"The Next Generation"

Materials Selection Case Report: Bioresorbable Vascular Scaffolds

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Index

Background

Coronary artery disease includes different diseases caused by arterial atherosclerosis, or narrowing of the artery due to the buildup of plaque. In 2015, there were 110 million cases worldwide, with 8.9 million deaths as a result [1]. Coronary interventions such as angioplasty and coronary stents are often utilized in severe cases to restore blood flow through the blocked artery, and the stent is left in the artery to ensure that it remains unblocked.

Drug-eluting stents (DES) are placed in the artery during angioplasty to address the problem of restenosis, or renarrowing of the artery after angioplasty has been performed. The DES slowly releases a drug that blocks cell proliferation, in order to prevent fibrosis as well as blood clots around the stent which could impede blood flow through the artery. After clinical trials had shown that drug-eluting stents are more effective at preventing restenosis than stents without a drug-eluting component [2], known as bare-metal stents, DES were approved by the FDA for clinical use. Currently, most DES consist of the metal structure that physically holds the artery open, as well as the elutable drug contained within a durable polymer matrix integrated within the metal scaffold [3].

Although DES are more effective in preventing restenosis, prolonged exposure to the drug has brought a new set of issues compared to the bare metal stents. Notably, the implementation of DES have caused the rate of stent thrombosis to rise, a complication that was very rarely seen with bare metal stents [4]. The current standard utilizes bioabsorbable polymers in the coating of the stent, which will eventually degrade to leave only a bare metal stent [5]. The first bioabsorbable polymer drug-eluting stent system (BP-DES), Boston Scientific's SYNERGY, was approved by the FDA in 2015. During its clinical trial, SYNERGY demonstrated 0% stent thrombosis throughout the four years of the trial. Both the drug coating and the polymer itself bioabsorb after the drug coating has finished eluting at three months, avoiding the complications that arise from long-term polymer exposure with DES. A comprehensive analysis of all stents for risk of stent thrombosis found that the SYNERGY BP-DES had the lowest relative risk of stent thrombosis [6]. Regardless, although DES with biocompatible or biodegradable polymer components address the issue of sustained polymer exposure, there are now concerns that these BP-DESs can cause neoatherosclerosis, which sometimes results in thrombosis [7]. Neoatherosclerosis is attributed to the chronic inflammation caused by the constant presence of a foreign body, in this case the permanent components of metallic DES.

Future Materials

A novel approach to drug-eluting stents that addresses the issue of neoatherosclerosis is a vascular scaffold system that is completely bioresorbable. Currently, the only FDA-approved bioresorbable vascular scaffold system (BVS) is the Absorb GT1 BVS, manufactured by Abbott Vascular and composed of the biodegradable polymer poly(L-lactic) acid (PLLA). However, long term results from ongoing clinical trials revealed that the Absorb BVS has a significantly higher risk of myocardial infarction, ischemia-driven repeat procedures, and scaffold thrombosis compared to Abbott's metallic drug-eluting stent [8]. This led the FDA to issue a safety alert to health care providers advising them of the increased risks of the Absorb BVS in March of this year, causing Abbott to announce that it will no longer sell the Absorb BVS due to "low commercial sales" [9]. The disappointing results from the studies of the Absorb BVS influenced Boston Scientific to abandon the development of its own BVS device, in favor of focusing on its current metallic DES instead [10]. However, over 20 companies are still working on their respective versions of a BVS [11].

REVA Medical's Fantom scaffold, unlike most BVS, doesn't utilize PLLA in its scaffold, instead consisting of a proprietary tyrosine polycarbonate polymer known as Tyrocore. As most BVS under development use PLLA, Fantom provides an important alternative to patients sensitive to PLLA. As a second generation BVS, its design addresses concerns raised during the testing of first generation BVS. The Fantom is radiopaque, eliminating the need for the platinum markers present in the radiolucent Absorb BVS, and making imaging and placement of the Fantom easier than its predecessors. The Fantom also has thinner struts (125 μm), as thicker struts (~150 μm) were previously required to maintain the necessary mechanical properties, but were linked to higher occurrence of restenosis and thrombosis. In the FANTOM II trial, after 6 months there was a 2.6% occurrence of major adverse cardiac events. The performance of the Fantom scaffold in preventing restenosis was promising, and on par with metallic DES [12].

