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Efficacy and Safety of the Absorb Everolimus-Eluting Bioresorbable Scaffold for Treatment of Patients with Diabetes Mellitus: Results of the Absorb Diabetic Substudy

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ABSTRACT

Objectives: To evaluate the efficacy and safety of Absorb everolimus-eluting bioresorbable vascular scaffold (BVS) in patients with diabetes mellitus.

Background: Randomized, controlled trials have demonstrated comparable clinical outcomes following percutaneous coronary intervention with either Absorb BVS or metallic Xience everolimus-eluting stent (EES). However, these trials lack power required to provide reliable treatment effect estimates in this high risk population.

Methods: In a pre-specified, powered analysis, patients with diabetes who received ≥1 Absorb were pooled from the ABSORB II, III and JAPAN randomized trials and from the single arm ABSORB EXTEND registry. The study composite primary endpoint was target lesion failure (TLF) at 1-year following Absorb BVS compared with a performance goal (PG) of 12.7%.

Results: Among 754 diabetic patients included in analysis (27.3% insulin-treated), the 1-year TLF rate was 8.3% (upper 1-sided 95% confidence limit 10.1%; p=0.0001 versus PG). Scaffold thrombosis (definite/probable) was observed in 2.3% of patients. Multivariable regression identified older age, insulin treatment and smaller pre-procedure reference vessel diameter as significant independent predictors of 1-year TLF.

Conclusions: The Absorb diabetic substudy suggests efficacy and safety of the Absorb BVS for treatment of patients with diabetes mellitus.

KEY WORDS: bioresorbable vascular scaffolds, diabetes, coronary artery disease

CONDENSED ABSTRACT

Target lesion failure (TLF) was evaluated at 1-year in 754 patients with diabetes mellitus who received ≥1 Absorb everolimus-eluting bioresorbable vascular scaffold (BVS), and compared to a pre-specified performance goal (PG) of 12.7%. At 1-year, Absorb BVS TLF was 8.3% (upper 1-sided 95% confidence limit 10.1%; p=0.0001 versus PG) and definite/probable scaffold thrombosis was observed in 2.3% of patients. This prespecified, powered substudy suggests efficacy and safety of Absorb BVS in patients with diabetes mellitus.

ABBREVIATIONS

ACS = acute coronary syndromes

ARC = Academic Research Consortium

BMS = bare metal stents

BRS = bioresorbable scaffolds

BVS = bioresorbable vascular scaffold

DES = drug-eluting stents

CEC = clinical events committee

CK-MB = creatine kinase isoenzyme MB

CL = confidence limit

DAPT = dual antiplatelet therapy

DSMB = data safety monitoring board

EES = everolimus-eluting stent

ID-TLR = ischemia driven target lesion revascularization

LAD = left anterior descending artery

MI = myocardial infarction

PCI = percutaneous coronary intervention

PG = performance goal

QCA = quantitative coronary angiography

RVD = reference vessel diameter

SIHD = stable ischemic heart disease

TLF = target lesion failure

TV-MI = target vessel myocardial infarction

ULN = upper limit of normal

US = United States

INTRODUCTION

The presence of diabetes mellitus remains a significant predictor of adverse clinical and angiographic outcomes following percutaneous coronary intervention (PCI) with contemporary drug-eluting stents (DES), with increased rates of myocardial infarction (MI), stent thrombosis, restenosis, and death.[1-4] This poor prognosis in patients with diabetes has been ascribed to a greater level of vascular inflammation, the presence of a pro-thrombotic state and more complex clinical and angiographic features.[5,6]

Among patients with diabetes undergoing PCI, both the severity of diabetes as reflected by the treatment required (insulin providing versus insulin sensitizing medications)[8] as well as the level of glucose control (as reflected by HbA1c or fasting blood glucose levels)[9,10] have been correlated with peri-procedural and late clinical outcomes. DES reduce angiographic as well as clinical restenosis (ischemia-driven target lesion and vessel revascularization) following PCI when compared with either bare metal stents (BMS) or balloon angioplasty in patients with or without diabetes.[11,12] Although iterations in metallic DES including novel alloy composition, reduced strut thickness and improved polymer biocompatibility and/or bioresorption have further improved outcomes compared with early generation DES,[13] concerns regarding incomplete endothelialization, polymer hypersensitivity, neoatherosclerosis and stent fracture persist.[14-16] Indeed, beyond 1 year after implant, current metallic DES are associated with a 2-4% ongoing annual incidence of target lesion failure events (TLF; composite occurrence of cardiac death, target vessel MI [TV-MI] and ischemia-driven target lesion revascularization [ID-TLR]), rates similar to that observed following either BMS or early generation DES.[17,18] The occurrence of this phenomenon with all stents may be due to the presence of a metallic implant that

mechanically distorts and constrains the vessel, thus preventing normalization of vasomotion, autoregulation and adaptive remodeling.[17,18]

