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Everolimus-Eluting Bioresorbable Scaffolds Versus Everolimus-Eluting Metallic Stents

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ABSTRACT

BACKGROUND Recent evidence suggests that bioresorbable vascular scaffolds (BVS) are associated with an excess of thrombotic complications compared with metallic everolimus-eluting stents (EES).

OBJECTIVES This study sought to investigate the comparative effectiveness of the Food and Drug Administration–approved BVS versus metallic EES in patients undergoing percutaneous coronary intervention at longest available follow-up.

METHODS The authors searched MEDLINE, Scopus, and web sources for randomized trials comparing BVS and EES. The primary efficacy and safety endpoints were target lesion failure and definite or probable stent thrombosis, respectively.

RESULTS Seven trials were included: in sum, 5,583 patients were randomized to receive either the study BVS (n = 3,261) or the EES (n = 2,322). Median time of follow-up was 2 years (range 2 to 3 years). Compared with metallic EES, risk of target lesion failure (9.6% vs. 7.2%; absolute risk difference: +2.4%; risk ratio: 1.32; 95% confidence interval: 1.10 to 1.59; number needed to harm: 41; p = 0.003; I^2 = 0%) and stent thrombosis (2.4% vs. 0.7%; absolute risk difference: +1.7%; risk ratio: 3.15; 95% confidence interval: 1.87 to 5.30; number needed to harm: 60; p < 0.0001; I^2 = 0%) were both significantly higher with BVS. There were no significant differences in all-cause or cardiovascular mortality between groups. The increased risk for ST associated with BVS was concordant across the early (<30 days), late (30 days to 1 year), and very late (>1 year) periods ($p_{interaction}$ = 0.49).

CONCLUSIONS Compared with metallic EES, the BVS appears to be associated with both lower efficacy and higher thrombotic risk over time. (Bioresorbable vascular scaffold compare to everolimus stents in long term follow up; CRD42017059993). (J Am Coll Cardiol 2017;69:3055–66) © 2017 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

ARD = absolute risk difference

BVS = bioresorbable vascular scaffold(s)

EES = everolimus-eluting stent(s)

FDA = Food and Drug Administration

ID-TLR = ischemia-driven target lesion revascularization

MI = myocardial infarction

NNH = number needed to harm

PCI = percutaneous coronary intervention

RCT = randomized controlled trial

RR = risk ratio

ST = stent thrombosis

TLF = target lesion failure

Bioresorbable vascular scaffolds (BVS) have emerged as a new technology in the field of percutaneous coronary intervention (PCI) (1). The pathobiological rationale that led to the creation of BVS developed from the concept of providing transient mechanical support and drug delivery early after PCI (within 6 to 12 months), followed by progressive bioresorption of the scaffold from the coronary artery (2). The potential advantages of the progressive dissolution of the scaffold (initially anticipated to be measured in months) include the ultimate return of cyclic pulsatility and vasoregulation of the native coronary artery, as well as the possibility of surgical coronary bypass of the target lesion. Therefore, the anticipated benefits of BVS versus conventional metallic drug-eluting stents were expected to emerge in the later period, after dissolution of the implanted scaffold. However, recent reports indicated that delays in reabsorption process of up to 3 years are associated with scaffold discontinuity and ensuing malapposition, restenosis, or thrombosis (3,4).

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Regulatory approval of the first BVS, the Absorb BVS (Abbott Vascular, Santa Clara, California), was achieved on the basis of noninferiority in terms of target lesion failure (TLF) at 1 year versus the comparator metallic, everolimus-eluting stent (EES), which was demonstrated in prior trials to be associated with low rates of stent thrombosis (ST) compared with first-generation drug-eluting stents (5). Recently, the 2-year follow-up of the ABSORB III (A Clinical Evaluation of Absorb™ BVS, the Everolimus Eluting Bioresorbable Vascular Scaffold in the Treatment of Subjects With de Novo Native Coronary Artery Lesions) trial demonstrated that BVS are associated with significantly higher rates of TLF and a nonsignificant greater absolute risk of ST compared with EES (6). In addition, BVS were associated with increased risk of thrombosis compared with metallic EES in the European AIDA (Amsterdam Investigator-initiateD Absorb Strategy All-comers) trial (7), leading to early study termination due to safety concerns.

On the basis of the 2-year data from the ABSORB III trial, the Food and Drug Administration (FDA) released a safety alert on the performances of BVS and recommended adherence to dual antiplatelet therapy to prevent major adverse cardiac events while further investigations are ongoing (8). The individual randomized controlled trials (RCTs) investigating BVS thus far have been underpowered to detect statistical differences in hard clinical endpoints, as most were powered only for angiographic outcomes and composite endpoints. Giving the overall clinical context, we have undertaken a systematic review and meta-analysis of the available evidence on BVS using the longest available follow-up to better characterize the performance of the currently FDA-approved BVS in comparison with metallic EES in patients undergoing PCI.

METHODS

STUDY DESIGN. In accordance with the PRISMA guidelines (9), we searched MEDLINE, Scopus, and oral presentations from the latest international conferences for papers published or posted until March 18, 2017 (Online Table 1). The following key words were used for the search: *bioresorbable vascular scaffold*, *bioresorbable stent*, *BVS*, *everolimus-eluting stent(s)*, and *randomized trial*. To avoid the effect of selection and confounding bias on treatment effect estimates, only RCTs comparing the FDA-approved BVS versus metallic EES were included. Full-length papers and meeting presentations were both included in the analysis. Main exclusion criteria were observational study design (including single-arm pilot studies), non-English-language studies, editorials, letters, expert opinions, case reports or series, studies with duplicated data, and studies using metallic stents with bioresorbable polymer coatings. Two authors (S.S. and M.F.) independently evaluated studies for eligibility, and discrepancies were resolved by a third reviewer (G.G.). Studies that met the inclusion criteria were selected for the analysis.

