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Bioresorbable vascular scaffolds versus everolimus-eluting metallic stents in patients with ST-segment elevation myocardial infarction: 5-year results of the BVS-EXAMINATION study

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KEYWORDS

- bioresorbable scaffolds
- drug-eluting stent
- STEMI

Abstract

Aims: The aim of this study was to compare five-year clinical outcomes between an everolimus-eluting bioresorbable scaffold (BRS) and an everolimus-eluting metallic stent (EES) in STEMI patients.

Methods and results: This observational and retrospective study included 235 consecutive STEMI patients treated with BRS, compared with 235 STEMI patients treated with EES from the EXAMINATION trial, by applying propensity score matching. The primary endpoint was a device-oriented endpoint (DOCE), including cardiac death, target vessel myocardial infarction and target lesion revascularisation at five-year follow-up. Device thrombosis, according to the ARC criteria, was also evaluated. Optical coherence tomography (OCT) analysis was also performed at five years in event-free BRS patients. The cumulative incidence of five-year DOCE was higher in the BRS group as compared to the EES group (13.2% vs 7.6%, HR 1.87, 95% CI: 0.94-3.44, p=0.071), mainly driven by a higher rate of TLR (7.6% vs 1.7%, HR 1.15, 95% CI: 0.44-2.30, p=0.004). The five-year definite BRS thrombosis rate was also higher as compared to EES (4.2% vs 1.2%, HR 3.49, 95% CI: 0.95-12.82, p=0.054). OCT analysis showed a high incidence of neoatherosclerosis in the BRS group.

Conclusions: The five-year event risk was higher with BRS versus EES in STEMI. This suggests that the probability of obtaining favourable results at very long-term follow-up is low. Whether better results will be obtained with new-generation BVS remains to be determined.

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Abbreviations

BRS bioresorbable scaffold
DOCE device-oriented composite endpoint
EES everolimus-eluting stent
MI myocardial infarction
STEMI ST-elevation myocardial infarction
TLR target lesion revascularisation

Introduction

Everolimus-eluting bioresorbable scaffolds (BRS) (Absorb™ bioresorbable vascular scaffold [BVS]; Abbott Vascular, Santa Clara, CA, USA) were designed to provide temporary mechanical support with antiproliferative responses to vascular injury similar to those of metallic drug-eluting stents but with complete resorption within several years, thereby restoring normal vascular function and potentially improving late outcomes[1].

Analysis of data from four major randomised trials using polylactide-based BRS (Absorb BVS) have shown non-inferior outcomes to contemporary metallic drug-eluting stents in patients with stable coronary artery disease at short-term follow-up. However, they raised concerns about increased rates of target vessel-related myocardial infarction (TV-MI) and device thrombosis at long-term follow-up[2,3]. Of note, a number of BRS-related events in these trials were reported between one and three years – the period of active scaffold bioresorption[4,5]. Because of these concerns, the manufacturer withdrew the Absorb BVS from the market.

Nevertheless, other BRS with differing designs and drugs are still available on the market for use in clinical studies. One of these – a magnesium-based BRS – is currently being tested in ST-segment elevation myocardial infarction (STEMI), where their physiological advantages, such as late lumen enlargement and vasomotion, appear particularly appealing[6,7]. Previous studies on BRS in STEMI have shown contrasting results with either a non-inferior vascular healing response with a low rate of events or a higher rate of early device thrombosis at one-year follow-up[8,9]. However, all these studies are limited by short-term follow-up and lack of data beyond three years where the scaffold bioresorption may have a role in scaffold collapse with subsequent thrombosis[10].

We therefore conducted a five-year follow-up of the BVS-EXAMINATION study, which matched consecutive STEMI patients receiving BRS with a cohort of STEMI patients receiving everolimus-eluting stents (EES) (XIENCE V®; Abbott Vascular) from the EXAMINATION randomised trial.

Editorial, see page 1397

Methods

STUDY POPULATION

The EXAMINATION trial was an all-comer STEMI, multicentre, controlled and randomised trial, which randomised 1:1 a total of 1,498 STEMI patients to an EES (n=751) (XIENCE) or MULTI-LINK VISION® bare metal stent (BMS; n=747) (both Abbott Vascular)[11,12]. Those patients randomised to an EES were used for propensity score matching with an observational and retrospective cohort of consecutive STEMI patients treated with BRS in various institutions. The BVS-EXAMINATION study was performed according to the privacy policy of the various participating institutions and to their regulations for the appropriate use of data in patient-oriented research, which are based on international regulations, including the Declaration of Helsinki.

All consecutive STEMI patients already included in the one-year follow-up of the BVS-EXAMINATION study were included in this analysis[8]. The investigators at each institution who had already participated in the study were invited to perform a five-year follow-up of their STEMI patients treated with BRS who had already been included in the one-year study. If they agreed, they were then asked to complete a structured patient-level database with clinical outcome data, similar to the EXAMINATION database. Such individual patient data were sent to the study coordinator (S. Brugaletta), who was responsible for data consistency checking and for final pooling in a single database. All STEMI patients included in the BVS-EXAMINATION study were already matched with patients from the EXAMINATION randomised trial[8]. Five-year follow-up was performed in the EXAMINATION patients by clinical visits and in the BRS patients either by clinical visit or by telephone call.

Details about the primary PCI procedure, definition of clinical outcomes and optical coherence tomography (OCT) analysis are reported in **Supplementary Appendix 1-Supplementary Appendix 3**.

STATISTICAL ANALYSIS

For the present analyses, individual data were pooled on a patient-level basis. Continuous variables are expressed as mean±SD and categorical variables are presented as absolute number and proportion (%). Details about propensity score matching analysis are reported in **Supplementary Appendix 4**.

Time-to-event variables are presented as Kaplan-Meier curves. Hazard ratios (HRs) of all events at 30 days, one year and five years were calculated using Cox proportional hazards models.

A two-sided p-value <0.05 was considered statistically significant. All statistical analyses were performed using SPSS, Version 25.0 (IBM Corp., Armonk, NY, USA).

Results

STUDY POPULATION

All but one of the participating institutions agreed to perform five-year clinical follow-up and to provide follow-up data. For these reasons, out of the 290 consecutive STEMI patients treated with BRS implantation originally included in the one-year follow-up of the BVS-EXAMINATION study, 235 patients were finally included for five-year follow-up. By applying the aforementioned methodology of propensity score matching, all of the 235 BVS patients were matched with 235 EES patients from the EXAMINATION trial, as previously shown[8]. The distribution of patient demographics and procedural characteristics between the two matched groups was similar to the one previously reported[8] **(Supplementary Table 1)**.

