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# Comparison of Everolimus- and Biolimus-Eluting Coronary Stents With Everolimus-Eluting Bioresorbable Vascular Scaffolds

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## ABSTRACT

**BACKGROUND** The first CE-approved bioresorbable vascular scaffold (BVS) is effective at treating simple lesions and stable coronary artery disease, but it has yet to be assessed versus the best-in-class drug-eluting stents (DES).

**OBJECTIVES** This study sought to compare the performance of a BVS with that of everolimus-eluting stents (EES) and biolimus-eluting stents (BES) in all-comer patients.

**METHODS** The EVERBIO II (Comparison of Everolimus- and Biolimus-Eluting Stents With Everolimus-Eluting Bioresorbable Vascular Scaffold Stents II) trial was a single-center, assessor-blinded study of 240 patients randomly assigned in a 1:1:1 ratio to EES, BES, or BVS. The only exclusion criterion was a reference vessel diameter >4.0 mm, which precluded treatment with BVS. The primary endpoint was angiographic late lumen loss (LLL) at 9 months. Secondary endpoints included patient-oriented major acute coronary events (MACE) (death, myocardial infarction [MI], and any revascularization), device-oriented MACE (cardiac death, MI, and target lesion revascularization), and stent thrombosis at the 9-month clinical follow-up.

**RESULTS** Follow-up angiography was performed in 216 patients (90.7%) at 9 months. In-stent LLL was similar between patients treated with BVS (0.28 ± 0.39 mm) and those treated with EES/BES (0.25 ± 0.36 mm; p = 0.30). Clinical outcomes were similar at 9 months: the patient-oriented MACE rate was 27% in BVS and 26% in the EES/BES group (p = 0.83) and the device-oriented MACE rate was 12% in BVS and 9% in the EES/BES group (p = 0.6).

**CONCLUSIONS** New-generation metallic DES (EES/BES) were not superior to BVS in terms of angiographic LLL and clinical outcomes. (Comparison of Everolimus- and Biolimus-Eluting Stents With Everolimus-Eluting Bioresorbable Vascular Scaffold Stents [EVERBIO II]; NCT01711931) (J Am Coll Cardiol 2015;65:791–801) © 2015 by the American College of Cardiology Foundation.

Drug-eluting stents (DES) have greatly reduced the risk of restenosis compared with bare-metal stents and have become the standard of care for patients undergoing percutaneous coronary intervention (PCI) (1). However, the durable polymer within the vessel is considered responsible for ongoing inflammation, leading to late complications such as stent thrombosis and

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**ABBREVIATIONS AND ACRONYMS**

**ACS** = acute coronary syndrome(s)

**ARC** = Academic Research Consortium

**BES** = biolimus-eluting stent(s)

**BVS** = bioresorbable vascular scaffold stent(s)

**DES** = drug-eluting stent(s)

**EES** = everolimus-eluting stent(s)

**LLL** = late lumen loss

**MACE** = major adverse coronary event(s)

**MI** = myocardial infarction

**PCI** = percutaneous coronary intervention

**ST** = stent thrombosis

**TLR** = target lesion revascularization

**TVR** = target vessel revascularization

neoatherogenesis (2). Not surprisingly, research and development in the field of interventional cardiology has concentrated on more biocompatible stents.

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From these innovations, the second-generation everolimus-eluting stent (EES) using a biocompatible durable polymer (fluorinated copolymer) with thin strut (81 μm) and the third-generation biolimus-eluting stent (BES) using an abluminally coated biodegradable polymer (polylactic acid) with relatively thick strut (112 μm) are currently considered the safest DES. Several trials have demonstrated the superiority of both EES and BES over earlier generations of DES in long-term clinical outcomes (3–10). Outcomes were similar, however, when EES was compared with BES (11,12). Furthermore, Natsuaki et al. (13) found BES to be noninferior to EES for in-stent late lumen loss (LLL) at 8 months.

More recently, everolimus-eluting bioresorbable vascular scaffold stents (BVS) have been developed with the aim to further improve late outcomes. The Absorb device (Abbott Vascular, Santa Clara, California) is the first CE-approved BVS. The prospective, open-label, 2-stage ABSORB study of 131 patients was conducted in Europe and New Zealand and led to approval of the Absorb BVS by the European Union in January 2011 to treat coronary artery lesions (14). The reported LLL was 0.27 mm at 12 months, and the composite endpoint major acute coronary event (MACE) rate was 6.8% at 2-year follow-up (15,16).

Due to its resorption kinetics, BVS radial strength is disturbed 6 to 12 months after implantation. This phenomenon could be responsible for the higher restenosis rate compared with metallic platforms at midterm, especially in complex lesions. Its noninferiority to EES is currently under investigation in the multicenter randomized ABSORB II trial, in which 500 patients are anticipated to enroll (17). Published head-to-head data on BVS compared with EES or BES are lacking. We therefore sought to compare the efficacy, at midterm, of the Absorb BVS, the Promus Element EES (Boston Scientific, Marlborough, Massachusetts), and Biomatrix Flex BES (Biosensors Europe SA, Morges, Switzerland) using LLL as an early marker of restenosis (18,19) in all-comer patients. Assuming similar outcomes for the primary endpoint of LLL between BES and EES as suggested by the NEXT (Nobori Biolimus-Eluting Versus Xience/Promus Everolimus-Eluting Stent Trial) (13), COMPARE II (A Trial of Everolimus-Eluting Stents and Paclitaxel-Eluting Stents for Coronary Revascularization in Daily Practice II) (11), and EVERBIO (Everolimus-Versus Biolimus-Eluting Stents in All-Comers) trial (12), which demonstrated similar target lesion revascularization (TLR) rates, both DES were unified as 1 comparator.

## METHODS

**STUDY DESIGN AND PATIENTS.** EVERBIO II was a single-center, assessor-blinded, randomized study (20). Between November 2012 and November 2013, 240 patients 18 years of age or older, capable of providing informed consent, with symptomatic coronary artery disease or silent ischemia were recruited at the Fribourg University and Hospital (Switzerland). The study protocol defined no limit for lesion length, number of target lesions, or number of vessels. The only exclusion criterion was a reference vessel size >4.0 mm that would have prevented the implantation of BVS. Patients with a known or presumed hypersensitivity to heparin, antiplatelet drugs, or contrast dye not controllable with standard premedication were excluded. The EVERBIO II study complied with the Helsinki Declaration and was approved by the local ethics committee of Fribourg University and Hospital (043/12-CER-FR). All patients provided written, informed consent for participation.

