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REVIEW

Mid- and Long-Term Outcome Comparisons of Everolimus-Eluting Bioresorbable Scaffolds Versus Everolimus-Eluting Metallic Stents

A Systematic Review and Meta-Analysis

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Background: Percutaneous coronary interventions to implant bioresorbable vascular scaffolds (BVSs) were designed to reduce the late thrombotic events that occur with metallic stents.

Purpose: To estimate the incidence of scaffold thrombosis after BVS implantation and compare everolimus-eluting BVSs with everolimus-eluting metallic stents (EESs) in terms of safety and efficacy at mid- and long-term follow-up in adults who had a percutaneous coronary intervention.

Data Sources: PubMed, EMBASE, the Cochrane Library, conference proceedings, and relevant Web sites from inception until 20 May 2017, without language restriction.

Study Selection: 7 randomized trials and 38 observational studies (each with a minimum of 6 months and 100 patient-years of follow-up) in adults with coronary artery disease who had a BVS or an EES and reported scaffold or stent thrombosis (main outcome) or other secondary outcomes (such as death, myocardial infarction, or revascularization).

Data Extraction: 2 reviewers independently extracted study data, rated study quality, and assessed strength of evidence.

Data Synthesis: The pooled incidence of definite or probable scaffold thrombosis after BVS implantation was 1.8% (95% CI, 1.5% to 2.2%) at a median follow-up of 1 year (41 studies, 21 884 patients) and 0.8% (CI, 0.5% to 1.3%) beyond 1 year (14 studies, 4688 patients). Seven trials involving 5578 patients that directly compared BVSs with EESs showed an increased risk for definite or probable scaffold thrombosis (odds ratio [OR], 3.40 [CI, 2.01 to 5.76]) with BVSs at a median follow-up of 25 months. Increased risks were present at early (prominently subacute), late, and very late stages, and odds beyond 1 year were almost double those seen within 1 year. Bioresorbably vascular scaffolds increased risks for myocardial infarction (OR, 1.63 [CI, 1.26 to 2.10]), target lesion revascularization (OR, 1.31 [CI, 1.03 to 1.67]), and target lesion failure (OR, 1.37 [CI, 1.12 to 1.66]); the odds for these 3 end points also increased over time. The incidences of all-cause, cardiac, and noncardiac death and of target vessel and any revascularization did not differ.

Limitation: Quality of observational studies was unclear, and some data were unpublished.

Conclusion: Compared with EESs, BVSs increased the risks for scaffold thrombosis and other thrombotic events at mid- and long-term follow-up, and risks increased over time.

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Drug-eluting stents reduce the rate of in-stent restenosis, myocardial infarction, and target lesion revascularization (TLR) compared with bare-metal stents for adults undergoing percutaneous coronary interventions, but concerns remain about the risk for late and very late stent thrombosis with drug-eluting stents (1, 2). Bioresorbable vascular scaffolds (BVSs) were designed to reduce the late thrombotic events associated with metallic stents. Early, modest-sized studies showed similar midterm cardiovascular safety with everolimus-eluting metallic stents (EESs) and BVSs (3–7), but meta-analyses published in 2016 suggested a possible increased midterm risk for scaffold or stent thrombosis and myocardial infarction with BVSs (8, 9).

Long-term follow-up data from comparative trials (10–18) and several large registries (19–25) were recently published or presented in conference proceedings. Results from some of the trials suggest that BVSs might increase the incidence of late cardiovascular events, as compared with EESs (10–12), but most trials were underpowered to detect rare outcomes, such as scaffold or stent thrombosis. Moreover, neither the long-term safety and efficacy nor the time courses of improvement or deterioration after BVS implantation are clearly established. We performed a meta-analysis of randomized controlled trials and observational studies to estimate the incidence of scaffold thrombosis after BVS implantation and to compare BVSs and EESs in terms of safety and efficacy at mid- and long-term follow-up. We also aimed to investigate the performance differences of BVSs at different time courses.

METHODS

This meta-analysis updates our previous review (9) and follows standard reporting guidelines (26).

Data Sources and Searches

We searched PubMed, EMBASE, the Cochrane Library, conference proceedings, and relevant Web sites (namely www.escardio.org, www.tctmd.com, www.

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Table 1. Pooled Rates of Clinical End Points, by Time of Occurrence and Study Design

Variable	Definite or Probable Scaffold Thrombosis			All-Cause Death			Cardiac Death		
	Incidence (95% CI), %	Clinical Events, *n*	Total Patients, *n*	Incidence (95% CI), %	Clinical Events, *n*	Total Patients, *n*	Incidence (95% CI), %	Clinical Events, *n*	Total Patients, *n*
Longest follow-up									
Overall	1.8 (1.5–2.2)	389	21 884	1.7 (1.3–2.3)	274	18 000	1.1 (0.8–1.4)	193	20 750
RCT	2.5 (1.7–3.4)	78	3237	2.0 (1.2–3.0)	64	3233	1.2 (0.7–1.8)	39	3242
Observational study	1.7 (1.4–2.1)	311	18 647	1.7 (1.2–2.4)	210	14 767	1.1 (0.8–1.5)	154	17 508
Within 1 y									
Overall	1.6 (1.3–1.9)	336	20 838	1.2 (0.9–1.5)	212	17 531	0.7 (0.6–0.9)	146	20 272
RCT	1.6 (0.9–2.2)	49	3063	0.8 (0.1–1.8)	36	3075	0.4 (0–1.0)	20	3075
Observational study	1.6 (1.3–2.0)	287	17 775	1.2 (1.0–1.5)	176	14 456	0.8 (0.6–0.9)	126	17 197
>1 y									
Overall	0.8 (0.5–1.3)	36	4688	1.5 (0.8–2.2)	44	2764	0.9 (0.6–1.4)	33	4269
RCT	1.1 (0.6–1.9)	28	3249	1.5 (1.0–2.1)	27	1927	0.6 (0.4–1.0)	18	3249
Observational study	0.5 (0.1–1.1)	8	1439	1.4 (0.3–3.2)	17	837	1.4 (0.4–2.7)	15	1020

RCT = randomized controlled trial; TLF = target lesion failure; TLR = target lesion revascularization; TVR = target vessel revascularization.

europcr.com, and www.acc.org). The search was an update to 20 May 2017 of our previous search (9), which was done from the inception of the databases to 20 January 2016. The following keywords were used: *bioresorbable*, *bioabsorbable*, *biodegradable*, *naturally dissolving*, *everolimus*, *stent*, and *scaffold*. One reviewer (X.L.Z.) hand-searched the reference lists of the retrieved trials and relevant reviews to identify additional studies. Searches were unrestricted regarding language and publication status.

Study Selection

Two reviewers (X.L.Z. and Q.Q.Z.) independently evaluated the eligibility of studies. Any disagreements were resolved by a third author (L.N.K.). Randomized controlled trials or observational studies, published in any language, involving adults with coronary artery disease who had a BVS implanted were included. Studies must have reported at least 1 outcome of interest and have a minimum of 6 months and 100 patient-years of follow-up.

