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Three-year clinical outcomes of the absorb bioresorbable vascular scaffold compared to Xience everolimus-eluting stent in routine PCI in patients with diabetes mellitus—AIDA sub-study

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Abstract

Background: In this prespecified AIDA-trial sub-study we investigate the clinical performance of absorb bioresorbable vascular scaffold (BVS) compared to Xience everolimus-eluting stent (EES) in routine percutaneous coronary intervention (PCI) in patients with diabetes mellitus (DM) at complete 3-year follow-up.

Methods and results: All 1,845 randomized patients were subdivided by medical history with DM or without DM. Of the 924 Absorb BVS patients, 171 (18.5%) patients had DM, of which 65 (38.0%) were treated with insulin (iTDM). Of the 921 Xience EES patients, 153 (16.6%) patients had DM, of which 45 (29.4%) were insulin-treated diabetes mellitus (iTDM). Target vessel failure (TVF), composite of cardiac death, target vessel myocardial infarction, and target vessel revascularization, occurred in 18.7% of diabetic patients treated with Absorb patients versus in 18.0% patients treated with Xience EES (p = .840). In nondiabetics the rates of TVF were 12.3% in Absorb BVS versus 11.0% in Xience EES (p = .391). Definite/probable device thrombosis occurred more frequently in Absorb BVS compared to Xience EES

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in both diabetic and nondiabetic patients (4.8% versus 0.7%; *p* = .028 and 3.2% vs. 0.5%; *p* < .001, respectively).

Conclusions: In routine PCI practice, both Absorb BVS and Xience EES have worse clinical outcomes in diabetic patients as compared to nondiabetic patients. Throughout all clinical presentations, Absorb BVS was associated with higher rates of device thrombosis at 3-year follow-up.

KEYWORDS
bioresorbable scaffolds, diabetes mellitus, drug eluting stents

1 | INTRODUCTION

Diabetic patients represent a major challenge for the interventional cardiologists as they have more rapidly progressing coronary artery disease, and more often have long coronary lesions, when compared to nondiabetic patients. Despite advances in pharmacotherapy, revascularization techniques, and advances in-stent technology, diabetes mellitus (DM) still remains a significant predictor of adverse clinical and angiographic outcomes after percutaneous coronary intervention (PCI).[1,2] This higher risk of adverse events may be due to their pronounced chronic coronary inflammation and abnormal vessel healing.[3,4]

The design of the absorb bioresorbable vascular scaffolds (BVS) is pinnacled around the concept of providing temporary coronary vessel scaffolding after PCI, and allowing for complete coronary vessel healing after the scaffold has been resorbed.[5] Given the increased peri-strut inflammation in patients with DM,[4,6,7] absorb BVS implantation might be associated with favorable clinical outcomes after PCI in diabetic patients, since the inflammation induced by the foreign body of the implant might be transient.[8,9] The Amsterdam Investigator-Initiated Absorb Strategy All-Comers (AIDA) trial is a randomized (1:1) clinical trial that compared the absorb BVS with the Xience everolimus-eluting stent (EES) in a population that reflects routine clinical PCI practice. At 2-year follow-up, Absorb BVS was noninferior to Xience EES for the primary endpoint of target vessel failure (TVF).[10] Absorb BVS was, however, associated with increased risk of device thrombosis that continued to accrue until 3-year follow-up.[11] The goal of the current AIDA-trial sub-study is to provide insights in the clinical outcomes in diabetic versus nondiabetic patients at complete 3-year follow-up; a significant landmark in the resorption progress of the absorb BVS.

2 | MATERIALS AND METHODS

2.1 | Study design AIDA trial

The AIDA trial was a multicenter, investigator-initiated, randomized controlled trial. The study design,[12] the preliminary safety report,[13] 2-year[10] and 3-year[11] results have been published previously. Briefly,

between August 2013 and December 1, 2015, 845 consecutive patients were randomized to either Absorb BVS (924) or Xience EES (921). The study design was in concordance with the provisions of the Declaration of Helsinki. The research ethics committee of Academic Medical Centre, Amsterdam approved the study protocol for all participating centers. All enrolled patients provided written informed consent.

