Stent thrombosis in patients treated with drug-eluting stents and bioresorbable vascular scaffolds

Mechanisms, long-term outcomes and sex differences

Kerkmeijer, L.S.M.

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CHAPTER 6

Final five-year results of the AIDA trial: a randomized trial comparing Absorb BVS with Xience EES in daily clinical practice

Kerkmeijer LSM, Renkens MPL, Tijssen RYG, Hofma SH, van der Schaaf RJ, Arkenbout KE, Kraak RP, Weevers A, Garcia-Garcia HM, Piek JJ, Tijssen JGP, Henriques JPS, de Winter RJ, Wykrzykowska JJ

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Abstract

Background: Absorb bioresorbable vascular scaffold (BVS) related events have been reported between 1 and 3 years – the period of active scaffold bioresorption. Data on the performance of Absorb BVS in daily clinical practice beyond this time point is scarce.

Aims: This report provides the final five-year clinical follow-up of the Absorb BVS in comparison with Xience everolimus-eluting stent (EES). In addition, we evaluated the effect of prolonged dual-antiplatelet therapy (DAPT) administration on events in the scaffold group.

Methods and Results: AIDA was a multicentre, investigator-initiated, non-inferiority trial, in which 1,845 unselected patients with coronary artery disease were randomly assigned to either Absorb BVS (n=924) or Xience EES (n=921). Through 5 years follow-up, there was no difference in target vessel failure, composite of cardiac death, target vessel myocardial infarction or target vessel revascularisation, between Absorb BVS (17.7%) and Xience EES (16.1%) (hazard ratio 1.31, 95% CI 0.90-1.41, p=0.302). Definite or probable device thrombosis (DT) occurred in 43 patients (4.8%) of the scaffold group compared to 13 patients (1.5%) of the stent group (hazard ratio 3.32; 95% CI 1.78-6.17; p<0.001). Device thrombosis between 3- and 4-years occurred six times in Absorb-arm versus three in Xience-arm. Between 4- and 5-years the incidence was 3 versus 2, respectively. Of those three DT in scaffold group, two occurred in Xience EES treated lesions. When scaffold thrombosis cases matched with controls and tested for effect of DAPT, the odds ratio of scaffold thrombosis in patients on DAPT compared to off DAPT throughout 5-year follow-up was 0.36 (95% CI 0.15-0.86).

Conclusion: The excess risk of Absorb BVS on late adverse events, in particular device thrombosis, in routine PCI continues up to 4-years. DAPT appears to mitigate the risk of scaffold thrombosis.

Introduction

Drug-eluting stents have an ongoing risk of device-related adverse events long after the implantation.(1) The pathogenesis of this ongoing annual hazard is thought to be the permanent presence of a metallic implant. To liberate the coronary artery of its permanent metallic cage and therefore remove the potential cause of restenosis and stent thrombosis, the bioresorbable vascular scaffolds (BVS) were developed. Theoretically, the function of the BVS is to scaffold the arterial wall after balloon dilatation to prevent acute vessel closure and late constrictive remodeling, afterwards it should dissolve over approximately 3 years' time to restore the native structure of the coronary artery. The most widely studied coronary scaffold is the Absorb BVS (Abbott Vascular, Santa Clara, USA), which, in a porcine model, completely resorbs and integrates in approximately 3 years.(2) However, in clinical practice, Absorb BVS was found to be associated with an increased risk of target-vessel myocardial infarction and device thrombosis during the time of reabsorption compared to everolimus-eluting metallic Xience stent (Abbott Vascular, Santa Clara, USA).(3-5) Beyond the 3-year time-point, data on safety and efficacy of the Absorb BVS is scarce.(6) In addition, it is unknown whether prolonged dual antiplatelet therapy (DAPT) benefits patients treated with Absorb BVS. Therefore, long-term outcomes are of interest. The Amsterdam Investigator-initiateD Absorb strategy (AIDA) randomized clinical trial compared the Absorb BVS with the everolimus-eluting metallic Xience stent (Xience EES; Abbott Vascular) in daily clinical practice.(7) Herein we report the final five-year clinical outcomes of Absorb BVS in comparison with Xience EES. In addition, we evaluate whether prolonged DAPT regimes mitigate the occurrence of scaffold thrombosis.

Methods

The study design, endpoint definitions, and results through 3 years have been previously described in detail.(3, 7-9) Briefly, the AIDA trial was an all-comers, multicentre, investigator-initiated, randomized controlled trial. Between August 2013 and December 2015, 1,845 consecutive patients with coronary artery disease undergoing percutaneous coronary intervention (PCI) of one or more target lesions suitable for drug-eluting stent implantation were enrolled. Follow-up was performed at regular intervals through 5 years. Quantitative coronary angiographic analyses were performed at a core laboratory. An independent clinical event committee adjudicated all major adverse cardiac events according to either Third Universal Myocardial Infarction definitions(10), or the Academic Research Consortium definitions.(11) The primary study endpoint was target vessel

failure (TVF), powered for non-inferiority at 2-years. TVF is a composite of cardiac death, target vessel myocardial infarction (TV-MI), or target vessel revascularisation. Secondary endpoints included TVF, its components, and device thrombosis at each follow-up period.

The protocol mandated use of DAPT for at least one-year post-PCI. In January 2017, the data and safety monitoring board (DSMB) noted higher rate of early and late scaffold thrombosis and recommended considering prolonged DAPT in all patients treated with Absorb BVS. Subsequently, this recommendation was implemented and referring cardiologists were advised to prescribe DAPT up to 3 years in all patients treated with Absorb BVS.

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 centres. All enrolled patients provided written informed consent.

Effect of DAPT

To assess the effect of DAPT on occurrence of scaffold thrombosis (ScT), every case with definite ScT was matched with one or two control case(s) based on age, sex, presenting with acute coronary syndrome, total number of stents, total stent length and enrolment date before October 1st 2014. At the time of ScT, use of DAPT was scored yes or no for the cases and their controls.

Statistical analysis

The current paper reports the pre-specified major outcomes at 5-year follow-up. All analyses were performed according to the intention-to-treat principle. Time-to-event curves were constructed by the Kaplan-Meier and compared with log-rank test. Hazard ratios were calculated using cox regression. Landmark analyses were performed at 3 and 4 years after index procedure. All ScT cases were matched fuzzy (1:2). Fuzz of 10 for age, 14 for days, 0.8 for total number of stents and 19 for total stent length were allowed. The effect of DAPT on the occurrence of ScT was assessed by calculating odds ratio, using multivariable logistic regression adjusting for age, total number of stents and total stent length. A p-value of ≤0.05 was considered statistically significant. All statistical analyses were performed with SPSS software, version 26.0 (IBM SPSS Statistics, IBM Chicago, IL, USA).

Results

From August 2013 until December 2015, 1,845 patients were enrolled at five sites throughout the Netherlands. In total, 924 patients were randomized Absorb BVS and 921 patients were randomized to Xience EES. Baseline patient, procedural and lesion characteristics were described in detail in previous reports (1, 5), and are shown in **supplementary table 1 and 2**. Briefly, baseline characteristics were well balanced between the two groups. A total of 54% patients presented with acute coronary syndrome at baseline; 25.2% ST-segment myocardial infarction, 20.4% non-ST-segment myocardial infarction and 8.5% unstable angina. SYNTAX score was available for 1,661 patients (90.0%) with a median of 11 (IQR 7-18). In total, 2,446 lesions were treated.