Outcome Measures

The main outcome of interest was definite or probable scaffold or stent thrombosis; secondary outcomes of interest included myocardial infarction, all-cause death, cardiac death, noncardiac death, TLR, target vessel revascularization (TVR), all revascularization, and target lesion failure (TLF). Target lesion failure was defined as a composite of cardiac death, target vessel myocardial infarction, or ischemia-driven TLR. Myocardial infarction was classified as Q-wave or non–Q-wave myocardial infarction. Scaffold or stent thrombosis was classified as definite or probable, definite, and acute (within 24 hours after percutaneous coronary intervention); subacute (1 day to 30 days); early (within 30 days); late (1 month to 1 year); or very late (beyond 1 year) according to the time of occurrence.

Data Extraction and Assessment of Study Quality and Strength of Evidence

Two investigators (X.L.Z. and Q.Q.Z.) independently extracted details about study characteristics, outcomes, and funding sources. Two reviewers (X.L.Z. and L.N.K.) independently appraised the potential risk of bias for each trial by using the Cochrane Collaboration tool (27) and used the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach to rate the quality of evidence for each outcome as high, moderate, low, or very low (28). The quality of observational studies was evaluated with a modified version of the Newcastle–Ottawa Scale (29).

Data Synthesis and Statistical Analysis

Data within 1 year, beyond 1 year, and with the longest follow-up were analyzed separately. A profile likelihood random-effects model was used to pool incidence data for each outcome after Freeman–Tukey double arcsine transformation (30, 31). The profile likelihood method was chosen because it captures the uncertainty associated with statistical heterogeneity better than the conventional DerSimonian–Laird method (30). Incidence analyses were stratified by study design and summarized by using an updated version of the *metaan* command in Stata (StataCorp) (**Supplement 1**, available at Annals.org). Odds ratios (ORs) and 95% CIs were used to compare and summarize safety and efficacy between BVSs and EESs. Because little statistical heterogeneity existed among the study-level effects, a fixed-effect model (Mantel–Haenszel method) was used to summarize the effectiveness of BVSs compared with that of EESs (32). When the number of events was zero in only 1 treatment group, the treatment group continuity correction was used for estimation, because it outperforms the conventional constant 0.5 correction (33). The *metan* command was used in comparative analysis. Statistical heterogeneity was assessed by the Cochran Q test and the I^2 statistic (34). Substantial het-

Table 1–Continued

Myocardial Infarction			TLR			TVR			TLF		
Incidence (95% CI), %	Clinical Events, *n*	Total Patients, *n*	Incidence (95% CI), %	Clinical Events, *n*	Total Patients, *n*	Incidence (95% CI), %	Clinical Events, *n*	Total Patients, *n*	Incidence (95% CI), %	Clinical Events, *n*	Total Patients, *n*
3.5 (2.8–4.2)	724	20 951	4.6 (3.6–5.6)	765	20 517	6.2 (4.8–7.9)	581	10 577	7.3 (5.9–8.8)	1210	19 998
6.6 (4.9–7.5)	213	3242	6.5 (4.6–9.4)	200	3242	8.0 (4.3–12.9)	232	3234	9.4 (6.5–12.9)	323	3242
3.0 (2.4–3.6)	511	17 709	4.1 (3.1–5.2)	565	17 275	5.5 (4.1–7.2)	349	7343	6.8 (5.4–8.5)	887	16 756
2.9 (2.4–3.5)	631	20 372	3.4 (2.7–4.2)	595	19 938	4.5 (3.6–5.6)	439	9779	5.7 (4.7–6.8)	974	19 419
4.5 (2.9–6.2)	159	3075	3.0 (1.9–4.1)	96	3075	4.8 (3.4–5.7)	147	3075	5.8 (3.9–7.4)	197	3075
2.7 (2.2–3.2)	472	17 297	3.5 (2.7–4.4)	500	16 863	4.6 (3.2–6.2)	292	6704	5.8 (4.7–7.1)	777	16 344
2.2 (1.5–2.9)	95	4688	3.5 (2.6–4.6)	146	4479	4.3 (2.5–6.6)	106	2469	4.2 (3.0–5.7)	199	4688
2.2 (1.5–3.2)	64	3249	3.6 (2.3–5.7)	98	3154	5.6 (3.2–9.4)	74	1594	3.8 (3.1–4.9)	122	3249
2.1 (0.9–3.6)	31	1439	3.4 (2.0–4.9)	48	1325	3.2 (1.0–6.3)	32	875	4.2 (1.9–7.2)	77	1439

erogeneity was considered present when the *P* value was less than 0.10 or the I^2 statistic was greater than 50%. We performed several tests for publication bias that found no positive results; however, these tests had limited ability to adequately assess small-study effects, because all involved a small number of trials. We performed metaregression analyses to determine the potential for effect modification of several important variables, including diabetes, complex (type B2/C) lesion, and postdilatation. All *P* values were 2-tailed, and those less than 0.050 were regarded as statistically significant. Analyses were performed with Stata, version 12.0.

Role of the Funding Source

The National Natural Science Foundation of China had no role in the study design, data collection and analysis, writing of the report, or decision to submit the manuscript for publication.

RESULTS

Study Selection and Characteristics

Of 3411 records, 45 studies presented in 88 citations met selection criteria (**Figure 1** and **Tables 1** to **4** of **Supplement 2**, available at Annals.org). Seven were randomized trials (3–7, 10, 35), and 38 were observational studies (19–25, 36–66). All studies, encompassing 22 850 patients who received a BVS, contributed to the incidence analysis. The median follow-up for the studies was 12 months (range, 6 to 36 months). Seven trials reported in 16 citations were included in the comparative analysis of BVSs versus EESs (3–7, 10–18, 35, 67). Trials involved 5578 patients (3258 with a BVS and 2320 with an EES). All trials reported outcomes occurring within 1 year, as well as those occurring within 2 to 3 years, of the procedures.

Studies included all-comer participants with coronary artery disease ($n = 29$), patients with ST-segment elevation myocardial infarction ($n = 4$), patients with stable or unstable angina pectoris ($n = 6$), and other populations ($n = 6$). Mean ages of study participants ranged from 57 to 67 years; 74% of participants were men. The prevalence of diabetes mellitus and past myocardial infarction was 25% and 20%, respectively. Roughly 62% of lesions were type B2/C according to the American College of Cardiology and American Heart Association criteria; 68% of patients received postdilatation in the percutaneous coronary intervention procedure with BVSs. All trials were deemed as having low risk of bias for all outcomes (**Table 5** of **Supplement 2**, available at Annals.org). Most observational studies were rated as good quality; however, some studies presented as abstracts were considered to be of unclear quality (**Table 6** of **Supplement 2**, available at Annals.org).

