Three-Year Outcomes With the Absorb Bioresorbable Scaffold

Individual-Patient-Data Meta-Analysis From the ABSORB Randomized Trials

BACKGROUND: The Absorb bioresorbable vascular scaffold (BVS) completely resorbs within 3 years after coronary artery implantation. The safety and effectiveness of BVS through this critical 3-year period have not been characterized.

METHODS: We performed an individual-patient-data pooled meta-analysis of the 4 randomized ABSORB trials in which 3389 patients with coronary artery disease were randomly assigned to everolimus-eluting Absorb BVS (n=2164) or cobalt-chromium everolimus-eluting stents (n=1225). The primary efficacy outcome measure was target lesion failure (cardiac mortality, target vessel myocardial infarction, or ischemia-driven target lesion revascularization), and the primary safety outcome measure was device thrombosis.

RESULTS: BVS compared with cobalt-chromium everolimus-eluting stents resulted in higher 3-year rates of target lesion failure (11.7% versus 8.1%; risk ratio [RR], 1.38; 95% confidence interval [CI], 1.10–1.73; *P*=0.006), driven by greater target vessel myocardial infarction (7.8% versus 4.2%; RR, 1.72; 95% CI, 1.26–2.35; *P*=0.0006) and ischemia-driven target lesion revascularization (6.6% versus 4.4%; RR, 1.44; 95% CI, 1.05–1.98; *P*=0.02), with comparable cardiac mortality (1.1% versus 1.1%; RR, 0.93; 95% CI, 0.47–1.88; *P*=0.85). Device thrombosis rates through 3 years were also higher with BVS (2.4% versus 0.6%; RR, 3.71; 95% CI, 1.70–8.11; *P*=0.001). Between 1 and 3 years, target lesion failure rates (6.1% versus 3.9%; *P*=0.02) and device thrombosis rates (1.1% versus 0.0%; *P*<0.0001) were higher with BVS than cobalt-chromium everolimus-eluting stents.

CONCLUSIONS: In the present individual-patient-data pooled meta-analysis of the ABSORB trials, BVS was associated with increased rates of target lesion failure and device thrombosis between 1 and 3 years and cumulatively through 3 years of follow-up compared with everolimus-eluting stents.

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Clinical Perspective

What Is New?

- The Absorb bioresorbable vascular scaffold (BVS) completely resorbs within 3 years after implantation. The safety and effectiveness of BVS through this period have not been characterized.
- Our individual-patient-data meta-analysis of the 4 randomized ABSORB trials demonstrates that compared with metallic everolimus-eluting stents, BVS have higher rates of target lesion failure and device thrombosis cumulatively to 3 years and between 1 and 3 years.
- Multivariable analysis identified the number of treated lesions, current tobacco use, and previous cardiac interventions as independent predictors of 3-year target lesion failure, whereas diabetes mellitus was predictive of 3-year device thrombosis in BVS-treated patients.

What Are the Clinical Implications?

- The current-generation Absorb BVS are associated with higher rates of adverse events cumulatively within 3 years but also between 1 and 3 years compared with metallic everolimus-eluting stents.
- The first-generation Absorb BVS is no longer being produced by the manufacturer.
- The impact of appropriate patient selection, device sizing, adequate lesion preparation, routine high-pressure postdilatation, and intravascular imaging on improving BVS outcomes needs to be carefully examined in other current and future iterations of BVS.

Contemporary drug-eluting stents (DES) have substantially improved event-free survival in patients with coronary artery disease compared with earlier devices.[1,2] However, the permanence of metallic DES may result in expansive remodeling, late strut fractures, abnormal vasomotion, and neoatherosclerosis, which collectively contribute to a 2% to 3% annual risk of stent-associated events beyond the first year after implantation, potentially for the life of the patient.[3–5] Drug-eluting bioresorbable vascular scaffolds (BVS) were designed to mitigate these very late risks of metallic stents by providing mechanical support only during the required period of stent-induced vascular remodeling, with complete bioresorption within several years thereafter. The temporary nature of BVS may also confer other advantages compared with permanent stents such as treatment of bifurcation lesions, long diffuse disease, and in-stent restenosis. However, although in randomized trials BVS met criteria for noninferiority compared with contemporary metallic DES within the first year after implantation,[6] an ongoing risk of adverse events between 1 and 2 years was identified,[7] resulting in increased patient-oriented and device-oriented adverse event rates with BVS compared with DES at cumulative 2-year follow-up.[8,9] Comprehensive analysis of BVS outcomes through 3-year follow-up has not been performed, in part because the 3-year results from the ABSORB III trial, the largest BVS randomized trial to date, have not been reported. In this regard, characterizing the safety and efficacy profile of BVS at 3 years, when its bioresorption is complete,[10] is essential to understanding the limitations of this first-generation device that must be overcome if the potential later advantages of BVS are to be realized. We therefore performed an individual-patient-data pooled meta-analysis of the Absorb BVS randomized trials, including the ABSORB III trial, through 3-year follow-up.

METHODS

Trials and Study Objectives

For inclusion in the present meta-analysis, we identified all studies comparing treatment with the Absorb BVS and the Xience cobalt-chromium everolimus-eluting stent (CoCr-EES; both devices manufactured by Abbott Vascular, Santa Clara, CA) in which at least 3-year clinical follow-up was available. Only randomized trials were included to control residual confounding. Four trials in which patients with coronary artery disease underwent percutaneous coronary intervention met these criteria: ABSORB II,[11,12] ABSORB Japan,[13] ABSORB China,[14] and ABSORB III.[15,16] Each trial was approved by the institutional review board or ethics committee at each participating center, and all patients signed written informed consent before randomization. The individual patient data from these 4 studies were merged into a single database. The principal objectives of the present study were to determine the safety and effectiveness of BVS compared with CoCr-EES at 3 years and in landmark periods between 1 to 3 years and 2 to 3 years, to determine the extent to which the excess in adverse events with BVS compared with CoCr-EES is attributable to increased device thrombosis, and to examine the multivariable predictors of adverse events after BVS treatment.

End Points and Definitions

The primary efficacy outcome measure for the present study was the device-oriented composite end point of target lesion failure (TLF; cardiac mortality, target vessel myocardial infarction [TV-MI], or ischemia-driven target lesion revascularization [ID-TLR]) at cumulative 3-year follow-up. The primary safety outcome measure was definite or probable device thrombosis, also at cumulative 3-year follow-up. Secondary end points included the patient-oriented composite end point of all-cause mortality, all MI, or all revascularization; all-cause mortality (also subclassified as cardiac or noncardiac); all MI (also subclassified as TV-MI or non–TV-MI); and all ischemia-driven revascularization (also subclassified as ID-TLR or ischemia-driven target vessel revascularization). We also examined these outcome measures in the landmark period between 1 and 3 years. All end points were assessed according to the

definitions reported in the original trial protocols as adjudicated by independent end point committees with the intention-to-treat principle.[11–16]

Statistical Analysis

Summary treatment effect estimates were derived for adverse events in the follow-up period cumulatively through 3 years after randomization and in the landmark period between 1 and 3 years. Patients were included in the 3-year follow-up and landmark analyses if 3-year follow-up was complete or if an event occurred during the follow-up period. Patients with events before 1 year were included in the landmark analyses between 1 and 3 years. Treatment outcomes were examined with both the DerSimonian and Laird random-effect model and Mantel-Haenszel fixed-effect model, the latter of which