Pre-specified data elements were extracted from each trial and included in a structured dataset; these elements included baseline population and procedural characteristics and clinical outcome at longest available follow up. The primary efficacy outcome was TLF (device-oriented composite endpoint) including cardiac death, target vessel myocardial infarction (MI), or ischemia-driven target lesion revascularization (ID-TLR). The primary safety endpoint was definite or probable ST or scaffold thrombosis according to the Academic Research Consortium criteria (10). Secondary efficacy endpoints were ID-TLR, any MI, and target vessel MI. Secondary safety endpoints were all-cause mortality, cardiovascular mortality, and a patient-oriented composite endpoint, including all-cause mortality, any MI, or any revascularization.

Risk for bias for each trial for both primary endpoints was evaluated using the Cochrane tool, as described by Higgins et al. (11). The following

potential sources of bias were evaluated: adequacy of random sequence generation (selection bias); allocation concealment (selection bias); blinding of participants and personnel (performance bias); blinding of outcome assessment (detection bias); description of incomplete outcome data (attrition bias); and selective reporting (reporting bias). For each element, a qualitative attribution of bias was given (low risk, intermediate risk, or high risk for bias) by 2 independent investigators (Online Table 2). All endpoints were assessed according the definitions reported in the original trial protocols, using the intention-to-treat principle. Risk of ST was evaluated in the early (1 month), late (1 to 12 months), and very late (beyond 1 year from implantation) periods.

STATISTICAL ANALYSIS. Crude event rates and numbers of events were extracted from the selected trials and entered into a pre-specified structured dataset. Pooled estimates of risk ratios (RRs) and 95% confidence intervals (CIs) were calculated as a summary statistic for the comparison of BVS versus EES. The primary analytic method was random effect according to the method of Mantel-Haenszel. We also calculated the risk estimations for the primary outcomes according to fixed-effects models. Heterogeneity among trials for each outcome was estimated with chi-square tests and quantified with I^2 statistics (<25% represented mild heterogeneity, 25% to 50% represented moderate heterogeneity, and higher than 50% represented severe heterogeneity) (12). The risk of publication bias was assessed by visual estimation of the Funnel plot and with the Harbord test (13). To evaluate the public health impact of BVS on safety outcomes, the absolute risk difference (ARD) and number needed to harm (NNH) were calculated (14). Risk for ST in the early (0 to 30 days), late (1 month to 1 year), and very late (>1 year) periods was estimated using a landmark population, censoring any patient experiencing an endpoint event, any death, or lost at follow-up preceding each specific landmark time point.

Study-specific influences on TLF and ST were estimated after exclusion of each trial from the analysis and subsequent evaluation of the change in significance, magnitude, and direction of the effect. We deemed p values <0.05 as significant. RevMan version 5.3 (The Cochrane Collaboration, Copenhagen, Denmark) and Stata version 11.2 (StataCorp LLC, College Station, Texas) were used for the statistical analyses. This study is registered in PROSPERO (CRD42017059993) (15).

RESULTS

SYSTEMATIC REVIEW. We included 7 trials (6,7,16-20) in which 5,583 patients were randomized to PCI with the BVS (n = 3,261) or the metallic EES (n = 2,322). The detailed study flow diagram is shown in Online Figure 1. Main characteristics of the included RCTs are reported in **Table 1**. Baseline clinical and procedural characteristics across trials are summarized in **Table 2 and** Online Table 3. In the metallic EES arm, the most frequently implanted stent (n = 2,242) was the cobalt-chromium stent with everolimus eluted via a durable fluoropolymer (Xience, Abbott Vascular, Santa Clara, California), whereas the remaining patients (n = 80) were treated with the platinum-chromium EES (Promus Element, Boston Scientific, Natick, Massachusetts). Median time of follow-up across trials was 2 years (range 2 to 3 years).

EFFICACY OUTCOMES. The risk of TLF (**Figure 1A**) was significantly higher with BVS than with EES, both on a relative (9.6% vs. 7.2%; RR: 1.32; 95% CI: 1.10 to 1.59; p = 0.003; I^2 = 0%) and on an absolute scale (ARD: +2.4%; 95% CI: 0.97% to 3.9%; NNH: 41). No evidence of publication bias was found for this outcome measure (Online Figure 2A). The magnitude and direction of the effect were also consistent with the study influence analysis (Online Figure 3A).

Use of BVS compared with EES was also associated with greater risk for ID-TLR (5.6% vs. 4.1%; RR: 1.39; 95% CI: 1.09 to 1.78; p = 0.009; I^2 = 0%) (**Figure 2A**), and of target vessel MI (5.8% vs. 3.2%; RR: 1.62; 95% CI: 1.24 to 2.12; p = 0.0004; I^2 = 0%) (**Figure 2B**). No evidence of publication bias was observed for the efficacy outcomes (Online Figure 4).

SAFETY OUTCOMES (SCAFFOLD THROMBOSIS OR ST). BVS was associated with a significantly increased risk for definite or probable ST (**Figure 1B**) on both a relative (2.4% vs. 0.7%; RR: 3.15; 95% CI: 1.87 to 5.30; p < 0.0001; I^2 = 0%) and an absolute scale (ARD: +1.7%; 95% CI: 1.0% to 2.3%; NNH: 60). No evidence of publication bias was found for this outcome (Online Figure 2B). Moreover, the magnitude and direction of the effect were consistent with the study influence analysis (Online Figure 3B). Risk for ST associated with BVS over time was concordant (**Central Illustration**) across the early (RR: 1.99; 95% CI: 1.04 to 3.78; p = 0.04; I^2 = 0%) (**Figure 3A**), late (RR: 3.12; 95% CI: 0.93 to 10.50; p = 0.07; I^2 = 0%) (**Figure 3B**), and very late periods (RR: 3.96; 95% CI: 1.47 to 10.66; p = 0.006; I^2 = 0%) (**Figure 3C**), without evidence of interaction ($p_{interaction}$ = 0.49). No evidence of publication bias was found for these outcomes (Online Figure 5).

