Commentary

Bioresorbable scaffold—the holy grail of percutaneous coronary intervention: fact or myth?

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When Grüntzig preformed the first balloon angioplasty in 1977 (1), it revolutionized the treatment of obstructive coronary artery disease (CAD) and provided an alternative to coronary bypass surgery. While a reasonable procedural and clinical outcome was achievable with balloon angioplasty alone, sustained arterial patency was ultimately undermined by elastic recoil, acute secondary closure and constrictive remodeling (2). The second technological leap in percutaneous coronary intervention (PCI) occurred with the advent of bare metal stents (BMS), which promised to overcome these issues by providing a mechanical scaffold within the coronary arteries (3). Longitudinal studies however have since demonstrated suboptimal long term outcomes with the use of BMS due primarily to the high incidence of in-stent restenosis (ISR) (4). The development of drug eluting stent (DES) represented the third paradigm shift in the field of interventional cardiology, whereby the coating of BMS with anti-proliferative agents resulted in a significant reduction in the incidence of ISR and improvement in patient outcome (5). The benefit was further enhanced by new stent designs and evolution in polymer technology (6), with the second generation DES now widely accepted as the percutaneous treatment of choice for obstructive CAD. The persistence of stent struts within the coronary artery remains a significant pitfall however, with ongoing issues relating to the risk of stent thrombosis (ST) (7), neoatherosclerosis (8), loss of vasomotion (9) and preclusion from future bypass surgery.

The development of bioresorbable scaffold (BRS) marks the beginning of a fourth revolution in PCI, providing an alternative stent platform that has the ability to deliver drugs locally, provide initial mechanical support, and degrades over time once its desired effect is achieved. Many such devices are currently under investigation, while two have received Conformité Européenne (CE)-mark approval for use in clinical practice. Of the two, the ABSORB bioresorbable vascular scaffold (BVS; Abbot Vascular, Santa Clara, CA, USA) was the first BRS to undergo comprehensive clinical evaluation and is now available for clinical use worldwide. ABSORB BVS is an everolimus-eluting BRS composed of poly-L-lactic acid (PLLA) and poly-DL-lactic acid (PDLLA). The polymeric BRS maintains its radial strength for 6 months after implantation and auto-hydrolyzes into carbon dioxide and water over a space of 2–4 years (10).

ABSORB BVS has been benchmarked against the cobalt-chromium based everolimus eluting metallic stent (CoCr-EES; Abbott Vascular, Santa Clara, CA, USA) in several clinical trials, with the latter being considered as the current gold standard in DES technology in terms of its efficacy and safety. Each individual trial however was relatively under-powered to detect small differences in low frequency events such as ST and death, while subgroup analyses were similarly precluded. With this in mind, Stone *et al*. performed a patient-level, pooled meta-analysis of four completed randomized trials of ABSORB BVS, and leveraged the improved statistical power to characterize the safety and efficacy of the BVS as compared with the CoCr-EES (11). The methodology was robust, and while the study was funded by the BVS manufacturer, the author had jurisdiction over the final report. Overall, 3,389 stable and stabilized patients with acute coronary syndrome were included in the analysis. In effect, the study demonstrated equipoise between the two devices in terms of the patient-

and device-oriented composite endpoints at 12 months, with no statistical differences in the relative rates of all-cause and cardiac mortality, all myocardial infarction (MI), ischemia-driven target lesion revascularization, and all revascularization. The authors concluded by stating that there was a non-significantly different rate of overall outcome at 1-year follow-up between the two devices.

While this represents a valuable contribution to the evidence base of ABSORB BVS, certain caveats need to be carefully considered. Specifically, both device (95.6% *vs*. 99.4%, P<0.0001) and procedural (94.9% *vs*. 97.0%, P=0.003) successes rates were significantly lower in the BVS arm. Secondly, numerically more early target lesion failure was observed with BVS (4.1% *vs*. 2.6%, P=0.051), likely reflecting early mechanical issues following device implantation. Lastly, there is a numerical trend towards higher incidence of definite/probable ST (1.3% *vs*. 0.6%) and MI (5.7% *vs*. 4.0%) at 12 months in the BVS arm, which echo observations made previously by other large clinical registries (12).