Clinical endpoints

Complete five-year follow-up was obtained in 95.1% of patients; a study flowchart is displayed in the **supplementary Figure 1**. Clinical outcomes through 5-year follow-up are shown in **Table 1**. Throughout 5 years, no significant difference in TVF-rate was found between patients treated with Absorb BVS (17.7%) versus Xience EES (16.1%) (HR 1.13, 95% CI 0.90-1.41, p =0.302) (**Figure 1**). The rates of TV-MI and target lesions revascularization (TLR) remained significantly increased in the Absorb-arm compared to the Xience-arm, with 5-year follow-up rates of TV-MI 7.7% vs 5.0% (HR 1.57, 95% CI 1.08-2.30; p =0.018) and TLR 10.1% vs 7.3% (HR 1.41, 95% CI 1.02-1.94; p=0.034), respectively.

Landmark analysis of clinical outcomes between 3- and 4-year, and 4- and 5-year follow-up are shown in **Table 2**. Clinical outcomes at 4-years follow-up are shown in **supplementary table 3**. Between 3- and 4-years, the rates of TV-MI were numerically higher in Absorb BVS compared to Xience EES, 1.1% vs. 0.4% HR 3.01, 95% CI 0.82-5.76, p=0.082). The rates of TLR were significantly higher in Absorb BVS compared to Xience EES, 1.6% vs. 0.5% (HR 3.27, 95% CI 1.07-10.02; p=0.028). This difference was mainly driven by TLR due to restenosis, 1.4% vs 0.4%, respectively (HR 3.61, 95% CI 1.01-12.93; p=0.035).

In contrast, between 4- and 5-years, the rates of TV-MI did not differ between Absorb BVS (0.7%) and Xience EES (0.8%) (HR 0.83, 95% CI 0.25-2.73; p=0.763). Also, the incidence of TLR did not differ between Absorb BVS and Xience EES, 0.8% vs. 1.1% (HR 0.75, 95% CI 0.26-9.02; p=0.602).

TABLE 1. Clinical Outcomes through 5-year follow-up

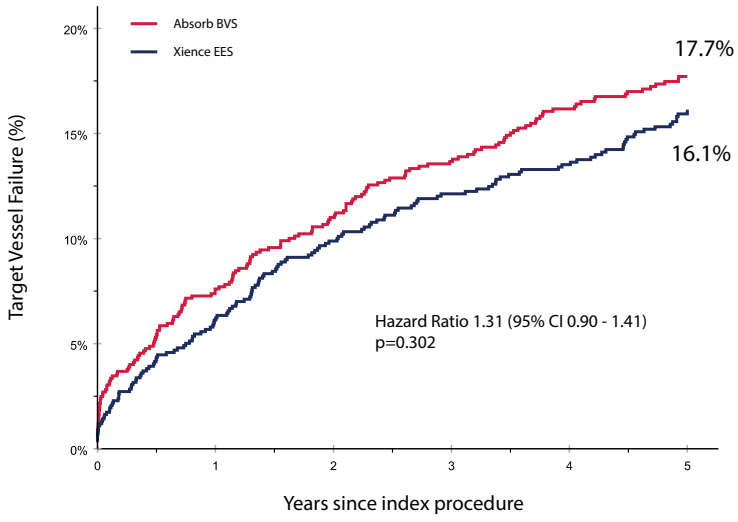
	At 5 years			
	Absorb BVS (n=924)	**Xience EES (n=921)**	**Hazard Ratio (95% CI)**	**p value$**
All-cause death	76 (8.4%)	88 (9.8%)	0.85 (0.63-1.16)	0.314
Cardiac death	34 (3.8%)	41 (4.7%)	0.82 (0.52-1.29)	0.396
Cardiovascular death	43 (4.8%)	47 (5.4%)	0.91 (0.60-1.37)	0.641
All myocardial infarction	96 (10.7%)	62 (7.1%)	1.56 (1.13-2.15)	0.006
Target vessel MI	69 (7.7%)	44 (5.0%)	1.57 (1.08-2.30)	0.018
Non-target vessel MI	27 (3.1%)	19 (2.2%)	1.41 (0.79-2.54)	0.246
Any revascularisation	179 (20.1%)	152 (17.3%)	1.18 (0.95-1.47)	0.127
Target vessel revascularisation	119 (13.4%)	94 (10.7%)	1.27 (0.97-1.66)	0.084
Target lesion revascularisation	90 (10.1%)	64 (7.3%)	1.41 (1.02-1.94)	0.034
Device thrombosis related	37 (4.1%)	9 (1.0%)	4.12 (1.99-8.54)	<0.001
Device stenosis related	58 (6.6%)	56 (6.4%)	1.02 (0.71-1.48)	0.896
Composite endpoints				
Target vessel failure	160 (17.7%)	143 (16.1%)	1.13 (0.90-1.41)	0.302
Target lesion failure†	135 (14.9%)	121 (13.7%)	1.12 (0.88-1.43)	0.356
Patient-oriented composite endpoint‡	259 (28.4%)	241 (26.6%)	1.09 (0.91-1.29)	0.351

$ p-values were calculated by the log-rank test. † Composite of cardiac death, target vessel myocardial infarction and target lesion revascularisation. ‡ Composite of death, myocardial infarction or any revascularisation. BVS = bioresorbable vascular scaffold; EES = everolimus-eluting stent; MI = myocardial infarction

TABLE 2. Landmark analysis for clinical Outcomes between 3- and 5-years follow-up

	Between 3 and 4 years				Between 4 and 5 years			
	Absorb BVS (n=924)	Xience EES (n=921)	Hazard Ratio (95% CI)	p value[$]	Absorb BVS (n=924)	Xience EES (n=921)	Hazard Ratio (95% CI)	p value[$]
All-cause death	14 (1.6%)	18 (2.1%)	0.77 (0.38-1.54)	0.453	16 (2.0%)	17 (2.2%)	0.93 (0.47-1.83)	0.828
Cardiac death	4 (0.5%)	7 (0.8%)	0.56 (0.16-1.92)	0.354	6 (0.7%)	8 (1.1%)	0.74 (0.26-2.13)	0.574
Cardiovascular death	5 (0.6%)	9 (1.1%)	0.55 (0.18-1.64)	0.274	9 (1.1%)	10 (1.3%)	0.89 (0.36-2.18)	0.793
All myocardial infarction	13 (1.6%)	6 (0.8%)	2.19 (0.83-5.76)	0.103	8 (1.1%)	7 (0.9%)	1.15 (0.42-3.18)	0.780
Target vessel MI	9 (1.1%)	3 (0.4%)	3.01 (0.82-11.13)	0.082	5 (0.7%)	6 (0.8%)	0.83 (0.25-2.73)	0.763
Non-target vessel MI	3 (0.4%)	3 (0.4%)	0.99 (0.20-4.91)	0.991	3 (0.4%)	2 (0.3%)	1.49 (0.25-8.90)	0.661
Any revascularisation	26 (3.6%)	14 (1.9%)	1.88 (0.98-3.60)	0.053	13 (2.0%)	18 (2.7%)	0.74 (0.36-1.50)	0.399
Target vessel revascularisation	20 (2.6%)	5 (0.7%)	4.01 (1.50-10.68)	0.003	9 (1.3%)	12 (1.7%)	0.76 (0.32-1.80)	0.526
Target lesion revascularisation	13 (1.6%)	4 (0.5%)	3.27 (1.07-10.02)	0.028	6 (0.8%)	8 (1.1%)	0.75 (0.26-2.18)	0.602
Device thrombosis related	5 (0.6%)	2 (0.2%)	2.51 (0.49-12.96)	0.254	3 (0.4%)	2 (0.3%)	1.51 (0.25-9.02)	0.651
Device stenosis related	11 (1.4%)	3 (0.4%)	3.61 (1.01-12.93)	0.035	4 (0.5%)	6 (0.8%)	0.66 (0.19-2.33)	0.514
Composite endpoints								
Target vessel failure	22 (2.9%)	12 (1.6%)	1.85 (0.91-3.73)	0.082	13 (1.8%)	21 (3.0%)	0.63 (0.31-1.25)	0.181
Target lesion failure†	16 (2.1%)	11 (1.4%)	1.47 (0.68-3.16)	0.324	10 (1.4%)	18 (2.5%)	0.56 (0.26-1.21)	0.136
Patient-oriented composite endpoint‡	35 (4.9%)	30 (4.2%)	1.19 (0.73-1.94)	0.481	26 (4.0%)	33 (5.0%)	0.81 (0.48-1.35)	0.415

