The euphoria, the warnings and the downfall of the current bioresorbable stents: could the journey be restarted?

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Bioresorbable scaffolds have been developed in an effort to avoid metals in the coronary arteries, to maintain vessel pulsatility and to diminish late and especially very late stent thrombosis. In the recent very interesting paper published in Korean Journal of Internal Medicine [1] concerning 105 consecutive patients with bioresorbable stent implantation neither stent thrombosis, nor deaths and urgent revascularizations occurred during hospitalization and the follow-up period. Whereas the mean follow-up was 105.4 ± 74.9 days, 43 patients had at least 6-month follow-up period and clinical follow-up at 6-month was available for all period-eligible patients. The patients received dual antiplatelet therapy with aspirin and an adenosine diphosphate receptor antagonist (clopidogrel, ticagrelor, or prasugrel) for at least 12 months and cilostazol had been added to the above therapy at the physician’s discretion. Could the latter have contributed to the above excellent results that making the journey to restart, for these devices, after the initial euphoria, warnings and final abandoning?

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THE INITIAL EUPHORIA: NIL STENT THROMBOSIS

The bioresorbable scaffolds were firstly implanted in animal models in 1980. Following this, the first bioresorbable stent implanted in humans was the Igaki-Tamai stent, that required a combination of thermal self-expansion and balloon expansion for its deployment. In an initial study of biodegradable poly-L-lactic acid stents that included 15 patients with 19 atherosclerotic lesions, no cases of stent thrombosis were reported [2].

Another prospective, open-label study randomized 30 patients with either stable, unstable, or silent ischaemia and a single de novo lesion revealed that the bioresorbable everolimus-eluting stents resulted in procedural success 100%, device success 94% (29/31 attempts at implantation of the stent). Notably, no target lesion revascularizations, no late stent thromboses and only negligible angiographic in-stent late loss were demonstrated (0.44 ± 0.35 mm [SD]). This was mainly due to a mild reduction of the stent area (−11.8%) as measured by intravascular ultrasound [3].

The first-in-human ABSORB trial, of a fully everolimus-eluting bioresorb-
able vascular scaffold (E-BVS, Abbott Vascular, Santa Clara, CA, USA) that completed in July 2006 at four clinical sites in Europe and New Zealand, studied 30 patients with a single de novo native coronary artery lesion demonstrating a sustained low major adverse cardiac events (3.4%) without any late stent thrombosis [4]. At 5 years, the ischemia-driven major adverse cardiac event rate of 3.4% remained unchanged. The authors concluded that the low event rate at 5 years suggests sustained safety after the implantation of a fully bioresorbable Absorb everolimus-eluting scaffold. Also, noninvasive assessment of the coronary artery together with functional assessment recommended as an alternative to invasive imaging following treatment with such a polymeric bioresorbable scaffold [5].

THE WARNINGS: REAL WORLD STENT THROMBOSIS

Despite that these studies reported nil incidence of bioabsorbable vascular scaffold thrombosis, none of these trials evaluated the incidence of such scaffold thrombosis in the real world. However, several reports had already started to appear in the medical literature concerning sub-acute stent thrombosis involving bioresorbable scaffolds in real-world practice, raising concerns in the cardiology community regarding the possible underlying mechanisms of these thrombotic episodes [6].

Therefore, in an editorial in 2014, we had sounded the alarm that further studies and strict adherence to U.S. Food and Drug Administration (FDA) recommendations would be of paramount importance [7]. Our initial concerns were based on clinical and experimental findings associated with the degradation of the relative poly(lactide-co-glycolide) based nanofibrous scaffolds, whose acidic degradation products (i.e., lactic and glycolic acid) could decrease the pH in the surrounding tissue and could further trigger inflammatory and foreign body reactions in vivo [8].

Indeed, symptoms, such as suddenly emerging pain, oedematous tissues, and even persistent fistula were observed during their clinical application [9]. Furthermore, a week after implantation, several cytokine expression (both in gene and protein level), such as tumor necrosis factor-α and transforming growth factor-β in gene level as well as growth-regulated oncogene- keratinocyte chemoattractant (GRO-KC) in protein level, were observed for all groups of implanted scaffolds.

In these experiments, the use of nanoapatitic particles with alkaline properties found to improve the tissue response during 4-week of subcutaneous implantation [10]. Apart from the impact on local pH reduction through degradation of the scaffold polymers—into lactic acid and finally into carbon dioxide and water via metabolism in the Krebs cycle, additional pathophysiologic factors stemming from bioresorbable scaffold components appeared to be associated with the development of symptoms and scaffold thrombosis. For example, the suddenly emerging pain could be attributed to lactic acid sensors on sensory neurons innervating the heart, while the low molecular weight poly(L-lactide) scaffold that is more susceptible to hydrolysis could further induce intense inflammatory reaction. In addition, the poly (L-lactide) and or poly(D,L-lactide) together with the eluted everolimus substance and the four platinum marker beads embedded at both the proximal and distal ends of the scaffold for fluoroscopic visualization could contribute to hypersensitivity inflammation reactions into the coronary artery [11,12].

THE DOWNFALL: END OF THE CURRENT BIORESORBABLE SCAFFOLDS

Recent studies comparing the Absorb everolimus-eluting bioresorbable scaffold with the everolimus-eluting metallic stent have demonstrated an alarming increase of 3.5 times higher rate of thrombosis with bioresorbable stents [13]. Furthermore, two recent meta-analyses with the same median follow-up time—1st and 2 years the first [14] and 2nd and 3rd years the second [15], the same number of patients (5,583), the same number of randomized trials (seven), five of which were conducted by the same authors reported the same results against the current bioresorbable scaffold. These results were attributed to a plethora of technical and structural causes as shown in the Table 1. Interestingly, none of these effects included pathophysiologic
causes such as foreign body reaction, local hypersensitivity inflammation to scaffold components or locally induced acidity by lactic acid and carbon dioxide.

The Abbott Vascular wisely announced that they will end all countries commercial sales of its Absorb bioresorbable vascular scaffold as of September 14, 2017 with the following statement: “Due to low commercial sales, Abbott will stop selling the first-generation bioresorbable Absorb coronary stent” but will continue the ongoing Absorb clinical trials to assess long-term outcomes after the scaffold has dissolved.

**CONCLUSIONS**

Although the magic bullet for the treatment of coronary artery disease has not been discovered as yet, the current results with bioresorbable scaffolds are certainly not end-game for this technology. Newer generation of bioresorbable scaffolds will be required to overcome current generation of technologically advanced drug eluting stents. Efforts to avoid and/or prevent local hypersensitivity inflammation, locally induced acidity and foreign body reactions, together with technical and structural improvement seem to be of paramount importance. FDA statements and device specific characteristics should be always taken into consideration.

**Conflict of interest**

No potential conflict of interest relevant to this article was reported.

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