Incidence Estimates After BVS Implantation

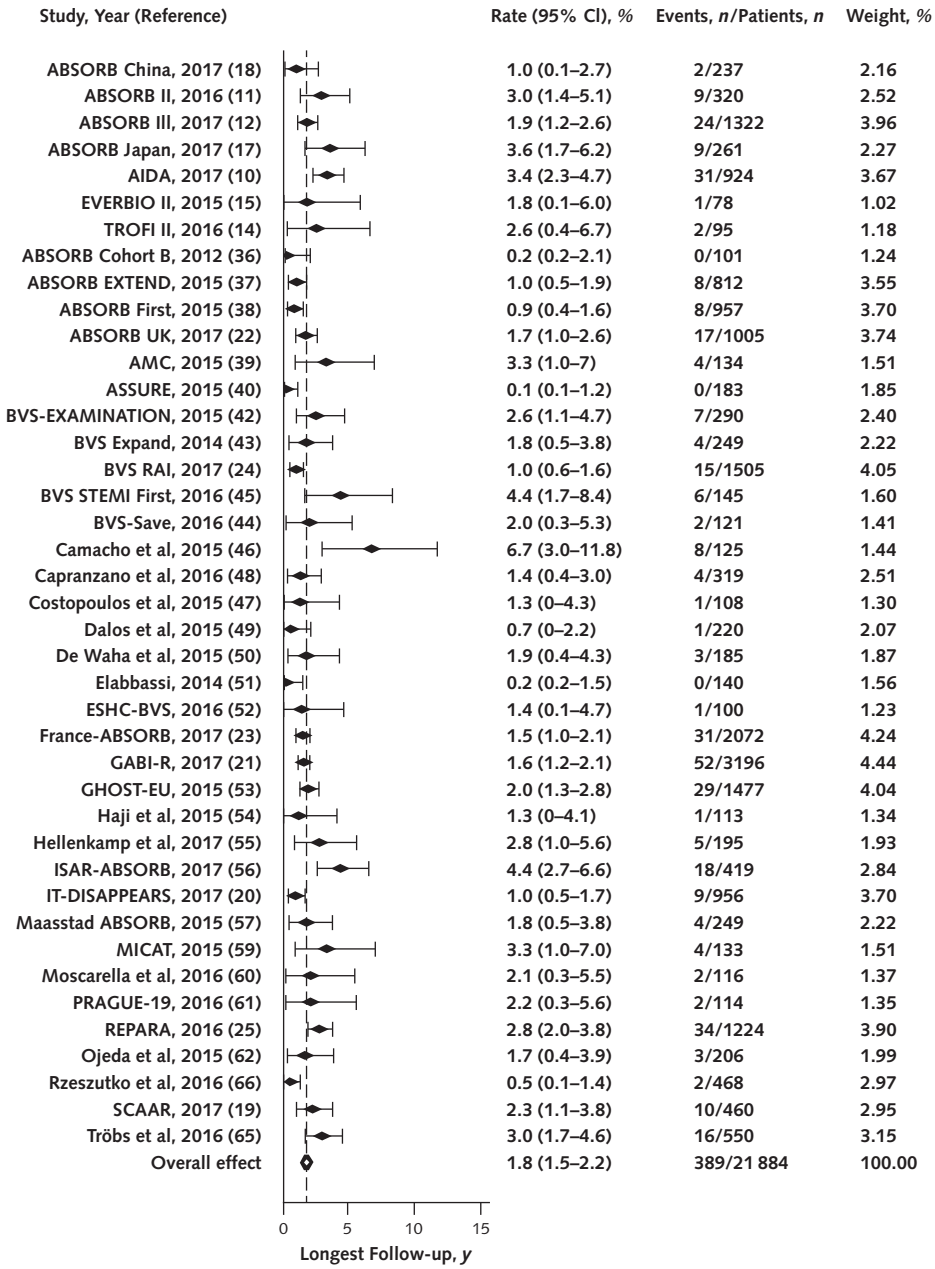
The incidence of definite or probable scaffold thrombosis was 1.8% (95% CI, 1.5% to 2.2%) at the longest follow-up (**Table 1** and **Figure 1**), 1.6% (CI, 1.3% to 1.9%) within 1 year (**Figure 2** of **Supplement 2**, available at Annals.org), and 0.8% (CI, 0.5% to 1.3%) beyond 1 year (**Figure 3** of **Supplement 2**, available at Annals.org). The incidence of definite thrombosis at the longest follow-up was 1.5% (CI, 1.1% to 2.0%). (For additional data on time of occurrence, see **Tables 7** and **8** of **Supplement 2**, available at Annals.org.)

The incidences of total and cardiac mortality were 1.7% (CI, 1.3% to 2.3%) and 1.1% (CI, 0.8% to 1.4%), respectively. The incidence of myocardial infarction was 3.5% (CI, 2.8% to 4.2%) at longest follow-up, 2.9% (CI, 2.4% to 3.5%) within 1 year, and 2.2% (CI, 1.5% to 2.9%) beyond 1 year (**Table 1**). The incidences of TLR, TVR, and TLF were 4.6% (CI, 3.6% to 5.6%), 6.2% (CI, 4.8% to 7.9%), and 7.3% (CI, 5.9% to 8.8%), respectively (**Table 1**). The incidences of these events beyond 1 year remained largely similar to those within 1 year.

Comparative Analysis of BVSs and EESs

Estimates of absolute effects of BVSs and GRADE assessments of confidence in estimates of effect de-

Figure 1. Pooled incidence of definite or probable stent thrombosis at longest follow-up in patients receiving a BVS.



ABSORB = Everolimus-Eluting Bioresorbable Scaffolds for Coronary Artery Disease; AIDA = Amsterdam Investigator-Initiated Absorb Strategy All-Comers Trial; AMC = Academic Medical Center; ASSURE = Postmarketing Surveillance Registry to Monitor the Everolimus-Eluting Bioresorbable Vascular Scaffold in Patients With Coronary Artery Disease; BVS = bioresorbable vascular scaffold; BVS-EXAMINATION = Bioresorbable Vascular Scaffold–A Clinical Evaluation of Everolimus Eluting Coronary Stents in the Treatment of Patients with ST-segment Elevation Myocardial Infarction; BVS EXPAND = Bioresorbable Vascular Scaffolds Expand registry; BVS-RAI = Italian Absorb Registry; BVS STEMI = Use of BVS in ST-segment Elevation Myocardial Infarction; BVS-Save = Bioresorbable Vascular Scaffolds for Small Vessel Coronary Disease; ESHC-BVS = Eastern and Sutherland Heart Clinic BVS registry; EVERBIO II = Comparison of Everolimus- and Biolimus-Eluting Stents With Everolimus-Eluting Bioresorbable Vascular Scaffold Stents; GABI-R = German-Austrian Register to Evaluate the Short and Long-term Safety and Therapy Outcomes of the ABSORB Everolimus-eluting Bioresorbable Vascular Scaffold System in Patients With Coronary Artery Stenosis; GHOST-EU = Gauging Coronary Healing With Bioresorbable Scaffolding Platforms in Europe; ISAR-ABSORB = Intracoronary Scaffold Assessment a Randomised Evaluation of Absorb; IT-DISAPPEARS = Italian Diffuse/Multivessel Disease Absorb Prospective Registry; MICAT = Mainz Intracoronary Database. The Coronary Slow-flow and Microvascular Diseases Registry; REPARA = Registry of Patients With Bioresorbable Device in Daily Clinical Practice; SCAAR = Swedish Coronary Angiography and Angioplasty Registry; TROFI II = Comparison of the Absorb Everolimus Eluting Bioresorbable Vascular Scaffold System With a Drug-Eluting Metal Stent (Xience) in Acute ST-Elevation Myocardial Infarction.

