Two-year Clinical Outcomes of Patients Treated with Overlapping Absorb Scaffolds: An Analysis of the ABSORB EXTEND Single-Arm Study

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ABSTRACT

Background: Pre-clinical data showed that overlapping (OVP) scaffolds might result in delayed healing and strut coverage compared to non-OVP scaffold segments. Furthermore, OVP in patients could result in increased peri-procedure myocardial infarction (MI) rate secondary to side branch occlusion; however, little is known whether this may have an impact on long-term clinical outcomes.

Methods: ABSORB EXTEND is a prospective, single-arm, open-label clinical study in which 812 patients were enrolled at 56 sites. In the present study, we compared the immediate and two-year clinical outcomes of patients with OVP scaffolds (n=115) to those of patients with non-OVP scaffolds (n=697). The primary objective was the comparison of MACE (cardiac death, MI and ischemic-driven TLR) and scaffold thrombosis (ST) rates up to 2 years.

Results: Baseline clinical and angiographic characteristics were comparable between cohorts except for longer lesions in the OVP patients as expected (16.7 ± 7.3 vs. 11.6 ± 4.4 mm, $p < 0.0001$), higher lesion complexity (B2) and numerically smaller vessel size. In-hospital, there was a marked increase in MACE in the OVP cohort (7.0% vs. 0.9%, $p = 0.002$), exclusively driven by a higher rate of peri-procedure MI (7.0% vs. 0.9%, $p = 0.002$). Long-term MACE did not significantly differ between groups (10.4% in the OVP cohort vs. 6.6% in the no-OVP group, $p = 0.1$) with comparable rates of cardiac death (0.9% vs. 1.2%, $p = 1.0$) and ischemia-driven TLR (1.7% vs. 2.5%, $p = 1.0$). Cumulative incidence of MI was higher in the OVP cohort (7.8% vs. 3.0%, $p = 0.02$). Of note, the rate of MI between hospital discharge and two-year follow-up was lower in the OVP cohort (0.8% vs. 2.1%, $p = 0.04$). Cumulative incidence of definite/probable ST was relatively low and comparable between groups (1.8% vs. 1.5%, $p = 0.7$).

Conclusions: In this low-to-moderate complex population treated with the ABSORB scaffold the OVP group showed a higher incidence of peri-procedure MI with no immediate or long-term increase in cardiac death, TLR or ST.

Key words: ABSORB, overlapping, MACE, single arm study.

Introduction

It is well established in the literature that metallic stent overlapping (OVP) is associated with higher peri-procedural myocardial infarction (MI), probably due to more side branch occlusion along the treated segment, an event linked also to the device design and strut thickness and width^{1,2}.

The advent of metallic drug-eluting stents (DES) increased the concern related to the double layer of polymer and double dose of the anti-proliferative drug accrued in the OVP segments. Finn et al. analyzed rabbit models treated with 1st-generation DES (Cypher™ [Cordis Corporation, NJ, USA] and Taxus™ [Boston Scientific, MA, USA]) and their analogous bare-metal stents (BxVelocity™ [Cordis Corporation] and Express™ [Boston Scientific]) and showed that, compared with bare-metal stents, 1st-generation DES further delay arterial healing and promote inflammation at sites of OVP³. Newer-generation DES, with thinner struts, open-cell design and more biocompatible or even biodegradable polymer coatings, contributed to minimize the negative impact of OVP and have been proven to be safer than 1st-generation DES^{4,5}.

In theory, the recent introduction of BVS has made OVP more attractive, since these devices will be ultimately absorbed and the functionality of the treated segment should be potentially restored. Nonetheless, it is important to keep in mind that the current generation of BVS is still bulky with strut thickness and width of about 150 µm and 200 µm, respectively, which are higher than those of the 1st-generation DES and may affect acute and long-term outcomes of this novel technology. In the present manuscript, we sought to compare acute and two-year outcomes of patients treated with ABSORB BVS with and without OVP scaffolds.

Methods

Study Design and Population

In the present analysis, we included all patients enrolled in the ABSORB EXTEND study. For comparison purposes, the entire population was divided according to the presence or not of OVP.

The details of the ABSORB EXTEND trial have been described elsewhere⁶. In brief, this was a prospective, single-arm, open-label clinical trial that enrolled 812 patients at 56

international sites outside of the US. Target arteries should have a reference vessel diameter (RVD) ≥ 2.0 mm and ≤ 3.8 mm, a maximum lesion length of ≤ 28 mm, a diameter stenosis $\geq 50\%$ and $< 100\%$. A maximum of two *de novo* native coronary artery lesions could be treated, each located in a different major epicardial vessel. Major exclusion criteria included a recent MI (< 72 hours before the index procedure) and target lesions located in the left main or within an arterial or saphenous vein graft. Also excluded were lesions with excessive tortuosity and/or heavy calcification.

Abbott Vascular (Santa Clara, CA) funded the study. The research ethics committee of each participating institution approved the protocol and all enrolled patients provided written informed consent before inclusion. The study is registered on clinicaltrials.gov (unique identifier NCT01023789).

Study Device

The study device (Abbott Vascular, Santa Clara, CA) is the same as that used in the ABSORB Cohort B trial, and has been described in detail previously^{7,8}. In brief, the balloon expandable Absorb BVS is comprised of a poly L-lactide (PLLA) backbone, coated with a matrix composed of the antiproliferative drug everolimus (Certican® Novartis Pharmaceuticals Corporation, Basel, Switzerland) and the polymer poly (D-lactide) (PDLLA) in a 1:1 ratio to form an amorphous drug-eluting coating matrix containing 100 μg everolimus/ cm^2 . Both PLLA and PDLLA are fully bioresorbable; PDLLA is expected to be completely absorbed by the body in 9 months and PLLA in approximately 24-36 months. During the resorption process, ester bonds in the PLLA and PDLLA chains are hydrolyzed, and small particles (≤ 2 μm in diameter) are phagocytosed by macrophages. The ultimate degradation product of both PLLA and PDLLA is lactic acid, which is biologically ubiquitous and metabolized via the Krebs cycle⁹.