3 | DESIGN OF THE CURRENT ANALYSIS

3.1 | Definitions

We compared the safety and efficacy of Absorb BVS with Xience EES in patients presenting with a medical history of DM. Diabetic patients were further subcategorized into treatment with oral medication or with insulin (oTDM vs. iTDM). The primary endpoint of the current analysis is TVF at 3-year after index procedure. Secondary endpoints were all-cause death, all myocardial infarction, all revascularizations and device thrombosis. To evaluate the impact of baseline procedural and lesion differences, predictors of lesion oriented clinical outcomes (LOCE) were calculated. LOCE is a composite of target vessel MI, target lesion revascularization (TLR) or definite device thrombosis. All events were adjudicated by an independent clinical event committee. Offline quantitative coronary angiography (QCA) was performed by an Academic Corelab that consisted of 12 experienced readers who were supervised by two expert cardiologists [YO and PWS]; all readers and supervising cardiologists were blinded for clinical events.

3.2 | Statistical analysis

All analyses were performed with outcomes that occurred between randomization and 3 years of follow-up by randomized device modality (Absorb BVS or Xience EES) according to the intention-to-treat principle. Baseline data are summarized with descriptive statistics using Fisher's exact test for binary variables and the independent *t*-test for continuous variables. Three-year event rates were based on Kaplan–Meier estimates in time-to-first-event analyses and were compared by means of the log rank test. Lesion level

based predictors of LOCE in diabetic patients were calculated by univariate and multivariate logistic regression. All statistical analyses were performed with use of SPSS software, version 23 (IBM Corp., Armonk NY).

4 | RESULTS

4.1 | Baseline, procedural, and QCA characteristics

In the absorb BVS group, 171 (18.5%) patients had DM, of which 95 (55.6%) patients were treated with oral medication (oTDM) and 65 (38.0%) patients were treated with insulin (iTDM). In the Xience EES group, 153 (16.6%) patients had DM, of which 97 (63.4%) patients were oTDM and 45 (29.4%) iTDM.

Compared with patients without DM, patients with DM were older and more frequently had coexisting cardiovascular risk factors including history of smoking, hypertension, and hyperlipidemia. Diabetic patients

presented less frequently with ST-segment elevation myocardial infarction (17.6 vs. 26.8%, $p < .001$) and more often with stable angina (48.5 vs. 37.7%, $p < .001$). The baseline demographic and clinical characteristics of the randomized absorb BVS- and Xience EES-treated groups were well matched in patients with and without DM (Table 1). Only Absorb BVS treated diabetics presented more often with ST-segment elevation myocardial infarctions compared with Xience EES diabetics.

In diabetic patients, the implantation rate of any assigned study device was lower compared to nondiabetics (96.0 vs. 98.8%, $p < .001$). Patients with DM had more often moderate/severe calcified lesions compared with patients without DM (37.8 vs. 24.8%, $p < .001$). Procedural and QCA characteristics are descripted in Table 2. In diabetic patients, post-dilatation was more frequently performed in Absorb BVS compared to Xience EES (Table 2). Among non-DM, lesions were less frequently moderate/severe calcified in Xience EES compared to Absorb BVS (Table 2). Other procedural and QCA characteristics did not differ among DM and non-DM patients treated with Absorb BVS and Xience EES. Multivariate analysis

