Editorial

Bioresorbable vascular scaffolds for complex coronary anatomies: "Icarus' flight" for interventional cardiologists?

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Provenance: This is a Guest Editorial commissioned by Section Editor Yue Liu, MD (Department of Cardiology, The First Affiliated Hospital of Harbin Medical University, Harbin, China).

Comment on: Kraak RP, Grundeken MJ, Hassell ME, *et al*. Two-year clinical outcomes of Absorb bioresorbable vascular scaffold implantation in complex coronary artery disease patients stratified by SYNTAX score and ABSORB II study enrolment criteria. EuroIntervention 2016;12:e557-65.

Submitted Oct 24, 2016. Accepted for publication Nov 30, 2016.
doi: 10.21037/cdt.2017.01.10
View this article at: http://dx.doi.org/10.21037/cdt.2017.01.10

In patients suffering from obstructive coronary artery disease (CAD) a percutaneous therapy with fully bioresorbable scaffolds ensures for the vessel a temporary support which dissolves into inert breakdown products after a certain amount of time. These coronary prostheses have been developed with the objective of improving vascular healing and remodeling, and restoring vasomotricity of the treated segment, once the dissolution process is absolved (1). By virtue of their transient nature, fully bioresorbable scaffolds are expected to avoid the late pathophysiological processes associated with permanent drug-eluting stent (DES) platforms, which have been found responsible for an accrual of adverse events over the long term (2).

In the last decade, fully bioresorbable scaffolds eluting antirestenotic drugs have been extensively investigated in CAD patients. By virtue of initial positive results in highly selected cohorts, the everolimus-eluting bioresorbable vascular scaffold (BVS/Absorb, Abbott Vascular, Santa Clara, CA, USA) has been the first among fully bioresorbable coronary prostheses deserving CE-mark approval (3). Thereafter, the favorable outcomes observed in two large-scale randomized controlled trials [ABSORB II (4) and ABSORB III (5)] comparing BVS versus the benchmark metallic everolimus-eluting stent (EES) (Xience; Abbott Vascular, Santa Clara, California, USA) vouched for BVS the Food and Drug Administration approval for clinical use in the United States since July 2016.

Notwithstanding the green light obtained from regulatory agencies on both sides of the Atlantic, investigations of BVS in moderately complex lesions demonstrated a risk of stent/scaffold thrombosis (ST) out to 1-year follow-up about twice as high in comparison with the benchmark metallic EES (6). Consistent findings have been observed in several registries including individuals with relatively more complex CAD (7). In consequence of these indicators of concern, a number of observations addressed the issue of whether a more proper selection of patients to implant may result in improved performance of current-generation BVS (8). In this respect, an interesting report published in *EuroIntervention* in 2016 has to be highlighted (9).

Kraak and co-workers presented the 2-year results of the Amsterdam Medical Center (AMC) Registry, a single-center study, which included 135 unselected CAD patients with 159 lesions treated with BVS implantation. The main purposes of this analysis were: firstly, to report the incidence of target vessel failure (TVF) 2 years after a successful percutaneous intervention with BVS in the overall population included; secondly, to investigate the incidence of TVF in participants grouped by adherence to inclusion criteria of ABSORB II trial or by baseline Synergy between PCI With TAXUS and Cardiac Surgery (SYNTAX) score. TVF, the primary endpoint of the analysis, was defined as the composite of

cardiac death, target vessel-related myocardial infarction, and target vessel revascularization (TVR) and occurred in a proportion of 14.4% participants at 2-year follow-up. At the same time point, TVR and definite ST occurred in a proportion of 11.3% and 3.0% patients, respectively. Interestingly, the rates of TVF and TVR were lower in patients who fitted the ABSORB II inclusion criteria as compared to those who did not. Moreover, being 11.5 the median baseline SYNTAX score of participants, TVF and TVR were less frequent in those patients totaling a score under the median value as compared to those with a score above this threshold. Despite the inherent limitations of a single-center, small-sized registry, in which BVS was implemented without optimal implantation technique or routine intracoronary imaging, the authors should be commended for this important undertaking and for the independent adjudication of outcomes data. However, some points need careful discussion.

