federico II", Naples, Italy; 18. Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands; 19. Cardiovascular European Research Center, Massy, France; 20. Cardialysis B.V., Rotterdam, the Netherlands; 21. Department of Cardiology, Radboud UMC, Nijmegen, the Netherlands.

Acknowledgements

All authors are indebted to Prof. Patrick W. Serruys (Imperial College London, London, UK) as a senior consultant to the trial and to Mrs Ute Windhovel (CERC, Massy, France) and Mrs Ria van Vliet (Maasstad CardioVascular Research, Rotterdam, the Netherlands) for assistance in coordinating the trial.

Funding

The trial sponsor was Maasstad Hospital, Rotterdam, the Netherlands, which received an institutional grant from Abbott Vascular. The grant giver was not involved in the conduct, data management, or data analysis of the trial, conducted by CERIC, Geneva, Switzerland, which contracted CERC and Cardialysis as clinical research organisation (CRO) and core lab.

Conflict of interest statement

P.C. Smits has received institutional research grants and speaker fees from Abbott Vascular, St. Jude Medical and Terumo. B. Chevalier has received grants and personal fees from Abbott Vascular during the conduct of the study, and personal fees from Medtronic, Terumo, and Biotronik, and is a shareholder and general director of CERC (CRO), outside the submitted work. N. West has received speaker fees from Abbott Vascular. T. Gori has received speaker fees from Abbott Vascular. E. Barbato has received personal fees from Boston Scientific, Abbott Vascular, Opsens Medical, and GE Healthcare, outside the submitted work. V. Kočka has received personal fees from Abbott Vascular, Medtronic, B Braun, and Terumo, outside the submitted work. J. Tijssen has received grants and personal fees from Abbott Vascular during the conduct of the study. M.C. Morice is the CEO of CERC, the CRO which conducted the trial. Y. Onuma was an advisory board member of Abbott Vascular. R.J. van Geuns reports grants and personal fees from Abbott Vascular, outside the submitted work. G. Tarantini reports personal fees from St. Jude Medical, personal fees from Edwards Lifesciences, Boston Scientific, Abbott Vascular, and AstraZeneca, outside the submitted work. J. Escaned reports consultancies and/or speaker fees at educational events for Abbott, Biotronik, Boston Scientific, Medtronic, Opsens, OrbusNeich, and Philips Healthcare. The other authors have no conflicts of interest to declare.

References

1. Ormiston JA, Serruys PW, Regar E, Dudek D, Thuesen L, Webster MW, Onuma Y, Garcia-Garcia HM, McGreevy R, Veldhof S. A bioabsorbable everolimus-eluting coronary stent system for patients with single de-novo coronary artery lesions (ABSORB): a prospective open-label trial. *Lancet.* 2008;371:899-907.

2. Serruys PW, Chevalier B, Dudek D, Cequier A, Carrie D, Iniguez A, Dominici M, van der Schaaf RJ, Haude M, Wasungu L, Veldhof S, Peng L, Staehr P, Grundeken MJ, Ishibashi Y, Garcia-Garcia HM, Onuma Y. 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.* 2015;385:43-54.

3. Ellis SG, Kereiakes DJ, Metzger DC, Caputo RP, Rizik DG, Teirstein PS, Litt MR, Kini A, Kabour A, Marx SO, Popma JJ, McGreevy R, Zhang Z,

Simonton C, Stone GW; ABSORB III Investigators. Everolimus-Eluting Bioresorbable Scaffolds for Coronary Artery Disease. *N Engl J Med.* 2015; 373:1905-15.

4. Felix CM, van den Berg VJ, Hoeks SE, Fam JM, Lenzen M, Boersma E, Smits PC, Serruys PW, Onuma Y, van Geuns RJM. Mid-term outcomes of the Absorb BVS versus second-generation DES: A systematic review and meta-analysis. *PLoS One.* 2018;13:e0197119.

5. Stone GW, Abizaid A, Onuma Y, Seth A, Gao R, Ormiston J, Kimura T, Chevalier B, Ben-Yehuda O, Dressler O, McAndrew T, Ellis SG, Kereiakes DJ, Serruys PW. Effect of Technique on Outcomes Following Bioresorbable Vascular Scaffold Implantation: Analysis From the ABSORB Trials. *J Am Coll Cardiol.* 2017;70:2863-74.

6. Kufner S, Joner M, Thannheimer A, Hoppmann P, Ibrahim T, Mayer K, Cassese S, Laugwitz KL, Schunkert H, Kastrati A, Byrne RA; ISAR-TEST 4 (Intracoronary Stenting and Angiographic Results: Test Efficacy of 3 Limus-Eluting Stents) Investigators. Ten-Year Clinical Outcomes From a Trial of Three Limus-Eluting Stents With Different Polymer Coatings in Patients With Coronary Artery Disease. *Circulation.* 2019;139:325-33.

7. Chang CC, Onuma Y, Achenbach S, Barbato E, Chevalier B, Cook S, Dudek D, Escaned J, Gori T, Kočka V, Tarantini G, West NEJ, Morice MC, Tijssen JGP, van Geuns RJ, Smits PC; COMPARE ABSORB trial investigators. Absorb Bioresorbable Scaffold Versus Xience Metallic Stent for Prevention of Restenosis Following Percutaneous Coronary Intervention in Patients at High Risk of Restenosis: Rationale and Design of the COMPARE ABSORB Trial. *Cardiovasc Revasc Med.* 2019;20:577-82.

8. Gori T, Weissner M, Gonner S, Wendling F, Ullrich H, Ellis S, Anadol R, Polimeni A, Münzel T. Characteristics, Predictors, and Mechanisms of Thrombosis in Coronary Bioresorbable Scaffolds: Differences Between Early and Late Events. *JACC Cardiovasc Interv.* 2017;10:2363-71.

