JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
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PUBLISHED BY ELSEVIER

VOL. 69, NO. 25, 2017
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2017.04.012

EDITORIAL COMMENT

First-Generation Bioresorbable Vascular Scaffolds

Disappearing Stents or Disappearing Evidence?*

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Significant progress in percutaneous coronary intervention (PCI) technology over the last 3 decades has provided contemporary drug-eluting stents (DES) that have a low risk of restenosis and a very low risk of stent thrombosis (1). In the small proportion of patients who develop in-stent restenosis, the risk of recurrent in-stent restenosis is high, whether treated with a second-generation DES or a drug-coated balloon, and the location of the stented segment may preclude coronary artery bypass graft placement. As such, bioresorbable vascular scaffolds (BVS) hold promise that the options for revascularization, including coronary artery bypass graft surgery, will be preserved after the scaffolds disappear. Several other theoretical advantages include: expansive remodeling and return of coronary vasomotion (2), with a consequent potential greater decrease in angina as a result of "uncaging" of the artery; and mitigation of stent-related adverse events and reduction in need for extended duration dual antiplatelet therapy (DAPT). As such, this therapy has been heralded as the next paradigm shift in PCI technology, and several hospitals have issued press releases touting the benefits of the BVS on the basis of these theoretical benefits. Although many bioerodible implants are currently in development, in 2016, the Absorb scaffold (Abbott Vascular, Santa Clara, California), a 150-μm-thick, first-generation scaffold, became the first to receive Food and Drug Administration approval. To justify its use, the scaffold should be proven at least noninferior to the current best available DES in the resorption phase

*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of *JACC* or the American College of Cardiology.

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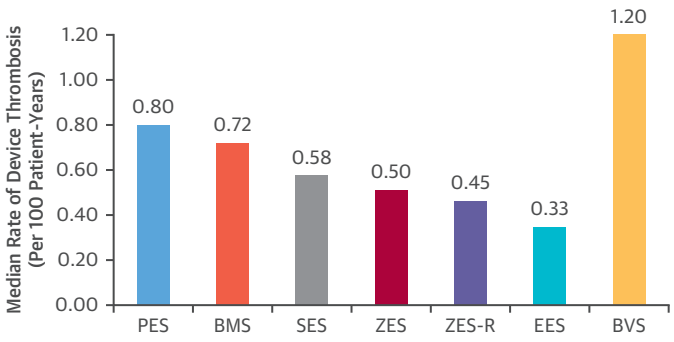
FIGURE 1 Rate of Device Thrombosis With Metallic Stents and BVS Scaffold



Rates of device thrombosis among various metallic stents (adapted from the meta-analysis by Bangalore et al. [1]) and the BVS scaffold (Abbott Vascular, Santa Clara, California) (adapted from the meta-analysis of Sorrentino et al. [4]). BMS = bare-metal stents; BVS = bioresorbable vascular scaffold; EES = everolimus-eluting stents; PES = paclitaxel-eluting stents; SES = sirolimus-eluting stents; ZES = zotarolimus-eluting stents; ZES-R = zotarolimus-eluting stent-Resolute.

(up to 3 years) and show superiority (for clinical outcomes or preservation of revascularization options) after resorption (3).

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In this issue of the *Journal*, another meta-analysis raises safety concerns with this BVS, with a significant increase in the risk of target lesion failure (driven by a significant increase in target vessel myocardial infarction and ischemia-driven target lesion revascularization) and scaffold thrombosis compared with the everolimus-eluting stent (EES) at a median follow-up of 2 years (4). This meta-analysis includes the very recent AIDA (Amsterdam Investigator-Initiated Absorb Strategy All-Comers Trial) trial, which published an early preliminary report on the basis of their Data Safety Monitoring Board's recommendation and reported an almost 4-fold increase in the risk of scaffold thrombosis compared with an EES (5). Particularly concerning from recent trials and this meta-analysis is the increased risk of not only early scaffold thrombosis, but also late and very late (>1 year) scaffold thrombosis, with persisting concern even at 3 years of follow-up, reminding physicians of similar concerns with first-generation DES (6). This is at a time when the guidelines have moved to recommend a shorter minimal required duration of DAPT (6 months) with metallic DES in elective PCI, and the concern for excessive very late stent thrombosis has largely dissipated with durable stents. Moreover, in the ABSORB II trial, the BVS had neither superior vasomotion nor greater benefit in angina relief compared with EES (7). Thus, recent trials and meta-analyses suggest that proof of noninferiority for efficacy and safety outcomes with the BVS compared with EES during the resorption phase remains elusive, and that the promise of added benefit for resorption has yet to be established.

A few hypotheses have been put forth for continued optimism despite the current sobering results, including the unexpected superior performance of the comparator in clinical trials and an as yet inadequately optimized BVS implantation procedure. In a sense, we may be stuck where we were when stents were introduced: fairly certain that the new technology (bare-metal stents first and then DES later) is superior to the predicate (balloon angioplasty first and then bare-metal stents), but unable to demonstrate benefit without changing the domain space in which comparisons are made or how the devices are designed or used. Alternatively, we may be where we were when brachytherapy was being celebrated: certain of the basic concepts at hand, but incapable of providing a coherent argument for logistical superiority against an established, working intervention.

