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Efficacy and Safety of the Absorb Bioresorbable Vascular Scaffold in Females and Males

Results of an Individual Patient-Level Pooled Meta-Analysis of Randomized Controlled Trials

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ABSTRACT

OBJECTIVES Because females are under-represented in coronary trials, this study sought to assess the relative safety and efficacy of Absorb bioresorbable vascular scaffold (BVS) (Abbott Vascular, Santa Clara, California) and the Xience everolimus-eluting stent in females compared with males.

BACKGROUND The Absorb everolimus-eluting BVS provides drug delivery and mechanical support similar to a metallic drug-eluting stent, followed by resorption and restoration of more normal vascular structure with the potential to improve late clinical outcomes.

METHODS The ABSORB II, ABSORB III, ABSORB Japan, and ABSORB China trials were pooled. Baseline clinical, angiography, procedural variables, and 2-year outcomes were analyzed by sex and device.

RESULTS Among 3,384 randomized patients, 932 (27.5%) were female. Females were older, more often had diabetes and hypertension, but had less everolimus-eluting stent, 3-vessel disease, and smoking compared with males (all $p \leq 0.001$). The 2-year rates of target lesion failure with BVS versus everolimus-eluting stent in females were 8.9% versus 6.2% (study-level adjusted hazard ratio: 1.47; 95% confidence interval [CI]: 0.88 to 2.46) and 8.9% versus 6.4% in males (HR: 1.40; 95% CI: 1.02 to 1.92; $p_{interaction} = 0.85$). There were no significant interactions between sex and device type for any of the components of target lesion failure.

CONCLUSIONS The relative treatment effects of BVS and everolimus-eluting stent for the 2-year rates of target lesion failure and other cardiovascular outcomes were consistent in females and males. (J Am Coll Cardiol Intv 2017;10:1881–90) © 2017 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

BVS = bioresorbable vascular scaffold

CI = confidence interval

EES = everolimus-eluting stent(s)

HR = hazard ratio

ID-TLR = ischemia-driven target lesion revascularization

PCI = percutaneous coronary intervention

QCA = quantitative coronary angiography

RVD = reference vessel diameter

ST = scaffold/stent thrombosis

TLF = target lesion failure

TVMI = target vessel myocardial infarction

Progressive improvements in clinical outcomes and angiographic measures of restenosis have accompanied the evolution in percutaneous coronary intervention (PCI) from balloon angioplasty to bare-metal stents and to drug-eluting stents (1,2). Nevertheless, a persistent 2% to 3% per year annual incidence of device-related events (target lesion failure [TLF], the composite of cardiac death, target vessel myocardial infarction [TVMI], or ischemia-driven target lesion revascularization [ID-TLR]) has been observed beyond 1 year following PCI regardless of stent type (bare-metal stent or first- or second-generation drug-eluting stent) (3,4). The pathogenesis of these events may be the common presence of a metallic frame that distorts and constrains the vessel, thus limiting vasomotion and adaptive vascular remodeling. The permanent metal frame may serve as a nidus for chronic inflammation, neoatherosclerosis, thrombosis, and strut fracture. With the intent of improving very late clinical outcomes, fully bioresorbable vascular scaffolds (BVS) have been developed that completely resorb several years after PCI, restoring more normal vascular structure and function (5). In randomized trials, the Absorb BVS (Abbott Vascular, Santa Clara, California), the most widely used such device, was demonstrated to be statistically noninferior for 1-year TLF when compared with the Xience cobalt chromium everolimus-eluting stent (EES) (Abbott Vascular) in the ABSORB III pivotal trial for U.S. regulatory approval (6). Long-term outcomes for BVS are presently being collected from this and other randomized trials.

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Although coronary heart disease remains the leading cause of mortality in females (7), women are underrepresented in trials of coronary stenting, including ABSORB III (29.5% females), so that analysis from any single trial lacks power to provide accurate estimates of device efficacy or safety in this subgroup. Furthermore, females enrolled into clinical trials are often distinguished by significant differences in baseline clinical and angiographic variables than their male counterparts, including older age, more frequent comorbid risk factors, and smaller coronary arteries (8). Meta-analysis of multiple randomized controlled trials accrues power to inform more definitive assessments of device efficacy and safety. In this context, we performed an individual patient data pooled analysis of 4 randomized trials from the ABSORB clinical trial program in which baseline clinical, angiographic, and procedural variables as well as 2-year clinical outcomes were analyzed by sex and device.

METHODS

STUDY POPULATION. For the present study, we pooled the individual patient data from the ABSORB II (9), ABSORB III (6), ABSORB China (10), and ABSORB Japan (11) trials into a common database following sponsor (Abbott Vascular) and principal investigator approval. These 4 randomized trials were chosen based on their availability of individual patient-level data through 2-year follow-up. In each trial patients with coronary artery disease undergoing PCI were randomized to treatment with the Absorb BVS versus the Xience EES. Major characteristics of the 4 trials have previously been described and are summarized in **Table 1**. The clinical definitions across the trials were similar as were trial inclusion/exclusion criteria. Allowable reference vessel diameter (RVD) was ≥2.5 mm to ≤3.75 mm and lesion length was limited to ≤24 mm in ABSORB Japan, ABSORB China, and ABSORB III. ABSORB II allowed an RVD of ≥2.25 mm to ≤3.8 mm with lesion lengths up to 48 mm and mandated use of quantitative coronary angiography (QCA), whereas the other 3 trials allowed visual angiographic assessment for lesion eligibility. All trials were approved by the institutional review boards of the participating centers and all patients signed informed consent before trial enrollment.

