Polymeric Degradable Cardiac Stents: Materials and Future Manufacturing

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Abstract

Cardiac stents are tubular protheses used widely in vascular interventions to treat coronary vessel stenosis. Bioresorbable stents serve the purpose of supporting the vessel during vascular healing before degrading, allowing the vessel to regain normal vasomotion and preventing in-stent restenosis. This review considers the potential choices of materials for polymeric degradable stents, with particular reference to the chemical and mechanical properties required, alongside the potential future use of 3D printing to create personalised cardiac stents. A polymer for use in a bioresorbable stent must be biocompatible and degrade in the correct amount of time. It must also produce a stent with high radial strength and stiffness to support the artery and prevent restenosis. Many 3D-printing technologies are being investigated for the production of stents, and μCLIP seems especially promising. Future research should combine what was learned from the promising results of Igaki-Tamai stents with what we know of the problems with the Absorb BVS, and consider the benefits of a novel production method such as μCLIP.

1 Introduction

Cardiac stents were introduced in the late 1980s to treat coronary heart disease; the first stent implantations were performed by Sigwart et al. in 1986 [1]. Stents were designed to prevent restenosis following angioplasty to widen the arteries around the heart. The notion of a bioresorbable stent was being considered as early as 1988, with research into a biodegradable stent device at Duke University Medical Centre being reported in The American Journal of Cardiology [2].

Bioresorbable stents were first researched due to concerns about stiff metal stents damaging artery walls [2], and this is still a major concern,

with a key advantage of bioresorbable stents being that they allow vessels to regain normal vasomotion [3]. Clinicians believe the role of stenting is limited to the vascular healing period, approximately the first 6 months after implantation [4]. In addition to this, it has been shown that arterial vessel remodelling around a metal can lead to restenosis, with the endothelium growing to cover the metal scaffold. A bioresorbable stent would resolve this issue by the scaffolds degrading, not allowing the vessel wall to grow inwards and narrow. Bioresorbable stents have the additional advantage of allowing future use of the vessel in bypass grafting, after degradation has occurred; durable stents preclude bypass grafting [3].

Traditionally stent manufacturing has been performed via laser machining of a hollow tube of the parent material. 3D-printing is a promising new avenue. It has the potential to allow cardiologists to design and print cardiac stents personalised to each patient, based on measurements from medical imaging [5]. Currently stents are chosen by being the "best-fit" option of an off the shelf product, and poor sizing increases the risk of complications [6]; a custom fit stent would prevent this. There are, however, still challenges in manufacturing 3D-printed devices with suitable mechanical properties with current technologies.

This review considers the potential choices of materials for polymeric degradable stents, with particular reference to the chemical and mechanical properties required, alongside the potential future use of 3D printing to create personalised cardiac stents.

2 Chemical Properties

There are two major considerations with regards to the chemical properties of a potential material: are it and its degradation products biocompatible and safe to be in the blood stream, and how long it will take to degrade. Both of these factors are researched using in vitro, ex vivo and in vivo tests.

2.1 Biocompatibility

Biocompatibility means a polymer provokes no adverse response from surrounding tissue when implanted in the body. In a vascular stent it is vital the polymer causes little inflammatory response, so tissue doesn't accumulate around the stent narrowing the artery which has just been widened. It is also important that the polymer is not thrombogenic: it doesn't cause formation of blood clots.

Van der Giessen et al. (1996) studied the marked inflammatory and

neointimal response to 5 biodegradable and 3 nonbiodegradable polymers after implantation in the porcine coronary artery [7]. The polymers chosen had known medical applications and favourable in vitro results. Polymer strips were cast over 90 °of an existing metal stent and then implanted in porcine coronary arteries. Unexpectedly, all the polymers tested provoked a severe inflammatory response and subsequent neointimal thickening. Van der Giessen et al. attributed this to a combination of parent polymer compound, biodegradation products, and possibly implant geometry. The biodegradable polymers that provoked the least severe responses were polyglycolic acid/polylactic acid copolymer PGLA, and polyethyleneoxide/polybutylene terephthalate copolymer PEO/PBTP.

