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Incidence and Potential Mechanism(s) of Post-Procedural Rise of Cardiac Biomarker in Patients With Coronary Artery Narrowing After Implantation of an Everolimus-Eluting Bioresorbable Vascular Scaffold or Everolimus-Eluting Metallic Stent

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ABSTRACT

OBJECTIVES This study sought to evaluate the mechanism of post-procedural cardiac biomarker (CB) rise following device implantation.

BACKGROUND A fully bioresorbable Absorb scaffold, compared with everolimus-eluting metallic stents (EES), might be associated with a higher incidence of periprocedural myocardial injury.

METHODS In 501 patients with stable or unstable angina randomized to either Absorb (335 patients) or EES (n = 166) in the ABSORB II trial, 3 types of CB (creatine kinase, creatine kinase-myocardial band, and troponin) were obtained before and after procedure. Per protocol, periprocedural myocardial infarction (PMI) was defined as creatine kinase rise >2× the upper limit of normal with creatine kinase-myocardial band rise.

RESULTS Incidence of side branch occlusion and any anatomic complications assessed by angiography was similar between the 2 treatment arms (side branch occlusion: Absorb: 5.3% vs. Xience: 7.6%, p = 0.07; any anatomic complication: Absorb: 16.4% vs. EES: 19.9%, p = 0.39). Fourteen patients who presented with recent myocardial infarction at entry with normalized creatine kinase-myocardial band according to the protocol were excluded for post-CB analysis. The overall compliance for CB was 97.8%. The CB rise subcategorized in 7 different ranges was comparable between the 2 treatment arms. PMI rate was numerically higher in the Absorb arm according to the per-protocol definitions, and treatment with overlapping devices was the only independent determinant of per-protocol PMI (odds ratio: 5.07, 95% confidence interval: 1.78 to 14.41, p = 0.002).

CONCLUSIONS There were no differences in the incidence of CB rise and PMI between Absorb and EES. Device overlap might be a precipitating factor of myocardial injury. (ABSORB II Randomized Clinical Trial: A 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 [ABSORB II]; NCT01425281). (J Am Coll Cardiol Intv 2015;8:1053–63)

ABBREVIATIONS AND ACRONYMS

CB = cardiac biomarker

CI = confidence interval

CK = creatine kinase

CK-MB = creatine kinase-myocardial band

EES = everolimus-eluting stent(s)

IVUS = intravascular ultrasound

OR = odds ratio

PMI = periprocedural myocardial infarction

RVD = reference vessel diameter

SBO = side branch occlusion

TIMI = Thrombolysis In Myocardial Infarction

ULN = upper limit of the normal

The bioresorbable everolimus-eluting scaffold (Absorb, Abbott Vascular, Santa Clara, California) was developed to provide a novel approach to treat coronary artery stenosis with transient vessel support and drug delivery (1–4). The performance of the second-generation Absorb was investigated in the ABSORB Cohort B trial (ABSORB Clinical Investigation, Cohort B), which reported excellent clinical results (5–7). However, the clinical relevance of this technology in comparison with metallic drug-eluting stents still remains a matter of debate due to the absence of randomized comparative data between the Absorb and conventional metallic drug-eluting stents. The ABSORB II (ABSORB II Randomized Clinical Trial: A 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) (8) is the first randomized clinical trial assessing the clinical outcomes in 501 patients treated with either the Absorb or the metallic everolimus-eluting stent (EES) (Xience, Abbott Vascular).

In a nonrandomized comparison using historical data, the Absorb scaffold was associated with a higher incidence of post-procedural side branch occlusion (SBO) than EES was (9). Given the increased strut thickness of Absorb, a potential concern exists that it might be associated with a higher incidence of periprocedural myocardial injury and periprocedural myocardial infarction (PMI) than newer-generations of DES are (9). Therefore, the aim of this study is to investigate the incidence and mechanism of post-procedural cardiac biomarker (CB) rise following Absorb scaffold versus metallic EES implantation.

METHODS

STUDY DESIGN. The ABSORB II randomized controlled trial design has been described in detail previously (8). In brief, the ABSORB II trial was prospective, multicenter, single-blinded, randomized controlled trial that compared the safety and efficacy of the Absorb versus the EES in patients with stable or unstable angina due to up to 2 de novo coronary artery lesions, each located in different major epicardial vessels, all with an angiographic maximal luminal diameter between 2.25 and 3.8 mm as estimated by online quantitative coronary angiography and a lesion length of ≤48 mm. The detail of both study devices is provided in the Online Appendix (2,10,11). A total of 501 patients were randomized 2:1 into either the Absorb arm or the EES arm in Europe and New Zealand.

QUALITATIVE AND QUANTITATIVE ANGIOGRAPHIC ASSESSMENT. SBO, occurrence of no-reflow, abrupt closure, dissection, and distal embolization in main and side branches were assessed qualitatively at preprocedure, after balloon pre-dilation, after device deployment, and after final balloon inflation. Coronary dissections were assessed using the National Heart, Lung and Blood Institute criteria (12,13). In the present study, according to the underlying "anatomic complications" (assessed by angiography), CB rise and PMI were classified into 3 types: type 1—CB rise and PMI due to SBO; type 2—CB rise and PMI due to other anatomic complications (e.g., slow flow or no-reflow, distal embolization, thrombus during procedure, flow-limiting dissection, coronary dissection of National Heart, Lung and Blood Institute type D or E, or disruption of collateral flow); type 3—CB rise and PMI without angiographically identifiable causes for the CB rise (**Figure 1**).