Patient randomization was performed after lesion preparation on the basis of computer-generated random numbers. Allocation was concealed in sealed nontransparent numbered envelopes. Only the outcome assessors and data analysts were blinded to the intervention.

The Absorb BVS (Abbott Vascular) has a poly-DL-lactide coating releasing everolimus. The scaffold body is semi-crystalline poly-L-lactide, which is completely degraded via hydrolysis and bioresorbed within 2 years via the Krebs cycle. The scaffold has 150-μm struts.

The Promus Element stent (Boston Scientific) consists of a platinum chromium alloy with everolimus (100 μg/cm$^2$) applied in a durable, biocompatible acrylic polymer and fluorinated copolymer.

The Biomatrix Flex stent (Biosensors Europe SA) consists of stainless steel (strut thickness of 112 μm) with only abluminal coating with a biodegradable polymer layer (20 μm) that dissolves 6 to 9 months after implantation and from which the lipophilic antiproliferative drug biolimus elutes.

Procedures were performed via the femoral or radial artery with a 5-F to 6-F guiding catheter.

Standard interventional techniques were used and performed according to practice guidelines. A preprocedural antithrombotic regimen was systematically achieved with aspirin (500 mg intravenous bolus for those not under treatment and 100 mg for those already on aspirin and then 100 mg/day for all) and unfractionated heparin (70 UI/kg), whereas a glycoprotein IIb/IIIa inhibitor was administered per operator discretion. All patients received either a minimum 600-mg loading dose of clopidogrel, 180 mg of ticagrelor, or 60 mg of prasugrel before or immediately after the procedure. Lifelong ≥100 mg daily aspirin and 75 mg daily clopidogrel, 90 mg twice daily ticagrelor, or 10 mg prasugrel for a minimum of 6 months were prescribed. For patients receiving oral anticoagulation therapy, we prescribed 100 mg of aspirin once daily for a minimum of 1 month and clopidogrel 75 mg daily for 12 months in addition to oral anticoagulation. Other medications were prescribed per standard of care. All patients were monitored for 4 to 12 h in an intermediate care unit and underwent baseline and 3- to 6-h cardiac biomarker measurements. A standard 12-lead electrocardiogram was recorded before and immediately after the procedure and with each biomarker measurement.

**STUDY ENDPOINTS.** The primary angiographic endpoint was in-stent LLL at 9 months. Based on previous reports (21,22), comparison of LLL between the BVS and EES or BES at 9 months would represent the "most unfavorable" timing for the bioabsorbable scaffold and would thus provide important information regarding its clinical effectiveness. The secondary angiographic endpoints were in-segment LLL, binary restenosis at 9 months, acute gain, minimal lumen diameter, and percent diameter stenosis.

The secondary clinical endpoints included a patient-oriented MACE rate (composite of death, myocardial infarction [MI], and any revascularization), a device-oriented MACE (composite of cardiac death, MI, and TLR), and stent thrombosis (ST) at 1 year. All clinical endpoints were defined according to Academic Research Consortium (ARC) criteria (23). Peri-procedural MI was defined according to the Global MI Task Force for the Universal Definition of Myocardial Infarction (24). Death was considered of cardiac origin when due to proximate cardiac cause, unwitnessed death, or death of unknown cause. TLR was defined as repeat revascularization within the stent or the 5-mm boarders proximal and distal to the stent. Target vessel revascularization (TVR) was defined as any revascularization in the stented vessel. TVR or TLR was considered ischemia driven if associated with a positive functional study, target vessel diameter, or stenosis ≥50% by core laboratory quantitative analysis with ischemic symptoms or a target vessel (or lesion) diameter stenosis ≥70% with or without documented ischemia. MI was defined as either the development of new pathological Q waves ≥0.04 s in duration in ≥2 contiguous leads or an elevation of creatine phosphokinase levels to >2 times normal with positive creatine phosphokinase-MB or troponin I levels. ST was considered definite if there was angiographic confirmation of thrombus, with or without vessel occlusion, associated with clinical or electrocardiographic signs of acute ischemia or elevation of creatine kinase levels to twice the normal value within 48 h of angiography. ST was classified as probable if unexplained death occurred within 30 days after the index procedure or if MI, occurring at any time after the index procedure, was documented in an area vascularized by the target vessel in the absence of angiographic ST confirmation. ST was considered possible in any unexplained death occurring more than 30 days after intracoronary stenting until end of follow-up.

Coronary angiograms were digitally recorded at baseline, immediately after the procedure, and at follow-up and were assessed at the angiographic core laboratory of the University of Fribourg. Angiogram readers were noncardiologists and were unaware of study endpoints. The projection that best showed the stenosis was used for all analyses. Patients received nitroglycerin before angiography, and measurements were performed on cineangiograms. The contrast-filled, nontapered tip of the catheter was used for calibration. Digital angiograms were analyzed with the use of an automated edge detection system (CAAS II, Pie Medical Imaging, Maastricht, the Netherlands). LLL was defined as the difference between the minimum lumen diameter post-procedure and at 9 months. In-stent was considered for measurements in the implanted stent, whereas in-segment embraced the complete target lesion in cases of multiple stent implantations. Binary restenosis was defined as >50% diameter stenosis. Any unscheduled angiogram after 6 months was considered as 9-month follow-up angiogram.

All in-hospital events were recorded before discharge. Clinical follow-up was scheduled at 3, 6, 9, and 12 months and at 2 and 5 years. If the patient was not accessible, data were retrieved from the referring physician or the hospital electronic database. An independent Clinical Events Adjudication Committee (CEAC), including interventional and noninterventional cardiologists, reviewed and adjudicated all reported events and endpoints and performed

computation and angiographic measurements. All CEAC members were blinded to stent allocation.

