A Review on Biodegradable and Bioabsorbable Stents for Coronary Artery Disease

Prathibha Ramadugu1*, Kanaka Latha Alikatte2 and Narendar Dhudipala2

1Kakatiya Institute of Pharmaceutical Sciences, Pembarthi, Warangal, India
2St. Peter’s Institute of Pharmaceutical Sciences, Warangal, India

Abstract

In the recent years Angioplasty has made a significant progress and is being widely used in the treatment of atherosclerotic vascular disease. Drug-eluting stents are not only effective but are also raising the concerns associated like restenosis. Biodegradable stents are being developed as an alternative to permanent stents which may be a potential alternative in solving the problem of in-stent restenosis. When compared to metallic stents with a thin coated drug, a fully degradable stent may be more potential in targeted drug delivery. Biodegradable materials like polycarbonates, polyesters, corrodbile metals and bacterial-derived polymers have been investigated by various research groups in designing stents. A biodegradable stent is considered to be perfect if it could be reliably deploy under the fluoroscopic guidance and locate the target lesion with an insignificant endovascular trauma. In addition to the stents based on the advances that are used in addition to or as an alternative to stents in the treatment of CAD and prevent the potential risks of restenosis.

Biodegradable and Bioabsorbable Stents

Despite the fact that stents are major breakthrough in the treatment of obstructive coronary artery disease, the device will remain as permanent implant/foreign body inside the artery after their intended use. There exists several questions till date; why should a device implanted just to prevent acute or sub-acute recoil occurring mainly after the initial days of procedure, and to deliver anti-proliferative drugs to prevent cell proliferation which is observed after 2-3 weeks of intervention, for life time? Issues with long term stay of stents in the artery include but not limited to, late restenosis, mechanical blockages, late development of malposition, etc. which made researchers to develop Biodegradable and Bioabsorbable stents.

Bio-degradable polymer based stents (BDS) have several advantages over permanent metallic stents [9]. Optimized polymer composition may facilitate more targeted drug delivery, limiting smooth muscle cell proliferation on the abluminal side, while simultaneously encouraging endothelialization on the luminal side [10,11]. Moreover, stents made of complete polymer may have a higher drug loading capacity. The magnetic resonance imaging/CT compatibility of BDS may result in more diagnostic interpretation since there is no interaction from...
metallic stents. In addition, the avoidance of metallic stents may allow repeated percutaneous revascularization or surgical intervention if required [12].

There are several conditions to consider when selecting a polymer for the BDS [13]. These include, but not limited to, bio-compatibililty of the polymer, the strength of the polymer to avoid immediate recoil and lack of toxicity. Questions in regards to radial strength loss were of concern as there may be increased risk of stent fracture and migration over a period of time [14-17]. Furthermore, the long term bio-compatibility of the breakdown products was relatively unknown [18]. Poly L-lactic acid (PLLA), polyglycolic acid (PGA), polycaprolactone (PCL) and poly (D, L-lactide/glycolide) copolymer (PDLA) are some of the suggested polymers for fabricating bio-absorbable stents. Each of these polymers was designed as either self-expanding or balloon expandable stents. Another proposed design is the hybrid stent, which combines polymeric absorbable stents with a metallic backbone to enable strength and prevent recoil [19-24].

Stack and colleagues at Duke University, Durham, NC, developed the first fully fabricated BDS, made of knitted poly-L-lactic acid (PLLA) [21]. This prototype stent could withstand up to 1000 mm Hg of crush pressure, kept its radial strength for 1 month and was almost completely degraded by 9 months [25]. Igaki and Tamai further refined the design to PLLA monofilaments (molecular weight, 183 kDa) in a zigzag helical coil configuration (Figure 1) [26]. This arrangement was associated with reduced vascular injury at the implantation site, which led to a reduction in initial thrombus deposition and neointimal proliferation [26]. PLLA with low molecular mass, was associated with an intense inflammatory reaction, whereas a minimal inflammatory reaction was observed with molecular mass >300 kDa [27].

Several clinical studies were performed on humans to assess the safety of Igaki-Tamai stent made of biodegradable polymer PLLA [28-34]. Initially, Igaki and co-workers have evaluated the safety and efficacy of PLLA stent implanted in 15 patients. The results from the study conclude that, the percent diameter stenosis decreased from 64% before stenting to 12% after stenting and the study also confirmed the PLLA stents might not be associated with intimal hyperplasia than stainless steel stents [30,35]. In another study, Tsugi et al. reported a 1 year follow-up study of 50 patients who underwent stent implantation successfully in 63 lesions. Restenosis rates were 21% at 6 months and 19% at 12 months. Overall, these findings suggest us that the use of PLLA stents is safe with acceptable efficacy in human coronaries [31].

The bio-absorbable vascular solutions (BVS) everolimus-eluting stent from Abbott Vascular, Santa Clara, CA utilized highly crystalline poly lactic acid (PLA) as backbone material, which allows the stent to achieve the radial strength of MULTI-LINK VISION metal stent. The surface of the stent is coated with 1:1 mixture of drug to amorphous PLA matrix, allowing 80% of the drug to be released in first 30 days (Figure 2). Results from the studies concluded that, the stent is bioabsorbed in ~ 18 months [36].