PLA (polylactic acid) has since been extensively studied, and used in many bioresorbable stent manufacture attempts. Soji Nishio et al. (2012) reported on the 10 year outcomes of patients who had been treated with a PLLA Igaki-Tamai stent and reported non of the increased inflammation observed in the Van der Giessen experiments; artery walls had smooth muscle cells throughout the stent location and no giant cell reaction to foreign bodies. [8]. Da Silva et al. (2018) stated that PLA was the most commonly used polymer in clinical applications at that time, and is considered safe in many biological uses.[9].

Williams and Martin (2005) reported on a different kind of biodegradable polymer: polyhydroxyalkanoates (PHAs) [10]. PHAs are a class of polyesters that are produced by micro-organisms. They state that PHA monomers naturally occur in the human body, and some low molecular weight P(3HB) (poly-R-3-hydroxybutyrate) has even been found in human tissue. The degradation pathways of PHA monomers often happen naturally in the body and so do not raise biocompatibility concerns. Implants of PHAs, for example P(3HB) and P(4HB) were found to provoke some foreign body response but be generally well tolerated in vivo. In a 2003 Martin and Williams studied the biocompatibility and possible applications of P(4HB) specifically, and compared it to PGA [11]. P(4HB) was found to be much better tolerated by the body.

2.2 Degradation

Degradation plays an important role in biocompatibility, and the way a product degrades is due to chemical considerations, but it also has important affects on the mechanical properties of the stent over time, so this will also be touched on in this section.

Da Silva et al. also reported on the biodegradation and excretion of PLA in medical implants [9]. PLA is naturally hydrolysed into lactic acid

or oligomers of lactic acid, which is a naturally ocuring compound processed as part of the Cori cycle. The degradation products are mainly excreted through urine or as carbon dioxide, and cause no adverse effect. Additionally it was found that PLA degradation was limited at low pH. Da Silva et al. further reported on the vastly variable degradation times of PLA in the body [9]. The time taken for degradation ranged from full degradation in 42 days for PLA fibres (unspecified chirality) to a PLA-Zn 0.05% material with 98% L chirality which lost only 9% of its weight in a year. Arteries require the support of a stent for 6 months; after 6 months enough stent must remain to still support the artery, so the stent must take longer than 6 months to totally degrade. The Igaki-Tamai stents were found to be completely degraded in approximately 3 years [8]. The radial strength of a stent can approach 0 long before total degradation, as discontinuities in the scaffold are created. It is after this point that the vessel can regain normal vasomotion [12].

The chirality of PLA has a marked effect on degradation, examined by Oberhauser et al. (2009) [12]. PDLLA is a random copolymer produced from an equimolar mixture of D-PLA and L-PLA, and the random chirality means the chains can not pack efficiently and the polymer is mostly amorphous. PLLA is a semicrystalline polymer whose degree of crystallinity and crystalline microstructure are dependent upon the thermal and deformation history during processing. The crystalline PLLA is less susceptible to degradation than amorphous PDLLA, and takes longer to degrade.

Wang et al. (2018) further investigated how the crystallinity of PLLA affects the degradation of a stent in an asymmetrical manner [13]. They demonstrated how the mechanical processes a stent undergoes during crimping and expansion can introduce local heterogeneity, with areas becoming crystalline due to local strains aligning chains. This leads to certain parts of the stent degrading faster than others, and leads to microstructural loss of integrity, rather than the macroscopic loss of structural integrity considered in metallic stents. Loss of uniformity in the stent can cause shifting of the stent and complications, while protruding bits of polymer, left when surrounds have degraded, can activate platelets and cause thrombosis. Degradation can also be greatly accelerated by microstructural defects (for example cracks) in the polymer, which often form during crimping, and thus structural failure can therefore happen early in the stent's lifetime, when support of the artery is crucial. The effect of thermal and deformation processing on a polymeric stent, and whether it is a symmetric effect, must be carefully considered and controlled during stent design and manufacture to avoid this.