The quantitative angiographic analysis by the 2-dimensional single-vessel quantitative coronary angiography (CAAS 5.10, Pie Medical BV, Maastricht,

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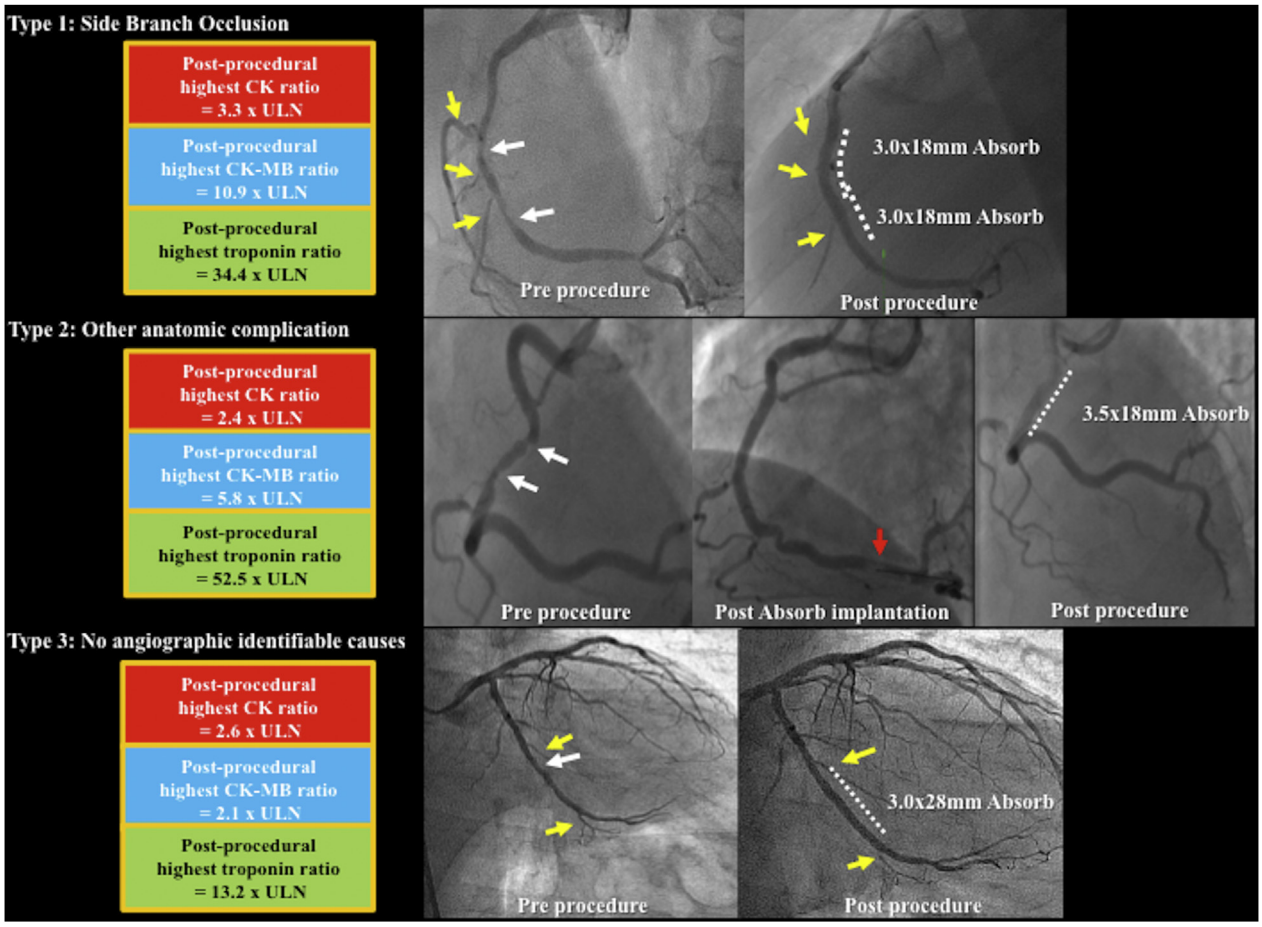
FIGURE 1 Classification According to Angiographic Mechanism After Revascularization



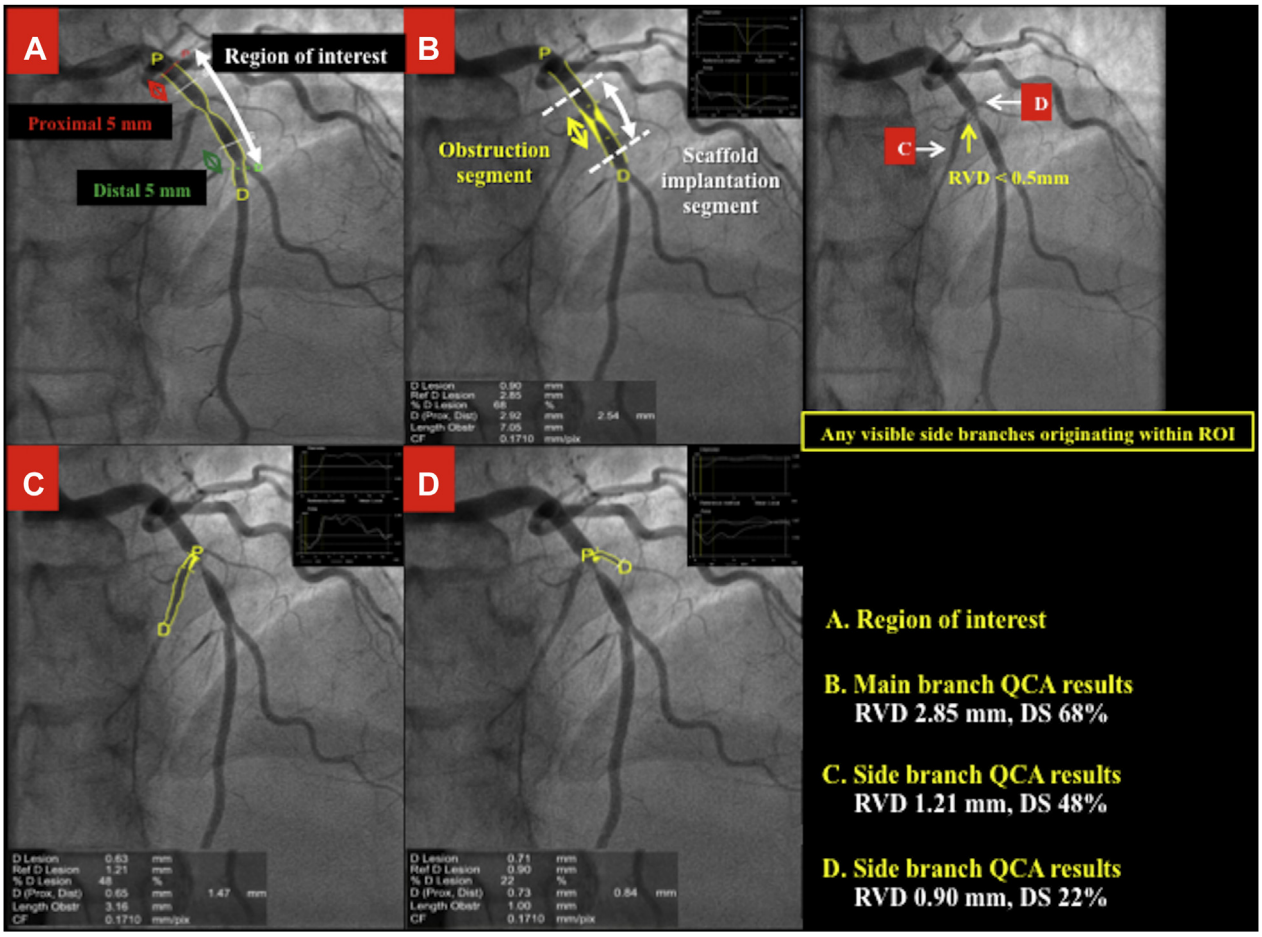
Type 1: cardiac biomarker rise due to side branch occlusion. Type 2: cardiac biomarker rise due to other anatomic complications. Type 3: cardiac biomarker rise without any identifiable anatomic causes in the coronary artery. Pre-procedure angiography showed a focal stenosis **(white arrows)**, side branches in the target lesion **(yellow arrows)**, and distal embolization was observed after device implantation **(red arrow)**.