**STATISTICAL ANALYSES.** This trial was powered for superiority of DES over BVS for the primary endpoint of LLL at 9 months. On the basis of published LLL data, we assumed a difference of 0.2 mm in LLL at 9 months (BES/EES 0.3 mm vs. BVS 0.5 mm; SD 0.5 mm). Of note, the assumed LLL of 0.5 mm in the BVS group was based on: 1) the hypothesis that LLL would be maximal at 6 to 12 months (LLL of 0.7 to 0.9 mm, with a peak in pigs at 3 to 6 months) (21); and 2) the hypothesis that LLL would be greater in complex lesions such as in the EVERBIO II trial than that expected in simple lesions such as in the ABSORB B cohort (LLL of 0.2 mm at 6 months) due to a higher rate of scaffold recoil (with or without premature fracture) (22). On the basis of these criteria, the sample size of 240 patients was considered to achieve a power of 90%. This allowed for a dropout rate of 20%, in which case the study would still yield a power of 83%. Sample size calculations were performed using Sample Power 3 (SPSS Inc., Chicago, Illinois) at a 2-tailed significance level of alpha = 0.05.

Baseline and procedural characteristics, as well as angiographic and clinical outcomes, were compared between patients receiving BVS and patients receiving EES/BES.

Categorical variables are reported as counts and percentages; continuous variables are reported as mean and SD or as median with 25% to 75% interquartile range according to their distribution. Normality was assessed by visual inspection of histograms and the computation of Q-Q plots. Categorical variables were compared using chi-square or Fisher exact test as appropriate. Continuous variables were analyzed using the Student *t* test or the Wilcoxon rank-sum test according to their distribution. For quantitative coronary angiography, data are reported as mean and SD, regardless of distribution. Pre-specified stratified analysis was performed according to the presence/absence of diabetes, acute coronary syndrome (ACS), and complex lesions. Survival free from the occurrence of clinical endpoints was compared using the log-rank test and plotted as Kaplan-Meier survival functions.

All statistical analyses were performed using dedicated software (Stata version 13, StataCorp LP, College Station, Texas) at a 2-tailed significance level of alpha = 0.05.

## RESULTS

**Figure 1** depicts patient flow. A total of 240 patients were enrolled and randomized to BVS (n = 80), EES (n = 80), or BES (n = 80) implantation. Two patients randomized to BVS were excluded due to important protocol violations (did not receive study stent). The total dropout rate was 9.2%, with 8 (10%) in the EES, 5 (6.3%) in the BES, and 9 (11.5%) in the BVS groups who withdrew consent for follow-up angiography; 216 patients (90.8%) underwent 9-month follow-up angiography. Baseline clinical characteristics were similar in both groups (**Table 1**). Mean age of participants was 65 ± 11 years, a majority of whom were men (79%); 23% had diabetes, 17% a prior history of MI, and 31% had already undergone PCI. The clinical presentation was ACS in 39% of cases.

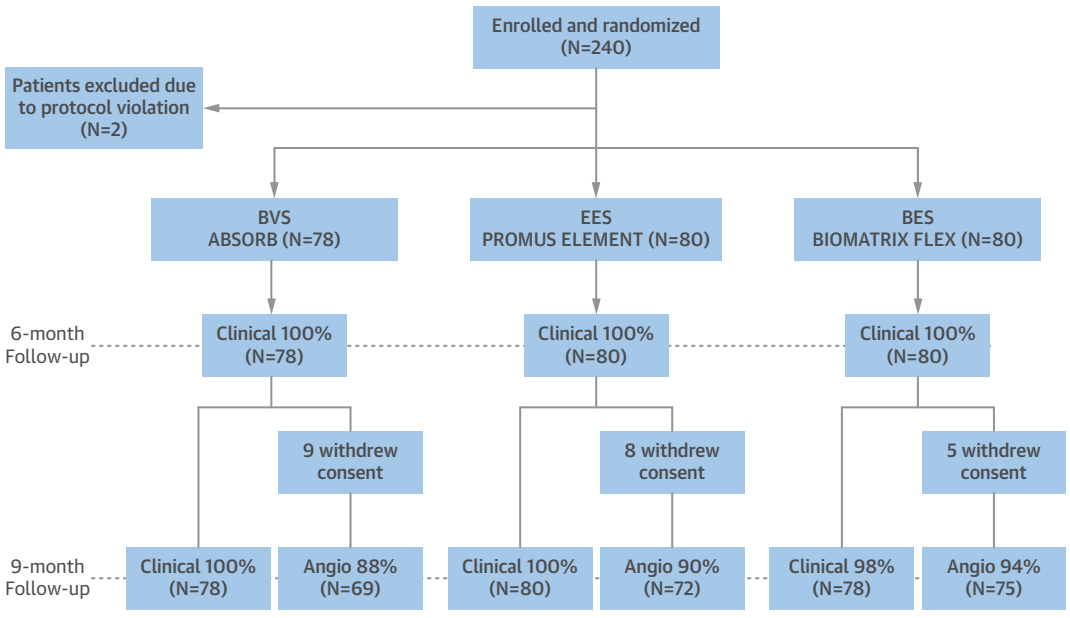
The baseline angiographic and procedural characteristics were generally well balanced (**Table 2**). Pre-procedural dimensions were similar except for reference vessel diameter (BVS 2.77 ± 0.60 mm vs. EES/BES 2.46 ± 0.78 mm; $p < 0.01$). Significant differences in PCI technique between BVS and EES/BES were observed: less direct stenting (3% vs. 17%; $p < 0.01$); higher incidence of hybrid PCI (defined as the concomitant implantation of 1 study and 1 nonstudy stent in the same lesion; 4% vs. 1%; $p = 0.03$); trend toward longer scaffold (22.8 ± 8.8 mm vs. 20.7 ± 12.1 mm; $p = 0.08$) of greater diameter (3.13 ± 0.37 mm vs. 2.99 ± 0.82 mm; $p = 0.03$).

Immediate post-procedural results are summarized in **Table 3**. Due to the longer scaffold with greater diameter, in-segment dimensions tended to be greater after BVS implantation than after EES/BES implantation. On the other hand, due to greater acute recoil in BVS (9.5 ± 6.5% vs. 6.6 ± 4.7%; $p < 0.01$), post-procedural in-stent dimensions tended to be lower with BVS compared with EES/BES.

