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Comparison of post-procedural rise of cardiac biomarkers after implantation of an everolimus-eluting bioresorbable vascular scaffold versus everolimus-eluting metallic stent in patients with long/diffuse LAD disease

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***Abstract*---**Objectives This study sought to evaluate the incidence and 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 Prospective nonrandomized comparative study enrolled 52 patients with stable myocardial ischemia with diffuse/ long LAD lesion for either an everolimus-eluting bioresorbable vascular (BVS) scaffold (22 patients) or an EES (30 patients), 3 types of CB (creatine kinase (CK), creatine kinase-myocardial band (CK-MB), and troponin) were obtained before and after procedure. Per protocol, periprocedural myocardial infarction (PMI) was defined as CK rise >2 the upper limit of normal with CK-MB rise.

Results Incidence of side branch occlusion (SBO) and any anatomic complications assessed by angiography was similar between the 2 treatment arms (SBO: Absorb: 4.5% vs. Xience: 6.7%, p=1; One PMI with acute instent thrombosis occurred in EES group. Dissection occurred in only 1 patient in BVS arm after stent implantation; this event was not associated with elevated cardiac biomarkers. One patient had PMI in BVS arm with no angiographic complications to explain it. Stent length and preprocedural TIMI flow grade were the independent determinants of per-protocol PMI (odds ratio (OR): 1.19, 95% confidence interval (CI): 1.033 to 1.376, P= 0.016; OR: 0.049, 95% CI: 0.002 to 1.22, P= 0.066; respectively). Conclusion: There were no difference in the incidence of CB rise and PMI between Absorb and EES. Stent length and preprocedural TIMI flow were the independent determinants for myocardial injury.

***Keywords*---**LAD disease, cardiac biomarkers, implantation, everolimus-eluting metallic stents.

Introduction

The bioresorbable everolimus-eluting scaffold (Absorb, Abbott Vascular, and Santa Clara, California) was developed to provide a novel approach to treat coronary artery stenosis with transient vessel support and drug delivery. (1) Effective from May 31, 2017, the device is only available in clinical registry setting at selected sites or institutions that plays a pivotal role in the monitoring of this technology. (2) Subsequently post marketing registries are being initiated in Europe and India to monitor implantation techniques for the Absorb dissolving stent, these E.U. registries will parallel post approval observational studies and training being conducted in other parts of the world including the ABSORB IV study of 3,000 patients in the united states to conform the effect of current implantation technique on clinical outcomes working on a small strut device; 99 micron strut bioresobable stent for reducing target lesion failure in the first year. The Absorb BVS was 150 microns, which caused delivery issues and problems in small vessels. (2)

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. (3) 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) 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). (4)

In a nonrandomized comparison using historical data, the Absorb scaffold was associated with a higher incidence of post-procedural SBO than EES was. 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 PMI than newer-generations of DES are. (5) The ABSORB III trial demonstrated noninferior rates of target lesion failure (TLF) (cardiac death, target vessel myocardial infarction [TVMI], or ischemia-driven target lesion revascularization) at 1 year in 2,008 patients with coronary artery disease randomized to BVS versus cobalt-chromium everolimus-eluting stents (EES). (6)

The ABSORB IV trial — a rigorously controlled study designed to overcome problems that may have marred results of earlier trials of the *Absorb* everolimus-eluting BVS (Abbott Vascular) — showed Absorb was noninferior to Abbott's metal *Xience* everolimus-eluting stent for the primary end point of TLF at 30 days and the secondary end points of TLF and angina at 1 year. (7) But despite the more careful patient selection and improved implantation techniques used in ABSORB IV, both 1-month and 1-year rates of myocardial infarction (MI), ischemia-drive target lesion revascularization, and device thrombosis were all higher with Absorb. Therefore, the aim of this study is to investigate the incidence and mechanism of post-procedural CB rise following Absorb scaffold versus metallic EES implantation.

Methods

This is a prospective nonrandomized comparative study compared the safety and efficacy of the Absorb versus the EES in patients with stable or unstable angina due to diffuse/ long LAD lesion measured > 20 mm**.** Fifty two patients admitted for elective PCI to LAD between January 2016 and May 2017. They were divided into 2 groups; 22 patients in group A (BVS) and 30 patients in group B (DES).

Angiographic assessment

SBO, occurrence of no-reflow, abrupt closure, dissection, and distal embolization in main and side branches were assessed qualitatively at pre-procedure, after balloon pre-dilation, after device deployment, and after final balloon inflation. SBO was defined as a reduction in the TIMI flow grade 0 to 1. 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 assessed in at least 2 different projections.