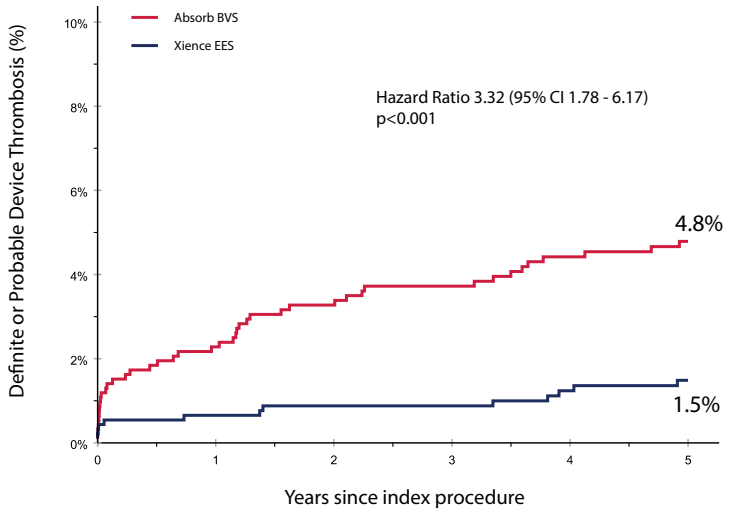
$ p-values were calculated by the log-rank test. † Composite of cardiac death, target vessel myocardial infarction and target lesion revascularisation. ‡ Composite of death, myocardial infarction or any revascularisation. BVS = bioresorbable vascular scaffold; EES = everolimus-eluting stent; MI = myocardial infarction



No. at risk

Absorb BVS	924	844	806	771	724	408
Xience EES	921	851	813	770	738	415

FIGURE 1. Kaplan-Meier curves for target vessel failure up to five-year follow-up per study arm



No. at risk

Absorb BVS	924	886	864	844	808	462
Xience EES	921	891	875	845	816	479

FIGURE 2. Kaplan-Meier curves for definite/probable device thrombosis to five-year follow-up per study arm

Device thrombosis

Device thrombosis (DT) rates are shown in **Table 3**. At 5-years, 38 Absorb BVS treated patients suffered from definite DT compared to 9 Xience EES treated patients (HR 4.24, 95% CI 2.05-8.77; p<0.001). Descriptive characteristics of the definite DT cases throughout 5-year follow-up are presented in **Supplementary Table 4 and 5**. The rate of definite/probable DT was significantly increased in Absorb BVS arm compared with Xience EES arm, with a 5-year rate of 4.8% (43 cases) versus 1.5% (13 cases) (HR 3.32, 95%CI 1.78-6.17; p<0.001) (**Figure 2**).

Between 3 and 4 years, five definite DT and one probable DT were noted in the Absorb BVS arm compared to three definite DT in the Xience EES arm. Of the five definite scaffold thrombosis cases, one case was treated with two-stent technique in a bifurcation lesion and the DT occurred at 1277 days post index PCI. The second very late scaffold thrombosis (VLST) was described as thrombosis on severe restenosis by the clinical event committee. The other three VLST cases had target lesion revascularization with a DES prior to the occurrence of DT. Between 4 and 5 years, three definite DT in Absorb-arm vs two in Xience-arm were noted. Two of these three DT cases were randomized at baseline to Absorb BVS but treated with Xience EES during index procedure.

TABLE 3. Incidence of device thrombosis through 5-year follow-up

	Absorb BVS (n=924)	Xience EES (n=921)	Hazard ratio (95% CI)	p value[$]
Definite	38 (4.3%)	9 (1.0%)	4.24 (2.05-8.77)	<0.001
Probable	5 (0.5%)	4 (0.5%)	1.24 (0.33-4.62)	0.747
Possible	16 (1.8%)	25 (3.0%)	0.63 (0.34-1.18)	0.150
Definite/probable	43 (4.8%)	13 (1.5%)	3.32 (1.78-6.17)	<0.001
≤ 24 hours (acute)	3	3		
>24 hours to 30 days (subacute)	10	2		
31 days to 1 year (Late)	8	1		
1 – 2 years (Very late)	9	2		
2 – 3 years (Very late)	4	0		
3 – 4 years (Very late)	6	3		
4 – 5 years (Very late)	3	2		
Any device thrombosis	58 (6.5%)	38 (4.4%)	1.53 (1.02-2.31)	0.039

$ p-values were calculated by the log-rank test. BVS = bioresorbable vascular scaffold; EES = everolimus-eluting stent

Effect of DAPT on Scaffold thrombosis

During 5-year follow-up, 21 very late definite scaffold thrombosis occurred in the Absorb arm. Only one of these 21 VLST (4.8%) was on DAPT at the time of the event. This is in stark contrast to early DT, where 12 of the 17 patients (70.6%) used DAPT at the time of the event (**Figure 3**). Patients were advised to prolong DAPT up to three years. **Figure 4** shows data on aspirin, P2Y12 inhibitors, DOAC and DAPT use at all follow-up points. All VLST between 3 and 4 years occurred in patients without use of DAPT regimens. These patients discontinued DAPT 331 days (range 119-632) prior to the event. Detailed information on DAPT status at the time of ScT can be found in **supplementary table 4.**

To make the effect of DAPT more transparent, the definite ScT cases were matched with control cases. Four of 38 ScT cases were not eligible; in two ScT cases the SYNTAX score was not available and DAPT-status was unknown in another two ScT cases. DAPT-status was also missing in three matched controls. Therefore, 34 ScT cases with 65 matched controls were included for analysis. Of those who suffered ScT, 13 patients were on DAPT and 21 patients off DAPT. Of those who did not develop ScT, 41 used DAPT and 24 did not. The odds ratio of ScT with the use of DAPT throughout 5-year follow-up was 0.36 (95% CI 0.15-0.86). Within the first year the OR of ScT was 0.14 (95% CI 0.02-0.85) and between 1- and 5-year follow-up the OR was 0.17 (95% CI 0.02-1.63) (**Figure 5)**.

Discussion

The main findings of this final five-year report on clinical outcomes of Absorb BVS in comparison with Xience EES from the AIDA-trial were as follows: 1) Absorb BVS was associated with a significantly increased risk of target-vessel myocardial infarction and device thrombosis compared to Xience EES tested in daily clinical practice; 2) landmark analysis has shown a plateauing of this excess risk with Absorb BVS starting at four-years; and 3) retrospective analysis indicates a reduced odds ratio of scaffold thrombosis in patients using DAPT regimen.