TABLE 1 Study Endpoints and Outcomes at the Maximum Available Follow-Up

Study Name (Ref. #)	Year	Study Group Size	Device Used	Main Inclusion/Exclusion Criteria	Primary Endpoints	Available/Planned Follow-Up (yrs)
ABSORB China (17)	2016	480	CoCr EES vs. BVS	Inclusion criteria Evidence of myocardial ischemia De novo coronary lesions (n ≤ 2) RVD ≥2.5 and ≤3.75 mm lesion length ≤24 mm Exclusion criteria Acute MI or recent MI ≤7 days (with positive cardiac markers) LVEF ≤30% GFR <30 ml/min/1.73 m^2 Previous PCI in the target vessel ≤1 yr Left main or ostial stenosis Bifurcation lesion with a side branch diameter >2.0 mm Calcified lesion (moderate/heavy) Myocardial bridge Thrombotic lesion Excessive vessel tortuosity	12-month angiographic in-segment late loss	2/5
ABSORB II (20)	2016	501	CoCr EES vs. BVS	Inclusion criteria Evidence of myocardial ischemia De novo coronary lesions (n ≤ 2) Exclusion criteria Acute MI or recent MI (with positive cardiac markers) LVEF ≤30% GFR <60 ml/min/1.73 m^2 Left main or ostial stenosis Bifurcation lesion with a side branch diameter >2.0 mm Myocardial bridge Total occlusion (TIMI flow grade 0) or thrombotic lesion Heavy calcification proximal to or within the target lesion Restenotic from previous intervention Excessive vessel tortuosity	1) 36-month vasomotion 2) Δ MLD	2/5
ABSORB III (6)	2017	2,008	CoCr EES vs. BVS	Inclusion criteria Evidence of myocardial ischemia De novo coronary lesions (n ≤ 2) RVD ≥2.5 and ≤3.75 mm Lesion length ≤24 mm Exclusion criteria Acute MI or recent MI ≤72 h (with positive cardiac markers) LVEF ≤30% GFR <30 ml/min/1.73 m^2 Previous PCI in the target vessel ≤1 yr Left main or ostial stenosis Bifurcation lesion with a side branch diameter >2.0 mm Calcified lesion (moderate/heavy) Thrombotic lesion Myocardial bridge Excessive vessel tortuosity	12-month TLF	2/5
ABSORB Japan (19)	2016	400	CoCr EES vs. BVS	Inclusion criteria Evidence of myocardial ischemia De novo coronary lesions (n ≤ 2) RVD ≥2.5 and ≤3.75 mm Lesion length ≤24 mm Exclusion criteria Acute MI or recent MI ≤72 h (with positive cardiac markers) LVEF ≤30% GFR <30 ml/min/1.73 m^2 Previous PCI in the target vessel ≤1 yr Left main or ostial stenosis Bifurcation lesion with a side branch diameter >2.0 mm Calcified lesion (moderate/heavy) Thrombotic lesion Excessive vessel tortuosity	12-month TLF	2/4

Continued on the next page

TABLE 1 Continued

Study Name (Ref. #)	Year	Study Group Size	Device Used	Main Inclusion/Exclusion Criteria	Primary Endpoints	Available/Planned Follow-Up (yrs)
AIDA (7)	2017	1,845	CoCr EES vs. BVS	Inclusion criteria Applicable guidelines on PCI and the instructions for use of the ABSORB BVS strategy and XIENCE family Exclusion criteria Lesions more than 70 mm in length RVD ≤2.5 and ≥4 mm Bifurcation lesions (≥ stent planned) In-stent restenosis	24-month TVF	2/5
EVERBIO II (16)	2016	158	PtCr EES vs. BVS	Inclusion criteria Stable or unstable ischemic heart disease Exclusion criteria (The study protocol defined no limits for lesion length, number of target lesions, or number of vessels.) RVD ≥4.0 mm	9-month angiographic in-device late loss	2/5
TROFI II (18)	2016	191	CoCr EES vs. BVS	Inclusion criteria STEMI ≤24 h RVD ≥2.25 and ≤3.8 mm Exclusion criteria Cardiogenic shock Calcified lesion (moderate/heavy) Inadequate vessel size (2.25 or 3.80 mm) Severe tortuosity Inadequate vessel size	6-month optical frequency domain imaging healing score	2/3

ABSORB = A Clinical Evaluation of Absorb™ BVS, the Everolimus Eluting Bioresorbable Vascular Scaffold in the Treatment of Subjects With de Novo Native Coronary Artery Lesions; AIDA = Amsterdam Investigator-initiateD Absorb Strategy All-comers; BVS = bioresorbable vascular scaffold; CoCr = cobalt-chromium; EES = everolimus-eluting stent; EVERBIO = Comparison of Everolimus- and Biolimus-Eluting Stents With Everolimus-Eluting Bioresorbable Vascular Scaffold Stents; GFR = glomerular filtration rate; LVEF = left ventricular ejection fraction; MI = myocardial infarction; MLD = minimal lumen diameter; PCI = percutaneous coronary intervention; PtCr = platinum-chromium; RVD = reference vessel diameter; STEMI = ST-segment elevation myocardial infarction; TIMI = Thrombolysis In Myocardial Infarction; TLF = target lesion failure; TROFI = Comparison of the ABSORB Everolimus Eluting Bioresorbable Vascular Scaffold System With a Drug-Eluting Metal Stent (Xience™) in Acute ST-Elevation Myocardial Infarction; TVF = target vessel failure.