Fully bioresorbable scaffolds (BRS) provide mechanical support and drug-delivery functions similar to metallic DES early (within 6-12 months) following PCI, followed by complete resorption with recovery of more normal vascular structure and function, with the consequent potential for improving very late clinical outcomes.[19] Recent randomized controlled clinical trials have demonstrated comparable 1-year clinical outcomes following PCI with the Absorb bioresorbable vascular scaffold (BVS) compared to the metallic Xience everolimus-eluting stent (EES) in patients with non-complex, stable ischemic heart disease (SIHD) and/or stabilized acute coronary syndromes (ACS), and long-term follow-up is ongoing.[20-22] However, subgroup analyses of patients with diabetes mellitus from these trials lack power required to provide reliable treatment effect estimates in this high risk population. Thus, a pre-specified formal substudy was performed to evaluate the 1-year safety and effectiveness of Absorb BVS in patients with diabetes mellitus.

METHODS

Design and Population. The present study represents a pre-specified, powered analysis designed in concert with the United States (US) Food and Drug Administration (FDA) to support a US diabetic indication for Absorb. The study cohort includes subjects with diabetes mellitus who were enrolled into the ABSORB II, ABSORB III and ABSORB JAPAN randomized trials,[20-22] plus the single arm, open-label ABSORB EXTEND registry.[23] The design of each study has been described previously.[20-23] Each trial included in this pooled analysis was conducted in accordance with the clinical investigational plan, the declaration of Helsinki, and applicable regulatory requirements. Institutional review boards/medical ethics committee

approval for the protocols and informed consents were obtained prior to site and subject participation. Clinical endpoints were adjudicated by an independent, central clinical events committee (CEC), and study oversight was provided by an independent data safety monitoring board (DSMB) for each study. A summary of key study design characteristics as well as the number of subjects with diabetes stratified by diabetic treatment are shown in supplemental.

All subjects included in the analysis cohort had Absorb BVS implanted in at least 1 target lesion ("as treated" population). For conformity of target lesion lengths across studies, subjects with lesion lengths > 24mm in ABSORB EXTEND and ABSORB II were excluded.

Endpoint Definitions. The powered primary endpoint for analysis is the incidence of TLF at 1-year in the Absorb BVS diabetic cohort. All endpoints in this analysis were defined the same as in the ABSORB III trial.[22]

Statistical Analysis. Patient level data from the four ABSORB studies were pooled into a common database. The powered primary endpoint of 1-year TLF rate of the pooled Absorb BVS diabetic cohort was tested against a pre-specified performance goal (PG). The analysis assumed the true 1-year TLF rate in the Absorb BVS diabetic cohort was 8.2%, which was derived from the historical XIENCE diabetic data from the SPIRIT IV trial.[24] (Supplemental Materials) The PG of 12.7% includes the 8.2% TLF estimate plus a 4.5% non-inferiority margin based on the "putative placebo" concept to preserve ≥50% of the treatment benefit for Xience versus bare metal stents.[25] Assuming a one-sided alpha = 0.05 and 5% loss to follow-up at 1-year, we estimated a total of approximately 700 Absorb BVS treated patients with diabetes mellitus would provide >95% power.

Patients who were lost to follow-up in whom no known event had occurred were not included in the denominator for calculations of binary endpoints. Exact test was used to compare

1-year primary endpoint of TLF against the performance goal. Chi-square test or Fisher's exact test (when Cochran's rule is not met) was used for between group comparisons of endpoint events. Poolability across the 4 ABSORB studies was examined via Chi-square test for the primary endpoint of TLF. In addition, a sensitivity analysis was also performed using both fixed and random effect meta-analysis for the primary endpoint. A multivariable Cox regression analysis of the primary endpoint of 1-year TLF was performed in the pooled Absorb BVS diabetic patients. Variables included in the model include age (5-year increment), gender (female vs. male), target vessel left anterior descending artery (LAD) (yes vs. no), pre-procedure reference vessel diameter (0.5 mm increment), lesion length (5 mm increment), insulin use (yes vs. no), lesion type (B2/C vs. A/B1), number of lesions treated (>2 vs. 1), and study (Absorb III vs. non-Absorb III patients). The graphical and numerical methods of Lin, Wei, and Ying[26] were used to assess the proportional hazards assumption. We used meta (version 4.3-2) in R version 3.2 to do the meta-analysis.[27] All other statistical analyses were performed with the use of SAS software, version 9.2 (SAS Institute).