STUDY OBJECTIVES AND ENDPOINT DEFINITIONS. The major objectives of the current study were to characterize the demographics of females versus males receiving BVS compared with EES, and to evaluate the sex-specific relative safety and efficacy of BVS compared with EES. The primary endpoint of the present analysis was the 2-year rate of TLF; secondary endpoints included TVMI, ID-TLR, and scaffold/stent thrombosis (ST) (Academic Research Consortium definite or probable definition) (12). For each trial, the pre-specified clinical endpoints were adjudicated by an independent clinical events committee. An independent core laboratory performed QCA as described previously (13). If ST was suspected, the angiographic core laboratory for each trial assessed whether thrombus was present.

STATISTICAL ANALYSIS. Patient-level data were aggregated into a single dataset and analysis was performed in the intention-to-treat population to examine sex-specific differences. Baseline clinical, demographic, and procedural characteristics were

TABLE 1 Characteristics of the Four Randomized Trials of Absorb BVS Versus Xience EES

	ABSORB II	ABSORB III	ABSORB China	ABSORB Japan
ClinicalTrials.gov ID	NCT01425281	NCT01751906	NCT01923740	NCT01844284
Centers	46	193	24	38
Randomized patients	501	2,008	480	400
Study lesions allowed	2	2	2	2
Reference vessel diameters allowed, mm	2.25–3.8	2.5–3.75	2.5–3.75	2.5–3.75
Target lesion length, mm	<48	<24	<24	<24
Primary endpoint	Angiographic vasomotion at 3 yrs	Target lesion failure at 1 yr	Angiographic in-segment late loss at 1 yr	Target lesion failure at 1 yr

BVS = bioresorbable vascular scaffold.

reported as mean ± SD for continuous variables and as proportions for categorical variables. Categorical variables were analyzed using the chi-square test or Fisher exact test. Continuous variables were compared with the Student *t* test. Time-to-first event curves were developed using Cox proportional hazard models in which study indicators were included as fixed effects. Adjusted survival rates were estimated using SAS procedure PHREG version 9.3 (SAS Institute Inc., Cary, North Carolina). The difference in event rates between 2 groups at a given time point was obtained by using the Z-test. Independent predictors of TLF and ST were determined by multivariable Cox proportional hazards regression, with the number of variables for each model chosen according to their historical association with the event in previous studies, with study indicators, sex, and treatment arm forced into each model. Formal interaction testing was performed to examine whether the relative rates of selected endpoints according to randomized treatment varied by sex. All p values were 2-sided, and a p value < 0.05 was considered statistically significant.

RESULTS

PATIENT CHARACTERISTICS. A total of 3,389 patients were enrolled in the 4 trials at 301 centers in Asia, Europe, and North America (Table 1). Five patients who withdrew consent and for whom sex information was not available were excluded from the analysis. Of the 3,384 analyzable patients, 932 (27.5%) were females, of which 593 (63.6%) were randomized to BVS. Among 2,452 males, 1,568 (63.9%) were randomized to BVS. Females were older than males, and more likely to be hypertensive and to have diabetes mellitus, particularly insulin-treated. Males were more likely than females to be active tobacco users, have had prior coronary intervention, and have 3 or more diseased major epicardial coronary arteries (Table 2). DAPT adherence (defined as no more than 1 day without DAPT therapy) during 2-year follow-up was 54.0% in males and 51.8% in females ($p = 0.25$).

Table 3 depicts the baseline and post-procedure angiographic findings according to sex. By QCA, females had a smaller baseline RVD compared with males and were more likely to have calcified lesions, whereas males had lesions that were longer and more often involved a bifurcation. Regarding procedural variables, there were no differences in the frequencies of pre-dilatation or post-dilatation between sexes, although procedure duration was slightly shorter and the requirement for bailout or unplanned stent or scaffold deployment was more frequent among females.

