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FOCUS ON BIORESORBABLE VASCULAR SCAFFOLDS

Clinical, Angiographic, and Procedural Correlates of Acute, Subacute, and Late Absorb Scaffold Thrombosis

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ABSTRACT

OBJECTIVES The authors sought to identify and verify independent correlates of device thrombosis from an analysis of multicenter trials and registries.

BACKGROUND Recent analyses suggest an increased risk of device thrombosis with Absorb bioresorbable vascular scaffold (Abbott Vascular, Santa Clara, California) implantation compared with metallic drug-eluting stents, and data from moderate size studies suggest a risk relationship to vessel size and technique.

METHODS From 8,771 consecutively treated patients, 105 patients (1.2%) were identified with scaffold thrombosis within 1 year of implantation. They were matched 2:1 with controls selected randomly from nonthrombosis patients. Data-restricted multiple logistic analysis was used to identify significant independent covariates of the outcome.

RESULTS Early (within 1 month) scaffold thrombosis occurred in 69 patients and late (1 to 12 months) thrombosis occurred in 36 patients. Modelling found significant correlations of thrombosis to be final minimal lumen diameter $<$1.85 mm (odds ratio [OR]: 3.1; $p = 0.004$), off dual antiplatelet therapy (DAPT) status (OR: 3.1 to 3.5; $p = 0.006$ to 0.053), no post-dilatation with $>$1.1:1 balloon/scaffold ratio (OR: 2.3; $p = 0.022$), and reference vessel diameter $<$2.40 mm (OR: 2.1; $p = 0.036$).

CONCLUSIONS Suboptimal vessel sizing, procedural technique, angiographic outcomes, and dual antiplatelet therapy discontinuation appear to be the principal determinants of Absorb scaffold thrombosis risk through 12 months after implantation. (J Am Coll Cardiol Intv 2017;10:1809–15) © 2017 Published by Elsevier on behalf of the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

BRS = bioresorbable scaffold

BVS = Abbott bioresorbable vascular scaffold

DAPT = dual antiplatelet therapy

DES = drug-eluting stent(s)

MLD = minimal lumen diameter

OR = odds ratio

QCA = quantitative coronary angiography

RVD = reference vessel diameter

Bioresorbable scaffolds (BRS) were developed with the hope that they would attenuate the 1.5% to 3.0% annual risk of adverse events beyond 1 year following implantation of metallic drug-eluting stents (DES) (1–3). However, the BRS with by far the most clinical experience, the Abbott Vascular Absorb scaffold (Abbott Vascular, Santa Clara, California), has been associated with a 2-fold excess risk of device thrombosis within the first year (4,5). Increased thrombosis risk has been attributed to an increased strut thickness and width relative to contemporary metallic DES, with associated flow disturbance-mediated platelet deposition (6). Furthermore, post hoc analyses have suggested that small reference vessel size, implantation technique, and final % stenosis affect thrombosis risk, but most of these data are derived from small-to-moderate size studies (7,8) or regression analyses without patient-level data (9). Therefore, we sought to rigorously define the principal risk factors for Absorb scaffold thrombosis occurring in the first year after its implantation.

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METHODS

STUDIES AND PATIENTS. In June 2016, we reviewed the contemporary published reports and contacted industry personnel to identify high-quality randomized clinical trials and registries enrolling with clinical follow-up in >95% to 12 months, and procedural quantitative coronary angiography (QCA) available either via the study directly or with willingness to send images to the Cleveland Clinic Core Angiographic laboratory for review (which was done masked to clinical outcome). Nineteen studies were identified, and 15 agreed to participate. Formal case report forms, with study-specific definitions were developed. Consecutive cases (Academic Research Consortium definite or probable scaffold thrombosis [10]) were identified. Control patients were selected 2:1 to cases, matched by site and requiring follow-up at least as long as their corresponding case, by a random number generator drawing from a consecutive list of nonthrombosis patients.