RESULTS

Patients and baseline characteristics. The analysis population was comprised of 754 patients with diabetes mellitus who were treated with at least 1 Absorb BVS in at least 1 target lesion. Baseline clinical, angiographic lesion characteristics and procedural data among these patients are shown in Table 1. At enrollment, 27.3% of subjects received insulin treatment and nearly 60% had HbA1c levels ≥7.0%. As expected from a global population in the pooled analysis, some geographic differences in the baseline patient demographic and risk factors were noted. In particular, the ABSORB III RCT diabetic population had a higher risk profile compared with other trials. Of note, 18% of all treated lesions in this analysis had a baseline reference vessel

diameter (RVD) of < 2.25 mm by quantitative coronary angiography (QCA), and ~60% had AHA/ACC type B2/C target lesion morphology (moderate to severe complexity). More than 70% of all scaffolds were post-dilated, and ~7% of lesions were treated with overlapping devices. Adherence to dual antiplatelet therapy (DAPT) is shown in supplemental.

Outcomes at one year. The primary endpoint of TLF at 1-year occurred in 8.3% of diabetic patients treated with Absorb BVS (Figure 1), with an upper one-sided 95% confidence limit (CL; exact method) of 10.1%, well below the prespecified PG of 12.7% (p for noninferiority = 0.0001). One-year TLF ranged from 4.4% to 10.9% by study (chi-square test for poolability p = 0.08). Sensitivity analyses using both fixed effect (Absorb 1-year TLF= 8.7%, upper one-sided 95% CL 10.6%; p for noninferiority = 0.0008) and random effect (Absorb 1-year TLF=7.1%, upper one sided 95% CL 10.5%; p for noninferiority = 0.006) meta-analysis models confirmed that 1-year TLF following Absorb BVS was significantly below the PG. Individual efficacy and safety outcomes to 1-year by trial and for the pooled diabetic cohort are shown in Table 2. Most outcomes including TLF, all MI, TV-MI, ischemia-driven target lesion and vessel revascularization and scaffold thrombosis were significantly increased among diabetic patients who were receiving insulin treatment compared with those who were not (Table 2).

Multivariable Cox regression analysis identified older age, insulin treatment and smaller pre-procedure RVD as significant independent predictors of 1-year TLF among subjects with diabetes mellitus (Figure 2) where the proportional hazards assumption was met for all variables included in the analysis. Clinical outcomes stratified by baseline QCA RVD < 2.25mm vs. ≥ 2.25mm demonstrates that adverse events were less frequent among diabetic subjects with RVD ≥ 2.25mm (Figure 3).

Although comparisons of outcomes between Absorb BVS and Xience treated patients with diabetes are limited by lack of randomization as well as the absence of a Xience treatment arm in the ABSORB EXTEND study, both 1-year TLF and device thrombosis rates appear similar among patients appropriate for trial enrollment (baseline QCA RVD ≥2.25 mm) by device type (1-year TLF 6.6% [N=40/606] vs. 6.5% [N=17/261]; device thrombosis 1.3% [N=8/603] vs. 0.4% [N=1/259] for Absorb BVS vs. Xience respectively).

DISCUSSION

The present pre-specified, prospective, pooled analysis is the largest outcome study of patients with diabetes mellitus treated with the Absorb BVS to date, and thus provides valuable insights into the efficacy and safety of this device in an important, increasingly prevalent high-risk subgroup. The major observations of this analysis include: 1) The powered primary endpoint of 1-year TLF following Absorb BVS in patients with diabetes was 8.3%, similar to the pre-specified TLF estimate of 8.2% and significantly less than the PG of 12.7%. In addition, achievement for the primary endpoint was confirmed in sensitivity analysis using formal meta-analysis. 2) Among patients with diabetes, the rates of TLF, and the TLF components of TV-MI and ID-TLR were significantly increased amongst diabetic patients treated with insulin compared to those who were not. A similar observation was made for scaffold thrombosis. 3) Multivariable regression analysis identified older age, smaller target vessel RVD by QCA, and insulin treatment as independent predictors of 1-year TLF.