TABLE 1 Baseline characteristics

		Diabetic patients			Nondiabetic patients		
		Absorb BVS (n = 171)	Xience EES (n = 153)	p-value	Absorb BVS (n = 753)	Xience EES (n = 768)	p-value
Age		66.14 ± 10.13	66.48 ± 9.43	.753	63.86 ± 10.70	64.46 ± 10.68	–
Male sex		112 (65.5%)	106 (69.3%)	.479	558 (74.1%)	594 (77.3%)	.151
Diabetic treatment	Oral medication	95 (55.6%)	97 (63.4%)	.174	n/a	n/a	n/a
	Insulin	65 (38.0%)	45 (29.4%)	.126	n/a	n/a	n/a
	None	8 (4.7%)	10 (6.5%)	.479	n/a	n/a	n/a
	Unknown	3 (1.8%)	1 (0.7%)	.625	n/a	n/a	n/a
Risk factors	Hypertension	123 (71.9%)	107 (70.4%)	.806	345 (46.1%)	357 (46.5%)	.877
	Hypercholesterolemia	98 (57.6%)	78 (51.3%)	.264	246 (33.0%)	272 (35.7%)	.279
	Family history of CAD	72 (42.1%)	74 (52.5%)	.169	379 (52.3%)	395 (51.4%)	.834
	Current smoker	38 (23.9%)	28 (19.9%)	.698	210 (29.7%)	245 (34.0%)	.176
History	Chronic renal failure	29 (17.0%)	31 (20.3%)	.476	41 (5.4%)	60 (7.8%)	.065
	Ejection fraction <30%	9 (5.3%)	31 (20.3%)	.150	13 (1.8%)	14 (1.9%)	1.000
	Previous myocardial infarction	44 (25.7%)	42 (27.5%)	.801	122 (16.2%)	130 (16.9%)	.730
	Previous PCI	60 (35.1%)	48 (31.4%)	.555	142 (18.9%)	136 (17.7%)	.596
	Previous CABG	6 (3.5%)	7 (4.6%)	.779	32 (4.2%)	19 (2.5%)	.064
Presentation	STEMI	38 (22.2%)	19 (12.4%)	.028	202 (26.8%)	206 (26.8%)	1.000
	NSTEMI	31 (18.1%)	28 (18.3%)	1.000	154 (20.5%)	164 (21.4%)	.705
	Unstable angina	10 (5.8%)	18 (11.8%)	.074	60 (8.0%)	69 (9.0%)	.520
	Stable angina	76 (44.4%)	81 (52.9%)	.148	285 (37.8%)	289 (37.6%)	.958
	Angiography driven	11 (6.4%)	7 (4.6%)	.682	40 (5.3%)	29 (3.8%)	.175
	Other	5 (2.9%)	0 (0%)	.062	12 (1.6%)	11 (1.4%)	.836
Syntax score	Mean	13.63 ± 8.95	12.94 ± 8.79	.506	13.06 ± 8.57	12.50 ± 8.35	.219
	Median (interquartile range)	11.5 (8.00–17.62)	11.00 (7.00–17.00)	.322	11.0 (7.00–18.00)	11.00 (7.00–17.00)	.219

Note: Table 1 shows the baseline characteristics of the two study arms within both diabetic and nondiabetic patients. Data are n (%) or mean ± SD.
Abbreviations: BVS, bioresorbable vascular scaffold; CABG, coronary artery bypass graft; CAD, coronary artery disease; EES, everolimus eluting stent; NSTEMI, non-ST-elevated myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction.