Martin and Williams have studied the degradation of PHAs, as well as the biocompatibility [11] [10]. Samples of P(4HB) of 0%, 50% and 80% porosity were implanted into rats and monitored over a 10 week period. It was found

that degradation rate was independent of configuration but the samples lost 20%, 50%, and almost 100% of their mass respectively, suggesting a correlation between degradation rate and surface area. This is significant as it is likely that the mechanical properties of P(4HB) will degrade gradually, rather than suddenly, since degradation is independent of configuration[11]. P(3HB) degrades much more slowly in vivo, being completely degraded after 24-30 months [10]. Furthermore, the products of the degradation of P(3HB) and P(4HB) are less acidic than the degradation products of PLA and PGA, and therefore do not provoke as strong foreign body reactions as PLA and PGA can during degradation[11].

3 Mechanical Properties

Arterial stents must be strong enough in the radial sense to support the artery they are implanted in and resist being dislodged. The stiffness must also be high enough that the force exerted by the artery on the stent can not elastically deform it so much that restenosis can occur. A stent must achieve sufficient strength and stiffness with stent strut thicknesses not so large as to not cause increased thrombogenicity. Furthermore, a stent must maintain suitable strength and stiffness throughout vascular healing, as degradation starts to occur. Additionally, depending on whether a stent is balloon deployed or self-expanding it must either be able to be plastically deformed first during crimping onto a balloon catheter then during balloon expansion, or it must self-expand to the full diameter of the vessel after prior balloon angioplasty.

3.1 Stent Strength and Stiffness

A stent with insufficient strength is liable to collapse, and a stent with insufficient stiffness will undergo too much elastic recoil; neither of these stents would effectively prevent restenosis [14]. Many experiments have been done to determine the mechanical properties of commercially available stents. Schrader and Beyer (1998) measured the radial strength and stiffness of 8 stents in clinical use expanded to 3 mm and 4 mm diameters [15]. They found that the radial strength of these stents when expanded to 4 mm ranged from 0.49–0.83 atm, and expanded to 3 mm ranged from 0.70–1.26 atm, although no values were recorded for 3 of the stents which either showed extreme variability in strength values or did not fail. The radial stiffnesses of the stents expanded to 4 mm ranged from 0.5–1.0 N mm^{-2}, and of the stents expanded to 3 mm ranged from 0.4–4.1 N mm^{-2}.

Qiu et al. (2018) performed similar analysis on 4 existing bioresorbable stents [14]. They found the radial strength of these stents, when expanded to their recommended diameter, ranged from 73–318 kPa (or 0.72 - 3.14 atm, for comparison with Schrader and Beyer). The radial stiffness of the bioresorbable stents ranged from 132–708 kPa mm^{-1}.

(Note on units: while Schrader and Beyer described stiffness in terms of the force applied to the stent per mm change in diameter, Qiu et al. worked with pressure applied per mm change. Pressure is perhaps more useful, as the stresses in the stent material, and therefore whether it will fail, depend on the area any force is applied over)

These values offer some guidance on what the strength and stiffness of the expanded stent should be, as they all apply to stents that have been approved for clinical use. Few tests, however, have been done to find the minimum strength and stiffness of a viable arterial stent. The maximum blood pressure expected inside an artery is 180 mmHg (or 24 kPa), as this is the maximum systolic blood pressure recorded in an adult not considered to be in hypertensive crisis [16]. If we consider the blood pressure to be in equilibrium with the vessel, the maximum compressive pressure exerted by the artery should be around 24 kPa. This is expected to be the minimum radial strength of a viable stent, though of course a safety factor should be applied. This value (including the safety factor) defines the minimum strut thickness of a stent for a given design in a given material.