This study was designed to support label expansion of Absorb in the US, and in this regard demonstrates efficacy and safety of Absorb BVS for the treatment of non-complex SIHD and stabilized ACS in patients with diabetes. Our study also provides important insights as to which diabetic patients will have a more or less favorable 1-year prognosis after Absorb. As

shown by the multivariable regression analysis, rates of 1-year TLF would be predictably lower in patients with diabetes who are younger, non-insulin treated and with larger baseline RVD. The higher TLF rate observed in the US ABSORB III trial (10.9%) was likely due to more complex patients included in this trial. After adjusting for the other patient and lesion risk factors, ABSORB III was not an independent predictor of 1-year TLF in this pooled diabetic analysis.

The overall 2.3% 1-year rate of scaffold thrombosis observed in the present study is not surprising as both diabetes and small vessel size are well established risk factors for stent thrombosis,[22,24,28] and ~1/5 of the diabetic patients had very small target vessels (QCA RVD < 2.25 mm, roughly correlating to a visually estimated RVD of < 2.5 mm). As in ABSORB III,[19, 29] baseline QCA RVD < 2.25mm was a powerful correlate of adverse outcomes, particularly TV-MI and scaffold thrombosis in the present pooled diabetic population. For diabetic patients with appropriately sized vessels (QCA RVD ≥ 2.25 mm), the scaffold thrombosis rate was lower (1.3%). Recent clinical experience suggests that an Absorb BVS specific deployment strategy that includes optimal target lesion preparation, fastidious scaffold to vessel sizing, and high-pressure post-dilatation with appropriately sized (≥1:1 but <0.5mm larger than scaffold) non-compliant balloons is effective in reducing BVS scaffold thrombosis.[30] Interestingly, the incidence of post-dilatation by trial in the present analysis ranged from 55.8% (ABSORB II) to 84.0% (ABSORB JAPAN), and was not clearly related to 1-year scaffold thrombosis rates of Absorb treated diabetic patients in these two trials (1.5% vs. 2.1% respectively). This apparent lack of correlation likely reflects play of chance due to the low frequency occurrence for scaffold thrombosis as well as the limited number of patients with diabetes mellitus contributed by each of the individual trials.

In the larger portion of patients with diabetes mellitus who did not require insulin treatment (n=548), the one year rate of scaffold thrombosis was 1.5%, similar to both the 1.5% rate observed for the overall Absorb patients enrolled into the ABSORB III trial (n=1322)[22] as well as the 1.4% rate observed in all Xience-treated patients with diabetes (n=224) in the ABSORB III trial.[31] These results are also consistent with a prior propensity-matched comparison of patients with diabetes mellitus treated with either the Absorb BVS or the Xience EES which noted comparable rates of 1-year TLF and thrombosis between devices.[32] It is noteworthy that in the present analysis, the smaller portion of patients who were insulin treated (27.3%) accounted for over 50% of the scaffold thrombosis events that occurred.

Several potential limitations of this work deserve mention. First, despite being the largest analysis of patients with diabetes treated with Absorb BVS to date, this study remains underpowered to precisely evaluate low frequency events such as scaffold thrombosis. Second, clinical outcomes and follow-up are limited to 1-year post PCI, a time frame when Absorb BVS resorption is incomplete. Third, the lack of randomized assignment of patients with diabetes to treatment with either Absorb BVS or EES precludes direct comparison of outcomes between the devices. Nevertheless, the powered primary endpoint of this study is not dependent on either a randomized (to EES) comparator group of patients with diabetes or comparison of device treatment by diabetic status. The study primary endpoint of 1-year TLF in Absorb BVS-treated patients with diabetes compared to a pre-specified PG was met with a high level of statistical significance which was confirmed in sensitivity analysis. Furthermore, consistency of Absorb BVS treatment (compared with EES) was previously demonstrated in the large-scale ABSORB III trial regardless of diabetic status.[22] Finally, it should be noted that for most investigators these studies reflect the first-time clinical use of Absorb BVS (compared with an extensive history

with Xience). As a first experience with a novel device, the results in a diabetic cohort are encouraging, and one would expect that as with all new medical procedures, results will improve over time with increased operator experience.

These limitations notwithstanding, this study suggests efficacy and safety of Absorb BVS in patients with diabetes mellitus particularly those with baseline RVD ≥ 2.25mm. Although this work represents the largest clinical outcomes analysis to date of diabetic patients treated with Absorb BVS, larger-scale direct comparative trials of Absorb verses Xience with long-term follow-up are required to better define the relative outcomes between these devices in patients with diabetes mellitus.

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PERSPECTIVES

WHAT IS KNOWN?