TABLE 2 Baseline Patient Characteristics

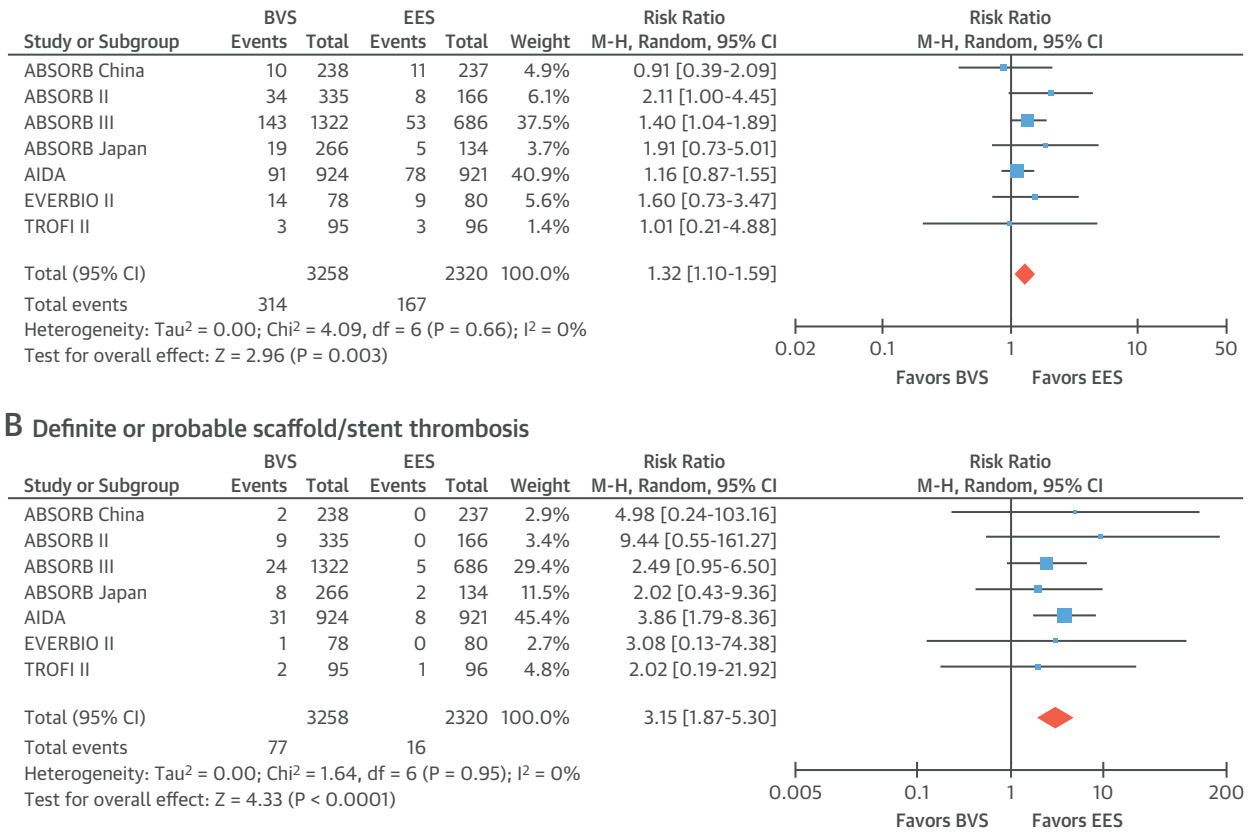
	ABSORB China		ABSORB II		ABSORB III		ABSORB Japan	
	BVS	EES	BVS	EES	BVS	EES	BVS	EES
Randomized study group	238	237	335	166	1,322	686	266	134
Age, yrs	57.2 ± 11.4	57.7 ± 9.6	61.5 ± 10.0	60.9 ± 10.0	63.5 ± 10.6	63.6 ± 10.3	67.1 ± 9.4	67.3 ± 9.6
Male	171 (71.8)	172 (72.6)	253 (76)	132 (80)	934 (70.7)	481 (70.1)	210 (78.9)	99 (73.9)
Smoker	78 (32.8)	84 (35.4)	79 (24)	36 (22)	281 (21.3)	142 (20.7)	53 (19.9)	29 (21.6)
Hypertension	140 (58.8)	143 (60.3)	231 (69)	119 (72)	1,122 (84.9)	583 (85.0)	208 (78.2)	107 (79.9)
Hyperlipidemia	101 (42.4)	91 (38.4)	252 (75)	133 (80)	1,140 (86.2)	592 (86.3)	218 (82.0)	110 (82.1)
Diabetes	60 (25.2)	55 (23.2)	80 (24)	40 (24)	416 (31.5)	224 (32.7)	96 (36.1)	48 (48)
Prior MI	40 (16.8)	38 (16.0)	93 (28)	48 (29)	282 (21.5)	150 (22.0)	42 (16)	32 (23.9)
SA	53 (22.3)	40 (16.9)	214 (64)	107 (64)	757 (57.3)	417 (60.8)	170 (63.9)	88 (65.7)
ACS	154 (64.7)	152 (64.1)	68 (20)	37 (22)	355 (26.9)	168 (24.5)	26 (9.8)	22 (16.4)

	AIDA		EVERBIO II		TROFI II	
	BVS	EES	BVS	EES	BVS	EES
Randomized study group	924	921	78	80	95	96
Age, yrs	64.3 ± 10.6	64 ± 10.5	65 ± 11	65 ± 11	59.1 ± 10.7	58.2 ± 9.6
Male	670 (72.5)	700 (76)	61 (78)	64 (80)	73 (76.8)	84 (87.5)
Smoker	248 (28.6)	273 (31.7)	28 (36)	30 (38)	46 (48.4)	47 (49.5)
Hypertension	468 (50.9)	464 (50.5)	43 (55)	51 (64)	41 (44.1)	35 (36.5)
Hyperlipidemia	344 (37.6)	350 (38.3)	44 (56)	50 (63)	60 (63.8)	55 (57.3)
Diabetes	171 (18.5)	153 (16.6)	17 (22)	13 (16)	18 (18.9)	14 (14.7)
Prior MI	166 (18)	172 (18.7)	11 (14)	14 (18)	2 (2.1)	3 (3.1)
SA	361 (39.1)	370 (40.2)	41 (53)	47 (59)	0 (0)	0 (0)
ACS	495 (53.6)	504 (54.6)	28 (35.9)	38 (47.5)	95 (100)	96 (100)

Values are mean ± SD or n (%). No significant differences were present between the BVS and EES groups.