3.2 Strut Thickness

Strut thickness has an important impact on the thrombogenicity of the stent. Kolandaivelu et al. (2011) carried out research into the effect of polymer coatings on the thrombogenicity of stents, during which they tested the effect of strut thickness [17]. They found that thick struts, which are less streamlined, cause blood to flow turbulently downstream of the scaffold. Turbulent flow causes platelet deposition, as well as thrombin and fibrin generation, causing so called coagulation cascade [3] and forming clots. This can be seen in Figure 1.

Kolandaivelu et al. showed that in general the thinner the strut, the less thrombogenic, though this also depends on how streamlined the strut design is, and whether any drug-elution is employed. It is unclear, however, how thin a strut must be to avoid causing problematic, and potentially fatal, thrombosis. A stent should be designed with struts as thin and streamlined as possible, and from there further tests can be performed on thrombogenicity.

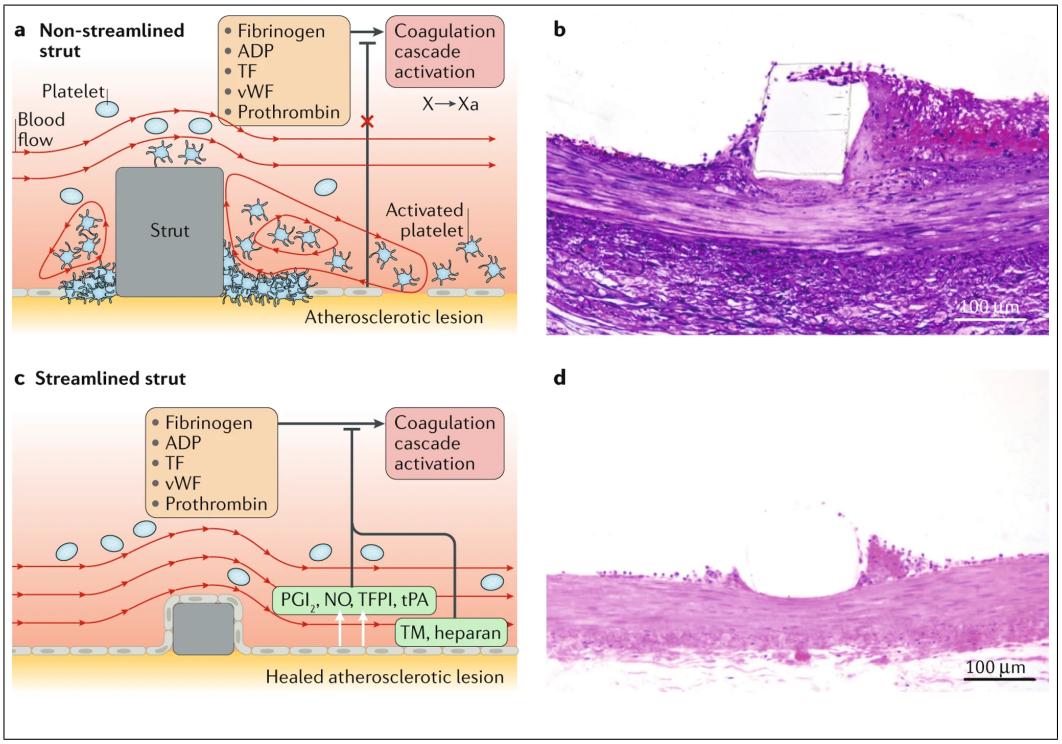

Figure 1: ***a*** *and* ***c*** *show how a non-streamlined thick strut provokes the coagulation cascade and generates a clot, while a streamlined strut causes no turbulent blood flow and so does not activate the coagulation cascade, causing less clotting.* *b and d are histological images demonstrating this effect; a large thrombus has formed downstream of the thick strut in b, while d shows less thrombus formation.* *Figure reproduced from Jinnouchi et al [3] with permission*

3.3 Geometry and Material Properties

Pauck and Reddy (2015) conducted a computational analysis of the mechanical performance of PLLA stents, testing 3 different geometries with a range of materials stiffnesses [18]. They tested the models against a desired radial strength of 300 mmHg (40.0 kPa). They referred to the three stent designs as S1, S2 and S3. S1 was based on the Absorb Bioresorbable Vascular Scaffold (produced by Abbot Vascular). S2 was based on a standard metallic stent. S3 was designed by Pauck and Reddy to maximise radial strength and stiffness. Strut width and thickness were kept to approximate 100 μm throughout this test.