Amaranth's third generation bioresorbable scaffold (BRS), Magnitude is composed of a proprietary ultra high molecular weight PLLA, granting it a greater elongation compared to other PLLA scaffolds. Magnitude also has thinner struts, less than 100 μm, to address the problems caused by thick struts in the first generation of BVS. However, its mechanical properties are still comparable to metallic DES, and it has an excellent fracture toughness [11]. Magnitude is currently in Phase 2 clinical trials, but the second generation BVS, Aptitude, had a major adverse cardiac event rate of 3.4%, with a clinical success rate of 98.3%.

Current research in animal models *in vivo* includes a 3 year study of Arterial Remodeling Technologies' BVS in a healthy porcine model. ART's BVS is composed of amorphous PLA [13]. Early lumen enlargement was observed, which is unique to ART's BVS and is not observed in other PLA-based BVS. Its safety profile was on par with the bare metal stent used as a control [14], which is promising for this BVS's future, as it is currently in clinical trials [13]. Another study compares the PLA XINSORB BVS to a metallic DES in a porcine model after 180 days. It was found that the XINSORB BVS has similar radial strength to a metallic DES, usually a major challenge in using polymers in stent applications [15]. However, a longer study is needed to fully characterize the resorption process of PLA, which can take up to 4 years.

	Bioabsorbable polymer drug eluting stents	Bioresorbable vascular scaffold
Pros	- Struts of metal stents can be thinner due to superior mechanical properties [16]	- Avoid late stent-related adverse events: thrombosis, myocardial infarction, restenosis [17] - Reduced neoatherosclerosis - No permanent metal component required - Reduce requirements for long-term dual antiplatelet therapy [18]
Cons	- Leaving metallic implant in vessel can cause late in-stent restenosis [16] - long-term dual antiplatelet use required [19]	- Some require cold storage and specific techniques for implantation - Thicker struts required to maintain necessary mechanical properties - Higher rates of early scaffold thrombosis and target vessel-related myocardial infarction

Table 1: Pros and Cons of Current and Future Materials for Treatment of Coronary Artery Disease after Angioplasty

Bioresorbable vascular scaffolds were conceived to avoid the complications inherent in metallic DES and permanently implanting a metallic component in the artery. BVS wouldn't require long-term antiplatelet therapy, and would biodegrade before late in-stent restenosis could become an issue. However, transitioning from metals to biodegradable polymers has been a major stumbling block, as polymers' inferior mechanical properties have required stents to have larger struts, introducing a new set of complications, including early thrombosis and myocardial infarction [16].

Material Selection Criteria

The initial starting point is the Bioengineering Level 3 database in EduPack. As I chose to focus on polymer-based BVS, I selected all polymers within EduPack's Material Universe. For the initial material selection, I chose three limits. For the first constraint, I set 18 MPa as the minimum value for tensile strength, as 18 MPa is the lowest tensile strength recorded for polymer-based BVS currently in development [16]. For the second limit, I set the minimum Young's modulus as 1 GPa, again because this is the lowest modulus recorded for current BVS [16]. For the third constraint, the maximum service temperature needed to be at least 40°C, as the scaffold will be implanted in the body and therefore must function for an extended period of time at body temperature [20].

