Special Report

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Bioabsorbable stents: nothing from something

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Percutaneous coronary intervention continues to develop at a rapid pace and has seen exciting developments in the last three decades. Percutaneous coronary intervention numbers have exceeded coronary bypass surgery worldwide and we now have long-term safety and efficacy data on the stents currently being used. However, there are unresolved issues relating to the optimal length of dual antiplatelet therapy, which represent a major concern due to the small but potentially catastrophic effect of stent thrombosis. The latest development in stent iteration is bioabsorbable stent technology. Bioabsorbable technology is still in its infancy; however, it holds promise for the future. This article delineates the progress made so far in this field and ponders its future applications.

Keywords: bioabsorbable stent • percutaneous coronary intervention

Coronary artery disease is a major public health problem with increasing incidence. However, due to improvements in both diagnosis and management, mortality rates are on the decline. Alongside advances in medical therapy, coronary revascularization has been instrumental in improving patient outcomes, with percutaneous coronary intervention (PCI) undergoing significant leaps in technological development during the last few decades. In this article, we describe the progress that has taken place in the field of PCI, which has led us to the fore of the bioabsorbable stent era – also termed by some as the fourth revolution in PCI.

The need for bioabsorbable stent

Greuntzig first described angioplasty in 1978 [1] and proposed it as a potential treatment strategy for patients with atheromatous obstructive coronary disease. Over the subsequent three decades, important technological advancements have been made. Balloon angioplasty gave way to bare-metal stents (BMS), which dramatically reduced acute complications such as abrupt vessel closure and need for emergency surgery. However, this came with a need for repeat revascularization due to balloon- and stent-induced injury to the vessel wall leading to restenosis and the need for repeat procedures. To overcome this particular setback, stents were coated with cytostatic drugs, such as sirolimus and paclitaxel, which attenuated regrowth of intima, thereby reducing the incidence of in-stent restenosis. The currently used second-generation drug-eluting stents (DES) have drug coatings of drugs such as everolimus and zotarolimus and are designed to be more deliverable due to thinner struts comprising newer materials (for example, cobalt chromium or platinum chromium). Unfortunately, a bystander effect of the drugs used to inhibit cell tissue growth, is inhibition of the beneficial effects of endothelial cell growth, resulting in prolonged stent strut exposure to circulating blood and platelets. Until the struts are covered by endothelium, patients must remain on antiplatelet therapy (typically aspirin and clopidogrel), which exposes them to the potential risks of bleeding, whilst prematurely discontinuing antiplatelet therapy (either due to poor compliance, bleeding or the need for surgery) may

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result in stent thrombosis (ST). It is now known that ST is a major predictor of adverse outcomes, including mortality, in up to 40% of patients. Currently, we have good follow-up data on the safety and efficacy of first-generation DES (of up to 5 years) [2,3]. Despite this, very late ST in DES is being increasingly recognized with positive remodeling of the vessel being one of the many possible causes.

Such considerations have driven research into the development of stents that require the patient to be exposed to a shorter duration of dual antiplatelet therapy. These include stents coated with more bioneutral polymers, stents that capture circulating endothelial cells and stents with bioabsorbable polymer (so that any inflammatory effects of the polymer are attenuated). However, most radical of all has been the design of newer stents that perform as well as conventional stents (for instance, keep the artery open, prevent vessel recoil and inhibit in-stent restenosis through drug elution) but then have the added benefit of being absorbed over time, ultimately leaving nothing behind in the vessel.

Bioabsorbable technology

Apart from a reduction in late ST, the disappearance of the scaffolding with bioabsorbable-stent technology may have other advantages over permanent metal stents. These include the prevention of late adverse remodeling – as there would be no space between the stent and the vessel wall, since there would be no stent. Furthermore, there is also the theoretical prevention of late stent strut fracture due to metal fatigue, less permanent side-branch occlusion and restoration of the vessel wall to function normally. It is known that metal *per se* causes impaired vasomotion [4] in coronary arteries, which has been linked to further atherosclerosis. Finally, another potential advantage over a permanent 'metal jacket' is that segments of the coronary tree treated with bioabsorbable stents may still be amenable to undergo coronary bypass grafting if the need arises in the future.