At 9 months, the primary angiographic endpoint of in-stent LLL was similar in both groups, with 0.28 ± 0.39 mm for BVS and 0.25 ± 0.36 mm for EES/BES (difference 0.04 mm; 95% CI: −0.06 to 0.13; $p = 0.30$). There was no difference for in-stent LLL between EES and BES ($p = 0.75$). Angiographic findings are depicted in the **Central Illustration** and **Figure 2**. Stratified analyses of in-stent LLL did not reveal significant differences in treatment effects between patients with and without diabetics (p for interaction = 0.33) nor between patients with and without ACS (p for interaction = 0.28). Moreover, treatment effect was not different for complex versus simple lesions (p for interaction = 0.94).

Furthermore, we performed a post-hoc noninferiority analysis based on the noninferiority margin published in the NEXT trial (0.195 mm) (13). The inclusion of 240 patients with an unequal

**FIGURE 1** Patient Study Flow




Patients were randomized 1:1:1 to 1 of 3 stent platforms. BES = biolimus-eluting stent(s); BVS = biovascular scaffold stent(s); EES = everolimus-eluting stent(s).

**TABLE 1** Baseline Patient Characteristics

| | EES (n = 80) | BES (n = 80) | EES and BES (n = 160) | BVS (n = 78) | p Value | | |
|---|---|---|---|---|---|---|---|
| | | | | | EES vs. BVS | BES vs. BVS | EES/BES vs. BVS |
| Male | 64 (80) | 64 (80) | 128 (80) | 61 (78) | 0.78 | 0.78 | 0.75 |
| Age, yrs | 65 ± 11 | 65 ± 10 | 65 ± 11 | 65 ± 11 | 0.78 | 0.99 | 0.88 |
| Hypertension | 51 (64) | 50 (63) | 101 (63) | 43 (55) | 0.27 | 0.35 | 0.24 |
| Diabetes | 13 (16) | 26 (33) | 39 (24) | 17 (22) | 0.37 | 0.13 | 0.66 |
| Non-insulin dependent | 8 (10) | 21 (26) | 29 (18) | 17 (22) | 0.04 | 0.51 | 0.50 |
| Smoking | 30 (38) | 25 (31) | 55 (34) | 28 (36) | 0.83 | 0.54 | 0.82 |
| Dyslipidemia | 50 (63) | 52 (65) | 102 (64) | 44 (56) | 0.44 | 0.27 | 0.28 |
| Family history of CAD | 23 (29) | 23 (29) | 46 (29) | 23 (30) | 0.92 | 0.92 | 0.91 |
| Previous PCI | 25 (31) | 23 (29) | 48 (30) | 25 (32) | 0.91 | 0.65 | 0.75 |
| Previous CABG | 11 (14) | 16 (20) | 27 (17) | 6 (8) | 0.22 | 0.03 | 0.07 |
| Previous MI | 14 (18) | 16 (20) | 30 (19) | 11 (14) | 0.56 | 0.33 | 0.37 |
| Indication for index procedure | | | | | 0.74 | 0.14 | 0.72 |
| Unstable angina | 5 (6) | 9 (11) | 14 (9) | 6 (8) | | | |
| NSTEMI | 16 (20) | 21 (26) | 37 (23) | 13 (17) | | | |
| STEMI | 6 (8) | 8 (10) | 14 (9) | 9 (12) | | | |
| Stable angina | 47 (59) | 27 (34) | 74 (46) | 41 (53) | | | |
| Silent ischemia | 6 (8) | 15 (19) | 21 (13) | 9 (12) | | | |
| LVEF, %* | 60 (55-65) | 58 (45-65) | 60 (48-65) | 61 (50-66) | 0.74 | 0.19 | 0.35 |

Values are n (%), mean ± SD, or median (interquartile range). *LVEF as assessed with ultrasound, cardiac magnetic resonance imaging, or left ventricular angiography.

BES = biolimus-eluting stent(s); BVS = bioresorbable vascular scaffold stent(s); CABG = coronary artery bypass grafting; CAD = coronary artery disease; EES = everolimus-eluting stent(s); LVEF = left ventricular ejection fraction; MI = myocardial infarction; NSTEMI = non-ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