Initial Material Selection

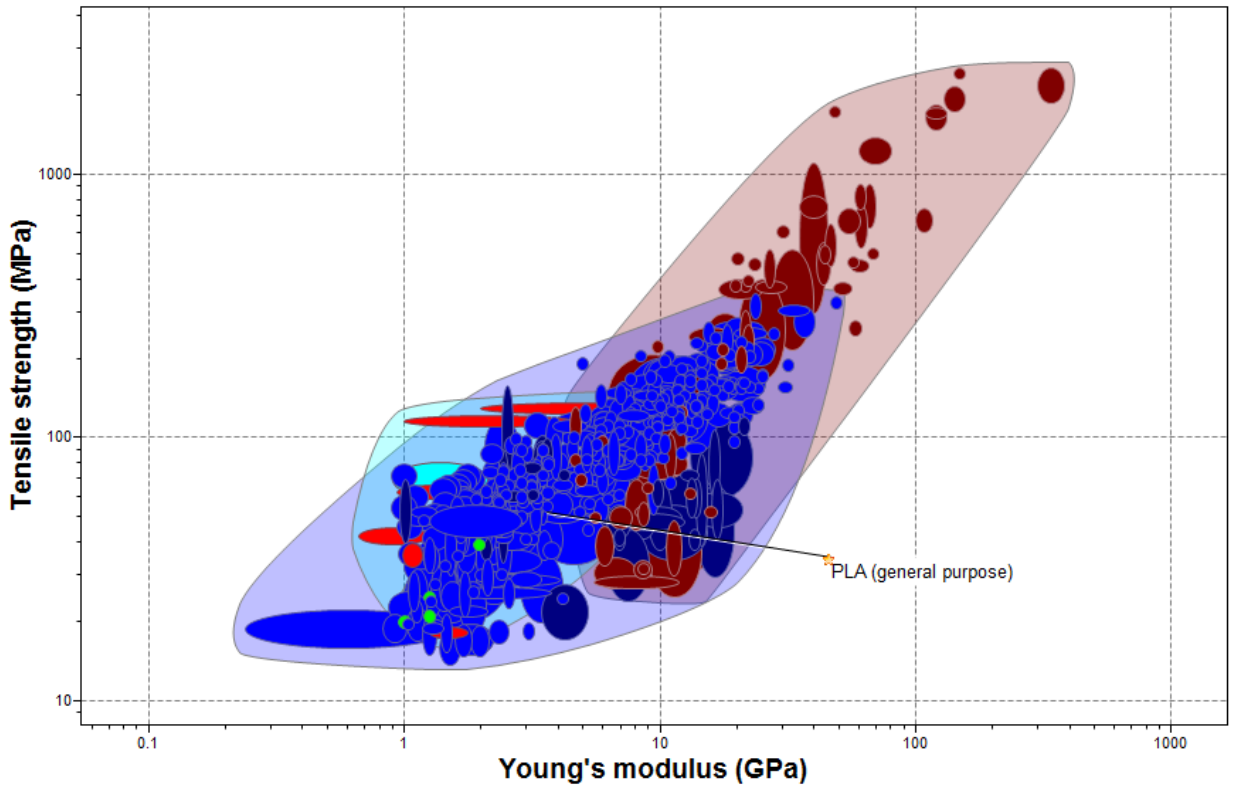

Figure 1: Initial Material Selection in EduPack: Tensile strength (mPa) vs. Young's modulus (GPa)

620 materials passed the criteria for the initial material selection. I marked PLA (general purpose) as my "favorite", as there are multiple commercially available PLA-based BVS [11]. PLA (general purpose) is on the lower side for both tensile strength and Young's modulus out of the materials that passed (Fig. 1). However, it seems to be a middling choice within the thermoplastics (royal blue). Materials within the composite subgroup (maroon) have the best mechanical properties of all the materials that passed the initial selection criteria. Most of the materials that passed, regardless of type, are clustered densely in the 1-20 GPa range for Young's modulus and the 10-500 MPa range for tensile strength. Along with the thermoplastics, the thermosets (dark blue), the thermoplastic elastomers (red), the foams (green), and the single thermoset elastomer (aqua) are also packed closely together.

Material Refinement

In refining my material selection, the most important criteria is that the material is biodegradable, filtered for in EduPack. Subsequently, I will generate a degradation and wear report in the ASM Medical Materials Database in order to analyze the time to complete resorption and toxicity of the degradation products. The time to complete resorption should be as short as possible while still preventing restenosis after angioplasty, around 6 to 12 months [21]. Minimizing the time to

complete resorption for BVS is crucial for preventing late events, a major issue in BP-DES [11]. For toxicity of the degradation products, there should not be systemic toxicity concerns, and the local toxicity of the degradation products should be minimal. Additionally, I will utilize the sterilizability data available in EduPack and generate a sterilization and imaging report in the ASM Medical Materials Database to ensure that a suitable sterilization method is available. In terms of importance, biodegradability of the material is naturally the highest priority, as biodegradability is inherent to this application. The availability of a suitable sterilization method is second priority, as the ability to effectively sterilize the material is crucial for the development of a clinically safe BVS. Third and fourth priority are systemic toxicity and local toxicity of the degradation products, respectively. Systemic toxicity is a crucial concern for developing a safe product. Local toxicity is slightly less important, as a foreign body reaction and subsequent inflammation is somewhat anticipated in the implantation of a biomaterial in the body. Finally, time to complete absorption is the lowest priority, as moderate variation within it is not crucial to the successful functioning or safety of a BVS, but is still important to consider.