Although patients with diabetes mellitus have worse clinical outcomes following percutaneous coronary revascularization, outcomes following bioresorbable vascular scaffold (BVS) deployment in this high risk population are not defined.

WHAT IS NEW?

A prospective prespecified, powered analysis of 1-year target lesion failure following Absorb BVS in patients with diabetes suggests efficacy and safety of this device with an observed TLF rate of 8.3% compared to a prespecified performance goal of 12.7% (p non-inferiority = 0.0001).

WHAT IS NEXT?

This study supports diabetic label expansion for Absorb BVS. Larger scale direct comparative trials (Absorb BVS versus Xience) with long-term follow-up are required to better define the relative outcomes between these devices in patients with diabetes mellitus.

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FIGURE LEGEND

Figure 1. One-Year Primary Endpoint.

The 1-year rate of TLF was 8.3%, significantly below the pre-specified performance goal of 12.7%.

Figure 2. Independent Predictors of One-year TLF.

Variables included in the Cox regression model were age (5-year increment), gender, LAD vs. non-LAD pre-procedure RVD (0.5 mm increment), lesion length (5 mm increment), insulin use, type B2/C vs. A/B1 lesion, 1 vs. 2 lesions treated, and Absorb III vs. non Absorb III study.

Figure 3. Clinical Outcomes by Pre-procedural Reference Vessel Diameter.

Clinical outcomes of target lesion failure (TLF), target vessel myocardial infarction (TV-MI) and scaffold thrombosis (ST; ARC definite/probable) stratified by pre-procedure reference vessel diameter (RVD) determined by quantitative coronary angiography (< 2.25 mm versus ≥ 2.25 mm). Adverse clinical outcomes were markedly lower in appropriately sized vessels (≥ 2.25 mm).

Table 1: Baseline and Procedure Characteristics

	ABSORB EXTEND (N=203) (N_L=214) (N_S=237)	**ABSORB II (N=68) (N_L=75) (N_S=86)**	**ABSORB III (N=388) (N_L=412) (N_S=437)**	**ABSORB Japan (N=95) (N_L=99) (N_S=100)**	**Pooled (N=754) (N_L=800) (N_S=860)**
Age (years)	61.4 ± 10.3	63.6 ± 9.5	63.8 ± 10.1	66.0 ± 9.9	63.4 ± 10.2
Male	146 (71.9%)	53 (77.9%)	238 (61.3%)	78 (82.1%)	515 (68.3)%
BMI (kg/m^2)	28.1 ± 4.7	29.1 ± 3.9	33.1 ± 6.6	24.9 ± 3.1	30.4 ± 6.3
Hypertension	161 (79.3%)	54 (79.4%)	352 (90.7%)	72 (75.8%)	639 (84.7%)
Hyperlipidemia	144 (70.9%)	49 (72.1%)	319 (82.2%)	71 (74.7%)	583 (77.3%)
Current smoker	46 (22.7%)	16 (23.5%)	72 (18.6%)	24 (25.3%)	158 (21.0%)
Treated with insulin	36 (17.7%)	15 (22.1%)	131 (33.8%)	24 (25.3%)	206 (27.3%)
Treated with oral hypoglycemic	168 (82.8%)	49 (72.1%)	284 (73.2%)	75 (78.9%)	576 (76.4%)
HbA1c level ≥ 7%	128 (69.6%)	30 (49.2%)	197 (54.6%)	46 (48.9%)	401 (57.3%)
Target lesion - LAD - LCX	 82 (38.3%) 60 (28.0%)	 30 (40.0%) 24 (32.0%)	 182 (44.2%) 111 (26.9%)	 40 (40.4%) 24 (24.2%)	 334 (41.8%) 219 (27.4%)

- RCA - LMCA	72 (33.6%) 0 (0.0%)	21 (28.0%) 0 (0.0%)	118 (28.6%) 1 (0.2%)	35 (35.4%) 0 (0.0%)	246 (30.8%) 1 (0.1%)
Lesion length (mm)	12.22 ± 4.53	12.29 ± 4.64	12.56 ± 5.27	13.99 ± 5.26	12.62 ± 5.04
RVD (mm) - < 2.25mm	2.64 ± 0.37 30 (14.1%)	2.61 ± 0.39 15 (20.0%)	2.63 ± 0.44 83 (20.2%)	2.70 ± 0.45 16 (16.2%)	2.64 ± 0.42 144 (18.1%)
Type B2/C lsns	92 (43.2%)	29 (38.7%)	283 (68.9%)	82 (82.8%)	486 (60.9%)
# devices (per pt)	1.2 ± 0.5	1.3 ± 0.6	1.1 ± 0.4	1.1 ± 0.2	1.1 ± 0.4
Post-dilatation (%, per scaffold)	179 (75.5%)	48 (55.8%)	304 (69.6%)	84 (84.0%)	615 (71.5%)
Overlapping devices (%, per lsn)	23 (10.7%)	9 (12.0%)	22 (5.3%)	1 (1.0%)	55 (6.9%)
Bailout device (%, per lesion)	2 (0.9%)	3 (4.0%)	21 (5.1%)	1 (1.0%)	27 (3.4%)

