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EDITORIAL COMMENT

Bioresorbable Vascular Scaffolds Restenosis

Pathophysiology and Predictors*

Fernando Alfonso, MD, PhD, Javier Cuesta, MD

Bioresorbablve vascular scaffolds (BVS) were introduced a decade ago with the aim of overcoming some limitations of metallic drug-eluting stents (DES) (1-3). BVS allow effective drug delivery with temporary scaffolding of the treated segment but eventually completely disappear from the vessel wall once their goal has been accomplished. BVS hold the promise of restoring coronary vasomotion, sealing vulnerable coronary plaques, and allowing the vessel lumen to benefit from plaque regression and adaptive remodeling (1-3). However, meeting most of these expectations has proved to be more challenging than initially anticipated (1-3).

Indeed, despite the favorable results of most early studies, safety and efficacy concerns arose when the information from the complete set of controlled studies with adequate long-term clinical follow-up became available (1-3). Aggregate analyses of these studies demonstrated a low yet statistically significant higher risk for thrombosis compared with new-generation DES (1-3). Moreover, poorer acute and late angiographic results were also demonstrated (2). In some trials, a higher rate of in-stent restenosis (ISR) was found. Recent meta-analyses suggested that compared with new-generation DES, BVS are associated with a 40% increase in ischemia-driven target lesion revascularization (3). Although much attention has been paid to identifying the pathophysiology of BVS thrombosis because of its dreadful clinical consequences (4,5), currently only limited information exists regarding the underlying mechanisms of BVS ISR (6-14).

PRESENT STUDY

In this issue of *JACC: Cardiovascular Interventions*, Polimeni et al. (15) report on a study in which they sought to assess the incidence, clinical presentation, and predictors of BVS ISR. In this retrospective single-center study, including 657 consecutive patients treated with 883 BVS, careful clinical follow-up (median 3 years) revealed the occurrence of clinical BVS ISR in 49 lesions in 41 patients. The incidence of ISR was 2.4%, 6.0%, and 9.0% at 12, 24, and 36 months, respectively. In most cases BVS ISR presentation was benign (stable symptoms or incidental finding), and only 19% of patients presented with acute coronary syndromes. One-half of these lesions had a nonfocal

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angiographic pattern. Although the potential influence of lesion length was not presented, long BVS and small vessels were associated with higher recurrence rates. On optical coherence tomography (OCT) (available in 27 lesions), the predominant underlying substrate was homogeneous high-intensity neointima. Only 4 cases showed neointima with low-intensity areas, but none was considered suggestive of neoatherosclerosis. Interestingly, images suggestive of BVS fracture were very frequent at follow-up (35% in patients without ISR vs. 61% in those developing ISR). Malapposition and evagination were less frequently found in patients with ISR. Importantly, prior revascularization, diabetes, type B2 or C lesions, and implantation technique emerged as independent predictors of BVS ISR. Notably, device oversizing or undersizing and final residual stenosis predicted an increased risk for ISR. Eventually, most patients

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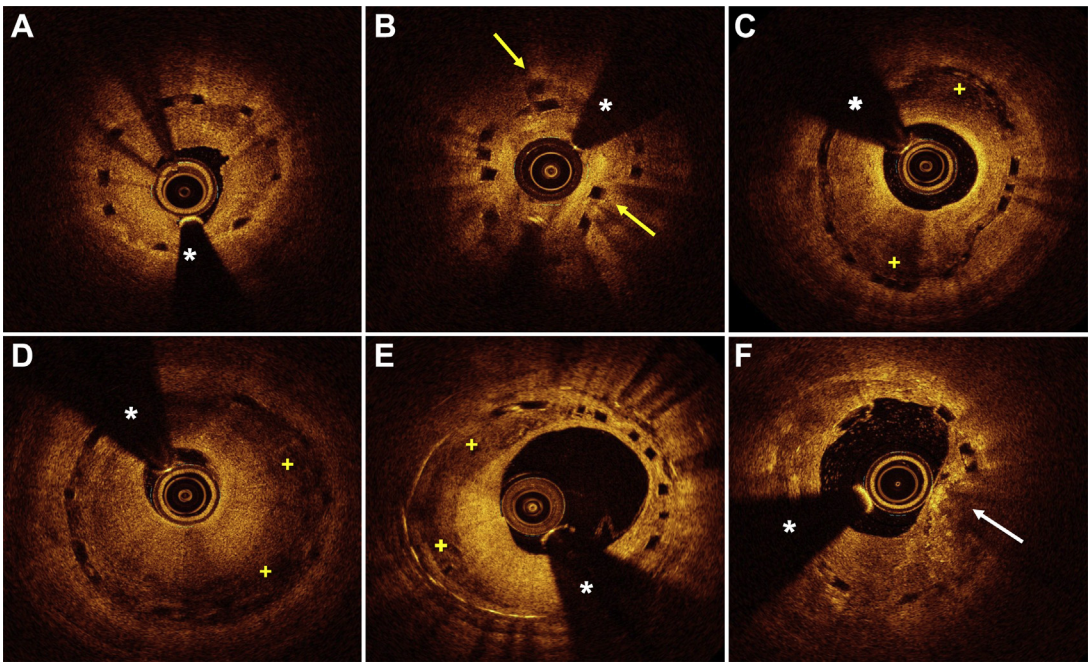
From the Department of Cardiology, Hospital Universitario de La Princesa, Madrid, Spain. Both authors have reported that they have no relationships relevant to the contents of this paper to disclose.