Study Procedure

Patients were enrolled through an interactive voice response system (Oracle America, Inc. Woburn, MA), following confirmation of angiographic inclusion criteria and delivery of the Absorb BVS device beyond the guiding catheter. Enrolled patients were to remain in the study until completion of the required follow-up period.

A maximum of two *de novo* native coronary artery lesions could be treated, each located in a different major epicardial vessel. The recommended range for target vessel diameter was assessed in terms of online quantitative coronary angiography (QCA) or

intravascular ultrasound parameters of distal Dmax and proximal Dmax, which refer to the maximum lumen diameter evaluated at the distal and proximal ends of the target segment to be scaffolded, respectively. Planned OVP of scaffolds was permitted in lesions >22 mm and ≤28 mm in length, with an OVP ranging between 1 mm and 4 mm. Although not mandatory, the “scaffold-to-scaffold” implantation technique was recommended to minimize OVP, which was achieved by placing the balloon marker of the proximal scaffold just before the scaffold marker of the distal scaffold¹⁰.

All target lesions were to be treated using standard interventional techniques with mandatory predilation and scaffold implantation at a pressure not exceeding the balloon rated burst pressure. Postdilatation was left to the discretion of the investigator; however, if performed, was to be done with a non-compliant balloon sized to fit within the boundaries of the scaffold (≤0.5mm of the nominal scaffold diameter).

All patients enrolled in the study were to be pre-treated with a loading dose of ≥300 mg of clopidogrel and ≥300 mg of aspirin, followed by 75 mg of clopidogrel daily for a minimum of 6 months and ≥75 mg of aspirin daily indefinitely.

Source document verification

Source document verification (SDV) was routinely performed in 100% of all reported events and 100% of patients through 30-day follow-up. Subsequently, SDV was performed in a random 20% of patients for the remaining follow-up visits.

Follow-up

Assessment of anginal status, data collection of adverse events, details of any subsequent coronary interventions, and use and changes in concomitant medications were collected at 30 days (±7 days), 180 days (±14 days) and at 1 and 2 years (± 28 days).

Study Endpoints and Definitions

In addition to acute success, which is comprised of clinical device (analyzed on a per lesion basis) and clinical procedure success (analyzed on a per subject basis), endpoints include the comparison of adjudicated scaffold thrombosis (ST), cardiac death, MI (target and non-target vessel), and revascularization (target lesion revascularization [TLR]/target

vessel revascularization [TVR]/all revascularizations) rates. The composite rates of ischemia-driven major adverse cardiac events (ID-MACE), ischemia-driven target vessel failure (ID-TVF), ischemia-driven target lesion revascularization (ID-TLR) and ischemia-driven target vessel revascularization (ID-TVR) were also compared between patients with and without OVP.

An independent Clinical Event Committee (CEC) adjudicated all study endpoint events according to either protocol definitions and/or the Academic Research Consortium (ARC) definitions. All adverse events were reported to an independent Data and Safety Monitoring Board (DSMB), which reviewed the data to identify any safety issues related to the conduct of the study.

Clinical device success was defined as successful delivery and deployment of the clinical investigation scaffold at the target lesion and successful withdrawal of the scaffold delivery system with attainment of a final residual stenosis <50% by QCA or by visual estimation if QCA was unavailable. Standard predilation and postdilatation balloon catheters (if applicable) could be used. Bailout patients were included as device success only if the above criteria for clinical device success were met.

Clinical procedure success was defined as successful delivery and deployment of the clinical investigation scaffold at the target lesion and successful withdrawal of the scaffold delivery system with attainment of a final residual stenosis of <50% by QCA or by visual estimation if QCA was unavailable, and/or using any adjunctive device without the occurrence of ID-MACE during hospital stay with a maximum of first seven days post index procedure. In a dual lesion setting, both lesions must have met clinical procedure success.

Cardiac death was defined as any death due to proximate cardiac cause (e.g., MI, low-output heart failure, fatal arrhythmia). Unwitnessed death and death of unknown cause were classified as cardiac death. This included all procedure-related deaths comprising those related to concomitant treatment.

Classification and criteria for MI diagnosis were defined according to the per protocol definition. Q-wave MI was the development of a new, pathological Q wave. Non-Q-wave MI was elevation of CK levels to $\geq$ two times the upper limit of normal with elevated CK-MB in the absence of new pathological Q waves.

Revascularization events were defined as: a) ID-MACE, composed of cardiac death, MI (Q-wave and non-Q-wave) and ID-TLR by CABG or PCI; b) ID-TVF, composed of cardiac death, MI (Q-wave and non-Q-wave); c) ID-TVR by CABG or PCI.

ID-TLR was defined as any repeat percutaneous intervention of the target lesion or bypass surgery of the target vessel with either positive functional ischemia study, ischemic symptoms and angiographic minimal lumen diameter stenosis $\geq 50\%$ by core laboratory QCA or revascularization of a target lesion with diameter stenosis $\geq 70\%$ by core laboratory QCA without either ischemic symptoms or a positive functional study.

ID-TVR was defined as any repeat percutaneous intervention or surgical bypass of any segment of the target vessel with either positive functional ischemia study or ischemic symptoms and an angiographic minimal lumen diameter stenosis $\geq 50\%$ by core laboratory or revascularization of a target vessel with diameter stenosis $\geq 70\%$ by core laboratory QCA without either ischemic symptoms or a positive functional study.

ST was categorized as acute (<1 day), subacute (1-30 days) and late (>30 days), and was defined according to the ARC guidelines¹¹ as follows: definite, acute coronary syndrome and angiographic or pathologic confirmation of scaffold thrombosis; probable, unexplained death ≤ 30 days or target vessel MI without angiographic information; and possible, unexplained death >30 days after scaffold placement.

Statistical Analysis

The sample size for ABSORB EXTEND rather than being defined based on an endpoint hypothesis was chosen to provide information on device performance and should be seen as hypothesis generating. All analyses were performed on the per treatment evaluable population.

