Bioresorbable Vascular Scaffolds Versus Drug-Eluting Stents for Diffuse Long Coronary Narrowings

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Clinical benefits of bioresorbable vascular scaffold (BVS) implantation for long coronary lesions were not sufficiently evaluated. The efficacy and safety of BVS and metallic everolimus-eluting stent (EES) were compared for the treatment of long coronary narrowings. A total of 341 patients with diffuse long lesions (requiring device length ≥28 mm) were randomized to receive either BVS (n = 171) or EES (n = 170) implantation. The primary endpoint was major adverse cardiovascular events which included death from cardiac cause, myocardial infarction, device thrombosis, or ischemia-driven target-lesion revascularization at 12 months. The trial was terminated early because the manufacturer stopped supplying BVS. The mean lesion length was 32.2 ± 13.1 mm in the BVS group and 35.3 ± 13.0 mm in the EES group. The 12-month follow-up was completed in 332 patients (97.4%). At 12 months, the primary endpoint events occurred in 2 patients (1.2%) in the BVS group and in 4 patients (2.4%) in the EES group (hazard ratio = 0.49, 95% confidence interval = 0.09 to 2.67, p = 0.398). Definite or probable device thrombosis occurred in 1 patient (0.6%) in the BVS group and 1 patient (0.6%) in the EES group (hazard ratio = 1.00, 95% confidence interval = 0.06 to 15.94, p = 0.998). In conclusion, in patients with long native coronary artery disease, significant differences between BVS and EES were not observed regarding the primary composite endpoint of death from cardiac cause, myocardial infarction, device thrombosis, or target-lesion revascularization at 12 months. However, due to the early termination of this trial and a low number of events, the results cannot be considered clinically relevant (clinicalTrials.gov Identifier: NCT02796157). **(Am J Cardiol 2020;125:1624−1630)**

Compared with a relatively short segment of coronary artery disease, long coronary narrowings remain at a higher risk of unfavorable outcomes after percutaneous coronary intervention (PCI) due to an increased risk of in-stent restenosis and stent thrombosis.[1−3] Although the safety for bioresorbable vascular scaffold (BVS) compared with contemporary drug-eluting stent (DES) was a concern in recent studies,[4−7] the scaffold can have potential advantages including early restoration of physiological processes and superior conformability.[5,8] These advantages may be more beneficial for diffuse long coronary lesions. Therefore, the safety and efficacy of BVS implantation compared with metallic everolimus-eluting stent (EES) implantation for patients with diffuse long coronary narrowings were evaluated.

Methods

This trial was an investigator-initiated, randomized, controlled, single-blinded, multicenter study conducted at nine hospitals in Korea. The patients who required a device ≥28 mm in length with reference vessel diameter 2.5 to 3.75 mm based on angiographic estimation for de novo lesions were enrolled. There was not an upper limit on the required device length. Patients were excluded if they had the following: (1) acute myocardial infarction (MI) with unstable hemodynamic status requiring inotropic agents, mechanical ventilation, or percutaneous cardiopulmonary support within 48 hours; (2) left main coronary artery disease; (3) true bifurcation lesion requiring the two-stent technique; (4) history of previous PCI with BVS or EES in the last three months; and (5) left ventricle ejection fraction <40%. The Institutional Review Board at each participating

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center approved the protocol. All patients provided written informed consent.

After coronary angiography, patients with eligible target long lesions were randomly assigned in a 1:1 ratio to receive one of the two study devices, everolimus-eluting BVS (Absorb, Abbott Vascular, Santa Clara, CA) or everolimus-eluting cobalt-chromium stent (Xience, Abbott Vascular), using a web-based program with stratified and block randomization based on participation sites. In patients with multiple lesions, the operator determined the hierarchy of lesions and chose the target lesion for each patient before the procedure. The same type of allocated stent was used for all lesions in patients with multiple lesions.