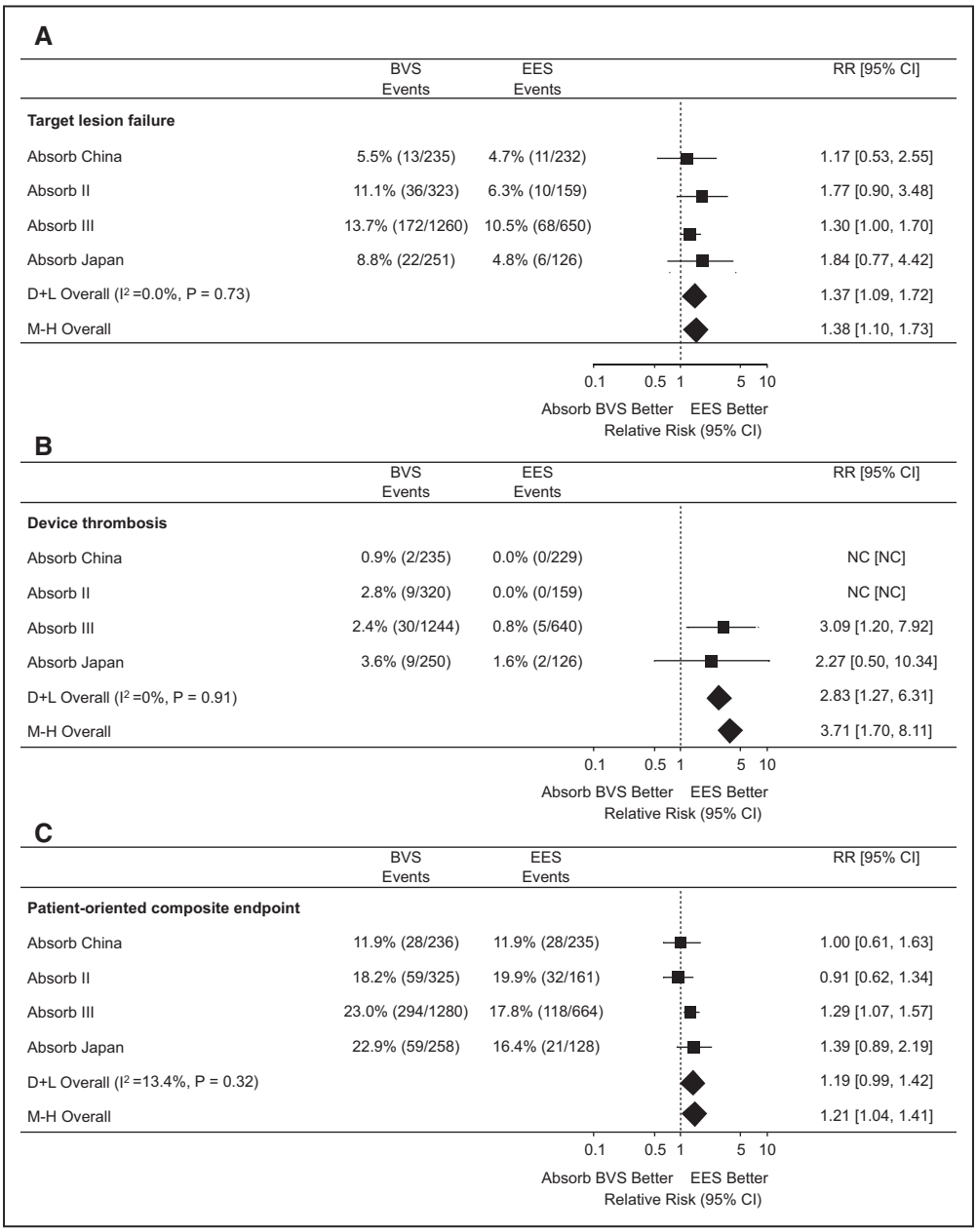
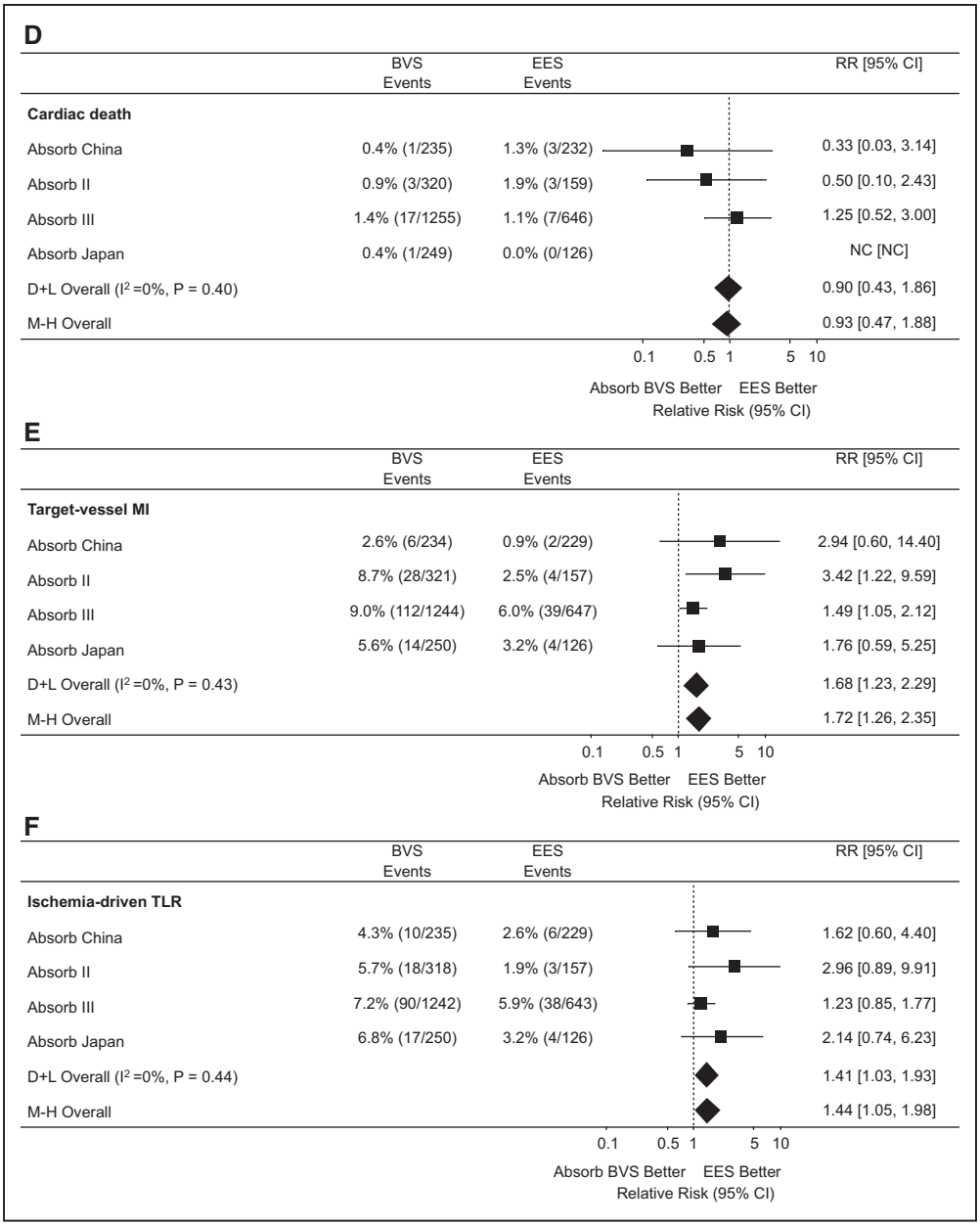


Figure 1. Three-year selected clinical outcomes for patients randomized to the Absorb BVS vs Xience CoCr-EES in the ABSORB randomized trials.

A, The device-oriented composite end point of target lesion failure (cardiac death, target vessel myocardial infarction, or ischemia-driven target lesion revascularization). **B**, Device thrombosis (definite or probable). **C**, Patient-oriented composite end point of death, myocardial infarction, or any revascularization. **D**, Cardiac mortality. **E**, Target vessel myocardial infarction (MI). **F**, Ischemia-driven target lesion revascularization. BVS indicates bioresorbable vascular scaffold; CI, confidence interval; D+L, DerSimonian and Laird random-effect model; EES, everolimus-eluting stent; M-H, Mantel-Haenszel fixed-effect model; NC, not calculated; and RR, relative risk.



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is preferred when few events (<5) are present in any of the treatment arms in the component trials (eg, as observed for device thrombosis).[17] Summary statistics are relative risks (RRs) with 95% confidence intervals (CIs). Heterogeneity between trials was evaluated with the Cochran Q test and the I^2 statistic (with <25%, 25%–50%, and >50% indicating low, moderate, and high heterogeneity, respectively).