Five-year follow-up was available in 100% of EES patients and in 98% of BRS patients, as four patients were lost at follow-up **(Figure 1)**.

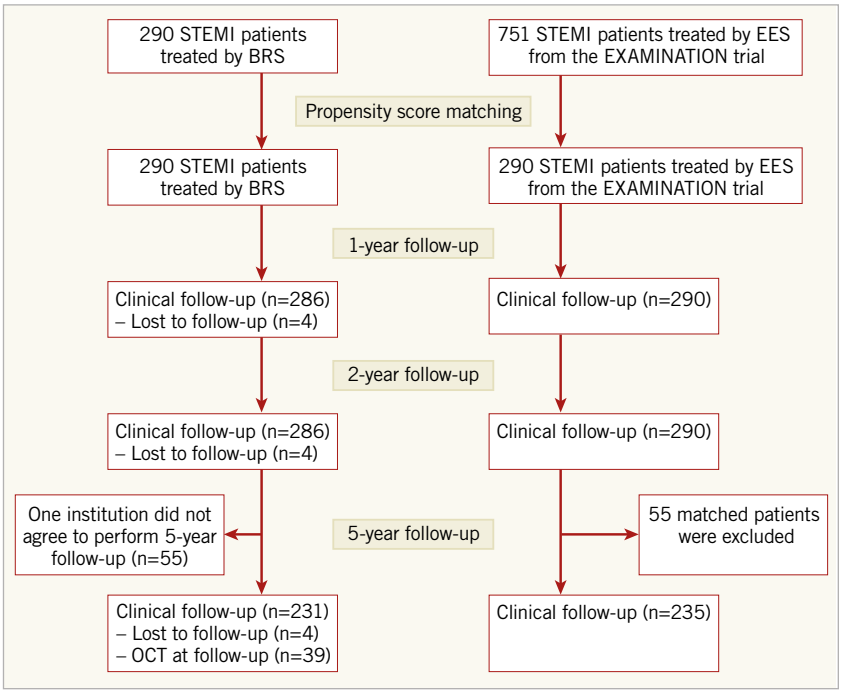

Figure 1. *Study flow chart.*

CLINICAL OUTCOMES BETWEEN BRS AND EES

At five years, the device-oriented composite endpoint (DOCE) was numerically higher, but not statistically significant in the BRS as compared to the EES group (13.2% vs 7.6%; HR 1.87, 95% CI: 0.94-3.44, p=0.071) **(Table 1)**. This difference was mainly driven by a higher rate of TV-MI (6.0% vs 2.5%, p=0.086) and target lesion revascularisation (TLR) (7.6% vs 1.7%, p=0.004) **(Figure 2)**.

The definite device thrombosis rate was also higher in the BRS as compared to the EES group at five years (4.2% vs 1.2%, HR 3.49, 95% CI: 0.95-12.82, p=0.054) **(Figure 3)**.

In a landmark analysis from one to five years, no differences were found between the BRS and EES groups in terms of DOCE (7.8% vs 4.3%, p=0.122) or cardiac death (6.0% vs 4.3%, p=0.574). A numerically higher rate of TV-MI (3.4% vs 1.7%, p=0.258) and definite device thrombosis (2.2% vs 0.9%, p=0.283) was found between one and five years in the BRS versus the EES group with a statistically significant higher incidence of TLR (5.2% vs 0.9%, p=0.006). No differences were found in terms of dual antiplatelet therapy between the BRS and EES groups at five years (3.4% vs 5.0%, p=0.647).

OCT DATA

A total of 88 patients were screened to participate in the OCT study. A total of 48 patients were excluded (4 patients died, 5 patients had a TLR, 4 patients had a TV-MI, 15 patients because of severe comorbidities, 2 patients because of oral anticoagulation, 18 patients refused to participate). Out of the 40 patients who agreed to participate, one patient had target lesion occlusion and therefore 39 patients were eventually included in the analysis. Baseline clinical and angiographic characteristics are reported in **Supplementary Table 2**.

Table 1. Clinical outcome at 30-day, 1-year and 5-year follow-up.

	BRS group (n=235)	EES group (n=235)	HR [95% CI]	*p*-value
Clinical outcome at 30 days				
DOCE	8 (3.4)	5 (2.1)	0.61 [0.20-1.86]	0.381
Cardiac death	5 (2.2)	4 (1.7)	1.27 [0.34-4.74]	0.717
TV-MI	4 (1.7)	0 (0)	0.15 [0.00-46.51]	0.060
TLR	4 (1.7)	0 (0)	0.15 [0.00-46.51]	0.060
Definite/probable device thrombosis	4 (1.7)	2 (0.9)	2.05 [0.37-11.20]	0.406
Definite device thrombosis	4 (1.7)	0 (0)	0.15 [0.00-46.51]	0.060
Clinical outcome at 1 year				
DOCE	10 (4.3)	8 (3.4)	1.86 [0.75-4.28]	0.186
Cardiac death	7 (3.0)	5 (2.1)	1.42 [0.45-4.50]	0.543
TV-MI	6 (2.6)	2 (0.9)	3.10 [0.63-15.38]	0.165
TLR	6 (2.6)	2 (0.9)	3.13 [0.63-15.53]	0.162
Definite/probable device thrombosis	6 (2.6)	4 (1.7)	1.80 [0.52-6.16]	0.346
Definite device thrombosis	5 (1.7)	1 (0.7)	5.16 [0.63-44.19]	0.092
Clinical outcome at 5 years				
DOCE	31 (13.2)	18 (7.6)	1.87 [0.94-3.44]	0.071
Cardiac death	14 (5.9)	10 (4.2)	1.44 [0.63-3.32]	0.366
TV-MI	14 (6.0)	6 (2.5)	2.33 [0.88-6.14]	0.086
TLR	18 (7.6)	4 (1.7)	4.86 [1.62-14.58]	0.004
Definite/probable device thrombosis	13 (5.5)	10 (4.2)	1.34 [0.57-3.11]	0.437
Definite device thrombosis	10 (4.2)	3 (1.2)	3.49 [0.95-12.82]	0.054

DOCE: device-oriented endpoint; MI: myocardial infarction; TLR: target lesion revascularisation; TV: target vessel