TABLE 2 Procedural and QCA characteristics

		Diabetic patients			Nondiabetic patients		
		Absorb BVS	**Xience EES**		**Absorb BVS**	**Xience EES**	
		(n = 171)	**(n = 153)**	**p-value**	**(n = 753)**	**(n = 768)**	**p-value**
Treated lesions per patient		1.32 ± 0.58	1.35 ± 0.61	.644	1.34 ± 0.64	1.31 ± 0.58	.438
Number of devices per patient		1.48 ± 0.76	1.48 ± 0.76	.977	1.56 ± 0.86	1.44 ± 0.79	.648
Total device length per patient, mm		30.12 ± 17.52	31.38 ± 21.35	.560	31.34 ± 20.00	29.34 ± 18.79	.232
Device implantation	Any assigned study device	158 (92.4%)	153 (100%)	<.001	737 (97.9%)	766 (99.7%)	1.000
	Only assigned study devices	152 (88.9%)	152 (99.3%)	<.001	707 (93.9%)	758 (98.7%)	.702
Treated lesions							
Total number eligible for QCA		**n = 182**	**n = 191**		**n = 172**	**n = 907**	
Reference vessel diameter pre-procedure–mm		2.46 ± 0.53	2.51 ± 0.64	.420	2.54 ± 0.59	2.51 ± 0.62	.992
Moderate/severe calcification–n(%)		67 (36.8%)	74 (38.7%)	.749	218 (25.0%)	224 (24.7%)	<.001
Predilatation performed–n(%)		175 (96.2%)	180 (94.2%)	.472	856 (98.2%)	833 (91.8%)	.299
Number of devices per lesion		1.14 ± 0.94	1.08 ± 0.30	.094	1.17 ± 0.41	1.10 ± 0.32	.478
Post-dilatation performed–n (%)		143 (78.6%)	100 (52.4%)	<.001	666 (76.4%)	438 (48.3%)	.339
Percentage diameter stenosis post-procedure		24.64 ± 10.42	25.51 ± 11.74	.463	22.68 ± 10.40	25.93 ± 11.40	.651
In segment MLD post-procedure–mm		1.93 ± 0.47	1.95 ± 0.47	.703	2.03 ± 0.56	1.95 ± 0.50	.934

Note: Table 2 shows the procedural characteristics of the two study arms within both diabetic and nondiabetic patients. Data are n (%) or mean ± *SD*.
Abbreviations: BVS, bioresorbable vascular scaffold; EES, everolimus eluting stent; MLD, minimum lumen diameter; ml, milliliter; mm, millimeter; QCA, quantitative coronary angiography; RVD, reference vessel diameter.

suggests that the procedural and QCA differences have no impact on the occurrence of LOCE (Supplementary Table 1).

4.2 | Clinical outcomes

Overall rates of TVF at 3-years were higher among DM compared to non-DM patients when pooled across Absorb BVS and Xience EES (18.3 vs. 11.6%; *p* = .002). Compared with patients without DM, patients with DM had higher rates of all-cause death (7.8 vs. 4.7%, *p* = .024), any revascularization (21.1 vs. 13.1%, *p* < .001) and TLR at 3 years (9.9 vs. 6.2%, *p* = .020).

The 3-year rates of TVF (Figure 1) and its individual endpoints were not significantly different between Absorb BVS and Xience EES in either DM or non-DM (Table 3). Results were similar in per protocol analysis (Supplementary Table 2). Figure 1b demonstrates that diabetic patients have similar results in the first year, but higher incidence of TVF between 1 and 3 years. No difference between the two devices for TVF was found. Definite or probable device thrombosis occurred more frequently in Absorb BVS compared to Xience EES in DM (4.8 vs. 0.7%, *p* = .028) and in non-DM (3.5 vs. 0.9%, *p* = .001). No significant interactions were found between DM status and treatment in any of the study outcomes.

4.3 | Outcomes in ITDM and OTDM patients

The baseline demographic, procedural and QCA characteristics of oTDM and iTMD patients were not different between

Absorb BVS and Xience EES, except for higher prevalence of presentation with STEMI in Absorb BVS compared to Xience EES in oTDM patients (Supplementary Table 3). In addition, post-dilatation was significantly more often performed in Absorb BVS compared to Xience EES among oTDM patients (Supplementary Table 4).

The clinical outcomes of oTDM patients and iTDM patients per randomized treatment strategy are shown in Supplementary Table 5. Within the oTDM patients, TVF occurred in 14.1% of absorb BVS patients and in 17.8% Xience EES patients (*p* = .531). Definite or probable device thrombosis occurred numerically more often in Absorb BVS patients (4.4%) than in Xience EES patients (1.0%) (*p* = .166). In iTDM patients, TVF occurred in 25.2% of absorb BVS patients versus 25.2% of Xience EES patients (*p* = .557). Definite or probable scaffold thrombosis occurred in 6.2% of the Absorb BVS iTDM patients whereas definite stent thrombosis did not occur in Xience EES iTDM patients (*p* = .949).