For the descriptive statistics, categorical data are presented as counts and percentages and continuous variables are presented as mean $\pm$ standard deviation (SD). Categorical variables were compared by the Chi-square test or Fisher's test when the Cochran's rule was not met. Continuous variables were compared by the Student *t* test. Time-to-event MACE is presented as a Kaplan-Meier curve.

To determine the independent predictors of MACE, TLR, MI and ST among patients treated with the ABSORB BVS, a multivariable logistic regression model was built using a stepwise (forward/backward) procedure, with independent variables entered into the model at the 0.20 significance level and removed at the 0.10 level. Variables were eligible for inclusion in the multivariable logistic regression model-building process if the variable was present for 90% of the subjects in the analyses, they had a p-value <0.2 from the univariable

analysis, and, if they highly correlated with another variable ($r > 0.5$ and $p < 0.05$), had the higher level of significance. Presence of OVP was included in the model.

A two-tailed p value < 0.05 was considered statistically significant. However, since p values presented here are for exploratory analysis only, they should therefore be interpreted cautiously.

RESULTS

Of the 812 patients (874 lesions) enrolled in the ABSORB EXTEND study, 115 (128 lesions, 14.2%) were treated with OVP. Patients had a mean age of 61 years and were predominantly men in both cohorts. Baseline clinical demographics (Table 1) did not significantly differ between patients with and without OVP, except for the initial clinical presentation, with stable coronary disease more prevalent among patients treated with OVP, while patients without OVP had more frequently acute coronary syndrome as the initial presentation.

Table 2 displays the relevant angiographic clinical characteristics. As expected, lesions in the OVP cohort were longer with a higher prevalence of increased complexity (B2 according to ACC/AHA classification) (66% vs. 38%, $p < 0.01$). Predilation was performed in almost all patients in both cohorts, while postdilation was more frequently performed among patients with OVP (77.4% vs. 68.2%, $p = 0.05$).

Procedure success was comparable between the cohorts. However, clinical success was slightly higher among patients without OVP, mainly due to more peri-procedure MI detected among them (94.3% vs. 90.4%, $p < 0.001$) (Table 3).

Notably, if we consider the current definition of good scaffold implantation (PSP = patients with pre-dilatation, and QCA RVD ≥ 2.25 mm ≤ 3.5 mm, and post-dilatation performed at ≥ 18 atm, with post-dilatation balloon diameter $>$ nominal scaffold diameter but $\leq$ nominal scaffold diameter + 0.5mm), this was achieved in only 20% of the OVP cohort and 13.7% of the control group ($p = 0.02$).

Incidence of other MACE components, including cardiac death and vessel revascularization as well as ST, TLF and TVF were comparable between groups at two-year follow-up (Tables 4 and 5). Of note, there was no case of definitive ST in the OVP cohort in the first year after the procedure, while in the non-OVP group a 1.1% rate was observed in the same period.

Figure 1 shows the temporal distribution of MACE between the two groups. As noticed, most of the adverse events in the OVP population occurred within the in-hospital period.

There was no independent predictor of MACE in the overall population. However, a trend toward more events was observed among patients with small reference vessel diameter (OR 0.90 IC95% [0.01, 1.04], $p=0.054$) and in those with prior MI history (OR 3.18 IC 95% [0.93, 10.84], $p=0.064$). The only independent predictor of MI was a prior history of MI (OR 5.15, IC95% [1.42, 18.70], $p=0.012$). Independent predictor of a new revascularization procedure was treatment of multivessel disease (OR 6.16, IC 95% [1.72, 22.11], $p=0.005$). There were no independent predictors of ST or death.

DISCUSSION

To the best of our knowledge, this is the largest long-term follow-up of patients undergoing treatment with OVP scaffolds. The results of this study should be interpreted with caution due to the differences in baseline lesion characteristics between the two groups. The main findings are the following: 1) there was a higher incidence of peri-procedure MI in the OVP patients who, however, had longer lesions, numerically smaller RVD, and greater B2 lesion complexity and; 2) two-year MACE including cardiac death, ID-TLR and ST were similar between these low-to-moderate complexity patient groups.

Treatment of long lesions with BVS frequently require scaffold OVP, since the maximum length of the commercially available devices is 28 mm. Development of longer devices, although possible, would face one of the current limitations of this technology. Since the device should not be postdilated more than 0.5 mm than its nominal diameter to prevent the risk of acute disruption, the development of longer scaffolds would make difficult to accommodate vessel tapering, which often results in differences >0.5 mm between the proximal and distal reference vessel segment in the scenario of long lesions.

Furthermore, it is not always technically easy or feasible to advance such bulky devices into each other to achieve OVP segments, especially when treating tortuous, and/or calcified vessels or when an unplanned OVP at the distal edge of a previously implanted BVS is needed. Use of tension/pressure to advance the device may result in dislodgement and damage to its integrity.

Once OVP is achieved, a segment with a 300-400- μ m layer of polymer will be created, which might impair local flow dynamic¹² and increase the risk of side branch occlusion. Muramatsu et al. have already demonstrated that deployment of the Absorb BVS

without OVP was associated with a higher incidence of post procedural side-branch occlusion when compared with a thin-strut new-generation DES (Xience V, Abbott Vascular)¹³. Despite the lack of abundant clinical data, we speculate that these findings may be aggravated in segments of double layers of BVS. In a recent publication of the ABSORB II trial, Ishibashi et al. reported that BVS OVP was the single independent predictor of per protocol peri-procedure MI (OR: 5.07, 95% CI: 1.78 to 14.41, $p=0.002$)¹⁴. A previous analysis of the ABSORB EXTEND study database pointed also to OVP as a predictor of peri-procedure MI¹⁵. The present analysis confirms this finding that is probably related to the occlusion of more side branches along the longer segments treated with OVP.