ACS = acute coronary syndrome; DAPT = dual antiplatelet therapy; DM = diabetes mellitus; SA = stable angina; other abbreviations as in Table 1.

FIGURE 1 Primary Safety and Efficacy Outcomes in BVS Versus EES



(A) Target lesion failure. **(B)** Definite or probable scaffold thrombosis or ST. ABSORB = A Clinical Evaluation of Absorb™ BVS, the Everolimus Eluting Bioresorbable Vascular Scaffold in the Treatment of Subjects With de Novo Native Coronary Artery Lesions; AIDA = Amsterdam Investigator-initiateD Absorb Strategy All-comers; BVS = bioresorbable vascular scaffold; CI = confidence interval; EES = everolimus-eluting stent; EVERBIO = Comparison of Everolimus- and Biolimus-Eluting Stents With Everolimus-Eluting Bioresorbable Vascular Scaffold Stents; M-H = Mantel-Haenszel; RR = risk ratio; TROFI = Comparison of the ABSORB Everolimus-Eluting Bioresorbable Vascular Scaffold System With a Drug-Eluting Metal Stent (Xience™) in Acute ST-Elevation Myocardial Infarction.

There were no significant differences in cardiac death (**Figure 4**), all-cause death, and patient-oriented composite endpoint (Online Figures 6A and 6C) between the 2 groups. However, the overall MI rate was higher in the BVS group (Online Figure 6B). No evidence of publication bias was found for the secondary endpoints of interest (Online Figure 7).

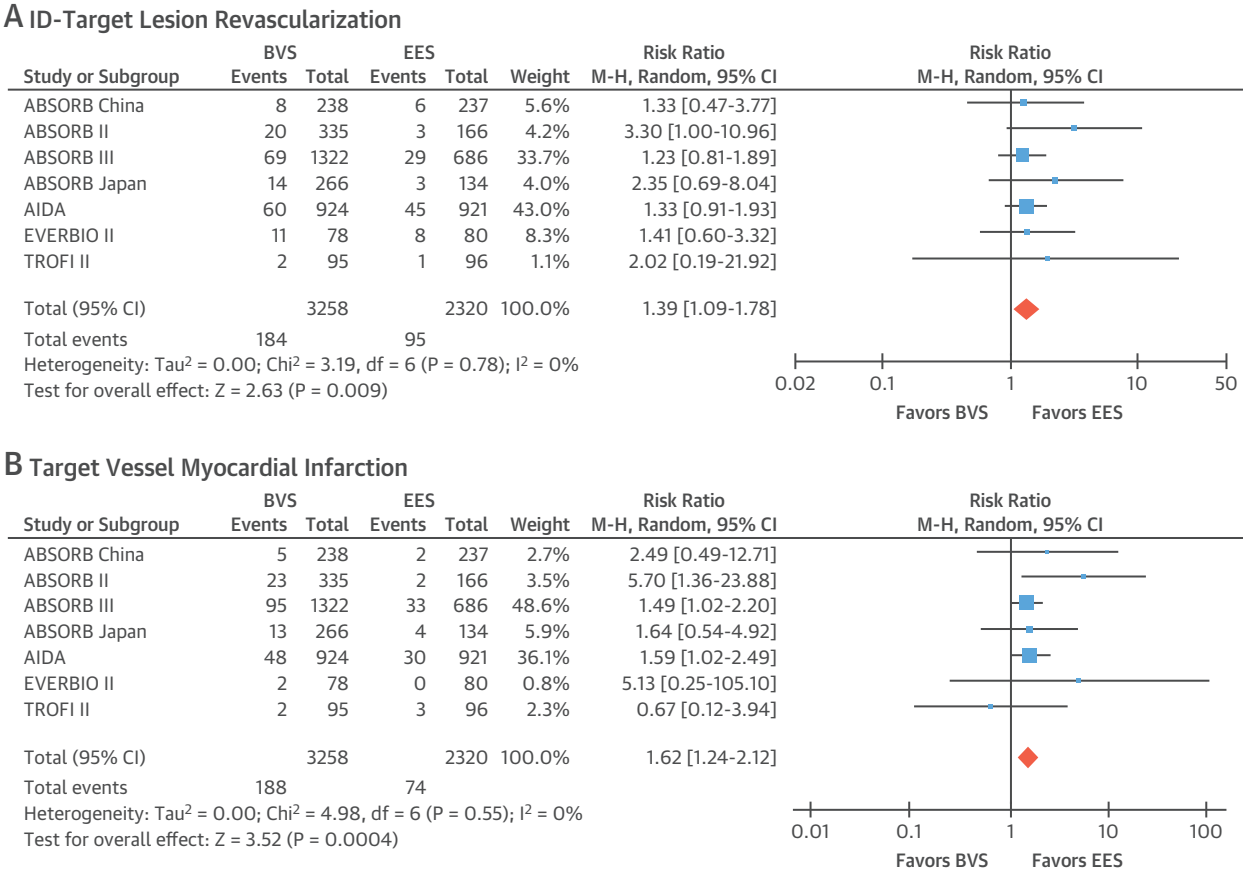
All of the results discussed previously were consistent using fixed effect models for both primary (Online Figures 8 and 9) and secondary endpoints (Online Figures 10 and 11).

DISCUSSION

The main findings of the present large-scale meta-analysis of 7 RCTs comparing the BVS with metallic EES in patients undergoing PCI are: 1) at a median time of follow-up of 2 years (range 2 to 3 years), BVS was associated with increased risk of TLF and ST compared with metallic EES; 2) the greater risk of ST associated with BVS was consistent across the early, late, and very late periods, with an overall NNH ≈60 with use of BVS compared to EES; 3) there were more MI events with BVS than with EES, but there were no significant differences in the risk of all-cause or cardiac mortality between the 2 groups.