TABLE 2 Baseline Demographic Characteristics by Sex

	Male (n = 2,452)	Female (n = 932)	p Value
Age, yrs	61.8 ± 10.5 (2,452)	65.4 ± 10.5 (932)	<0.0001
>65, %	41.9 (1,028/2,452)	55.6 (518/932)	<0.0001
Current tobacco use, %	25.0 (613/2,452)	18.0 (168/932)	<0.0001
Hypertension, %	76.9 (1,886/2,452)	82.3 (767/932)	0.0007
Dyslipidemia, %	77.7 (1,904/2,452)	79.0 (736/932)	0.41
Diabetes mellitus, %	28.4 (697/2,450)	34.7 (323/932)	0.0004
Treated with insulin, %	8.3 (203/2,450)	13.3 (124/932)	<0.0001
Prior coronary intervention, %	36.1 (885/2,452)	27.5 (256/930)	<0.0001
Prior MI, %	22.7 (554/2,436)	18.7 (173/925)	0.01
Renal insufficiency, %	8.1 (143/1,756)	10.8 (78/723)	0.04
Number of diseased vessels, %			
Single	68.5 (1,468/2,143)	73.1 (615/841)	0.01
Double	23.0 (492/2,143)	21.9 (184/841)	0.53
Triple	8.5 (183/2,143)	5.0 (42/841)	0.001
Clinical presentation, %			
Recent MI	3.4 (84/2,451)	3.3 (31/932)	0.88
Post-MI angina	0.5 (13/2,451)	1.1 (10/932)	0.09
Stable angina	54.1 (1,327/2,451)	55.8 (520/932)	0.39
Unstable angina	28.6 (701/2,451)	30.5 (284/932)	0.28
Silent ischemia	12.1 (297/2,451)	8.4 (78/932)	0.002
No evidence of ischemia	1.2 (29/2,451)	1.0 (9/932)	0.59

MI = myocardial infarction.

TABLE 3 Index Procedure Variables and Angiographic Results

	Male (n = 2,452) (L = 2,583) (S = 2,787)	Female (n = 932) (L = 976) (S = 1,602)	p Value
Index procedure variables			
Number of stents/scaffolds implanted (per target lesion)	1.1 ± 0.3 (2,580)	1.1 ± 0.3 (975)	0.46
Maximum diameter of stent/scaffold implanted (per target lesion)	3.08 ± 0.37 (2,580)	3.00 ± 0.38 (975)	<0.0001
Total stented/scaffolded length (per target lesion)	19.12 ± 6.85 (2,569)	19.09 ± 7.20 (970)	0.92
Number of target lesions treated			
Mean ± SD, n	1.1 ± 0.2 (2,452)	1.0 ± 0.2 (932)	0.46
1 target lesion, %	94.6 (2,319/2,452)	95.3 (888/932)	0.41
2 target lesions, %	5.4 (132/2,452)	4.7 (44/932)	0.44
Number of target vessels treated			
Mean ± SD, n	1.1 ± 0.2 (2,452)	1.0 ± 0.2 (932)	0.65
1 target vessel, %	94.8 (2,325/2,452)	95.3 (888/932)	0.59
2 target vessels, %	5.1 (126/2,452)	4.7 (44/932)	0.62
Procedure duration, min	42.9 ± 23.1 (2,067)	40.7 ± 22.7 (816)	0.02
Procedure complications (per target lesion), %	4.5 (98/2,163)	5.4 (46/850)	0.31
IVUS/OCT (per target lesion), %	27.3 (597/2,188)	24.4 (203/833)	0.10
Bailout stent/scaffold use during procedure (per target lesion), %	4.4 (113/2,583)	6.1 (60/976)	0.03
Pre-dilatation performed (per target lesion), %	99.6 (2,572/2,583)	99.8 (974/976)	0.53
Post-dilatation performed (per target lesion), %	61.6 (1,592/2,583)	63.8 (623/976)	0.23
Procedural QCA results			
Target vessel, %			
LAD	45.5 (1,174/2,583)	45.8 (447/976)	0.85
Left circumflex/ramus	27.3 (704/2,583)	24.0 (234/976)	0.048
RCA	27.3 (704/2,583)	30.2 (295/976)	0.08
Lesion length, mm	13.4 ± 5.8 (2,570)	12.7 ± 5.3 (972)	0.0008
Long lesions (>24), %	4.9 (125/2,570)	3.2 (31/972)	0.03
Pre-procedure RVD, mm	2.7 ± 0.5 (2,572)	2.6 ± 0.4 (972)	<0.0001
RVD <2.25: BVS, %	16.0 (250/1,562)	21.6 (128/592)	0.002
RVD <2.25: EES, %	14.6 (128/878)	22.6 (76/337)	0.0009
Pre-procedure MLD, mm	0.95 ± 0.4 (2,574)	0.96 ± 0.4 (972)	0.86
Pre-procedure %DS	64.6 ± 12.3 (2,574)	63.3 ± 12.1 (972)	0.005
Bifurcation, %	35.0 (899/2,570)	31.0 (301/972)	0.02
Calcification (moderate or severe), %	25.7 (662/2,571)	30.8 (300/973)	0.002
ACC/AHA lesion class B2/C, %	67.7 (1,741/2,573)	67.5 (657/973)	0.94
Post-procedure in-segment MLD, mm	2.2 ± 0.4 (2,569)	2.1 ± 0.4 (971)	<0.0001
Post-procedure in-device MLD, mm	2.5 ± 0.4 (2,569)	2.4 ± 0.4 (970)	<0.0001
Post-procedure in-segment %DS	19.9 ± 8.0 (2,569)	20.0 ± 7.8 (971)	0.86
Post-procedure in-device %DS	10.9 ± 8.4 (2,564)	10.0 ± 8.9 (967)	0.006
Post-procedure in-segment acute gain	1.2 ± 0.5 (2,567)	1.2 ± 0.4 (970)	<0.0001
Post-procedure in-device acute gain	1.5 ± 0.5 (2,567)	1.4 ± 0.4 (969)	<0.0001

Values are mean ± SD (N) or % (n/N).