Regarding long-term outcomes, the presence of scaffold OVP has also been associated with negative findings, at least in the pre-clinical scenario. Farooq et al. examined 41 OVP performed with the ABSORB BVS or the everolimus-eluting metallic DES in pigs and showed that strut coverage at 28 days was delayed in the OVP scaffolds because of the overlay configuration of the thicker ABSORB BVS struts. However, at 90 days OVP of both ABSORB BVS and metallic DES showed comparable strut coverage¹⁶. It is noteworthy that the pre-clinical observation of delayed strut coverage did not translate into an increased occurrence of serious untoward events in our clinical evaluation. This might be related to adherence to the dual antiplatelet therapy (roughly 96% at 6 months and 79% at one year, for both groups), the frequent optimization of the procedure with postdilation (especially in the OVP group) and the low-to-moderate complexity of the enrolled population. Furthermore, in our present study, use of OVP also did not turn out as an independent predictor of MACE, TLF, MI, TLR or ST.

It is also important to bear in mind that this study was conceived and primarily conducted prior to the current recommendations for optimal scaffold deployment, including the endorsement for performing routine postdilation with high-pressure non-compliant balloons within the limits of expansion of the device, as recently published by Ortega-Paz et al.¹⁷.

Recently, Sotomi et al. published the results of 14 patients treated with ABSORB OVP and evaluated with OCT at two years¹⁸. They compared the results in the segments with and without OVP. Notably, lumen area and endoluminal scaffold areas were similar in both segments despite the neointimal area being larger in the overlap segments. The neointimal coverage was essentially fully complete in both non-overlap ($99.4\pm0.8\%$) and overlap segments ($99.8\pm0.4\%$) at two-year follow-up. The flow area in the overlap segments was not different from the flow area in the non-overlap segments, despite the neointimal response

being greater in the overlap segments. Consequently, the treated segments showed a homogeneous lumen area through the scaffold segment. These results might support the feasibility of overlapping scaffolds when needed for longer lesions if acute lumen expansion is achieved in a similar extent as in the non-overlap segments using good implantation techniques.

LIMITATIONS

This post-hoc analysis was performed from a non-randomized study. No correction has been made regarding differences in baseline characteristics between the two comparison groups. These differences could have heavily contributed to the results. The study was underpowered for low-frequency events, like ST. The implantation technique used in the ABSORB Extend was outdated. Indeed, the PSP (vessel predilation, sizing and postdilation) implant strategy is highly recommended and followed today. Finally, the lack of a control arm with a metallic DES does not allow for comparison of the devices.

CONCLUSIONS

In this low-to-moderate complex population treated with the BVS in the ABSORB EXTEND study, scaffold OVP was associated with an increase of peri-procedure MI but without any immediate or long-term effect on cardiac death, TLR or ST occurrence.

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Figure Legend

Figure 1. Cumulative incidence of MACE in patients treated with and without ABSORB overlapping. On the left the two-year curve for both groups and, on the right, the landmark analysis with the in hospital events.

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Table 1. Baseline characteristics of the study patients

Variables	Total N=812 pts	OVP scaffolds N=115 pts	Non-OVP scaffolds N=697 pts	P-value*
Age (years)	61± 4.3	61±4.7	61±3.9	0.71
Gender male, n (%)	603 (74)	82 (71)	523 (75)	0.43
Active smoking, n (%)	468 (58)	66(57)	402 (58)	0.95
Diabetes Mellitus, n (%)		28 (24)	187 (27)	0.58
Hypertension**, n (%)	563 (69)	80 (70)	483 (69)	0.95
Hypercholesterolemia**, n (%)	550 (68)	82 (71)	468 (67)	0.38
CAD in family, n (%)	276 (37)	45 (42)	231 (36)	0.25
Prior MI, n (%)	230 (29)	31 (27)	199 (29)	0.74
Clinical Presentation, n (%)				
- Silent ischemia	49 (6)	9 (8)	40 (6)	0.39
- Stable angina	461 (57)	83 (72)	378 (54)	0.00
- Unstable angina	215 (27)	20 (17)	195 (28)	0.02
- Non STEMI	87 (10)	3 (3)	84 (12)	<0.01

OVP: overlapping
* Between OVP and non OVP
** Requiring medication

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Table 2. Angiographic and procedure characteristics

	Total population N=874 lesions	OVP scaffolds N=128 lesions	Non-OVP scaffolds N=746 lesions	P-value
Vessel treated, n (%)				
- RCA (%)	250 (29)	39 (31)	211 (28)	0.61
- LAD (%)	395 (45)	67 (52)	328 (44)	0.08
- LCX (%)	228 (26)	22 (17)	206 (28)	0.01
Tortuosity >45°, n (%)	26 (3)	6 (5)	20 (3)	0.25
Calcification ≥moderate, n (%)	121 (14)	23 (18)	98 (13)	0.25
Thrombus, n (%)	14 (2)	2 (2)	12 (2)	1.00
Reference vessel diameter, mean ± SD	2.64 ± 0.39	2.59 ± 0.34	2.66 ± 0.39	0.06
Lesion length (mm), mean ± SD	12.33 ± 5.26	16.7± 7.32	11.6± 4.42	<0.001
ACC/AHA lesion classification, n (%)				
- Type A (%)	19 (2)	0 (0)	19 (3)	0.09
- Type B1 (%)	459 (53)	39 (31)	420 (57)	<0.001
- Type B2 (%)	363 (42)	83 (66)	280 (38)	<0.001

- Type C (%)	23 (3)	4 (3)	19 (3)	0.76
Lesion length >20 mm (%)	74 (9)	33 (41/125)	5 (33/734)	<0.001
Predilation, n (%)	872 (99.8)	128 (100%)	744 (99.7)	1.0
Postdilation, n (%)	609 (69.7)	99 (77.4)	510 (68.2)	0.05
Device success, (%)	98.4	97.6	99.1	0.16
Procedure success, (%)	94.3	90.4	98.1	<0.001
Use of dual antiplatelet therapy, %				
- At 30 days	98.8%	98.3%	99.3%	0.26
- At 180 days	96.2%	95.7%	96.6%	0.59
- At 365 days	79%	80.0%	78.0%	0.64
- At 720 days	46.7%	47.8%	45.6%	0.67