the Netherlands) included the reference size of the side branch and the percentage of diameter stenosis of any side branch lesion as well as the side branch TIMI (Thrombolysis In Myocardial Infarction) flow grade at the following time points: pre-procedure; after pre-dilation; after post-dilation; and post-procedure (9). The region of interest was defined as the study device implantation site and the 5-mm proximal and distal margins in the main branch (**Figure 2**). A detailed side branch analysis was performed of all side branches identified within the region of interest pre-procedurally, during the course of the intervention to capture any transient complications, and post-procedure. SBO was defined as a reduction in the TIMI flow grade 0 to 1. Accordingly, side branches with pre-procedural TIMI flow grade 0 or 1 were excluded. Transient or final SBO was defined as SBO that occurred during the procedure and either disappeared or persisted at the end of the procedure. Angiographic assessment of the side branch was based on the consensus of 3 experienced cardiologists (Y.I., T.M., and Y.C.) and assessed in at least 2 different projections, with angiographic assessment for each side branch.

IVUS IMAGE ACQUISITION. Intravascular ultrasound (IVUS) was mandatory before and after the procedure. The detail of an image acquisition is described in Online Figure 1.

BLOOD SAMPLING. The protocol mandated that blood sampling for cardiac enzymes was to be collected within 6 h before the index percutaneous

FIGURE 2 Detailed Analysis of SBO



The QCA analysis delineates 5-mm proximal **(A) (red double arrow)** and distal segment **(A) (green double arrow)** to the intended device implantation site **(B) (white double arrow)**. Any visible side branches originating from this region of interest were analyzed. The conventional QCA analysis automatically delineates an obstruction segment in the main branch **(B) (yellow double arrow)**. An example of side branch analysis is shown in **C** and **D**. DS = diameter stenosis; QCA = quantitative coronary angiography; RVD = reference vessel diameter; SBO = side branch occlusion.

coronary intervention procedure and at 6, 12, and 18 h after the procedure or at hospital discharge, whichever came first. These blood samples were sent to the central core laboratory (ICON Laboratories, Dublin, Ireland) and to local hospital laboratories for analysis. Whenever clinically indicated, additional sampling could be taken and analyzed by the local hospital laboratories.

This yielded a mixture of local and central laboratories' biomarker results with different upper limits of normal (ULN). When both local and central laboratories' cardiac enzyme data were available at the same time, the clinical events committee used the central laboratories' results for the adjudication of MI.

DEFINITIONS OF PERIPROCEDURAL MYOCARDIAL INFARCTION. In this study protocol, MI was defined according to the following definitions (14–16): 1) per-protocol (modified World Health Organization) definition; and 2) extended historical definition (14). In the protocol, MI without distinction of being spontaneous or PMI is defined by elevation of total creatine kinase (CK) to >2× ULN along with elevated or "positive" creatine kinase-myocardial band (CK-MB). A hierarchical approach was used for the adjudication of PMI based on CB availability when an analyzable CB was missing (extended historical definition: CK-MB mass when CK was not available, cardiac troponin when CK and CK-MB mass were not available). All protocol defined clinical outcomes were

adjudicated by an independent Clinical Events Committee. Fourteen patients presented with recent MI at entry with normalized CK-MB according to the protocol, but with/without troponin elevation. These patients were excluded for post-CB analysis. Post-hoc adjudication was performed according to Society of Cardiovascular Angiography and Interventions definition and the universal third definition. The details are described in the Online Appendix.

STATISTICAL ANALYSIS. All analyses were performed on the intention-to-treat basis, using all patients randomized in the study, regardless of the treatment actually received. The counts of PMI are summarized and tabulated according to the frequency. Categorical variables were compared by Fisher exact test. Continuous variables are presented as mean ± SD and were compared by nonparametric test. The logistic regression model was performed for **Table 5**. Detail of statistical analysis is provided in the Online Appendix. In addition to the device type, significant variables ($p < 0.10$) in the univariate analysis were forced into a multivariate logistic regression model to predict PMI. All statistical tests were performed with SPSS (version 22.0 for Windows, SPSS, Chicago, Illinois). A 2-sided p value of <0.05 was considered to indicate statistical significance.

RESULTS

PATIENT AND PROCEDURAL CHARACTERISTICS. Patient demographics were comparable in both arms (**Table 1**). The lesion characteristics such as type B2/C lesions, bifurcation lesions, eccentricity, moderate/severe tortuosity, thrombus, and moderate/severe calcification were similar between the 2-treatment arms.