Univariable determinates of cumulative 3-year and 1- to 3-year adverse events were determined with the Wald χ^2 test from a univariable Cox regression, adjusted by study level as a fixed effect. The independent predictors of cumulative 3-year and 1- to 3-year events were determined by multivariable logistic regression using stepwise selection, adjusted by study, with the number of variables for each model sparingly chosen according to their historical relationship to each outcome measure in previous studies to avoid overfitting (at least 10 events per variable).[18] Variables entered into each model appear in the footnote of the corresponding results table. The Pearson goodness-of-fit test verified the stability of each of the models. Demographic and baseline characteristics are summarized by treatment group with means and SDs for continuous variables and were compared by two-way ANOVA. Binary data were compared by the Mantel-Haenzel fixed-effect model. Time to first event curves are displayed with Kaplan-Meier estimates, with between-group differences compared by hazard ratio and 95% CI, tested with the Wald χ^2 test, and adjusted by study. The consistency of the treatment effect on the RR for selected end points in subgroups (adjusted for study level) was examined with formal multiplicative interaction testing. Metafor (version 1.9–7) in R version 3.2 was used to perform the meta-analysis. All other statistical analyses were performed with SAS version 9.2 (SAS Institute, Cary, NC).

RESULTS

Patients and Procedures

A total of 3389 patients were enrolled at 301 centers from North America, Europe, and Asia into the 4 ABSORB trials (Table I in the online-only Data Supplement), of whom 2164 and 1255 patients were randomly assigned to BVS and CoCr-EES, respectively. Three-year follow-up was complete in 2096 BVS-treated patients (96.9%) and 1189 CoCr-EES–treated patients (97.1%). Baseline clinical features, antiplatelet regimens, and angiographic data according to randomized device are shown in Tables II and III in the online-only Data Supplement and were well matched between groups. Procedural and angiographic results for the randomized groups are shown in Table IV in the online-only Data Supplement. The proportion of patients maintained on dual antiplatelet therapy (both aspirin and a $P2Y_{12}$ inhibitor) at 3 years was higher in BVS-treated patients than CoCr-EES–treated patients (1000 of 2158 [46.3%] versus 510 of 1222 [41.7%]; *P*=0.01).

Cumulative Outcomes Through 3 Years After Randomization

A summary of adverse events in the 4 studies occurring from randomization through 3 years appears in Figures 1 and 2 and Table 1. The 3-year relative rates of the primary efficacy end point of TLF were higher with BVS compared with EES (11.7% versus 8.1%; RR, 1.38; 95% CI, 1.10–1.73; *P*=0.006). These differences were driven by increased rates of TV-MI (7.8% versus 4.2%; RR, 1.72; 95% CI, 1.26–2.35; *P*=0.0006) and ID-TLR (6.6% versus 4.4%; RR, 1.44; 95% CI, 1.05–1.98; *P*=0.02) with BVS, but not cardiac death (1.1% versus 1.1%; RR, 0.93; 95% CI, 0.47–1.88; *P*=0.85). The primary safety end point of device thrombosis through 3 years occurred more commonly with BVS than EES (2.4% versus 0.6%; RR, 3.71; 95% CI, 1.70–8.11; *P*=0.001). The patient-oriented composite end point at 3 years was also greater with BVS compared with EES, driven by increased rates of MI with BVS. No significant heterogeneity was present between the 4 studies for any of the evaluated end points.

By multivariable analysis, among BVS-treated patients, the number of treated lesions, current tobacco use, previous coronary interventions, and participation in ABSORB China versus ABSORB III were independent predictors of 3-year TLF, whereas the presence of diabetes mellitus was predictive of 3-year device thrombosis (Table 2). Multivariable predictors of 3-year TLF and device thrombosis in the entire study population are shown in Table V in the online-only Data Supplement.

Table 1. Meta-Analysis Summary for Ischemic End Points Occurring From Randomization Through 3 Years in the ABSORB Trials

	BVS, % (n/N)	CoCr-EES, % (n/N)	Fixed-Effect RR (95% CI)	*P* Value, Fixed Effect	Random-Effect RR (95% CI)	*P* Value, Random Effect	I^2, %	*P* Value, Heterogeneity
TLF	11.7 (243/2069)	8.1 (95/1167)	1.38 (1.10–1.73)	0.006	1.37 (1.09–1.72)	0.01	0	0.73
Patient-oriented composite end point	21.0 (440/2099)	16.8 (199/1188)	1.21 (1.04–1.41)	0.02	1.19 (0.99–1.42)	0.06	13.4	0.33
All-cause mortality	2.6 (54/2089)	3.0 (35/1185)	0.84 (0.55–1.29)	0.43	0.84 (0.55–1.30)	0.45	0	0.46
Cardiac	1.1 (22/2059)	1.1 (13/1163)	0.93 (0.47–1.88)	0.85	0.90 (0.43–1.86)	0.77	0	0.40
Noncardiac	1.5 (32/2068)	1.9 (22/1173)	0.78 (0.45–1.35)	0.38	0.79 (0.45–1.36)	0.39	0	0.74
All MI	9.2 (189/2049)	5.7 (66/1162)	1.53 (1.17–2.00)	0.002	1.51 (1.15–1.98)	0.003	0	0.63
TV-MI	7.8 (160/2049)	4.2 (49/1159)	1.72 (1.26–2.35)	0.0006	1.68 (1.23–2.29)	0.001	0	0.43
Periprocedural	3.2 (66/2042)	2.6 (30/1156)	1.17 (0.76–1.79)	0.47	1.15 (0.75–1.77)	0.52	0	0.71
Nonperiprocedural	6.2 (127/2046)	3.4 (39/1158)	1.74 (1.22–2.47)	0.002	1.71 (1.20–2.44)	0.003	0	0.83
Non–TV-MI	1.8 (37/2040)	1.8 (21/1155)	0.96 (0.56–1.64)	0.88	0.96 (0.56–1.64)	0.87	0	0.95
All revascularization	15.0 (319/2126)	12.2 (147/1202)	1.19 (0.99–1.43)	0.06	1.15 (0.89–1.48)	0.29	34.0	0.21
Ischemia-driven revascularization	13.7 (281/2048)	10.9 (126/1158)	1.21 (1.00–1.48)	0.05	1.17 (0.89–1.56)	0.26	29.0	0.24
ID-TLR	6.6 (135/2045)	4.4 (51/1155)	1.44 (1.05–1.98)	0.02	1.41 (1.03–1.93)	0.03	0	0.44
ID-TVR	10.0 (205/2048)	6.7 (77/1156)	1.45 (1.12–1.86)	0.004	1.44 (1.12–1.86)	0.005	0	0.71
Device thrombosis	2.4 (50/2049)	0.6 (7/1154)	3.71 (1.70–8.11)	0.001	2.83 (1.27–6.31)	0.01	0	0.91
Definite	2.2 (46/2049)	0.5 (6/1154)	3.95 (1.70–9.20)	0.001	3.12 (1.32–7.37)	0.01	0	0.93
Probable	0.2 (4/2049)	0.1 (1/1154)	2.26 (0.28–18.4)	0.44	1.67 (1.23–2.29)	0.001	0	1.0

BVS indicates bioresorbable vascular scaffold; CI, confidence interval; CoCr-EES, cobalt-chromium everolimus-eluting stent; ID-TLR, ischemia-driven target lesion revascularization; ID-TVR, ischemia-driven target vessel revascularization; MI, myocardial infarction; RR, relative risk; TLF, target lesion failure; and TV-MI, target-vessel myocardial infarction.

Significant interactions were present between device type and hypertension, reference vessel diameter, target vessel, and in-segment minimal lumen diameter for the 3-year TLF end point (Table VI in the online-only Data Supplement) and between device type and sex for the 3-year occurrence of device thrombosis (Table VII in the online-only Data Supplement).

Very Late Outcomes

As shown in Figures 3 and 4, and Table 3, between 1 and 3 years, the rate of TLF was higher with BVS than CoCr-EES (6.1% versus 3.9%; RR, 1.50; 95% CI, 1.07–2.08; *P*=0.02), driven by greater TV-MI (2.7% versus 1.0%; RR, 2.40; 95% CI, 1.29–4.44; *P*=0.006) and ID-TLR (4.5% versus 2.6%; RR, 1.65; 95% CI, 1.10–2.47; *P*=0.01) with BVS, without significant differences in cardiac death (0.7% versus 0.8%; RR, 0.88; 95% CI, 0.39–1.98; *P*=0.75). In this period, 22 definite device thromboses occurred in 2042 BVS-treated patients (11 [0.5%] between 1 and 2 years and 11 [0.5%] between 2 and 3 years) compared with no thrombosis events between 1 and 3 years in 1152 CoCr-EES–treated patients (1.1% versus 0.0%; *P*<0.0001). By multivariable analysis, among BVS-treated patients, the number of treated lesions, a larger baseline minimal lumen diameter, and sex were independent predictors of 1- to 3-year TLF, and diabetes mellitus was a predictor of 1- to 3-year device thrombosis (Table 2). Multivariable predictors of outcomes between 1 and 3 years in the entire study population are shown in Table V in the online-only Data Supplement.