Table 2. GRADE Assessment of Confidence in Estimates of Effect

Outcome	Participants, *n*	Trials, *n*	Risk of Bias	Consistency	Directness
Scaffold thrombosis	5540	7	No serious limitations	No serious limitations	No serious limitations
Myocardial infarction	5553	7	No serious limitations	No serious limitations	No serious limitations
All-cause death	5535	7	No serious limitations	No serious limitations	No serious limitations
Cardiac death	5553	7	No serious limitations	No serious limitations	No serious limitations
TLR	5553	7	No serious limitations	No serious limitations	No serious limitations
TLF	5553	7	No serious limitations	No serious limitations	No serious limitations

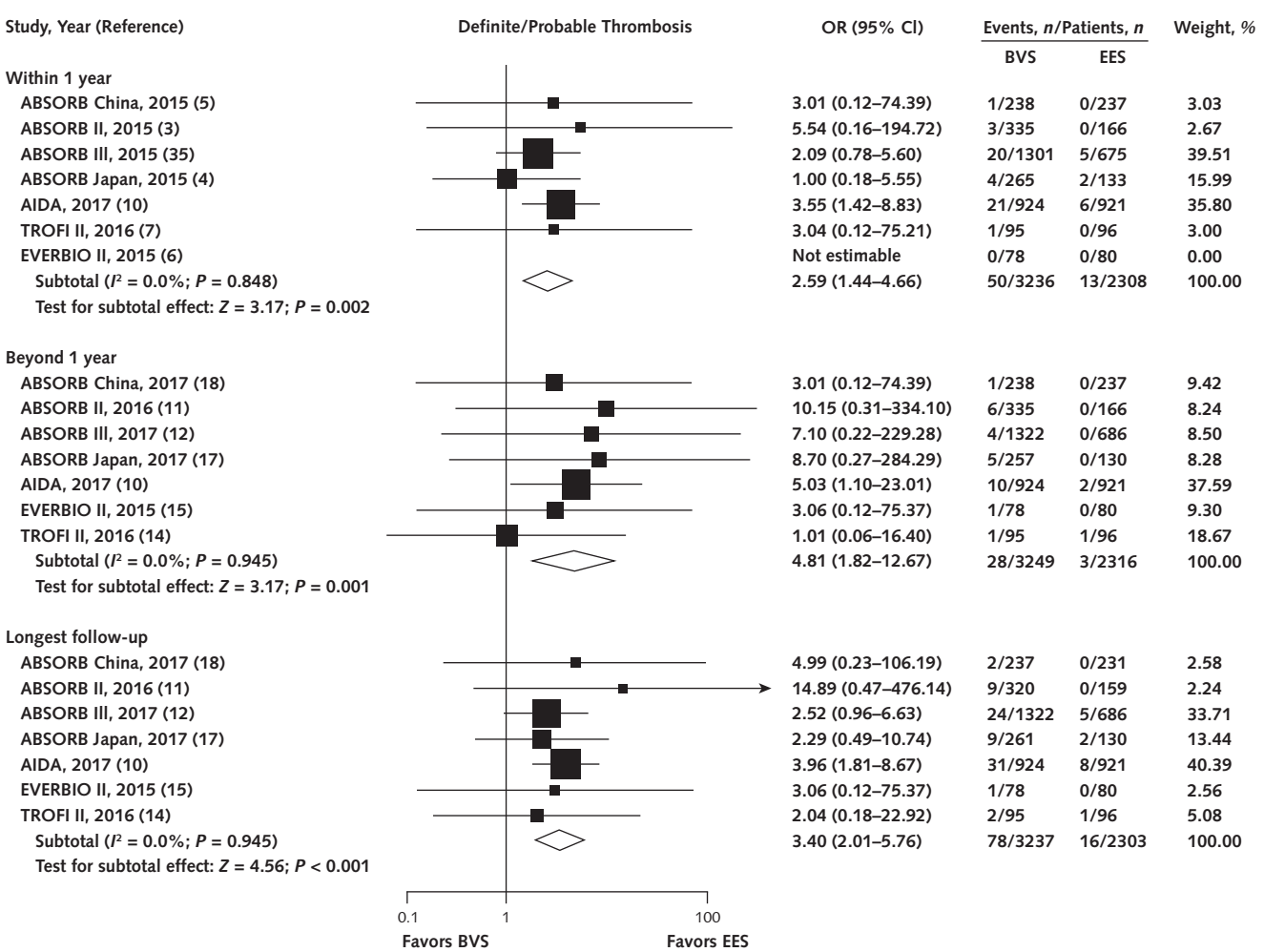
BVS = bioresorbable vascular scaffold; GRADE = Grading of Recommendations Assessment, Development and Evaluation; OR = odds ratio; TLF = target lesion failure; TLR = target lesion revascularization.
* Baseline risk for each outcome in the control group derived from event rates among patients with complete data in the everolimus-eluting metallic stent group of the ABSORB III (Everolimus-Eluting Bioresorbable Scaffolds for Coronary Artery Disease III) trial (normalized to 1 y).

rived from the comparative trials are shown in Table 2. A discussion of the results for each outcome follow.

Scaffold or Stent Thrombosis

Pooled analysis showed an increased risk for definite or probable scaffold or stent thrombosis with BVSs (OR, 3.40 [CI, 2.01 to 5.76]; $P < 0.001$) (Figure 2). The risk was greater for early (prominently subacute), late, and very late thrombosis (Figures 4 and 5 of Supplement 2, available at Annals.org). The odds of definite or probable scaffold or stent thrombosis almost doubled beyond 1 year (OR, 4.81 [CI, 1.82 to 12.67]; $P = 0.001$) compared with those observed within 1 year (OR, 2.59

Figure 2. Pooled risk for definite or probable stent thrombosis, by time of occurrence.



ABSORB = Everolimus-Eluting Bioresorbable Scaffolds for Coronary Artery Disease; AIDA = Amsterdam Investigator-Initiated Absorb Strategy All-Comers Trial; BVS = bioresorbable vascular scaffold; EES = everolimus-eluting stent; EVERBIO II = Comparison of Everolimus- and Biolimus-Eluting Stents With Everolimus-Eluting Bioresorbable Vascular Scaffold Stents; OR = odds ratio; TROFI II = Comparison of the Absorb Everolimus Eluting Bioresorbable Vascular Scaffold System With a Drug-Eluting Metal Stent (Xience) in Acute ST-Elevation Myocardial Infarction.