ACC = American College of Cardiology; AHA = American Heart Association; EES = everolimus-eluting stent(s); IVUS = intravascular ultrasound; L = number of lesions; LAD = left anterior descending; MLD = minimal lumen diameter; OCT = optical coherence tomography; %DS = percent diameter stenosis; QCA = quantitative coronary angiography; RCA = right coronary artery; RVD = reference vessel diameter; S = number of devices; other abbreviations as in Table 1.

CLINICAL OUTCOMES BY SEX AND DEVICE. Two-year outcomes are shown in Figures 1 and 2 and Table 4. The 2-year rates of TLF with BVS versus EES in females were 8.9% versus 6.2% (study-level adjusted hazard ratio [HR]: 1.47; 95% confidence interval [CI]: 0.88 to 2.46) and 8.9% vs. 6.4% in males (HR: 1.40; 95% CI: 1.02 to 1.92; $p_{interaction} = 0.85$). There were no significant interactions between sex and device type for any of the components of TLF. A borderline interaction was present between sex and device for the 2-year rate of ST BVS versus EES, 1.3% versus 1.2% in females (HR: 1.07; 95% CI: 0.32 to 3.55) and 2.0% vs. 0.4% in males (HR: 5.54; 95% CI: 1.69 to 18.14; $p_{interaction} = 0.06$).

The 1- and 2-year TLF and ST outcomes stratified by sex and device randomization for patients having at least 1 target lesion with baseline RVD <2.25 mm versus those who had the baseline RVD of all target

lesions >2.25 mm are shown in **Table 5**. Although no statistically significant interactions between sex and device type for TLF were observed, a borderline interaction ($p_{interaction}$ = 0.046) was present for the occurrence of 2-year ST according to vessel size.

By multivariable analysis in the entire study population, device type but not sex was an independent predictor of TLF after adjusting for baseline differences in comorbidities and angiographic measures (**Central Illustration**, panel A). The only independent predictors of ST were device type, diabetes, and preprocedure RVD (**Central Illustration**, panel B). Multivariable correlates of 2-year TLF and ST by sex are shown in **Figure 3**. Device type was an independent predictor of TLF in males but not females, although the adjusted HRs were directionally similar (1.39 vs. 1.55, respectively). Device type was also an independent predictor of ST in males but not females, although the adjusted HR was higher in males (5.67 vs. 1.13, respectively).

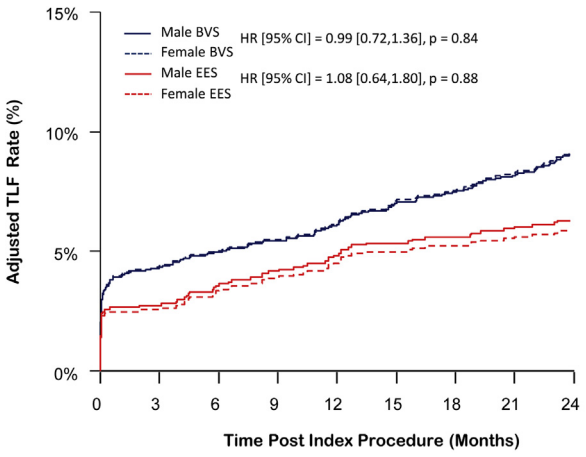
DISCUSSION

The principal observations from the present analysis of 4 randomized controlled trials comparing Absorb BVS with the Xience EES in 3,384 patients undergoing PCI are: 1) males and females with coronary artery disease enrolled in these trials had different baseline clinical and angiographic characteristics; 2) nonetheless, consistency of device treatment effects were observed between the sexes for most 2-year outcomes; and 3) by multivariable analysis, sex was not predictive of TLF, the components of TLF, or ST at 2 years.

As in prior studies (14-18), we found that females undergoing PCI had a different risk profile than males. Females were more likely to be older, have diabetes and hypertension, and have smaller target vessels. Males were more likely to be tobacco users, have 3-vessel disease, and to have had prior coronary interventions. These differences in comorbidities contribute to the worse outcomes observed in many studies in females after PCI, although most prior studies were done in the pre-stent era, included small numbers of female patients, and were retrospective (19-21). In the present analysis, sex was not an independent predictor of the 2-year rate of either TLF or ST. Nonetheless, even with 3,384 patients, the present analysis remains underpowered to exclude an effect of sex on outcomes.