STATISTICAL ANALYSES. Continuous variables are presented as mean ± SD or median, as appropriate, and were compared with Student *t* or Kruskal Wallis test, as appropriate. Categorical variables are presented as counts and percentages, and were compared using parametric or nonparametric testing (chi square, Fisher exact, or Kolmogorov-Smirnov test). For control patients undergoing bioresorbable vascular scaffold (BVS) implantation at multiple sites, 1 was selected randomly to be the site of interest. Potential covariates were prioritized a priori for data analysis using an approximate 1:10 covariate/case ratio to minimize overmodeling (11). Chosen potential covariates were acute coronary syndrome presentation, diabetes, intravascular imaging, in-segment minimal lumen diameter (MLD), in-segment % stenosis, on/off dual antiplatelet therapy (DAPT), post-dilatation (≥16 atm, ≥1:1 balloon:scaffold ratio), reference vessel diameter (RVD), and scaffold length. Continuous variables were assessing for possible dichotomization primarily by inspection of quintile data and also by spline analysis. Univariate and multivariable Cox proportional hazards analyses were performed to identify parameters possibly correlated to the endpoint. Models were assessed by multiple statistics, including log-likelihood, receiver-operating characteristic curve c-statistic and McFadden's Rho-squared testing. Interaction testing was performed to assess imbalances by study, and to compare modeling for events 0 to 1 month versus 2 to 12 months. Analyses were performed using SYSTAT software, version 13.0 (SYSTAT, Richmond, California).

RESULTS

Patients were drawn from studies with a variety of entry criteria, ranging from those with relatively simple anatomy and no acute coronary syndrome (e.g., the ABSORB III trial [ABSORB III Randomized Controlled Trial]), to all-comers (e.g., the Compare Absorb [ABSORB Bioresorbable Scaffold vs. Xience Metallic Stent for Prevention of Restenosis in Patients at High Risk of Restenosis]; NCT02486068), to ST-segment elevation myocardial infarction only (e.g., the BVS EXAMINATION [Bioresorbable Vascular Scaffold-A Clinical Evaluation of Everolimus Eluting Coronary Stents in the Treatment of

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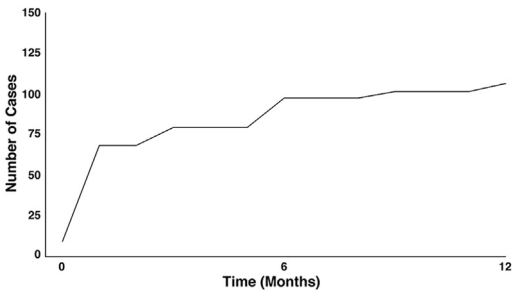
FIGURE 1 Timing of the Cases Studied



Patients With ST-Segment Elevation Myocardial Infarction] trial) (see the Online Appendix for a list of studies). Of 8,771 consecutively treated BVS implant patients with available data, 105 (1.2%) had definite or probable scaffold thrombosis within 12 months. The timing of scaffold thrombosis in this series is shown in **Figure 1**. The majority of events (65.7%) occurred in the first month after device implantation. Baseline patient characteristics are provided in **Tables 1 and 2** and procedural details and outcomes are provided in **Table 3**. Data for selected pre-specified covariates for study are shown in **Figure 2**. Independent covariates for scaffold thrombosis at 12 months, and also for 0 to 1 month and 2 to 12 months are shown in **Table 4**. Two models are provided because they performed nearly identically and are, in a sense, complementary, with model 1 emphasizing implantation technique and model 2 emphasizing the final angiographic result.

Additionally, spline analysis for RVD as a risk factor found a low-risk group (RVD > 3.15 mm, odds ratio [OR]: 0.72) a moderate-risk group (RVD 2.60 to 3.15, OR: 0.95) a high-risk group (RVD 2.08 to 2.59, OR: 1.17) and a very high-risk group (RVD <2.06, OR: 1.61). Spline analysis for in-segment final MLD found a low-risk group (MLD >2.14 mm, OR: 0.85), a moderate-risk

TABLE 1 Baseline Clinical Characteristics

	Cases (n = 105)	Controls (n = 210)	p Value
Age, yrs	59 ± 11	60 ± 11	0.71
Clinical presentation			
AMI	43.3	36.7	0.26
Unstable angina	17.3	18.1	0.86
Stable angina/ischemia	29.8	36.2	0.26
Diabetes	38.5	27.8	0.054
Hyperlipidemia	63.5	59.1	0.49
Hypertension	63.8	63.9	0.98
LVEF	52 ± 11	54 ± 10	0.68
Male	78.1	73.8	0.41
Prior CABG	5.3	2.9	0.29
Smoking, current	33.3	36.8	0.54

Values are mean ± SD or %.