Table 2–Continued

Precision	Publication Bias	Quality	OR (95% CI)	Absolute Effect of BVS per 1000 Patients Treated per Year (95% CI)*
No serious limitations	Not detected	High	3.40 (2.01–5.76)	9 more events (4 more to 19 more events)
No serious limitations	Not detected	High	1.63 (1.26–2.10)	15 more events (6 more to 25 more events)
Serious limitations	Not detected	Moderate	0.83 (0.58–1.19)	0 fewer events (1 fewer to 0 more events)
Serious limitations	Not detected	Moderate	0.92 (0.57–1.46)	0 fewer events (1 fewer to 1 more events)
No serious limitations	Not detected	High	1.31 (1.03–1.67)	6 more events (1 more to 14 more events)
No serious limitations	Not detected	High	1.37 (1.12–1.66)	14 more events (4 more to 24 more events)

[CI, 1.44 to 4.66]; $P = 0.002$) (Figure 2). With the observed rate of thrombosis in the EES group of the largest ABSORB III (Everolimus-Eluting Bioresorbable Scaffolds for Coronary Artery Disease III) trial used as the baseline, BVSs were associated with 9 more thromboses (CI, 4 to 19 more events) per 1000 persons treated per year (Table 2). Analysis refined to definite scaffold or stent thrombosis showed similar results (Figure 6 of Supplement 2, available at Annals.org).

Myocardial Infarction

Bioresorbable vascular scaffolds were associated with an increased risk for myocardial infarction (OR, 1.63 [CI, 1.26 to 2.10]; $P < 0.001$) (Figure 3, *top*), which was present within 1 year (OR, 1.40 [CI, 1.06 to 1.86]; $P = 0.019$) and slightly higher beyond 1 year (OR, 1.79 [CI, 1.13 to 2.83]; $P = 0.013$). When the observed rate of myocardial infarction in the EES group of the ABSORB III trial was used as the baseline value, BVSs

Figure 3. Pooled risk for myocardial infarction (*top*) and cardiac death (*bottom*), by time of occurrence.

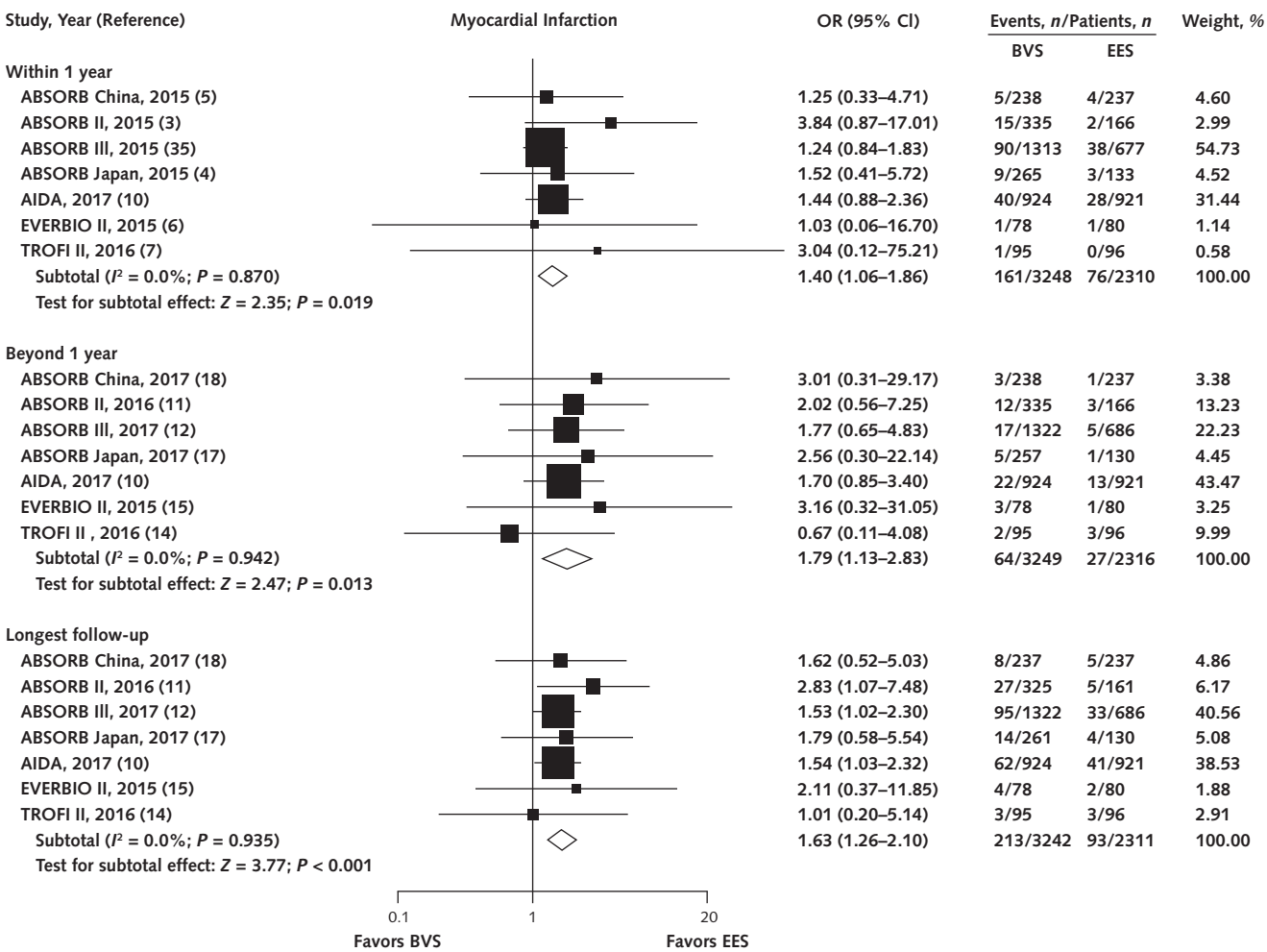
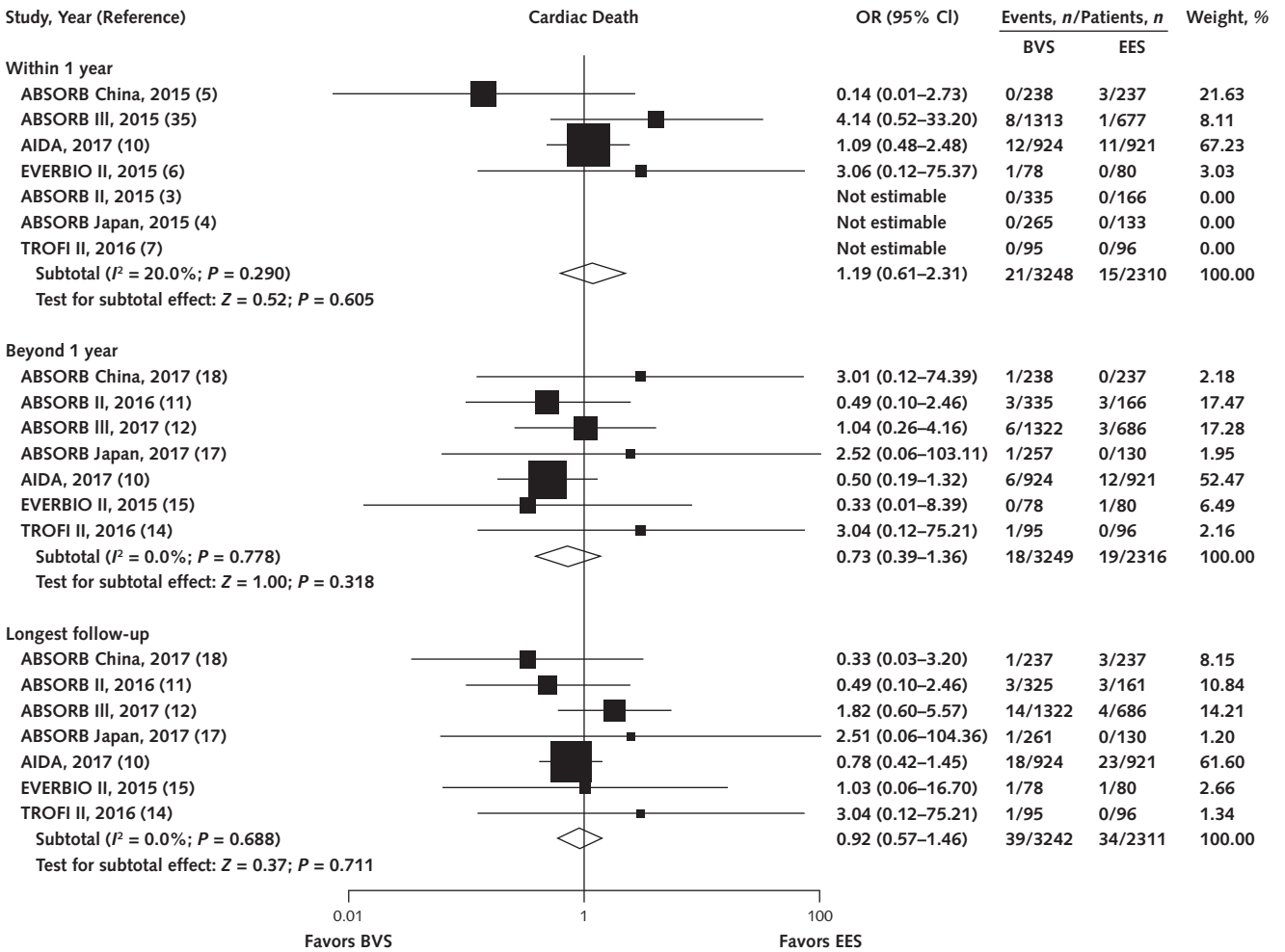