The S1 geometry performed best no matter the stiffness of the material tested, but only the material stiffness of 9 GPa in the S1 geometry was able to reach the threshold of 300 mmHg radial strength. It had a radial strength

Table 1: *Mechanical properties of some typical stent materials. Stainless steel, cobalt chromium and nitinol are used in permanent stents, while iron and magnesium are bioresorbable metals, and the polymers are all bioresorbable. Table adapted from Grabow et al (2009) [20], with values for PDLLA taken from Engelberg and Kohn (1991) [21].*

Material	Tensile Modulus (GPa)	Tensile Strength (MPa)	Elongation at break (%)
Stainless Steel (316 L)	190	670	45
Cobalt Chromium (L605)	240	1100	50
Nitinol	83	895	8.5
Iron	211	210	<10
Magnesium	45	250	25
PGA	6.9	70	<3
PLLA	2.1	45	<10
PDLLA	1.9	29	4
P(3HB)	3.7	36	1
P(4HB)	0.7	50	1000

of 322 mmHg, so does not represent an absolute minimum, and could be further reduced by altering the strut width and thickness (without significantly increasing thrombogenicity). Typical stiffness and strength values for stent materials are given in Table 1. The value given for PLLA represents an average stiffness, however, and Pauck and Reddy believe PLLA fibres, with a high crystallinity, may reach sufficiently high modulus to create 300 mmHg radial strength geometry.

The S1 geometry represents a suitable starting point for future stent design, with adjustment for the specific material used to maximise strength. None of the average stiffness value for typical bioresorbable polymers used in stents (given in Table 1) reach the suggested 9 GPa stiffness, but the polymers have a very wide range of values, depending on molecular weight and crystallinity, and chain orientation. Moduli of up to 7 GPa were measured in PLLA fibres by Agrawal and Bhalla (1992) [19], so this may be a suitable material for stent manufacture.

4 3D-Printing

3D-printing opens up many possibilities for the future of cardiac stents. Moore et al. (2016) [5] outline the potential benefits and upcoming challenges. Their vision is of a system wherein a cardiologist could take scans from a patients heart, use measurements these to design a stent, and then

have it printed in under 20 minutes, ready to deploy. There are, however, some key challenges: firstly, surface finish, the stent must be smooth to not cause inflammation in the artery; secondly, strength, the stent must be strong enough to support the artery throughout it's life; thirdly, speed, any manufacturing method must produce a stent with sufficiently good strength and surface finish in under 20 minutes. Some forms of 3D-printing offer superior control of the microstructure of the polymer by giving good thermal control during production, or offer better control of defects, which could help combat some of the issues raised by Wang et al., discussed in section 2.2.

4.1 Poly-Jet

Moore et al report on initial results using a Poly-Jet technology 3D-printing process [5]. This was just initial experimentation, with the stents created not being designed for any further use. The time taken to print a stent and purge the system was 45 minutes, though this test was done with non-sterile, non-bioresorbable polypropylene, and was never intended for clinical use: it is unknown how long this method would take with these considerations. The surface finish was stated to be relatively good. An issue arose, however, due to the layer-by-layer method of printing; the strength within the layers is significantly higher than the strength between layers, and so when expansion of the stents was attempted strut failure occurred in all stents due to delamination of layers parallel to print bed. Failure occurred no matter the orientation to the print bed the stent was printed in. This issue of delamination is a potential problem in many 3D-printing methods, as so many depend on point-by-point scanning of the material to polymerize each fabrication layer.

