Editorial

Adverse events with bioresorbable vascular scaffolds in routine percutaneous coronary interventions: "coup de théâtre" or unfinished play?

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Bioresorbable scaffolds are percutaneous coronary prostheses designed to ensure transient support of the dilated vessel and dissolution into inert breakdown products overtime (1). By leaving the coronary artery without a permanent metallic implant, bioresorbable scaffolds have been developed to absolve three main commitments: improve long-term vessel healing and remodelling, restore vasomotor function of the treated segment, and reduce the burden of angina symptoms in comparison with conventional drug-eluting stent (DES) platforms.

The encouraging short-term data from four industry-sponsored randomized controlled trials granted the everolimus-eluting bioresorbable vascular scaffold (BVS/Absorb, Abbott Vascular, Santa Clara, CA, USA) the approval from regulatory agencies for clinical use in Europe, USA, China and Japan (2). In these pivotal trials, patients with moderately complex obstructive coronary artery disease (CAD) treated with either BVS or everolimus-eluting metallic stent (EES) showed broadly comparable clinical outcomes at 12 months. However, a meta-analysis (3) and a large registry of individuals with relatively more complex CAD (4) displayed a thrombotic risk at 6- to 12-month follow-up with BVS about twice as high in comparison with the benchmark metallic EES. More disappointingly, recent follow-up data beyond 1 year from those trials (5,6) originally designed to support the regulatory approval of BVS in Europe and Japan failed to demonstrate either physiological or clinical advantages with BVS as compared to EES. At the opposite, BVS was associated with a risk of failure, which accrued with the time.

In line with these considerations, the results of the Amsterdam Investigator-initiateD Absorb strategy all-comers (AIDA) trial published in the *New England Journal of Medicine* in 2017 have to be highlighted (7). The AIDA trial was a single blind, multicentre, investigator-initiated, non-inferiority, randomized clinical trial, which included 1,845 unselected CAD patients with 2,446 lesions assigned to either BVS or EES therapy. The primary endpoint was target vessel failure (TVF) the composite of cardiac death, target vessel related myocardial infarction (TV-MI) or target vessel revascularization at 2 years. Device thrombosis at 2 years was a main secondary endpoint. Among those enrolled, 54.1% of patients presented an acute coronary syndrome at admission (including one-fourth of participants with ST-segment elevation MI) and 52.8% of lesions treated had a complex morphology. In this report, the authors provided descriptive outcomes data released after a median follow-up duration of 2 years since the data and safety monitoring board recommended early reporting of results owing to safety concerns. The main findings of AIDA trial were as follows: at 2-year follow-up (I) BVS was associated with a risk of TVF comparable to that of EES;

(II) however, BVS had an approximately 3.5 times higher risk of thrombosis and a higher risk of TV-MI as compared to EES; (III) notably, nearly one-third of BVS thromboses occurred in the period beyond 1 year after implantation. These results deserve an in-depth discussion.

First, although the acronym of the trial by Wykrzykowska *et al.* recalls the name of the Nubian princess protagonist of the homonymous play by Giuseppe Verdi, the results of the AIDA trial do not represent a "coup de théâtre". Indeed, 10 days before the *New England Journal of Medicine* posted online the results of this trial, the 2-year data from the ABSORB III trial presented during the 2017 American College of Cardiology Congress reported a higher risk for device failure and thrombosis associated with BVS as compared to EES (8). Similarly, the majority of recently published meta-analyses (1,9-18) investigating the clinical outcomes beyond 1 year of CAD patients treated with either BVS or EES display a consistent higher risk of failure and/or thrombosis with fully-bioresorbable scaffolds regardless of the availability of the AIDA trial for pooled risk estimates (*Table 1*).

Second, although some enthusiastic proponents of BVS technology continue to argue that a suboptimal implantation technique accounts for the observed unfavourable results (19), there is no evidence from randomized trials or meta-analyses of individual data in support of this claim. Investigators of AIDA trial were experienced in BVS technology at time of study inception and conduction, as indicated from the high proportion (96.9%) of patients in the BVS group in which at least one assigned study device was implanted, the few number of devices implemented in vessels <2.25 mm in diameter and the proportions of pre- and post-dilation in the group of patients treated with BVS (96.9% and 74%, respectively). These percentages were significantly higher than those of the group of patients treated with EES and among the highest reported within randomized trials studying this technology (18). Notably in this trial, BVS failure occurred regardless of pre- and post-dilation and of the use of a specific protocol dedicated to BVS implantation (pre-dilation, appropriate vessel sizing, and high-pressure post-dilation) suggesting that device failure may not only depend on technical issues (20). In addition, although the adoption of BVS implantation protocols targeted at improving acute mechanical results may hypothetically impact on short-term outcomes (21), whether such protocols can modify rates of late thrombotic events remains to be demonstrated.