All patients were administered a loading dose of 300 mg of aspirin and a loading dose of $P2Y_{12}$ inhibitors 24 hours before PCI. Other medications were administered based on standard practice. All operators were well-experienced with BVS implantation previous to commencement of the study. After implantation of one of the two devices, high-pressure postdilatation using a noncompliant balloon up to 0.5 mm above the nominal scaffold diameter was performed to achieve residual stenosis <10%. Intravascular imaging studies were performed at physicians' discretion. Dual-antiplatelet agent was prescribed for at least six months after PCI. All coronary angiography images were analyzed at a core laboratory by qualified analysts who were blinded to patient and procedural information (Cardiovascular Research Center, Seoul, Korea). Severe tortuosity was defined as follows; one or more bends of 90° or more, or three or more bends of 45° to 90° proximal to the diseased segment.[9] Heavy calcifications were defined as multiple persisting opacifications in more than one projection.[9]

The primary endpoint of this trial was a composite of major adverse cardiac events including cardiac death, MI, device thrombosis, or ischemia-driven target-lesion revascularization at 12 months. Clinical events were defined according to the Academic Research Consortium.[10] All deaths were considered cardiac deaths unless a definite non-cardiac cause could be established. Acute MI after hospital discharge was defined as the presence of clinical symptoms, electrocardiographic changes, or abnormal imaging findings of MI, combined with an increase in the creatine kinase myocardial band fraction above the upper normal limits or an increase in troponin-T/troponin-I to >99th percentile of the upper normal limit.[11] Device thrombosis was defined according to the recommendations of the Academic Research Consortium.[10] Ischemia-driven target lesion revascularization was defined as a repeat PCI or bypass surgery of the target lesions with either of the following: (1) ischemic symptoms or a positive stress test and angiographic diameter stenosis ≥50%, or (2) angiographic diameter stenosis ≥70% regardless of symptoms or a positive stress test.

Patients were followed up at outpatient clinics at 1, 3, 6, and 12 months. At each follow-up visit, physical examination was performed, vital signs taken, and patients were asked about interim clinical events, the use of cardiovascular medications, and adverse reactions to medication. At each participating center, patient data were recorded prospectively on electronic, standard case report forms and stored at the central data management center (Cardiovascular Research Center, Seoul, Korea). All adverse clinical events were adjudicated by independent clinicians blinded to the treatment assignment.

The trial was a non-inferiority study and based on the hypothesis that BVS was not inferior to EES regarding the primary endpoint. For the sample size calculation, the incidence of the primary endpoint at one year was assumed to be 6% based on previous studies.[12,13] With a noninferiority margin of 4.5% for the lower boundary of the 90% confidence interval (CI), a total of 876 patients were needed to achieve a one-sided alpha error rate of 2.5% and 80% power with a one-sided type 1 error rate of 0.025. However, the recruitment was prematurely terminated in March 2018 after enrollment of 341 patients because the manufacturer stopped supplying BVS. Therefore, this report provides descriptive information on endpoint events without formal hypothesis testing. The primary evaluation was performed using intention-to-treat analysis. The cumulative event rate was estimated using the Kaplan-Meier method and compared with the log-rank test. For time-to-event analysis, hazard ratios with 95%CI were determined. All analyses were conducted using SAS version 9.2 (SAS Institute Inc). All tests were two-sided and a p value <0.05 was considered statistically significant.

Results

A total of 341 patients were enrolled in this trial conducted between June 2016 and January 2018; 171 patients were randomly assigned to receive BVS implantation and 170 patients were assigned to receive EES implantation. In the BVS group, 3 patients received EES instead of BVS due to delivery failure of BVS in the target lesion and 4 patients received additional EES at distal segment after BVS implantation because of distal dissection (n = 2) or uncovered lesion (n = 2). In the EES group (n = 170), 1 patient received another DES instead of EES because of failure of device delivery, and 1 patient received BVS due to the patient's strong insistence on receiving a BVS (Figure 1).

Baseline demographic and clinical characteristics are presented in Table 1. Clinical characteristics were well balanced between the groups, except cilostazol use was more frequent in the BVS group than in the EES group. Angiographic and procedural characteristics are shown in Table 2. The use of intravascular imaging (intravascular ultrasound or optical coherence tomography) was more frequent in the BVS group than in the EES group. The mean device diameter was larger in the BVS group than in the EES group. Final balloon size was significantly larger in the BVS group than in the EES group.