Iterations in metallic drug-eluting stents, including improved polymer biocompatibility, drug release kinetics, reduced strut thickness, and improved alloy composition, overcame the limitations of first-generation drug-eluting stents, including in high-risk patient subsets (21-27). However, even with the current metallic EES, phenomena such as incomplete

FIGURE 2 Secondary Efficacy Endpoints in BVS Versus EES



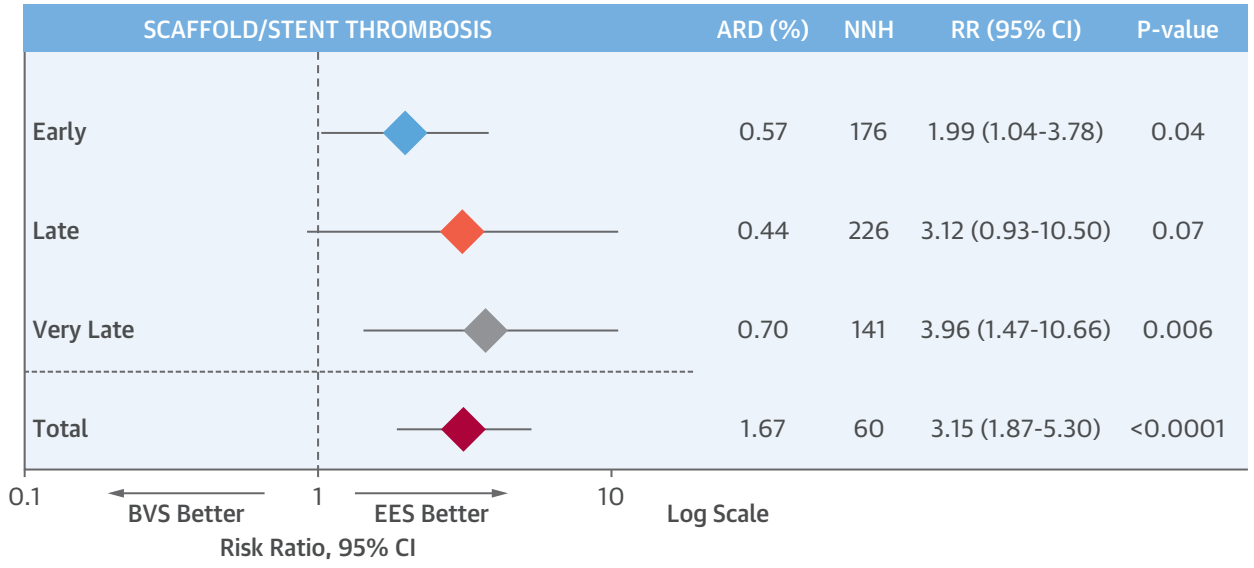
(A) Ischemia-driven (ID) target lesion revascularization. **(B)** Target vessel myocardial infarction. Abbreviations as in Figure 1.

endothelialization, polymer hypersensitivity, and neoatherosclerosis may still occur, and lead to accrual of TLF events over time (28). The main mechanism underlying these pathological processes is believed to be related to the persistence of the metallic implant within the coronary artery, which alters endothelial function and physiological vasomotion (28). The conception of the BVS technology occurred in the first-generation drug-eluting stent era, and they were created with the intent of providing transient mechanical support coupled with release of an antiproliferative drug to prevent restenosis (within 1 year), followed by complete scaffold bioresorption in the very late periods, resulting in recovery of vascular integrity and physiology, as well as freedom for possible use of the artery for future coronary bypass surgery (28). According to the BVS development theory, timely and complete reabsorption of the scaffold would permit a physiological vascular remodeling process, a lower risk of very late ST, and reduce the necessity of prolonged dual antiplatelet therapy. However, the strut thickness of the currently approved BVS and variability in absorption kinetics in atheromatous human coronary arteries antagonized the previously described potential favorable effects that were observed ex vivo and in experimental animal models. In fact, recent evidence from large RCTs suggested that BVS are associated with a higher risk of complications compared with metallic EES (28–30).

In line with the initial observations, this large meta-analysis (encompassing the totality of the evidence from RCTs) indicates that the use of BVS is associated with a significantly greater risk of TLF, MI, and ST compared with metallic EES. Importantly, the increased risk of ST appears to start early and to be durable over time.

The findings of our study should be carefully evaluated. First, in this meta-analysis, the TLF and ST rates

CENTRAL ILLUSTRATION **Bioresorbable Scaffolds Versus Metallic Stent Thrombosis Across Different Time Points**



Sorrentino, S. et al. J Am Coll Cardiol. 2017;69(25):3055-66.

The risk of device thrombosis observed with bioresorbable vascular scaffold (BVS) compared with everolimus-eluting stent (EES) appeared to be concordant across the early, late, and very late periods. ARD = absolute risk difference; CI = confidence interval; NNH = number needed to harm; RR = risk ratio.