AMI = acute myocardial infarction; CABG = coronary artery bypass grafting; LVEF = left ventricular ejection fraction.

TABLE 2 Angiographic Characteristics

	QCA Cases (n = 86)	QCA Controls (n = 169)	p Value
Lesion length, mm	18.6 ± 11.1	16.7 ± 8.6	0.13
Lesion morphology			
Bifurcation	30.4	26.6	0.48
Calcium, moderate-severe	15.7	18.4	0.59
Thrombus	27.2	14.5	0.017
In-segment RVD, mm	2.70 ± 0.47	2.81 ± 0.46	0.09
Vessel			
LMT	2.9	0.5	0.76
LAD	65.9	51.2	0.002
LCX	10.5	22.5	0.010
RCA	16.2	29.5	0.025

Values are mean ± SD or %.

LAD = left anterior descending coronary artery; LCX = left circumflex coronary artery; LMT = left main trunk coronary artery; QCA = quantitative coronary angiography; RCA = right coronary artery; RVD = reference vessel diameter.

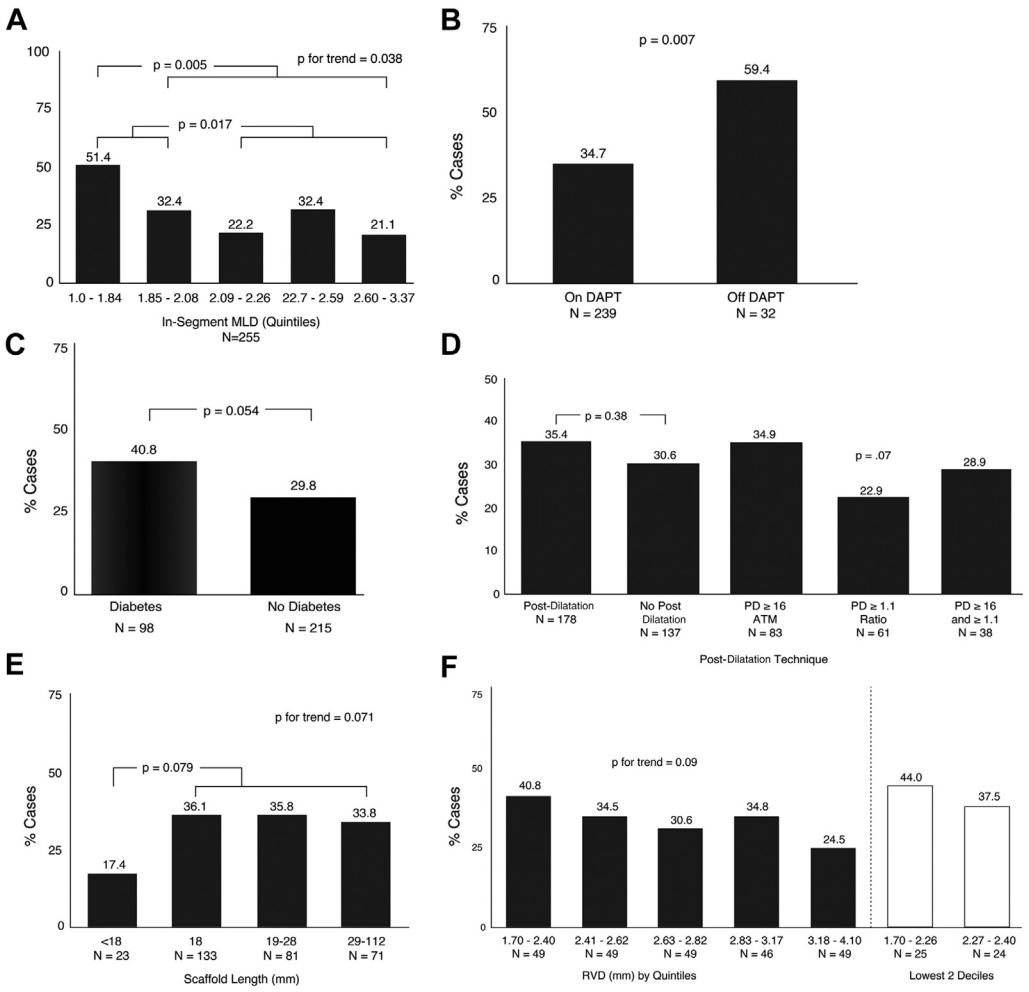
TABLE 3 Procedural Characteristics and Outcomes