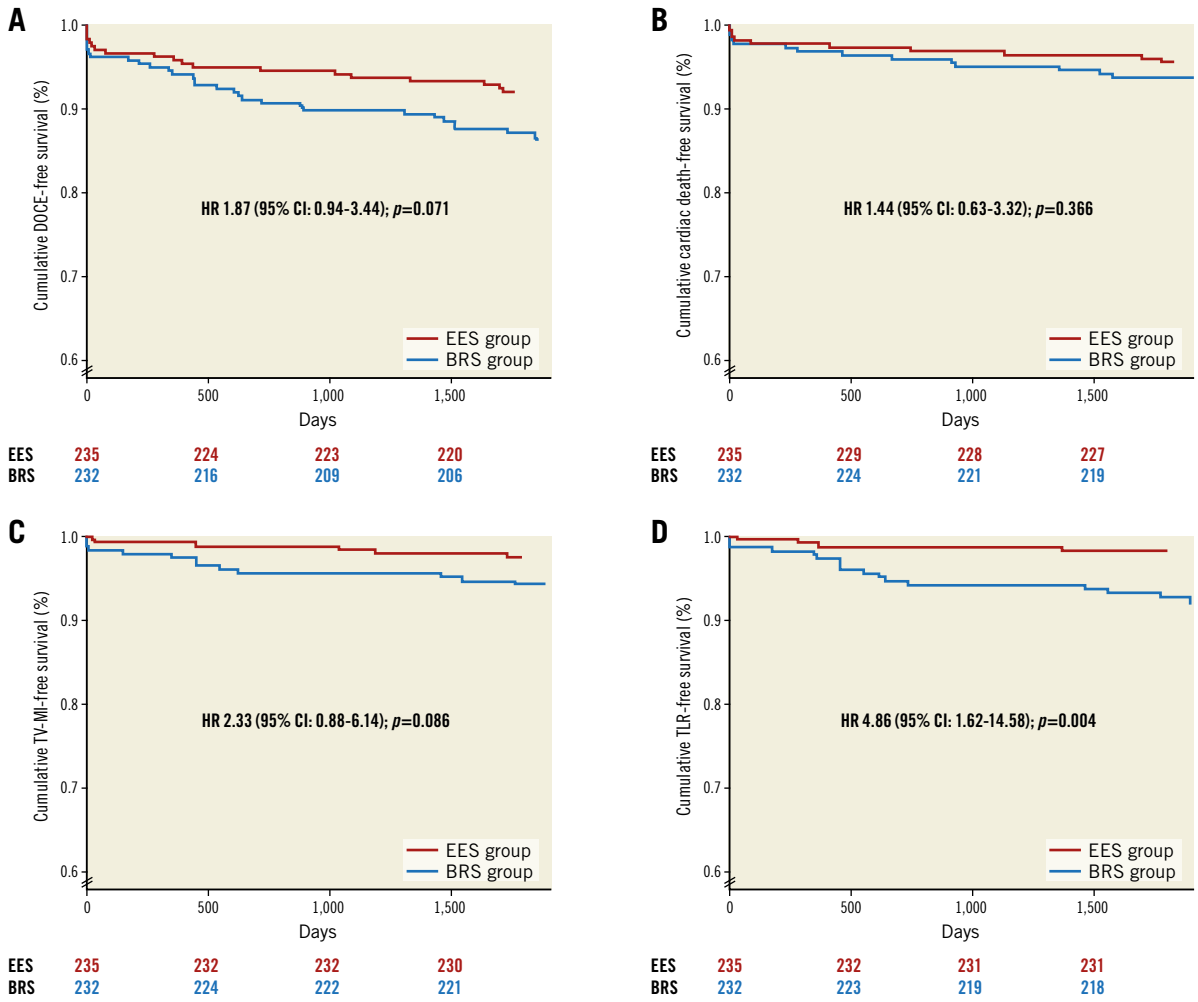

Figure 2. *Kaplan-Meier curves. A) Kaplan-Meier event curves comparing BRS and EES for the composite device-oriented endpoint (DOCE) of cardiac death, target vessel myocardial infarction and target lesion revascularisation. B) Kaplan-Meier event curves comparing BRS and EES for cardiac death. C) Kaplan-Meier event curves comparing BRS and EES for target vessel myocardial infarction (TV-MI). D) Kaplan-Meier event curves comparing BRS and EES for target lesion revascularisation (TLR).*

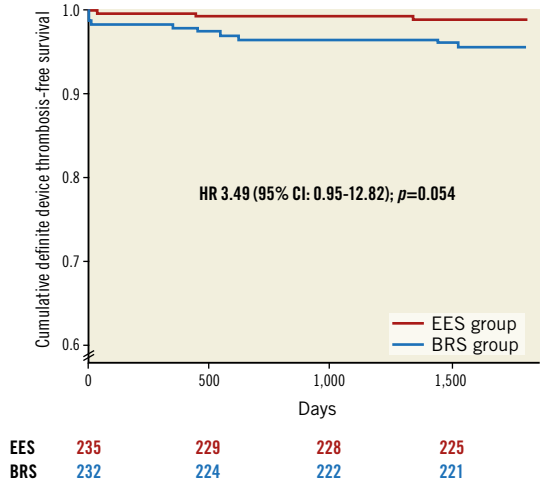

Figure 3. *Kaplan-Meier event curves comparing BRS and EES for definite device thrombosis.*

OCT data, as well as the combinations of lipid, calcification, and neovascularisation, as major atherosclerotic findings in this study, are shown in **Table 2**.

Overall, 31 patients (79%) exhibited at least one major finding of neoatherosclerosis. In particular, 8 (20%) patients had one major finding of atherosclerosis in the intima at five years. Two major findings were present in 9 (22%) patients and all three major findings of atherosclerosis were present in 13 (33%) patients **(Figure 4)**.

Discussion

This is the first study comparing five-year long-term follow-up of BRS versus EES in STEMI patients. The main findings can be summarised as follows: 1) the five-year DOCE rate was higher in the BRS versus the EES group, mainly driven by a higher rate of TLR, which was especially concentrated between one and five years; 2) the rate of long-term definite device thrombosis was also

Table 2. OCT data of the BRS patients included in the OCT substudy.