In males, the 2-year rates of TLF, TVMI, and ST were higher after treatment with BVS compared with EES, with a trend toward greater ID-TLR. In females,

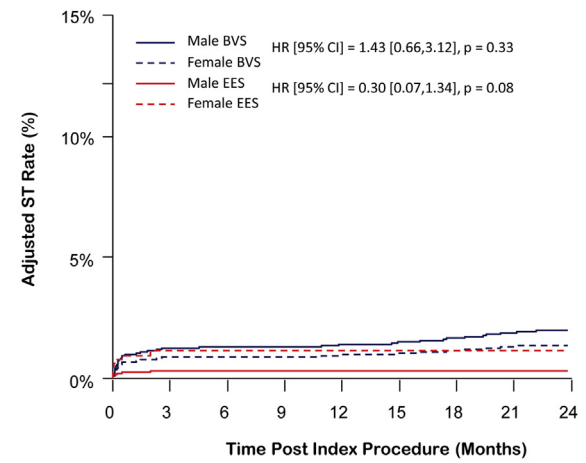
FIGURE 1 Time-to-First Event Curves Target Lesion Failure



# at risk	0	12M	24M
Male BVS	1568	1460	1388
Female BVS	593	541	523
Male EES	884	835	808
Female EES	339	316	306

Time-to-first event curves for target lesion failure from the index procedure to 2 years by sex and device. BVS = bioresorbable vascular scaffold; CI = confidence interval; EES = everolimus-eluting stent(s); HR = hazard ratio; TLF = target lesion failure.

FIGURE 2 Time-to-First Event Curves for Definite or Probable Stent Thrombosis



# at risk	0	12M	24M
Male BVS	1568	1520	1483
Female BVS	593	576	565
Male EES	884	869	854
Female EES	339	328	320

Time-to-first event curves for definite or probable stent thrombosis from the index procedure to 2 years. Stent thrombosis was defined according to the Academic Research Consortium definite or probable criteria. ST = stent/scaffold thrombosis; other abbreviations as in **Figure 1**.

TABLE 4 1- and 2-Year Study-Level Adjusted Clinical Outcomes in the Randomized Groups Stratified by Sex

		1-Year Outcomes				2-Year Outcomes			
	Sex	BVS	EES	Adjusted HR (95% CI)	Adjusted $p_{interaction}$	BVS	EES	Adjusted HR (95% CI)	Adjusted $p_{interaction}$
TLF	Male	5.5 (87)	4.6 (40)	1.19 (0.82–1.73)	0.67	8.9 (140)	6.4 (55)	1.40 (1.02–1.92)	0.85
	Female	7.4 (45)	5.5 (18)	1.36 (0.79–2.36)		8.9 (54)	6.2 (20)	1.47 (0.88–2.46)	
TVF	Male	6.8 (108)	5.8 (50)	1.19 (0.85–1.66)	0.49	11.2 (176)	8.7 (74)	1.31 (1.00–1.72)	0.74
	Female	9.6 (58)	6.7 (22)	1.45 (0.88–2.37)		11.9 (72)	8.6 (28)	1.42 (0.92–2.20)	
MACE	Male	6.1 (96)	5.1 (44)	1.20 (0.84–1.71)	0.60	9.6 (151)	7.2 (62)	1.34 (1.00–1.81)	0.81
	Female	8.1 (49)	5.8 (19)	1.41 (0.83–2.39)		9.9 (60)	7.1 (23)	1.42 (0.88–2.30)	
All death	Male	0.8 (13)	0.7 (6)	1.25 (0.47–3.31)	0.42	1.7 (26)	1.3 (11)	1.35 (0.66–2.74)	0.07
	Female	0.5 (3)	0.8 (3)	0.66 (0.13–3.31)		1.2 (7)	2.7 (9)	0.45 (0.17–1.21)	
Cardiac death	Male	0.4 (6)	0.3 (3)	1.21 (0.30–4.90)	0.66	0.9 (14)	0.6 (5)	1.63 (0.58–4.56)	0.35
	Female	0.2 (1)	0.3 (1)	0.71 (0.04–11.77)		0.3 (2)	0.6 (2)	0.61 (0.08–4.41)	
All MI	Male	5.0 (79)	3.8 (33)	1.30 (0.87–1.96)	0.65	6.6 (104)	4.2 (36)	1.58 (1.08–2.30)	0.92
	Female	6.8 (42)	4.7 (15)	1.47 (0.81–2.65)		8.2 (50)	5.7 (18)	1.46 (0.85–2.51)	
TVMI	Male	4.4 (70)	3.2 (27)	1.39 (0.89–2.17)	0.74	5.7 (91)	3.2 (27)	1.81 (1.18–2.78)	0.87
	Female	6.1 (38)	4.1 (13)	1.52 (0.81–2.87)		7.1 (44)	4.4 (14)	1.65 (0.90–3.01)	
ID-TLR	Male	2.2 (34)	1.7 (15)	1.26 (0.68–2.32)	0.91	4.8 (74)	3.5 (30)	1.37 (0.90–2.11)	0.78
	Female	2.9 (17)	2.4 (8)	1.23 (0.53–2.85)		3.7 (22)	3.0 (10)	1.24 (0.59–2.63)	
ID-TVR	Male	3.6 (56)	2.7 (23)	1.35 (0.83–2.20)	0.95	7.3 (113)	5.2 (44)	1.42 (1.00–2.01)	0.79
	Female	4.4 (26)	3.3 (11)	1.35 (0.66–2.74)		6.0 (35)	4.5 (15)	1.33 (0.72–2.44)	
ST	Male	1.3 (21)	0.4 (3)	3.70 (1.10–12.42)	0.12	2.0 (31)	0.4 (3)	5.54 (1.69–18.14)	0.06
	Female	1.2 (7)	1.2 (4)	0.93 (0.27–3.19)		1.3 (8)	1.2 (4)	1.07 (0.32–3.55)	

Event rates are derived from Kaplan-Meier analysis and presented as Kaplan-Meier % (n) where n is the number of events.