9. Ali ZA, Serruys PW, Kimura T, Gao R, Ellis SG, Kereiakes DJ, Onuma Y, Simonton C, Zhang Z, Stone GW. 2-year outcomes with the Absorb bioresorbable scaffold for treatment of coronary artery disease: a systematic review and meta-analysis of seven randomised trials with an individual patient data substudy. *Lancet.* 2017;390:760-72.

10. Okamura T, Onuma Y, Garcia-Garcia HM, van Geuns RJ, Wykrzykowska JJ, Schultz C, van der Giessen WJ, Ligthart J, Regar E, Serruys PW. First-in-man evaluation of intravascular optical frequency domain imaging (OFDI) of Terumo: a comparison with intravascular ultrasound and quantitative coronary angiography. *EuroIntervention.* 2011;6:1037-45.

11. Kereiakes DJ, Ellis SG, Popma JJ, Fitzgerald PJ, Samady H, Jones-McMeans J, Zhang Z, Cheong WF, Su X, Ben-Yehuda O, Stone GW. Evaluation of a fully bioresorbable vascular scaffold in patients with coronary artery disease: design of and rationale for the ABSORB III randomized trial. *Am Heart J.* 2015;170:641-51.

Supplementary data

Supplementary Appendix 1. Methods.

Supplementary Figure 1. Stratified analyses according to optimal implantation technique.

Supplementary Figure 2. Distribution of correct sizing and definite device thrombosis in the BVS group.

Supplementary Table 1. Number of patients randomised per site.

Supplementary Table 2. Inclusion and exclusion criteria.

Supplementary Table 3. Study organisation.

Supplementary Table 4. Study endpoints and definitions.

Supplementary Table 5. Definition of optimal implantation techniques.

Supplementary Table 6. Dual antiplatelet treatment.

Supplementary Table 7. Quality of life reported at one-year follow-up.

Supplementary Table 8. Correct sizing according to post-procedural quantitative angiographic analysis.

Supplementary Table 9. Angiographic analysis in bioresorbable vascular scaffold trials.

The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-19-01079

Supplementary data

Supplementary Appendix 1. Methods

Randomisation

Patients were 1:1 randomly assigned to receive either BVS (Absorb™; Abbott Vascular, Santa Clara, CA, USA) or EES (XIENCE; Abbott Vascular). Randomisation was performed after successful passage of the guidewire across the first target lesion. Randomisation was stratified by study site and study arm. Each site had its own dedicated randomisation lists for both arms, respecting the 1:1 ratio. Each randomisation list was built dynamically by the Electronic Data Capture (EDC) system whenever a new study site was declared within the system. The algorithm used when building a randomisation list was based on the standard algorithm of Blocked Randomization with Randomly Selected Block Sizes.

Procedures

A dedicated implantation technique was defined in the protocol: predilatation using non-compliant balloons of the same diameter as the reference vessel diameter and post-scaffold high-pressure (≥16 atm) dilatation were mandatory in the BVS group. Scaffold to vessel sizing was based on the instructions for use allowing a margin of plus or minus 0.25 between nominal device diameter and visual vessel reference diameter as established by the operator.

Study hypotheses and endpoints

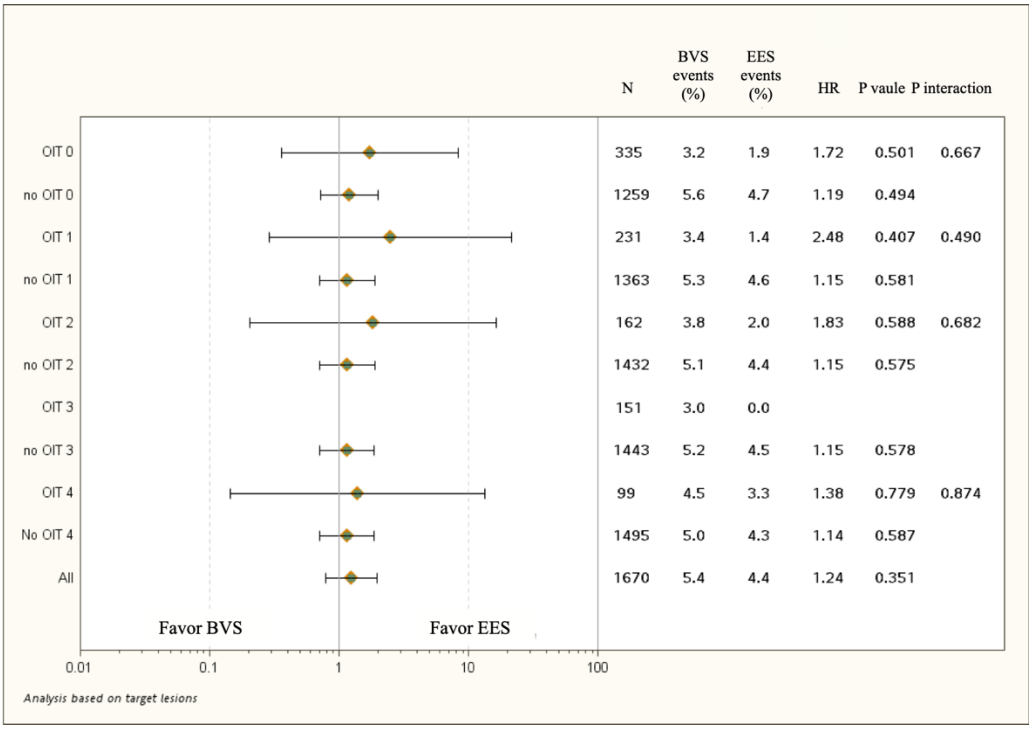
The short-term primary hypothesis of the study was non-inferiority of the BVS group compared with the EES group in terms of the primary endpoint, TLF (a composite of cardiac death, myocardial infarction in the target vessel territory and clinically indicated target lesion

revascularisation) at one year. Additional study endpoints and definitions are presented in **Supplementary Table 4**.