		BRS group (n=39)
Mean lumen area, mm^2		4.97±1.96
Proximal reference lumen area, mm^2		7.38±2.43
Distal reference lumen area, mm^2		6.54±3.04
Lipid, n (%)		27 (69)
Calcification, n (%)		19 (48)
Thrombi, n (%)		2 (0.5)
Internal rupture, n (%)		6 (15)
Neovascularisation, n (%)		19 (48)
TCFA, n (%)		6 (15)
Macrophage, n (%)		15 (38)
None of the 3 major findings, n (%)		8 (20)
One finding, n (%)	Lipid only	7 (18)
	Calcification only	0 (0)
	Neovascularisation only	1 (2.5)
Two findings, n (%)	Lipid+calcification	4 (10)
	Lipid+neovascularisation	3 (7)
	Calcification+neovascularisation	2 (5)
All 3 findings, n (%)		13 (33)

BRS: bioresorbable scaffold; OCT: optical coherence tomography; TCFA: thin-cap fibroatheroma

higher in the BRS versus the EES group; 3) in event-free patients, the incidence of neoatherosclerosis was remarkably high.

After initial enthusiasm in relation to bioresorbable scaffolds, long-term data together with BRS use in more complex lesions have shown not only a lack of superiority but even inferiority in terms of hard clinical endpoints as compared to drug-eluting metallic stents[13,14]. For these reasons, the Absorb BVS has been withdrawn from the market and the use of other BRS has been restricted to clinical studies[15].

Against this background, the usefulness of BRS in STEMI is still controversial. From the clinical point of view, previous STEMI studies on BRS have shown comparable angiographic and OCT performance to everolimus-eluting metallic stents without a clear inferiority of BRS versus EES, with only higher device thrombosis especially in the early phase and without data beyond three-year follow-up, when scaffold bioresorption is complete[8,9]. The TROFI II trial, which is the only randomised STEMI trial of BRS versus EES, showed low rates of DOCE and device thrombosis at three years, in line with the favourable vascular healing process observed at six months[16,17].

The MAGSTEMI trial, which randomised STEMI patients to a magnesium-based BRS (Magmaris®; Biotronik, Bülach, Switzerland) versus a metallic drug-eluting stent (DES) (Orsiro; Biotronik), recently showed a higher one-year vasodilation of the treated coronary segment after intracoronary nitroglycerine administration with Magmaris versus Orsiro[18].

In this five-year follow-up of the BVS-EXAMINATION trial, we found a higher rate of DOCE in the BRS versus the EES arm, mainly driven by a higher rate of TLR. The difference in terms of TLR between the groups became more important between one and five years. The incidence of device thrombosis was also higher in the BRS versus the EES group; this difference was already evident in the early phase and continued to increase up to five years. No differences were found between the groups in terms of dual antiplatelet therapy at five years, with a very low rate in both groups.

It is noteworthy that device-related clinical events continue to accrue yearly and that, whereas almost 90% of the five-year EES TLR were due to device thrombosis, only 55% of the BRS TLR

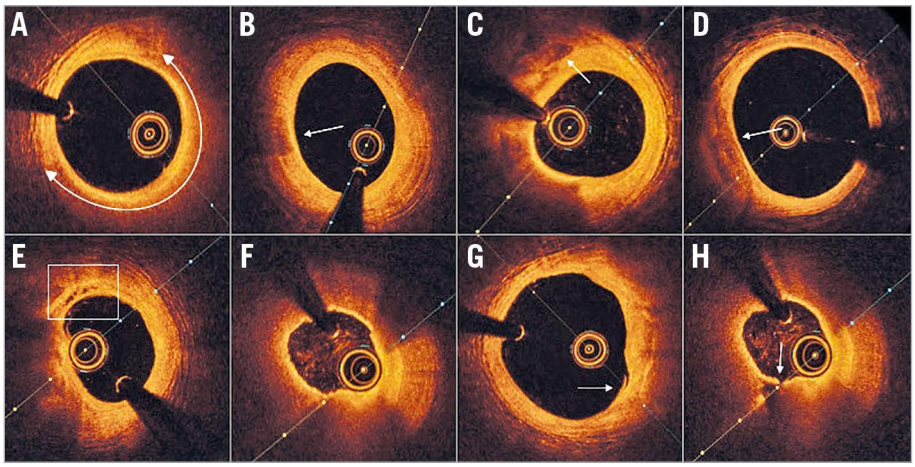

Figure 4. *Five-year OCT findings in STEMI patients treated with BRS. A) Lipid-laden intima (bidirectional white arc). B) Macrophage infiltration (white arrow). C) Deep calcium deposition (white arrow) >200 mm from the end-luminal border. D) Neointimal calcification (white arrow) <200 mm from the end-luminal border. E) Neovascularisation (white box). F) TCFA containing lipidic neointima. G) Intimal rupture (white arrow). H) Plaque rupture (white arrow) and empty cavity. OCT: optical coherence tomography; TCFA: thin-cap fibroatheroma*

were caused by device thrombosis. This means that different mechanisms may play a role in determining these events between metallic and bioresorbable devices. Mechanical causes, such as scaffold dismantling, and also neoatherosclerosis should be considered. Whereas scaffold dismantling is known to be important for device thrombosis, neoatherosclerosis may play a role either in thrombosis or in restenosis[10,19] **(Figure 5)**. In the case of metallic stents, neoatherosclerosis was known to contribute to the so-called late catch-up phenomenon. Although BRS were created to reduce this phenomenon, neoatherosclerosis following BRS implantation is not only qualitatively similar to that of DES, mainly composed of lipid, calcification and neovascularisation, but also seems to have a higher incidence[19,20]. Whereas in the RE-EXAMINATION study the incidence of neoatherosclerosis in STEMI patients who received EES was 22.6% at five years, in the present study we found, for example, a higher incidence (79%) in STEMI patients treated with BRS[21]. This high incidence confirms a previous observation in a group of stable angina patients enrolled in the ABSORB EXTEND study with OCT analysis at five years[19]. Data from other BRS platforms would be interesting in order to understand whether this phenomenon is related only to a specific BRS or if it is a class effect.

Last but not least, a previous study suggested that, despite the increased risk of early events, BRS may still provide a theoretical net clinical benefit to patients in the very long term, but only if the risk of BRS failure beyond three years is substantially reduced as compared with EES[22]. However, our study shows that this event risk of BRS versus EES is maintained beyond four years, despite being performed in STEMI, a setting which is theoretically favourable to BRS[17]. Given this small degree of benefit that clinicians and decision makers may expect from the first-generation BRS at the current risk not only of device thrombosis but overall of target lesion failure, we guess that very long-term follow-up of the first-generation BRS has a very low probability of giving positive results. Whether different results will be obtained with new-generation BRS remains to be determined.