We must then learn from our legacy and allow time-tested methods to declare how we should consider this new technology. It is therefore time to increase our sophisticated clinical trials and spur greater investment in nonclinical studies and design refinement such that we allow a potential promise to play out before being accepted without question or rejected prematurely. If the less than expected results with the BVS are due to better than expected performance of the comparator (with very low stent thrombosis, better vasomotion, and greater angina relief with EES than in prior studies), then time will tell. Furthermore, if scaffold thrombosis in the Absorb trials is in the range observed with first-generation DES or bare-metal stents (**Figure 1**), and unacceptable in current-day practice because of unrefined design or technique, then additional investigation is required. Now is the time to ask if pre-dilation, sizing, post-dilation (PSP) can indeed normalize adverse events, as suggested in some post hoc analyses. The ABSORB IV trial is one of the few large-scale trials in the PSP era, and early blinded, interim, pooled stent-scaffold thrombosis data at 1 year show a very competitive, low rate of 0.5%, which is encouraging (8). However, in the AIDA trial, pre-dilation and post-dilation were performed in the majority of patients (98.6% and 74%, respectively) in the BVS group, yet the 2-year rate of definite or probable scaffold thrombosis remained unacceptably high, at 3.5% (5). Moreover, vessel size 2.25 mm or smaller, inadequate device sizing, and lack of post-dilation

were not predictive of scaffold thrombosis in that trial, and the excess risk with the BVS seemed present in all patients studied in the AIDA trial (5). Thus, now is the time to double down on investigation of what was appreciated relatively late in the DES era: that stent dimensions, rather than material characteristics, were dominant determinants of adverse effects. The first-generation BVS has a scaffold thickness of 150 μm, as thick as the Cypher stent (Cordis, Fremont, California). Greater strut thickness increases the risk of stent thrombosis (9) and it is therefore not surprising that the device, in general, would be more thrombogenic than a comparator thin-strut DES. Moreover, this stent becomes less forgiving in small vessels, with less than optimal deployment techniques, and perhaps with less than optimal adherence and duration of DAPT.

In summary, the well-done meta-analysis by Sorrentino et al. (4) further elevates the safety concerns with the first-generation BVS, and perhaps should kindle renewed research into revision of design and procedure. In the interim, it is prudent to apply the highest standards of appropriate patient selection (vessel size ≥2.5 mm, compliance with long-term DAPT for at least 3 years), and appropriate deployment techniques (including PSP). Still, hospitals, physicians, and patients should carefully weigh whether the increased procedural duration, complexity, and cost of the BVS, with likely a need for prolonged DAPT, are worth the theoretical, though appealing, long-term potential of a coronary artery returning to its native state. Perhaps this meta-analysis is also a call to end the first phase of analysis and proceed to the second. The legacy of technology assessment and evaluation that has developed side by side with the evolution of remarkable cardiovascular interventional innovation over the last half-century provides us with a platform to renew efforts to determine and define the limits of emerging technology. New materials, designs, and implantation techniques must be considered, as it is a community responsibility to learn as much as we can before we bury a promise or accept a flawed early incarnation of potential. In the meantime, let us hope that we do not repeat the history of the overly exuberant early adoption of first-generation DES without understanding the greater stent thrombosis risk they posed compared with bare-metal stents, with early reports having difficulty getting published, and then initially being ignored (6) until the evidence became overwhelming, which perhaps led to an overreaction to the small, but real safety issue (6,10). Research on BVS should not stop—indeed, research should be redoubled. Thinner scaffolds, for example, may greatly improve deliverability of the BVS and reduce scaffold thrombosis risks as well. However, any newer BVS needs to undergo proper long-term evaluation in randomized trials versus the best second-generation DES before clinical adoption.

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REFERENCES

1. Bangalore S, Kumar S, Fusaro M, et al. Short- and long-term outcomes with drug-eluting and bare-metal coronary stents: a mixed-treatment comparison analysis of 117 762 patient-years of follow-up from randomized trials. Circulation 2012;125:2873–91.

2. Onuma Y, Collet C, van Geuns RJ, et al., ABSORB Investigators. Long-term serial non-invasive multislice computed tomography angiography with functional evaluation after coronary implantation of a bioresorbable everolimus-eluting scaffold: the ABSORB cohort B MSCT substudy. Eur Heart J Cardiovasc Imaging 2017 Mar 16 [E-pub ahead of print].

3. Bangalore S, Toklu B, Bhatt DL. Outcomes with bioabsorbable vascular scaffolds versus everolimus eluting stents: insights from randomized trials. Int J Cardiol 2016;212:214–22.

4. Sorrentino S, Giustino G, Mehran R, et al. Everolimus-eluting bioresorbable scaffolds versus everolimus-eluting metallic stents. J Am Coll Cardiol 2017;69:3055–66.

5. Wykrzykowska JJ, Kraak RP, Hofma SH, et al., AIDA Investigators. Bioresorbable scaffolds versus metallic stents in routine PCI. N Engl J Med 2017 Mar 29 [E-pub ahead of print].

6. Bavry AA, Kumbhani DJ, Helton TJ, Borek PP, Mood GR, Bhatt DL. Late thrombosis of drug-eluting stents: a meta-analysis of randomized clinical trials. Am J Med 2006;119:1056–61.

7. 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.

8. Ellis SG. Everolimus-eluting bioresorbable vascular scaffolds in patients with coronary artery disease: ABSORB III trial 2-year results. Paper presented at: ACC 2017; March 18, 2017; Washington, DC.

9. Kolandaivelu K, Swaminathan R, Gibson WJ, et al. Stent thrombogenicity early in high-risk interventional settings is driven by stent design and deployment and protected by polymer-drug coatings. Circulation 2011;123:1400–9.

10. Bangalore S, Gupta N, Guo Y, Feit F. Trend in the use of drug eluting stents in the United States: insight from over 8.1 million coronary interventions. Int J Cardiol 2014;175:108–19.

KEY WORDS drug-eluting stents, myocardial infarction, percutaneous coronary intervention, thrombosis