AVAILABILITY OF CARDIAC BIOMARKERS OF MYOCARDIAL INJURY. Within 24 h before the index procedure, 920 blood time points for the assessment of CB were available with 458 central and 462 local biomarker data. At least 1 of the 3 CB was available in 486 patients (97.0%) within 6 h and in 495 patients (98.8%) within 24 h before the index procedure. At least 1 of the 3 CB was available in 490 patients (97.8%) within 48 h after the index procedure. In the serial sample analysis, 1,446 blood time points for the assessment of CB were available with 572 central and 874 local biomarker data (**Figure 3**). A total of 3,813 blood samples with 1,257 CK, 1,253 CK-MB, and 1,303 troponin values were available. For the post-procedural peak-level assessment of each CB, the central biomarker data was used in 58.4% for CK (271 of 464), 70.9% for CK-MB (337 of 475), and 45.0% for troponin (213 of 473). The availability of paired biomarkers (CK and CK-MB) for per-protocol PMI adjudication at post-procedure was available in 93.4% (313 of 335) of the Absorb arm and 96.4% (160 of 166) of the EES arm. Troponin was available in 98.8% (325 of 335) of the Absorb arm and 97.6% (160 of 166) of the EES arm.

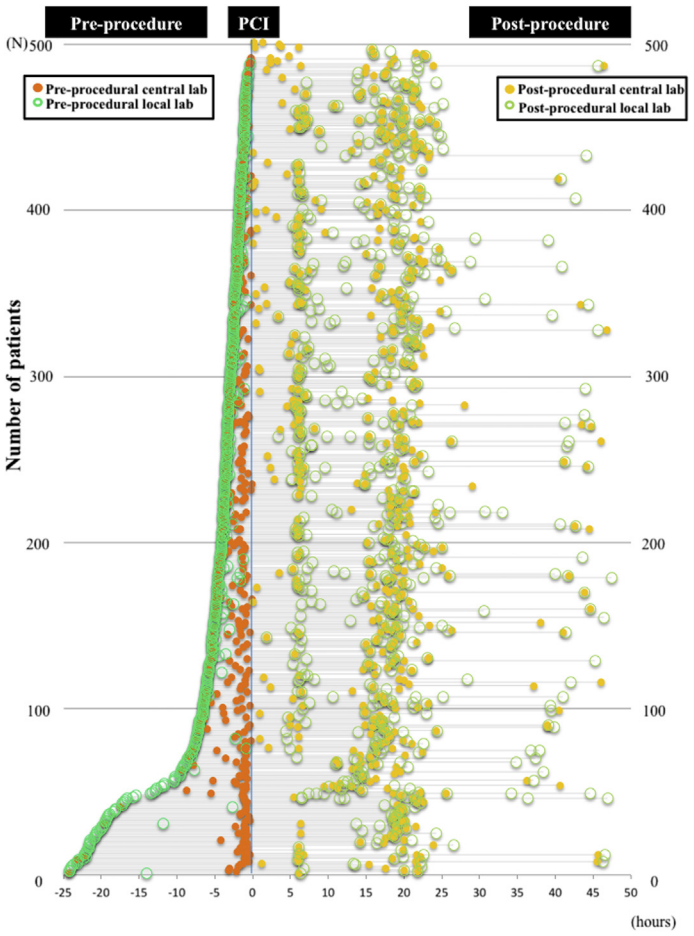
TABLE 1 Baseline Demographic Data and Angiographic Characteristics in Patients

	Absorb (335 Patients, 364 Lesions)	EES (166 Patients, 182 Lesions)	p Value
Age, yrs	61.5 ± 10.0	60.9 ± 10.0	0.51
Male	253 (75.5)	132 (79.5)	0.32
Body mass index, kg/m^2	27.9 ± 4.1	28.1 ± 3.7	0.56
Current smoker	79 (23.6)	36 (21.7)	0.64
Hypertension requiring treatment	220 (65.7)	112 (67.5)	0.69
Dyslipidemia requiring treatment	238 (71.0)	123 (74.1)	0.47
Any diabetes mellitus	80 (23.9)	40 (24.1)	0.96
Unstable angina	68 (20.3)	37 (22.3)	0.61
Family history of coronary artery disease	112 (36.6)	64 (41.3)	0.33
Previous history of myocardial infarction	93 (28.0)	48 (28.9)	0.83
Number of lesions/patient	1.1 ± 0.3	1.1 ± 0.3	0.81
Lesion location			
Right coronary artery	95 (26.1)	56 (30.8)	0.25
Left anterior descending artery	163 (44.8)	84 (46.2)	0.76
Left circumflex artery or ramus	106 (29.1)	42 (23.1)	0.13
ACC/AHA lesion complexity			
A	5 (1.4)	1 (0.6)	0.67
B1	193 (53.2)	90 (50.0)	0.49
B2	159 (43.8)	87 (48.3)	0.32
C	6 (1.7)	2 (1.1)	1.00
TIMI flow grade 0 or 1	1 (0.3)	2 (1.1)	0.26
Calcification, moderate or severe	46 (12.7)	28 (15.5)	0.37
Tortuosity, moderate or severe	34 (9.4)	13 (7.2)	0.39
Eccentric	357 (98.3)	178 (99.4)	0.43
Thrombus	5 (1.4)	4 (2.2)	0.49
Bifurcation	13 (3.6)	5 (2.8)	0.62
Reference vessel diameter, mm	2.59 ± 0.38	2.63 ± 0.40	0.36
Percentage of diameter stenosis	58.6 ± 11.1	59.7 ± 11.6	0.30
Obstruction lesion length, mm	13.8 ± 6.5	13.8 ± 6.6	1.00

Values are mean ± SD or n (%).
ACC = American College of Cardiology; AHA = American Heart Association; EES = everolimus-eluting stent(s).

QUALITATIVE AND QUANTITATIVE ANGIOGRAPHIC ASSESSMENT. The frequencies of "angiographic complications" are shown in **Table 2**. In the present analysis, 335 patients with 988 side branches in the Absorb arm and 166 patients with 503 side branches in the EES arm were assessed. Incidence of any "angiographic complications" and SBO was similar between the 2 treatment arms (any complications: Absorb: 16.4% vs. EES: 19.9%, $p = 0.39$; SBO: 5.3% vs. 7.6%, $p = 0.07$). The incidence of post-procedural SBO in the obstruction segment was significantly lower in the Absorb arm than in the EES arm (4.3% vs. 6.8%,

FIGURE 3 Time Points and Availability for the Assessment of CB Pre- and Post-Procedure



A total of 920 blood time points for the assessment of cardiac biomarkers (CB) were available with 458 central and 462 local biomarker data within 24 h before the index procedure. At least 1 of the 3 CB was available in 486 patients (97.0%) within 6 h and 495 patients (98.8%) within 24 h before the index procedure. At least 1 of the 3 CB was available in 490 patients (97.8%) within 48 h after the index procedure. In the serial sample analysis, 1,446 blood time points for the assessment of CB were available with 572 central and 874 local biomarker data.

p = 0.046), although there were no significant differences in the incidence of SBO according to the reference vessel diameter (RVD) size (RVD ≤ 0.5 mm, 0.5 mm < RVD ≤ 1.0 mm, 1.0 mm < RVD). Each type (type 1, type 2, and type 3) of "anatomic complications" after revascularization was similar between the 2 treatment arms. However, 2 abrupt occlusions were documented after EES implantation (Table 2).