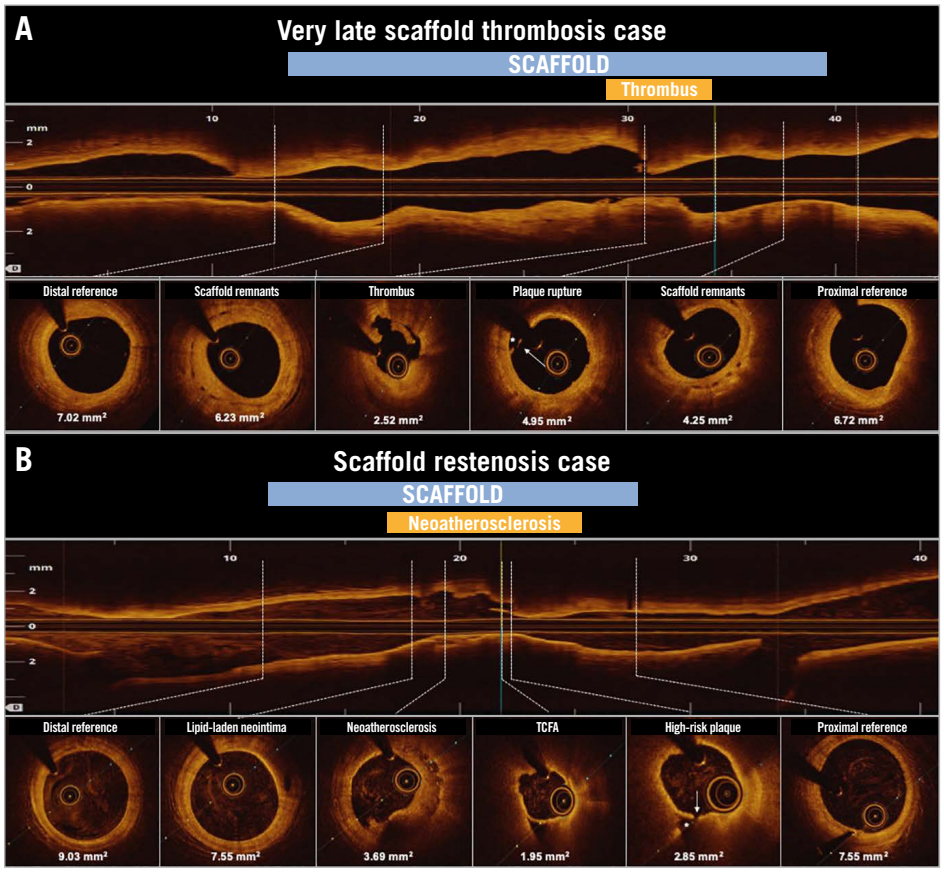

Figure 5. *Examples of events caused by neoatherosclerosis following BRS implantation in STEMI. A) A case of BRS VLST at 1,550 days (4.25 years) after the index procedure. The main OCT finding related to the thrombosis was neoatherosclerosis with plaque rupture (white arrow and asterisk), visible also in the OCT longitudinal view. Near to the proximal and distal references, scaffold remnants were still observed. B) A case of scaffold restenosis due to neoatherosclerosis. A TCFA with cap rupture (white arrow and asterisk) was identified without thrombus. An FFR of 0.74 was measured. For both panels, in the longitudinal view the dotted lines correspond to the cross-section images. Minimum lumen area is shown per each cross-section. BRS: bioresorbable scaffold; FFR: fractional flow reserve; OCT: optical coherence tomography; TCFA: thin-cap fibroatheroma; VLST: very late scaffold thrombosis*

Limitations

Several limitations of the study should be acknowledged. Due to the limited number of patients and events, and because the study was not randomised but based on a propensity score analysis, caution should be exercised in reaching firm conclusions. Dual antiplatelet therapy in STEMI patients with Absorb BVS implantation did not include guideline-oriented prasugrel or ticagrelor, and the duration was not according to the recommendations of the EAPCI Task Force. Of note, post-dilatation was performed in a relatively low number of patients. The nature of the clinical follow-up (clinical visit or phone call) differed in both clinical arms. Nevertheless, this study currently represents the largest cohort of STEMI patients treated with BRS compared with a control arm.

Conclusions

At five-year follow-up, STEMI patients treated with BRS showed a higher rate of DOCE compared with STEMI patients treated with EES, mainly driven by a higher rate of TLR, especially concentrated between one and five years. The incidence of BRS thrombosis was also higher as compared to EES. In event-free BRS patients, a high incidence of neoatherosclerosis, composed of lipid, including thin-cap fibroatheroma (TCFA), calcification and neovascularisation, was found at five years. Our five-year event risk of BRS versus EES suggests that the probability of obtaining positive results at very long-term follow-up is low. Whether better results will be obtained with new-generation BRS remains to be determined.

Impact on daily practice

This is the first study to investigate five-year outcomes in STEMI patients between BRS and best-in-class second-generation DES. STEMI patients treated with BRS have a higher incidence of DOCE, mainly driven by TLR clustered between one and five years. Device thrombosis is higher in BRS. OCT analysis also showed a high rate of neoatherosclerosis in BRS patients. This five-year event risk of BRS versus EES suggests a very low probability of positive results at very long-term follow-up. Effort should be concentrated on obtaining data from new-generation BRS.

Appendix. Study collaborators

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Guest Editor

This paper was guest edited by Alec Vahanian, MD, PhD; Department of Cardiology, Hôpital Bichat-Claude Bernard, and University Paris VII, Paris, France.

Conflict of interest statement

S. Brugaletta is a member of the advisory board of Boston Scientific and iVascular. T. Gori has received lecture fees from Abbott Vascular. V. Kocka has received personal fees from Abbott Vascular, Medtronic, B Braun, and Terumo. A. Cequier reports grants and personal fees from Abbott Vascular, Biosensors, Boston Scientific, and Medtronic, and grants from OrbusNeich, outside the submitted work. P.W. Serruys is a member of the advisory board of Abbott Vascular. M. Sabaté is a member of the advisory board of Abbott Vascular and iVascular. The other authors have no conflicts of interest to declare. The study collaborators have no conflicts of interest to declare. The Guest Editor is a consultant for Edwards Lifesciences.

References

1. Brugaletta S, Garcia-Garcia HM, Onuma Y, Serruys PW. Everolimus-eluting ABSORB bioresorbable vascular scaffold: present and future perspectives. *Expert Rev Med Devices*. 2012;9:327-38.