Contribution of Device Thrombosis to TLF Events

Among the 338 randomized patients in whom TLF developed within 3 years, 48 (14.2%) also had device thrombosis (including 42 BVS- and 6 CoCr-EES–treated patients; Table 4). After the exclusion of these 48 patients, the 3-year rate of TV-MI remained higher in BVS-treated patients (5.7% versus 3.7%; *P*=0.04).

DISCUSSION

The major findings from the present individual-patient-data pooled meta-analysis of the 4 randomized ABSORB trials at the 3-year follow-up are as follows: First, compared with Xience CoCr-EES, Absorb BVS resulted in higher 3-year rates of TLF, patient-oriented composite end point, all MI, TV-MI, ID-TLR, ischemia-driven target vessel revascularization, and device thrombosis, with no significant differences between devices in the 3-year cumulative relative rates of all-cause, cardiac, or noncardiac death or all or ischemia-driven revascu-

Table 2. Independent Predictors of Ischemic Events by Logistic Regression Among Patients Randomized to BVS and CoCr-EES in the 4 ABSORB Trials

	RR (95% CI)	*P* Value
3-y Cumulative		
BVS group		
TLF		
No. of treated lesions (2 vs 1)	1.42 (1.06–1.90)	0.02
Current tobacco use	1.31 (1.01–1.70)	0.04
Previous coronary intervention	1.30 (1.03–1.65)	0.04
ABSORB China vs ABSORB III	0.43 (0.25–0.74)	0.02
Device thrombosis (definite or probable)		
Diabetes mellitus present	2.71 (1.57–4.68)	0.0004
CoCr-EES group		
TLF		
Diabetes mellitus present	1.94 (1.33–2.83)	0.0008
Previous coronary interventions	1.96 (1.32–2.89)	0.0005
Any ACC/AHA class (B2 or C lesion vs A or B1)	1.79 (1.09–2.93)	0.02
Preprocedure RVD (<2.25 vs ≥2.25 mm)*	1.83 (1.20–2.79)	0.006
Target vessel (LAD)	1.61 (1.09–2.39)	0.02
Between 1 and 3 y		
BVS group		
TLF		
No. of treated lesions (2 vs 1)	1.83 (1.23–2.74)	0.004
Preprocedure MLD (median, 0.93 mm)*	0.67 (0.47–0.94)	0.02
Female sex	0.60 (0.39–0.94)	0.02
Device thrombosis (definite or probable)		
Diabetes mellitus present	2.31 (1.01–5.30)	0.048
CoCr-EES group		
TLF		
Previous coronary intervention	2.73 (1.50–4.95)	0.0006
Preprocedure RVD (<2.25 vs ≥2.25 mm)*	2.30 (1.28–4.13)	0.004
Target vessel (LAD)	2.09 (1.15–3.79)	0.01
Diabetes mellitus present	2.05 (1.16–3.60)	0.009

ACC/AHA indicates American College of Cardiology/American Heart Association; BVS, bioresorbable vascular scaffold; CI, confidence interval; CoCr-EES, cobalt-chromium everolimus-eluting stent; MLD, minimal lumen diameter; LAD, left anterior descending artery; RR, relative risk; RVD, reference vessel diameter; and TLF, target lesion failure.

*Angiographic core laboratory determination. The following variables were entered into the models for TLF: ACC/AHA lesion class, age (median, 63 years), calcification (moderate/severe), previous coronary intervention, any diabetes mellitus, hypercholesterolemia requiring treatment, sex, hypertension requiring treatment, presentation (acute coronary syndrome versus stable ischemia), bifurcation, target vessel (LAD versus non-LAD), target lesion length (median, 12.16 mm), preprocedure MLD (median, 0.93 mm), number of treated lesions, $P2Y_{12}$ receptor antagonist (loading), preprocedure RVD (<2.25 versus ≥2.25 mm), and current tobacco use.

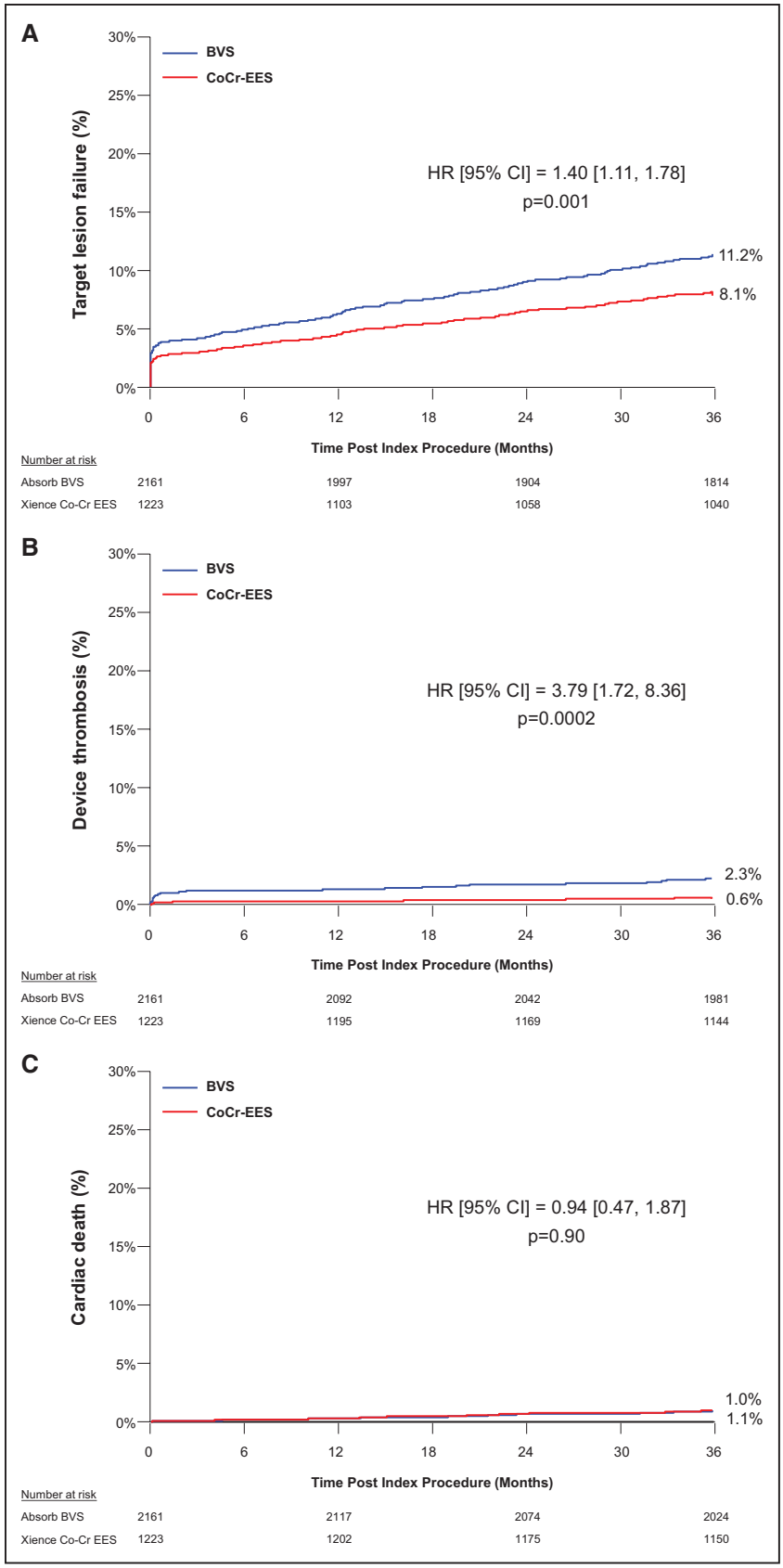
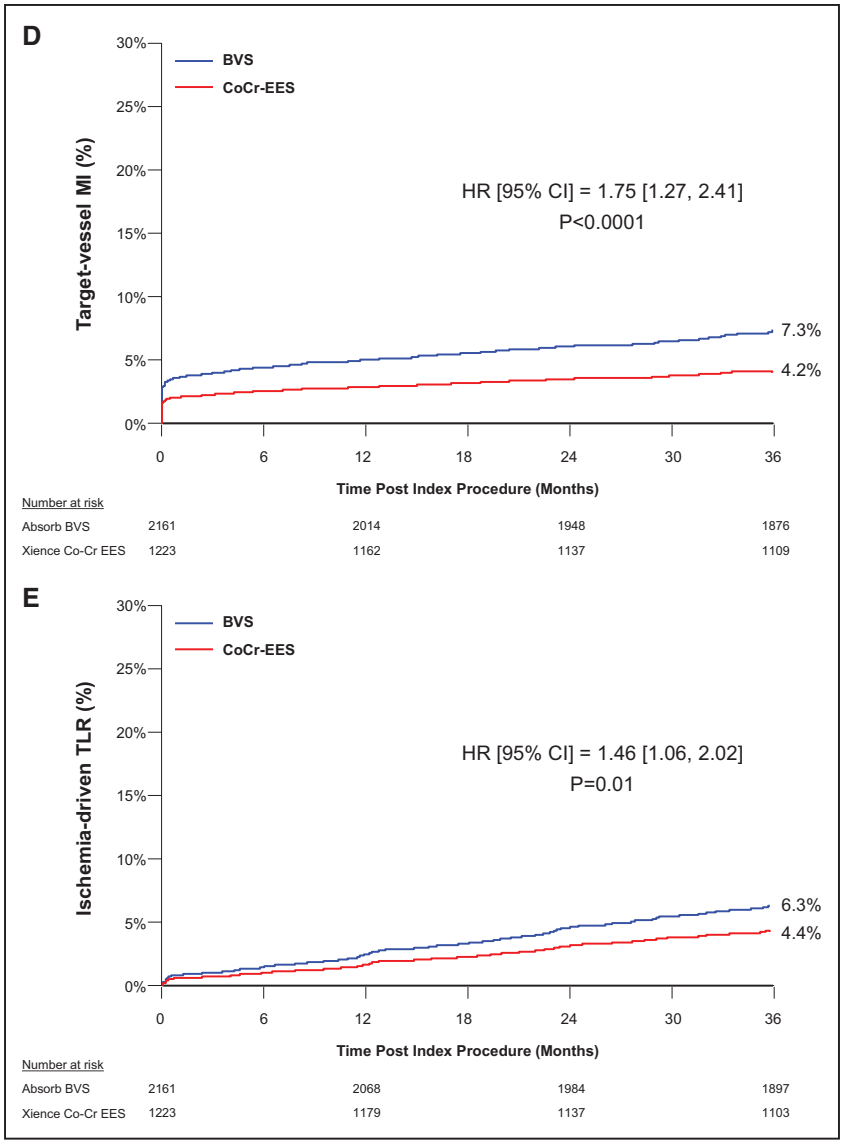