in the metallic EES control group were very low and "exceeded the individual trial investigators' expectations" (21-27). The excellent outcomes observed with EES may be due to the improved deliverability, implantation technique, and overall familiarity of the operators with this particular device, as well as the low overall risk of the patients included in these RCTs. Additionally, the durable fluoropolymer may offer intrinsic thromboprotection (31). Second, the instruction for implanting BVS devices did not initially include routine intracoronary imaging and the (currently recommended) pre-dilation, appropriate vessel sizing, and high-pressure post-dilation protocol, probably in fear of causing scaffold deformation or fracture. This implantation technique was advised toward the end of RCT enrollment, after initial unfavorable early safety reports were observed in the ABSORB II (Clinical Evaluation to Compare the Safety, Efficacy and Performance of ABSORB Everolimus Eluting Bioresorbable Vascular Scaffold System Against XIENCE Everolimus Eluting Coronary Stent System in the Treatment of Subjects With Ischemic Heart Disease Caused by de Novo Native Coronary Artery Lesions) trial (32). Interestingly, the pre-dilation, appropriate vessel sizing, and high-pressure post-dilation protocol techniques are similar to those described by Colombo et al. (33) in the original landmark report supporting the use of intravascular imaging and high-pressure balloon inflation to avoid routine anticoagulation and prevent thrombosis after bare-metal stent implantation (33,34). Third, the currently FDA-approved BVS device has thick struts, deformation risk with high-pressure post-dilation, more delayed than expected (on the basis of animal models) absorption kinetics, and limited radial strength; newer-generation or new BVS models currently under investigations or approved outside of the United States should attempt to overcome these limitations (Online Table 4). Fourth, it must be considered that the control group for the included trials received an advanced-generation metallic drug-eluting stent with a durable fluoropolymer, whereas the currently tested BVS type remains a first-generation device with room for future improvement in both implantation technique and device engineering characteristics, as explained earlier.

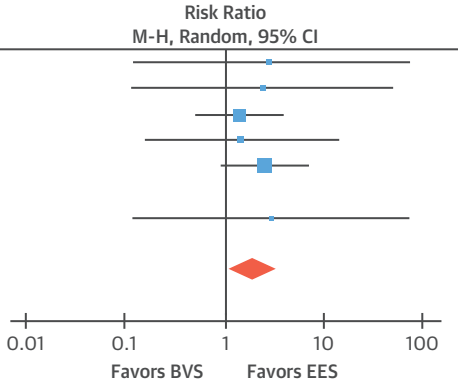
The main causes of BVS thrombosis require further investigation. As previously described for the metallic stents, mechanisms of BVS thrombosis related to the scaffold may include: BVS undersizing with respect to the reference vessel diameter; inadequate lesion preparation and poor BVS expansion; late scaffold recoil or compression; excessive positive vessel remodeling; invagination; or late scaffold fracture or

FIGURE 3 **BVS Versus EES risk of ST in Early (1 Month), Late (1 to 12 Months), and Very Late (Beyond 1 Year From Implantation) Periods**

A Early Scaffold/Stent Thrombosis

Study or Subgroup	BVS Events	BVS Total	EES Events	EES Total	Weight	Risk Ratio M-H, Random, 95% CI
ABSORB China	1	238	0	237	4.1%	2.99 [0.12-72.97]
ABSORB II	2	335	0	166	4.5%	2.49 [0.12-51.47]
ABSORB III	14	1322	5	686	40.0%	1.45 [0.53-4.02]
ABSORB Japan	3	266	1	134	8.1%	1.51 [0.16-14.39]
AIDA	13	924	5	921	39.2%	2.59 [0.93-7.24]
EVERBIO II	0	78	0	80		Not estimable
TROFI II	1	95	0	96	4.1%	3.03 [0.13-73.49]
Total (95% CI)		3258		2320	100.0%	1.99 [1.04-3.78]
Total events	34		11			

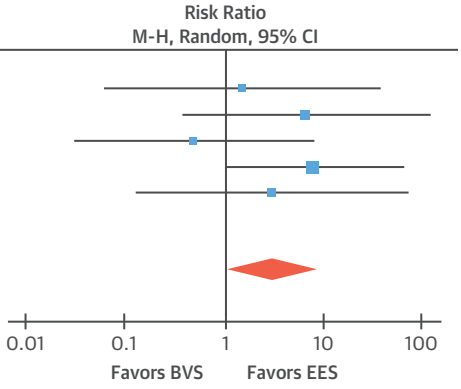
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.83$, df = 5 (P = 0.98); $I^2 = 0\%$
Test for overall effect: Z = 2.09 (P = 0.04)



B Late Scaffold/Stent Thrombosis

Study or Subgroup	BVS Events	BVS Total	EES Events	EES Total	Weight	Risk Ratio M-H, Random, 95% CI
ABSORB China	0	237	0	237		Not estimable
ABSORB II	1	331	0	166	14.4%	1.51 [0.06-36.84]
ABSORB III	6	1299	0	675	17.8%	6.76 [0.38-119.82]
ABSORB Japan	1	263	1	132	19.2%	0.50 [0.03-7.96]
AIDA	8	909	1	911	34.1%	8.02 [1.00-63.97]
EVERBIO II	1	78	0	80	14.5%	3.08 [0.13-74.38]
TROFI II	0	94	0	96		Not estimable
Total (95% CI)		3211		2297	100.0%	3.12 [0.93-10.50]
Total events	17		2			

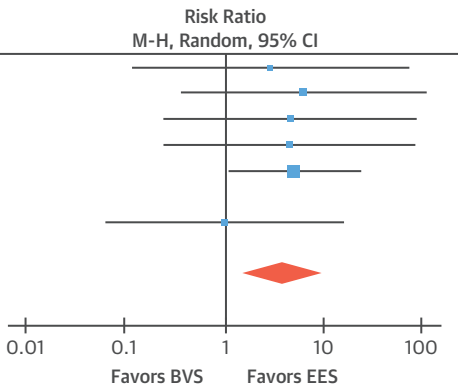
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 3.04$, df = 4 (P = 0.55); $I^2 = 0\%$
Test for overall effect: Z = 1.84 (P = 0.07)



C Very-late Scaffold/Stent Thrombosis

Study or Subgroup	BVS Events	BVS Total	EES Events	EES Total	Weight	Risk Ratio M-H, Random, 95% CI
ABSORB China	1	237	0	232	9.6%	2.94 [0.12-71.73]
ABSORB II	6	328	0	163	11.9%	6.48 [0.37-114.33]
ABSORB III	4	1284	0	675	11.5%	4.73 [0.26-87.81]
ABSORB Japan	4	256	0	130	11.5%	4.59 [0.25-84.56]
AIDA	10	812	2	828	42.6%	5.10 [1.12-23.20]
EVERBIO II	0	77	0	77		Not estimable
TROFI II	1	94	1	96	12.9%	1.02 [0.06-16.09]
Total (95% CI)		3088		2201	100.0%	3.96 [1.47-10.66]
Total events	26		3			