Data are n (%) or mean ±SD. N = number of patients; N_L= number of lesions; N_S = number of scaffolds. BMI = body mass index; HbA1C = hemoglobin A1c; LAD = left anterior descending artery; LCX = left circumflex artery; RCA = right coronary artery; LMCA = left main coronary artery; RVD = reference vessel diameter

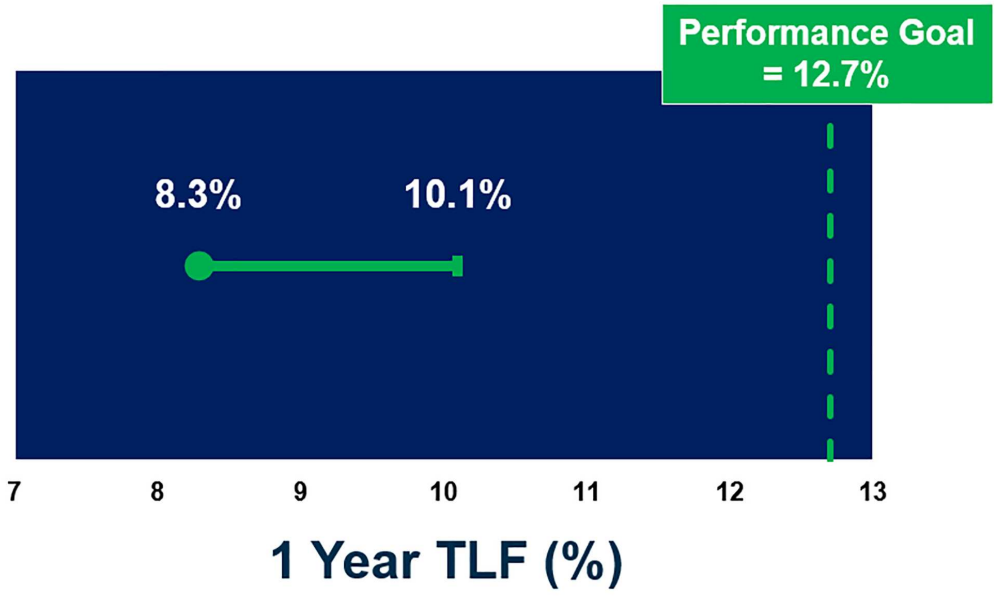
Table 2: One-Year Clinical Outcomes

	ABSORB EXTEND (N=203)	**ABSORB II (N=68)**	**ABSORB III (N=388)**	**ABSORB Japan (N=95)**	**Pooled Diabetic (N=754)**	**Insulin Treated (N=206)**	**Non-Insulin Treated (N=548)**	**P value***
TLF	12 (5.9%)	3 (4.4%)	42 (10.9%)	5 (5.3%)	62 (8.3%)	28 (13.7%)	34 (6.2%)	0.001
All-cause death	2 (1.0%)	0 (0.0%)	4 (1.0%)	0 (0.0%)	6 (0.8%)	1 (0.5%)	5 (0.9%)	1.00
- Cardiac	1 (0.5%)	0 (0.0%)	2 (0.5%)	0 (0.0%)	3 (0.4%)	1 (0.5%)	2 (0.4%)	1.00
All MI	9 (4.4%)	3 (4.4%)	38 (9.9%)	3 (3.2%)	53 (7.1%)	26 (12.7%)	27 (4.9%)	0.0002
- TV-MI	8 (3.9%)	3 (4.4%)	35 (9.1%)	3 (3.2%)	49 (6.5%)	25 (12.2%)	24 (4.4%)	0.0001
ID-TLR	6 (3.0%)	0 (0.0%)	22 (5.7%)	4 (4.2%)	32 (4.3%)	15 (7.3%)	17 (3.1%)	0.01
ID-TVR	6 (3.0%)	1 (1.5%)	31 (8.1%)	7 (7.4%)	45 (6.0%)	20 (9.8%)	25 (4.6%)	0.008
Scaffold thrombosis (ARC	2 (1.0%)	1 (1.5%)	12 (3.2%)	2 (2.1%)	17 (2.3%)	9 (4.4%)	8 (1.5%)	0.03