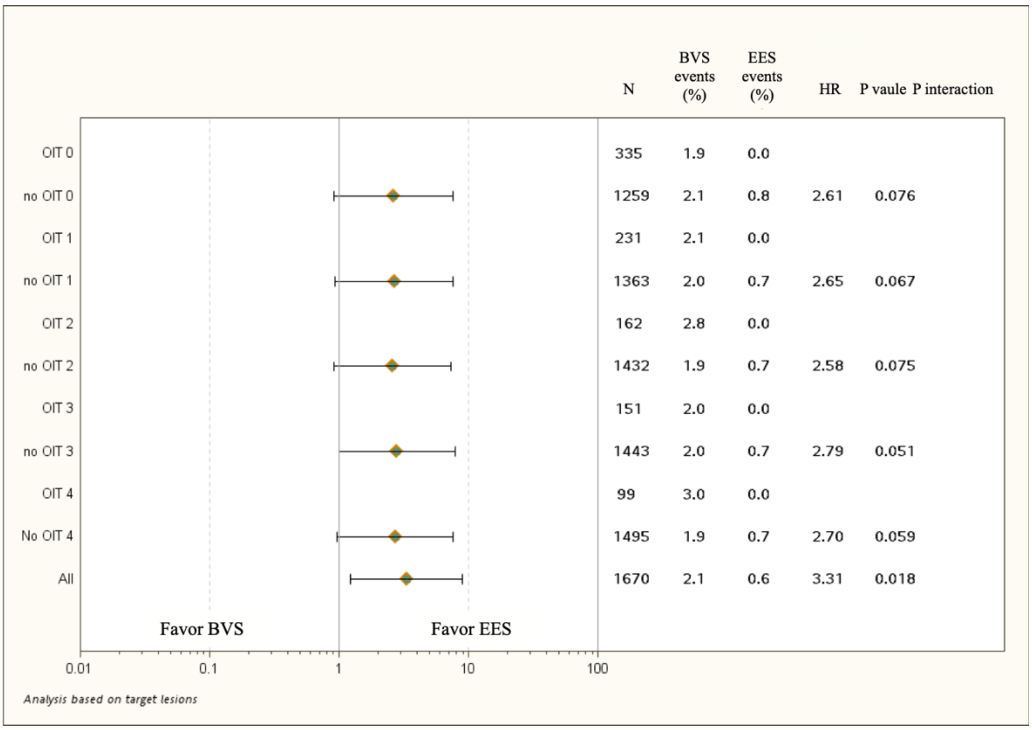
Protocol revisions

In the original protocol, the long-term hypothesis was the superiority of BVS over EES in TLF between one and five years. During enrolment for the study, follow-up results of early randomised trials suggested that the potential benefits of BVS might only become apparent beyond three years, after completion of bioresorption. Therefore, the timing of landmark analysis of the long-term hypothesis was adjusted to between three and seven years. The other change in the protocol was the inclusion criteria for small vessels. The initial protocol allowed inclusion of target vessels with reference diameter equal to 2.25 mm on visual estimation. However, because of evolving safety concerns regarding use of BVS in small vessels, the Steering Committee decided to exclude lesions with reference vessel diameter less than 2.5 mm and recommended additional quantitative sizing tools for vessels below 2.75 mm [7]. Owing to an observed second phase of increased risk of scaffold thrombosis between two and three years [8], the Steering Committee advised prolongation of the duration of dual antiplatelet treatment from the original 12 months to 36 months in the BVS group and the timing of landmark analysis of the long-term hypothesis was adjusted to between three and seven years. On 31 August 2017, the Steering Committee stopped enrolment prematurely based on the recommendation of the DSMB.

A.

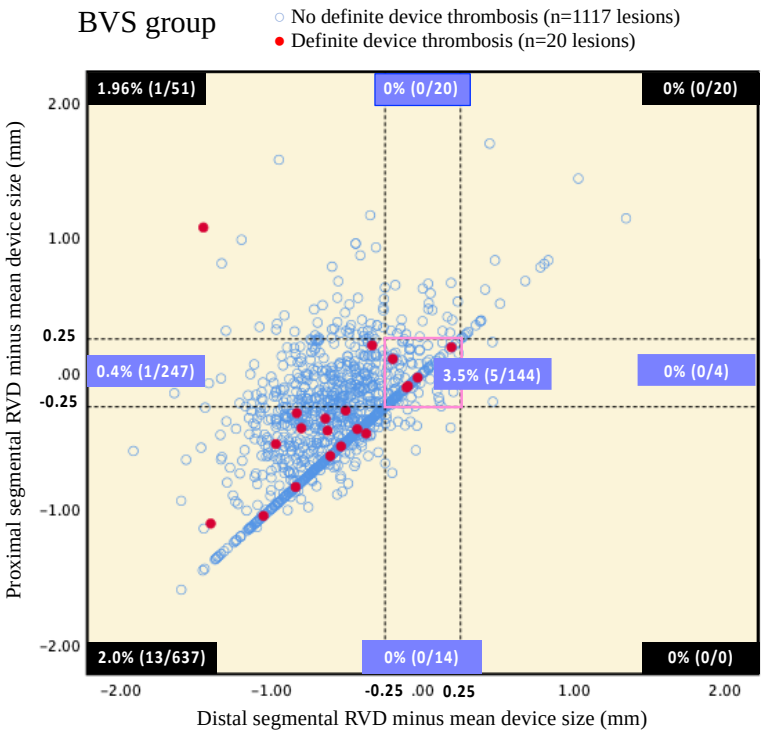


B.