Figure 3–Continued



ABSORB = Everolimus-Eluting Bioresorbable Scaffolds for Coronary Artery Disease; AIDA = Amsterdam Investigator-Initiated Absorb Strategy All-Comers Trial; BVS = bioresorbable vascular scaffold; EES = everolimus-eluting stent; EVERBIO II = Comparison of Everolimus- and Biolimus-Eluting Stents With Everolimus-Eluting Bioresorbable Vascular Scaffold Stents; OR = odds ratio; TROFI II = Comparison of the Absorb Everolimus Eluting Bioresorbable Vascular Scaffold System With a Drug-Eluting Metal Stent (Xience) in Acute ST-Elevation Myocardial Infarction.

were associated with 15 more myocardial infarctions (CI, 6 to 25 more events) per 1000 persons treated per year (Table 2). Data within 1 year suggested that Q-wave myocardial infarction was numerically increased in patients with a BVS (OR, 2.54 [CI, 0.88 to 7.35]; *P* = 0.085) (Figure 7 of Supplement 2, available at Annals.org).

Total, Cardiac, and Noncardiac Mortality

The incidences of total (OR, 0.83 [CI, 0.58 to 1.19]) (Figure 8 of Supplement 2, available at Annals.org), cardiac (OR, 0.92 [CI, 0.57 to 1.46]) (Figure 3, *bottom*), and noncardiac (OR, 0.78 [CI, 0.47 to 1.29]) (Figure 9 of Supplement 2, available at Annals.org) mortality were not statistically significantly different between patients receiving a BVS and those receiving an EES. Stratified analysis showed no statistically significant differences in these 3 end points, either within or beyond 1 year.

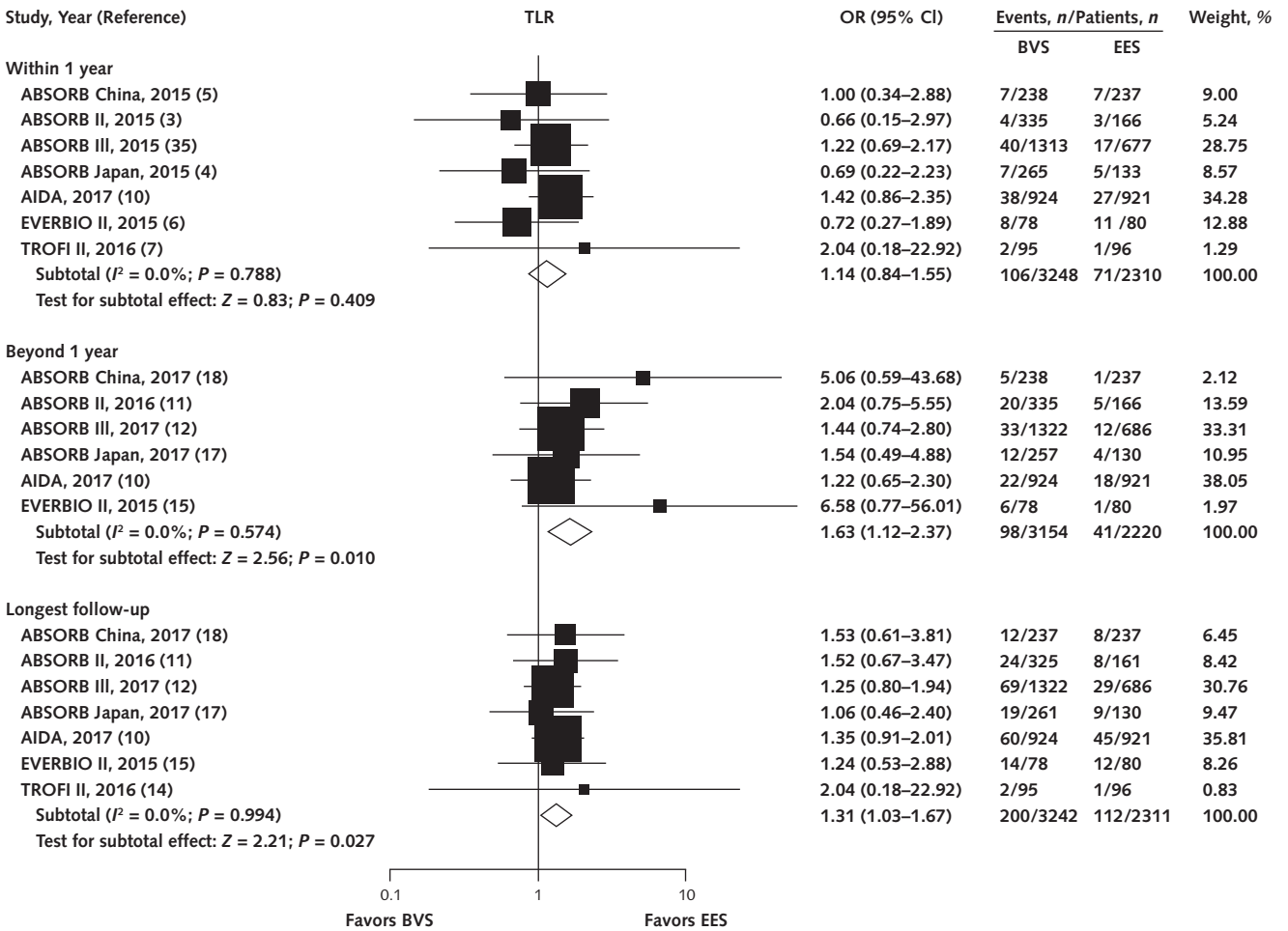
TLR, TVR, All Revascularization, and TLF