5 | DISCUSSION

In the AIDA trial, Absorb BVS was associated with higher rates of target vessel myocardial infarction (TV-MI) and device thrombosis at 3 years compared to Xience EES.[11] In this sub-study, we found that (1) DM is associated with higher rates of all-cause death, revascularization and TLR, (2) TVF and its individual components were not different between absorb BVS and Xience EES in both DM and non-DM, (3) Absorb BVS implantation lead to higher rates of device thrombosis in patients both with and without DM, and (4) rates of TVF were

FIGURE 1 Figure 1 shows the Kaplan–Meier curves of target vessel failure among diabetic and nondiabetic patients randomly assigned to Absorb BVS or Xience EES throughout (a) 3 years and (b) with landmark at 1 year. Target vessel failure is defined as a composite of cardiac death, target vessel myocardial infarction or target vessel revascularization. BVS, bioresorbable vascular scaffold; EES, everolimus-eluting stent [Color figure can be viewed at wileyonlinelibrary.com]
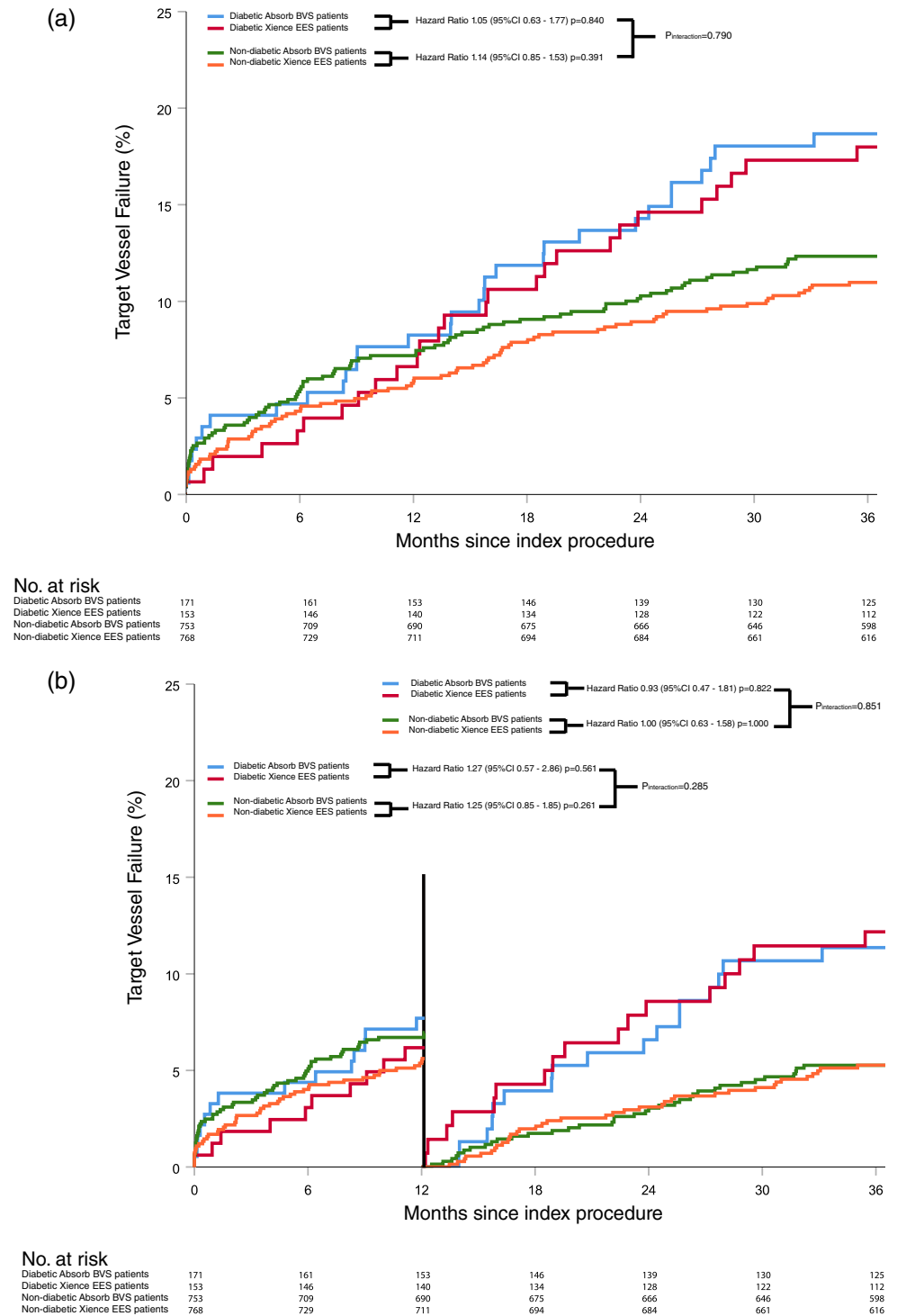
highest in iTDM patients, both for absorb BVS versus Xience EES (25.2 vs. 20.5%, respectively).