Blood sampling

The protocol mandated that blood sampling for cardiac enzymes was to be collected within 6 h before the index percutaneous coronary intervention procedure and at 8 h after the procedure or at hospital discharge which is at least 6 h after procedure.

Definition of periprocedural myocardial infarction

In this study protocol, MI was defined according to the modified World Health Organization which is defined by elevation of total CK to >2× ULN along with elevated or “positive” CK-MB.(8)

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 median (IQR) and were compared by nonparametric test as the data was not normalized. 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). A 2-sided p value of <0.05 was considered to indicate statistical significance.

Results

Patient demographics were comparable in both arms (Table 1). The lesion characteristics such as type B /C lesions, bifurcation lesions, eccentricity, tortuosity, thrombus, and calcification were similar between the 2-treatment arms.

Table 1
Baseline Demographic Data and Angiographic Characteristics in Patients

	BVS n=22	DES n=30	P value
Age, median(IQR)	58 (50-62)	58 (55-62)	0.59
Body Mass Index (BMI), median(IQR)	25.3 (23.1-26.1)	25.32 (24.2-28.7)	0.36
Male, n(%)	17 (77.3)	21 (70)	0.56
Current smoker, n (%)	17 (77.3)	15 (50)	0.046
Hypertension (HTN), n (%)	15 (68.2)	24 (80)	0.33
Dyslipidemia requiring treatment, n (%)	17 (77.3)	17 (56.7)	0.12
Diabetes Mellitus (DM), n (%) IDDM NIDDM	12 (54.5) 3 (13.6) 9 (40.9)	20 (66.7) 6 (20) 14 (46.7)	0.38
Family history of coronary artery disease, n (%)	11 (50)	17(56.7)	0.63
Previous history of MI, n (%)	1(4.5)	1 (3.3)	1.0
ACC/AHA lesion complexity, n (%) B1 B2 C	 1 (4.5) 7 (31.8) 14 (63.6)	 1 (4.5) 7 (23.3) 22 (73.3)	0.77
TIMI flow grade 2 3	 0 22 (100)	 5 (16.7) 25 (83.3)	0.065
Calcification, n (%) Absent Mild Moderate	 10 (45.5) 12 (54.5) 0	 15 (50) 11 (36.7) 4 (13.3)	0.17
Tortuosity, n (%) Absent	 4 (18.2)	 4 (13.3)	0.87

Mild Moderate	10 (45.5) 8 (36.4)	14 (46.7) 12 (40)	
Eccentric, n (%)	1 (4.5)	5 (16.7)	0.23
Thrombus, n	0	0	-
Bifurcation, n	0	0	-
Percentage of diameter stenosis, median	85	85	0.54
Obstruction lesion length, mm, median	24.5	25	0.14

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

In both groups, there was statistically significant increase in CK and CK MB, but no increase in troponin. However, this increase was not clinically significant. (table 2) Comparing the rise in cardiac enzymes between both groups showed a statistically significant difference in CK MB (BVS< DES). However, this difference was not clinically significant (less than 2 ULN). (table 3. Figure 1)

Table (2): Comparison between the study groups as regards cardiac enzymes

	BVS			DES		
	Median (IQR) before procedure	Median (IQR) after procedure	*p	Median (IQR) before procedure	Median (IQR) after procedure	*p
CK	88 (70-110)	88 (80-119)	0.031	80 (70-97)	96 (75-130)	0.003
CK MB	19 (14-20)	20 (18-22)	0.005	15 (14-18)	19 (18-23)	<0.001
Troponin	.09 (0.08-0.12)	.09 (0.08-0.1)	0.97	.07 (0.05-0.09)	.08 (.05-0.09)	0.44

Table (3): Comparison between cardiac enzymes in both study groups

	CK			CK MB			Troponin		
	BVS	DES	P value	BVS	DES	P value	BVS	DES	P value
Δ cardiac enzymes, median	5.0 (-2,15)	8.5 (-2,29)	0.17	1.5 (-1,3)	4.0 (2,6)	0.008	0.00 (-0.01,0.01)	0.00 (-0.02,0.02)	0.8
Δ% cardiac enzymes, median	6.62 (-2.4,21.4)	13.3 (-2.86,42.03)	0.37	8.61 (-4.35,20)	26.67 (8.7,66.67)	0.01	0 (-18.18,66.67)	0 (-9.09,12.5)	0.9
> 2 ULN	2 (9.1)	3 (10)	1.0	0	1 (3.3)	1.0	0	1 (3.3)	1.0
> 5 ULN	0	0	-	0	0	-	0	0	-