Clinical follow-up at 12 months was completed in 332 patients (97.4%). Twelve-month clinical outcomes are presented in Table 3 and Figure 2. At 12 months, primary composite endpoint of major adverse cardiac events occurred in 2 patients (1.2%) in the BVS group and in 4 patients (2.4%) in the EES group (hazard ratio = 0.49, 95%CI = 0.09 to 2.67, p = 0.398). The between-group difference was not observed regarding the individual component of death from cardiac cause, MI, device thrombosis, or ischemic-driven target-vessel revascularization. Device thrombosis occurred in 1 patient (0.6%) in the BVS group and 1 patient (0.6%)

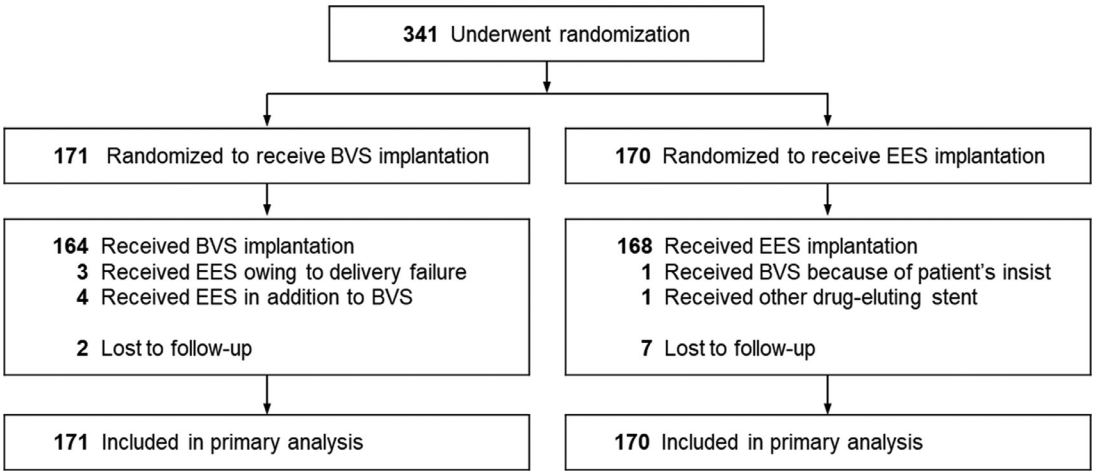

Figure 1. Trial flow diagram. BVS, bioresorbable vascular scaffold; EES, everolimus-eluting stent.

in the EES group. Ischemic-driven target-lesion revascularization was required in 1 patient in the BVS group and 1 patient in the EES group.

Discussion

In this trial, the safety and efficacy of BVS and EES for the treatment of diffuse long coronary narrowings requiring a device length ≥28 mm were compared. Although the study may have been underpowered to conclude the planned non-inferiority due to premature termination, the incidence of primary endpoint of major adverse cardiac events at 12 months was not significantly different between the BVS and the EES groups.

Several points of the trial deserve comment. First, the intravascular imaging guidance was more frequently used in the BVS group than in the EES group. Intravascular imaging-guided implantation for BVS is important for