Supplementary Figure 1. Stratified analyses according to optimal implantation technique. A) Target lesion failure. B) Definite/probable device thrombosis.

BVS: bioresorbable vascular scaffold; EES: everolimus-eluting stent; HR: hazard ratio; N: number of patients; OIT: optimal implantation technique



Supplementary Figure 2. Distribution of correct sizing and definite device thrombosis in the BVS group.

Distribution of proximal and distal segment reference vessel diameters minus the device size in lesions with or without definite device thrombosis is shown. Correct sizing is the mean diameter of the distal or proximal segment within the range of the device size±0.25 mm. The differences between the proximal/distal segment and device size are plotted on the y-axis and x-axis, respectively. The definite device thrombosis rates of different quadrants/rectangles are shown. The definite device thrombosis rates had no significant differences between lesions with or without a correct vessel sizing (1.36% [6/439] vs 2.0% [14/698], p=0.494).

BVS: bioresorbable vascular scaffold; RVD: reference vessel diameter

Supplementary Table 1. Number of patients randomised per site (total number of patients: 1,670).

Site name	PI	Location	Number of patients enrolled
MAASSTAD ZIEKENHUIS	P. SMITS	ROTTERDAM	201
MIEDZIOWE CENTRUM ZDROWIA SA	A. WLODARCZAK	LUBIN	178
HÔPITAL PRIVÉ JACQUES CARTIER	B. CHEVALIER	MASSY	99
PAPWORTH HOSPITAL	S. HOOLE	CAMBRIDGE	89
UNIVERSITATSMEDIZIN MAINZ	T. GORI	MAINZ	72
SEGEBERGER KLINIKEN	M. ABDEL-WAHAB	BAD SEGEBERG	67
CARDIOVASCULAR CENTER AALST OLV HOSPITAL	E. BARBATO	AALST	66
UNIVERSITA DEGLI STUDI DI NAPOLI FEDERICO	G. ESPOSITO	NAPLES	62
ERASMUS MEDISCH CENTRUM	R. VAN GEUNS	ROTTERDAM	55
FREEMAN HOSPITAL	M. EGRED	NEWCASTLE	50
AZIENDA OSPEDALIERA DI PADOVA	G. TARANTINI	PADUA	47
HOSPITAL DEL MAR	B. VAQUERIZO MONTILLA	BARCELONA	47
CARDIOCENTRE, UNIVERSITY HOSPITAL KRALOVS	V. KOCKA	PRAGUE	43
ROYAL BOURNEMOUTH HOSPITAL	P. O'KANE	BOURNEMOUTH	39
AMERICAN HEART OF POLAND	P. BUSZMAN	CHRZANOW	36
UNIVERSITY HOSPITAL BRNO	P. KALA	BRNO	34
UNIVERSITATSKLINIKUM ERLANGEN	S. ACHENBACH	ERLANGEN	33
CENTRAL MILITARY HOSPITAL	M. MALY	PRAGUE	30
AMERICAN HEART OF POLAND	K. MILEWSKI	TYCHY	30
CHARITÉ CAMPUS BENJAMIN FRANKLIN	U. LANDMESSER	BERLIN	29
ALBERT SCHWEITZER HOSPITAL	S. IJSSELMUIDEN	DORDRECHT	29
ELISABETHKRANKENHAUS ESSEN	C. NABER	ESSEN	28
CATHARINA ZIEKENHUIS	P. TONINO	EINDHOVEN	26
CHU CLERMONT-FERRAND	P. MOTREFF	CLERMONT FERRAND	25
UNIVERSITATSKLINIKUM GIESSEN	H. NEF	GIESSEN	25
UNIVERSITY HOSPITAL KRAKOW	D. DUDEK	KRAKOW	25

CLINIQUE RHÔNE DURANCE	J. SAINSOUS	AVIGNON	24
HOSPITAL CLINIC	S. BRUGALETTA	BARCELONA	21
CHR DE LA CITADELLE	G. SAAD	LIEGE	19
KERCKHOFF KLINIK	C. LIEBETRAU	BAD NAUHEIM	19
UNIVERSITARIA DI PARMA	A. MENOZZI	PARMA	17
CLINIQUE PASTEUR	J. FAJADET	TOULOUSE	15
OSPEDALE SAN GIACOMO	C. CERNETTI	CASTELFRANCO VENETO	13
OSPEDALE PAPA GIOVANNI XXIII	O. VALSECCHI	BERGAMO	12
UNIVERSITATSKLINIKUM KOLN	T. RUDOLPH	KOLN	11
AMPHIA ZIEKENHUIS	M. MEUWISSEN	BREDA	11
HOSPITAL CLINICO SAN CARLOS	J. ESCANED	MADRID	11
UNIVERSITA DEGLI STUDI MAGNA GRAECIA	C. INDOLFI	CATANZARO	6
AZIENDA OSPEDALIERA BROTZU	B. LOI	CAGLIARI	6
UZ LEUVEN	W. DESMET	LEUVEN	4
CLINIQUE SAINT HILAIRE	R. KONING	ROUEN	4
KLINIKUM DER UNIVERSITÄT MÜNCHEN	J. MEHILLI	MUNCHEN	3
UNIVERSITÄTSKLINIKUM LEIPZIG	P. LURZ	LEIPZIG	3
ARNAS CIVICO PALERMO	M. CARUSO	PALERMO	3
HOSPITAL UNIVERSITARIO MARQUES DE VALD	J.M. DE LA TORRE HERNANDEZ	SANTANDER	3

Supplementary Table 2. Inclusion and exclusion criteria (latest protocol version).