The excess risk of Absorb BVS thrombosis

Randomized clinical trials, comparing Absorb BVS with Xience EES, have identified an increased risk with Absorb BVS on TV-MI and DT up to 3 years after implantation. Stone et al.(12) demonstrated in a pooled analysis of the Absorb trials that this excess risk with Absorb BVS was no longer apparent beyond 3 years. Compared to the first 3 years, the hazard ratios of target lesion failure dropped from 1.42 to 0.92 and the hazard ratio of DT dropped from 3.86 to 0.44 between 3 and 5 years.(12) Our results, however,

show a continued excess risk up to 4-years. Between 3-4 years, the hazard ratio of target lesion failure increased from 1.13(3) to 1.22 at 4 years and the increased risk of device thrombosis diminished but did not disappear (HR dropped from 6.02(3) to 2.52. It was only after four years that the excess risk with Absorb BVS was no longer apparent. The hazard ratio of target lesion failure dropped to 0.56, and for DT it dropped to 1.51. However, two of the three device thrombosis cases between four and five years occurred in Xience EES treated lesions instead of the randomized device, scaffold. Therefore, the hazard ratio is overestimated.

The difference in outcomes between the ABSORB trials and AIDA might be partly explained by the difference in study population; the study population of the ABSORB trials mainly consisted of patients with simple lesions and low risk of restenosis. In comparison, the AIDA trial represented the daily clinical practice and included patients with complex lesions and patients who had presented with acute coronary syndrome including ST-segment elevation myocardial infarction. It might be that the resorption of the Absorb BVS is prolonged in these complex and severe diseased lesions and thereby creates a longer lasting risk of device-related events.(13) A better understanding of this resorption process and the factors that influences it could help us to improve next generation BRS devices.

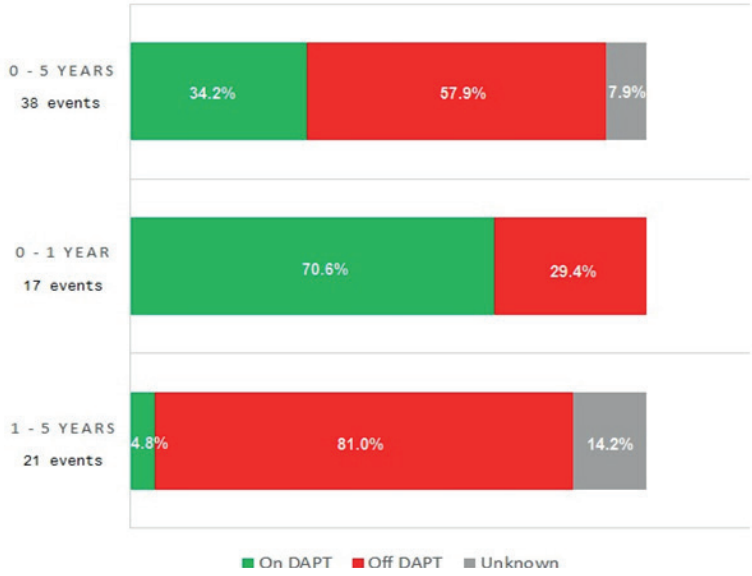


FIGURE 3. Relationship between definite device thrombosis and dual antiplatelet therapy (DAPT) status at the time of the event during 5-year follow-up

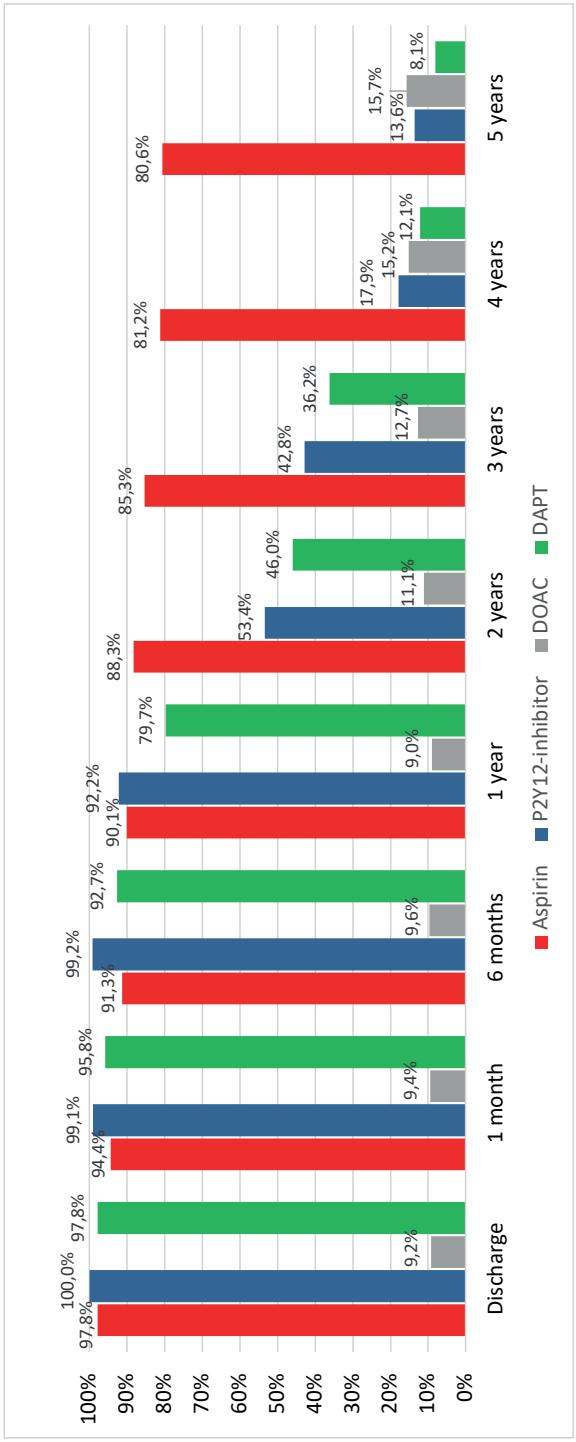


FIGURE 4. Antiplatelet therapy per follow-up in Absorb BVS-group.

Effect of DAPT

Device thrombosis is a serious complication with high morbidity and mortality.(14) DAPT significantly reduces the risk of stent thrombosis in DES.(15, 16) The introduction of bioresorbable scaffolds led to the question on whether current DAPT recommendations after DES implantation are also applicable to this different technology. A prolonged ischemic risk period could be expected due to its larger footprint (strut thickness 157um) compared with contemporary second-generation DES (60 to 90um), which may lead to greater platelet activation and delayed endothelialisation.(17, 18) In addition, intraluminal dismantling of Absorb BVS at sites without complete endothelialisation during the resorption process has been suggested as a new mechanism of device thrombosis.(19) Indeed, our results demonstrated an increased ischemic risk period of four years with Absorb BVS compared to Xience EES. Especially high complex PCI, as bifurcation stenting, long lesions or double layer stents, led to ischemic events long after the index procedure. Therefore, prolonged DAPT may be justified and outweigh an increased bleeding risk particularly after complex PCI. Although our analyses are retrospective and should be interpreted with caution, the odd ratios of DAPT on ScT are suggestive of possible effect. In addition, there was no temporal relationship between DAPT discontinuation and VLST. For example, all ScT between 3- and 4-years follow-up occurred on average 331 days after DAPT cessation. Well-apposed and embedded struts at baseline can still protrude into the lumen later on during the reabsorption process.(20) It is also plausible that good apposition at baseline would not prevent the occurrence of acquired malapposition, as large plaque burden continues to exert an inner force on the progressively weaker resorbing device. So, a cause of scaffold thrombosis may occur at any time during the reabsorption process, rather than being present continuously and cause thrombosis after DAPT discontinuation.