Table 1
Patient baseline clinical and angiographic characteristics

Variable	BVS (n = 171)	EES (n = 170)	P-value
Age (years)	63 ± 10	62 ± 10	0.468
Men	129 (75%)	138 (81%)	0.199
Hypertension	88 (52%)	97 (58%)	0.300
Diabetes mellitus	53 (31%)	53 (31%)	0.971
Dyslipidemia	138 (81%)	144 (85%)	0.328
Current smoker	32 (19%)	32 (19%)	0.979
Prior percutaneous coronary intervention	27 (16%)	22 (13%)	0.453
Left ventricular ejection fraction (%)	63.5 ± 9.1	63.4 ± 9.0	0.993
Clinical presentation			0.698
Stable angina pectoris	93 (54%)	95 (56%)	
Unstable angina pectoris	69 (41%)	63 (37%)	
Acute myocardial infarction	9 (5%)	12 (7%)	
Number of narrowed coronary arteries			0.481
1	68 (40%)	57 (34%)	
2	57 (33%)	64 (38%)	
3	46 (27%)	49 (28%)	
Number of treated narrowings per patient	1.2 ± 0.4	1.3 ± 0.5	0.559
Medication at discharge			
Aspirin	165 (97%)	161 (95%)	0.421
Clopidogrel	146 (85%)	142 (84%)	0.637
Ticagrelor	22 (13%)	19 (11%)	0.632
Prasugrel	1 (1%)	4 (2%)	0.174
Cilostazol	23 (14%)	6 (4%)	<0.001
Statin	167 (98%)	159 (94%)	0.063
Beta blockers	104 (61%)	113 (67%)	0.278
Angiotensin converting enzyme inhibitors	47 (28%)	38 (22%)	0.273
Angiotensin II receptor blockers	43 (25%)	65 (38%)	0.009
Calcium channel blockers	75 (44%)	67 (39%)	0.405

Data are presented as mean ± standard deviation or number (percentage). BVS = bioresorbable vascular scaffold; EES = everolimus-eluting stent.

Table 2
Angiographic and procedural characteristics

Variables	BVS	EES	p value
Target lesions			
Number of coronary narrowings	171	170	
Coronary arteries			0.277
Left anterior descending	100 (59%)	108 (64%)	
Left circumflex	20 (12%)	24 (14%)	
Right	51 (30%)	38 (22%)	
Baseline QCA data			
Reference vessel diameter (mm)	2.96 ± 0.47	2.88 ± 0.43	0.086
Minimum lumen diameter (mm)	0.92 ± 0.53	0.81 ± 0.54	0.062
Diameter stenosis (%)	68.5 ± 18.1	71.7 ± 18.3	0.105
Lesion length (mm)	32.2 ± 13.1	35.3 ± 13.0	0.027
Use of intravascular imaging	97 (57%)	71 (42%)	0.006
Use of intravascular ultrasound	40 (23%)	57 (34%)	0.038
Use of optical coherence tomography	57 (33%)	14 (8%)	<0.001
Chronic total occlusions	25 (15%)	23 (14%)	0.772
Heavy calcification	12 (7%)	14 (8%)	0.672
Use of atherectomy	1 (0.6%)	2 (1.2%)	0.559
Severe tortuosity	18 (11%)	16 (9%)	0.731
Mean device diameter (mm)	3.31 ± 0.27	3.19 ± 0.23	<0.001
Total implanted device length (mm)	34.3 ± 11.4	39.4 ± 13.5	<0.001
Adjunct post-dilatation	117 (68%)	100 (59%)	0.065
Final balloon size (mm)	3.43 ± 0.36	3.18 ± 0.48	<0.001
Maximal inflation pressure (atm)	18.5 ± 4.4	16.8 ± 4.0	0.014
Overlapping stent	31 (18%)	25 (15%)	0.394
Number of stents per lesion	1.5 ± 0.7	1.4 ± 0.6	0.161
Post-intervention QCA data			
Reference vessel diameter (mm)	3.12 ± 0.36	3.03 ± 0.38	0.043
Minimum lumen diameter (mm)	2.58 ± 0.36	2.58 ± 0.38	0.894
Diameter stenosis (%)	17.0 ± 8.0	14.7 ± 9.2	0.015
All treated lesions			
Number of lesions	209	213	
Coronary arteries			0.660
Left anterior descending	120 (57%)	121 (57%)	
Left circumflex	30 (14%)	41 (19%)	
Right	59 (28%)	51 (24%)	
Baseline QCA data			
Reference vessel diameter (mm)	2.95 ± 0.49	2.87 ± 0.44	0.086
Minimum lumen diameter (mm)	0.94 ± 0.54	0.83 ± 0.53	0.040
Diameter stenosis (%)	67.7 ± 18.1	71.0 ± 18.1	0.079
Lesion length (mm)	31.1 ± 13.1	33.7 ± 13.6	0.059
Chronic total occlusions	29 (14%)	24 (11%)	0.419
Total implanted device length (mm)	32.0 ± 12.2	36.6 ± 14.2	<0.001
Adjunct post-dilatation	139 (67%)	115 (54%)	0.009
Final balloon size (mm)	3.41 ± 0.35	3.18 ± 0.48	<0.001
Maximal inflation pressure (atm)	18.1 ± 4.3	17.0 ± 4.0	0.056
Overlapping stent	34 (16%)	28 (13%)	0.365
Number of stents per lesion	1.4 ± 0.6	1.3 ± 0.6	0.166
Post-intervention QCA data			
Reference vessel diameter (mm)	3.11 ± 0.39	3.03 ± 0.39	0.036
Minimum lumen diameter (mm)	2.58 ± 0.39	2.59 ± 0.39	0.780
Diameter stenosis (%)	17.1 ± 8.3	14.2 ± 9.5	0.002