2. 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.

3. Kimura T, Kozuma K, Tanabe K, Nakamura S, Yamane M, Muramatsu T, Saito S, Yajima J, Hagiwara N, Mitsudo K, Popma JJ, Serruys PW, Onuma Y, Ying S, Cao S, Staehr P, Cheong WF, Kusano H, Stone GW; ABSORB Japan Investigators. A randomized trial evaluating everolimus-eluting Absorb bioresorbable scaffolds vs. everolimus-eluting metallic stents in patients with coronary artery disease: ABSORB Japan. *Eur Heart J*. 2015;36:3332-42.

4. Serruys PW, Chevalier B, Sotomi Y, Cequier A, Carrié D, Piek JJ, Van Boven AJ, Dominici M, Dudek D, McClean D, Helqvist S, Haude M, Reith S, de Sousa Almeida M, Campo G, Iniguez A, Sabaté M, Windecker S, Onuma Y. Comparison of an everolimus-eluting bioresorbable scaffold with an everolimus-eluting metallic stent for the treatment of coronary artery stenosis (ABSORB II): a 3 year, randomised, controlled, single-blind, multicentre clinical trial. *Lancet*. 2016;388:2479-91.

5. Toyota T, Morimoto T, Shiomi H, Yoshikawa Y, Yaku H, Yamashita Y, Kimura T. Very Late Scaffold Thrombosis of Bioresorbable Vascular Scaffold: Systematic Review and a Meta-Analysis. *JACC Cardiovasc Interv*. 2017;10:27-37.

6. Brugaletta S, Radu MD, Garcia-Garcia HM, Heo JH, Farooq V, Girasis C, van Geuns RJ, Thuesen L, McClean D, Chevalier B, Windecker S, Koolen J, Rapoza R, Miquel-Hebert K, Ormiston J, Serruys PW. Circumferential evaluation of the neointima by optical coherence tomography after ABSORB bioresorbable vascular scaffold implantation: can the scaffold cap the plaque? *Atherosclerosis*. 2012;221:106-12.

7. Brugaletta S, Cequier A, Alfonso F, Iniguez A, Romani S, Serra A, Salinas P, Goicolea J, Bordes P, Del Blanco BG, Hernandez-Antolin R, Pernigotti A, Gomez-Lara J, Sabaté M. MAGnesium-based bioresorbable scaffold and vasomotor function in patients with acute ST segment elevation myocardial infarction: The MAGSTEMI trial: Rationale and design. *Catheter Cardiovasc Interv*. 2019;93:64-70.

8. Brugaletta S, Gori T, Low AF, Tousek P, Pinar E, Gomez-Lara J, Scalone G, Schulz E, Chan MY, Kocka V, Hurtado J, Gomez-Hospital JA, Münzel T, Lee CH, Cequier A, Valdes M, Widimsky P, Serruys PW, Sabaté M. Absorb bioresorbable vascular scaffold versus everolimus-eluting metallic stent in ST-segment elevation myocardial infarction: 1-year results of a propensity score matching comparison: the BVS-EXAMINATION Study (bioresorbable vascular scaffold-a clinical evaluation of everolimus eluting coronary stents in

the treatment of patients with ST-segment elevation myocardial infarction). *JACC Cardiovasc Interv.* 2015;8:189-97.

9. Cassese S, Katagiri Y, Byrne RA, Brugaletta S, Alfonso F, Räber L, Maeng M, Iniguez A, Kretov E, Onuma Y, Joner M, Sabaté M, Laugwitz KL, Windecker S, Kastrati A, Serruys PW. Angiographic and clinical outcomes of STEMI patients treated with bioresorbable or metallic everolimus-eluting stents: a pooled analysis of individual patient data. *EuroIntervention.* 2020;15:1451-7.

10. Räber L, Brugaletta S, Yamaji K, O'Sullivan CJ, Otsuki S, Koppara T, Taniwaki M, Onuma Y, Freixa X, Eberli FR, Serruys PW, Joner M, Sabaté M, Windecker S. Very Late Scaffold Thrombosis: Intracoronary Imaging and Histopathological and Spectroscopic Findings. *J Am Coll Cardiol.* 2015;66:1901-14.

11. Sabaté M, Brugaletta S, Cequier A, Iniguez A, Serra A, Jiménez-Quevedo P, Mainar V, Campo G, Tespili M, den Heijer P, Bethencourt A, Vazquez N, van Es GA, Backx B, Valgimigli M, Serruys PW. Clinical outcomes in patients with ST-segment elevation myocardial infarction treated with everolimus-eluting stents versus bare-metal stents (EXAMINATION): 5-year results of a randomised trial. *Lancet.* 2016;387:357-66.

12. Sabaté M, Cequier A, Iniguez A, Serra A, Hernandez-Antolin R, Mainar V, Valgimigli M, Tespili M, den Heijer P, Bethencourt A, Vazquez N, Gomez-Hospital JA, Baz JA, Martin-Yuste V, van Geuns RJ, Alfonso F, Bordes P, Tebaldi M, Masotti M, Silvestro A, Backx B, Brugaletta S, van Es GA, Serruys PW. Everolimus-eluting stent versus bare-metal stent in ST-segment elevation myocardial infarction (EXAMINATION): 1 year results of a randomised controlled trial. *Lancet.* 2012;380:1482-90.

13. Kereiakes DJ, Ellis SG, Metzger C, 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. 3-Year Clinical Outcomes With Everolimus-Eluting Bioresorbable Coronary Scaffolds: The ABSORB III Trial. *J Am Coll Cardiol.* 2017;70:2852-62.

14. Chevalier B, Cequier A, Dudek D, Haude M, Carrie D, Sabaté M, Windecker S, Reith S, de Sousa Almeida M, Campo G, Iniguez A, Onuma Y, Serruys PW. Four-year follow-up of the randomised comparison between an everolimus-eluting bioresorbable scaffold and an everolimus-eluting metallic stent for the treatment of coronary artery stenosis (ABSORB II Trial). *EuroIntervention.* 2018;13:1561-4.

15. 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.

16. Katagiri Y, Onuma Y, Asano T, Iniguez A, Jensen LO, Cequier A, Hofma SH, Christiansen EH, Suttorp M, Brugaletta S, Räber L, Sabaté M, Windecker S, Serruys PW. Three-year follow-up of the randomised comparison between an everolimus-eluting bioresorbable scaffold and a durable polymer everolimus-eluting metallic stent in patients with ST-segment elevation myocardial infarction (TROFI II trial). *EuroIntervention.* 2018;14:e1224-6.

