EDITORIAL

Korean J Intern Med 2018;33:879-882
https://doi.org/10.3904/kjim.2018.060

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

Nicholas G. Kounis[1], Ioanna Koniari[2], Emmanouil Chourdakis[3], Dimitrios Velissaris[4], and George Hahalis[1]

[1]Department of Cardiology, University of Patras Medical School, Patras, Greece; [2]Department of Cardiology, Royal Bromptom Hospital, London, England; [3]Krankenhaus der Barmherzigen Brüder Trier, Trier, Germany; [4]Department of Internal Medicine, University of Patras Medical School, Patras, Greece

See Article on Page 922-932

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?

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-

Received: February 12, 2018
Accepted: April 4, 2018

Correspondence to
Nicholas G. Kounis, M.D.
Department of Cardiology, University of Patras Medical School, Queen Olgas Square, 7 Aratou St, Patras 26221, Greece
Tel: +30-2610279579
Fax: +30-2610279579
E-mail: ngkounis@otenet.gr

pISSN 1226-3303
eISSN 2005-6648
http://www.kjim.org

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 bioresorbale 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-coglycolide) 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

https://doi.org/10.3904/kjim.2018.060

Table 1. Technical and structural causes of bioresorbable scaffold thrombosis

Acute disruption
Device degradation
Early discontinuation of dual antiplatelet therapy
Edge-related progression
Incomplete lesion coverage
Late discontinuity (abrupt loss on longitudinal scaffold between two adjacent frames)
Malposition
Neoatherosclerosis
Peristrut low-intensity area
Poor scaffold expansion
Recoil
Restenosis
Strut thickness
Uncovered strut
Under-deployment
Very small vessel

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 in 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.

REFERENCES

1. Kwon O, Ahn JM, Kang DY, et al. Early experience and favorable clinical outcomes of everolimus-eluting bioresorbable scaffolds for coronary artery disease in Korea. Korean J Intern Med 2018;33:922-932.
2. Tamai H, Igaki K, Kyo E, et al. Initial and 6-month results of biodegradable poly-l-lactic acid coronary stents in humans. Circulation 2000;102:399-404.
3. Ormiston JA, Serruys PW, Regar E, et al. A bioabsorbable everolimus-eluting coronary stent system for patients with single de-novo coronary artery lesions (ABSORB): a prospective open-label trial. Lancet 2008;371:899-907.
4. Onuma Y, Serruys PW, Ormiston JA, et al. Three-year results of clinical follow-up after a bioresorbable everolimus-eluting scaffold in patients with de novo coronary artery disease: the ABSORB trial. EuroIntervention 2010;6:447-453.
5. Onuma Y, Dudek D, Thuesen L, et al. Five-year clinical and functional multislice computed tomography angiographic results after coronary implantation of the fully resorbable polymeric everolimus-eluting scaffold in patients with de novo coronary artery disease: the ABSORB cohort A trial. JACC Cardiovasc Interv 2013;6:999-1009.
6. Ho HH, Er Ching M, Ong PJ, Ooi YW. Subacute bioresorbable vascular scaffold thrombosis: a report of 2 cases. Heart Vessels 2015;30:545-548.
7. Kounis NG, Soufras GD, Tsigkas G, Hahalis G. Bioabsorbable stent thrombosis Quo Vadis: is Kounis syndrome still present? Int J Cardiol 2014;176:305-306.
8. Lendlein A, Langer R. Biodegradable, elastic shape-memory polymers for potential biomedical applications. Science 2002;296:1673-1676.
9. Bostman O, Pihlajamaki H. Clinical biocompatibility of biodegradable orthopaedic implants for internal fixation: a review. Biomaterials 2000;21:2615-2621.

10. Ji W, Yang F, Seyednejad H, et al. Biocompatibility and degradation characteristics of PLGA-based electrospun nanofibrous scaffolds with nanoapatite incorporation. Biomaterials 2012;33:6604-6614.
11. Kounis NG, Koniari I, Tsigkas G, Soufras GD, Hahalis G. Where are the secrets of increased thrombosis and aneurysm formation with the current bioresorbable vascular scaffolds hidden? Circ J 2018;82:608-609.
12. Kounis NG, Koniari I, Davlouros P, Soufras G, Tsigkas G, Hahalis G. Bioresorbable stents: quo vantis? J Thorac Dis 2017;9:E1032-E1034.
13. Wykrzykowska JJ, Kraak RP, Hofma SH, et al. Bioresorbable scaffolds versus metallic stents in routine PCI. N Engl J Med 2017;376:2319-2328.
14. Ali ZA, Serruys PW, Kimura T, et al. 2-Year outcomes with the absorb bioresorbable scaffold for treatment of coronary artery disease: a systematic review and meta-analysis of seven randomised trials with an individual patient data substudy. Lancet 2017;390:760-772.
15. Sorrentino S, Giustino G, Mehran R, et al. Everolimus-eluting bioresorbable scaffolds versus everolimus-eluting metallic stents. J Am Coll Cardiol 2017;69:3055-3066.

https://doi.org/10.3904/kjim.2018.060