	Cases (n = 105/86)	Controls (n = 210/169)	p Value
Procedure			
Intravascular imaging			
IVUS	12.6	6.7	0.081
OCT	6.3	7.6	0.68
Balloon/scaffold ratio	1.11 ± 0.15	1.09 ± 0.16	0.50
Post-dilatation			
Yes	60.0	54.8	0.38
≥16 atm	29.9	27.3	0.64
≥1.1 sizing	16.3	26.2	0.071
Scaffold length, mm	29.1 ± 17.8	25.9 ± 12.9	0.097
Scaffold overlap	19.0	18.2	0.65
Initial angiographic outcome			
Diameter stenosis			
In-scaffold	13.3 ± 10.4	12.1 ± 9.6	0.36
In-segment	22.1 ± 8.6	20.3 ± 7.8	0.18
MLD			
In-scaffold	2.28 ± 0.45	2.42 ± 0.42	0.035
In-segment	2.11 ± 0.47	2.27 ± 0.45	0.04
Edge dissection	1.4	1.4	0.98

Values are % or mean ± SD.

IVUS = intravascular ultrasound; MLD = minimal lumen diameter; OCT = optical coherence tomography.

FIGURE 2 Univariate Results for All Pre-Designated Potential Covariates



Bar graph depiction of **(A)** minimal lumen diameter (MLD), **(B)** on/off dual antiplatelet therapy (DAPT), **(C)** diabetes, **(D)** post-dilatation (PD) with balloon/scaffold diameter ratio >1.1, **(E)** scaffold length, **(F)** reference vessel diameter (RVD).