Another biodegradable polymer tyrosine polye poly (desaminotyrosyl–tyrosine ethyl ester) carbonate was utilized to make REVA stent by Reva Medical, with polycarbonate backbone. The REVA stent has a unique slide and locking design that provides both flexibility and strength (Figure 3). This design with polycarbonate backbone imparts high tensile strength and apparently negligible recoil with balloon deployment. From the human clinical trials it suggested that there is no recoil observed at the end of 6 months [37-41].

The IDEAL™ biodegradable stent from Bioabsorbable Therapeutics Inc. was made from Poly-anhydride ester (PAE) with sirolimus and salicylic acid incorporated, to provide both anti-inflammatory and anti-proliferative property (Figure 4). Initial human clinical study demonstrated the structural integrity with no evidence of recoil. But, the stents failed to show the anti-proliferative property which could be due to lesser drug load. Therefore, second generation IDEAL™ stents with higher drug load and slower drug release were under investigation [42].

Another interesting concept is the multi-layered biodegradable stent designed by Eury et al. which is made of various polymers such as PLLA, PGA, PCL, poly-orthoesters or poly-anhydrides [43]. The unique feature of this stent is that 1 layer addresses the structural requirements of the stent and an additional layer controls the drug release.

**Limitation of Biodegradable Stents**

Despite the clinical advantages associated with biodegradable polymer stents, there exist several limitations. The polymer stents are associated with significant degree of local inflammation. These stents are not as strong as metal stents, which may result in recoil and may
require strong backbone, especially in small vessels. These polymer stents may require special storage conditions and have a shorter shelf life [7].

**Bioabsorbable Stents**

Metal bioabsorbable stents are becoming attractive since they have the potential to overcome the limitations of biodegradable polymer based stents and to perform similarly to stainless steel metal stents. So far, only two classes of materials have been proposed and studied in humans include magnesium (Mg) and Iron (Fe). Use of both Mg and Fe metals as bioabsorbable stents can be justified by the well-known human metabolism. The systemic toxicity of Mg and Fe was very well documented. Therefore, bioabsorbable stents have gain more interest than the polymer stents [44-51].

Several Mg alloys have been investigated so far by several research groups. Mg alloys have very limited ductility compared with most Fe alloys. Advance processing techniques may improve the ductility of Mg alloys, for e.g. Hot Melt Extrusion of Mg-Ga showed better strength and ductility [52]. Several clinical investigations have been studied using Mg alloys as bioabsorbable metal stent. Heublein and co-workers have tested Mg alloy (AE 21) in porcine coronary arteries [53]. From the studies, they observed that, there was over stretch injury in the arteries because of asymmetrical expansion of stent and strut positioned within adventia caused inflammation and exaggerated intimal hyperplasia. But, the natural process of arterial growth was not disturbed in young pigs and the in-stent area increased from 3.28 mm$^2$ at 35 days to 6.15 mm$^2$ at 56 days.

Another most promising and most studied bioabsorbable metal stent is Fe. However, pure Fe unlike most other metals its shows ferromagnetic property, which may interfere with magnetic resonance imaging observation. Therefore, this property was altered by alloying with manganese (Mn) which resulted in anti-ferromagnetic property, while improving its mechanical properties [50]. Since the in vivo degradation of the Fe stent is slow, the cytotoxic property of Fe was found to be insignificant [49]. Relatively small amount of Fe (∼40 mg) was found in stent when compared to systemic availability (447 mg/L) makes it least toxic systemically. Peuster and co-workers have studied and reported the experimental studies of bioabsorbable Fe stent (∼41 mg) into the aorta of New Zealand white rabbits (Figure 5). The results showed there was no adverse side effects resulted during the study period. Moreover, there was neither pronounced neointimal proliferation nor significant inflammatory response.

The important clinical application for bioabsorbable metal stent (AMS) is for pediatric use. Schranz et al. [54] first reported the use of AMS for acute treatment of a new-born baby with severely impaired heart function. A recent study revealed early restenosis following AMS implantation in 2 months old girl. This study demands the further improvements in the field of Mg alloys stent technology [55]. PROGRESS-AMS (Clinical Performance and Angiographic Results of Coronary Stent) study was the first human coronary clinical trials reported. The study showed the AMS stents can be safely delivered and expanded at high pressure in simple coronary artery lesions with good mechanical scaffolding similar to that obtained from BMS. In conclusion from several clinical studies, implantation of AMS-1 is safe in human coronary and peripheral arteries and is associated with high procedural success rate. Degradation rate of the metal stents was as expected without any adverse events. But, however implantation was associated with higher restenosis rate than expected [54-57].

**Conclusion**

With increasing trends in the people affected by coronary heart diseases and the advances in technology the treatments for CRD using intervention techniques will increase. Intervention treatments may also be followed by the physicians for patients with multi-vessel disease, diabetes, etc. Despite the advantages from intervention therapies there are also limitations like restenosis which can be solved by using different non intervention therapies. More research advances addressing the limitations associated with the existing therapies will further benefit the population that is affected by CRD.

**References**

everolimus-versus sirolimus-eluting stents in patients with coronary artery disease: 3-year outcomes from a randomized clinical trial. J Am Coll Cardiol 58: 1325-1331.