BVS, bioresorbable vascular scaffold; EES, everolimus-eluting stent; IVUS, intravascular ultrasound; QCA, quantitative coronary angiographic.
Data are presented as mean ± standard deviation, or number (percentage).

selecting the optimal BVS size due to the limitation of BVS overexpansion and prevention of increased footprint.[14] Tanaka et al reported the final residual percentage stenosis was lower if intravascular imaging was used to guide BVS implantation despite containing more complex lesions.[14] In addition, underexpansion, incomplete lesion coverage, and malapposition were the main causes of scaffold thrombosis.[15] Therefore, the use of intravascular imaging, particularly for long lesions, may be helpful to improve clinical outcomes with appropriate device selection and device optimization, which can be more important particularly for the BVS implantation. Further studies are needed to show whether intravascular imaging guidance for BVS implantation for long lesions improves clinical outcomes. Second, although

Table 3
Clinical outcome at 12 months

Clinical events	BVS (n = 171)	EES (n = 170)	HR (95% CI)	p value
Major adverse cardiac event	2 (1.2%)	4 (2.4%)	0.49 (0.09–2.67)	0.398
Cardiac death	0 (0%)	1 (0.6%)	–	0.307
Myocardial infarction	2 (1.2%)	3 (1.8%)	0.66 (0.11–3.92)	0.641
Device thrombosis	1 (0.6%)	1 (0.6%)	1.00 (0.06–15.94)	0.998
Definite	1		–	
Probable		1	–	
Ischemia-driven target-lesion revascularization	1 (0.6%)	1 (0.6%)	1.00 (0.06–15.94)	0.998

BVS, bioresorbable vascular scaffold; CI, confidence interval; EES, everolimus-eluting stent; HR, hazard ratio.

Major adverse cardiac event was defined as a composite of death from cardiac cause, MI, device thrombosis, or ischemia-driven target-lesion revascularization.

the patients had diffuse long lesions, the average reference vessel diameter was 2.96 ± 0.47 mm. Therefore, the device with a relatively large diameter could be implanted. The average BVS diameter was 3.31 ± 0.27 mm and the minimum diameter was 3.26 ± 0.31 mm. In the AIDA trials, a relatively higher incidence of device thrombosis rate of 3.5% was observed with a significantly higher rate than with metallic stents after 2 years of follow-up; the minimum device diameter per patient was 2.75 ± 0.27 mm.[7] Based on all-comer, multicenter registry regarding scaffold thrombosis, quantitative coronary angiographic features of small vessels were a hallmark of scaffold thrombosis, and suboptimal post-procedural angiographic results with even small deviations from the nominal BVS diameter were associated with exponential increases in the risk of scaffold thrombosis.[16] Last, cilostazol was more frequently used in the BVS group. Although the present study was randomized, the use of medication was at the physicians' discretion. More frequent use of cilostazol in addition to dual antiplatelet therapy could have produced better outcomes, particularly in the BVS group. Cilostazol was administered to 14% of the patients in the BVS group and to only 4% in the EES group. In several randomized studies and meta-analyses, adding cilostazol to dual-antiplatelet therapy after DESs provided additional clinical benefits by reducing the stent thrombosis and in-stent restenosis rates.[17–20]

The present study had several limitations. First, the trial was terminated early. Therefore, formal statistical testing for the primary hypothesis was not feasible. Second, due to the limited number of patients and clinical events, the present trial was underpowered to detect the difference in terms of clinically relevant outcomes. Third, treating physicians and analyzers in the core lab were not blinded to the devices used, resulting in the failure to balance the procedural and post-procedural treatment between the two groups. Finally, the present study provided 1-year of clinical follow-up data. Further clinical follow-up will provide information regarding possible ongoing risk over a longer period of time.

