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EDITORIAL COMMENT

Bioabsorbable Stents

A Solution in Search of a Problem?*

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The emergence of the bioabsorbable vascular scaffold (BVS) is a technical tour de force in the world of biomechanical engineering and deserves recognition as a major accomplishment. However, the ultimate value of any technical advent lies in the improvement it offers our patients balanced against potential risks. The introduction of angioplasty itself presented such a dilemma. Early attempts at balloon angioplasty were marked by substantial risk of abrupt vessel closure and need for emergent surgery. Yet the advantage of avoiding an open surgical procedure in the well-selected patient was obvious. The introduction of bare-metal stents (BMS) was marked by legitimate concern for stent thrombosis, especially before the widespread use of dual antiplatelet therapy. Yet, the dramatic improvement in procedural safety and efficacy was compelling. The introduction of drug-eluting stents (DES) was hailed as a landmark event for reductions in restenosis. Even after press reports of late stent thrombosis were widely compared to having a "time bomb" in the heart, their use persisted because practitioners understood the risk-benefit ratio favored DES. The concept of the fully absorbable stent has obvious appeal, but does it satisfy this risk benefit relationship?

There are both patient and physician perceived benefits of the bioabsorbable stent. The notion of allowing the coronary vasculature to return to a more "natural state" with the ability to retain aspects of normal vascular function has been argued as beneficial. In addition, a lack of a permanent scaffold removes potential barriers to future surgical revascularization. However, the greatest appeal is the oft-cited preference of not having a permanent indwelling implant, and thereby avoiding some of the long-term risks of DES. It merits emphasis that the excellent performance of newer generation DES raises the bar considerably for this latter contention. The results of the ABSORB trials to date have shown both promise and risk. The ABSORB II trial was the first randomized trial to compare the Absorb BVS (Abbott Vascular, Santa Clara, California) against an everolimus-eluting stent (EES). There were 2 primary endpoints: superiority of BVS in terms of angiographic vasomotor reactivity and noninferiority of late lumen loss. Neither of these endpoints was met at 3-year follow-up (1). The pivotal ABSORB III trial used the composite endpoint of target lesion failure, cardiac death, target vessel myocardial infarction, and ischemia-driven target-vessel revascularization. At 1 year, noninferiority was met for BVS versus EES (7.8% vs. 6.1%; p for noninferiority = 0.007) (2). By 2 years, however, BVS subjects had increased target lesion failure (11.0% vs. 7.9%; p = 0.03) (3). Other concerns have arisen around thrombotic complications. In the ABSORB II trial, 3-year rates of definite or probable stent thrombosis were statistically higher for BVS (2.8% vs. 0.0%; p = 0.0331) (1). In the ABSORB III trial, rates of stent thrombosis did not appear different, although by 2 years, rates of target vessel myocardial infarction were statistically higher in BVS (7.3% vs. 4.9%; p = 0.04) (3). Coincident with the release of these data, the U.S. Food and Drug Administration released a letter informing health care providers of higher rates of major adverse cardiac events with the Absorb BVS.

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In this issue of *JACC: Cardiovascular Interventions*, Alfonso et al. (4) present data from the RIBS VI (Restenosis Intrastent: Biosresorbable Vascular

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Scaffolds Treatment) study examining the use of BVS in patients with in stent restenosis. Could this represent a niche for BVS? It certainly is one of the more complex lesion subsets. Many of us have encountered the particularly vexing issue of patients with refractory restenosis in which we have to consider placing multiple stents in the same arterial segment. A solution that is not dependent on a second or even third permanent layer of stent is attractive. The RIBS VI study is based on a prospective registry and results were compared to similar registries examining the use of EES and drug-eluting balloon (DEB) for in stent restenosis. Although not randomized, the studies have mandated angiographic follow-up and used identical entry criteria. Using both in segment late lumen loss and target lesion revascularization rates, the authors report that EES was superior to both DEB and BVS. There was no appreciable difference demonstrated between BVS and DEB. Safety was excellent with only 1 patient in the BVS arm experiencing stent thrombosis and this was in the setting of premature dual antiplatelet therapy discontinuation.