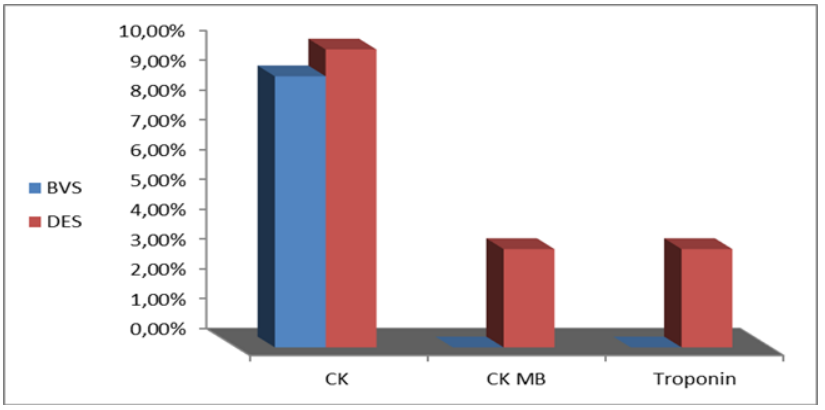

Figure 1: Comparison between cardiac enzymes > 2 ULN in both study groups

The frequencies of "angiographic complications" are shown in Table 4. In the present analysis, incidence of any "angiographic complications" and SBO was similar between the 2 treatment arms (any complications: Absorb: 9% vs. EES: 10%, p = 1.0; SBO: 4.5% vs. 6.7%, p = 1). The incidence of SBO in the obstruction segment was lower in the Absorb arm than in the EES arm, although there were no statistically significant differences.

Table 4
Anatomic Complications Assessed by Angiography

		BVS	DES	P value
		Number (%)	Number (%)	
SBO	Incidence of SBO	1 (4.5)	2 (6.7)	1
	Inside stent	1 (4.5)	2 (6.7)	0.36
	Outside stent	0	0	-
	After predilation	0	0	-
	After device implantation	1 (4.5)	2 (6.7)	0.12
	After procedure	0	0	-
	Improved after nitroglycerin	1 (4.5)	1 (3.3)	0.63
Abrupt closure		0	0	-
Distal embolization		0	0	-
Coronary perforation		0	0	-
Flow-limiting dissection		0	0	-
Coronary dissection after pre-dilation		0	0	-
Coronary dissection after device implantation		1 (4.5)	0	0.42
Acute instent thrombosis		0	1 (3.3)	1
Disruption of collateral flow		0	0	-

Values are % (n).
EES = everolimus-eluting stent(s); SBO = side branch occlusion.

Per-protocol PMI (World Health Organization definition) occurred in 2of 22 patients (9.1%) in the Absorb arm and 3 of 30patients (10%) in the EES arm (p =

1.0). Incidence of PMI per protocol according to “anatomic complications” assessed by angiography was similar between the 2 treatment arms (Table 5).

Table 5
Incidence of Per-Protocol PMI According to Anatomic Complications Assessed by Angiography

	Absorb (n = 22)	EES (n = 30)	p Value
Per-protocol PMI	9.1(2)	10 (3)	1
SBO	4.5 (1)	6.7 (2)	1
SBO after pre-dilation	0 (0)	0 (0)	1.00
SBO after device implantation	4.5 (1)	6.7 (2)	0.12
SBO improvement after NTG	4.5(1)	3.3 (1)	0.63
SBO after procedure	0 (0)	0 (0)	1.00
Type 2: angiographic other complication	4.5(1)	3.3 (1)	0.63
Abrupt closure	0 (0)	0(0)	1.00
Distal embolization	0 (0)	0 (0)	1.00
Coronary perforation	0 (0)	0 (0)	1.00
Coronary dissection after pre-dilation	0 (0)	0 (0)	1.00
Coronary dissection after device implantation	4.5(1)	0 (0)	0.42
Acute instent thrombosis	0 (0)	3.3 (1)	1.00
Disruption of collateral flow	0 (0)	0 (0)	1.00
Nonindentifiable mechanism causes	4.5 (1)	0 (0)	0.42

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; SBO = side branch occlusion.
In the multivariable analyses, stent length and preprocedural TIMI flow grade were the independent determinants of per-protocol PMI (odds ratio (OR): 1 . 1 9 , 95% confidence interval (CI): 1.033 to 1.376, P= 0.016; OR: 0.049, 95% CI: 0.002 to 1.22, P= 0.066; respectively)