INCIDENCE OF CARDIAC BIOMARKER RISE AND PERIPROCEDURAL MI. As recently described (17), we compared the peak value of the 3 CB values post-procedure according to 5 rise categories (CB: >2× ULN, >5× ULN, >10× ULN, > 35× ULN, and >70× ULN) after scaffold or stent implantation. In the present study, the rise of 3 CB subcategorized in 7 different ranges was comparable between the 2 treatment arms (Table 3).

Per-protocol PMI (World Health Organization definition) occurred in 13 of 335 patients (3.9%) in the Absorb arm and 2 of 166 patients (1.2%) in the EES arm (p = 0.16). Incidence of PMI per protocol according to "anatomic complications" assessed by angiography was similar between the 2 treatment arms (Table 4). In the post-hoc adjudication, the PMI rates according to the third universal definition and the Society of Cardiovascular Angiography and Interventions definition were 14.2% versus 10.6% (p = 0.31) and 0.6% versus 0.6% (p = 1.00), respectively.

CARDIAC BIOMARKER RISE, ANGIOGRAPHY, AND GRAYSCALE/RADIOFREQUENCY IVUS. Figure 4 shows the magnitude of post-procedural CB rise in patients with "anatomic complications" (type 1 and type 2) assessed by angiography. CB rise subcategorized in 5 different ranges was similar between the 2 treatment arms in the patients with "anatomic complications." Incidence of CB rise assessed by IVUS (data not shown) was similar between the 2 treatment arms as well as "angiographic complications." There was no statistical significance between IVUS finding and post-procedure CB rising (Online Appendix).

PREDICTORS OF PERIPROCEDURAL MYOCARDIAL INFARCTION. In the multivariable analyses, treatment with overlapping devices was the only independent determinant of per-protocol PMI (odds ratio [OR]: 5.07, 95% confidence interval [CI]: 1.78 to 14.41, p = 0.002) (Table 5).

DISCUSSION

The present study is the first randomized clinical trial to analyze the difference in frequencies of PMI and CB rise after implantation of Absorb scaffold or EES. The main findings of this study follow: 1) Incidence of any anatomic complications including SBO assessed by angiography was similar between the 2 treatment arms (Absorb: 16.4% vs. EES: 19.9%, p = 0.39). 2) Per-protocol PMI (World Health Organization definition) occurred in 13 of 335 patients (3.9%) in the Absorb arm and 2 of 166 patients (1.2%) in the EES arm (p = 0.16). Of 15 patients with per-protocol PMI, 10 PMI (66.7%) were caused by SBO, whereas 3 (20.0%) were due to other anatomical complications. 3) Treatment with overlapping devices was an independent

determinant of per-protocol PMI (OR: 5.07, 95% CI: 1.78 to 14.41, p = 0.002). 4) The CB rise subcategorized in 7 different ranges was comparable between the 2 treatment arms.

AVAILABILITY OF CARDIAC BIOMARKER AND PERIPROCEDURAL CARDIAC BIOMARKER RISE. This is the first scaffold or metallic stent study in which 3 different CB values were available at a central core laboratory, the compliance of enzyme collection was high (CK: 95.3%, CK-MB: 97.5%, troponin: 97.1%). Of note, in the RESOLUTE-All Comers (A Randomized Comparison of a Zotarolimus-Eluting Stent With an Everolimus-Eluting Stent for Percutaneous Coronary Intervention) trial (14), an analyzable dataset for cardiac troponin was available in 55.3% (1,173 of 2,121) of patients. In addition, 44.1% (935 of 2,121) of patients had an analyzable dataset for both cardiac troponin and CK-MB (14). In 10 patients, 3 CB simultaneously increased, whereas in 127 patients, discordance in CB rise was documented, suggesting that the sensitivity of CB to detect myocardial damage varies according to the criteria and type of CB (Online Figure 2).

The prognostic relevance of CB rise is shown by Park et al. (18), in a large cohort of 23,604 patients, the prognostic implication of a CK-MB rise 3× to 5× ULN. Myint et al. (19) reported that prognostic significance of troponin in acute coronary syndrome attenuates with increased age and that older age is associated with a worse prognosis compared with the prognosis of younger counterparts given the same level of troponin rise, even at very low levels of troponin.

TABLE 2 Anatomic Complications Assessed by Angiography

Per-Patient Analysis	Absorb (n = 335)	EES (n = 166)	p Value
Any anatomic complications assessed by angiography	16.4 (56)	19.9 (33)	0.39
Type 1 anatomic complication assessed by angiography			
SBO	12.5 (43)	15.7 (26)	0.41
SBO after pre-dilation	0 (0)	0 (0)	1.00
SBO after device implantation	12.5 (43)	15.7 (26)	0.41
SBO improvement after NTG	0.9 (3)	0 (0)	0.55
SBO after procedure	11.6 (40)	15.7 (26)	0.26
Type 2 anatomic complication assessed by angiography			
Abrupt closure	0 (0)	1.8 (2)	0.11
Distal embolization	0.3 (1)	0 (0)	1.00
Coronary perforation	0.6 (2)	0 (0)	1.00
Flow-limiting dissection (NHLBI type F)	0.3 (1)	0 (0)	1.00
Coronary dissection after pre-dilation (NHLBI type D or E)	1.8 (6)	1.2 (2)	1.00
Coronary dissection after device implantation	0.3 (1)	0.6 (1)	1.00
Thrombus during procedure	0.3 (1)	0 (0)	1.00
Disruption of collateral flow	0.3 (1)	1.2 (2)	0.26
Per-Side Branch Analysis	**(n = 998)**	**(n = 503)**	
Incidence of SBO after procedure	5.3 (52)	7.6 (39)	0.07
Location of occluded side branch			
Outside scaffold segment	0 (0)	0 (0)	1.00
To-be-scaffold segment outside obstruction	0.9 (9)	1.0 (5)	1.00
Obstruction segment	4.3 (42)	6.8 (34)	0.046
RVD of occluded side branch			
RVD > 1.0 mm	0.9 (9)	1.2 (6)	0.59
0.5 mm < RVD ≤ 1.0 mm	2.9 (29)	4.2 (21)	0.22
RVD ≤ 0.5 mm	1.3 (13)	2.4 (12)	0.14

Values are % (n).