In conclusion, significant differences between BVS and EES regarding the primary composite outcome of major adverse cardiac events at 12 months were not observed in this preliminary trial. However, due to the early termination of this trial and a low number of events, the results cannot be considered clinically relevant.

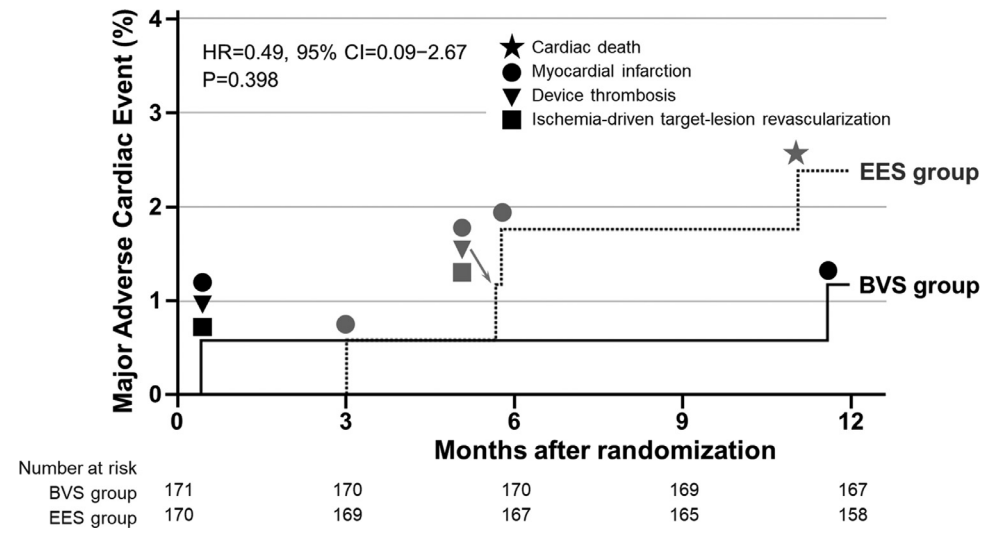

Figure 2. Kaplan-Meier curve of the primary outcome of major adverse cardiac events. Major adverse cardiac event was defined as a composite of death from cardiac cause, MI, device thrombosis, or ischemia-driven target-lesion revascularization. BVS, bioresorbable vascular scaffold; CI, confidence interval; EES, everolimus-eluting stent; HR, hazard ratio; MI, myocardial infarction.

Authors' Contribution

Jongkwon Seo:conceptualization, formal analysis, investigation, writing-original draft; Jung-Min Ahn:conceptualization, formal analysis, investigation, writing-original draft; Sung-Jin Hong:conceptualization, formal analysis, investigation, writing-original draft; Do-Yoon Kang:conceptualization, investigation, writing-review and editing; Soon Jun Hong:conceptualization, investigation, writing-review and editing; Ae-Young Her:conceptualization, investigation, writing-review and editing; Yong Hoon Kim:conceptualization, investigation, writing-review and editing; Chul-Min Ahn:conceptualization, investigation, writing-review and editing; Jung-Sun Kim:conceptualization, investigation, writing-review and editing; Byeong-Keuk Kim:conceptualization, investigation, writing-review and editing; Young-Guk Ko:conceptualization, investigation, writing-review and editing; Donghoon Choi:conceptualization, investigation, writing-review and editing; Yangsoo Jang:supervision, project administration;Seung-Jung Park:supervision, project administration; Duk-Woo Park:supervision, project administration; Myeong-Ki Hong:supervision, project administration.

Disclosures

The authors have no conflicts of interest to disclose.

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