FIGURE 1 Optical Coherence Tomographic Findings in Patients With Bioresorbable Vascular Scaffold In-Stent Restenosis



(A) Underexpanded bioresorbable vascular scaffold (BVS) with bright homogeneous neointimal proliferation. **(B)** Severely underexpanded BVS showing distorted struts **(arrows)** within a high-backscatter uniform neointima. **(C)** Glistening superficial neointima overlying dark areas with diffuse borders **(plus signs)**. **(D)** Massive tissue obstruction in a nicely expanded BVS. Notice a layered heterogeneous pattern with peristrut low-intensity areas **(plus signs)**. **(E)** The tissue obstructing this BVS shows dark areas with sharply delineated edges **(plus signs)**. **(F)** Highly heterogeneous tissue encompassing some punctuated bright areas casting dorsal shadowing **(arrow)**. In all these cases of BVS in-stent restenosis (time to restenosis 132 to 649 days), the "black boxes" corresponding to the BVS struts are still clearly recognizable. **Asterisk** denotes wire artifact.

(67%) were treated with DES, and midterm clinical outcomes were favorable (15).

This investigation, the largest series currently available focusing on BVS ISR, is of major interest. Discussing some methodological issues and study findings appears warranted to disclose what the study adds to current knowledge.

First, although systematic late angiographic evaluation is necessary to ascertain the true incidence of ISR, and this was not performed in the present study, the analysis of "clinical" ISR is highly relevant. Moreover, the present study, describing the incidence of clinical ISR in a complex all-comers clinical setting, may be better suited to understand the efficacy of BVS in relatively unselected patients treated in everyday clinical practice than data coming from controlled studies including highly selected patients and mandated angiographic surveillance. Nevertheless, even in this study, the use of BVS was discouraged in patients with tortuous or heavily calcified vessels, major bifurcations, vein grafts, and ostial and ISR lesions.

Second, OCT revealed that the principal mechanism of BVS ISR was severe neointima proliferation. These findings suggest progressive growth of benign fibrotic neointima. Conversely, other studies using OCT have found that neoatherosclerosis plays a major role in this setting (14). Time to BVS ISR presentation might be implicated. Different criteria to define neoatherosclerosis could also help explain the differences. This elusive pathological substrate might be overestimated when liberal definitions are selected. Alternatively, some images from the present study, depicting large low-intensity areas obscuring most BVS struts (15), might have been interpreted as neoatherosclerosis by other investigators (**Figure 1**).

Third, stent underexpansion remains the most robust predictor of ISR and thrombosis, even with new-generations DES (16). In this study, patients with BVS ISR had significantly smaller minimal scaffold

TABLE 1 Pathophysiology of Bioresorbable Vascular Scaffold Restenosis

1. Excessive neointimal proliferation*
2. Neoatherosclerosis
   - Stable (gradual, progressive development)
   - Complicated (ruptured capsule with associated thrombosis)
3. BVS underexpansion with preserved structure
4. Small target vessel (≤2.25 mm; strut overcrowding)
5. BVS structural changes
   - Acute
     - BVS damage during implantation or inappropriate over-expansion (BVS fracture)
     - Secondary to insufficient radial strength (acute recoil)
   - Late: related to programmed bioresorption
     - Within the vessel wall: loss of structural support
       - Initial configuration preserved
       - With displacement or disruption (late recoil); loss of alignment or circularity
     - With disrupted elements floating within the lumen (malapposition)
       - Initial configuration preserved
       - Modified spatial configuration; loss of alignment or circularity, overhung struts (BVS "dismantling")
6. "Delayed" BVS resorption; very late (>3 to 4 years) persistence of structural elements in the vessel wall
7. Resistance to the antiproliferative drug
8. Disease in adjacent coronary segments not covered by the BVS (5-mm edges)
   - Disease progression (several plaque types) at the initially untreated BVS edges
   - Progression of atherosclerotic plaque at segments treated (injured) but uncovered by the BVS ("geographic miss")
   - Overlap failure ("gap") between 2 separate BVS
9. Excessive overlap of 2 adjacent BVS (long lesions†)
10. Associated with BVS-related aneurysm formation