EES = everolimus-eluting stent(s); NHLBI = National Heart, Lung, and Blood Institute; NTG = nitroglycerin; RVD = reference vessel diameter; SBO = side branch occlusion.

ANATOMIC COMPLICATIONS ASSESSED BY ANGIOGRAPHY/IVUS AND PERIPROCEDURAL CARDIAC BIOMARKER RISE WITH ABSORB OR EES. In the previous publication using the data of the Absorb Extend registries with a matched cohort from SPIRIT (Clinical Evaluation of the Xience V Everolimus Eluting Coronary Stent System) trials (9), it was reported that the Absorb scaffold was associated with a higher SBO rate than Xience was. The difference was more pronounced with small side branches with an RVD ≤0.5 mm. However, there was no significant difference in the incidence of post-procedure CK-MB elevation. It was hypothesized that the difference in SBO was due to the difference in the design of the 2 devices. The Absorb scaffold has thicker (156 μm) and wider struts (up to 800 μm) with a higher surface coverage ratio (26% to 32%) than Xience does (thickness: 90 μm, widths: up to 428 μm, surface coverage: 13%). Therefore small side branches could be more frequently occluded by the implantation of Absorb scaffold. At variance with the report by Muramatsu et al. (9), the Absorb, compared with EES, showed a trend toward lower incidence of post-procedural SBO. Of note, most of the SBO occurred in small side branches of RVD <1.0 mm in both of treatment arms (**Table 2**). Although the nominal sizes of devices used (3.01 ± 0.31 mm vs. 3.05 ± 0.28 mm, p = 0.10) and frequency of post-device dilation were comparable (60.7% vs. 58.8%, p = 0.67), the nominal balloon size and the pressure used during either implantation or post-dilation was larger and higher in the EES arm, so that the expected balloon diameter tended to be larger accordingly (3.29 ± 0.35 mm vs. 3.35 ± 0.37 mm, p = 0.15) (17), the acute gain in minimal lumen diameter (quantitative coronary angiography measurement by the core laboratory) was significantly larger in the EES arm (1.15 ± 0.38 mm vs. 1.46 ± 0.38 mm, p < 0.001) (17). Whether the aggressive (post)-dilation may have resulted in a higher incidence

TABLE 3 Comparison of the Peak Value of Cardiac Enzyme Rise Post-Procedure Using Central Lab and/or Local Lab Results

	CK n = 464 of 487 (95.3%)			CK-MB* n = 475 of 487 (97.5%)			cTn n = 473 of 487 (97.1%)		
	Absorb (n = 306)	Xience (n = 158)	p Value	Absorb (n = 315)	Xience (n = 160)	p Value	Absorb (n = 316)	Xience (n = 157)	p Value
Mean ± SD	0.71 ± 0.63	0.65 ± 0.64	0.380	1.33 ± 2.12	1.09 ± 1.65	0.180	12.09 ± 30.24	8.28 ± 20.20	0.138
>2× ULN	5.2 (16)	1.9 (3)	0.135	13.7 (43)	10.0 (16)	0.304	48.1 (152)	45.9 (72)	0.696
>5× ULN	0 (0)	0.6 (1)	0.341	5.1 (16)	2.5 (4)	0.232	29.7 (94)	25.5 (40)	0.386
>10× ULN	0 (0)	0 (0)	1.000	0.6 (2)	0.6 (1)	1.000	19.0 (60)	15.3 (24)	0.372
>35× ULN	0 (0)	0 (0)	1.000	0 (0)	0 (0)	1.000	6.0 (19)	3.8 (6)	0.387
>70× ULN	0 (0)	0 (0)	1.000	0 (0)	0 (0)	1.000	3.5 (11)	1.3 (2)	0.236

Values are % (n) unless otherwise indicated. *Fourteen patients presented with recent myocardial infarction at entry with normalized CKMB according to the protocol were excluded for post CB analysis.

CK = creatine kinase; CK-MB = creatine kinase-myocardial band; cTn = cardiac troponin; EES = everolimus-eluting stent(s); ULN = upper limit of normal.

of post-procedural SBO in the EES arm—due to the presence of the bifurcation carina shift and/or plaque shift into the orifice of side branch (16,20)—remains speculative. Among the patients with post-dilation, the peak ratio of CK-MB post-procedure was significantly higher in the Absorb arm than in the EES arm (1.43 ± 2.41 vs. 1.00 ± 1.89, p = 0.02). The current protocol did not recommend post-dilation of the Absorb device with a balloon larger than 0.25 mm with respect to the nominal size of the device. The post-procedural CB rise with the patients who underwent post-dilation seems to justify retrospectively this conservative recommendation.

TABLE 4 Incidence of Per-Protocol PMI According to Anatomic Complications Assessed by Angiography

	Absorb (n = 335)	EES (n = 166)	p Value
Per-protocol PMI	3.9 (13)	1.2 (2)	0.16
Type 1: SBO	2.7 (9)	0.6 (1)	0.18
SBO after pre-dilation	0 (0)	0 (0)	1.00
SBO after device implantation	2.7 (9)	0.6 (1)	0.18
SBO improvement after NTG	0 (0)	0 (0)	1.00
SBO after procedure	2.7 (9)	0.6 (1)	0.18
Type 2: angiographic other complication	0.6 (2)	0.6 (1)	1.00
Abrupt closure	0 (0)	0.6 (1)	1.00
Distal embolization	0.3 (1)	0 (0)	1.00
Coronary perforation	0 (0)	0 (0)	1.00
Flow-limiting dissection, NHLBI type F	0 (0)	0 (0)	1.00
Coronary dissection after pre-dilation, NHLBI type D or E	0.3 (1)	0 (0)	1.00
Coronary dissection after device implantation	0 (0)	0 (0)	1.00
Thrombus during procedure	0 (0)	0 (0)	1.00
Disruption of collateral flow	0 (0)	0 (0)	1.00
Nonindentifiable mechanism causes	0.6 (2)	0 (0)	1.00

Per-protocol PMI is defined as the elevation of total CK to >2× ULN along with elevated or "positive" CK-MB without clinical symptom and electrocardiogram change.