**TABLE 2 Procedural Characteristics**

| | EES (n = 80) | BES (n = 80) | EES and BES (n = 160) | BVS (n = 78) | p Value EES vs. BVS | p Value BES vs. BVS | p Value EES/BES vs. BVS |
|---|---|---|---|---|---|---|---|
| Vessels diseased per patient | 1.9 ± 0.8 | 1.9 ± 0.8 | 1.9 ± 0.6 | 1.9 ± 0.7 | 0.74 | 0.67 | 0.67 |
| Vessels treated per patient | 1.2 ± 0.4 | 1.1 ± 0.4 | 1.1 ± 0.4 | 1.1 ± 0.3 | 0.51 | 0.83 | 0.50 |
| Lesions per patient | 2.1 ± 1.3 | 2.2 ± 1.4 | 2.2 ± 1.3 | 2.1 ± 1.4 | 0.98 | 0.75 | 0.77 |
| Lesions treated per patient | 1.5 ± 0.8 | 1.4 ± 0.6 | 1.4 ± 0.7 | 1.3 ± 0.5 | 0.3 | 0.85 | 0.60 |
| | (n = 112) | (n = 117) | (n = 229) | (n = 96) | | | |
| Target coronary artery | | | | | 0.31 | 0.05 | 0.19 |
| LM | 1 (1) | 1 (1) | 2 (1) | 0 (0) | | | |
| LAD | 44 (39) | 34 (29) | 78 (34) | 44 (46) | | | |
| LCX | 21 (19) | 27 (23) | 48 (21) | 24 (25) | | | |
| RCA | 40 (36) | 48 (41) | 88 (38) | 24 (25) | | | |
| Arterial graft | 2 (2) | 1 (1) | 3 (1) | 0 (0) | | | |
| Vein graft | 4 (4) | 6 (5) | 10 (4) | 4 (4) | | | |
| Type of intervention per lesion | | | | | | | |
| Pure study stent implantation | 111 (1) | 117 (100) | 228 (99) | 92 (96) | 0.18 | 0.03 | 0.03 |
| Hybrid with other DES implantation | 1 (1) | 0 (0) | 1 (1) | 4 (4) | 0.18 | 0.03 | 0.03 |
| Hybrid with BMS implantation | 0 (0) | 0 (0) | 0 (0) | 0 (0) | | | |
| Lesion complexity | | | | | | | |
| A | 28 (25) | 34 (29) | 62 (27) | 19 (20) | 0.41 | 0.15 | 0.21 |
| B1 | 45 (40) | 49 (42) | 94 (41) | 49 (51) | 0.13 | 0.21 | 0.11 |
| B2 | 19 (17) | 17 (15) | 36 (16) | 13 (14) | 0.57 | 1 | 0.74 |
| C | 20 (18) | 17 (15) | 37 (16) | 15 (16) | 0.71 | 0.85 | 1 |
| TIMI flow post-intervention per lesion | 3 (3-3) | 3 (3-3) | 3 (3-3) | 3 (3-3) | 0.35 | 1 | 0.52 |
| Restenotic lesion | 2 (2) | 3 (3) | 5 (2) | 1 (1) | 1.00 | 0.63 | 0.50 |
| Chronic total occlusion | 7 (6) | 5 (4) | 12 (5) | 1 (1) | 0.07 | 0.16 | 0.12 |
| Thrombus aspiration | 5 (4) | 7 (6) | 12 (5) | 7 (7) | 0.38 | 0.70 | 0.47 |
| Number of stents per lesion | 1.3 ± 0.7 | 1.1 ± 0.4 | 1.2 ± 0.6 | 1.2 ± 0.5 | 0.04 | 0.14 | 0.55 |
| Total stent length per lesion, mm | 22.1 ± 13.8 | 19.3 ± 10.0 | 20.7 ± 12.1 | 22.8 ± 8.8 | 0.67 | <0.01 | 0.08 |
| Maximum stent diameter per lesion, mm | 3.0 ± 1.0 | 3.0 ± 0.6 | 3.0 ± 0.8 | 3.1 ± 0.4 | 0.31 | <0.01 | 0.03 |
| Maximum pressure per lesion, atm | 14.6 ± 2.9 | 13.8 ± 3.0 | 14.2 ± 3.0 | 13.6 ± 2.8 | 0.04 | 0.67 | 0.09 |
| Overlapping stents per lesion | 26 (23) | 14 (12) | 40 (17) | 16 (17) | 0.24 | 0.33 | 0.86 |
| Direct stenting per lesion | 16 (14) | 23 (20) | 39 (17) | 3 (3) | <0.01 | <0.01 | <0.01 |
| Post-dilation per lesion | 35 (31) | 35 (30) | 70 (31) | 33 (34) | 0.63 | 0.49 | 0.50 |

Values are mean ± SD, n (%), or median (interquartile range).

BMS = bare-metal stent(s); DES = drug-eluting stent(s); LAD = left anterior descending; LCX = left circumflex; LM = left main; RCA = right coronary artery; TIMI = Thrombolysis In Myocardial Infarction; other abbreviations as in Table 1.

treatment assignment of 2:1 would have yielded a power of 82% to detect noninferiority at a 1-sided alpha level of 0.025 with a noninferiority margin of 0.195 ± 0.49 mm for the outcomes in both treatment arms. This retrospective analysis was done for illustrative purposes only. The difference of 0.04 mm (95% CI: −0.06 to 0.13) in favor of the metallic stents significantly demonstrated BVS noninferiority (p = 0.001) for in-stent LLL at 9 months.

The secondary angiographic endpoint of in-segment LLL, however, was slightly but significantly higher in BVS (0.30 ± 0.44 mm) versus EES/BES (0.19 ± 0.42 mm; p = 0.03). Taken separately, there was no difference between EES and BES (p = 0.72).

At 9 months, there were no differences in the secondary endpoints of device-oriented MACE (EES/BES 12% vs. BVS 9%; p = 0.60) or patient-oriented MACE (EES/BES 26% vs. BVS 27%; p = 0.83). Clinically driven TLR also was similar, occurring in 6% of patients receiving EES/BES and 8% of patients receiving BVS (p = 0.54), as was clinically driven TVR in 8% for EES/BES and 10% for BVS (p = 0.59). Non-TVR was similar in both groups, 11% versus 12% (p = 0.83) for EES/BES and BVS, respectively, and non-target vessel-related MI occurred once in each group, but there were no target vessel-related MIs. Overall, mortality was 2%. One death of unknown cause occurred in the BVS group at 238 days post-procedure and was, according to ARC criteria, considered a

