Editorial

Bioresorbable scaffolds versus metallic stents in routine PCI: the plot thickens

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The story so far: from plain old balloon angioplasty to the preliminary release of the AIDA trial results

The evolution of percutaneous coronary revascularization, after this treatment was introduced in clinical practice in the form of balloon angioplasty, has been characterized by three landmarks, corresponding to the development and application of an equal number of specific device types. In terms of chronologic appearance, these developments can be broadly categorized as bare metal stents, drug eluting stents (DES) and finally bioresorbable scaffolds (BRS). Bare metal stents were able to overcome some of the major drawbacks of balloon angioplasty, most importantly acute vessel closure and recoil, but their application was still plagued by significant rates of restenosis. The introduction of DES, and most importantly their further development in the second generation iterations, effectively managed the problem of restenosis and also reduced to clinically acceptable levels the incidence of an unexpected problem encountered during the long-term follow-up of the first generation DES, namely late stent thrombosis. Further developments in the design of DES, including reductions in strut thickness, more biocompatible coatings and novel anti-proliferative agents, have led to the currently used versions of DES in clinical practice, collectively referred to as new generation DES. New generation DES are considered the best currently available technology in percutaneous coronary intervention, but room for improvement still exists. This room is associated with the permanent implant that is left in the coronary arteries after metallic stent implantation and has been the driving force for the development of BRS. The promise of BRS is that after the bioresorption process is completed, restoration of functionality and normal geometry of the vessel could take place (1). At the clinical level, these theoretical advantages could be translated in the elimination of the risk of device thrombosis and in-scaffold neo-atherosclerosis and the broadening of the clinical indications of stenting to include the passivation of non-obstructive, vulnerable plaques. Despite the disappointing results of the first, preclinical investigations of synthetic polymers for developing BRS (2), subsequent advances in the field were rapid and more promising, testing an ever increasing number of new, polymer or metal, alloys and culminating in the development of the first BRS which achieved the CE mark for clinical use in coronary interventions. The BVS 1.1 iteration of Abbott's BRS achieved the CE mark in 2010, based on the results of the single-arm ABSORB trial—101 patients with no evidence of thrombosis during a follow-up out to 5 years (3), and became the first BRS to achieve this status. This milestone was accompanied a few years later by another first, the achievement of FDA approval in 2016, based on the 1 year results of ABSORB III (4). The most important characteristic of Abbott's Absorb BRS however, is that it is the only available BRS that has been evaluated in randomized, controlled trials so far, meaning that

the specific device currently serves as the only available mean to test the true potential of BRS. Hence, inevitably, when it comes to the question metallic stents or BRS for percutaneous coronary intervention, the discussion focuses on the ABSORB trials series.

Collectively, seven randomized controlled trials (RCT) evaluating the Absorb scaffold (Absorb, Abbott Vascular) *vs.* the cobalt-chromium everolimus-eluting metallic stent (Xience, Abbott Vascular) in a total of 5,583 patients have completed enrolment and one (ABSORB IV) is currently recruiting. Until the release of the preliminary results of AIDA trial, interim clinical results had been presented for ABSORB II (5,6), ABSORB III (4,7), ABSORB Japan (8) ABSORB China (9), EVERBIO II (10,11) and TROFI II (12) trials. None of these trials reported a difference in cardiac mortality between the two devices. In addition, in ABSORB II, ABSORB China, ABSORB Japan, and EVERBIO II, the 2 years clinical results were comparable between ABSORB and Xience for all clinical end-points. However, in all of the aforementioned trials, the rates of target lesion failure (TLF) and/or scaffold/stent thrombosis (ST), despite statistically non-significant differences, were numerically higher in the BRS group. This unfavourable trend eventually turned into a statistically significant difference, when the 2 years follow-up results of the ABSORB III (7) and the 3 years follow-up of ABSORB II (6) were published. These results, in conjunction with registry based data demonstrating increased thrombotic events with Absorb (13), prompted the data and safety monitoring board of the AIDA trial to recommend the release of an early report of the study's data at 2 years follow-up, owing to safety concerns. These preliminary results were published in the March 29th, 2017 issue of the New England Journal of Medicine (14).