However, many challenges need to be overcome before an ideal absorbable DES scaffold achieves the same utility as current DES

So what are the needs before a polymer DES can be made and tested in man? First, the polymer has to be modified so that it can act as a rigid scaffold for the artery and resist recoil – in other words, once delivered it has to have the radial strength of the metal it is replacing. Then it needs to be able to be cut in such a way that allows for it to be crimped onto a balloon so that it has a profile allowing deliverability to the coronary stenosis. This was not so difficult since the designs that had allowed the previous metal stents to be crimped onto a balloon could be copied. However, the designs have had to be modified after the first absorbable stents showed unacceptable results, not least the struts were too thick and the design that suited the metal stent did not necessarily suit the polymer stent. Next it is essential in bench testing to ensure the stent could be delivered into arteries, be balloon-expandable, provide good radial strength to prevent potential vessel recoil, be able to release drug in the concentrations required and over the appropriate time (usually needed to be released over several months). In addition, it needs to dissolve over a period of time that will allow it to have done its job in supporting the artery (~2 years) leaving nothing behind (with the breakdown constituents being bioneutral) and allow the artery to return to a normal physiology. The designs that have been tested so far are elaborated on in the following sections.

Igaki–Tamai stent

The first bioabsorbable stent to report on safety, efficacy and feasibility was the Igaki–Tamai stent, the struts of which were made of poly-L-lactic acid [5]. The struts had a thickness of 170 μm, strut to artery coverage of 24%, with a duration of radial support of approximately 6 months and absorption time of 24 months. The stents had no drug elution and were self expanding with heated balloon. The first-in-man study of the Igaki–Tamai stent (15 patients, and 25 stents), demonstrated no major adverse clinical events (MACE) and notably no ST events within 30 days, and need for one repeat PCI at 6 months follow up. The late loss, which is an index of tissue growth within the stent, was 0.48 mm. This is comparable to BMS, as opposed to values of 0.19 mm in current DES [6]. Favorable long-term clinical results have been reported at 3- and 10-year follow up, which currently represents the longest available evaluation of an absorbable stent. This study has recently reported on the long term (> 10 years) clinical outcome and the complete absence of stent struts on Intravascular Ultrasound at 3-year follow up, together with a mean angiographic diameter stenosis of 25% [7].

REVA stent

The REVA stent (REVA Medical, Inc., San Diego, CA, USA) is a polycarbonate stent that degrades to water, carbon dioxide and ethanol, leaving iodinated-desaminotyrosine, which is absorbed and excreted from the body. The strut thickness is approximately 125 μm and has a resorption time of approximately 36 months. This stent also does not have a drug elution and is deployed over a balloon. The first version had a slide-and-locking design and benchwork data indicate that acute stent recoil is minimal, and the radial force of the device is comparable with a BMS [8].

The RESORB FIM study which recruited 27 patients with *de novo* lesions demonstrated good acute reduction in diameter stenosis following stent deployment; although the study demonstrated a significantly high target lesion revascularization rate of 66.7%, which was attributed to mechanical failures driven by polymer embrittlement [9]. The second-generation ReZolve™ stent is currently undergoing clinical trial [101,10], with primary outcome measures being ischaemia and clinically driven target lesion revascularization, and is expected to report 2017. This stent has a more robust polymer, a spiral 'slide-and-lock' mechanism to improve clinical performance and a coating of sirolimus.

Biodegradable metallic stent technology

An alternative to using polymers that dissolve over time is to use absorbable metals. The AMS-1 BRS (Biotronik, Berlin, Germany) is a balloon-expandable stent that is composed of 93% magnesium and 7% rare earth metals. It has a strut thickness of 165 µm, high mechanical strength, low elastic recoil (<8%), a high collapse pressure (0.8 bar) and minimal shortening after inflation (<5%) [11,12]. The magnesium degrades within 4 months and it is hypothesized that the negative charge produced by such degradation enhances stent hypothrombogenicity. The PROGRESS AMS study was a multicenter, nonrandomized, prospective study, assessing the efficacy and safety of the AMS-1 stent in 63 patients (71 stents) with single *de novo* lesions [13]. Although the 12-month outcome data confirmed the safety of the stent, there was a high incidence of target lesion revascularization proving it to be not as efficacious as the current DES. The new generations of stents, AMS-2 and -3 alloy are modifications of the AMS-1. They incorporate changes such as reduced strut thickness and, specifically for AMS-3, bioresorbable matrix for the controlled release of an antiproliferative drug, is being investigated in the ongoing BIOSOLVE-I FIM study.

Abbott Vascular bioabsorbable vascular scaffold

The Abbot Vascular everolimus-eluting bioresorbable vascular scaffold (BVS; Abbott Vascular, Santa Clara, CA, USA) has a backbone of poly-L-lactic acid, which is subsequently coated with a thin layer of a 1:1 mixture of an amorphous matrix of poly-D,L-lactide and 8.2 µg/mm of the antiproliferative drug everolimus. The poly-D,L-lactide enables controlled release of everolimus, such that 80% is eluted by 30 days. This drug elution is similar to that from the permanent polymer on the metallic Xience V stent used in the Spirit trials [14,15].