Nevertheless, lacking data on major bleedings precludes us from commenting on the net clinical benefit of prolonged DAPT. Further research for the recommendation on DAPT duration after implantation of scaffolds, a completely different technology than metallic DES, is warranted.

Causes of scaffold thrombosis

The causes of very late scaffold thrombosis are not yet fully understood. It is thought that the underlying mechanism of very late scaffold thrombosis is mostly scaffold dismantling, followed by malappostion and neoatherosclerosis(21). The current data uncovered another possible mechanism of scaffold thrombosis. Three very late scaffold thrombosis occurred in lesions previously treated for restenosis with Xience EES. Lack of Optical Coherence Tomography images precludes us from making a more definitive conclusion about the

mechanisms of these particular cases and allows us only to speculate. It is possible that the DES itself caused device thrombosis. However, it cannot be excluded that resorption of the underlying BVS caused device thrombosis due to protrusion of the thrombogenic material or that it caused acquired malapposition of the DES. As new generations of scaffolds are being developed, it is important to further investigate whether it is safe to implant a metallic stent over the scaffold.

Overcome very late device-related events

Bioresorbable scaffold were designed to overcome very late device-related events often caused by neoatherosclerosis.(22) However, neoatherosclerosis did also appear in Absorb BVS treated lesions (23) and led to at least one scaffold thrombosis. Neoatherosclerosis will eventually occur within any device if sufficiently potent risk factors remain active and Absorb BVS is not immune to the progression of neoatherosclerosis. In addition, the incidence of patient-oriented and device-related adverse events in the Xience EES group reported in the current article are not negligible. Target lesion failure-rate within the first year was 5.2%, afterwards an annual rate of ±2.2%, and a total of 16.1% target lesion failure-rate at 5-year follow-up. Patient-oriented composite endpoint in Xience-arm within first year was 10.6%, afterwards an annual rate of ±+/- 4.0%, and 26.6% at 5-year follow-up. Therefore, regardless of the stent platform, more effort on secondary prevention is needed.

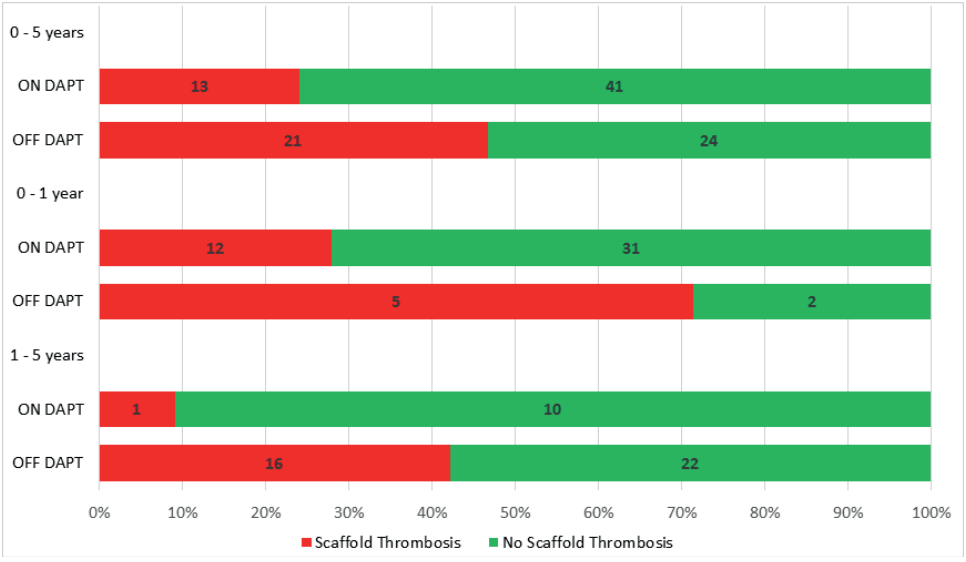


FIGURE 5. Effect of DAPT on occurrence of Scaffold Thrombosis

Limitations

The present study has several limitations. First, the AIDA trial was powered for the primary endpoint of TVF at 2 years. All secondary analyses on individual components of the primary endpoint such as scaffold thrombosis should be considered hypothesis generating. Second, the lack of systematic intravascular imaging in patients with clinical events, preclude more definite conclusions about the mechanisms related to BVS failure at different time points. Third, restarting or prolonging DAPT through three 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 compared to patients who were treated according to the applicable guidelines and IFU. Fourth, patients and clinicians were unblinded to treatment assignment after the report of concerns about the safety of Absorb BVS upon the recommendation of the DSMB. Fifth, bleeding events were not monitored or adjudicated by clinical event committee and therefore it precludes us from assessing the net benefit of prolonged DAPT.

Conclusions

In addition to previous reports, the increased risk for device related myocardial infarction and revascularization in patients treated with the Absorb bioresorbable vascular scaffold continues up to 4 years after index PCI and seems to plateau afterwards. Retrospective analyses indicate a reduction of odds with the use of prolonged DAPT on scaffold thrombosis. The later, however, would have to be weighted against the risk of bleeding in individual patients and needs further investigation.

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Supplementary material

SUPPLEMENTARY TABLE 1. Characteristics of the Patients at Baseline*

	Absorb BVS (N=924)		Xience EES (N=921)	
Age - years	64.3	±10.6	64.0	±10.5
Male sex – n (%)	670	(73%)	700	(76%)
Risk factors – n/ total n (%)				
Diabetes mellitus	171/924	(19%)	153/921	(17%)
Requiring oral medication	95/171	(56%)	97/153	(63%)
Requiring insulin	65/171	(38%)	45/153	(37%)
Hypertension	468/920	(51%)	464/919	(51%)
Hypercholesterolemia	344/915	(38%)	350/914	(38%)
Family history of coronary artery disease	451/886	(51%)	469/886	(53%)
Current smoker	248/867	(29%)	273/861	(32%)
History – n/ total n (%)				
Chronic renal failure	70/924	(8%)	91/921	(10%)
Ejection fraction < 30%	22/910	(2%)	17/900	(2%)
Previous stroke or transient ischemic attack	46/923	(5%)	58/921	(6%)
Peripheral vascular disease	65/924	(7%)	56/918	(6%)
Previous myocardial infarction	166/924	(18%)	172/921	(19%)
Previous percutaneous coronary intervention	202/924	(22%)	184/921	(20%)
Previous bypass surgery	38/924	(4%)	26/921	(3%)
Clinical presentation – n (%)				
ST-segment elevation myocardial infarction	240	(26%)	225	(24%)
Non ST-segment elevation myocardial infarction	185	(20%)	192	(21%)
Unstable angina	70	(8%)	87	(9%)
Stable angina and/or documented ischemia	361	(39%)	370	(40%)
Angiographic driven	51	(6%)	36	(4%)
Other	17	(2%)	11	(1%)
SYNTAX score				
Mean	13.2	±8.6	12.6	±8.4
Median	11	(7-18)	11	(7-17)

** plus-minus values are means ± SD. Absorb BVS: Absorb bioresorbable vascular scaffold; n:number; Xience EES: Xience everolimus-eluting stent*