CI = confidence interval; HR = hazard ratio; ID-TLR = ischemia-driven target lesion revascularization; MACE = major adverse cardiac event(s); ST = scaffold/stent thrombosis; TLF = target lesion failure; TVF = target vessel failure; TVMI = target vessel myocardial infarction; other abbreviations as in Tables 1 to 3.

the rates of TLF, TVMI, and ID-TLR were also numerically higher following treatment with BVS compared with EES, although the differences did not reach statistical significance. In both males and females, the increased risk of TLF following BVS was present at 1 year, with continued divergence of the cumulative event curves between years 1 and 2. There were no significant interactions between device treatment and sex for any outcome measure at 2 years for all randomized patients. Acknowledging the fact that subgroup analysis is inherently underpowered (even with 3,384 patients), the most appropriate and conservative interpretation is that there are no significant differences in the relative treatment effects

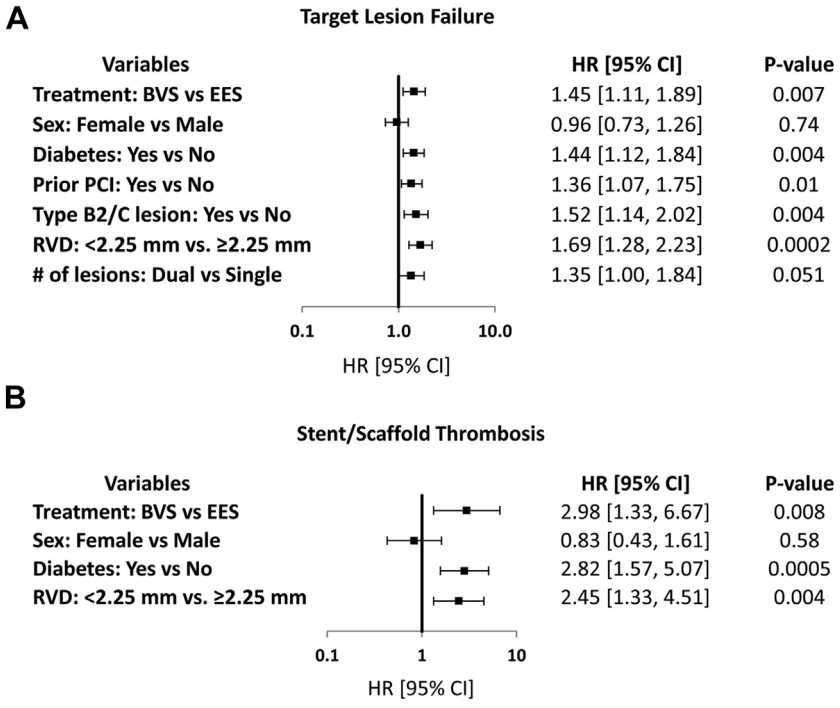
TABLE 5 1- and 2-Year Study-Level Adjusted Target Lesion Failure and Device Thrombosis Rates in the Randomized Groups Stratified by Sex and Pre-Procedural Reference Vessel Diameter

		1-Year Outcomes				2-Year Outcomes			
	Sex	BVS	EES	Adjusted HR (95% CI)	Adjusted $p_{interaction}$	BVS	EES	Adjusted HR (95% CI)	Adjusted $p_{interaction}$
RVD ≥2.25 mm*									
TLF	Male	5.0 (67)	4.5 (33)	1.13 (0.74–1.71)	0.59	8.2 (108)	5.9 (43)	1.41 (0.99–2.01)	0.92
	Female	5.7 (27)	4.0 (10)	1.43 (0.69–2.96)		6.9 (33)	4.9 (12)	1.44 (0.74–2.79)	
ST	Male	1.0 (14)	0.3 (2)	3.79 (0.86–16.71)	0.07	1.8 (24)	0.3 (2)	6.59 (1.55–27.96)	0.046
	Female	0.2 (1)	0.8 (2)	0.24 (0.02–2.65)		0.4 (2)	0.9 (2)	0.48 (0.07–3.40)	
RVD <2.25 mm†									
TLF	Male	7.9 (20)	5.6 (7)	1.44 (0.61–3.42)	0.97	12.6 (32)	9.8 (12)	1.32 (0.68–2.57)	0.66
	Female	14.3 (18)	10.1 (8)	1.45 (0.62–3.35)		16.7 (21)	10.2 (8)	1.71 (0.76–3.89)	
ST	Male	2.7 (7)	0.8 (1)	3.30 (0.41–26.84)	0.69	2.7 (7)	0.8 (1)	3.30 (0.41–26.84)	0.69
	Female	4.9 (6)	2.5 (2)	2.02 (0.41–10.06)		4.9 (6)	2.5 (2)	2.02 (0.41–10.06)	

Event rates are derived from Kaplan-Meier analysis and presented as Kaplan Meier % (n) where n is the number of events. *Subjects with all target lesions with pre-procedural RVD ≥2.25 mm. †Subjects with at least 1 target lesion with pre-procedural RVD <2.25 mm.