It is important to note that current data pertains exclusively to first generation ABSORB BVS, which has a relatively thick strut (157 microns)—a design feature considered necessary to maintain its radial strength. The crimping process further increases its crossing profile (1.4 mm), which is considerably larger than a contemporary metallic stent (1.0 mm) (13). This limits the deliverability, trackability and pushability of these devices and may explain the differences observed in procedure duration, procedural as well as device success rate, and a numerical increase in the incidence of ST and MI at 12 months. The outcome is further compounded by the variation in operators' experience, with optimal scaffold implantation potentially undermined by inconsistencies in device sizing, lesion preparation, routine high pressure post-dilatation and guidance with intra-coronary imaging. Only 66.2% of patients in the ABSORB arm had post-dilation, while 23.9% underwent intracoronary imaging. Indeed, the importance of proper implantation technique including pre-implantation plaque modification, routine high pressure scaffold post-dilatation with non-compliant balloons, and liberal use of intracoronary imaging such as optic coherent tomography (OCT) to evaluate scaffold apposition and coverage have since been appreciated and advocated.

Furthermore, the manufacturer's restriction on scaffold size has not been universally observed, with a significant proportion of BVS being implanted in vessels with a reference diameter of <2.5 mm. In ABSORB III, if vessels smaller than 2.25 mm were excluded from the analysis, the incidence of ST were in fact equivalent between the two arms (14). Adherence to vessel sizing guidelines may therefore further off-set target lesion failure by reducing the incidence of recurrent MI and ST both at 30 days and 1 year. Notably, while the target vessel related MI was higher in the ABSORB arm, it was due in part to a higher incidence of peri-procedural myocardial infarction (PMI). This may be related to higher degree of residual diameter stenosis and scaffold mal-apposition, though other factors may be at play such as small side-branch occlusion. Importantly however, the incidence of clinically significant PMI as defined by the Society of Cardiac Angiography and Intervention (15) did not vary significantly between the two arms. The clinical relevance of this observation therefore remains unclear.

Another pertinent point to consider relates to the short follow-up in this study. While the outcomes are similar between the two study arms at 12 months, most of the anticipated benefits of BVS are not expected to become apparent until 3–5 years after implantation when the treated arteries are completely "uncaged", leading to restoration of vessel geometry, physiological vasomotion, late luminal gain and late expansive remodeling (16). This is particularly important in younger patients undergoing PCI, with annualized rate of target lesion failure with second generation DES remaining at around 1.8% with no observable plateau (7). Further, studies thus far have focused primarily on relatively uncomplicated lesions and clinical contexts, with deliberate exclusion of patients with heavily calcified vessels, left main diseases, chronic total occlusions, and acute coronary syndromes. In its current form, BVS have several practical limitations including its deliverability that may restrict its use in these scenarios, and penalties such as longer procedural time, need for more aggressive lesion preparation, higher incidence of PMI, and significantly lower procedural success have been observed (17). However, a number of studies focusing on real life application of the BVS technology have now demonstrated its feasibility in a broad range of clinical contexts including calcified and bifurcational lesions, particularly with meticulous implantation techniques (17,18). The long term implications of off-label application of BVS however need to be further delineated by prospective trials (COMPARE ABSORB, NCT02486068) before its generalized adoption could be encouraged in routine clinical practice.

Several questions remain unanswered by this analysis, such as the interaction between patients' outcome and the choice of P2Y12 antiplatelet therapy as well as their

baseline attribute including diabetes. These will require further exploration with long term and adequately powered randomized trials (Absorb IV, NCT02173379). The impact of optimal implantation techniques and improved strut design also needs to be ascertained, incorporating features such as thinner struts, improved expansile capability, and earlier strut degradation, which may improve the outcomes further compared with current iteration of BVS. Finally, a cost-effective analysis needs to be performed to assess the benefit of BVS in a wider population context.

The ability to liberate the coronary vessels from permanent metallic caging is an inherently appealing concept, and the present study has helped push it one step closer to reality by demonstrating equipoise in both the efficacy and safety endpoints between an established gold standard and the ABSORB BVS, notwithstanding the limitations of a first generational device. With ongoing randomized trials still many years away from completion, the results of the current analysis should be treated with respect and embraced with a degree of cautious optimism. It is hoped that further studies will eventually confirm the sustained benefit as well as the versatility of ABSORB BVS, and indeed the technology BRS as a whole, and complete the fourth wave of revolution in the field of interventional cardiology.

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Footnote

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Conflicts of Interest: N Jepson has received speaker's fees from Abbott Vascular. K Liou has no conflicts of interest to declare.

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