This study is the first to report the clinical outcomes of Absorb BVS and Xience EES treatment strategies in diabetic or nondiabetic patients at complete three-year follow-up. Previously, in low to medium risk patients, absorb BVS showed acceptable safety and efficacy in patients with DM at 1-year follow-up.[9] We showed that diabetics have increased risk of adverse events after the first year compared with nondiabetics. In addition, the AIDA population is a more complex population that reflects routine PCI practice. At complete 3-year follow-up, among diabetic patients, similar rates of TVF in absorb BVS compared to Xience EES were observed. However, rates of device thrombosis were significantly higher in the absorb BVS group compared to the Xience EES, regardless of diabetic status. It can be concluded that safety concerns that were previously put forward by the unpredictable occurrence of very late scaffold thrombosis, are also seen in diabetic patients within AIDA. The exact cause of the increased rates of scaffold thrombosis remains party

TABLE 3 Outcomes at 3 years

	Diabetic patients			Nondiabetic patients			
	Absorb BVS (n = 171)	Xience EES (n = 153)	p-value	Absorb BVS (n = 753)	Xience EES (n = 768)	p-value	P_{interaction}
Clinical events							
All-cause death	7.8% (13)	7.9% (12)	.971	4.1% (31)	5.3% (40)	.309	0.621
Cardiac death	3.1% (5)	4.7% (7)	.463	2.4% (18)	2.5% (19)	.904	0.562
Any myocardial infarction	8.6% (14)	5.4% (8)	.273	**8.1% (60)**	**5.5% (41)**	**.042**	0.897
Target vessel myocardial infarction	6.1% (10)	4.1% (6)	.398	5.9% (44)	3.9% (29)	.062	0.971
Any revascularization	22.7% (37)	19.4% (29)	.538	14.0% (103)	12.2% (91)	.309	0.987
Target vessel revascularization	14.1% (23)	12.8% (19)	.744	9.1% (67)	7.8% (58)	.351	0.849
Target lesion revascularization	11.1% (18)	8.7% (13)	.527	7.2% (53)	5.2% (39)	.114	0.804
Device thrombosis related	3.7% (6)	0.7% (1)	.076	**3.1% (23)**	**0.5% (4)**	**<.001**	0.947
Device stenosis related	7.4% (12)	8.1% (12)	.794	4.2% (31)	4.7% (35)	.660	0.992
Composite endpoints							
Target vessel failure	18.7% (31)	18.0% (27)	.840	12.3% (92)	11.0% (83)	.391	0.790
Target lesion failure	15.7% (26)	15.3% (23)	.915	10.9% (81)	9.1% (69)	.248	0.623
Patient-oriented composite endpoint	30.3% (51)	27.0% (41)	.522	19.2% (144)	17.8% (136)	.472	0.854
Device thrombosis							
Definite	3.7% (6)	0.7% (1)	.076	**3.2% (24)**	**0.5% (4)**	**<.001**	0.918
Probable	1.2% (2)	0 (0%)	.181	0.3% (2)	0.4% (3)	.669	0.914
Definite/probable	**4.8% (8)**	**0.7% (1)**	**.028**	**3.5% (26)**	**0.9% (7)**	**.001**	0.575