The AIDA trial: results and clinical implications

AIDA is a single-blind, multicenter, investigator-initiated, non-inferiority, randomized, clinical trial funded by Abbot (which however had no role in the design of the study, the collection or management of the data, or the statistical analysis) comparing the Absorb BRS *vs.* the Xience stent in patients undergoing PCI for one or more target lesions considered suitable for drug-eluting stent implantation on the basis of clinical judgment. Key exclusion criteria are target lesions more than 70 mm in length, a reference vessel diameter of less than 2.5 mm or more than 4.0 mm (as estimated visually), bifurcation lesions for which the use of two stents or scaffolds was planned, and in-stent restenosis. The primary end point of target-vessel failure was a composite of cardiac death, target-vessel myocardial infarction, or target-vessel revascularization.

At the time that the release of preliminary results was decided, a total of 1,845 patients had been enrolled and clinical follow-up had been completed in 899 patients in the scaffold group (97.3%) and 894 patients in the stent group (97.1%). The results of this trial, in brief, demonstrated that after a median follow-up duration of 707 days, the Absorb BRS compared to the Xience stent demonstrated: (I) no significant differences in the rates of target-vessel failure (= primary end point) (11.7% *vs.* 10.7%, P=0.43), TLF (10.3% *vs.* 8.9%, P=0.31), cardiac death (2% *vs.* 2.7%, P=0.43) and target-lesion revascularization (7.0% *vs.* 5.2%, HR =1.33, P=0.15); and (II) a higher incidence of definite or probable device thrombosis (3.5% *vs.* 0.9%, P<0.001) and target-vessel myocardial infarction (5.5% *vs.* 3.2%, P=0.04). Furthermore, no major predictors of device thrombosis were found and when the researchers performed a landmark analysis of ST at 30 days, the risk of definite and probable ST was ongoing in the Absorb arm. Unfortunately, routine intravascular imaging at the time of implantation and device thrombosis was not performed, limiting the insights of the researchers into the mechanisms of device thrombosis and this was the single most important limitation of the trial. Finally, another interesting observation was that scaffold implantation was associated with increased procedural time and use of contrast material, and a lower likelihood of receiving the assigned device. These findings are indicative of the delivery challenges encountered with scaffold implantation.

The 2-year results of AIDA, build on the 2 years results of ABSORB III and the 3 years results of ABSORB II, to establish the increased mid-term risk of ST with Absorb as a consistent finding. Although the results at 2 years from ABSORB China, ABSORB Japan, and EVERBIO II trials do not support this conclusion, the population of ABSORB II, ABSORB III and AIDA combined accounts for 78% of the patients included in the ABSORB series of RCTs with complete enrolment. Furthermore, the AIDA results lend themselves to the most updated meta-analysis including the totality of currently available evidence (median follow-up 2 years), which demonstrated significantly increased rates of TLF and definite or probable ST with Absorb BRS *vs.* new generation DES (Xience in 96.5% of the cases) (15). Hence, although the 2 years landmark is not the time-point to use for drawing the final conclusions, AIDA completes a picture

showing quite convincingly that Absorb is associated with increased thrombotic complications at mid-term follow-up. Since the theoretical advantage of a BRS *vs.* durable polymer platforms manifests beyond the 3 years' time frame, the game is still on for Absorb BRS, but at present the results are disappointing.

The observation of increased ST in AIDA could be considered as a double blow for the case of Absorb, as it seems that it is not only associated with increased thrombotic complications but also that we don't know what is causing this phenomenon and most important how to deal with it.

AIDA had very limited exclusion criteria, hence its population was as close as possible to the real-life patients treated in every day clinical practice, including patients presenting with ACS (54%) and classic high risk and challenging lesions subsets, such as by-pass grafts, heavily calcified lesions and CTOs. Also, although vessel size <2.25 mm was an exclusion criterion, in total, 220 patients received a scaffold in such a vessel. However, no interaction with respect to device thrombosis was seen between the study groups and presenting symptoms, age, cardiovascular risk factors, lesion characteristics, vessel calibre (small and large vessels, using 2.75 mm as a cut-off) or QCA parameters. There was also no significant difference in device thrombosis between patients with a scaffold in a vessel $\leqslant$2.25 mm and patients with Absorb in larger vessels (2.9% *vs.* 3.3%, P=0.67). Investigators also stratified patients according to their SYNTAX risk score. In patients with low SYNTAX scores, the rate of scaffold thrombosis among Absorb-treated patients was 1.1%, which could be considered clinically acceptable as an absolute number, but still, it was significantly higher than the rate in the Xience-treated patients with low SYNTAX scores (0.3%).