Figure 2. Three-year cumulative time to first event curves for patients randomized to the Absorb bioresorbable vascular scaffold (BVS) vs Xience cobalt-chromium everolimus-eluting stent (CoCr-EES) in the ABSORB randomized trials. **A**, Device-oriented composite end point of target lesion failure (cardiac death, target vessel myocardial infarction [MI], or ischemia-driven target lesion revascularization [TLR]). **B**, Device thrombosis (definite or probable). **C**, Cardiac mortality. **D**, Target vessel MI. **E**, Ischemia-driven TLR. Follow-up is censored at the time of first event, at last follow-up, or at exactly 36 months (whichever occurred first), and thus, these rates differ slightly from binary event rates. Analysis by 1-stage meta-analysis, adjusted by study level. CI indicates confidence interval; and HR, hazard ratio.



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larization. Second, between 1 and 3 years after device implantation, a greater number of TLF and device thrombosis events accrued in patients treated with BVS than patients treated with CoCr-EES. Finally, after the exclusion of patients with device thrombosis, the 3-year rates of TV-MI remained more frequent with BVS.

BVS were designed to overcome the limitations arising from the permanent presence of a metallic DES frame in the coronary circulation. Very late TLF events from device thrombosis or restenosis that may occur with metallic DES as a result of loss of vascular adaptive responses, compliance mismatch, inflammation, neoatherosclerosis, and strut fracture may be mitigated with complete BVS bioresorption. Early observational studies,[19] followed by randomized trials,[6,11,13–15] individually reported that that BVS had noninferior 1-year rates of safety and effectiveness measures compared with CoCr-EES, leading to regulatory approval and clinical adoption of the device. However, initial enthusiasm was tempered by the findings of 2-year meta-analysis demonstrating an increased risk of MI and device thrombosis with BVS.[7] For the late benefits of BVS after its complete bioresorption to be realized, its full safety and effectiveness profile (including characterizing its absolute risk and RR) before this time point (≈3 years) must be placed into perspective. We therefore performed the present individual-patient-data pooled analysis from the 4 randomized ABSORB trials now with complete follow-up data through 3 years.

The BVS bulk erosion process results in reduction of the molecular weight of the poly-L-lactic acid scaffold during the first year, with loss of radial strength beginning at 6 months, followed by accelerated mass loss, with complete bioresorption at ≈3 years.[20] Landmark analysis of clinical outcomes at these different time points (a major advantage of individual patient-

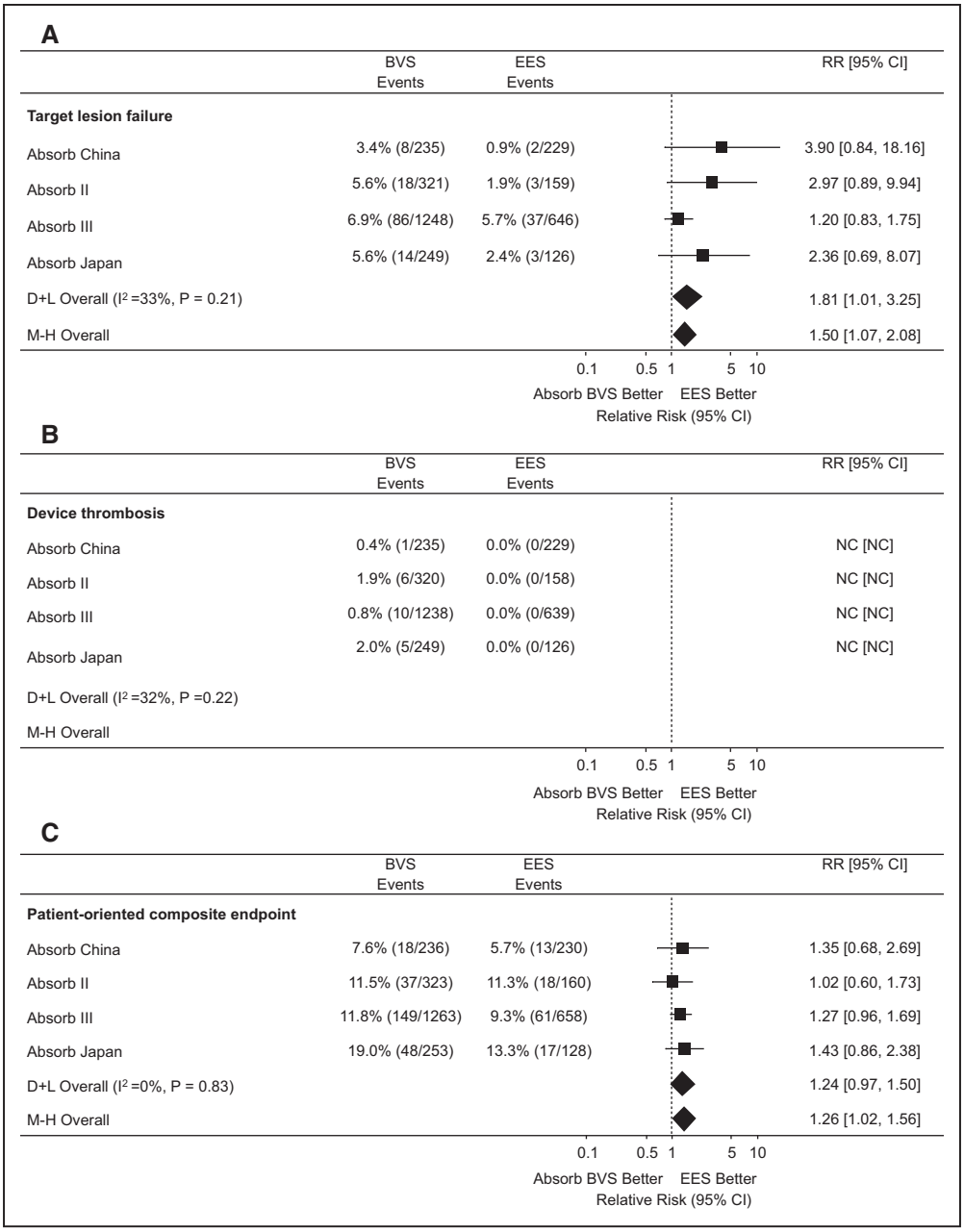

Figure 3. One- to 3-year selected clinical outcomes for patients randomized to the Absorb bioresorbable vascular scaffold (BVS) vs Xience cobalt-chromium everolimus-eluting stent (CoCr-EES) in the ABSORB randomized trials.