Bioresorbable vascular scaffolds were associated with a higher rate of TLR (OR, 1.31 [CI, 1.03 to 1.67]; *P* = 0.027) compared with EESs (Figure 4, *top*), which was evident beyond 1 year (OR, 1.63 [CI, 1.12 to 2.37]; *P* = 0.010) but not within 1 year (OR, 1.14 [CI, 0.84 to 1.55]; *P* = 0.409).

The incidences of TVR (OR, 1.12 [CI, 0.90 to 1.39]) (Figure 10 of Supplement 2, available at Annals.org) and all revascularization (OR, 1.08 [CI, 0.91 to 1.28]) (Figure 11 of Supplement 2, available at Annals.org) were not statistically significantly different between patients receiving BVSs and those receiving EESs, either within or beyond 1 year.

The incidence of TLF was greater in patients with a BVS than those with an EES (OR, 1.37 [CI, 1.12 to 1.66]; *P* = 0.002) (Figure 4, *bottom*). The OR also increased over time, showing an increased risk beyond 1 year

Figure 4. Pooled risk for target lesion revascularization (*top*) and target lesion failure (*bottom*), by time of occurrence.



(OR, 1.51 [CI, 1.09 to 2.09]; $P = 0.012$) and a nonstatistically significantly increased risk within 1 year (OR, 1.23 [CI, 0.97 to 1.55]; $P = 0.088$).

Additional Analyses

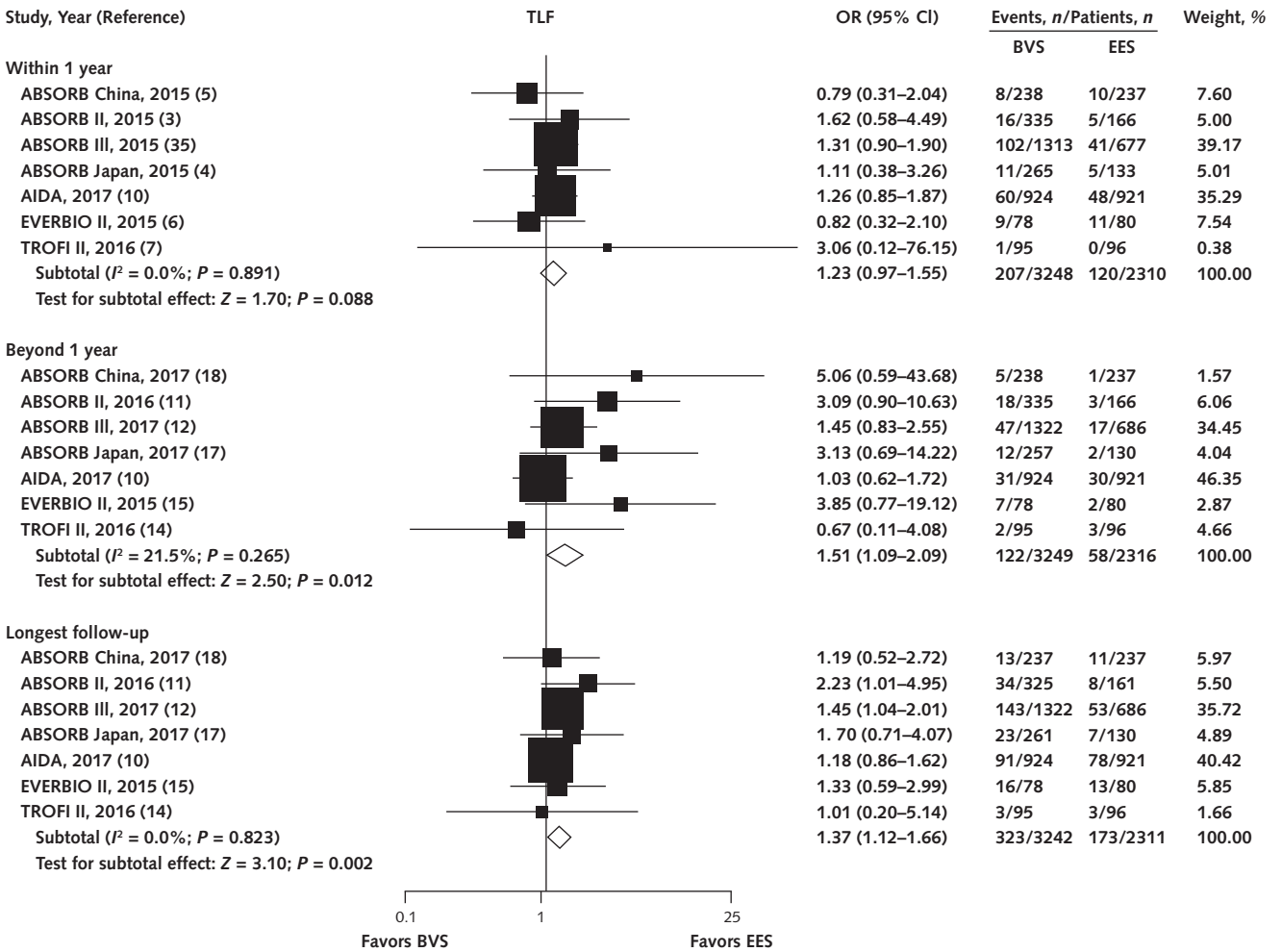
Publication bias tests were negative for all analyses (Table 9 of Supplement 2, available at Annals.org). Metaregression analyses did not show a statistically significant effect of postdilatation, diabetes, or complex lesion on outcomes (Table 10 of Supplement 2, available at Annals.org).

Discussion

Our meta-analysis had several main findings. First, the pooled incidence of definite or probable scaffold thrombosis after BVS implantation was 1.8% (CI, 1.5% to 2.2%) at a median follow-up of 1 year and 0.8% beyond 1 year. Second, compared with EESs, BVSs were associated with a higher incidence of scaffold thrombosis at all time courses (early, late, and very late), and relative risks seemed to increase over time. Third, BVSs increased risks for myocardial infarction, TLR, and TLF, with such relative risks also increasing over time. Fourth, risks for all-cause, cardiac, and noncardiac death; TVR; and all revascularization were not statistically significantly different between patients with a BVS and those with an EES.