Third, the accrual of thrombotic events after the discontinuation of dual antiplatelet therapy (DAPT) observed in this as well as in other randomized trials of BVS versus metallic DES, has prompted the AIDA investigators (22) and certain professional associations (23) to recommend the prolongation of DAPT up to 36 months or even the re-introduction of DAPT in all patients treated with BVS if not contra-indicated. Moreover, some experts have suggested intensifying platelet inhibition with more potent P2Y12-receptor antagonists in patients treated with BVS at low risk of bleeding (24). However, these recommendations are based on experts' consensus rather than on a solid evidence. In this regard, despite the ABSORB II trial did not report late thrombotic events after BVS implantation in patients that never interrupted DAPT out to 3 years (6), a recent meta-analysis found a higher thrombotic risk with BVS both at 12- and 24-month follow-up, irrespectively of the proportions of patients on DAPT at each timepoint (18). Moreover, the well-known increased risk of bleeding associated with a prolonged DAPT (25) may nullify the potential long-term benefits of fully-bioresorbable platforms, which are expected some years after implantation.

In consideration of these indicators of concern, the Food and Drug Administration warned all practitioners in the USA against the higher risk of adverse events associated with BVS, recommending a careful patient selection and the implementation of implantation protocols specific to this technology. Concomitantly, after advising in conjunction with the European Regulatory Agency all physicians regarding the worrisome mid-term outcomes of BVS, the manufacturer has discontinued the normal commercial sale of BVS in Europe and restricted its usage to centres participating in carefully monitored registries. Notwithstanding this, the fact that the performance of current BVS does not reflect initial enthusiastic expectations should not jeopardize further investigations in this field, leaving the technology of fully-bioresorbable scaffolds as an "unfinished play". The knowledge of intrinsic limitations of current devices should encourage a continuous iteration towards new-generation fully-bioresorbable scaffolds, which are in advanced phases of development (1). The hypothesis that refinements of implantation protocols and ancillary therapies might reduce adverse events in patients treated with current BVS generation is under investigation in ongoing large-scale randomized trials (NCT02173379, NCT02486068). In the meantime, long-term follow-up data (>5 to 10 years) of completed studies and future comparative studies of new-generation fully-bioresorbable platforms remain fundamental to disclose

Table 1 Published meta-analyses investigating TLF and definite/probable ST beyond 1 year with BVS versus EES

First Author	RCTs included	Follow-up duration, months	Statistical model for risk estimates	Risk estimates (95% CI) with BVS versus EES		Other features
				TLF	Definite/probable ST	
Toyota (9)	ABSORB China; ABSORB II ABSORB Japan	16.2 (median)	RE (DL)	OR 1.08 (0.76–1.54)	OR 2.08 (1.02–4.26)	7 comparative observational studies and 14 single-arm registries included in the analysis; limited 3-year follow-up data (1 trial)
Nairooz (12)	ABSORB China; ABSORB II ABSORB Japan	24	FE/RE (DL)	OR 1.53 (1.06–2.23)	OR 2.85 (0.81–9.99)	2 comparative observational propensity matched registries included in the analysis; limited 3-year follow-up data (1 trial)
Ha (15)	ABSORB China; ABSORB II ABSORB Japan	24	N/R	OR 1.31 (0.93–1.83)	OR 2.35 (1.14–4.86)	2 comparative observational registries included in the analysis; limited 3-year follow-up data (1 trial)
Sotomi (1)	ABSORB China; ABSORB II; ABSORB Japan; EVERBIO; TROFI II	24 (median)	FE (Peto)	OR 1.47 (1.00–2.17)	OR 3.07 (1.34–7.02)	time-to-event analysis restricted to definite/probable ST; limited 3-year follow-up data (1 trial)
Collet (17)	ABSORB China; ABSORB II; ABSORB Japan; EVERBIO; TROFI II	24 (median)	RE (DL/HK)	OR 1.48 (0.90–2.42)	OR 2.93 (1.37–6.26)	time-to-event analysis restricted to definite/probable ST; limited 3-year follow-up data (1 trial)
Sorrentino (10)	ABSORB China; ABSORB II; ABSORB III; ABSORB Japan; AIDA; EVERBIO; TROFI II	24 (median)	FE/RE (DL)	RR 1.32 (1.10–1.59)	RR 3.15 (1.87–5.30)	time-to-event analysis restricted to definite/probable ST; RCTs with variable follow-up duration (1 to 3 years) available for certain outcomes (i.e., all-cause death, TLR, MI); limited 3-year follow-up data (1 trial)
Mahmoud (14)	ABSORB China; ABSORB II; ABSORB III; ABSORB Japan; AIDA; EVERBIO	25 (median)	RE (DL, Peto)	RR 1.33 (1.11–1.58)	RR 3.22 (1.89–5.49)	time-to-event analysis restricted to definite/probable ST; limited 3-year follow-up data (1 trial)
Montone (13)	ABSORB China; ABSORB II; ABSORB III; ABSORB Japan; AIDA; EVERBIO; TROFI II	24 (median)	FE (MH)	OR 1.35 (1.11–1.65)	OR 3.33 (1.97–5.62)	time-to-event analysis restricted to TLF and definite/probable ST; RCTs with variable follow-up duration (1 to 3 years) available for certain outcomes (i.e., TLF); limited 3-year follow-up data (1 trial)
Polimeni (11)	ABSORB China; ABSORB II; ABSORB III; ABSORB Japan; AIDA	24	RE (DL)	OR 1.33 (1.07–1.63)	OR 3.22 (1.86–5.56)	time-to-event analysis restricted to definite/probable ST; limited 3-year follow-up data (1 trial)