Abbreviations as in Tables 1, 3, and 4.

CENTRAL ILLUSTRATION **Multivariable Predictors of TLF and Stent/Scaffold Thrombosis at 2 Years**



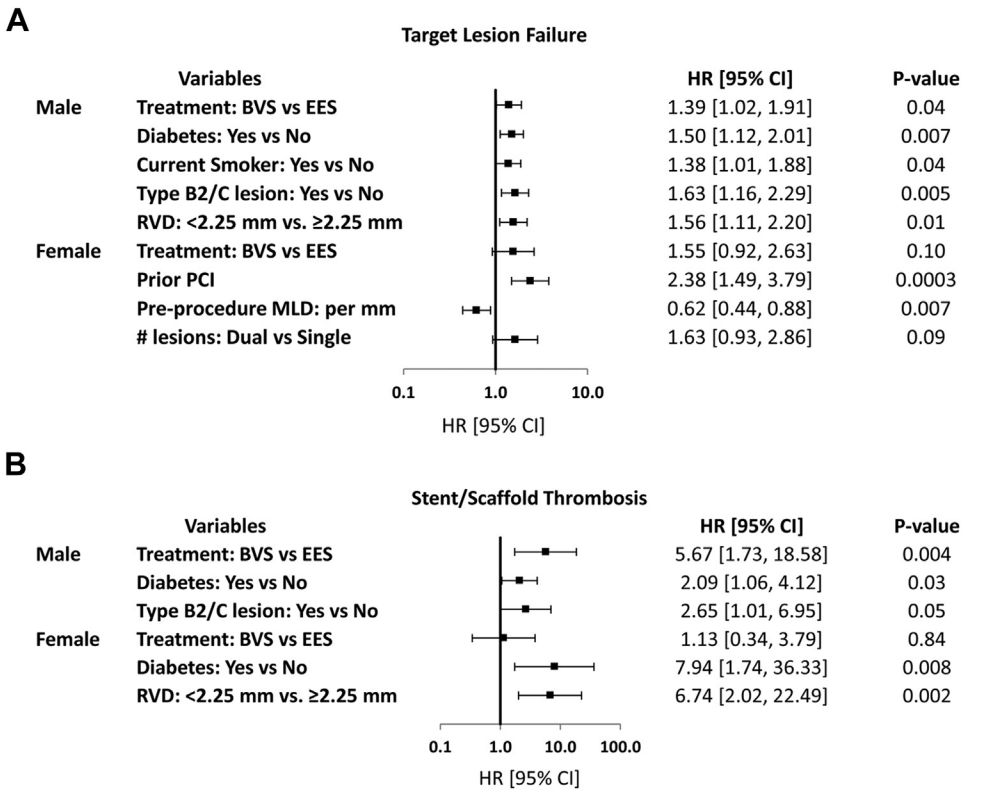
Shreenivas, S. et al. J Am Coll Cardiol Intv. 2017;10(18):1881–90.

Multivariable predictors of **(A)** target lesion failure and **(B)** stent/scaffold thrombosis at 2 years. Variables entered into the target lesion failure model included treatment arm, sex, any diabetes, type B2/C lesions, presentation (unstable angina/recent myocardial infarction vs. any stable ischemic syndrome), calcification, target vessel (left anterior descending vs. non–left anterior descending), pre-procedural reference vessel diameter (<2.25 mm vs. ≥2.25 mm), number of treated lesions, bifurcation, current smoker, initial prasugrel or ticagrelor, prior cardiac intervention, prior myocardial infarction, DAPT interruption during 2 years, age (years), target lesion length (mm), and pre-procedural minimal lumen diameter (mm). Variables entered into the stent/scaffold thrombosis model included treatment arm, sex, any diabetes, type B2/C lesions, presentation (unstable angina/recent myocardial infarction vs. any stable ischemic syndrome), pre-procedural reference vessel diameter (<2.25 mm vs. ≥2.25 mm), initial prasugrel or ticagrelor, DAPT interruption during 2 years, and target lesion length (mm). Sex and randomization arm were forced into each model. BVS = bioresorbable vascular scaffold; CI = confidence interval; EES = everolimus-eluting stent(s); HR = hazard ratio; PCI = percutaneous coronary intervention; RVD = reference vessel diameter.

of BVS versus EES on 2-year outcomes in females and males undergoing PCI.