TABLE 4 Independent Correlates of 0- to 12-Month Scaffold Thrombosis

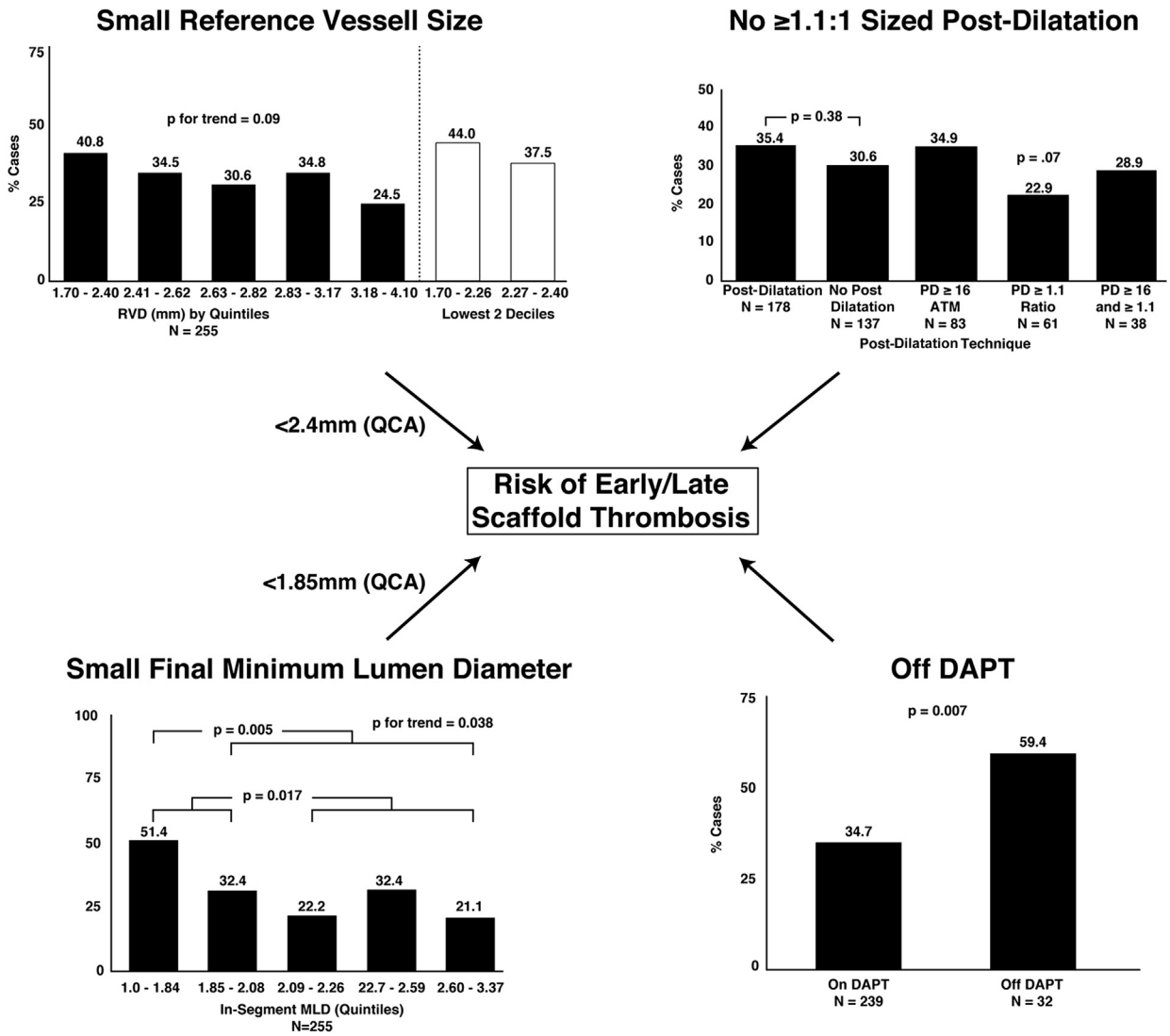
	Odds Ratio (95% CI)	p Value
Model 1		
Off DAPT	3.47 (1.42–8.49)	0.006
No post-dilatation ≥1.1	2.29 (1.13–4.60)	0.022
RVD <2.40 mm	2.12 (1.05–4.27)	0.036
Model p = 0.002	McFadden's Rho-sq 0.052	c-statistic 0.64
Model 2		
MLD <1.85 mm	3.07 (1.44–6.55)	0.004
Off DAPT	2.49 (0.99–6.27)	0.053
Model p = 0.003	McFadden's Rho-sq 0.051	c statistic 0.63

CI = confidence interval; DAPT = dual antiplatelet therapy; other abbreviations as in Tables 2 and 3.

group (MLD 1.87 to 2.14 mm, OR: 1.06) and a high-risk group (MLD <1.86 mm, OR: 1.6). Within the cohort with post-dilatation balloon/scaffold ratio ≥1.1, there was no impact of balloon pressure (range 6 to 24 atm) on outcome. Estimated 1-year thrombosis risk for patients kept on DAPT with final MLD >1.85 mm yielded an OR of 0.58, translating to an absolute risk of approximately 0.7%.

Models performed nearly the same for 0 to 1-month and 1 to 12-month scaffold thrombosis (model 1 c-statistics 0.62 and 0.70; model 2 c-statistics 0.61 and 0.67, respectively) and interaction testing for the components of each model across timing of the thrombosis failed to show even a trend for differences (all p > 0.20).

CENTRAL ILLUSTRATION **Principal Risk Factors for Absorb Scaffold Thrombosis**



Ellis, S.G. et al. J Am Coll Cardiol Intv. 2017;10(18):1809–15.