**TABLE 3** Quantitative Coronary Angiography Measurements

| | EES (n = 103) | BES (n = 106) | EES/BES (n = 209) | BVS (n = 75) | p Value* | | |
|---|---|---|---|---|---|---|---|
| | | | | | EES vs. BVS | BES vs. BVS | EES/BES vs. BVS |
| Pre-procedure | | | | | | | |
| MLD, mm | 0.52 ± 0.42 | 0.59 ± 0.50 | 0.55 ± 0.46 | 0.60 ± 0.58 | 0.58 | 0.99 | 0.75 |
| Diameter stenosis, % | 79.78 ± 15.3 | 78.7 ± 15.3 | 79.2 ± 15.7 | 81.3 ± 16.2 | 0.48 | 0.30 | 0.33 |
| RVD, mm | 2.39 ± 0.70 | 2.53 ± 0.84 | 2.46 ± 0.78 | 2.77 ± 0.60 | <0.01 | 0.04 | <0.01 |
| Post-procedure | | | | | | | |
| MLD, in-stent, mm | 2.62 ± 0.40 | 2.72 ± 0.53 | 2.67 ± 0.47 | 2.56 ± 0.43 | 0.36 | 0.08 | 0.18 |
| MLD, in-segment, mm | 2.11 ± 0.45 | 2.24 ± 0.60 | 2.17 ± 0.53 | 2.35 ± 0.51 | <0.01 | 0.20 | 0.01 |
| Diameter stenosis, in-stent, % | 8.1 ± 4.8 | 7.1 ± 5.8 | 7.6 ± 5.3 | 9.3 ± 5.7 | 0.28 | <0.01 | 0.04 |
| Diameter stenosis, in-segment, % | 12.9 ± 10.4 | 12.3 ± 9.4 | 12.6 ± 9.9 | 11.8 ± 7.4 | 0.44 | 0.50 | 0.41 |
| Acute gain, in-stent, mm | 2.09 ± 0.49 | 2.12 ± 0.53 | 2.11 ± 0.51 | 1.97 ± 0.66 | 0.47 | 0.21 | 0.35 |
| Acute gain, in-segment, mm | 1.59 ± 0.49 | 1.65 ± 0.58 | 1.62 ± 0.53 | 1.76 ± 0.73 | 0.07 | 0.41 | 0.12 |
| Acute recoil, % | 6.2 ± 4.2 | 6.9 ± 5.2 | 6.6 ± 4.7 | 9.5 ± 6.5 | <0.01 | <0.01 | <0.01 |
| 9 months | | | | | | | |
| MLD, in-stent, mm | 2.38 ± 0.47 | 2.57 ± 0.65 | 2.42 ± 0.56 | 2.28 ± 0.51 | 0.17 | 0.02 | 0.07 |
| MLD, in-segment, mm | 1.91 ± 0.48 | 2.06 ± 0.63 | 1.99 ± 0.58 | 2.05 ± 0.51 | 0.19 | 0.86 | 0.42 |
| Diameter stenosis, in-stent, % | 11.3 ± 9.8 | 12.6 ± 14.9 | 11.9 ± 12.5 | 16.9 ± 11.6 | <0.01 | <0.01 | <0.01 |
| Diameter stenosis, in-segment, % | 15.5 ± 11.0 | 16.1 ± 17.2 | 15.8 ± 14.3 | 17.8 ± 11.7 | 0.17 | 0.01 | 0.03 |
| RVD, mm | 2.68 ± 0.51 | 2.66 ± 0.48 | 2.67 ± 0.37 | 2.83 ± 0.51 | 0.07 | 0.04 | 0.03 |
| Late loss, in-stent, mm | 0.24 ± 0.32 | 0.25 ± 0.41 | 0.25 ± 0.36 | 0.28 ± 0.39 | 0.40 | 0.31 | 0.30 |
| Late loss, in-segment, mm | 0.20 ± 0.43 | 0.17 ± 0.40 | 0.19 ± 0.42 | 0.30 ± 0.44 | 0.08 | 0.03 | 0.03 |
| Binary restenosis, in-stent | 4 (4) | 5 (5) | 9 (4) | 4 (5) | 0.64 | 0.85 | 0.71 |
| Binary restenosis, in-segment | 9 (9) | 11 (10) | 20 (10) | 8 (11) | 0.67 | 1.00 | 0.78 |

Values are mean ± SD or n (%). *p values are from Fisher exact, Student *t* test, or Wilcoxon rank-sum test, as appropriate.
MLD = minimal lumen diameter; RVD = reference vessel diameter; other abbreviations as in Table 1.

cardiac death as well as possible ST. However, there was no ARC-defined definite or probable ST during follow-up. Clinical outcomes are summarized in Table 4, Central Illustration, and Figure 3.

## DISCUSSION

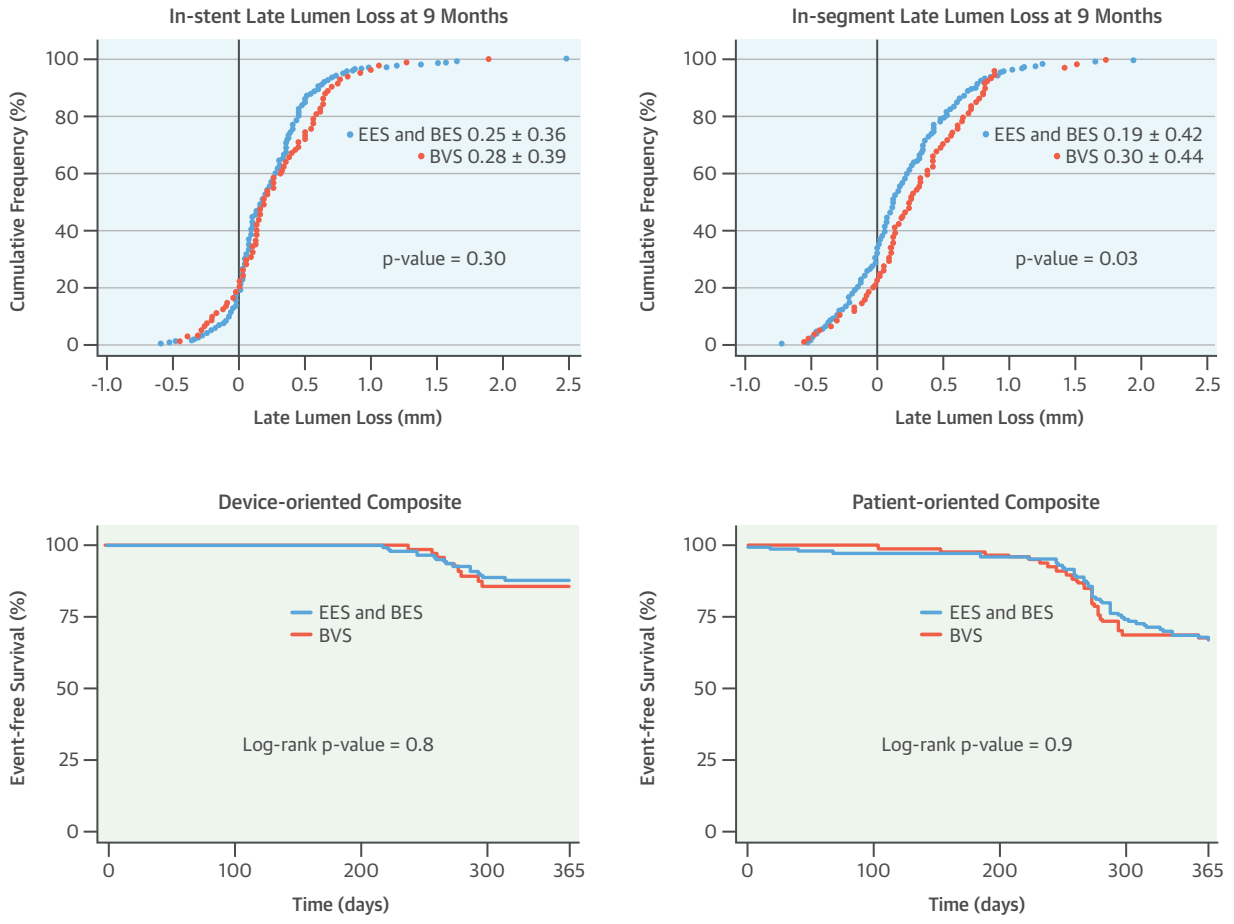
This randomized, controlled, single-center, assessor-blinded study investigated the angiographic and clinical outcomes in 238 patients assigned to BVS, EES, or BES implantation over a 9-month follow-up period. The major finding was no significant differences between the 2 treatment arms for the primary angiographic endpoint of in-stent LLL at 9-month follow-up or in any of the secondary clinical endpoints (Central Illustration).