Inclusion criteria

Patients aged 18-75 years with at least one of the following:

1. High-risk characteristics for restenosis

- Medically treated diabetes (oral medication or insulin) and/or multivessel disease of which more than one de novo target lesion to be treated with the study scaffold/stent.

2. Complex target lesion

Single de novo target lesion satisfying at least one of the following:

- Lesion length >28 mm
- Small vessels: target lesion reference vessel diameter ≥2.5 mm and ≤2.75 mm
- Lesion with pre-existing total occlusion (preprocedural TIMI=0)
- Bifurcation with single stent strategy

Exclusion criteria

1. Age <18 years, or >75 years
2. Patients incapable of giving informed consent
3. Patients under judicial protection, tutorship or curatorship
4. Known comorbidities which make patients unable to complete seven years of follow-up
5. Female of childbearing potential (and last menstruation within the last 12 months), who did not undergo tubal ligation, ovariectomy or hysterectomy
6. Pregnant woman
7. Breastfeeding woman
8. Known intolerance to aspirin, heparin, PLLA, everolimus, contrast material
9. Cardiogenic shock (Killip >2)
10. PCI with implantation of stents/scaffolds within previous 30 days
11. Active bleeding or coagulopathy
12. Subject is currently participating in another clinical trial that has not yet completed its primary endpoint
13. Renal insufficiency (GFR <45 ml/min)
14. Life expectancy <7 years
15. Known non-adherence to dual antiplatelet therapy
16. Patients on oral anticoagulation therapy (including novel oral anticoagulant such as dabigatran, rivaroxaban, apixaban and edoxaban)
17. Known impaired left ventricular function (left ventricular ejection fraction <30%)
18. Patients at high bleeding risk who are not suitable for long-term DAPT
19. Following lesion characteristics:
    - Target lesion with reference vessel diameter (RVD) <2.50 mm and >4.0 mm
    - STEMI with RVD of >3.5 mm of the culprit target lesion
    - Target lesion with in-stent/scaffold thrombosis
    - Graft lesions as target lesions
    - Lesion involving left main trunk
    - Severe tortuosity of target vessel
    - Aorto-ostial lesion(s)
    - In-scaffold/in-stent restenosis
    - Bifurcation target lesion with intended two stent/scaffold strategy
20. Non-target lesion and target lesion in the same epicardial coronary artery (right coronary artery, left circumflex artery or left anterior descending artery)

Supplementary Table 3. Study organisation.

Principal investigator
Pieter C. Smits
Co-principal investigator
Robert-Jan van Geuns
Executive Committee
Pieter C. Smits Robert-Jan van Geuns Marie-Claude Morice Yoshinobu Onuma
Steering Committee members
Pieter C. Smits Robert-Jan van Geuns Jan Tijssen Victor Kocka Dariusz Dudek Bernard Chevalier Tommaso Gori Stephan Achenbach Giuseppe Tarantini Emanuele Barbato Nick West Javier Escaned Marie-Claude Morice Yoshinobu Onuma
Data Safety Monitoring Board (DSMB)
Stefan James (chairman) Eric Boersma Michel Bertrand
Safety reporting
The CRO CERC (7 rue du Théâtre, 91300 Massy, France) is responsible for entering all serious adverse events (SAEs) including the assessment regarding relationship to the device (SADEs) or to the procedure from the eCRF in a safety database and for reporting these SAEs and SADEs according to the MEDDEV 2.7/3 guidelines and national requirements.
Data management, site management and monitoring
Data management, site management and monitoring were conducted by the clinical research organisation (CRO) CERC (7, rue du theatre, 91300 Massy, France).
Clinical Event Adjudication Committee
Eugene McFadden Pascal Vranckx Joanna Wykrzykowska Ernest Spitzer
Core laboratories
The independent angiography and intravascular ultrasound imaging Core Lab at Cardialysis (Cardialysis B.V., PO Box 2125, 3000 CC Rotterdam, the Netherlands) analysed angiograms obtained during and/or before procedure. Members of the Angiographic/IVUS Core Lab were not involved as investigators or co-investigators in this study.
Statistical analysis
Cardialysis (Cardialysis B.V., PO Box 2125, 3000 CC Rotterdam, the Netherlands) is responsible for the statistical analysis.

Supplementary Table 4. Study endpoints and definitions.

Primary endpoints

Target lesion failure (TLF) is defined as a composite of

- Cardiac death
- Myocardial infarction (MI) in target vessel territory
- Clinically indicated target lesion revascularisation

Secondary endpoints

- Components of primary endpoints
- Target vessel failure and its components
- All-cause mortality
- Periprocedural MI and spontaneous MI
- All revascularisation
- Definite or probable stent/scaffold thrombosis (per the ARC definition)
- Cumulative recurrent or worsening angina at 12 months, excluding the angina episodes that occurred during index hospitalisation or in the 7 days post index procedure, whichever comes first
- Healthcare cost related to diagnostic workup of presumed coronary ischaemia and therapies in the first 12 months
- Healthcare costs related to target vessel failure up to 7 years
- Angina status at 1, 6, 12 months and at the time of any recurrent event assessed by Seattle angina questionnaire
- Quality of life at 1, 6, 12 months and at the time of any recurrent event assessed by EQ5D
- For STEMI patients, TIMI flow, myocardial blush and ST-segment resolution on ECG

Definitions of endpoints

Death

The deaths were adjudicated per the ARC definition. All deaths are considered cardiac unless an unequivocal non-cardiac cause can be established. Specifically, any unexpected death even in patients with coexisting potentially fatal non-cardiac disease (e.g., cancer, infection) should be classified as cardiac.

