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Review Article

Bioresorbable Vascular Scaffold technology, the rise and fall in clinical practice

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ABSTRACT

In 1977, interventional treatment of coronary artery disease was heralded by Andreas Gruntzig who started balloon angioplasty. Then in 1996 Schömig et al.[3] introduced dual anti-platelet therapy instead of anticoagulant therapy. In 2001 Surrey et al.[4] published first report on 45 patients who had negligible neo-intinal hyperplasia, one year after implanting Sirolimus eluting Bx VELOCITY stents. In 2006, Ormiston J et al. reported on the first in man implantation at mid LAD position.[13] In 2008 the ABBSORB FIRST[8] reported on 30 patients with single denovo coronary lesions with 94% device success. Then came the ABSORB II and currently patients in ABSORB III and IV are being followed. Initial results upto one year have shown encouraging results in terms of no inferiority to bench mark drug eluting stents. However results at 2–5 years have shown increased risk of target vessel revascularization and importantly a new risk of late scaffold thrombosis that emerged as a worry.

The treatment of bioresorbable scaffold as a regular stent with similar sizing and implantation technique to other drug eluting stent has contributed to these results and better attention to proper sizing through more use of imaging, as well as more emphasis on post-dilatation has shown in subgroup analysis that it delivers better results. Furthermore avoiding use of BVS in small vessels and in complicated vessel lesions such as bifurcation or heavily calcified helps in ensuring a better long-term result.

This remains to be seen in long-term results from ABSORB III and ABSORB IV studies as well as national registries. Currently use of BVS has been curtailed to within the scope of such big registries or in the theme of a study.

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1. Introduction

In 1977, Andreas Gruntzig performed the first human balloon angioplasty and ushered in the era of percutaneous treatment for coronary artery disease. Initial enthusiasm though was tampered down by reports of acute vessel occlusion due to dissections[1] and late constrictive remodeling. The next large leap was the introduction of bare metal stents. The BENESTENT trial[2] reported reduced vessel restenosis (22% vs. 32%, $p = 0.02$), and the need for repeat coronary angioplasty (relative risk, 0.58; $p = 0.005$) in patients treated with bare metal stents. In addition, the rate of sub-acute vessel occlusion was 1.5% which reduced the need for emergency bypass surgery.

In 1996 Schömig et al.[3] introduced dual anti-platelet therapy instead of anticoagulant therapy, which resulted in 82% lower risk of MI and 78% reduction in need for repeat interventions (MACE relative risk, 0.25; 95% CI, 0.06–0.77).

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In 2001 Surrey et al.[4] first reported the potential benefits of drug eluting stents; he described 45 patients treated with Sirolimus eluting Bx VELOCITY stents who developed negligible neo-intimal hyperplasia on one year follow up. Following which the RAVEL trial[5] reported lower mean late luminal loss (−0.01 mm vs. 0.80 mm, $p < 0.001$) and no recurrent revascularization attempts (26% in the control group). However, reports about the risk of late stent thrombosis surfaced[6] and later increased to 3.5% at 4 years.[7] Therefore as far as long term outcomes are concerned, drug eluting stents are still not the perfect solution and the search for a better alternative continues.

2. The promise of bioresorbable scaffolds

Initial attempts by Tamai et al.,[9] examined the feasibility of a bio-absorbable poly-L-lactic acid (PLLA) Igaki-Tamai stents (Igakl Medical, Kyoto, Japan), which had a thickness of 0.17 mm, a zigzag helical coil pattern, and was not drug eluted. They reported 18% repeat revascularization at 4 years,[10] and 28% target vessel revascularization at 10 years. One case of definite stent thrombosis was reported.[25,28] Similarly, Di Mario et al.[11] reported on the use of magnesium stents among denovo coronary lesions, with only modest results (1-year target lesion revascularization rate 45%).

The Bioresorbable Vascular Scaffold (BVS) (Abbott Vascular, California) consists of a processed poly-L-lactic acid (PLLA) backbone covered with an amorphous Everolimus/PLA matrix coating for controlled drug release (1:1 ratio). In everyday clinical practice, use of polylactic acid and its copolymers is widespread ranging from absorbable sutures to orthopedic screws and dermatology fillers. The safety of PLLA is supported by the benign vascular response to its use in Angioseal closure devices for femoral arterial punctures. PDLLA (poly(D,L-lactide), the polymer used for controlled release of Everolimus, has also been used previously.[14] Everolimus (Novartis, Switzerland) is a semi-synthetic macrolide immunosuppressant which blocks cell proliferation by causing cell division to arrest in G1-S phase. BVS contains an Everolimus dose of 8.2 mcg/mm of which 80% is released within 30 days, similar to the Xience V stent. The safety and efficacy of Everolimus eluting stents are attested by the SPIRIT and FUTURE first trials.[14–16]

The BVS stent strives to perform comparably to others: its crossing profile at 1.4 mm is comparable to that of BX Velocity stent. At 37 degree Celsius, its radial strength is similar to that MULTILINK stent.[12] Its balloon delivery system is the same as that used for MULTI LINK, VISION and XIENCE V stents. An advantage over other metallic platform coronary stents, BVS shows higher conformability to vessel structure.[30]