Table 3. In-hospital clinical outcomes

	Total population N=812 pts	OVP scaffolds N=115 pts	Non-OVP scaffolds N=697 pts	P-value
NON-HIERARCHICAL MACE, n (%)				
- Cardiac death	0	0	0	N/A
- Myocardial infarction*	14 (1.7)			
- Q-wave MI	0	0	0	N/A
- Non-Q-wave MI	14 (1.7)			
- Ischemia driven TVR	0	0	0	N/A
- Ischemia driven TLR	0	0	0	N/A
HIERARCHICAL, n (%)				
- MACE*	14 (1.7)	8 (7.0)	6 (0.9)	<0.01
- TVF**	14 (1.7)	8 (7.0)	6 (0.9)	<0.01
- TLF***	14 (1.7)	8 (7.0)	6 (0.9)	<0.01

OVP: overlapping; MACE: major adverse cardiac events; MI: myocardial infarction; TVR: target vessel revascularization; TLR: target lesion revascularization; TVF: target vessel failure; TLF: target lesion failure.

*per protocol (please refer to study definition of MI in the methods section)

Table 4. Two-year clinical outcomes

	Total population N=812 pts	OVP scaffolds N=115 pts	Non-OVP scaffolds N=697 pts	P-value
NON-HIERARCHICAL MACE, n (%)				
- Cardiac death	9 (1.1)	1 (0.9)	8 (1.2)	1.0
- Myocardial infarction*	35 (12.3)	10 (8.7)	25 (3.6)	0.02
- Q wave MI	10 (1.2)	2 (1.7)	8 (1.1)	0.6
- Non Q wave MI	25 (3.1)	8 (6.9)	17 (2.4)	0.02
- Ischemia driven TVR	46 (5.7)	1 (0.9)	22 (3.1)	0.2
- Ischemia driven TLR	34 (4.2)	1 (0.9)	18 (2.6)	0.5
HIERARCHICAL, n (%)				
- MACE*	58 (7.2)	12 (10.4)	46 (6.6)	0.1
- TVF**	68 (8.4)	13 (11.3)	55 (7.9)	0.2
- TLF***	57 (7.1)	12 (10.4)	45 (6.5)	0.1

OVP: overlapping; MACE: major adverse cardiac events; MI: myocardial infarction; TVR: target vessel revascularization; TLR: target lesion revascularization; TVF: target vessel failure; TLF: target lesion failure.

*per protocol (please refer to study definition of MI in the methods section)

Table 5. Cumulative two-year scaffold thrombosis

Scaffold thrombosis (%)	Total population N=812 pts	OVP scaffolds N=115 pts	Non-OVP scaffolds N=697 pts	P-value
0-30 days				
- Early definite	4 (0.5)	1 (0.9)	3 (0.4)	0.5
- Early definite/probable	5 (0.6)	2 (1.7)	3 (0.4)	0.1
31-365 days				
- Late definite	3 (0.4)	0	3 (0.4)	1.0
- Late definite/probable	3 (0.4)	0	6 (0.9)	1.0
366-758 days				
Very Late definite	4 (0.5)	0	3 (0.4)	1.0
Very Late definite/probable	4 (0.5)	0	4 (0.6)	1.0

OVP: overlapping.

Figure 1. Cumulative incidence of MACE in patients treated with and without ABSORB overlapping. On the left the two-year curve for both groups and, on the right, the landmark analysis with the in hospital events.

338x166mm (300 x 300 DPI)

Accepted

Two-year Clinical Outcomes of Patients Treated with Overlapping Absorb Scaffolds: An Analysis of the ABSORB EXTEND Single-Arm Study

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ABSTRACT

Background: Pre-clinical data showed that overlapping (OVP) scaffolds might result in delayed healing and strut coverage compared to non-OVP scaffold segments. Furthermore, OVP in patients could result in increased peri-procedure myocardial infarction (MI) rate secondary to side branch occlusion; however, little is known whether this may have an impact on long-term clinical outcomes.

Methods: ABSORB EXTEND is a prospective, single-arm, open-label clinical study in which 812 patients were enrolled at 56 sites. In the present study, we compared the immediate and two-year clinical outcomes of patients with OVP scaffolds (n=115) to those of patients with non-OVP scaffolds (n=697). The primary objective was the comparison of MACE (cardiac death, MI and ischemic-driven TLR) and scaffold thrombosis (ST) rates up to 2 years.

Results: Baseline clinical and angiographic characteristics were comparable between cohorts except for longer lesions in the OVP patients as expected (16.7 ± 7.3 vs. 11.6 ± 4.4 mm, $p < 0.0001$), higher lesion complexity (B2) and numerically smaller vessel size. In-hospital, there was a marked increase in MACE in the OVP cohort (7.0% vs. 0.9%, $p = 0.002$), exclusively driven by a higher rate of peri-procedure MI (7.0% vs. 0.9%, $p = 0.002$). Long-term MACE did not significantly differ between groups (10.4% in the OVP cohort vs. 6.6% in the no-OVP group, $p = 0.1$) with comparable rates of cardiac death (0.9% vs. 1.2%, $p = 1.0$) and ischemia-driven TLR (1.7% vs. 2.5%, $p = 1.0$). Cumulative incidence of MI was higher in the OVP cohort (7.8% vs. 3.0%, $p = 0.02$). Of note, the rate of MI between hospital discharge and two-year follow-up was lower in the OVP cohort (0.8% vs. 2.1%, $p = 0.04$). Cumulative incidence of definite/probable ST was relatively low and comparable between groups (1.8% vs. 1.5%, $p = 0.7$).

Conclusions: In this low-to-moderate complex population treated with the ABSORB scaffold the OVP group showed a higher incidence of peri-procedure MI with no immediate or long-term increase in cardiac death, TLR or ST.

Key words: ABSORB, overlapping, MACE, single arm study.

Introduction

It is well established in the literature that metallic stent overlapping (OVP) is associated with higher peri-procedural myocardial infarction (MI), probably due to more side branch occlusion along the treated segment, an event linked also to the device design and strut thickness and width^{1,2}.