- **Cardiac death**: Any death due to proximate cardiac cause (e.g., MI, low-output failure, fatal arrhythmia), unwitnessed death and death of unknown cause, all study procedure-related deaths including those related to concomitant treatment.
- **Vascular death**: Death due to non-coronary vascular causes such as cerebrovascular disease, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular cause.
- **Non-cardiovascular death**: Any death not covered by the above definitions such as death caused by infection, malignancy, sepsis, pulmonary causes, accident, suicide or trauma.

Myocardial infarction

Spontaneous myocardial infarction (MI) is defined based on the third universal definition of myocardial infarction, while periprocedural MI is defined according to the SCAI definition.

- **Spontaneous MI (>48 hours after intervention, MI type I):** Symptoms suggestive of ischaemia/infarction in association with ECG, cardiac biomarker or pathologic evidence of infarction as follows: detection of a rise and/or fall of cardiac biomarker values (preferably cardiac troponin T or I) with at least one value above the 99th percentile upper reference limit and with at least one of the following:
    - Symptoms of ischaemia
    - New or presumed new significant ST-segment-T wave (ST-T) changes or new LBBB
    - Development of new Q-waves in the ECG
    - Evidence of new loss of viable myocardium or new regional wall motion abnormality
    - Identification of an intracoronary thrombus by angiography or autopsy

  Spontaneous MI typically occurs after the periprocedural period and may be secondary to late stent complications or progression of native disease (e.g., non-culprit lesion plaque rupture). Performance of ECG and angiography supports adjudication to either a target or non-target vessel or lesion in most cases.

- **Periprocedural** MI after PCI (within 48 hours after PCI, MI type 4a [post PCI] and 5 [post CABG])

  Periprocedural MI is defined based on the SCAI definitions as follows:
  In patients with normal baseline CK-MB: the peak CK-MB measured within 48 hours of the procedure rises to ≥10x the local laboratory ULN, or to ≥5x ULN with new pathologic Q-waves in ≥2 contiguous leads or new persistent LBBB, OR in the absence of CK-MB measurements and a normal baseline cTn,

a cTn (I or T) level measured within 48 hours of the PCI rises to ≥70x the local laboratory ULN, or ≥35x ULN with new pathologic Q-waves in ≥2 contiguous leads or new persistent LBBB.
In patients with elevated baseline CK-MB (or cTn) in whom the biomarker levels are stable or falling: the CK-MB (or cTn) rises by an absolute increment equal to those levels recommended above from the most recent pre-procedure level.
In patients with elevated CK-MB (or cTn) in whom the biomarker levels have not been shown to be stable or falling: the CK-MB (or cTn) rises by an absolute increment equal to those levels recommended above plus new ST-segment elevation or depression plus signs consistent with a clinically relevant MI, such as new onset or worsening heart failure or sustained hypotension.

- **Target**-vessel vs non-target vessel MI: any MI not clearly attributable to a non-target vessel will be considered as target vessel MI.

[Revascularisation]

The revascularisations were adjudicated per the ARC definition.

- **Target lesion revascularisation (TLR)**

  TLR is defined as any repeat percutaneous intervention of the target lesion or bypass surgery of the target vessel performed for restenosis or other complication of the target lesion. All TLR should be classified prospectively as clinically indicated [CI] or not clinically indicated by the investigator prior to repeat angiography. The target lesion is defined as the treated segment from 5 mm proximal to the stent and to 5 mm distal to the stent/scaffold.

- **Target vessel revascularisation (TVR)**

  TVR is defined as any repeat percutaneous intervention or surgical bypass of any segment of the target vessel. The target vessel is defined as the entire major coronary vessel proximal and distal to the target lesion which includes upstream and downstream branches and the target lesion itself

- **Non-target lesion revascularisation (Non-TLR)**

  Any revascularisation in the target vessel for a lesion other than the target lesion is considered a non-TLR.

- **Non-target vessel revascularisation (Non-TVR)**

  Revascularisation of the vessel identified and treated as the non-target vessel at the time of the index procedure.

  Note: TLR and TVR were adjudicated by the angiographic core laboratory.

- **Ischaemia-driven revascularisation (CI-TLR/TVR)**

  A revascularisation is considered clinically indicated if associated with any of the following:
  Positive functional ischaemia study including positive FFR
  Ischaemic symptoms and angiographic diameter stenosis ≥50% by core laboratory QCA
  Angiographic diameter stenosis ≥70% by core laboratory QCA without angina or positive functional study

Supplementary Table 5. Definition of optimal implantation techniques (OIT).

OIT-0

- Correct sizing by post-procedural QCA defined as the mean diameter of the distal or proximal segment within the range of the implanted device size±0.25 mm.
- Predilatation performed.
- Any post-dilatation.

OIT-1

- Correct sizing by post-procedural QCA defined as the mean diameter of the distal or proximal segment within the range of the implanted device size±0.25 mm.
- Predilatation performed.
- Post-dilatation with non-compliant balloon, maximum pressure ≥16 atm.

OIT-2

- Correct sizing by post-procedural QCA defined as the mean diameter of the distal or proximal segment within the range of the implanted device size±0.25 mm.
- Minimal reference vessel diameter 2.5 mm by QCA.
- Predilatation performed.
- Post-dilatation with non-compliant balloon, maximum pressure ≥16 atm.

OIT-3

- Correct sizing by post-procedural QCA defined as the mean diameter of the distal or proximal segment within the range of the implanted device size±0.25 mm.
- Minimal reference vessel diameter 2.5 mm by QCA.
- Predilatation performed.
- Post-dilatation with non-compliant balloon, pressure ≥16 atm, balloon diameter between device diameter and device diameter+0.5 mm

OIT-4

- Correct sizing by post-procedural QCA defined as the mean diameter of the distal or proximal segment within the range of the implanted device size±0.25 mm.
- Minimal reference vessel diameter 2.5 mm by QCA.
- Predilatation performed.
- Post-dilatation with non-compliant balloon, maximum pressure ≥16 atm, balloon diameter ≥device diameter+0.25 mm.