17. Sabaté M, Windecker S, Iniguez A, Okkels-Jensen L, Cequier A, Brugaletta S, Hofma SH, Räber L, Christiansen EH, Suttorp M, Pilgrim T, Anne van Es G, Sotomi Y, Garcia-Garcia HM, Onuma Y, Serruys PW. Everolimus-eluting bioresorbable stent vs. durable polymer everolimus-eluting metallic stent in patients with ST-segment elevation myocardial infarction: results of the randomized ABSORB ST-segment elevation myocardial infarction-TROFI II trial. *Eur Heart J.* 2016;37:229-40.

18. Sabaté M, Alfonso F, Cequier A, Romani S, Bordes P, Serra A, Iniguez A, Salinas P, Garcia Del Blanco B, Goicolea J, Hernandez-Antolin R, Cuesta J, Gomez-Hospital JA, Ortega-Paz L, Gomez-Lara J, Brugaletta S. Magnesium-Based Resorbable Scaffold versus Permanent Metallic Sirolimus-Eluting Stent in Patients with ST-Segment Elevation Myocardial Infarction: The MAGSTEMI Randomized Clinical Trial. *Circulation.* 2019;140:1904-16.

19. Moriyama N, Shishido K, Tanaka Y, Yokota S, Hayashi T, Miyashita H, Koike T, Yokoyama H, Takada T, Nishimoto T, Ochiai T, Tobita K, Yamanaka F, Mizuno S, Murakami M, Takahashi S, Saito S. Neoatherosclerosis 5 Years After Bioresorbable Vascular Scaffold Implantation. *J Am Coll Cardiol.* 2018;71:1882-93.

20. Vergallo R, Yonetsu T, Uemura S, Park SJ, Lee S, Kato K, Jia H, Abtahian F, Tian J, Hu S, Lee H, McNulty I, Prasad A, Yu B, Zhang S, Porto I, Biasucci LM, Crea F, Jang IK. Correlation between degree of neointimal hyperplasia and incidence and characteristics of neoatherosclerosis as assessed by optical coherence tomography. *Am J Cardiol.* 2013;112:1315-21.

21. Gomez-Lara J, Brugaletta S, Jacobi F, Ortega-Paz L, Nato M, Roura G, Romaguera R, Ferreiro JL, Teruel L, Gracida M, Martin-Yuste V, Freixa X, Masotti M, Gomez-Hospital JA, Sabate M, Cequier A. Five-Year Optical Coherence Tomography in Patients With ST-Segment-Elevation Myocardial Infarction Treated With Bare-Metal Versus Everolimus-Eluting Stents. *Circ Cardiovasc Interv.* 2016 Oct;9(10).

22. Capodanno D, Buccheri S, Romano S, Capranzano P, Francaviglia B, Tamburino C. Decision Analytic Markov Model Weighting Expected Benefits and Current Limitations of First-Generation Bioresorbable Vascular Scaffolds: Implications for Manufacturers and Next Device Iterations. *Circ Cardiovasc Interv.* 2018;11:e005768.

Supplementary data

Supplementary Appendix 1. Primary PCI procedure.

Supplementary Appendix 2. Definition of clinical outcomes.

Supplementary Appendix 3. Optical coherence tomography analysis.

Supplementary Appendix 4. Propensity score matching analysis.

Supplementary Table 1. Baseline clinical and procedural characteristics.

Supplementary Table 2. Baseline clinical and procedural characteristics of BRS patients included in the OCT substudy.

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Supplementary data

Supplementary Appendix 1. Primary PCI procedure

Primary percutaneous coronary intervention (PCI) was performed according to conventional clinical practice: manual thrombus aspiration, glycoprotein (GP) IIb/IIIa inhibitors, heparin and bivalirudin administration were performed according to the operator's choice. Balloon predilatation was not mandatory but recommended for BRS implantation, according to BRS instructions for use. Dual antiplatelet therapy with aspirin plus clopidogrel, ticagrelor or prasugrel was prescribed in all patients for 12 months. Of note, neither prasugrel nor ticagrelor was approved during the recruitment period of the EXAMINATION trial.

Supplementary Appendix 2. Definition of clinical outcomes

The primary endpoint of this analysis was defined as a combined device-oriented composite endpoint (DOCE), including cardiac death, target vessel myocardial infarction (TV-MI) and target lesion revascularisation (TLR). All the individual components and device thrombosis (stent/scaffold), defined by the Academic Research Consortium (ARC) criteria, were also analysed. Whereas all the events in the EXAMINATION trial were adjudicated by an independent clinical events committee, blinded to stent assignment after review of original source documentation, all the events in the BRS group were adjudicated by investigators collecting any relevant medical records, discharge letters and documentation of hospital stay from the hospitals providing treatment and physicians in private practice, using the same definitions of events applied in the EXAMINATION trial.

Supplementary Appendix 3. Optical coherence tomography analysis

Three participating institutions (n=88 patients) agreed to participate in a specific optical coherence tomography (OCT) substudy, which consisted of a five-year angiographic and OCT follow-up. Those event-free patients included in the BRS arm of the BVS-EXAMINATION study in these institutions were screened to participate in the OCT analysis. The exclusion criteria were death, target lesion myocardial infarction or target lesion revascularisation during the five years following stent implantation. Patients with creatinine clearance <45 ml/min/m^2, known hypersensitivity or allergic reaction to contrast, chronic oral anticoagulation, left ventricular ejection fraction ≤30%, platelet count <75,000/mm^3 or >70,0000/mm^3, life-threatening disease, inability to provide informed consent, pregnant or breast feeding were also excluded.

All suitable patients were contacted by phone and were invited to participate in the study. Patients accepting the protocol were cited to the outpatient clinic and signed written informed consent. This study was approved by the local ethics committee of all participating institutions and was conducted in accordance with the Declaration of Helsinki.

OCT analysis was performed by a dedicated core laboratory (BARCICORE-lab, Barcelona, Spain), using specific software for analysis (LightLab Imaging, Westford, MA, USA). The following analyses were performed:

- identification of the previously treated segment by identifying the radiopaque markers of the BRS;
- quantitative OCT analysis of the mean lumen area of the scaffolded segment, according to standard core laboratory procedures with analysis each 1 mm cross-section;
- qualitative OCT analysis at scaffold level.