The 4 principal risk factors for Absorb scaffold thrombosis are illustrated with supporting data: small reference vessel size and final minimal lumen diameter (MLD) (by quintile and with optimal cutpoint), implantation technique, and specifically, no post-dilatation (PD) with >1.1:1–sized balloon, and being off dual antiplatelet therapy (DAPT) at the time of thrombosis or matching follow-up time. QCA = quantitative coronary angiography; RVD = reference vessel diameter.

DISCUSSION

The principal findings of this study are that several risk factors for Absorb scaffold thrombosis can be identified or confirmed: final in-segment MLD <1.85 mm, DAPT discontinuation, no post-dilatation with a balloon-to-scaffold ratio ≥1.1, and RVD by QCA <2.4 mm. Risk factors for 0 to 1-month and 1 to 12-month thrombosis appear to be similar, as reflected by the fact that interaction testing by time did not approach statistical significance for any of these parameters (Central Illustration).

The principal strengths of this paper are that it includes a relatively large number of scaffold thrombosis patients (we believe this is the largest analysis to date) and that potential covariates were prespecified in limited number so as to minimize the risk for overmodeling.

Concern regarding scaffold thrombosis risk following BVS surfaced first in the GHOST EU (Gauging Coronary Healing With Bioresorbable Scaffolding Platforms in Europe) registry report (12) and has been substantiated by multiple meta-analyses (4,5). The importance of small vessels as a risk factor for scaffold thrombosis was first identified in a post hoc analysis from the ABSORB III trial (13), which suggested that a baseline RVD by QCA of <2.25 mm conferred increased thrombosis risk. This and the importance of final MLD were subsequently found to be risk factors from the important Mainz reports of Gori et al. (7) and Puricel et al. (8). Building on these observations, the combined importance of predilatation, vessel sizing, and post-dilatation to minimize the risk of thrombosis was suggested by Ortega-Paz et al. (12). However, potential covariates were not pre-specified in these reports, and the sum total of thrombosis events analyzed with patient-specific data consisted of fewer than 50 patients. Our finding regarding the importance of DAPT discontinuation may be intuitive based upon data from DES patients (14), and although noted in anecdotal reports (usually with very late scaffold thrombosis) (15–17), it has not previously been statistically verified as a risk factor in BVS patients.

CONCLUSIONS

The clinical implications of these findings are largely self-evident. BVS should not be placed into small-diameter coronary arteries (approximately <2.4-mm diameter by QCA); post-dilatation with a slightly oversized balloon should be done to achieve an in-segment MLD >1.85, and DAPT should be continued for at least 1 year. Larger diameters (both RVD >3.15 mm and MLD >2.14 mm) would appear to correlate with greater safety.

STUDY LIMITATIONS. First, quantitative coronary angiography was not available on all patients, the QCA data analyzed originates from several different core angiographic laboratories, and results may vary slightly between laboratories. Second, we are unable to ascertain whether or not post-dilatation and the use of intracoronary imaging were done on a routine basis or for cause (suboptimal angiographic results). Third, we did not formally evaluate other potential risk factors such as device oversizing (reported by Puricel et al. [8] and Ishibashi et al. [18] as a thrombosis risk factor) or the presence of angiographic thrombus at baseline (**Table 2**). Fourth, we do not address the issue of very late scaffold thrombosis (beyond 1 year). Lastly, even with 105 thrombosis cases in the present analysis, conclusions remain limited by sample size.

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PERSPECTIVES

WHAT IS KNOWN? The Absorb bioresorbable scaffold is associated with a greater risk of device thrombosis during the first year after implantation than second-generation DES, but the causes and correlates of this problem are not fully understood.

WHAT IS NEW? Risk of thrombosis is most closely related to small reference vessel size and final MLD, no post-dilatation with balloon sized ≥1.1:1 compared with scaffold diameter, and being off DAPT.

WHAT IS NEXT? These findings require verification from other studies, but they imply a remediable cause and hence possible better long-term results with this, and possibly similar, BRS.

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KEY WORDS Absorb, bioresorbable scaffold, thrombosis

APPENDIX For a list of the studies in this analysis, please see the online version of this article.