A, Device-oriented composite end point of target lesion failure (cardiac death, target vessel myocardial infarction [MI], or ischemia-driven target lesion revascularization [TLR]). **B**, Device thrombosis (definite or probable). **C**, Patient-oriented composite end point of death, MI, or any revascularization. **D**, Cardiac mortality. **E**, Target vessel MI. **F**, Ischemia-driven TLR. CI indicates confidence interval; D+L, DerSimonian and Laird random-effects model; M-H, Mantel-Haenszel fixed-effect model; NC, not calculated; and RR, relative risk.

data-pooled analyses) is thus particularly relevant. The rates of TLF and the patient-oriented composite end point were not significantly different between BVS and CoCr-EES in the first year after treatment,[6] although TV-MI was increased with BVS and a trend toward greater scaffold thrombosis was present. In this early period, the more aggressive vessel preparation required for BVS implantation, particularly in complex lesions,[21] and the larger footprint of BVS, leading to occlusion of small side branches, may increase the risk for periprocedural MI.[22,23] The thicker, wider scaffold struts may also result in nonlaminar flow and altered shear stress before the scaffold is covered by neointima,[24] activating platelets and increasing the risk for

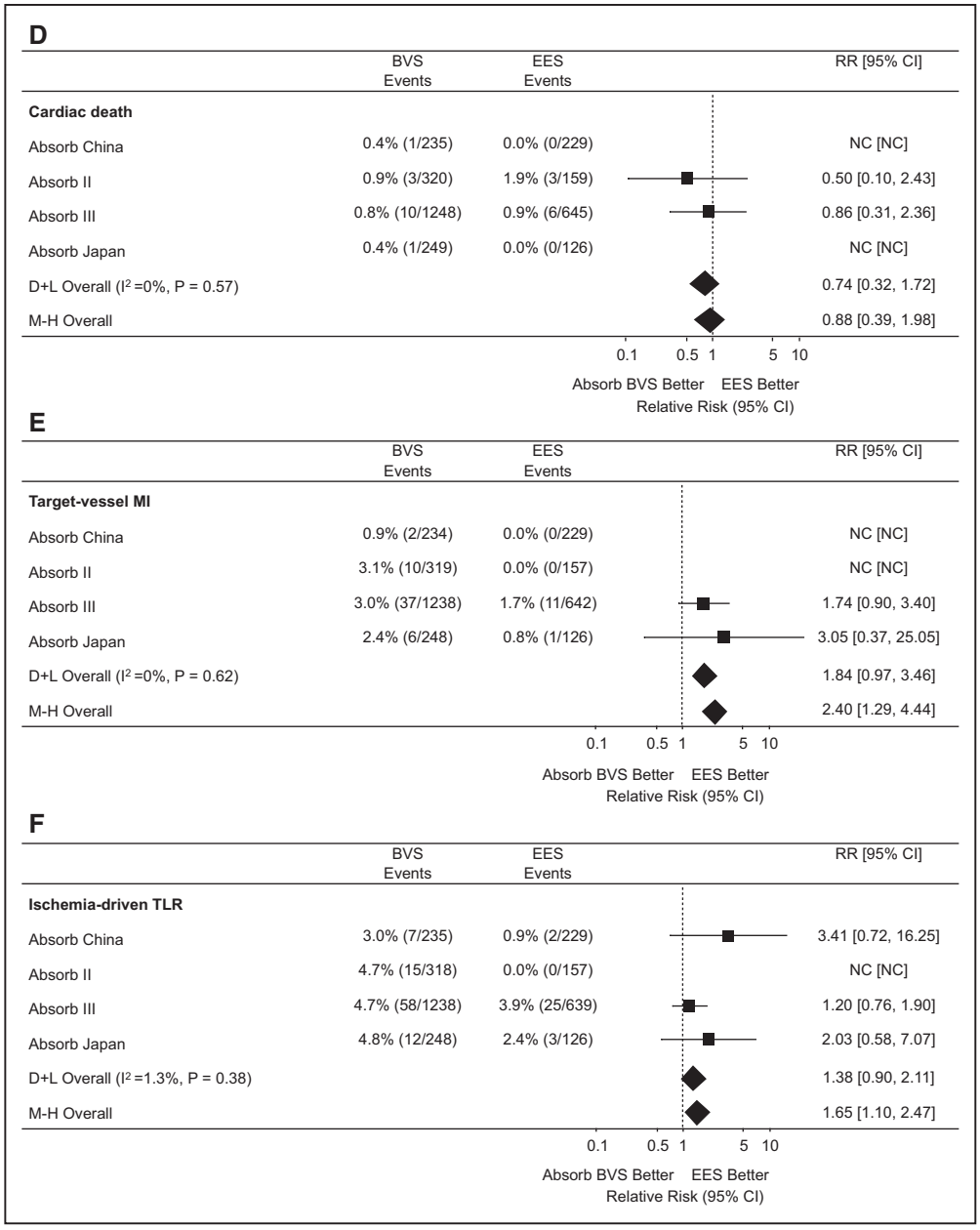

Figure 3 Continued.

TV-MI and device thrombosis, especially with BVS implantation in very small vessels.[23,25]

A previous meta-analysis demonstrated increased rates of TLF and device thrombosis between years 1 and 2 with BVS compared with CoCr-EES.[7] During the accelerated mass loss phase between years 1 and 3, programmed disintegration of the polymeric scaffold struts occurs, which, if not adequately restrained by neointima, may result in scaffold discontinuities with endoluminal dislocation (intraluminal scaffold dismantling),[20,26] with subsequent device thrombosis and TV-MI.[27,28] Although the biological consequences of polymeric crystal conversion to proteoglycan matrix within neointima appear minimal,[20] the intraluminal presence of the provisional matrix as a result of malapposition or translocation may serve as a nidus for thrombus formation[27,28] and is responsible for a substantial proportion of very late scaffold thromboses.[29]

The increased 3-year event rates with BVS compared with CoCr-EES were attributable to excess adverse events resulting from device thrombosis and non–thrombosis-related TV-MI. Future prospective studies are warranted to determine whether the differences between BVS and CoCr-EES may be lessened by interventions to reduce scaffold thrombosis (as suggested in previous retrospective studies), including improved scaffold implantation technique[23,30] to ensure maximal scaffold expansion with strut embedding,[31,32] avoidance of acute malap-

Table 3. Meta-Analysis Summary for Ischemic End Points Occurring From Randomization to Between 1 and 3 Years in the ABSORB Trials