As previously reported, we defined lipid-laden intima as a diffusely bordered, signal-poor region with overlying signal-rich bands in the intima. Calcification was defined as a well-delineated, signal-poor region with sharp borders. Calcium deposition at a superficial position (<200 mm from the end-luminal border) showing a sharply delineated region was calculated as neointimal calcification. Thrombi were described as masses protruding into the lumen and discontinuous from the surface of the vessel wall. Intimal rupture was defined as discontinuity of the fibrous cap connecting the lumen. Neovascularisation was defined as the presence of signal-poor holes or tubular structures with a diameter of 50 to 300 mm that were not connected to the vessel lumen. Thin-cap fibroatheroma (TCFA)-containing intima was defined as fibrous cap thickness <=65 mm at the thinnest segment and an angle of lipid tissue >=180°. Macrophage infiltration was described as a bright spot with a high signal variance from the surrounding tissue.

Neoatherosclerosis was defined as lipid-laden plaque including TCFA with or without intimal rupture and/or thrombi, and/or calcific plaque with or without neovascularisation and/or macrophage.

Supplementary Appendix 4. Propensity score matching analysis

Propensity score matching was applied to compare the five-year device-oriented primary endpoint of STEMI patients treated with BRS and those treated with EES. In the previous one-year

comparison, a propensity score matching was performed using a proprietary macro developed and tested for SPSS 20.0 (www.unc.edu/~painter), as previously shown. First, the program performed a logistic regression to score all patients according to the treatment (BRS vs EES), using as covariates clinical and procedural parameters that were clinically relevant for the endpoint: age (years), sex (male/female), diabetes mellitus (yes/no), culprit vessel and stent/scaffold length and diameter (mm). Secondly, the macro searched and selected the best match case of the EES group for every BRS case according to the absolute value of the difference between the propensity score of EES and BRS cases under consideration. Patients in the two groups were matched through a greedy algorithm based on local optimisation. The control selected for a particular case was the one closest to the case in terms of distance, whereby the maximum allowed distance for matching was set to 0.10. Analyses were then performed on the two matched groups (EES vs BRS), stratified by pairs to account for propensity score matching; as one institution did not agree to participate in this long-term follow-up, the EES patients matched with those BRS patients of that institution were excluded.

Supplementary Table 1. Baseline clinical and procedural characteristics.

	BVS group (n=235)	**EES group (n=235)**	***p*-value**
Age, years	56.0±12.9	57.5±12.0	0.624
Male sex	185 (78.7)	194 (82.6)	0.293
Smoking history	150 (63.8)	181 (77.0)	0.002
Hypertension	120 (51.1)	106 (45.1)	0.196
Diabetes	30 (12.8)	30 (12.8)	1.000
Dyslipidaemia	83 (35.3)	115 (48.9)	0.003
Previous MI	5 (2.1)	9 (3.8)	0.281
Previous PCI	7 (3.0)	10 (4.3)	0.459
Previous CABG	2 (0.9)	1 (0.4)	0.557
Previous stroke	5 (2.1)	4 (1.7)	0.736
Infarct-related artery			0.106
LAD	94 (40.0)	105 (44.7)	
RCA	116 (49.4)	92 (39.1)	
LCx	24 (10.2)	36 (15.3)	
SVG	0	0	
Left main	1 (0.2)	2 (0.9)	
Thrombectomy device use	163 (69.4)	162 (68.9)	0.920
Predilatation	181 (77.0)	67 (28.9)	<0.001
IIb/IIIa inhibitor	161 (68.5)	124 (52.8)	<0.001
Bivalirudin	0 (0)	18 (7.7)	<0.001
Unfractionated heparin	235 (100)	182 (77.4)	<0.001
Number of stents/scaffolds	1.1±0.4	1.1±0.3	0.911
Stent/scaffold diameter, mm	3.3±0.4	3.2±0.4	0.475
Stent/scaffold length, mm	21.9±8.4	22.0±9.0	0.672
Post-dilatation	54 (23.1)	30 (12.8)	0.004
TIMI pre			0.007
- 0	165 (70.2)	128 (54.9)	
- 1	9 (3.8)	17 (7.3)	

	BVS group (n=235)	**EES group (n=235)**	***p*-value**
- 2	25 (10.6)	36 (15.5)	
- 3	36 (15.3)	52 (22.3)	
TIMI post			0.353
- 0	1 (0.4)	4 (1.7)	
- 1	1 (0.4)	1 (0.4)	
- 2	11 (4.7)	6 (2.6)	
- 3	222 (94.5)	222 (94.5)	

Data are expressed as mean±SD or number (%). The p-values are from paired t-tests for continuous data and conditional logistic regression for dichotomous and ordinal data.

CABG: coronary artery bypass graft; LAD: left anterior descending artery; LCx: left circumflex artery; MI: myocardial infarction; PCI: percutaneous coronary intervention; RCA: right coronary artery; SD: standard deviation; SVG: saphenous vein graft

Supplementary Table 2. Baseline clinical and procedural characteristics of BRS patients included in the OCT substudy.

	Overall BRS group (n=235)	**OCT BRS group (n=39)**	***p*-value**
Age, years	56.0±12.9	57.1±11.0	0.921
Male sex	185 (78.7)	26 (70.3)	0.289
Smoking history	150 (63.8)	26 (66.6)	0.579
Hypertension	120 (51.1)	14 (37.8)	0.158
Diabetes	30 (12.8)	4 (10.8)	1.000
Dyslipidaemia	83 (35.3)	11 (29.7)	0.580
Previous MI	5 (2.1)	2 (5.4)	0.245
Previous PCI	7 (3.0)	1 (2.7)	1.000
Previous CABG	2 (0.9)	0 (0)	1.000
Previous stroke	5 (2.1)	0 (0)	1.000
Infarct-related artery			0.489
LAD	94 (40.0)	12 (32.4)	
RCA	116 (49.4)	23 (62.2)	
LCx	24 (10.2)	2 (5.4)	
Left main	1 (0.2)	0 (0)	
Thrombectomy device use	163 (69.4)	20 (54.1)	0.089
Predilatation	181 (77.0)	18 (48.6)	<0.001
Number of scaffolds implanted	1.1±0.4	1.1±0.5	0.822
Scaffold diameter, mm	3.3±0.4	3.4±0.4	0.842
Scaffold length, mm	21.9±8.4	22.4±8.1	0.752
Post-dilatation	54 (23.1)	12 (33.3)	0.211