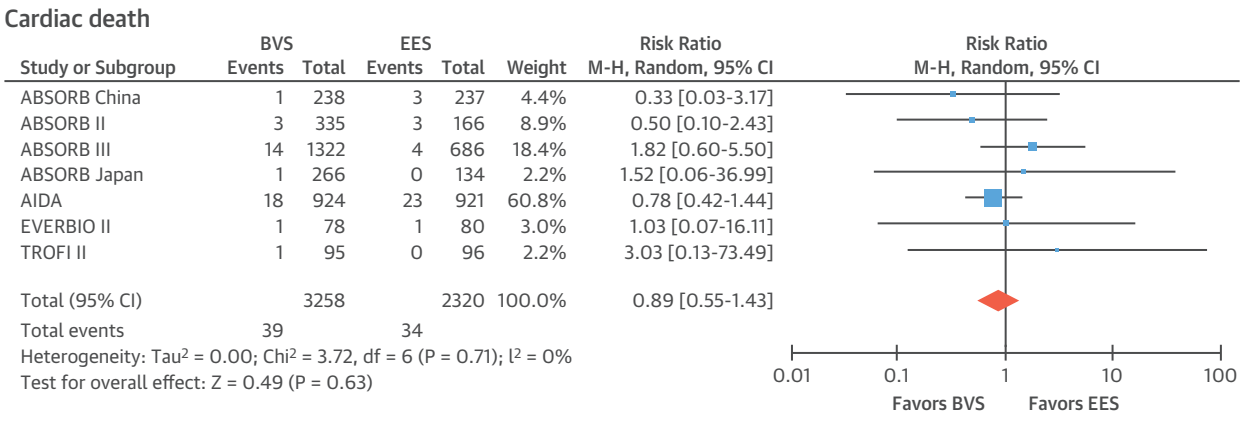
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.22$, df = 5 (P = 0.94); $I^2 = 0\%$
Test for overall effect: Z = 2.73 (P = 0.006)



(A) Early, **(B)** late, or **(C)** very late scaffold thrombosis or stent thrombosis (ST). Abbreviations as in Figure 1.

discontinuity (28). Of note, in a recent report in which causes of very late BVS thrombosis were investigated with use of optical coherence tomography imaging, scaffold malapposition appeared to be the most common underlying mechanism (4,23). Recent studies underlined the importance of optimal scaffold implantation (with intracoronary imaging for verification) through which the risk of BVS thrombosis may be reduced with routine balloon post-dilation and achievement of a greater scaffold expansion (35,36).

FIGURE 4 Secondary Safety Endpoint in BVS Versus EES at Longest Available Follow-Up



Abbreviations as in Figure 1.

In the present study, we demonstrated a consistently higher risk of BVS thrombosis across the early (up to 30 days), late (between 1 month and 1 year), and very late (beyond 1 year) periods. Prior studies and meta-analyses investigating the risk of BVS thrombosis were limited by the inclusion of a shorter time of follow-up (29) or nonrandomized studies (30). By including the latest evidence from RCTs using the longest follow-up available, we were able to more accurately characterize the risk of BVS thrombosis over time, particularly in the very late period. For example, in the study of Toyota et al. (30), BVS had an elevated risk of ST in the very late period compared with EES, but without statistical significance. In the present analysis, with enhanced statistical power, we observed a highly significant greater risk of BVS thrombosis beyond 1 year.

Given the persistent high risk of scaffold thrombosis over time (**Central Illustration**), and in line with the recent FDA safety alert recommendation (8), a prolonged period of dual antiplatelet therapy should be advised for all patients who receive the currently FDA-approved BVS. Notably, in the ABSORB II trial, patients experiencing late or very late scaffold thrombosis were not on dual antiplatelet therapy at the time of the event (20). Similarly, in the Absorb BVS (Clinical Evaluation of AVJ-301), ABSORB Japan (Everolimus Eluting Bioresorbable Vascular Scaffold in the Treatment of Subjects With de Novo Native Coronary Artery Lesions in Japanese Population) trial, 3 of 4 patients experiencing very late scaffold thrombosis were not on dual antiplatelet therapy (19).

STUDY LIMITATIONS. First, the present findings are subject to the inherent limitations of the included RCTs due to study design, follow-up, dropout, and endpoint ascertainment. Second, 4 of 7 RCTs included in this analysis were available as meeting presentations, rather than as full-length papers; this may be due to analysis delays or to publication bias secondary to trials' negative results. Third, despite the lack of measured heterogeneity, included studies differed in terms of inclusion or exclusion criteria and primary endpoint definitions. Fourth, a quantitative evaluation of the robustness of the main findings through a trial sequential analysis was not performed. Five, only 1 type of BVS was evaluated in this study. Therefore, the present results are not generalizable to all types of BVS. Finally, the clinical benefits of BVS may extend beyond the standard clinical endpoints implemented in coronary stent trials (i.e., future surgical revascularization, recurrent angina, possibility of coronary artery disease progression monitoring with noninvasive imaging, and patient preference), and remain to be explored and documented in future and longer-term clinical investigations.

CONCLUSIONS

Compared with metallic EES, the currently approved BVS is associated with lower efficacy and higher thrombotic complications at a median time of follow-up of 2 years. The observed risk of ST was evident across the early, late, and very late follow-up periods.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: The FDA-approved BVS is associated with greater risks of TLF, ST, and MI compared with metallic EES.

TRANSLATIONAL OUTLOOK: Further studies are needed to understand the mechanisms underlying thrombosis of BVS and to develop devices that overcome these limitations.

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KEY WORDS bioresorbable vascular scaffold, everolimus-eluting stents, percutaneous coronary intervention, thrombosis

APPENDIX For supplemental tables and figures, please see the online version of this article.