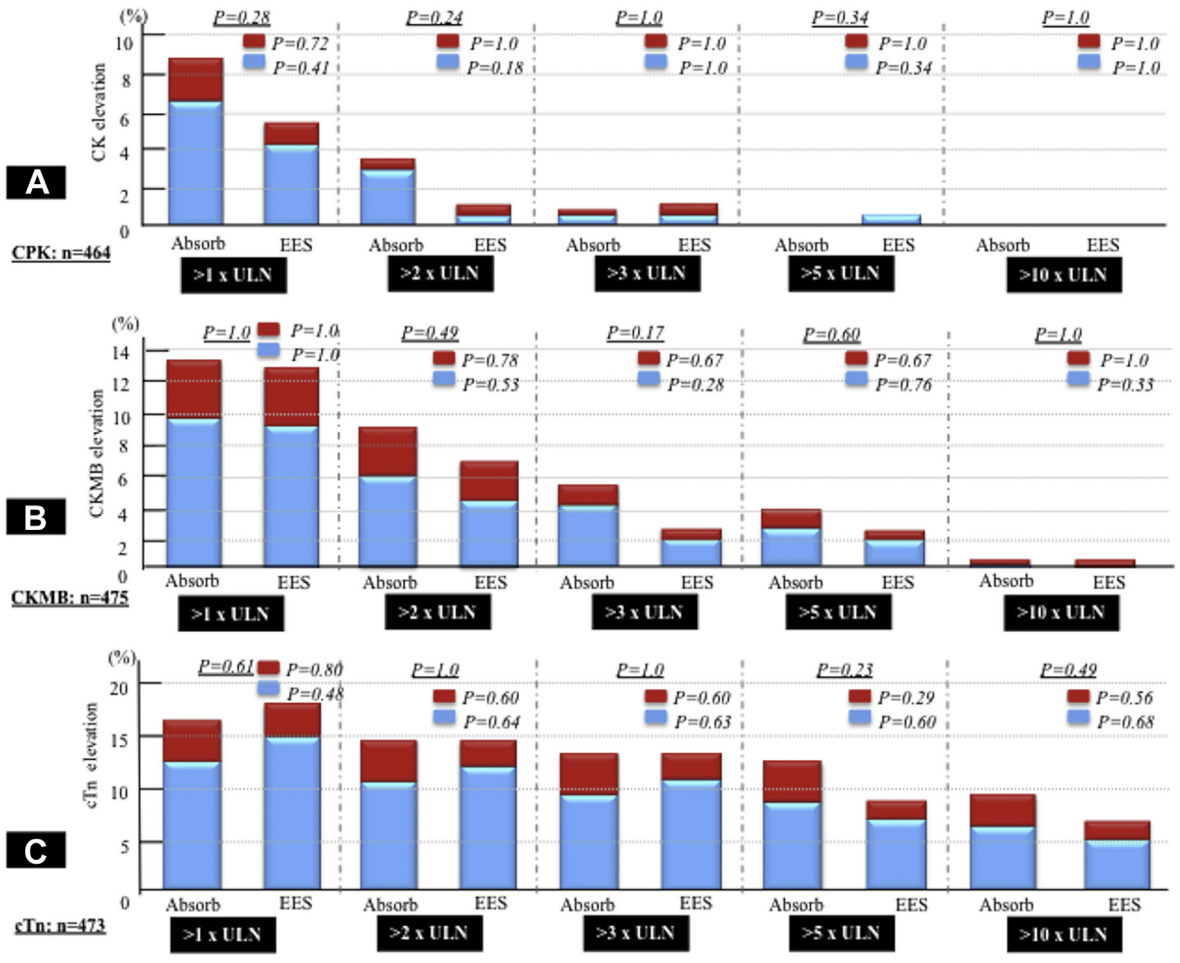
PMI = periprocedural myocardial infarction; other abbreviations as in Tables 1 to 3.

As previously reported, atherosclerotic plaque burden pre-intervention is correlated with an increased rate of PMI as evidenced by subsequent CB rise (21). Atherosclerotic plaque with larger necrotic core are at higher risk of plaque rupture and microembolization during percutaneous coronary intervention with subsequent CB rise (22,23). The present study also documented that dyslipidemia requiring treatment was protective for troponin rise >5× ULN, whereas the incidence of CB rise assessed by IVUS was similar between the 2 treatment arms. It has been hypothesized that statins may exert anti-inflammatory effects, resulting in reduction of microembolization by stabilizing the underlying plaque (24).

ANATOMIC COMPLICATIONS ASSESSED BY ANGIOGRAPHY AND PERIPROCEDURAL MI WITH ABSORB OR EES. Previous studies revealed that SBO was the most common cause of PMI (20,25). In the present study, 15 patients with per-protocol PMI, 10 (66.7%) were angiographically classified as type 1 (SBO) whereas 3 (20.0%) were type 2 (other anatomic complication). In 2 patients (13.3%), no angiographic complications could be identified. Thus, our results are in concordance with previous studies (16,26,27).