*If multiple devices were used, the largest device should be correlated to the mean diameter of the proximal segment whereas the smallest device should be correlated to the mean diameter of the distal segment as defined above.

Supplementary Table 6. Dual antiplatelet treatment.

Characteristic	BVS (N=848)	EES (N=822)	Difference (95% CI)	*p*-value
Discharge				
ASA	98.0% (831/848)	98.7% (811/822)	-0.7% [-1.9%, 0.6%]	0.3425
Clopidogrel	50.8% (431/848)	58.6% (482/822)	-7.8% [-12.6%, -3.1%]	0.0014
Prasugrel	12.6% (107/848)	9.0% (74/822)	3.6% [0.6%, 6.6%]	0.0182
Ticagrelor	38.3% (325/848)	34.2% (281/822)	4.1% [-0.5%, 8.7%]	0.0836
DAPT (ASA+Clopi)	49.9% (423/848)	57.9% (476/822)	-8.0% [-12.8%, -3.3%]	0.0012
DAPT (ASA+Tica or Prasu)	50.2% (426/848)	42.6% (350/822)	7.7% [2.9%, 12.4%]	0.0020
DAPT (ASA+Clopi or Tica or Prasu)	97.2% (824/848)	97.9% (805/822)	-0.8% [-2.2%, 0.7%]	0.3453
OAC alone	2.1% (18/848)	2.6% (21/822)	-0.4% [-1.9%, 1.0%]	0.6281
OAC and (ASA or Clopi or Tica or Prasu)	2.1% (18/848)	2.6% (21/822)	-0.4% [-1.9%, 1.0%]	0.6281
1 month				
ASA	98.1% (806/822)	98.5% (790/802)	-0.5% [-1.7%, 0.8%]	0.5690
Clopidogrel	51.6% (424/822)	58.2% (467/802)	-6.6% [-11.5%, -1.8%]	0.0082
Prasugrel	12.8% (105/822)	9.2% (74/802)	3.5% [0.5%, 6.6%]	0.0263
Ticagrelor	38.0% (312/822)	33.5% (269/802)	4.4% [-0.2%, 9.1%]	0.0699
DAPT (ASA+Clopi)	50.1% (412/822)	57.4% (460/802)	-7.2% [-12.1%, -2.4%]	0.0039
DAPT (ASA+Tica or Prasu)	50.0% (411/822)	41.9% (336/802)	8.1% [3.3%, 12.9%]	0.0012
DAPT (ASA+Clopi or Tica or Prasu)	97.6% (802/822)	97.4% (781/802)	0.2% [-1.3%, 1.7%]	0.8749
OAC alone	2.8% (23/822)	2.6% (21/802)	0.2% [-1.4%, 1.8%]	0.8792
OAC and (ASA or Clopi or Tica or Prasu)	2.8% (23/822)	2.6% (21/802)	0.2% [-1.4%, 1.8%]	0.8792
6 months				
ASA	97.4% (790/811)	98.1% (768/783)	-0.7% [-2.1%, 0.8%]	0.4023
Clopidogrel	53.4% (433/811)	57.7% (452/783)	-4.3% [-9.2%, 0.5%]	0.0866
Prasugrel	11.8% (96/811)	8.3% (65/783)	3.5% [0.6%, 6.5%]	0.0200
Ticagrelor	36.4% (295/811)	31.8% (249/783)	4.6% [-0.1%, 9.2%]	0.0572
DAPT (ASA+Clopi)	51.3% (416/811)	56.6% (443/783)	-5.3% [-10.2%, -0.4%]	0.0350
DAPT (ASA+Tica or Prasu)	47.6% (386/811)	39.6% (310/783)	8.0% [3.2%, 12.9%]	0.0015
DAPT (ASA+Clopi or Tica or Prasu)	96.4% (782/811)	94.6% (741/783)	1.8% [-0.2%, 3.8%]	0.0898
OAC alone	3.2% (26/811)	2.8% (22/783)	0.4% [-1.3%, 2.1%]	0.6630
OAC and (ASA or Clopi or Tica or Prasu)	3.0% (24/811)	2.8% (22/783)	0.1% [-1.5%, 1.8%]	0.8821
12 months				
ASA	96.6% (785/813)	96.5% (766/794)	0.1% [-1.7%, 1.9%]	1.0000
Clopidogrel	49.2% (400/813)	43.8% (348/794)	5.4% [0.5%, 10.2%]	0.0316
Prasugrel	7.7% (63/813)	5.9% (47/794)	1.8% [-0.6%, 4.3%]	0.1666
Ticagrelor	29.0% (236/813)	24.2% (192/794)	4.8% [0.5%, 9.2%]	0.0319
DAPT (ASA+Clopi)	47.2% (384/813)	41.9% (333/794)	5.3% [0.4%, 10.1%]	0.0351
DAPT (ASA+Tica or Prasu)	36.2% (294/813)	29.8% (237/794)	6.3% [1.7%, 10.9%]	0.0080
DAPT (ASA+Clopi or Tica or Prasu)	80.0% (650/813)	70.8% (562/794)	9.2% [5.0%, 13.4%]	<0.0001
OAC alone	4.1% (33/813)	3.0% (24/794)	1.0% [-0.8%, 2.8%]	0.2825

Characteristic	BVS (N=848)	EES (N=822)	Difference (95% CI)	*p*-value
OAC and (ASA or Clopi or Tica or Prasu)	3.4% (28/813)	2.3% (18/794)	1.2% [-0.4%, 2.8%]	0.1790

ASA: aspirin; BVS: bioresorbable vascular scaffold; Clopi: clopidogrel; DAPT: dual antiplatelet therapy; EES: everolimus-eluting stent; OAC: oral anticoagulants; Prasu: prasugrel; Tica: ticagrelor

Supplementary Table 7. Quality of life reported at one-year follow-up.

