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EDITORIAL COMMENT

What Have We Learned From the ABSORB Trials?*

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In this issue of *JACC: Cardiovascular Interventions*, Han et al. (1) reported the efficacy and safety of the NeoVas bioresorbable scaffold (BRS) (Lepu Medical Technology, Beijing, China) relative to a metallic cobalt-chromium everolimus-eluting stent (CoCr-EES). The NeoVas BRS is a new poly-L-lactic acid-based BRS of 160 μm thickness, which elutes sirolimus (15.3 μg/mm) from a poly-D, L-lactide coating of 10 μm thickness. The present prospective single-blind, multicenter randomized controlled trial was designed to enable approval of the NeoVas BRS by the China Food and Drug Administration, in which 560 patients at 32 centers in China were randomly assigned to treatment with the NeoVas (n = 278) versus the CoCr-EES (n = 282). The primary endpoint of the difference of angiographic in-segment late loss at 1 year between NeoVas and CoCr-EES was 0.03 mm (upper 1-sided 97.5% confidence interval: 0.09 mm; p for noninferiority <0.0001 for the noninferiority margin of 0.195 mm). Clinical outcomes at 1 year were similar in the 2 groups without raising major safety concerns. The investigators should be congratulated for this well-conducted pivotal study of the NeoVas BRS.

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This is the first pivotal study for a new BRS other than the ABSORB BRS (Abbott Vascular, Santa Clara, California), which was designed to demonstrate that new BRS is comparable to the best-in-class metallic drug-eluting stent (DES) in terms of midterm efficacy (prevention of restenosis) using a surrogate endpoint of angiographic late loss. The use of a surrogate endpoint would be inevitable, considering the inability to conduct a larger and longer-term pivotal study before approval. However, the NeoVas BRS has product specifications very similar to the ABSORB BRS in terms of polymer material and strut thickness except for the drug. The design, patient and lesion characteristics, and the clinical and angiographic outcomes in the present study were very similar to those in the ABSORB China trial in which the ABSORB BRS was compared with the CoCr-EES in 480 patients (2). Therefore, it may be pertinent to look back the story of the ABSORB BRS.

Small pilot imaging studies for up to 5 years after ABSORB BRS implantation have suggested those favorable vascular responses, including restoration of vasomotion and endothelium dependent vasodilation, late lumen enlargement with plaque regression and vessel remodeling, and formation of a stable-appearing neointima (3). These favorable imaging observations made the interventional cardiology community very enthusiastic for the concept of "nothing left alone" strategy in percutaneous coronary intervention. However, even if BRS demonstrates long-term advantages compared with metallic DES, it is important to confirm at least comparable short-term and midterm safety and efficacy profiles. Based on the pivotal ABSORB III and ABSORB Japan trials demonstrating noninferiority of the ABSORB BRS relative to the CoCr-EES in terms of target lesion failure at 1 year, the ABSORB BRS was approved in both the United States and Japan, despite the presence of some signals suggesting inferiority of the ABSORB BRS relative to the CoCr-EES (4,5). The rate of device thrombosis was numerically higher with the ABSORB BRS than with the CoCr-EES in both the ABSORB III and ABSORB Japan trials. Based on the finding in the subgroup analysis suggesting

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excess device thrombosis risk with ABSORB BRS only in small vessels, the interventional cardiology community and regulatory agencies were optimistic about prevention of scaffold thrombosis by appropriate lesion selection and improved implantation technique. As another limitation of the ABSORB BRS, device success rate was consistently lower with the ABSORB BRS than with the CoCr-EES in both the ABSORB III and ABSORB Japan trials, which has not been adequately discussed, but is a crucially important issue in the real clinical practice. Furthermore, thick strut of the prototype ABSORB BRS was a serious limitation in cases of device overlapping and side branch selection, which we encounter frequently in daily practice. Finally, the limited expansion range of the prototype ABSORB BRS made the procedures more inconvenient.

The real challenge for the ABSORB BRS came with the reports of very late scaffold thrombosis beyond 1 year. In a meta-analysis of 7 randomized trials including 5,583 patients, very late scaffold thrombosis between 1 and 2 years occurred only in the ABSORB BRS group (6). The cumulative 2-year incidence of device thrombosis was higher with the ABSORB BRS than with the CoCr-EES (2.3% vs. 0.7%; relative risk: 3.35; 95% confidence interval: 1.96 to 5.72; $p < 0.0001$). The most frightening aspect of very late scaffold thrombosis was its possible etiology linked to intraluminal scaffold dismantling, which is related to the intrinsic process of the scaffold bioresorption (7). The excess risk of the ABSORB BRS for very late scaffold thrombosis sustained up to 3 years after implantation (8). Even with perfect strut apposition under optical coherence tomographic imaging guidance, we could not deny the possibility of positive vessel remodeling with late acquired strut malapposition leading to intraluminal scaffold dismantling and scaffold thrombosis. The enthusiasm of the interventional cardiology community for the ABSORB BRS rapidly faded away. Abbott Vascular recently called a halt to sale the ABSORB Gt1 BRS due to the very low market penetration after approval in the United States and Japan. However, many interventional cardiologists still believe that the "nothing left alone" strategy would be the ultimate goal of coronary device development. We should wait for the development of the new-generation BRS overcoming the limitations of the prototype ABSORB BRS and also the confirmation of the superiority of BRS over metallic DES in the very long term. The requirements for the new-generation BRS are many, including thinner strut, less footprint, improved deliverability, wider expansion range, optimal time course of bioresorption to minimize inflammation, and solutions to avoid the intraluminal scaffold dismantling. Currently, it is only imaginary for us to expect improved clinical outcomes with the "nothing left alone" strategy. We should demonstrate that a BRS outperforms the CoCr-EES after complete scaffold bioresorption. The rates of very late stent thrombosis are very low with use of the new-generation metallic DES with more biocompatible durable polymer or biodegradable polymer. It will take many years for a BRS to demonstrate a meaningful improvement in clinical outcomes over the CoCr-EES. It is unprecedented for us to have such a large number of patients already enrolled in the randomized trials comparing the first-in-class new coronary device (ABSORB BRS) with the standard-of-care coronary device (metallic DES). It is crucially important to extend the follow-up duration as long as possible beyond the current schedule of 5 years.

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