Discussion

The present study is the first nonrandomized clinical trial in Egypt to analyze the difference in frequencies of PMI and CB rise after implantation of Absorb scaffold or EES. The main findings of this study revealed insignificant statistical difference between BVS and EES regards PMI that occurred in 5 patients (9.6%); 2 of 22 patients (9.1%) in the Absorb arm and 3 of 30 patients (10%) in the EES arm (p =1.0). Our results of PMI are higher than similar studies. In the ABSORB II trial, PMI incidence was 2.99% and there was no significant difference between

both stent types too (BVS: 3.9% vs EES: 1.2%, p= 0.16). (9) In ABSORB cohort B trial (45 patients with single BVS), PMI occurred in only 1 patient (2.2%). (10) Our PMI rates were higher than ABSORB II trial possibly because of higher percentage of smokers, DM, family history of CAD and diameter stenosis percentage in both BVS and DES. We also had higher PMI than Cohort B study as we treated longer lesions ≥ 20 mm (vs < 14 mm in Cohort B) and we had higher percentage of smokers and DM as well.

In our study, the incidence of any anatomic procedural complications was similar between the two treatment arms (9% in BVS vs 10% in EES, p=1.0). SBO was responsible for 60% of PMI (3 patients) with no significant differences between both groups (4.5% in BVS vs 6.7% in EES, p=1.0). One PMI with acute instent thrombosis occurred in EES which responded to intracoronary eptifibatide. Dissection occurred in only 1 patient in BVS arm after stent implantation and was sealed with another DES; this event was not associated with elevated cardiac biomarkers. One patient had PMI with no angiographic complications to explain it. The other studies showed higher rate of anatomic complications with no difference between BVS and EES as well. SBO and any anatomic complications assessed by angiography were similar between the 2 treatment arms in a study by Ishibashi Y et al (any anatomic complication: 16.4% vs19.9%, p = 0.39, SBO: 5.3% vs 7.6%, p = 0.07). PMI was caused by SBO in 66.7% whereas 20.0% were due to other anatomical complications; (13.3% due to distal embolization and coronary dissection in the BVS arm and 6.67% due to abrupt closure in the EES arm. (11)

On contrary, in a previous publication comparing data of the Absorb Extend registries (435 patients) with a matched cohort from SPIRIT trials (237 patients), BVS was associated with a higher SBO rate than EES (6% vs 4.1%, p=0.09). The difference was more pronounced with small side branches with an RVD ≤0.5 mm. PMI (according to WHO definition) was higher in SBO group than in non- SBO group (6.5% vs 0.5%, p< 0.01). 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 (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. (12) However, our study showed the opposite: a lower but non significant SBO rate in the Absorb group.

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. In the present study, stent length and TIMI grade were the only independent determinants of PMI by multivariate analysis; (OR: 1.19, 95% CI: 1.033 to 1.376, p=0.016; for stent length, and OR: 0.049, 95% CI: 0.002 to 1.22, p=0.066 for TIMI grade, respectively) Similarly, SPIRIT IV trial reported that total stent length was a strong predictor of PMI (OR: 1.03, 95% CI: 1.02 to 1.04, *P*<0.01) but they added the number of treated lesions as another strong predictor of PMI (OR: 1.83, 95% CI: 1.41 to 2.37, *P*<0.001). (8)

Study limitations

In the current study, the number of patients was relatively small in comparison with other studies and trials due to withdrawal of the stent from the market starting from May 2017. The study was not powered to detect difference in clinical events as our protocol definition of PMI did not include clinical symptoms or electrocardiographic changes. The present study relied on a nonrandomized comparison of different study populations. Consequently, there were significant differences in several baseline characteristics, and the possibility of results being affected by unknown confounding factors cannot be excluded. The current study enrolled a highly selected patient population with mainly stable CAD and single de novo non-complex target lesions. As such, the study results should not be generalized to complex lesions which are often encountered in clinical practice, such as bifurcations, heavily calcified lesions, diffuse disease and thrombus. The incidence of SBO would be expected to be higher in more complex lesions. However, this may be acceptable as the aim of study was to assess only the safety and efficacy of BVS. Long term follow up is required to determine whether the temporary scaffolding properties of BVSs are associated with similar or better outcomes compared with a permanent metallic DES particularly after the complete disappearance of the BVS struts which is anticipated in 2-3 years.

Conclusion

BVS and DES stents have similar rates of PMI that is determined mainly by stent length and preprocedural TIMI flow.

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