4.2 Selective Laser Melting

Flege et al (2012) used selective laser melting to produce PLLA and PLLA-co-poly-ϵ-caprolactone (PCL) degradable stents [22]. SLM tends to produce a part with a poor surface finish, so the stents required additional spray- and dip-coating to smooth the surface. The biocompatibility tests performed had promising results, with no inflammatory reactions or thrombi produced. However, no mechanical testing was performed, and in particular stent crimping/expansion was not attempted; SLM is performed in successive layers, and therefore delamination leading to strut failure is a major concern. No reference was made by Flege et al to the total time taken to manufacture, however the spray- and dip-coating process will add significant time, and it is unlikely this method could reach required speeds.

4.3 Rapid Prototyping with Electrospinning

Park et al (2015) used an electrospinning method (detailed in their 2011 report [23]) which creates a nanofiber web with high surface area to fabricate a stent [24]. The stent was fabricated from PCL fibres and coated with the drug sirolimus mixed with PGLA, and polyethylene glycol (PEG). They mainly investigated how the 3D-printing could affect the drug eluting properties of the stent. This method, which involves spinning fibres around a cylindrical form avoids the layered structure produced in most 3D-printing methods, but requires the stents conform to the form surface, limiting design flexibility and customisability. This stent too must be coated after printing to smooth the surface, and then must be dried for 24 hrs. While Park et al. did not report on the printing speed, this drying time clearly prevents this stent from acheiving the 20 minute production time aimed for.

4.4 Fused Deposition Modelling

Zhang et al (2019) manufactured a PLLA-sirolimus 5% stent using fused deposition modelling. They found the mechanical properties of the stent varied greatly depending on extrusion rate, but that the maximum radial strength (128.7 $\pm$7.1 kPa) and flexibility were similar to the Absorb Bioresorbable Vascular Scaffold. Mechanical tests were also carried out after 8 months in vitro degradation, and the stent with initially 128.7 $\pm$7.1 kPa radial strength was found to have retained 30 kPa strength (higher than the calculated 24 kPa minimum for arterial support). This demonstrates that it would retain strength to support the artery throughout vascular healing. Interestingly Zhang et al. found that after 1 month "degradation" in a phosphate-buffered saline solution the radial strength of the stent actually increased due to water uptake, which gives increased confidence in the performance of this stent during the crucial early healing. While fused deposition modelling is a layered method stents were successfully expanded and no delamination was reported. Relative extrusion rates were reported, but no overall time for manufacture, so it is unknown if fused deposition modelling can reach the required speed of manufacture. Otherwise, these results are very promising.

4.5 micro-Continuous Liquid Interface Production

CLIP is an additive manufacturing process devised by Tumbleston et al. (2015) [25]. It utilises the polymer setting properties of UV light and the polymer setting inhibiting properties of oxygen. A pool of UV-curable resin has an oxygen permeable window in its base. A continuous series of UV

images are projected through the window, and cure the resin above a "dead zone", caused by oxygen permeating into the resin. The depth of this dead zone can be altered by altering the thickness of the window, and the pressure of oxygen in the environment. Ware et al. (2017) developed micro-CLIP or μCLIP, a process to allow for 3D printing of biomedical devices with micron-scale precision [26]. They manufactured high-resolution bioresorbable scaffolds using μCLIP with a bioresorbable photopolymerizable biomaterial (B-Ink). The B-Ink is a combination of a prepolymer methacrylated poly(1-12 dodecamethylene citrate) (mPDC); solvent (Ethanol); photoinitiator (Irgacure 819, BASF Corporation); co-initiator Ethyl 4-dimethylamino benzoate (EDAB); and UV absorber (Tinuvin 171, Sigma Aldrich Corp). The proportions of mPDC and EDAB were varied throughout the study to optimise the properties. The speed achievable by this method depends on the resolution and precision required, but also majorly on the intensity of UV light projection. While in theory CLIP is a continuous process the CAD model was still sliced into layers for projection of the UV light, and so layer slice thickness can be varied. The thickest 15 μm layers used in this experiment led to a build time of 11.25 minutes, followed by a 2 minute UV flood, keeping the total manufacturing time under 20 minutes. The cost of this incredibly fast speed is that it negatively effects the surface finish. In a perfect CLIP system the surface would be totally smooth, but as the model is cut into layers some degree of "stepping" is observed on the angled edges of struts, especially at larger layer thicknesses. This doesn't affect the vertical surfaces of the inside and outside of the scaffold, which are very smooth.