Initial version of the stent (Revision 1.0) had to be stored at temperatures of −20 degrees to avoid device instability and undesirable cracks upon deployment. This was improved in the second generation (Revision 1.1) which is capable of being stored at room temperature.[23] It previously had different polymer treatment and a different scaffold design; which is now replaced with in-phase zigzag hoops linked by bridges, allowing for more uniform strut distribution, higher radial support, less vessel recoil and more uniform drug distribution.[29]

The BVS is composed of repeating units of PLLA/PDLLA. After implantation, the bonds between these repeating units start to get hydrolyzed producing lactic acid, which are metabolized via krebs cycle. Residual small particles (less than 2 micrometers diameter) get phagocytosed by macrophages. The time for complete reabsorption of the backbone is 2–3 years, whereas the coating polymer absorbs much faster.

Chemically, scaffold resorption process takes place in three phases; initially water diffuses into the less dense regions and hydrolyze the ester bonds; decreasing the stent's molecular weight. In the second stage there is scission of the chains linking crystalline regions, resulting in decline of the stent's radial strength. Finally in the third stage, the remaining polymer chains become short and diffuse out of the device to get reabsorbed into blood stream.

The degradation of the PLLA scaffold governs its mechanical performance, which is also divided into three phases. In the initial "revascularization phase" it acts like the mainstream drug eluting stents (comparable deliverability, minimal acute recoil and high acute radial strength). At the restoration phase there is an initial hydrolysis at amorphous regions followed then by hydrolysis at connecting points, causing a gradual decline in radial strength. This decline happens at a variable rate, but in cases studied[56,57] the process takes about three months to start. During the last "resorption phase" the BVS becomes discontinuous and ceases to act as a scaffold while its hydrolysis into L- and D- lactate continues.[21] This may take up to 24 months. Inside the vessel wall, the stent strut sites eventually become occupied by proteoglycan material, while the strut outline becomes surrounded by areas of calcification.[22] Encouraging results were observed in preclinical animal studies. There was complete luminal endothelialization and minimal inflammatory response, comparable to earlier reports with Cipher stent (J&J, Miami, FL).[12] At 6 months these arteries were still splinted; and at 12 months the vessel became capable of auto-vasomotion.[12,23]

The stent is transparent to conventional coronary fluoroscopy, apart from radiopaque markers at both edges.

In 2006, Ormiston J et al. reported the first in man implantation at mid LAD position.[13] In 2008 the ABBSORB FIRST[8] reported on 30 patients with single de-novo coronary lesions with 94% device success rate. At one-year one patient developed a non Q wave MI and had the target vessel revascularized. IVUS showed post-procedural incomplete strut apposition in 6 patients. At 6 months, the OCT sub-study showed 99% of struts were covered by tissue. These patients had higher acute stent recoil than everolimus eluting stents (6.9% vs. 4.3% historical data from SPIRIT FIRST and SPIRIT II; $p = 0.25$)[17]. IVUS data also noted significant late stent recoil (7.6%[18] vs. 0.03% Xience V at 6 months[15,8]) and at 2 years there was 34.5% decrease in strut thickness.[23] This translated into 0.44 mm late lumen loss at six months. Part of this was due to neo-intimal hyperplasia while the rest was due to reduction in inside stent area. Hyperplasia was comparable to Xience stents and better than that reported for BMS.[15] Reduction in inside stent area was due to a combination of acute stent recoil, non-uniform vessel wall support and loss of radial strength through scaffold resorption. In-stent restenosis rate was 11.5% in these patients, albeit it not necessitating re-intervention.

From 6 months to 2 years there was a reduction in plaque area,[23] while the vessel size remained the same leading to an overall gain in lumen area with no scaffold mal-apposition.[24] At 3 and 5 years,[25,31] the ischemia-driven major adverse cardiac event rate was 3.4%. Scaffold thrombosis was not reported.

The ABSORB II trial enrolled 501 patients with myocardial ischemia and one or two de-novo native vessel disease to receive BVS or Xience (Abbott Vascular, Santa Clara, CA, USA). Acute recoil post implantation was similar but acute lumen gain was lower for BVS (IVUS: 2.85 mm^2 vs. 3.60 mm^2, $p < 0.0001$). Composite device orientated endpoint at 1-year (Overall 5% vs.3%, $p = 0.35$), myocardial infarction (4% vs. 1%) and target-lesion revascularization (1% vs.2%)[47] was similar. Scaffold thrombosis started to surface when three patients from BVS group had definite or probable scaffold thrombosis, compared with none from the metallic stent group. Further disappointing at three years[56] was when BVS showed no favorable difference in vasomotor reactivity (BRS 0.047 mm vs. Xience 0.056 mm; p for superiority 0.49). Late luminal loss was larger for BVS (0.37 mm vs. 0.25 mm; p for non-inferiority 0.78)