The advent of metallic drug-eluting stents (DES) increased the concern related to the double layer of polymer and double dose of the anti-proliferative drug accrued in the OVP segments. Finn et al. analyzed rabbit models treated with 1st-generation DES (Cypher™ [Cordis Corporation, NJ, USA] and Taxus™ [Boston Scientific, MA, USA]) and their analogous bare-metal stents (BxVelocity™ [Cordis Corporation] and Express™ [Boston Scientific]) and showed that, compared with bare-metal stents, 1st-generation DES further delay arterial healing and promote inflammation at sites of OVP³. Newer-generation DES, with thinner struts, open-cell design and more biocompatible or even biodegradable polymer coatings, contributed to minimize the negative impact of OVP and have been proven to be safer than 1st-generation DES^{4,5}.

In theory, the recent introduction of BVS has made OVP more attractive, since these devices will be ultimately absorbed and the functionality of the treated segment should be potentially restored. Nonetheless, it is important to keep in mind that the current generation of BVS is still bulky with strut thickness and width of about 150 µm and 200 µm, respectively, which are higher than those of the 1st-generation DES and may affect acute and long-term outcomes of this novel technology. In the present manuscript, we sought to compare acute and two-year outcomes of patients treated with ABSORB BVS with and without OVP scaffolds.

Methods

Study Design and Population

In the present analysis, we included all patients enrolled in the ABSORB EXTEND study. For comparison purposes, the entire population was divided according to the presence or not of OVP.

The details of the ABSORB EXTEND trial have been described elsewhere⁶. In brief, this was a prospective, single-arm, open-label clinical trial that enrolled 812 patients at 56

international sites outside of the US. Target arteries should have a reference vessel diameter (RVD) ≥ 2.0 mm and ≤ 3.8 mm, a maximum lesion length of ≤ 28 mm, a diameter stenosis $\geq 50\%$ and $< 100\%$. A maximum of two *de novo* native coronary artery lesions could be treated, each located in a different major epicardial vessel. Major exclusion criteria included a recent MI (< 72 hours before the index procedure) and target lesions located in the left main or within an arterial or saphenous vein graft. Also excluded were lesions with excessive tortuosity and/or heavy calcification.

Abbott Vascular (Santa Clara, CA) funded the study. The research ethics committee of each participating institution approved the protocol and all enrolled patients provided written informed consent before inclusion. The study is registered on clinicaltrials.gov (unique identifier NCT01023789).

Study Device

The study device (Abbott Vascular, Santa Clara, CA) is the same as that used in the ABSORB Cohort B trial, and has been described in detail previously^{7,8}. In brief, the balloon expandable Absorb BVS is comprised of a poly L-lactide (PLLA) backbone, coated with a matrix composed of the antiproliferative drug everolimus (Certican® Novartis Pharmaceuticals Corporation, Basel, Switzerland) and the polymer poly (D-lactide) (PDLLA) in a 1:1 ratio to form an amorphous drug-eluting coating matrix containing 100 μg everolimus/ cm^2 . Both PLLA and PDLLA are fully bioresorbable; PDLLA is expected to be completely absorbed by the body in 9 months and PLLA in approximately 24-36 months. During the resorption process, ester bonds in the PLLA and PDLLA chains are hydrolyzed, and small particles (≤ 2 μm in diameter) are phagocytosed by macrophages. The ultimate degradation product of both PLLA and PDLLA is lactic acid, which is biologically ubiquitous and metabolized via the Krebs cycle⁹.

Study Procedure

Patients were enrolled through an interactive voice response system (Oracle America, Inc. Woburn, MA), following confirmation of angiographic inclusion criteria and delivery of the Absorb BVS device beyond the guiding catheter. Enrolled patients were to remain in the study until completion of the required follow-up period.

A maximum of two *de novo* native coronary artery lesions could be treated, each located in a different major epicardial vessel. The recommended range for target vessel diameter was assessed in terms of online quantitative coronary angiography (QCA) or

intravascular ultrasound parameters of distal Dmax and proximal Dmax, which refer to the maximum lumen diameter evaluated at the distal and proximal ends of the target segment to be scaffolded, respectively. Planned OVP of scaffolds was permitted in lesions >22 mm and ≤28 mm in length, with an OVP ranging between 1 mm and 4 mm. Although not mandatory, the “scaffold-to-scaffold” implantation technique was recommended to minimize OVP, which was achieved by placing the balloon marker of the proximal scaffold just before the scaffold marker of the distal scaffold¹⁰.

All target lesions were to be treated using standard interventional techniques with mandatory predilation and scaffold implantation at a pressure not exceeding the balloon rated burst pressure. Postdilatation was left to the discretion of the investigator; however, if performed, was to be done with a non-compliant balloon sized to fit within the boundaries of the scaffold (≤0.5mm of the nominal scaffold diameter).

All patients enrolled in the study were to be pre-treated with a loading dose of ≥300 mg of clopidogrel and ≥300 mg of aspirin, followed by 75 mg of clopidogrel daily for a minimum of 6 months and ≥75 mg of aspirin daily indefinitely.

Source document verification

Source document verification (SDV) was routinely performed in 100% of all reported events and 100% of patients through 30-day follow-up. Subsequently, SDV was performed in a random 20% of patients for the remaining follow-up visits.

Follow-up

Assessment of anginal status, data collection of adverse events, details of any subsequent coronary interventions, and use and changes in concomitant medications were collected at 30 days (±7 days), 180 days (±14 days) and at 1 and 2 years (± 28 days).

Study Endpoints and Definitions

In addition to acute success, which is comprised of clinical device (analyzed on a per lesion basis) and clinical procedure success (analyzed on a per subject basis), endpoints include the comparison of adjudicated scaffold thrombosis (ST), cardiac death, MI (target and non-target vessel), and revascularization (target lesion revascularization [TLR]/target

vessel revascularization [TVR]/all revascularizations) rates. The composite rates of ischemia-driven major adverse cardiac events (ID-MACE), ischemia-driven target vessel failure (ID-TVF), ischemia-driven target lesion revascularization (ID-TLR) and ischemia-driven target vessel revascularization (ID-TVR) were also compared between patients with and without OVP.