The most significant uncertainty that has arisen from the AIDA results, however, is the one about the impact of the implantation technique in the post-acute phase outcomes. Proponents of the PSP (pre-dilate, size and post-dilate) strategy (16), argue for the mitigation of ST risk with good implantation techniques (17,18). However, in AIDA, there was no difference in the use of device sizing, pre- and post-dilatation among patients with and without definite scaffold thrombosis. On the other hand, it should be noted that during the first year of enrolment, post-dilation was performed in only 63% of the lesions in the scaffold group, as implantation of the scaffolds did not include mandatory post-dilation (as per manufacturer's instructions) at that time. The steering committee recommended routine post-dilation of the scaffold device from October 1, 2014, onward. The authors claim that this fact had no impact on the outcomes, since "patients treated early in the randomization process had similar outcomes in terms of ST with patients treated at later dates, when operators gained experience and understanding of the importance of good implantation techniques". However, this observation is not sufficient to discard the hypothesis of improved results with strict adherence to optimal implantation technique. On the contrary, if there is one good news for Absorb from the AIDA trial is that this hypothesis remains alive and might be the only thing that can still save the game. The on-going ABSORB IV trial will probably be the final judge of this theory and anecdotal data from participants randomized so far show a markedly lower overall rate of ST at 30 days and 1 year compared with the ABSORB III, attributed to improved operator technique.

Unfortunately, until further trials conclude on this hypothesis, interventional cardiologists will be faced with uncertainty about the use of the Absorb BRS in new patients. The most important uncertainty that cardiologists will be faced with however, is the management of patients that have already been exposed to the increased, mid-term risk of ST of Absorb. The data and safety monitoring board of AIDA recommended that extended dual antiplatelet therapy (DAPT) should be considered for recipients of the Absorb BRS and this recommendation is already applied in the trials participants. However, how long should be DAPT prolonged? Some experts advocate the prolongation of DAPT for 3 years in patients who can tolerate it and the reinstitution of DAPT in patients who completed a one year-round of DAPT and are currently on aspirin mono-therapy. This, of course, is not the ideal solution, since it is well documented that the reduction in ischemic events comes at the cost of an increase in bleeding events (19), but at present it appears like the only solution. It is conceivable, that if Absorb finally achieves the desired long-term results accompanied by guidelines recommending prolonged DAPT, this would be a Pyrrhic victory.

Where do we go from here?

The most important message from AIDA trial is that Absorb BRS is a non-working horse device, in search for a setting to demonstrate clinical benefit over new generation DES. The favourable effects of this scaffold in vasomotion, endothelial stress, late luminal expansion and angina alleviation, observed in previous trials (20), did not materialize, while an increase in ST at 2 years was established. The latter

observation will be the determining factor for the fate of this scaffold, if it is reproduced in the long-term follow-up results of the ABSORB RCT series. This process, however, will be probably completed around 2025, when the final release of the ABSORB IV results is expected. All involved pieces in the BRS chessboard are repositioned, waiting for that day. On March 24, 2017, FDA issued a safety alert for Absorb, emphasizing the importance of good implantation technique and adherence to recommended DAPT, reflecting a "wait for more data" approach on the issue, while further investigations are on-going. This was based on the 2-year results of ABSORB III, which showed significantly increased rates of TLF and non-significantly increased rates of ST for Absorb, an inverse of what was observed in the 2-year results of the Dutch-based AIDA trial. Abbott took one step further in Europe, by limiting the supply of the Absorb BRS only in patients enrolled in clinical registries, in the hope that the results of longer term follow-up combined with strict adherence to proper implantation technique will eventually turn the tide. Finally, other manufacturers of BRS, claiming improved technical characteristics compared to Absorb BRS are warming up their engines to take the long, hard step of transitioning from clinical studies designed for the achievement of the CE mark to randomized studies aiming at non-inferiority *vs.* new generation DES (21). In the evolutionary history of DES, the problem of increased thrombotic complications of the first generation was managed with the development of the second generation. Whether this will be the case with the evolution of BRS as well or another scenario will emerge, as long-term follow-up data are accumulated, remains to be seen.

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Footnote

Conflicts of Interest: PW Serruys is a member of the international advisory board for Abbott. A Katsikis has no conflicts of interest to declare.

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