	ABSORB EXTEND (N=203)	**ABSORB II (N=68)**	**ABSORB III (N=388)**	**ABSORB Japan (N=95)**	**Pooled Diabetic (N=754)**	**Insulin Treated (N=206)**	**Non-Insulin Treated (N=548)**	**P value***
def/prob)								
Early (≤30 days)	1 (0.5%)	0 (0.0%)	8 (2.1%)	1 (1.1%)	10 (1.3%)	6 (2.9%)	4 (0.7%)	0.03
Late (31-365 days)	1 (0.5%)	1 (1.5%)	4 (1.1%)	1 (1.1%)	7 (0.9%)	3 (1.5%)	4 (0.7%)	0.40
Definite	2 (1.0%)	0 (0.0%)	12 (3.2%)	2 (2.1%)	16 (2.1%)	9 (4.4%)	7 (1.3%)	0.02
Probable	0 (0.0%)	1 (1.5%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.2%)	1.00

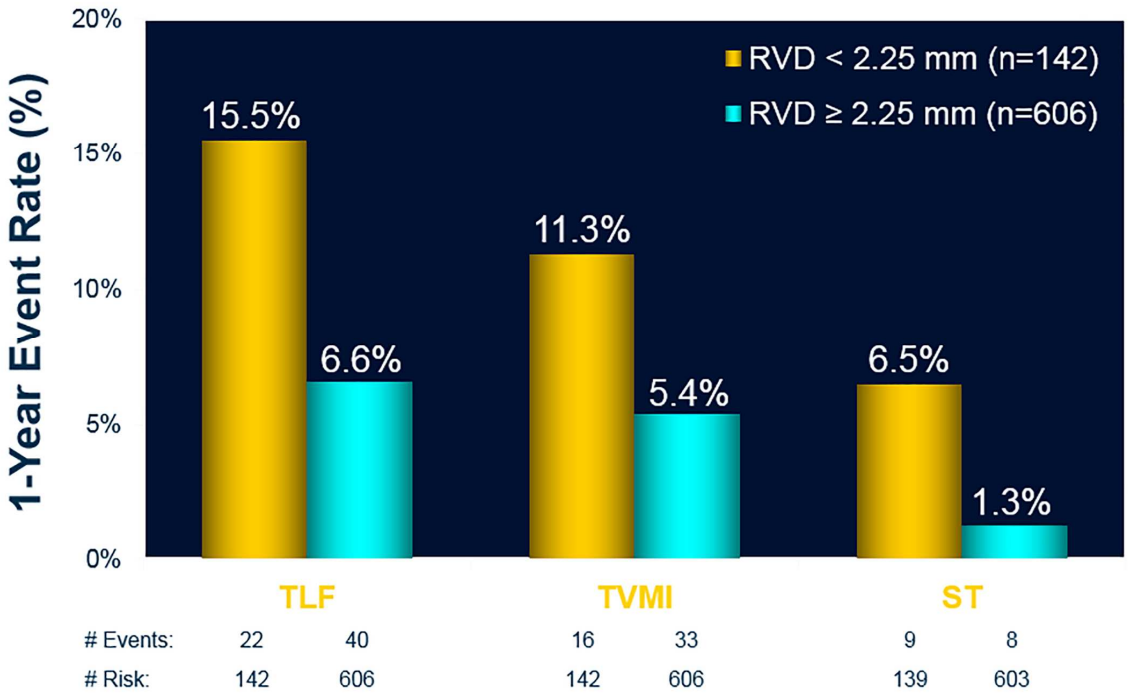
* Insulin vs. non-insulin. Data are n (%). N = number of patients. TLF = target lesion failure; MI = myocardial infarction; TV-MI = target vessel myocardial infarction; ID-TLR = ischemia-driven target lesion revascularization; ID-TVR = ischemia-driven target vessel revascularization; ARC = Academic Research Consortium

	Absorb N=754 n / N	%	Upper 1-sided 95% CL	p-value
TLF	62 / 751	8.3%	10.1%	0.0001



TLF: cardiac death, TV-MI, or ID-TLR	HR [95%CI]	P value
Age (increment of 5 years)	1.23 [1.08, 1.40]	0.001
Diabetes treated with insulin (yes vs. no)	2.24 [1.34, 3.74]	0.002
Pre-procedure RVD (increment of 0.5 mm)	0.61 [0.43, 0.87]	0.007