SUPPLEMENTARY TABLE 2. Procedural Characteristics.*

Outcome	Absorb BVS		Xience EES		P Value
Patients					
Total no.	**924**		**921**		
Treated lesions per patient	1.34	±0.63	1.31	±0.59	0.360
Number of devices per patient	1.54	±0.84	1.45	±0.79	0.014
Total device length per patient – mm	31.1	±19.6	29.7	±19.2	0.113
Minimum device diameter per patient - mm	2.73	±0.27	2.88	±0.35	0.050
Device implantation - n (%)					
Any assigned study device	895	(96.9%)	919	(99.8%)	<0.001
Only assigned study devices	859	(93.0%)	910	(98.8%)	<0.001
Any unassigned device	65	(7.0%)	11	(1.2%)	<0.001
Only unassigned devices	29	(3.1%)	2	(0.2%)	<0.001
After failure assigned device	20		1		
Unassigned device first choice	9		1		
Procedure time – min mean (total n) ± SD	49 (919)	±26	44 (918)	±23	<0.001
Contrast use – ml mean (total n) ± SD	160 (902)	±74	151 (897)	±72	0.016
Pre-dilatation first treated lesion – n/ total n of target lesions (%)	911	(99%)	892	(97%)	0.012
Procedure success	834	(90%)	889	(97%)	<0.001
Treated lesions¶					
Total no.	**1237**		**1209**		
Rotational atherectomy – n/ total n of target lesions (%)	24/1232	(1.9%)	26/1208	(2.2%)	0.776
Pre-dilatation performed – n (%)	1199	(97%)	1103	(91%)	<0.001
Total number of devices implanted	1425		1336		
Number of devices per lesion	1.15	±0.40	1.11	±0.34	0.001
Post-dilatation performed – no. (%)	915	(74%)	594	(49%)	<0.001

** Plus-minus values are means ± SD. # Listed is the diameter of the used pre-dilatation balloon, implanted stent or scaffold, and the used post-dilatation balloon. ¥ Listed is the maximum pressure of the pre-dilatation balloon, the stent or scaffold delivery-system balloon, and the post-dilatation balloon. ¶ All treated lesions at time of randomization and scheduled staged procedures. All abbreviations as in supplementary table 1.*

SUPPLEMENTARY TABLE 3. Clinical Outcomes per study arm at 4 years follow-up

	At 4 years			
	Absorb BVS (n=924)	**Xience EES (n=921)**	**Hazard Ratio (95% CI)**	**p value[$]**
All-cause death	60 (6.6%)	71 (7.8%)	0.84 (0.59-1.18)	0.309
Cardiac death	28 (3.1%)	33 (3.7%)	0.84 (0.51-1.39)	0.502
Cardiovascular death	34 (3.7%)	37 (4.1%)	0.91 (0.57-1.45)	0.697
All myocardial infarction	88 (9.8%)	55 (6.2%)	1.61 (1.15-2.26)	0.005
Target vessel MI	64 (7.1%)	38 (4.3%)	1.69 (1.13-2.53)	0.009
Non-target vessel MI	24 (2.7%)	17 (1.9%)	1.40 (0.75-2.61)	0.282
Any revascularisation	166 (18.5%)	134 (15.0%)	1.24 (0.99-1.56)	0.061
Target vessel revascularisation	110 (12.3%)	82 (9.2%)	1.34 (1.01-1.79)	0.042
Target lesion revascularisation	84 (9.4%)	56 (6.3%)	1.50 (1.07-2.11)	0.017
Device thrombosis related	34 (3.8%)	7 (0.8%)	4.87 (2.16-10.99)	<0.001
Device stenosis related	54 (6.1%)	50 (5.6%)	1.07 (0.73-1.57)	0.734
Composite endpoints				
Target vessel failure	147 (16.2%)	122 (13.5%)	1.21 (0.95-1.54)	0.116
Target lesion failure†	125 (13.7%)	103 (11.4%)	1.22 (0.94-1.58)	0.133
Patient-oriented composite endpoint‡	233 (25.4%)	208 (22.8%)	1.13 (0.94-1.36)	0.197
Device thrombosis				
Definite device thrombosis				
Probable device thrombosis				
Definite/probable device thrombosis				

$ p-values were calculated by the log-rank test. † Composite of cardiac death, target vessel myocardial infarction and target lesion revascularisation. ‡ Composite of death, myocardial infarction or any revascularisation. BVS = bioresorbable vascular scaffold; EES = everolimus-eluting stent; MI = myocardial infarction

SUPPLEMENTARY TABLE 4. Descriptive characteristics of cases of definite device thrombosis

Case	Device	Initial PCI Indication	Treated Vessel	Lesion type	Ref size (mm)	Pre-dilatation (atm)	Stent size (atm)	Post-dilatation (atm)	Initial DAPT therapy	Days to DT	DAPT therapy Time of DT	Clinical outcome (worst)	Patients note
1	Absorb BVS	STEMI	Mid RCA	B2	4.0x15	3.0x15 (12)	3.5x18 (13)	4.0x12 (13)	ASA Ticagrelor	0	ASA Ticagrelor	Myocardial infarction	Dissection distal of stent (OCT)
2	Absorb BVS	STEMI	Prox LAD	B2	3.5x18	3.5x20 (6)	3.5x18 (14)	3.5x12 (20)	ASA Ticagrelor	1	ASA Ticagrelor	Myocardial infarction	Distal edge dissection (OCT)
3	Absorb BVS	AP	Mid RCA	B2	3.0x15	3.0x15 (10)	3.5x18 (14)	4.0x12 (14)	ASA Clopidogrel	2	ASA Clopidogrel	Myocardial infarction	Malapposition stent (OCT)
4	Absorb BVS	AP	Mid RCA	C	3.0x46	2.5x20 (16)	3.0x28 (12) 3.0x18 (14)	3.0x20 (18)	ASA Clopidogrel	3	ASA Clopidogrel	Myocardial infarction	
5	Absorb BVS	STEMI	Prox LAD	C	3.5x21	2.0x12 (12)	3.0x15 (14) 3.5x12 (16)	3.75x15 (22)	ASA Clopidogrel	4	ASA Clopidogrel	Myocardial infarction	
6	Absorb BVS	AP	Distal RcX	B2	2.5x28	2.5x20 (10)	2.5x28 (10)	2.5x20 (14)	ASA Clopidogrel	5	ASA Clopidogrel	Myocardial infarction	Possible to low therapy compliance
7	Absorb BVS	Stabilized STEMI	Prox RCA	C	3.0x30	3.5x15 (12) Rotablation	3.5x18 (14) 3.5x18 (14)	3.5x15 (14)	ASA Ticagrelor	6	ASA	Myocardial infarction	Patient forgot to take Ticagrelor
8	Absorb BVS	NSTEMI	Prox LAD	B2	2.5x15	2.5x15(UN)	2.5x18 (10)	3.0x12 (12)	ASA Ticagrelor	11	ASA Ticagrelor	Myocardial infarction	
9	Absorb BVS	STEMI	Prox LAD Distal RCA Mid RCA Mid RCA	C C C C	3.0x25 2.7x25 2.7x25 2.7x25	2.5x20 (8) 3.5x20 (12) 2.5x20 (10) 3.5x20 (10)	3.0x28 (10) 2.5x28 (14) 3.0x28 (14) 2.5x28 (14)	3.5x15 (10) No No No	ASA Ticagrelor	29	ASA Ticagrelor	Myocardial infarction	DT in both LAD and RCA