An independent Clinical Event Committee (CEC) adjudicated all study endpoint events according to either protocol definitions and/or the Academic Research Consortium (ARC) definitions. All adverse events were reported to an independent Data and Safety Monitoring Board (DSMB), which reviewed the data to identify any safety issues related to the conduct of the study.

Clinical device success was defined as successful delivery and deployment of the clinical investigation scaffold at the target lesion and successful withdrawal of the scaffold delivery system with attainment of a final residual stenosis <50% by QCA or by visual estimation if QCA was unavailable. Standard predilation and postdilatation balloon catheters (if applicable) could be used. Bailout patients were included as device success only if the above criteria for clinical device success were met.

Clinical procedure success was defined as successful delivery and deployment of the clinical investigation scaffold at the target lesion and successful withdrawal of the scaffold delivery system with attainment of a final residual stenosis of <50% by QCA or by visual estimation if QCA was unavailable, and/or using any adjunctive device without the occurrence of ID-MACE during hospital stay with a maximum of first seven days post index procedure. In a dual lesion setting, both lesions must have met clinical procedure success.

Cardiac death was defined as any death due to proximate cardiac cause (e.g., MI, low-output heart failure, fatal arrhythmia). Unwitnessed death and death of unknown cause were classified as cardiac death. This included all procedure-related deaths comprising those related to concomitant treatment.

Classification and criteria for MI diagnosis were defined according to the per protocol definition. Q-wave MI was the development of a new, pathological Q wave. Non-Q-wave MI was elevation of CK levels to $\geq$ two times the upper limit of normal with elevated CK-MB in the absence of new pathological Q waves.

Revascularization events were defined as: a) ID-MACE, composed of cardiac death, MI (Q-wave and non-Q-wave) and ID-TLR by CABG or PCI; b) ID-TVF, composed of cardiac death, MI (Q-wave and non-Q-wave); c) ID-TVR by CABG or PCI.

ID-TLR was defined as any repeat percutaneous intervention of the target lesion or bypass surgery of the target vessel with either positive functional ischemia study, ischemic symptoms and angiographic minimal lumen diameter stenosis $\geq 50\%$ by core laboratory QCA or revascularization of a target lesion with diameter stenosis $\geq 70\%$ by core laboratory QCA without either ischemic symptoms or a positive functional study.

ID-TVR was defined as any repeat percutaneous intervention or surgical bypass of any segment of the target vessel with either positive functional ischemia study or ischemic symptoms and an angiographic minimal lumen diameter stenosis $\geq 50\%$ by core laboratory or revascularization of a target vessel with diameter stenosis $\geq 70\%$ by core laboratory QCA without either ischemic symptoms or a positive functional study.

ST was categorized as acute (<1 day), subacute (1-30 days) and late (>30 days), and was defined according to the ARC guidelines¹¹ as follows: definite, acute coronary syndrome and angiographic or pathologic confirmation of scaffold thrombosis; probable, unexplained death ≤ 30 days or target vessel MI without angiographic information; and possible, unexplained death >30 days after scaffold placement.

Statistical Analysis

The sample size for ABSORB EXTEND rather than being defined based on an endpoint hypothesis was chosen to provide information on device performance and should be seen as hypothesis generating. All analyses were performed on the per treatment evaluable population.

For the descriptive statistics, categorical data are presented as counts and percentages and continuous variables are presented as mean $\pm$ standard deviation (SD). Categorical variables were compared by the Chi-square test or Fisher's test when the Cochran's rule was not met. Continuous variables were compared by the Student *t* test. Time-to-event MACE is presented as a Kaplan-Meier curve.

To determine the independent predictors of MACE, TLR, MI and ST among patients treated with the ABSORB BVS, a multivariable logistic regression model was built using a stepwise (forward/backward) procedure, with independent variables entered into the model at the 0.20 significance level and removed at the 0.10 level. Variables were eligible for inclusion in the multivariable logistic regression model-building process if the variable was present for 90% of the subjects in the analyses, they had a p-value <0.2 from the univariable

analysis, and, if they highly correlated with another variable ($r > 0.5$ and $p < 0.05$), had the higher level of significance. Presence of OVP was included in the model.

A two-tailed p value < 0.05 was considered statistically significant. However, since p values presented here are for exploratory analysis only, they should therefore be interpreted cautiously.

RESULTS

Of the 812 patients (874 lesions) enrolled in the ABSORB EXTEND study, 115 (128 lesions, 14.2%) were treated with OVP. Patients had a mean age of 61 years and were predominantly men in both cohorts. Baseline clinical demographics (Table 1) did not significantly differ between patients with and without OVP, except for the initial clinical presentation, with stable coronary disease more prevalent among patients treated with OVP, while patients without OVP had more frequently acute coronary syndrome as the initial presentation.

Table 2 displays the relevant angiographic clinical characteristics. As expected, lesions in the OVP cohort were longer with a higher prevalence of increased complexity (B2 according to ACC/AHA classification) (66% vs. 38%, $p < 0.01$). Predilation was performed in almost all patients in both cohorts, while postdilation was more frequently performed among patients with OVP (77.4% vs. 68.2%, $p = 0.05$).

Procedure success was comparable between the cohorts. However, clinical success was slightly higher among patients without OVP, mainly due to more peri-procedure MI detected among them (94.3% vs. 90.4%, $p < 0.001$) (Table 3).

Notably, if we consider the current definition of good scaffold implantation (PSP = patients with pre-dilatation, and QCA RVD ≥ 2.25 mm ≤ 3.5 mm, and post-dilatation performed at ≥ 18 atm, with post-dilatation balloon diameter $>$ nominal scaffold diameter but $\leq$ nominal scaffold diameter + 0.5mm), this was achieved in only 20% of the OVP cohort and 13.7% of the control group ($p = 0.02$)

Incidence of other MACE components, including cardiac death and vessel revascularization as well as ST, TLF and TVF were comparable between groups at two-year follow-up (Tables 4 and 5). Of note, there was no case of definitive ST in the OVP cohort in the first year after the procedure, while in the non-OVP group a 1.1% rate was observed in the same period.