PREDICTORS FOR PERIPROCEDURAL RISE OF CARDIAC BIOMARKER FOR INJURY. The predictors of PMI can be broadly categorized as patient-, lesion-, and procedure-related risk factors (16,20). In the SPIRIT IV trial, which randomized 3,687 patients in a 2:1 fashion to receive either EES or PES, the total stent length was a strong predictor of PMI by criteria using CK or troponin (16). In the present study, by multivariable analysis, treatment with overlapping devices was the independent determinant of per-protocol PMI (OR: 5.07, 95% CI: 1.78 to 14.41, p = 0.002), whereas there was overall no significant difference in PMI between the 2 device types (Absorb vs. EES). In the Absorb

FIGURE 4 Anatomic Complication Assessed by Angiography and Periprocedural CB Rise



The figure shows magnitude of post-procedural CB rise—**(A)** CK, **(B)** CK-MB, **(C)** cTn—for the patients with side branch occlusion after percutaneous coronary intervention **(blue bars)** and those with the other anatomical complications **(red bars)**. *Fourteen patients presented with recent myocardial infarction at entry with normalized CK-MB according to the protocol were excluded for post-CB analysis. CB = cardiac biomarkers; CK = creatine kinase; CK-MB = creatine kinase-myocardial band; cTn = cardiac troponin.

arm, the treatment with overlapping was associated with risk of PMI with a 3.59 OR (p = 0.03), whereas in the EES arm, OR was 5.07 (p = 0.28) in the EES arm. The p value for interaction was not significantly different (p = 0.65), suggesting that overlapping is associated with higher risk of MI in both the Absorb and Xience arms. One MI (non-Q-wave) was attributed to definite scaffold thrombosis involving overlapping scaffolds. Of note, in a juvenile porcine model (28), overlapping Absorb scaffolds, compared with nonoverlapping scaffolds, showed delayed healing on histology and optical coherence tomography and slower tissue coverage: the coverage of the overlapping segment was 80.1% and 99.5% at 28 and 90 days after implantation respectively, suggesting that complete coverage in humans may take up to 18 months. Similar findings (29,30)—delayed healing and promotion of inflammation at sites of overlap—have been reported in the atherosclerotic rabbit model implanted with EES, suggesting the general detrimental effect and potential biohazard of overlapping devices. Adjacent implantation of scaffolds instead of true overlapping may circumvent this problem.

STUDY LIMITATIONS. The results of the current substudy are a post-hoc analysis. The study was not powered to detect difference in clinical events such as PMI and per-protocol definition of PMI does not include clinical symptoms or electrocardiographic changes. Given the mixture and wide range of troponin assays used across participating hospitals,

TABLE 5 Predictors of Per-Protocol PMI

	Univariate Logistic Regression		Multivariate Model (I, II, III, IV,V and Device Type)	
	OR (95% CI)	p Value	OR (95% CI)	p Value
Patient-related factors				
Age, yrs	1.02 (0.96–1.07)	0.56	–	–
Male	1.21 (0.34–4.37)	0.77	–	–
Body mass index, kg/m^2	0.94 (0.81–1.08)	0.36	–	–
Current smoker	1.71 (0.57–5.11)	0.34	–	–
Hypertension requiring treatment	0.43 (0.15–1.22)	0.11	–	–
Dyslipidemia requiring treatment	0.57 (0.20–1.64)	0.30	–	–
Any diabetes mellitus	0.48 (0.11–2.16)	0.34	–	–
Unstable angina	0.94 (0.26–3.40)	0.93	–	–
Lesion-related factors assessed by angiography				
Pre-procedural diameter stenosis, %	0.98 (0.93–1.02)	0.28	–	–
Pre-procedural minimal lumen diameter, mm	1.38 (0.28–6.72)	0.69	–	–
Pre-procedural reference diameter, mm	0.48 (0.12–1.92)	0.30	–	–
Obstruction length, mm	0.99 (0.92–1.08)	0.85	–	–
Pre-procedural curvature, cm^{-1}	0.20 (0.19–2.16)	0.19	–	–
Lesion-related factors assessed by grayscale IVUS				
Pre-procedural minimal lumen area, mm^2	0.78 (0.35–1.70)	0.53	–	–
Pre-procedural EEM, mm^2	0.99 (0.86–1.16)	0.98	–	–
Pre-procedural mean total plaque area in treated region, mm^2	1.05 (0.88–1.27)	0.58	–	–
Pre-procedural total plaque volume in treated region, mm^3	1.00 (1.00–1.01)	0.22	–	–
Pre-procedural plaque burden in treated region, %	1.03 (0.99–1.07)	0.14	–	–
Lesion-related factors assessed by IVUS-VH				
Pre-procedural dense calcium, mm^2	1.86 (0.15–23.83)	0.63	–	–
Pre-procedural necrotic core, mm^2	1.16 (0.34–3.99)	0.81	–	–
Pre-procedural fibrotic tissue, mm^2	1.33 (0.70–2.51)	0.39	–	–
Pre-procedural fibro-fatty tissue, mm^2	0.92 (0.63–1.34)	0.67	–	–
Treatment-related factors				
Treatment with overlapping devices	5.32 (1.88–15.05)	<0.01	5.07 (1.78–14.41)	0.002
Device type, Absorb vs. EES	0.30 (0.07–1.35)	0.12	3.03 (0.67–13.74)	0.150
Post-dilation	1.18 (0.40–3.50)	0.77	–	–
Bail-out	3.79 (0.45–31.96)	0.22	–	–
Expected balloon diameter of the last balloon, mm	3.06 (0.76–12.33)	0.12	–	–

Dashes indicate that there were no applicable data.

CI = confidence interval; IVUS = intravascular ultrasound; OR = odds ratio; VH = virtual histology; other abbreviations as in Tables 1 and 4.

the proportion of elevated troponin and periprocedural rise could be depended on the proportion of contemporary or sensitive assays compared with conventional troponin assays. The difference in the health care system could influence the long-term clinical outcomes, however, such variances are less relevant to the current analysis focusing on the acute procedural outcomes.

CONCLUSIONS

There were no statistically significant differences in the incidence of CB rise and PMI between Absorb and EES. Overlapping of scaffolds or stents might be a precipitating factor of myocardial injury. Larger randomized trials are currently ongoing to confirm these findings. As demonstrated in the present study, which collected all 3 CB, binary definition of PMI is not only dependent on the selection of CB but also on the thresholds of the CB rise which are arbitrarily chosen.

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PERSPECTIVES

WHAT IS KNOWN? A potential concern exists that a bioresorbable vascular scaffold, compared with newer-generations of DES, might be associated with a higher incidence of periprocedural myocardial injury and PMI.

WHAT IS NEW? Our results confirmed that there were no differences in the incidence of CB rise and PMI between Absorb and EES.

WHAT IS NEXT? Device overlap might be a precipitating factor of myocardial injury.

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KEY WORDS bioresorbable scaffold, cardiac biomarker, device overlap, periprocedural myocardial infarction

APPENDIX For the Protocol and Statistical Analysis Plan as well as supplemental tables and figures, please see the online version of this paper.