	BVS, % (n/N)	CoCr-EES, % (n/N)	Fixed-Effect RR (95% CI)	*P* Value, Fixed Effect	Random-Effect RR (95% CI)	*P* Value, Random Effect	I^2, %	*P* Value, Heterogeneity
TLF	6.1 (126/2053)	3.9 (45/1160)	1.50 (1.07–2.08)	0.02	1.81 (1.01–3.25)	0.04	33.0	0.21
Patient-oriented composite end point	12.1 (252/2075)	9.3 (109/1176)	1.26 (1.02–1.56)	0.03	1.26 (1.02–1.56)	0.03	0	0.83
All-cause mortality	1.8 (38/2073)	2.2 (26/1176)	0.78 (0.48–1.27)	0.32	0.77 (0.47–1.26)	0.30	0.0	0.78
Cardiac	0.7 (15/2052)	0.8 (9/1159)	0.88 (0.39–1.98)	0.75	0.74 (0.31–1.72)	0.48	0.0	0.57
Noncardiac	1.1 (23/2059)	1.5 (17/1168)	0.72 (0.39–1.34)	0.30	0.71 (0.38–1.34)	0.29	0.0	0.84
All MI	3.8 (78/2040)	2.0 (23/1156)	1.79 (1.13–2.83)	0.01	1.75 (1.10–2.77)	0.02	0.0	0.73
TV-MI	2.7 (55/2039)	1.0 (12/1154)	2.40 (1.29–4.44)	0.006	1.84 (0.97–3.46)	0.06	0.0	0.82
Non–TV-MI	1.2 (24/2039)	1.0 (11/1153)	1.16 (0.57–2.37)	0.68	1.06 (0.51–2.19)	0.88	0.0	0.76
All revascularization	9.5 (202/2122)	6.9 (83/1202)	1.34 (1.05–1.72)	0.02	1.34 (1.05–1.72)	0.02	0.0	0.87
Ischemia-driven revascularization	8.4 (171/2040)	6.0 (69/1154)	1.35 (1.03–1.76)	0.03	1.34 (1.02–1.75)	0.03	0.0	0.70
ID-TLR	4.5 (92/2039)	2.6 (30/1151)	1.65 (1.10–2.47)	0.01	1.38 (0.90–2.11)	0.14	1.3	0.36
ID-TVR	6.7 (136/2039)	4.2 (48/1153)	1.52 (1.11–2.10)	0.01	1.52 (1.10–2.09)	0.01	0.0	0.88
Device thrombosis (definite or probable)	1.1 (22/2042)	0.0 (0/1152)	…	<0.0001	0.51 (0.14–1.79)	0.29	0	1.0
Definite	1.1 (22/2042)	0.0 (0/1152)	…	<0.0001	1.67 (1.23–2.29)	0.001	0	1.0
Probable	0.0 (0/2042)	0.0 (0/1152)	…	…	…	…	0	1.0

BVS indicates bioresorbable vascular scaffold; CI, confidence interval; CoCr-EES, cobalt-chromium everolimus-eluting stent; ID-TLR, ischemia-driven target lesion revascularization; ID-TVR, ischemia-driven target vessel revascularization; MI, myocardial infarction; RR, relative risk; TLF, target lesion failure; and TV-MI, target-vessel myocardial infarction.

position, which may impair neointimal tissue coverage of the scaffold during healing,[29] and the development of next-generation devices with thinner struts and improved expansion characteristics.[33] Further studies are required to determine whether improved outcomes may also be achieved with intravascular imaging guidance to ensure optimal scaffold implantation[34] and perhaps by prolonged dual antiplatelet therapy through the 3-year process of BVS bioresorption.[35] Notably, the observed difference in very late device thrombosis between BVS and CoCr-EES was accentuated by the absence of any thrombosis events with CoCr-EES after 1 year, attributable in part to the thromboresistant properties of the fluorinated polymer (which is absent in BVS).[1,36–38] Nevertheless, even after the exclusion of patients with device thrombosis, TV-MI rates were still increased with BVS compared with CoCr-EES, especially after the first year, possibly because of factors that may also be addressable with future scaffold design advancements.

Our study has a number of limitations. First, we were unable to include 3 randomized BVS trials[39–42] because of a lack of reported 3-year follow-up. Their addition would have increased the overall power to detect small differences between devices, but because they are based on reported 2-year data, they likely would not have changed our study conclusions. Second, BVS was used for the first time by most of the investigators in these studies, and consistent with other new technologies, outcomes are expected to improve as experience accrues. Moreover, the extent to which specific implantation techniques may improve BVS clinical outcomes became appreciated only after enrollment in these studies.[23,30,31] Similarly, intravascular imaging guidance was used in the minority of patients in these trials, and the manner in which it was applied to guide device implantation was not collected. Third, the 4 ABSORB studies excluded high-risk patients and complex lesions, including chronic total occlusions, long lesions, bifurcations with large side branches, and ST-segment–elevation MI. Dedicated studies have been performed or are underway to determine the performance of BVS in these scenarios. Fourth, the present study results apply strictly to the first-generation Absorb BVS (which is no longer being manufactured), not to other currently available or future bioabsorbable scaffolds. Fifth, procedural and technique-related factors that may affect the outcomes of BVS implantation were not considered in the present analysis. Sixth, a borderline interaction was present between sex and device type for the 3-year rate of device thrombosis, although this effect was not adjusted for

Table 4. TLF Rates With and Without Inclusion of Device Thrombosis in the ABSORB Trials

	All Patients				Excluding Patients With Device Thrombosis*			
	BVS, % (n/N)	CoCr-EES, % (n/N)	RR (95% CI)	*P* Value	BVS, % (n/N)	CoCr-EES, % (n/N)	RR (95% CI)	*P* Value
0–3 y								
TLF	11.7 (243/2069)	8.1 (95/1167)	1.38 (1.10–1.73)	0.006	9.7 (201/2063)	7.6 (89/1167)	1.22 (0.96–1.56)	0.10
Cardiac mortality	1.1 (22/2059)	1.1 (13/1163)	0.93 (0.47–1.88)	0.85	1.0 (20/2057)	1.1 (13/1163)	0.85 (0.42–1.73)	0.66
TV-MI	7.8 (160/2049)	4.2 (49/1159)	1.72 (1.26–2.35)	0.0006	5.7 (116/2045)	3.7 (43/1158)	1.43 (1.01–2.01)	0.04
ID-TLR	6.6 (135/2045)	4.4 (51/1155)	1.44 (1.05–1.98)	0.02	4.6 (93/2040)	3.9 (45/1154)	1.15 (0.81–1.62)	0.44
0–1 y								
TLF	6.2 (132/2134)	4.9 (59/1207)	1.22 (0.90–1.65)	0.20	4.9 (105/2131)	4.3 (52/1207)	1.11 (0.80–1.54)	0.54
Cardiac mortality	0.3 (7/2129)	0.3 (4/1206)	1.10 (0.28–4.36)	0.89	0.2 (5/2127)	0.3 (4/1206)	0.79 (0.18–3.45)	0.75
TV-MI	5.1 (108/2127)	3.4 (41/1203)	1.40 (0.98–1.98)	0.06	4.0 (85/2126)	2.9 (35/1203)	1.29 (0.88–1.90)	0.20
ID-TLR	2.4 (51/2124)	1.9 (23/1202)	1.24 (0.76–2.02)	0.40	1.3 (27/2123)	1.4 (17/1202)	0.93 (0.51–1.70)	0.81
1–3 y								
TLF	6.1 (126/2053)	3.9 (45/1160)	1.50 (1.07–2.08)	0.02	5.2 (107/2053)	3.9 (45/1160)	1.27 (0.91–1.78)	0.16
Cardiac mortality	0.7 (15/2052)	0.8 (9/1159)	0.88 (0.39–1.98)	0.75	0.7 (15/2052)	0.8 (9/1159)	0.88 (0.39–1.98)	0.75
TV-MI	2.7 (55/2039)	1.0 (12/1154)	2.40 (1.29–4.44)	0.006	1.6 (33/2039)	1.0 (12/1154)	1.44 (0.75–2.76)	0.28
ID-TLR	4.5 (92/2039)	2.6 (30/1151)	1.65 (1.10–2.47)	0.01	3.5 (72/2039)	2.6 (30/1151)	1.30 (0.86–1.97)	0.22

BVS indicates bioresorbable vascular scaffold; CI, confidence interval; CoCr-EES, cobalt-chromium everolimus-eluting stent; ID-TLR, ischemia-driven target lesion revascularization; RR, relative risk; TLF, target lesion failure; and TV-MI, target-vessel myocardial infarction.

*For the 0- to 3-year and 1- to 3-year analyses, patients with device thrombosis within 3 years were excluded. For the 0- to 1-year analysis, patients with device thrombosis within 1 year were excluded.

multiple comparisons. Further studies are warranted to determine whether sex has any novel influence on BVS outcomes. Finally, longer-term follow-up from these studies (perhaps through 10 years, as currently planned in ABSORB III and IV) is necessary to place into perspective the lifelong risk-to-benefit ratio of this novel technology after its complete bioresorption.

CONCLUSIONS

In this individual-patient-data pooled meta-analysis of the ABSORB trials, BVS was associated with higher 3-year rates of TLF compared with CoCr-EES, a difference attributable to an increased rate of device thrombosis and non–thrombosis-related TV-MI.