Use of BVS compared with EES was an independent predictor of 2-year ST among males but not in females, with a borderline nonsignificant interaction present ($p_{interaction}$ = 0.06). Of note, no patient treated with EES had ST after year 1, and only 1 patient treated with BVS (a female) experienced ST between Year 1 and 2. The increase in very late ST with BVS compared with EES was primarily driven by males treated with BVS, all of whom had all target lesion RVDs 2.25 mm or greater. In this regard, like in most prior reports, females had smaller RVDs than males in our study, a finding that has been associated with increased post-PCI complications (22). Thinner struts of newer drug-eluting stent have been associated with improved clinical outcomes in females (14). Absorb BVS has greater strut width and thickness compared with EES, and smaller vessel size in females remains a theoretical concern for BVS. However, in the present study, the interaction between sex and device for 2-year ST was confined to patients who had the RVD of all target lesions >2.25 mm ($p_{interaction}$ = 0.046). In contrast, although the 2-year ST rates were generally higher in patients with treated target lesions RVD <2.25 mm, there was no interaction between device type and sex

FIGURE 3 Multivariable Predictors of Target Lesion Failure and Stent/Scaffold Thrombosis



Multivariable predictors of **(A)** target lesion failure and **(B)** stent/scaffold thrombosis at 2 years in males and females. Variables entered into the target lesion failure model included treatment arm, any diabetes, type B2/C lesions, presentation (unstable angina/recent myocardial infarction vs. any stable ischemic syndrome), calcification, target vessel (left anterior descending vs. non–left anterior descending), pre-procedural reference vessel diameter (<2.25 mm vs. ≥2.25 mm), number of treated lesions, bifurcation, current smoker, initial prasugrel or ticagrelor, prior cardiac intervention, prior myocardial infarction, DAPT interruption during 2 years, age (years), target lesion length (mm), and pre-procedural minimal lumen diameter (mm). Variables entered into the stent/scaffold thrombosis model included treatment arm, any diabetes, type B2/C lesions, presentation (unstable angina/recent myocardial infarction vs. any stable ischemic syndrome), pre-procedural reference vessel diameter (<2.25 mm vs. ≥2.25 mm), initial prasugrel or ticagrelor, DAPT interruption during 2 years, and target lesion length (mm). Randomization arm was forced into each model. MLD = minimal lumen diameter; other abbreviations as in Figure 1.

in this high-risk subgroup. However, all subgroup analyses are inherently underpowered, and statistical adjustments were not made for multiple comparisons. These findings may thus be caused by chance, especially because they represent subgroups within subgroups (sex stratified by baseline target RVD). Larger studies are required to determine if there is a varying propensity for ST after BVS between men and women, and if so, whether this relationship is affected by target lesion RVD. Nevertheless, event rates were consistently higher for both sexes when Absorb BVS was implanted in small vessels (RVD <2.25 mm), underscoring the importance of staying within the indicated ranges of vessel size (2.5 mm to 3.75 mm) in both men and women.

STUDY LIMITATIONS. Although the inclusion and exclusion criteria were similar between the trials, small differences in lesion length and vessel size between studies were present. In addition, the different geographic regions enrolling in each study may yield heterogeneous patient populations and treatments. None of the 4 trials stratified randomization by sex so comparisons of results between males and females should be done with caution (although our findings were adjusted by study). Although this report represents the largest analysis to date of Absorb BVS compared with EES in females, it still lacks power to detect differences in low-frequency events, such as ST. Subgroup analyses including the small vessel cohort (QCA

RVD <2.25 mm) are further underpowered to examine clinical event rates. The 4 component trials enrolled only patients with stable coronary artery disease or stabilized acute coronary syndromes, and extrapolation of these findings to patients with unstable syndromes and more complex lesion morphology should be avoided. Finally, longer-term follow-up is required to determine whether differences in outcomes between males and females emerge over time.

CONCLUSIONS

In the present individual patient data pooled analysis of 4 randomized trials comparing Absorb BVS with Xience EES, despite the varying cardiovascular risk profile of females, the treatment effect of Absorb BVS was consistent in both females and males with respect to 2-year clinical outcomes.

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PERSPECTIVES

WHAT IS KNOWN? The Absorb BVS provides drug delivery and mechanical support similar to a metallic drug-eluting stent, followed by resorption and the potential to restore more normal vascular structure and function, with improvement in very late clinical outcomes. Females are underrepresented in coronary stent trials, and the relative safety and efficacy of Absorb BVS in females versus males is not known.

WHAT IS NEW? Despite differing baseline clinical and angiographic characteristics, the relative treatment effects of Absorb BVS and everolimus-eluting stents on 2-year target lesion failure and other cardiovascular outcomes were consistent in males and females.

WHAT IS NEXT? Although this patient-level pooled analysis of 4 prospective trials is the largest to date to compare Absorb BVS and everolimus-eluting stents in females, device randomization was not stratified by sex, and our study is underpowered to detect differences in low-frequency events, such as device thrombosis. Larger prospective analyses in more complex patient cohorts and with longer-term follow-up are warranted.

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