Encouragingly, studies have indicated that the BVS has comparable acute vessel recoil to the metal everolimus-eluting stent (Xience V), inferring similar initial radial strength [16,17]. There are two platinum markers at each end of the scaffold to allow easier visualization on angiography and other imaging modalities. The first BVS device (Revision 1.0) had a strut thickness of 150 µm and was balloon expandable. The absorption time was approximately 24 months. In the first-in-man ABSORB study (prospective, open-label, multicenter study), Cohort A was the first to measure the safety and feasibility of this novel stent in 30 low-risk patients with *de novo* lesions who were suitable for a 3 mm stent of either 12 or 18 mm length. The stent had to be kept stored below -20°C to prevent physical aging of the polymer and to ensure device stability, which was both inconvenient and limited the shelf life to 8 weeks. There was 100% procedural and 94% device success at implantation and MACE at 1 year was 3.3%, with no late ST recorded. At 6-month follow up, angiographic in-stent late loss was 0.44 ± 0.35 mm [18], which is significantly greater than late loss associated with current-generation DES (~0.13 mm). Recently, the 4-year follow up from cohort A of ABSORB study has continued to show a low MACE rate (3.4%) without any late complications such as ST [19].

The late luminal loss from the original stent was largely attributed to strut shrinkage and subsequent revisions to the first iteration were made. The second-generation scaffold (revision 1.1) underwent evaluation in 101 patients forming Cohort B of the ABSORB study. The modifications meant that the device could be stored at room temperature with a shelf life of 6 months. Importantly, 6-month angiographic and clinical outcome data in a subgroup of 45 patients showed a late loss of 0.19 ± 0.18 mm [20] and 12-month MACE was 7.1%, comparable to the Xience V metallic stent. Compared with other bioabsorbable stents, The ABBOTT BVS seems therefore to have the lowest restenosis rate of all the tested bioabsorbable stents.

A currently ongoing study with the latest iteration of this device is the ABSORB EXTEND trial, which is a multicenter, single-arm registry and aims to recruit approximately 1000 patients from 50 centers worldwide [102]. The study incorporates multimodality imaging such as angiography, intravascular ultrasound, optical coherence tomography, and multislice CT, and is expected to complete in December 2015. The first randomized trial of BVS versus conventional metallic stents is currently underway in Europe and New Zealand (ABSORB 2) [103]. Patients are to be randomized to either BVS or Xience Prime DES and approximately 150 out of a target of 500 patients have

been recruited so far. Alongside standard measurements of MACE, patients will also undergo angiographic follow up. It is important to emphasize that while initial results are encouraging, these have so far been in stable angina patients with simple lesions. The performance of BVS in more complex lesions (including acute coronary syndromes) such as deliverability, efficacy and safety are as yet untested.

Future perspective

While it is still early days and data have only been generated from simple lesions in a small number of patients with short-term follow up, bioabsorbable stents appear to hold real promise. The early angiographic and clinical outcomes are comparable to the currently used second-generation DES, although the results of a head-to-head randomized trial are awaited from the ABSORB 2 study. There is an expectation that long-term results will be even more promising, especially if patients can avoid the need for long-term antiplatelet therapy and the associated bleeding complications. However, these early data must be interpreted with caution as the studies have been in selected patient cohorts with stable angina and simple lesions. This new technology has a long way to go before being used routinely as we currently have no data in complex lesions and in acute coronary syndromes. In addition, what remains to be proven is the long-term safety of bioabsorbable stents, particularly in relation to ST. Finally, the selection of patients most suited to this type of novel stent are still unclear and cost issues, especially important in a cost-constrained health economy such as the NHS. What the future holds for this promising technology is eagerly awaited by the interventional community.

Financial & competing interests disclosure

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Executive summary

- Percutaneous coronary intervention is widely performed the world over for coronary revascularization in both acute and elective situations.
- Percutaneous coronary intervention has undergone tremendous technical refinements and technology continues to underpin its development.
- Currently used drug-eluting stents have good safety and efficacy profiles that could in theory be improved further if the metal used to scaffold could somehow disappear when it is no longer needed.
- Different bioabsorbable technologies tested to date have been described in this review.
- The unfolding future of this fascinating technology is being eagerly watched by the interventional cardiology community and it is to be seen whether it delivers what it promises.

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