SUPPLEMENTARY TABLE 4. Continued

Case	Device	Initial PCI Indication	Treated Vessel	Lesion type	Ref size (mm)	Pre-dilatation (atm)	Stent size (atm)	Post-dilatation (atm)	Initial DAPT therapy	Days to DT	DAPT therapy Time of DT	Clinical outcome (worst)	Patients note
10	Absorb BVS	NSTEMI	Mid LAD Prox LAD	B2 B1	3.0x45 4.0x15	2.5x20 (14) 2.5x20 (14)	2.5x23 (16) 3.0x28 (18) 3.5x18 (18)	4.0x15 (18) 4.0x15 (18)	ASA Ticagrelor OAC	46	Clopidogrel OAC	Myocardial infarction	Malapposition stent (OCT)
11	Absorb BVS	UAP	Mid LAD	B1	3.0x12	2.5x15 (10)	3.0x18 (12)	No	ASA Ticagrelor	86	ASA	Myocardial infarction	Interaction Ticagrelor and HIV medication
12	Absorb BVS	NSTEMI	Prox RCA	B1	3.5x10	3.0x15 (12)	3.5x12 (14)	3.5x8 (22)	ASA Clopidogrel OAC	100	Clopidogrel OAC	Non-fatal MI followed by cardiac death	
13	Absorb BVS	UAP	Mid LAD	B1	3.5x15	2.0x15 (18)	3.5x18 (10)	3.5x15 (16)	ASA Ticagrelor	161	None	Myocardial infarction	DAPT cessation during surgery
14	Absorb BVS	NSTEMI	Prox RcX	B2	3.0x28	2.5x15 (12)	3.0x28 (14)	3.5x15 (14)	ASA Ticagrelor	185	None	Myocardial infarction	DAPT cessation during surgery
15	Absorb BVS	STEMI	Mid LAD	B1	2.5x23	2.0x20 (14)	2.5x23 (14)	2.5x15 (18)	ASA Ticagrelor	234	ASA Ticagrelor	Myocardial infarction	
16	Absorb BVS	AP	RcX, OM	B1	2.5x12	2.5x15 (8)	2.5x18 (6)	No	ASA Ticagrelor	249	ASA	Myocardial infarction	History of low therapy compliance
17	Absorb BVS	NSTEMI	Prox RcX	B2	2.5x15	2.5x15 (8) Rotablation	2.5x18 (14)	2.75x15 (16)	ASA Ticagrelor	352	ASA	Myocardial infarction	Dissection after stent implantation (angio)
18	Absorb BVS	AP	Mid RCA Distal RCA	B2 B2	3.5x25 3.0x15	2.5x20 (12) 2.5x20 (12)	3.5x28 (12) 3.0x18 (14)	4.0x15 (10) No	ASA Ticagrelor	376	ASA	Myocardial infarction	Malapposition distal stent (OCT)
19	Absorb BVS	STEMI	Distal RCA	B2	3.0x24	2.0x20 (10)	3.0x27 (8)	3.5x15 (18)	ASA Ticagrelor	419	ASA	Myocardial infarction	

SUPPLEMENTARY TABLE 4. Continued

Case	Device	Initial PCI Indication	Treated Vessel	Lesion type	Ref size (mm)	Pre-dilatation (atm)	Stent size (atm)	Post-dilatation (atm)	Initial DAPT therapy	Days to DT	DAPT therapy Time of DT	Clinical outcome (worst)	Patients note
20	Absorb BVS	AP	Dist RcX	B1	3.0x10	3.0x15 (18)	3.0x18 (12)	No	ASA Ticagrelor OAC	427	OAC	Myocardial infarction	
21	Absorb BVS	STEMI	Mid RCA	B2	3.5x23	3.5x20 (10)	3.5x28 (12)	3.5x15 (12)	ASA Prasugrel OAC ASA stop after 3 months	430	None	Non-fatal MI followed by cardiac death	OAC cessation during surgery (Clexane)
22	Absorb BVS	Angio-driven	Prox RCA Prox RcX	B1 A	4.0x16 3.5x12	3.0x20 (16) 3.0x12 (14)	3.5x28 (16) 3.0x23 (16)	4.0x20 (12) 3.5x40 (16)	ASA Clopidogrel	437	Unknown	Myocardial infarction	
23	Absorb BVS	STEMI Staged	Prox RCA Prox RcX	B2 B1	2.5x15 3.0x12	2.5x15 (10) 3.0x15 (10)	3.0x18 (12) 3.0x18 (14)	No No	ASA Ticagrelor	461	ASA	Myocardial infarction	
24	Absorb BVS	AP	Distal LAD Prox LAD	B1 A	3.0x28 3.5x12	2.5x28 (14) 3.0x12 (14)	3.0x28 (14) 3.5x12 (14)	3.0x28 (14) 3.5x14 (14)	ASA Ticagrelor	471	ASA Ticagrelor	Myocardial infarction	
25	Absorb BVS	STEMI	Prox RCA	C	3.5x18	3.0x15 (12)	3.5x23 (16)	4.0x20 (16)	ASA Prasugrel	567	ASA	Myocardial infarction	
26	Absorb BVS	STEMI	Mid RCA	B2	3.0x25	3.0x15 (12)	3.0x28 (10)	2.25x20 (13)	ASA Ticagrelor	593	ASA	Myocardial infarction	
27	Absorb BVS	STEMI	Prox LAD	C	3.5x21	2.5x20 (10)	3.5x23 (18)	3.5x15 (18)	ASA Ticagrelor	733	ASA	Myocardial infarction	Patient refused re-start DAPT
28	Absorb BVS	NSTEMI	AO-MO graft	B2	3.0x18	2.0x15 (12)	3.0x18 (10)	3.0x12 (14)	ASA Clopidogrel	769	ASA	Myocardial infarction	