Although this appears to be a setback for BVS use for in-stent restenosis, arguments can be made to withhold judgment. One of the arguments made consistently regarding BVS is that poor procedural technique has hampered the performance of the stent in clinical trials. Much has been made about the importance of the so-called PSP technique (emphasizing predilation, appropriate vessel sizing, and high-pressure post-dilation). What was the procedural performance in the RIBS VI study? The authors report that in the study, 97% of patients underwent pre-dilation. In the ABSORB III trial, the eligibility criteria included vessels with reference diameters from 2.5 mm to 3.75 mm. Yet, 19% of patients had a target lesion treated with a reference vessel diameter (RVD) of $<$2.25 mm by quantitative angiography. Post hoc analysis suggested that these patients were at greatest risk for adverse events (3). In comparison, the percent of patients in the RIBS VI study with RVDs $<$2.25 mm is not specifically given, but the average RVD was 2.69 $\pm$ 0.40 mm, and results are stratified by RVD $<$3 mm or $>$3 mm and seem to show no difference. Finally, the authors report that the majority (66%) of patients in the RIBS VI study underwent post-dilation. One could posit that more uniform post-dilation might have made a difference in outcome. However, what is likely to happen in the real world with widespread adoption of BVS? Although we should emphasize optimum technique for all procedures, it is not clear that such rigor will be widely applied to an extent that would match the RIBS VI study proceduralists.

Another argument that is frequently made regarding BVS is that the clinical benefits will not be readily discernible until the bioresorption process is complete, estimated to be approximately 3 years. The RIBS VI study only reports events until 1 year and it is plausible that 3-year follow-up will demonstrate a different and beneficial outcome. Yet it is also plausible that late detrimental effects will be encountered akin to the late stent thromboses seen in the years following the introduction of first-generation DES. The local pharmacokinetics and pharmacodynamics of drug delivery are complex and incompletely understood. BVS adds the complexity of the biology of resorption. To assume that we will not encounter possible late adverse reactions is premature.

Perhaps the most compelling argument to withhold judgment on the potential of BVS is that these are first-generation devices and will undoubtedly improve with further development. After all, current generation DES are demonstrably superior to first-generation DES with stent thrombosis rates lower than BMS (5). The RIBS VI study perhaps demonstrates areas for potential improvement in BVS. Immediately following implantation, EES achieve a statistically significant larger acute luminal gain than BVS do, a phenomenon seen in earlier ABSORB studies. This suggests the polymer does not have the same radial strength afforded by the cobalt chromium scaffold of the EES. Struts of current generation BVS are thicker than typical metal alloy stents. These physical characteristics can be improved and polymer and drug advancements will surely occur as well.

What lessons do we learn from the RIBS VI study? At first glance, it does not appear that treatment of in stent restenosis is a natural niche for use of BVS given similar outcomes with DEB. Yet, DEB are not currently Food and Drug Administration–approved for coronary use in the United States so in the interim, BVS may be an attractive choice. Until longer-term data are available, it will remain unclear in what patients BVS may offer a demonstrable advantage. At a larger level, with prior advents in interventional cardiology the goals have always been clear; better effectiveness and safety with BMS and reduced restenosis with DES. But with BVS, the goals have been noninferiority in the short term and a less well defined and unproven long-term advantage related to returning a vessel to its “natural state.” Such goals are too vague and articulating specific patient relevant endpoints will be critical to the design of future BVS randomized trials. In the meantime, it remains to be seen whether economic considerations allow industry to invest in the research to refine BVS to overcome some of the early shortcomings.

Despite the excellent performance of the current generation of DES, the field of interventional cardiology should not rest on its laurels, but rather should continue to innovate. Clinical trials clearly point to patients where outcomes are less than desirable. This includes patients with multivessel disease and diabetes where coronary artery bypass grafting continues to show superiority. It has recently been recognized that in many patients, lesions will develop neoatherosclerosis within stents and are prone to the same thrombotic complications as de novo atherosclerosis. Clearly our work is not done. However, our questions need to be clear and relevant, and our investigations need to be focused. It is premature to discount the promise of BVS, but the role of this impressive technologic achievement is still not clear.

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REFERENCES

1. Serruys PW, Chevalier B, Sotomi Y, et al. Comparison of an everolimus-eluting bioresorbable scaffold with an everolimus-eluting metallic stent for the treatment of coronary artery stenosis (ABSORB II): a 3 year, randomised, controlled, single-blind, multicentre clinical trial. Lancet 2016;388:2479–91.

2. Ellis SG, Kereiakes DJ, Metzger DC, et al. Everolimus-eluting bioresorbable scaffolds for coronary artery disease. N Engl J Med 2015;373:1905–15.

3. Ellis SG, Kereiakes DJ, Metzger DC. Everolimus-eluting bioresorbable vascular scaffolds in patients with coronary artery disease: ABSORB III trial 2-year results. Presented at: Annual Meeting of the American College of Cardiology, March 18, 2017; Washington, DC.

4. Alfonso F, Cuesta J, Pérez-Vizcayno MJ, et al. Bioresorbable vascular scaffolds for patients with in-stent restenosis: the RIBS VI study. J Am Coll Cardiol Intv 2017;10:1841–51.

5. Giustino G, Baber U, Sartori S, et al. Duration of dual antiplatelet therapy after drug-eluting stent implantation: a systematic review and meta-analysis of randomized controlled trials. J Am Coll Cardiol 2015;65:1298–310.

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