Table 1 *(continued)*

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First Author	RCTs included	Follow-up duration, months	Statistical model for risk estimates	Risk estimates (95% CI) with BVS versus EES		Other features
				TLF	Definite/probable ST	
Cassese (18)	ABSORB China; ABSORB II; ABSORB III; ABSORB Japan; AIDA; EVERBIO; TROFI II	26.6 (median)	FE/RE (MH/DL/HK)	OR 1.35 (1.11–1.65)	3.24 (1.92–5.49)	time-to-event analysis for TLF, definite/probable ST, definite ST, TLR and TV-MI; RCTs with homogeneous follow-up durations available for all outcomes; 3-year follow-up data available for 3 out of 7 trials

TLF, target lesion failure; ST, stent (scaffold) thrombosis; BVS, bioresorbable vascular scaffold; EES, everolimus-eluting stent; RCT, randomized controlled trial; RE, random effect; DL, DerSimonian and Laird; (TV)-MI, (target vessel) myocardial infarction; TLR, target lesion revascularization; FE, fixed effect; HK, Knapp-Hartung adjustment; MH, Mantel-Haenszel; OR, odds ratio; RR, risk ratio. Official titles and acronyms, ABSORB China, A Clinical Evaluation of Absorb™ Bioresorbable Vascular Scaffold (Absorb™ BVS) System in Chinese Population; ABSORB II, A Clinical Evaluation to Compare the Safety, Efficacy and Performance of ABSORB Everolimus Eluting Bioresorbable Vascular Scaffold System Against XIENCE Everolimus Eluting Coronary Stent System in the Treatment of Subjects With Ischemic Heart Disease Caused by de Novo Native Coronary Artery Lesions; ABSORB III, A Clinical Evaluation of Absorb™ BVS, the Everolimus Eluting Bioresorbable Vascular Scaffold in the Treatment of Subjects With de Novo Native Coronary Artery Lesions; ABSORB Japan, A Clinical Evaluation of AVJ-301 (Absorb™ BVS), the Everolimus Eluting Bioresorbable Vascular Scaffold in the Treatment of Subjects With de Novo Native Coronary Artery Lesions in Japanese Population; AIDA, Amsterdam Investigator-initiateD Absorb strategy all-comers trial; EVERBIO II, Comparison of Everolimus- and Biolimus-Eluting Stents With Everolimus-Eluting Bioresorbable Vascular Scaffold Stents; TROFI II, Comparison of the ABSORB™ Everolimus Eluting Bioresorbable Vascular Scaffold System With a Drug- Eluting Metal Stent (Xience™) in Acute ST-Elevation Myocardial Infarction.

possible advantages of this technology in comparison with contemporary high-performance metallic DES. Until further data will be available, current benchmark metallic DES should be further regarded as standard comparator for studies investigating the relative safety and efficacy of different percutaneous technologies for patients undergoing revascularization because of obstructive CAD.

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Footnote

Conflicts of Interest: A Kastrati has submitted patents in relation to DES technologies. The other authors have no conflicts of interest to declare.

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