Characteristic	BVS (N=848)	EES (N=822)	*p*-value
Seattle Angina Questionnaire			
Physical limitation	84.9±19.5 (742)	85.0±19.7 (718)	0.93
Anginal stability	55.3±17.8 (776)	54.6±16.8 (755)	0.40
Angina frequency	93.8±13.0 (776)	93.4±14.0 (756)	0.57
Treatment satisfaction	89.1±18.7 (761)	88.6±19.1 (739)	0.60
Disease perception	78.9±20.2 (753)	78.0±20.9 (728)	0.40
Euro Qol			
Mobility			0.89
No problem in walking about	71.8% (562/783)	71.2% (541/760)	
Slight problems in walking about	15.8% (124/783)	17.0% (129/760)	
Moderate problems in walking about	8.2% (64/783)	7.9% (60/760)	
Severe problems in walking about	3.2% (25/783)	3.4% (26/760)	
Not able to walk about	1.0% (8/783)	0.5% (4/760)	
Self-care			0.95
No problems washing or dressing myself	89.1% (701/787)	88.9% (684/769)	
Slight problems washing or dressing myself	7.4% (58/787)	7.7% (59/769)	
Moderate problems washing or dressing myself	2.9% (23/787)	2.7% (21/769)	
Severe problems washing or dressing myself	0.6% (5/787)	0.5% (4/769)	
Unable to wash or dress myself	0.0% (0/787)	0.1% (1/769)	
Usual activity			0.73
No problems doing my usual activity	74.5% (587/788)	73.7% (566/768)	
Slight problems doing my usual activity	15.4% (121/788)	15.6% (120/768)	
Moderate problems doing my usual activity	6.9% (54/788)	7.9% (61/768)	
Severe problems doing my usual activity	2.9% (23/788)	2.5% (19/768)	
Unable to do my usual activities	0.4% (3/788)	0.3% (2/768)	
Pain/discomfort			0.14
No pain or discomfort	60.2% (473/786)	64.2% (493/768)	
Slight pain or discomfort	25.2% (198/786)	22.0% (169/768)	
Moderate pain or discomfort	11.2% (88/786)	10.7% (82/768)	
Severe pain or discomfort	2.7% (21/786)	2.6% (20/768)	
Extreme pain or discomfort	0.8% (6/786)	0.5% (4/768)	
Anxiety/depression			0.79
Not anxious or depressed	64.8% (508/784)	65.7% (504/767)	
Slightly anxious or depressed	25.0% (196/784)	23.5% (180/767)	
Moderately anxious or depressed	7.4% (58/784)	8.2% (63/767)	
Severely anxious or depressed	1.8% (14/784)	2.3% (18/767)	
Extremely anxious or depressed	1.0% (8/784)	0.3% (2/767)	
Health state (0-100)	77.9±15.6 (782)	77.8±15.2 (762)	0.91

BVS: bioresorbable vascular scaffold; EES: everolimus-eluting stent

Supplementary Table 8. Correct sizing according to post-procedural quantitative angiographic analysis.

Correct sizing*	**BVS** N=1,137 lesions	**EES** N=1,139 lesions
Proximal segment +, distal segment +	11.5% (131/1,137)	17.3% (197/1,139)
Proximal segment +, distal segment -	20.6% (862/1,137)	21.7% (743/1,139)
Proximal segment -, distal segment +	6.5% (74/1,137)	7.3% (83/1,139)
Proximal segment -, distal segment -	61.4% (698/1,137)	53.7% (612/1,139)

*Please refer to the definition of correct sizing (Supplementary Table 5).

"+": meet the criteria of correct sizing, "- ": do not meet the criteria of correct sizing,

BVS: bioresorbable vascular scaffold; EES: everolimus-eluting stent; OIT: optimal implantation technique

Supplementary Table 9. Angiographic analysis in bioresorbable vascular scaffold trials.

Study	COMPARE ABSORB		ABSORB IV		ABSORB III	
Device	**BVS**	**EES**	**BVS**	**EES**	**BVS**	**EES**
Reference vessel diameter (mm)	2.51±0.50	2.49±0.49	NA	NA	NA	NA
Pre-procedure MLD (mm)	0.89±0.49	0.89±0.50	NA	NA	NA	NA
Post-procedure MLD (mm)	2.21±0.41	2.32±0.39*	2.66±0.39	2.74±0.41*	2.37±0.40	2.49±0.40*
Acute gain (mm)	1.33±0.57	1.42±0.53*	1.85±0.46	1.92±0.46*	1.45±0.45	1.59±0.44*

Study	ABSORB II		ABSORB Japan		ABSORB China	
Device	**BVS**	**EES**	**BVS**	**EES**	**BVS**	**EES**
Reference vessel diameter (mm)	2.59±0.38	2.63±0.40	2.72±0.44	2.79±0.46	2.81±0.03	2.82±0.03
Pre-procedure MLD (mm)	1.07±0.32	1.05±0.32	0.96±0.33	0.99±0.36	0.98±0.03	1.01±0.03
Post-procedure MLD (mm)	2.22±0.33	2.50±0.33*	2.42±0.38	2.64±0.40*	2.48±0.02	2.59±0.03*
Acute gain (mm)	1.15±0.38	1.46±0.38*	1.46±0.40	1.65±0.40*	1.51±0.03	1.59±0.03*

*p<0.05 (BVS vs EES).

BVS: bioresorbable vascular scaffold; EES: everolimus-eluting stent; MLD: minimal lumen diameter; NA: not applicable