In-stent LLL is considered a particularly robust endpoint for discrimination of new coronary stents for which binary rates are anticipated to be low. It is highly predictive of clinical revascularization rates, correlating with binary restenosis and TLR, and especially useful for "early" trials, such as ours, with limited sample size (19,25).

To better analyze BVS effectiveness in complex patients, we deliberately chose to compare it with the best competitors and at its weakest time point. On the basis of animal evidence, we speculated that BVS failure would be 6 to 12 months post-implantation. As reported by Otsuka et al. (21), BVS in-stent LLL peaked and was significantly higher than that of EES in-stent LLL (6-month LLL: BVS 0.69 ± 0.18 mm vs. EES 0.38 ± 0.15 mm; p = 0.01) at the 3- to 6-month follow-up in a mini-pig model but declined thereafter with coronary remodeling (e.g., 42-month LLL: BVS −0.42 ± 0.35 mm vs. EES −0.12 ± 0.31 mm; p = 0.06). This is supported by the following: 1) BVS resorption kinetics that significantly disturb radial strength and the mechanical aptitude of the platform 6 months after implantation based on the model of Prabhu and Hossainy (26); and 2) after a given time point (18 to 24 months based on the ABSORB [27] and ABSORB-EXTEND [28] trials), additional benefits are expected from BVS compared with metallic DES. Among these late putative advantages are a lowered risk of delayed complications (ST, neoatherosclerosis), partial restoration of vasomotion, plaque sealing/capping, and plaque remodeling/resorption (29).

Our reassuring findings revealed excellent in-stent LLL for both groups in a patient population with a

**CENTRAL ILLUSTRATION** **Comparison of Everolimus- and Biolimus-Eluting Coronary Stents With Everolimus-Eluting Bioresorbable Vascular Scaffolds: Clinical and Angiographic Endpoints**



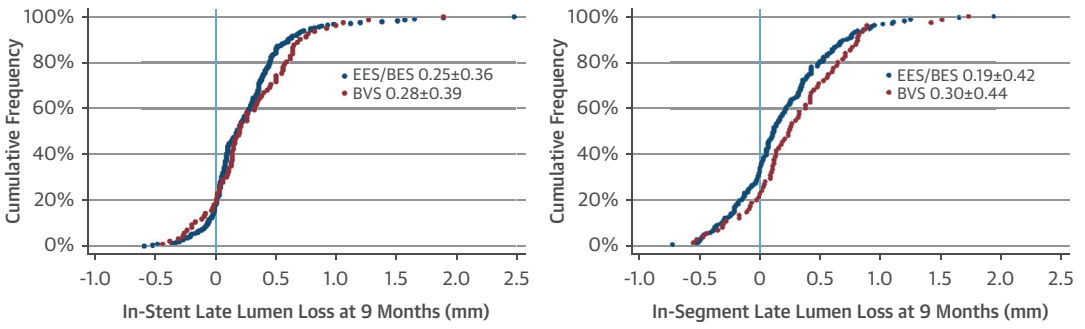

Puricel, S. et al. J Am Coll Cardiol. 2015; 65(8):791–801.

When compared with contemporary metallic stents, the biovascular scaffold stent (BVS) was noninferior for in-stent late lumen loss but produced significantly higher in-segment late lumen loss. Clinical endpoints relating both to devices and patients were similar between study arms. BES = biolimus-eluting stent(s); EES = everolimus-eluting stent(s).

substantial number of ACS events and complex lesion characteristics. The BVS matched the in-stent LLL and clinical outcomes of the safest DES on the market. This should be emphasized because EES previously was demonstrated to be noninferior to sirolimus-eluting stents and superior to paclitaxel-eluting stents (3–6).

One propensity score–matched registry (LESSON-1 [Long-Term Comparison of Everolimus-Eluting and Sirolimus-Eluting Stents for Coronary Revascularization-1]) showed a trend toward a lower risk of death, MI, and TVR with EES compared with sirolimus-eluting stents during a 3-year follow-up (7). Similarly, BES proved to be superior to SES at the 5-year follow-up in the LEADERS (Limus Eluted From a Durable Versus Erodable Stent Coating) trial, with fewer episodes of very late ST (0.7% vs. 2.5%; p = 0.003) and a lower rate of composite clinical outcomes (10). As suggested by Moreno et al. (18) in a meta-analysis of 8,641 patients from 21 trials, a 0.1-mm reduction in mean in-stent LLL (DES compared with bare-metal stent) was associated with a

**FIGURE 2** Cumulative Frequency Distribution of In-Stent and In-Segment LLL




At 9 months, metallic stents were not superior to BVS for in-stent late lumen loss (LLL); in-segment LLL was higher with BVS, significantly so versus BES ($p = 0.03$). Abbreviations as in Figure 1.

1.2-fold decrease in the number needed to treat for TLR (18). Thus, the 0.06-mm increase observed in the present trial (BVS in-stent LLL compared with EES/BES in-stent LLL) would indicate a marginal increase in TLR for the BVS group. Moreover, accumulating evidence demonstrates a late catch-up phenomenon with metallic DES not yet observed with BVS.

In-segment LLL was slightly but significantly higher in BVS compared with EES/BES, reinforcing our primary hypothesis of DES superiority within the 6- to 12-month time frame. A possible explanation for this difference may be the modest and transient constrictive effect found at scaffold edges (30). From a patient perspective, in-segment LLL is meaningful because it encompasses the entire treated lesion, including its edges. However, the clinical impact of in-segment LLL is uncertain and has not been clearly demonstrated for metallic platforms. In DES, in-segment LLL has not correlated with TLR as well as in-stent LLL (19,25). The challenges in accurately detecting BVS edges make in-stent—namely "in-scaffold"—LLL a complex and uncertain measure. In-segment may therefore be more sensitive than in-stent parameters. Although we believe particular attention should be paid to patients receiving BVS during the intermediate phase and possibly up to 2 years, the accumulated evidence of improved angiographic parameters 18 to 24 months after BVS implantation suggests a low clinical impact of in-segment LLL.