Note: Table 3 shows the 3-year clinical outcomes by randomized device modality in both diabetic and nondiabetic patients. Data are presented in % (n).
Abbreviations: BVS, bioresorbable vascular scaffold; EES, everolimus eluting stent.

understood. It has been hypothesized that implantation techniques might mitigate the risk of increased occurrence of stent thrombosis,[14-16] however, results and definition of these strategies have been varying.[17,18]

The availability of second-generation DES improved safety and efficacy compared with first-generation DES.[19] However, this improvement in clinical outcomes does not extend to diabetic patients. A patient-pooled analysis of data from four randomized trials—SPIRIT II, III, IV and COMPARE—found that in nondiabetic patients, the use of Xience EES significantly reduced the rates of cardiac death, MI and TLR at 2 years compared to paclitaxel-eluting stent (6.2 vs. 11.4%; Odds Ratio 0.53; 95% CI [0.43–0.65]).[19] However, in diabetic patients, there was no difference between the two stents (10.1 vs. 10.3%; Odds Ratio 0.94; 95% CI [0.68–1.30]).[19] And still nowadays, diabetic patients seem to benefit less from the improvements in technology and stent technique. In the present trial, both the absorb BVS and the Xience EES have worse clinical outcomes after PCI in diabetic patients compared to nondiabetic patients.

This AIDA-trial sub-study, as other sub-studies, highlights the unmet need of clinical outcome improvements with current-generation DES technology, as well as the Absorb BVS, in diabetic patients. Two hypotheses have emerged for the relative ineffectiveness of -limus drug. One reason is the direct resistance of vascular smooth muscle cells to mammalian target of rapamycin (mTOR) inhibition in diabetic patients.[20,21] Another reason is the effect of leptin.

The body mass index strongly correlates with risk of DM. Obesity is associated with elevated levels of the hormone leptin, which has been found to promote vascular remodeling and neointimal growth in animal studies.[22] Increased leptin levels have been associated with in-stent restenosis.[23] DM has reached pandemic proportions; as the worldwide prevalence of DM has increased over the last decades from 108 million people in 1980 to 422 million people in 2014.[24] Due to this increased prevalence and the undesirable PCI outcomes in diabetic-patients, there is an urgent need to enhance stent technology tailored to the needs of the diabetic patients.

6 | LIMITATIONS

The current study has limitations. As any subgroup analysis, this study might be subject to under powering (especially in the low number of insulin-treated diabetic patients). Based on the TVF rate in this study, and a noninferiority boundary of 5%, this study needed a sample size of 1,003 patients per group to have at least 80% power. Second, the AIDA population reflects routine PCI. In routine PCI, intracoronary imaging is not mandatory, and therefore it is not possible to quantify successful lesion preparation and/or device implantation. Third, inflammatory and immunologic markers, in order to understand the role of both inflammation and cell proliferation in restenosis, have not been collected. Fourth, as a post-hoc analysis, information on HbA1C

is lacking which would have provide better insights. Fifth, restarting or prolonging DAPT through 3 years after scaffold implantation was recommended at the request of the DSMB. This recommendation might have influenced the occurrence of thrombosis-related outcomes in patients on prolonged or restarted DAPT. Exact information on the duration of DAPT in every patient would have given greater insights.

7 | CONCLUSIONS

In routine PCI practice, both absorb BVS and Xience EES have worse clinical outcomes in diabetic patients as compared to nondiabetics. Specifically insulin-treated diabetics are at higher risk of adverse clinical events. Throughout all clinical presentations, Absorb BVS was associated with higher rates of device thrombosis at 3-year follow-up.

DATA AVAILABILITY STATEMENT

Data available at request

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.