To the Editor:
The bioresorbable vascular scaffold (BVS) technology has been developed in an effort to reduce or even to abolish late and mainly very late stent thrombotic risk. It has the potential advantage of progressive early re-absorption and maintaining the cyclic pulsatility and vasomotion that could not be offered by the metallic drug-eluting stents (DES). However, scaffold remnants have been traced even 44 months after bioresorbable scaffold implantation, and there is increasing evidence that aneurysm formation, restenosis and thrombosis are frequent with this technology. Indeed, several recent meta-analyses and reports comparing bioresorbable scaffolds and metallic DES have shown that the rate of thrombosis was nearly 3.5-fold higher in the bioresorbable scaffolds.

In the very interesting review published in the Journal, the authors speculate on the intensity and duration of dual antiplatelet therapy as well as on technical and procedural factors. However, although they referred to the Food & Drug Administration (FDA) approval letter for the Absorb BVS (Abbott Vascular, Santa Clara, CA, USA), they did not elaborate on the safety warnings and contraindications that were included in that letter. Therefore, the following issues concerning the increased incidence of restenosis and thrombosis associated with the BVS need clarification.

The BVS Components and the Corresponding Hypersensitivity Inflammation
The Absorb GT1 BVS system has the following components.
1. Biodegradable poly (L-lactide) (PLLA) coated by biodegradable polylactide (PDLLA) containing the antineoplastic substance, everolimus. However, PLLA acid screws, used in orthopedics, have induced systemic hypersensitivity reactions proven by positive skin tests and necessitated removal of the screws. Furthermore, PLLA gel injections can induce granulomatous reactions. The eluted everolimus substance from the Absorb stent has already been associated with the development of hypersensitivity pneumonitis, atopic dermatitis, exanthema and generalized as well as lingual angioedema.

2. 4 platinum marker beads, 2 embedded at both the proximal and distal ends of the scaffold that are used for fluoroscopic visualization. Hypersensitivity reactions to platinum salts and taxanes have been associated with hypersensitivity reactions, which have been confirmed by skin tests.

The Pathophysiology Secrets
The BVS degradation process takes up to 2 years to complete, although polymer remnants have been traced, by Fourier transform IR spectroscopy, 44 months after scaffold implantation. Both of the polymers are eventually degraded into lactic acid and finally into carbon dioxide and water through metabolism in the Krebs cycle with the following consequences: (1) the lactic acid accumulates and decreases the pH of the surrounding intima, media and adventitia coronary tissue; (2) lactic acid sensors on sensory neurons innervating the heart are stimulated, which induces the same pain as in angina and myocardial infarction; (3) carbon dioxide can enhance acidosis, which can cause thrombosis, as has occurred in open thorax surgery; (4) acidosis has been shown to decrease activated partial thromboplastin time thus facilitating thrombosis; and (5) acidosis can decrease clot lysis, thus maintaining thrombus formation.

The FDA Warnings
The FDA has issued the following warnings and precautions, which can be found in the Absorb GT1 BVS system labeling: (1) the Absorb GT1 BVS system is contraindicated for use in patients who cannot tolerate allergy or hypersensitivity to procedural anticoagulation or the post-procedural antiplatelet regimen; (2) furthermore, this system is contraindicated for use in patients with hypersensitivity or contraindication to everolimus or structurally related compounds, or known hypersensitivity to scaffold components (PLLA, PDLLA, platinum) or with contrast material sensitivity.

Conclusions
We suggest that in order to prevent and avoid all of the above dangerous consequences, there should be strict adherence to the FDA recommendations, careful reading of the system’s labeling, further technical procedure improvement, improvement of current device technology, increasing efforts to invent new inert materials and long-term clinical data before routine implantation of the BVS system.

References
5. Mastrokalos DS, Paesler HH. Allergic reaction to biodegradable...

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Where Are the Secrets of Increased Thrombosis and Aneurysm Formation With the Current Bioreabsorbable Vascular Scaffolds Hidden? — Reply —

We thank Dr. Kounis and colleagues for their interest in our article.1 They raise issues concerning the increased incidence of restenosis and thrombosis associated with bioreabsorbable vascular scaffolds (BVS) and suggest that hypersensitivity to PLLA/PDLLA, everolimus and the 4 platinum markers induce systemic reactions, which may induce restenosis and thrombosis. Also, they suggest that the acidosis induced by the PLLA degradation process may eventually decrease activated partial thromboplastin and thus provoke thrombus formation. Although this is a very important issue to understand in the physiology of BVS, we would like to point out some erroneous assumptions that may be misleading.

First, regarding hypersensitivity to PLLA, the incidence of hypersensitive reactions to PLLA screws is very low compared with the vast amount of orthopedic procedures performed. Also, the “dose” or size of a bioreabsorbable implant is important in inducing a biological response. In other words, unlike bone screws which have a large volume and mass, the largest Absorb scaffold (3.5×28 mm) contains approximately 18.8 mg of the polylactide polymer (PLLA), which is a small amount to induce a systemic hypersensitivity. Moreover, in the case series report of allergic granulomatous reaction to injectable PLLA gel, the authors of that case series mentioned that other dermal implants (e.g., collagen, silicone, polyalkylimide, polyacrylamide, hyaluronic acid, Gore-Tex and methacrylate) also elicited a granulomatous reaction. This was also mentioned in a review paper by Lowe et al.,2 who stated that granuloma formation is influenced by the implantation technique and the concentration of the injected material.

Second, everolimus is the active pharmaceutical ingredient used in various DES, with established safety and efficacy. Although Kounis et al provide a reference for hypersensitivity reactions to everolimus, the dose of a pharmaceutical is important in inducing a biological response. Hypersensitivity reactions have been reported in cancer and immunosuppressive therapies, which used a daily dose of 1–10 mg everolimus for extended periods.3,4 In comparison, the everolimus dose on the largest Absorb scaffold is approximately 0.31 mg and present as a single controlled-release dose. In particular, everolimus is used in the Xience stent, which has been the active comparator in various studies, meaning that everolimus cannot be the cause of “increased” adverse effects.

Third, Kounis et al provide examples of hypersensitivity to platinum salts. However, the platinum markers in Absorb are made of the pure metal, which is a noble metal with high resistance to corrosion.5 Platinum salt and pure