Several mechanisms may be involved in the same patient. Classic factors such as diabetes (*) and lesion length (†) always emerge as risk factors for restenosis independently of the selected treatment. Modified with permission from Alfonso and García-Guimaraes (6).

BVS = bioresorbable vascular scaffold.

areas at follow-up compared with patients without ISR. Unfortunately, a detailed analysis of BVS expansion by OCT was not provided, as this parameter was only assessed using the angiographic reference vessel diameter. Furthermore, the lack of OCT at the time of BVS implantation prevents dismissing the potential influence of early or late BVS recoil on these findings (8).

Fourth, the presence of images suggestive of BVS fracture (stacked, overhung, or disrupted intraluminal struts) was higher than in previous studies (14). Indeed, two-thirds of patients with ISR showed features consistent with BVS fracture. Nevertheless, the investigators fail to discuss in depth the potential meaning of these striking findings. Some images suggesting fracture might actually correspond to structural discontinuities resulting from the programmed BVS dissolution process. In this regard, additional morphological information (late structural discontinuity vs. true BVS "dismantling") would have been most valuable. Importantly, dismantling have been associated with an abnormal bioresorption process, leading to adverse clinical events (5,10).

Last but not least, an "optimal technique" for BVS implantation was defined as 1:1 pre-dilatation and post-dilation with noncompliant balloons appropriately sized (using quantitative coronary angiography) for the reference vessel diameter (ranging from 2.5 to 3.5 mm) and a final residual diameter stenosis <20%. This is appealing, as patients treated using this strategy obtained better clinical outcomes. Optimism, however, should be cautiously tempered, because studies indicate that even with the use of optimal implantation techniques, BVS might still show higher rates of device failure compared with new-generation DES.

DISTINCT PERSPECTIVES ON BVS FAILURE

Multiple mechanisms potentially leading to BVS ISR have been described (6–14) (**Table 1**). Most of these have been also implicated in BVS thrombosis (4,5) and in ISR after DES implantation (16). However, some specific characteristic inherent to the polymeric BVS could promote distinct pathophysiologic mechanisms. These would include: 1) the thick struts, required to achieve the necessary initial radial force, generate adverse rheological profiles and uneven shear stress, stimulating neointimal proliferation; 2) the progressive loss of structural support during the bioresorption process might favor BVS collapse and vessel recoil; 3) the complete disappearance of the BVS opens a brand new scenario in which the vessel may either keep healing (with some studies suggesting plaque regression), or, alternatively, the underlying disease may progress (neoplaque formation) without any structural barrier preventing lumen encroachment. However, the prevalence and characteristics of restenosis occurring in this later scenario (complete resorption without any remaining scaffold structure) have not yet been established and will require longer follow-up and detailed intracoronary imaging studies.

CLOSING REMARKS

The study of Polimeni et al. (15) provides novel insight into the causes and predictors of BVS failure that may help inform treatment decisions in clinical practice. Whether the risk for BVS ISR may be significantly reduced by avoiding particularly challenging lesions, by the use of specific implantation techniques, or by the systematic use of intracoronary imaging (especially to tackle underexpansion)

remains controversial (6). Larger trials with extended follow-up are essential to expand our knowledge and improve treatment of patients with BVS ISR. Whether the risk for BVS thrombosis and ISR will be mitigated with the advent of device iterations also remains speculative. The potential benefits of complete restoration of vascular physiology should be contemplated with healthy scientific skepticism until compelling clinical evidence confirms that BVS offer at least similar long-term safety and efficacy compared with new-generation DES.

ADDRESS FOR CORRESPONDENCE: Dr. Fernando Alfonso, Department of Cardiology, Hospital Universitario de La Princesa, Universidad Autónoma de Madrid, Instituto de Investigación Sanitaria Princesa, Diego de León 62, Madrid 28006, Spain. E-mail: falf@hotmail.com.

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