Figure 1 shows the temporal distribution of MACE between the two groups. As noticed, most of the adverse events in the OVP population occurred within the in-hospital period.

There was no independent predictor of MACE in the overall population. However, a trend toward more events was observed among patients with small reference vessel diameter (OR 0.90 IC95% [0.01, 1.04], $p=0.054$) and in those with prior MI history (OR 3.18 IC 95% [0.93, 10.84], $p=0.064$). The only independent predictor of MI was a prior history of MI (OR 5.15, IC95% [1.42, 18.70], $p=0.012$). Independent predictor of a new revascularization procedure was treatment of multivessel disease (OR 6.16, IC 95% [1.72, 22.11], $p=0.005$). There were no independent predictors of ST or death.

DISCUSSION

To the best of our knowledge, this is the largest long-term follow-up of patients undergoing treatment with OVP scaffolds. The results of this study should be interpreted with caution due to the differences in baseline lesion characteristics between the two groups. The main findings are the following: 1) there was a higher incidence of peri-procedure MI in the OVP patients who, however, had longer lesions, numerically smaller RVD, and greater B2 lesion complexity and; 2) two-year MACE including cardiac death, ID-TLR and ST were similar between these low-to-moderate complexity patient groups.

Treatment of long lesions with BVS frequently require scaffold OVP, since the maximum length of the commercially available devices is 28 mm. Development of longer devices, although possible, would face one of the current limitations of this technology. Since the device should not be postdilated more than 0.5 mm than its nominal diameter to prevent the risk of acute disruption, the development of longer scaffolds would make difficult to accommodate vessel tapering, which often results in differences >0.5 mm between the proximal and distal reference vessel segment in the scenario of long lesions.

Furthermore, it is not always technically easy or feasible to advance such bulky devices into each other to achieve OVP segments, especially when treating tortuous, and/or calcified vessels or when an unplanned OVP at the distal edge of a previously implanted BVS is needed. Use of tension/pressure to advance the device may result in dislodgement and damage to its integrity.

Once OVP is achieved, a segment with a 300-400- μ m layer of polymer will be created, which might impair local flow dynamic¹² and increase the risk of side branch occlusion. Muramatsu et al. have already demonstrated that deployment of the Absorb BVS

without OVP was associated with a higher incidence of post procedural side-branch occlusion when compared with a thin-strut new-generation DES (Xience V, Abbott Vascular)¹³. Despite the lack of abundant clinical data, we speculate that these findings may be aggravated in segments of double layers of BVS. In a recent publication of the ABSORB II trial, Ishibashi et al. reported that BVS OVP was the single independent predictor of per protocol peri-procedure MI (OR: 5.07, 95% CI: 1.78 to 14.41, $p=0.002$)¹⁴. A previous analysis of the ABSORB EXTEND study database pointed also to OVP as a predictor of peri-procedure MI¹⁵. The present analysis confirms this finding that is probably related to the occlusion of more side branches along the longer segments treated with OVP.

Regarding long-term outcomes, the presence of scaffold OVP has also been associated with negative findings, at least in the pre-clinical scenario. Farooq et al. examined 41 OVP performed with the ABSORB BVS or the everolimus-eluting metallic DES in pigs and showed that strut coverage at 28 days was delayed in the OVP scaffolds because of the overlay configuration of the thicker ABSORB BVS struts. However, at 90 days OVP of both ABSORB BVS and metallic DES showed comparable strut coverage¹⁶. It is noteworthy that the pre-clinical observation of delayed strut coverage did not translate into an increased occurrence of serious untoward events in our clinical evaluation. This might be related to adherence to the dual antiplatelet therapy (roughly 96% at 6 months and 79% at one year, for both groups), the frequent optimization of the procedure with postdilation (especially in the OVP group) and the low-to-moderate complexity of the enrolled population. Furthermore, in our present study, use of OVP also did not turn out as an independent predictor of MACE, TLF, MI, TLR or ST.

It is also important to bear in mind that this study was conceived and primarily conducted prior to the current recommendations for optimal scaffold deployment, including the endorsement for performing routine postdilation with high-pressure non-compliant balloons within the limits of expansion of the device, as recently published by Ortega-Paz et al.¹⁷

Recently, Sotomi et al. published the results of 14 patients treated with ABSORB OVP and evaluated with OCT at two years¹⁸. They compared the results in the segments with and without OVP. Notably, lumen area and endoluminal scaffold areas were similar in both segments despite the neointimal area being larger in the overlap segments. The neointimal coverage was essentially fully complete in both non-overlap ($99.4\pm0.8\%$) and overlap segments ($99.8\pm0.4\%$) at two-year follow-up. The flow area in the overlap segments was not different from the flow area in the non-overlap segments, despite the neointimal response

being greater in the overlap segments. Consequently, the treated segments showed a homogeneous lumen area through the scaffold segment. These results might support the feasibility of overlapping scaffolds when needed for longer lesions if acute lumen expansion is achieved in a similar extent as in the non-overlap segments using good implantation techniques.

LIMITATIONS

This post-hoc analysis was performed from a non-randomized study. No correction has been made regarding differences in baseline characteristics between the two comparison groups. These differences could have heavily contributed to the results. The study was underpowered for low-frequency events, like ST. The implantation technique used in the ABSORB Extend was outdated. Indeed, the PSP (vessel predilation, sizing and postdilation) implant strategy is highly recommended and followed today. Finally, the lack of a control arm with a metallic DES does not allow for comparison of the devices.

CONCLUSIONS

In this low-to-moderate complex population treated with the BVS in the ABSORB EXTEND study, scaffold OVP was associated with an increase of peri-procedure MI but without any immediate or long-term effect on cardiac death, TLR or ST occurrence.

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Figure Legend

Figure 1. Cumulative incidence of MACE in patients treated with and without ABSORB overlapping. On the left the two-year curve for both groups and, on the right, the landmark analysis with the in hospital events.

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