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EDITORIAL COMMENT

Long-Term Favorable Coronary Healing After Bioresorbable Scaffold Implantation

Insights From OCT*

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Vascular response after coronary angioplasty varies according to the technique. Acute response after balloon angioplasty is characterized by luminal gain in most cases, although dissection can occur during the procedure, putting coronary artery patency at risk. Arterial "elastic recoil" sometimes follows this acute luminal gain, resulting in some degree of restenosis.

Bare-metal stents represented a great advance because they overcame these 2 main limitations of balloon angioplasty. However, vascular damage created by bare-metal stent implantation can result in intense tissue proliferation around the struts, leading to another form of restenosis: proliferative rather than mechanical recoil. Drug-eluting stents (DES) were developed to overcome this limitation by incorporating antiproliferative drugs. First-generation DES changed the post-stenting healing process; however, the lack of coverage of a substantial amount of DES struts was shown to contribute substantially to stent thrombosis (1).

Within the past few years, it has been recognized that the tissue covering stent struts can undergo changes resembling the atherosclerotic process, something known as post-stent *neoatherosclerosis* (2). Intravascular imaging modalities, such as optical coherence tomography (OCT), have been fundamental to our understanding of this phenomenon in living patients (3). There has been intense interest in developing a device to induce a more "natural" healing of the post-stented vessel. In this regard, drug-eluting bioresorbable vascular scaffolds (BVS) have been proposed because of their ability to provide mechanical scaffolding during the healing process only to disappear afterward, which allows recovery of vessel functionality.

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In this issue of the *Journal*, Karanasos et al. (4) report a long-term OCT evaluation of the vascular response after first-generation BVS implantation. The study provides a detailed analysis of 8 patients from cohort A of the ABSORB (A bioabsorbable everolimus-eluting coronary stent system) study who were evaluated with OCT 5 years after BVS implantation. Main findings include complete device resorption with no discernible struts, a progressive vessel lumen enlargement, presence of a signal-rich layer of tissue around the lumen, and patency of all small side branches initially "jailed" by the scaffold. The present report is important because the performance of long-term follow-up in asymptomatic subjects with invasive imaging modalities after BVS implantation is complicated; it is difficult to envision larger cohorts with such a long follow-up with OCT.

Two-year follow-up of cohort A demonstrated a significant reduction (34%) in the OCT-discernible number of struts (5). This new report further shows complete resorption, with no struts visible at 5 years. The lumen enlargement observed by these investigators confirms the trend seen in the 2-year data. The late lumen enlargement seen also appeared to be associated with late positive remodeling of a vessel that was not caged by a stent and by plaque

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regression, which was supported by intravascular ultrasound data. Despite being consistent with previous reports using different imaging modalities (6), the OCT data relating to luminal dimensions in this study should be considered cautiously because the OCT system and acquisition technique used at baseline and initial follow-ups differed from the one used at 5-year follow-up, which possibly influenced the results (7).

The most exciting data presented by Karanasos et al. (4) relate to the pattern of vessel healing 5 years after BVS implantation. The systematic appearance of a signal-rich layer, showing a continuum with the native intimal layer (together forming a "neoplaque"), suggests that a BVS implant can produce a favorable tissue response. The presence of a thin fibrous cap has been consistently associated with plaque vulnerability; vascular reaction after stent implantation includes fibrous cap thickening, which suggests that "plaque passivation" happens after stenting. In this regard, BVS could offer unique advantages over metallic scaffolds, because the healing process appears to incorporate initial generation of a new fibrous cap and subsequent scaffold dissolution, leaving an uncaged coronary segment (5).

We must acknowledge several limitations of the present study. Its clearest drawback is the extremely small sample size: 8 patients. As the authors recognize, any conclusion from a study with such a limited sample size is hypothesis generating at best. Additionally, the highly selected study population most probably does not represent the real-life population currently receiving these scaffolds. Importantly, with no information about plaque characteristics before BVS implantation, any conclusion about the device's behavior when implanted over plaques with vulnerable features remains speculative.

It has been demonstrated that the healing response is determined by the underlying plaque characteristics, with evidence showing that stents implanted in patients with acute coronary syndromes (ACS) have less tissue coverage at follow-up, probably related to strut apposition over a necrotic core and thrombus influence on drug distribution (1,8). All the long-term benefits claimed to be associated with BVS implantation (signal-rich layer followed by neoplaque, uncaged artery, and so on) seem to fit perfectly with the needs of some patients presenting with ACS. Unfortunately, the present study did not include ACS patients, who are more prone to have plaques with vulnerable characteristics. Therefore, the application of the present findings to a wider population with a more "vulnerable" phenotype is an exercise of belief. Finally, the fact that "only" 8 of the 14 living patients originally enrolled underwent 5-year follow-up might represent a selection bias.

The signal-rich layer of tissue separating the plaque from the lumen is claimed as an imaging surrogate of favorable vascular healing, but in reality, it simply reflects a thicker barrier between the plaque core and the bloodstream with no struts embedded. We have no evidence that this type of tissue response exerts a clinically relevant protective role. The stability of the fibrous cap may depend not only on its thickness but also on its collagen content and organization; these parameters should be evaluated in the signal-rich layer in future studies. The lack of neoatherosclerosis in the signal-rich layer is also mentioned as an advantage over metallic stents, but the authors provide no serial data regarding the evolution over time of signal-rich layer thickness and plaque characteristics. Therefore, no definite conclusions about neoatherosclerosis formation in the tissue originally covering the scaffold can be drawn. In this regard, we want to highlight a different unfavorable healing response (plaque progression, cap thinning, and thrombus formation) in the scaffolded segment in 1 patient; in such a small population, it clouds the conclusion that BVS implantation results in long-term, favorable healing. The small sample size precludes a real perspective on this phenomenon. While we await future studies, the already demonstrated recovery of endothelial function of the tissue overlying the scaffold shown in patients 2 years after BVS implantation (9) supports the hypothesis of favorable healing.

Another aspect not yet investigated is the impact of the bioabsorbable scaffolds on bifurcation lesions. In fact, bifurcation lesion was an exclusion criterion in the present study, yet this abundant type of lesion has been difficult to target with metallic stents that usually compromise ("jail") the side branch. The patency of all small side branches initially jailed by the scaffold in the present study is the closest information in this regard, albeit these cannot be considered true bifurcations (from the interventional perspective). The 3-dimensional evaluation provided a comprehensive way of approaching side-branch analysis and demonstrated patency of the ostium with thinning of the neointimal bridges initially formed. No explanation was provided for this phenomenon, but future studies evaluating the relation with vessel biomechanics would be of great interest. The potential for disappearance of the jailing struts over time would intuitively benefit the treated vessels and dependent myocardium.

Another relevant aspect that deserves mention is that the device used in cohort A (BVS 1.0) is different

from the one currently available for clinical use. The latter shows a markedly higher initial mechanical stability and longer resorption time. We cannot envision a different healing pattern with the new BVS scaffold (10), but again, this must be proved. Future studies with the current device in a wider and less selected population and in comparison with new-generation drug-eluting stent are needed to confirm the premises here proposed.

In summary, the report by Karanasos et al. (4) is original and of great scientific relevance in constructing the field of evidence concerning these new devices that are emerging as an alternative to metallic stents. Yet the data presented here must be taken as hypothesis generating.

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