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DISCLOSURES

Dr Ali reports grants from St. Jude Medical and personal fees from St. Jude Medical (now Abbott Vascular), and his employer, Columbia University, receives royalties from the sale of the MitraClip. Dr Gao has a research grant from Abbott Vascular. Dr Kimura is an advisory board member for Abbott Vascular. Drs Onuma, Kereiakes, Ellis, Chevalier, and Serruys report serving as consultants to Abbott Vascular. Drs Vu, Zhang, and Simonton are full-time employees of Abbott Vascular. Dr Stone is a consultant to Reva Medical, and his employer, Columbia University, receives royalties from the sale of the MitraClip.

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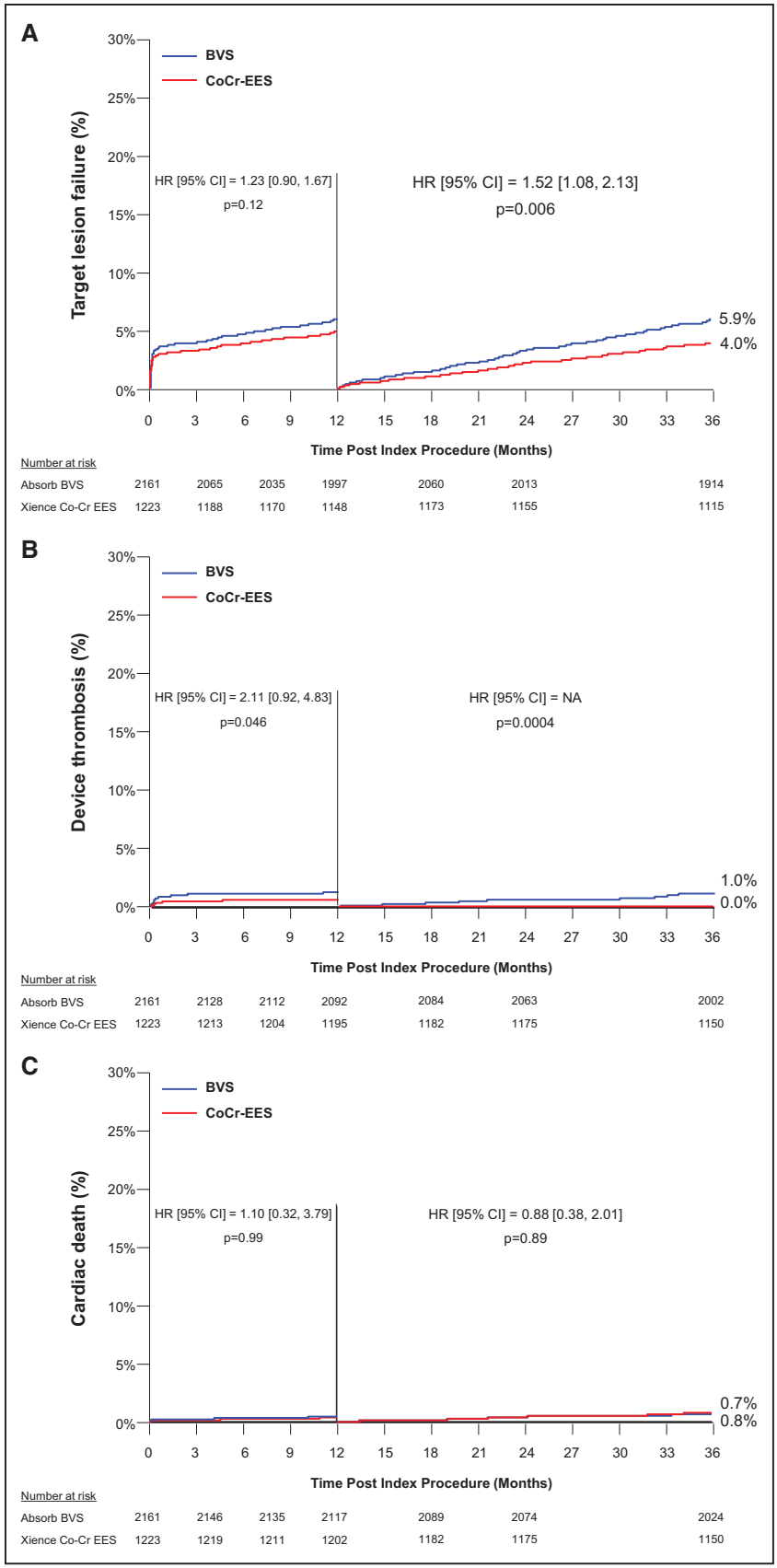

Figure 4. One- to 3-year cumulative time to first event curves for patients randomized to the Absorb bioresorbable vascular scaffold (BVS) vs Xience cobalt-chromium everolimus-eluting stent (CoCr-EES) in the ABSORB randomized trials. **A**, Device-oriented composite end point of target lesion failure (cardiac death, target vessel myocardial infarction [MI], or ischemia-driven target lesion revascularization [TLR]). **B**, Device thrombosis (definite or probable). **C**, Cardiac mortality. **D**, Target vessel MI. **E**, Ischemia-driven TLR. Follow-up is censored at the time of first event, at last follow-up, or at exactly 36 months (whichever occurred first), and thus, these rates differ slightly from binary event rates. Analysis by 1-stage meta-analysis, adjusted by study level. CI indicates confidence interval; and HR, hazard ratio.

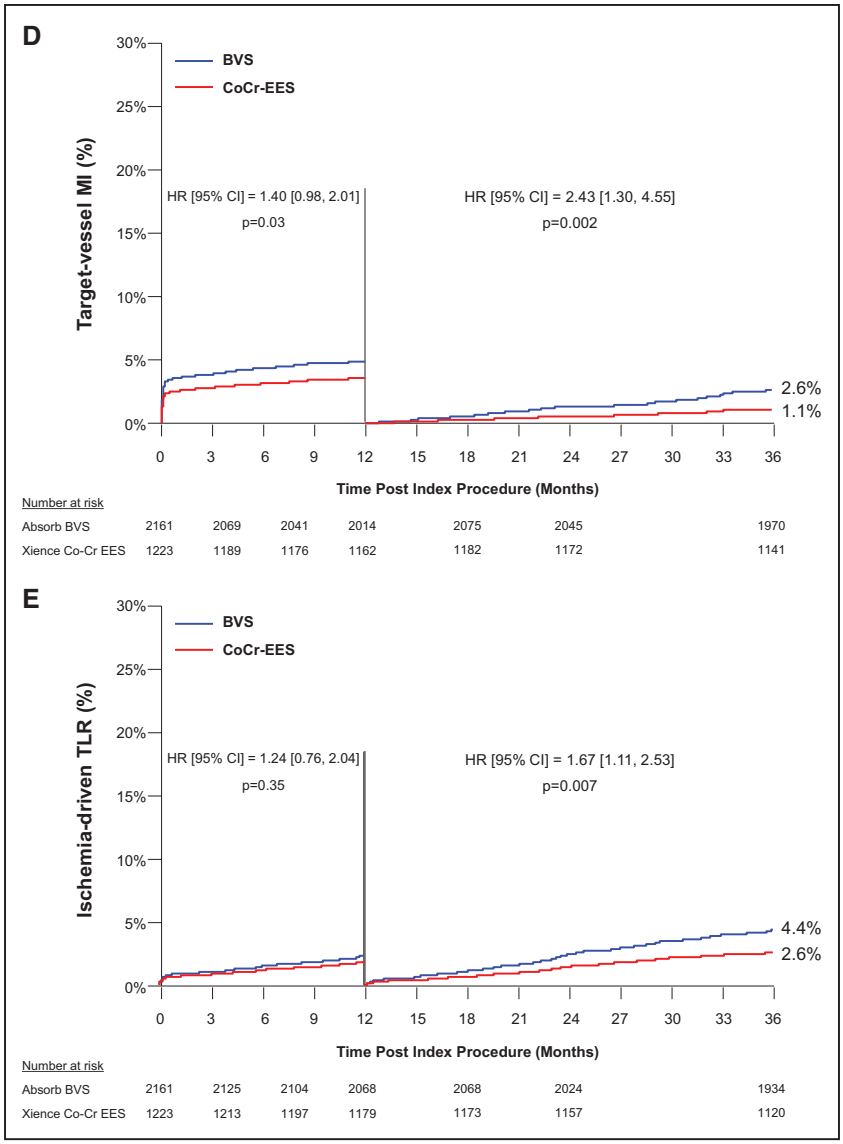

Figure 4 Continued.

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FOOTNOTES

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