First, the rates of TVR and definite ST reported in the AMC Registry are in keeping with recent studies of unselected CAD individuals treated with BVS (10-13), displaying rates of TVR between 2.4% and 10.1% and rates of definite ST between 0.9% and 3.3% >1 year after index procedure. Although these studies had no independent adjudication of clinical outcomes available, the common denominator was that TVR and definite ST attributable to the use of BVS in broadly inclusive CAD populations remain fairly higher than we have accustomed to with contemporary metallic DESs. In this regard, a recent pooled analysis of 4,554 patients treated with contemporary metallic DESs in four randomized trials with "all-comers" design (14) reported a 2-year risk for TVR and definite ST associated as high as 6.4% and 0.9%, respectively.

Second, Kraak and colleagues documented a circa 10 times lower rates of TVF and TVR in patients fitting the ABSORB II criteria as compared to those with more complex coronary anatomies and comorbidities, though the rate of definite ST remained unaffected. Consistent with all other coronary platforms (15), BVS efficacy remains a straightforward function of CAD complexity. In contrast, the safety of BVS in less complex patient and lesion populations cannot be easily discounted. The early and very late thrombotic risk associated with current BVS generation remains a matter of concern, irrespectively of CAD complexity. A recent meta-analysis demonstrated a higher risk of subacute ST in patients with moderately complex lesions treated with BVS therapy (6). In addition, the 2-year follow-up of the ABSORB II (16) and the ABSORB Japan (17) trials, enrolling highly selected CAD populations, reported some cases of ST beyond 1 year, while no case was observed in patients treated with metallic EES, suggesting a possible risk of very late events while the scaffold is dissolving.

Finally, by grouping patients into low or high CAD complexity with the median SYNTAX score as discriminant, Kraak *et al*. reported higher 2-year rates of TVF and TVR in patients totaling a SYNTAX score >11.5. Interestingly, a recent analysis, in which CAD complexity was defined by means of a SYNTAX score threshold similar to that used in the AMC Registry, found contemporary metallic DESs in patients with higher SYNTAX score values (>11) associated with 2-year rates of TVR and definite ST of 7.6% and 1.0%, respectively (14). These results diverge substantially from those of patients with high CAD complexity treated with BVS in the AMC Registry (TVR 21.8%; definite ST 3.1%).

In virtue of these considerations, the behavior of interventional cardiologists with respect to BVSs resembles the myth of the "Icarus' flight". According to Greek mythology, while attempting to escape from Crete by means of wings constructed from feathers and wax, Icarus ignored the warning of his father Daedalus not to fly too close to the sun, and fell into the sea. The literary interpretation has found in this myth the structure and the consequence of over-confidence. In the same way, contemporary operators have prematurely challenged the BVS technology with complex patients and lesion subsets, which they confidently managed with metallic DES, in the absence of robust evidence supporting this practice. On the contrary, a mounting body of evidence suggests that current BVS technology is immature to supply all CAD patients encountered in the routine clinical practice and that the broader is the clinical use of BVS, the more technical shortcomings emerge (17).

As further data from clinical trials investigating BVS is expected in the years to come, the uncertainty regarding early performance and late benefits of these platforms should not feed a skeptical behavior. At the opposite, continuous investigations in patients enrolled in carefully supervised randomized trials remain pivotal to allow current BVS technology being competitive against contemporary best-in-class metallic DESs at least for simple to moderately complex CAD. Although the iterations of current BVS platforms in terms of scaffold design and backbone components are expected to overcome present technical shortcomings and to improve clinical outcomes, operators should be discouraged to handle contemporary

BVSs as metallic DESs. On the contrary, the use of BVS should follow protocols of implantation specific to this technology (18,19), by including a more liberal use of intravascular imaging, which has proved to increase the performance of these devices (20). This represents the only way to ascertain whether BVS implantation will translate into tangible clinical benefit for CAD patients as compared to contemporary high-performance metallic DES platforms, without prematurely dismantling a technology, which may be a potential breakthrough in the field of interventional cardiology.

Acknowledgements

None.

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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Cite this article as: Cassese S, Kastrati A, Fusaro M. Bioresorbable vascular scaffolds for complex coronary anatomies: "Icarus' flight" for interventional cardiologists? Cardiovasc Diagn Ther 2017;7(Suppl 2):S98-S101. doi: 10.21037/cdt.2017.01.10