We searched PubMed (in July 2017) for other relevant meta-analyses and found 4 that reported 2-year outcome comparisons between BVSs and EESs (68–71). Our comparative findings at long-term follow-up were similar to those of 1 recently published meta-analysis that included the same 7 trials (68). However, the follow-up of 3 trials was updated in our analysis to 3 years (11, 17, 18); follow-up of these trials was 2 years in the other analyses (13, 16, 67). We also performed several additional analyses. First, we assessed the difference in BVS performance within versus beyond 1 year and found that the effect of BVSs on individual and composite thrombotic events likely would be worse over time. Second, we rated the quality of evidence for each outcome by using the GRADE system and provided estimates of absolute effects of BVSs from the comparative trials. Third, we provided comprehensive

***Figure 4*–Continued**



ABSORB = Everolimus-Eluting Bioresorbable Scaffolds for Coronary Artery Disease; AIDA = Amsterdam Investigator-Initiated Absorb Strategy All-Comers Trial; BVS = bioresorbable vascular scaffold; EES = everolimus-eluting stent; EVERBIO II = Comparison of Everolimus- and Biolimus-Eluting Stents With Everolimus-Eluting Bioresorbable Vascular Scaffold Stents; OR = odds ratio; TROFI II = Comparison of the Absorb Everolimus Eluting Bioresorbable Vascular Scaffold System With a Drug-Eluting Metal Stent (Xience) in Acute ST-Elevation Myocardial Infarction.

incidence estimates of all clinical outcomes at different time courses, involving nearly 23 000 patients receiving BVSs in randomized trials and observational studies. These incidence analyses comprise mid- to long-term data of almost all registered large observational studies and largely may represent the last evidence on first-generation BVSs. The other 3 meta-analyses (69–71) included only 3 trials or a few comparative observational studies, some of which were not adjusted for important confounding factors. Pooled analyses from randomized trials in these 3 studies did not show or showed only borderline statistically significant differences in clinical outcomes, some with directional disparity (69).

Concern about increased risk for scaffold thrombosis was first raised by researchers from the all-comer GHOST-EU (Gauging Coronary Healing With Bioresorbable Scaffolding Platforms in Europe) registry (53), who reported an incidence of scaffold thrombosis up to 2.1% at 6 months of follow-up (53). Similarly, another large all-comer registry reported a 1-year rate of scaffold thrombosis of 3.0% (72). These findings later were confirmed in randomized trials. Three-year data from the ABSORB II trial showed an increased risk for scaffold thrombosis associated with BVSs (OR, 2.81), which was maintained to very late stage (11). In AIDA (Amsterdam Investigator-Initiated Absorb Strategy All-Comers Trial), the 2-year rate of scaffold thrombosis in the BVS group was 4 times greater than in the EES group (10). In addition, our previous meta-analysis, as well as meta-analyses of others, showed a 1-year scaffold thrombosis rate up to 1.5% to 1.8% (9, 73), which was remarkably higher than that reported for EESs (2). In agreement with these observations, our present, updated analysis confirmed the concerns of increased midterm risk for scaffold thrombosis and other thrombotic events with BVSs and extended these concerns to long-term follow-up, showing consistently higher risk at all time courses. The increased relative risk seemed to increase further

over time. Indeed, the Kaplan–Meier event curves for TLF separated shortly after BVS or EES implantation, and this separation seemed to continue to augment in favor of EESs at the end of 2 years in the ABSORB III trial (12) and 3 years in the ABSORB II trial (11).

The mechanisms underlying the increased risk for thrombotic events associated with BVSs may involve several factors, including malapposition, incomplete coverage of lesions, poor scaffold expansion, underdeployment, acute disruption, late discontinuity, and neoatherosclerosis (74). Although complete resorption of the scaffold, which occurs within 3 to 4 years after BVS implantation, theoretically might reduce the risk for long-term scaffold thrombosis to some extent, optimized strategies should be taken to improve mid- to long-term BVS outcomes, given that accumulated evidence has shown inferior performance for BVSs. A BVS-specific implantation protocol called PSP (predilation, scaffold sizing, and postdilation) (75) has been reported to substantially reduce the incidence of 1-year scaffold thrombosis from 3.3% to 1.0% (72). Meanwhile, prolonging the duration of dual antiplatelet therapy (DAPT) and the selection of antiplatelet treatment regimens (P2Y12 receptor inhibitors) also have been reemphasized after BVS implantation. Interruption of DAPT was seen in one third of patients with BVS thrombosis (76). In the ABSORB II trial, no late or very late scaffold thrombosis event occurred in 63 patients who continued DAPT for up to 3 years (11). On the basis of current evidence, which is limited, DAPT is recommended for at least 12 months (77) and prasugrel or ticagrelor is preferred over clopidogrel after BVS implantation (77, 78). Two randomized trials, BVS LATE (Optimal Duration of Antiplatelet Therapy After Bioresorbable Vascular Scaffold Implantation to Reduce Late Coronary Arterial Thrombotic Events [ClinicalTrials.gov: NCT02939872]) and SMART-CHOICEII (P2Y12 Inhibitor Monotherapy Versus Extended DAPT in Patients Treated With Bioresorbable Scaffold [ClinicalTrials.gov: NCT03119012]) have just been launched to investigate the use of DAPT in patients with a BVS.

In light of the early and late safety concerns of BVSs, the U.S. Food and Drug Administration recently issued a safety alert for the Absorb BVS (Abbott) (79). The first-generation BVSs are unlikely to be used widely around the world in the future. Next-generation BVSs with an improved design, including thinner struts, greater radial strength, and faster resorption, might overcome the shortcomings of first-generation BVSs (80). An Abbott next-generation BVS with a strut thickness of less than 100 μm is under investigation. Short- to midterm clinical and imaging outcomes of several other kinds of next-generation BVSs from single-group pilot studies with small numbers of patients have just been reported, with some showing encouraging early results (81–87). A ClinicalTrials.gov search currently identifies only 1 registered randomized trial comparing the cardiovascular safety and efficacy of next-generation BVSs with those of conventional drug-eluting stents or first-generation BVSs—namely FUTURE-II (A Trial of Firesorb in Patients With Coronary Artery Disease [ClinicalTrials.gov: NCT02890160]), which started in October 2016 and likely will be completed by October 2022—however, we expect a growing body of such research in the next few years.

Our study has limitations. Several observational studies and trials were available only as meeting presentations. Our negative tests for publication bias based on a small number of trials could not adequately assess small-study effects. Our analyses were based only on studies of the Absorb BVS; therefore, our conclusions are not generalizable to other kinds of BVSs. Follow-up in our comparative analysis was limited to a median of 25 months; longer-term follow-up data from patients in whom the scaffold completely resorbed is still needed to determine whether BVSs have potential late advantages.

Compared with EESs, BVSs were associated with consistently increased risks for scaffold or stent thrombosis and other thrombotic events at mid- and long-term follow-up. All these observed increased risks increased further over time. Optimal scaffold-specific techniques and better-designed scaffolds are needed to improve the clinical outcomes of BVSs.

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