Variables included in the Cox regression model = age (5 year increment), gender, LAD vs. non-LAD, pre-procedure RVD (0.5 mm increment), lesion length (5mm increment), insulin use, type B2/C vs A/B1 lesion, 1 vs. 2 lesions treated, Absorb III vs. non Absorb III study



Supplementary Materials

I. Statistical Analysis: Derivation of Performance Goal

The assumed 1-year TLF rate of 8.2% for patients with diabetes was derived from the 7.0% assumed 1-year TLF used for both devices in the ABSORB III randomized controlled trial (RCT) plus 1.2% (observed absolute difference in 1-year TLF rates among subjects with non-complex anatomic characteristics between Xience treated patients with diabetes versus all Xience treated patients in the SPIRIT IV trial).[1] The delta 4.5% was similar to that used in the ABSORB III RCT and represents the 90% lower confidence limit of the derived treatment effect difference between XIENCE vs. bare metal stent (BMS; putative placebo concept in accordance with FDA guidance document on non-inferiority trials).[2]

Supplemental Table 1: Absorb Diabetic Study Component Trials

	ABSORB EXTEND	ABSORB II	ABSORB III	ABSORB Japan
ClinicalTrials.gov identifier	NCT01023789	NCT01425281	NCT01751906	NCT01844284
Study design	Single arm Open label	Randomized (2:1), single-blind	Randomized (2:1), single-blind	Randomized (2:1), single-blind
Geography	Europe, Middle East, Asia Pacific/Japan, Canada, Latin America	Europe, Israel, New Zealand	US, Australia	Japan
Target lesion RVD (mm)	$D_{max/}$ D_{mean} 2.0 to 3.3 by online QCA	D_{max} 2.25 to 3.8 by online QCA	RVD ≥2.5 to ≤3.75 by visual assessment	D_{max} ≥2.5 to ≤3.75 by online QCA or visual assessment
Target lesion length (mm)	≤28	≤48	≤24	≤24
Overlap allowed	Yes	Yes	Bailout only	Bailout only
Clinical follow-up	3 years	5 years	5 years	5 years
Angiographic follow-up	At 2 years for OCT subgroup	At 3 years	At 3 years for a separate imaging subgroup	At 13 months and 3 years
Primary endpoint	None	Vasomotion at 3 years	TLF at 1 year	TLF at 1 year

	ABSORB EXTEND	ABSORB II	ABSORB III	ABSORB Japan
Number of total patients	812	501 (Absorb 335; XIENCE 166)	2008 (Absorb 1322; XIENCE 686)	400 (Absorb 266; XIENCE 134)
Analysis Diabetic Cohort – ITDM	36	15	131	24
Analysis Diabetic Cohort – NITDM	167	53	257	71
Analysis Diabetic Cohort – Total DM	203	68	388	95

ITDM: insulin treated diabetes mellitus; NITDM: non-insulin treated diabetes mellitus; DM: diabetes mellitus;

RVD: reference vessel diameter; D_{max}: maximum lumen diameter; QCA; quantitative coronary angiography

Supplemental Table 2: Aspirin, P2Y12 Inhibitor and Dual Antiplatelet Therapy Adherence to 1 Year

	ABSORB EXTEND (N=203)	ABSORB II (N=68)	ABSORB III (N=388)	ABSORB Japan (N=95)	Pooled (N=754)
Aspirin	197 (97.0%)	63 (92.6%)	370 (95.4%)	95 (100.0%)	725 (96.2%)
P2Y12 receptor antagonist	164 (80.8%)	55 (80.9%)	367 (94.6%)	94 (98.9%)	680 (90.2%)
- Ticlopidine	2 (1.0%)	0 (0.0%)	0 (0.0%)	3 (3.2%)	5 (0.7%)
- Clopidogrel	146 (71.9%)	49 (72.1%)	275 (70.9%)	91 (95.8%)	561 (74.4%)
- Prasugrel	14 (6.9%)	2 (2.9%)	66 (17.0%)	0 (0.0%)	82 (10.9%)
- Ticagrelor	2 (1.0%)	4 (5.9%)	26 (6.7%)	0 (0.0%)	32 (4.2%)
DAPT	161 (79.3%)	51 (75.0%)	358 (92.3%)	94 (98.9%)	664 (88.1%)

Data are n (%). N: number of patients. DAPT: dual antiplatelet therapy

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