Mechanical tests were performed after stents were soaked in water for at least 12 hrs, to simulate the operating environment. . It was shown that the B-Ink formulation consisting of 60% mPDC and 3% EDAB produced stents that could exceed the stiffness of a nitinol control stent, however this was with a strut thickness of 400 μm, not suitable for a coronary stent. In a later study (2018) Ware et al. aimed to reduce strut thickness and test biocompatibility of their stents [27]. They achieved a stent with a stiffness surpassing the nitinol control stent with strut thickness and width of just 150 μm, far more suitable for use in coronary arteries. This was achieved using post-processing with either UV flood post-fabrication-cure or convection heat post-fabrication-cure. UV flood was much faster, requiring only 60s for the stent to achieve nitinol comparable stiffness. The B-Ink was shown to be biocompatible and raised no concerns. Further work is ongoing to make production a completely continuous process, eliminating the layers and their accompanying speed limits, however with 11.25 minute build time the work demonstrates the plausibility of the use of customized, 3D printed vascular scaffold for patients in emergency settings.

5 Conclusions

Research into bioresorbable vascular stents has been happening for over 30 years, yet there has been little success. In 2002 50 patients were treated with Igaki-Tamai stents, and 10 years on in 2012 Nishio Soji et al demonstrated that the evidence showed the long-term safety of these stents, and their comparable outcomes to bare metal stents [8]. Yet these stents were never made commercially available, perhaps due to focus switching to the development of drug eluting stents, which successfully reduced restenosis, improving outcomes over bare metal stents [28].

The Absorb Bioresorbable Vascular Scaffold (Absorb BVS, produced by Abbott Vascular) is a more recent bioresorbable stent attempt, a drug eluting bioresorbable stent which received the CE mark in Europe in 2010, and was FDA approved for use in 2015. But evidence began mounting that the Absorb BVS led to more complications in the 3 years post-implantation compared to more conventional durable drug eluting stents, and use of the device never gained sufficient momemntum to be commercially viable, so it was withdrawn from the market in 2017 [3] . Evidence is still being collected from those treated with the system, however, and it is thought that the benefits of a bioresorbable stent over a durable one are after it has fully degraded, around 3 years after implantation. So it is possible that after 10 years the evidence will show comparable outcomes between the Absorb BVS and conventional stents, after the benefits of the stents being bioresorbable take effect.

If we are to continue the development of bioresorbable stents despite discouraging outcomes, the most promising materials for this are PLA and PHAs, in particular P(3HB) and P(4HB). These show good biocompatibility, and are used in existing medical devices [10] [29]. These polymers can be used in combination, e.g. one for the scaffold and one for the coating, or in some other configuration, to tailor degradation time, and speed of drug elution, while maintaining good mechanical properties.

3D-Printing, and particularly μCLIP, presents the possibility of producing personalised bioresorbable stents with mechanical properties comparable to stents currently in use [6], and a good surface finish (preventing increased foreign body response). It is hoped the personalisation of size of the stent will prevent some of the problems encountered by Absorb BVS, of scaffold thrombosis due to malapposition or under expansion [3] [5]. In vivo tests are yet to be performed with this technology, however, so it is yet to be seen whether μCLIP produced stents will give superior outcomes.

Huge volumes of research have been produced on this topic in the last 30 years, and it is unclear where future development is heading. Future research

would do well to combine what was learned in the promising early tests of the Igaki-Tamai stents with the more discouraging outcomes of the Absorb BVS, and perhaps consider the benefits of a novel production method such as μCLIP. It is possible, however, that polymeric degradable vascular stents which deliver on what was promised aren't currently achievable, and progress requires a whole new outlook on the issue.

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