SUPPLEMENTARY TABLE 4. Continued

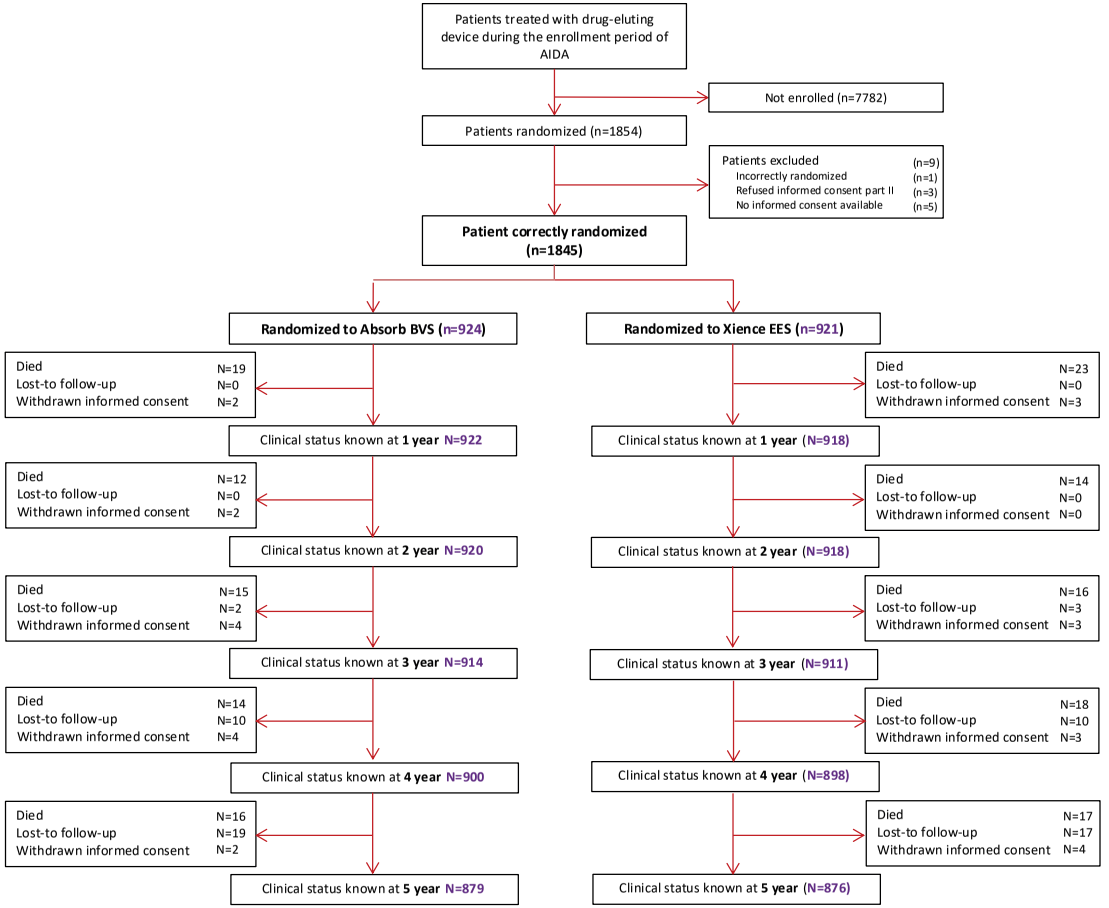
Case	Device	Initial PCI Indication	Treated Vessel	Lesion type	Ref size (mm)	Pre-dilatation (atm)	Stent size (atm)	Post-dilatation (atm)	Initial DAPT therapy	Days to DT	DAPT therapy Time of DT	Clinical outcome (worst)	Patients note
29	Absorb BVS	AP	Prox LAD	A	3.5x8	3.0x15 (12)	2.5x12 (12)	3.5x8 (20)	ASA Clopidogrel	817	ASA	Myocardial infarction	Malapposed non-covered struts distally (OCT)
30	Absorb BVS	NSTEMI	RcX, MO	B1	2.5x10	2.5x15 (20)	2.5x12 (16)	2.75x15 (18)	ASA Ticagrelor	825	ASA	Myocardial infarction	
31	Absorb BVS	NSTEMI	Mid RcX Prox RCA Distal RCA	B1 B1 B1	3.0x28 3.5x18 2.5x28	2.5x15 (14) 2.0x20 (10) 2.0x20 (10)	3.0x28 (16) 3.5x18 (8) 2.5x29 (12)	3.0x28 (18) 4.0x12 (20) 3.0x12 (10)	ASA Ticagrelor	1223	ASA	Post NSTEMI	RcX prox occluded; TLR Cx Xience at 790 days
32	Absorb BVS	Stabilized STEMI	Mid LAD First Diagonal	C B2	2.5x45 2.5x45 2.5x45 3.5x12	2.5x30 (12) 2.5x30 (12) 2.5x30 (12) 3.5x15 (16)	2.5x28 (16) 2.5x28 (16) 2.5x18 (16) 3.5x12 (14)	No No No 4.0x9 (14)	ASA Ticagrelor	1,277	Unknown	Myocardial infarction	DT in LAD
33	Absorb BVS	AP	Distal RcX Prox LAD	B1 B1	3.5x18 3.0x18	3.0x15 (12) 2.5x15 (12)	3.5x18 (14) 2.5x18 (12)	3.5x12 (16) 2.5x12 (16)	ASA Ticagrelor	1,312	ASA	Myocardial infarction	TLR with Xience at 2 days
34	Absorb BVS	UAP	Mid LAD First Diagonal	B1 B2	3.5x15 2.5x10	3.0x15 (12) 2.5x10 (10)	3.5x18 (12) 2.5x12 (12)	4.0x15 (12) No	ASA Clopidogrel	1,330	ASA	Myocardial infarction	DT in LAD, TLR with Xience at 668 days
35	Absorb BVS	UAP	Prox RCA Distal RCA	C C	3.5x23 2.5x23	2.5x15 (12) 2.5x15 (10)	3.5x23 (14) 2.5x23 (12)	3.5x12 (16) 2.5x12 (16)	ASA Ticagrelor	1,377	ASA	Myocardial infarction	Acute DT on severe scaffold-restenosis
36	Absorb BVS Xience EES	AP	Prox LAD Mid RcX	B1 B1	3.0x18 2.5x15	2.5x20 (20) 2.0x20 (16)	3.0x23 (20) 2.5x23 (16)	3.0x15 (20) No	ASA Clopidogrel	1,506	Unknown	Myocardial infarction	Subtotal lesion RcX proximal of stent
37	Absorb BVS	STEMI	LAD Mid	C1	3.0x20	2.0x20 (10)	3.0x23 (18)	3.0x15 (16)	ASA Ticagrelor	1,711	ASA	Myocardial infarction	

SUPPLEMENTARY TABLE 4. Continued

Case	Device	Initial PCI Indication	Treated Vessel	Lesion type	Ref size (mm)	Pre-dilatation (atm)	Stent size (atm)	Post-dilatation (atm)	Initial DAPT therapy	Days to DT	DAPT therapy Time of DT	Clinical outcome (worst)	Patients note
38	Absorb BVS	NSTEMI	LAD Mid	B1	3.3x15	3.0x15 (10)	3.0x18 (12)	3.5x15 (12)	ASA	1,798	ASA		ST in D1
	Xience EES		D1	B2	3.0x20	3.0x15 (6)	3.0x23 (10)	No	Ticagrelor				

SUPPLEMENTARY TABLE 5. Descriptive characteristics of cases of definite device thrombosis

Case	Device	Initial PCI Indication	Treated Vessel	Lesion type	Ref size (mm)	Pre-dilatation (atm)	Stent size (atm)	Post-dilatation (atm)	Initial DAPT therapy	Days to DT	DAPT therapy Time of DT	Clinical outcome (worst)	Patients note
1	Xience	Stabilized	Mid RCA	B2	3.5x15	No	3,5x10 (18)	3.5x18 (14)	ASA Ticagrelor	0	ASA Ticagrelor	Myocardial Infarction	
		STEMI	Dist RCA	C	2.5x25	2.5x20 (14)	2,75x28 (14)	2.5x15 (8)					
2	Xience	STEMI	Prox LAD	B2	3.0x28	3.0x20 (6)	3.0x38 (14)	3.5x15 (12)	ASA Ticagrelor	0	ASA Ticagrelor	Myocardial Infarction	
3	Xience	STEMI	Prox LAD	B2	3.5x15	3.0x15 (16)	3.5x15 (12)	No	ASA Ticagrelor	1	ASA Ticagrelor	Myocardial Infarction	Jailing stent (Angio)
4	Xience	AP	Distal RcX	A	3.0x15	2.5x15 (10)	3.0x18 (12)	No	ASA Clopidogrel	3	ASA Clopidogrel	Myocardial Infarction	
5	Xience	STEMI	Prox RCA	B2	3.0x15	3.0x15 (10)	3.0x12(16)	No	ASA Prasugrel	511	ASA	Myocardial Infarction	Malapposition proximal stent-strut (OCT)
6	Xience	STEMI	Mid LAD	B1	3.0x16	3.0x15 (6)	3.0x18 (12)	No	ASA Ticagrelor	1,222	ASA	OHCA	
7	Xience	UAP	Distal RCA	B1	3.0x10	2.5x10 (13)	3.0x15 (14)	No	ASA Clopidogrel	1,391	ASA Clopidogrel	Myocardial Infarction	TLR at 176 days
8	Xience	AP	Mid LAD	B1	3.0x15	2.5x12 (10)	3.0x18 (12)	No	ASA Prasugrel	1,472	ASA	Myocardial infarction	
9	Xience	STEMI	RCA mid	A1	3.0x10	2.5x15 (18)	3.0x12 (18)	No	ASA	1,792	none	Myocardial infarction	ST in MO1
			MO1	A1	2.5x12	2.5x15 (16)	2.5x15 (16)	No	Ticagrelor				Cessation NOAC 1 month prior



SUPPLEMENTARY FIGURE 1. Study Flowchart