Overall, the current data are reassuring and demonstrate a satisfactory BVS safety profile in all-comer patients with broad clinical presentations. This is of paramount importance given other published data in all-comer patients (31,32) and the continuous increase in BVS implantation worldwide.

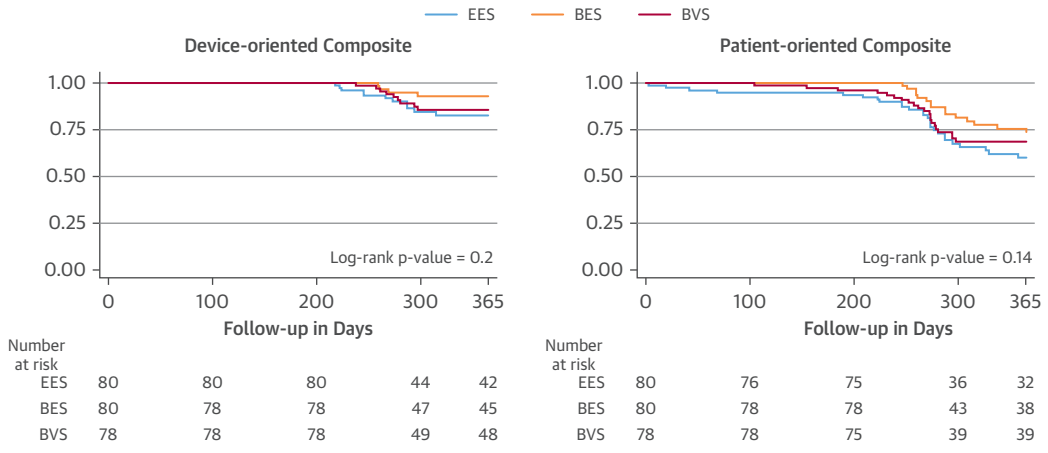
**STUDY LIMITATIONS.** Although the present prospective study boasts a substantial rate of angiographic follow-up, with few dropouts and the unprecedented comparison of BVS with 2 of the newest DES, it has several important limitations. First, it is limited in size, with a primary angiographic outcome, and was not powered to detect differences in clinical event rates. Given the uncertainty around point estimations, extrapolations should be drawn with caution. Second, because it was conducted in a single center with PCI performed by 5 operators with uniform procedural strategies, generalizations to other centers become limited. Third, a bias in lesion selection and implantation technique for the

**TABLE 4** Clinical Outcomes at 9 Months

| | EES (n = 80) | BES (n = 80) | EES/BES (n = 160) | BVS (n = 78) | p Value: EES vs. BVS | p Value: BES vs. BVS | p Value: EES/BES vs. BVS |
|---|---|---|---|---|---|---|---|
| Device-oriented composite | 11 (14) | 4 (5) | 15 (9) | 9 (12) | 0.68 | 0.14 | 0.60 |
| Cardiac death | 0 (0) | 0 (0) | 0 (0) | 1 (1) | 0.49 | 0.49 | 0.33 |
| MI of the target vessel | 0 (0) | 0 (0) | 0 (0) | 0 (0) | – | – | – |
| TLR | 11 (14) | 4 (5) | 15 (9) | 8 (10) | 0.50 | 0.21 | 0.83 |
| Clinically indicated | 7 (9) | 2 (3) | 9 (6) | 6 (8) | 0.81 | 0.16 | 0.54 |
| Patient-oriented composite | 26 (33) | 15 (19) | 41 (26) | 21 (27) | 0.44 | 0.22 | 0.83 |
| All-cause mortality | 3 (4) | 0 (0) | 3 (2) | 1 (1) | 0.62 | 0.49 | 1.00 |
| Any MI | 1 (1) | 0 (0) | 1 (1) | 1 (1) | 1.00 | 0.49 | 0.55 |
| Repeat revascularization | 24 (30) | 15 (19) | 39 (24) | 19 (24) | 0.43 | 0.39 | 0.99 |
| TVR | 14 (18) | 8 (10) | 22 (14) | 11 (14) | 0.56 | 0.43 | 0.94 |
| Clinically indicated | 8 (10) | 5 (6) | 13 (8) | 8 (10) | 0.96 | 0.36 | 0.59 |
| Stent thrombosis (possible) | 0 (0) | 0 (0) | 0 (0) | 1 (1) | 0.49 | 0.49 | 0.33 |

Values are n (%).
TLR = target lesion revascularization; TVR = target vessel revascularization; other abbreviations as in Table 1.

**FIGURE 3 Composite Clinical Endpoints**




The Kaplan-Meier curves demonstrate no significant differences between the individual stent cohorts for either device- or patient-oriented composite clinical endpoints. Device-oriented composite = cardiac death, myocardial infarction of the target vessel, and target vessel revascularization; patient-oriented composite = all-cause mortality, any myocardial infarction, and any repeat revascularization. Abbreviations as in Figure 1.

BVS group cannot be excluded given the single-blinded study design. Finally, we did not address whether the bioabsorbable polymer in BES or the bioresorbable vascular scaffold reduced thrombotic risk.

## CONCLUSIONS

New-generation metallic DES (EES/BES) were not superior to BVS in terms of angiographic LLL. There were no significant differences between these devices regarding clinical outcomes. The slight in-segment LLL differences at 9 months deserve close clinical follow-up during the 6- to 18-month period. Long-term benefit requires further investigation.

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## PERSPECTIVES

**COMPETENCY IN MEDICAL KNOWLEDGE:** Short-term angiographic outcomes following deployment of the latest types of DES with BVS compare favorably with those with late-generation DES.

**TRANSLATIONAL OUTLOOK:** Longer-term experience and evaluation of clinical outcomes are needed to inform a better assessment of the comparative benefits of metallic versus BVS in patients undergoing percutaneous coronary intervention.

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**KEY WORDS** coronary artery disease, drug-eluting stent(s), late lumen loss, myocardial infarction, percutaneous coronary intervention