Material Recommendations

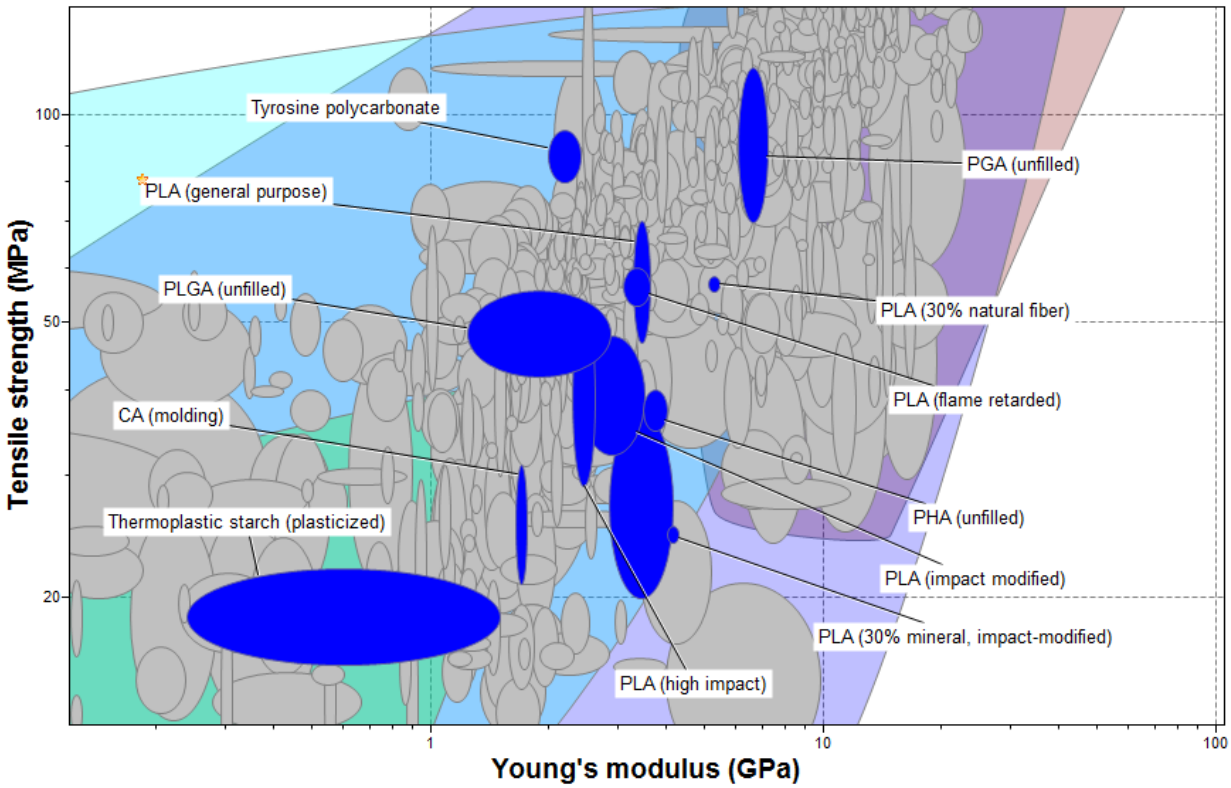

Figure 2: Refining of Material Selection: Tensile strength (mPa) vs. Young's modulus (GPa)

After applying my new criteria for biodegradability in EduPack, 13 individual material listings passed this limit (Fig. 2). However, as 7 of these were different versions of PLA, in actuality 7 materials passed: cellulose acetate (CA), polyhydroxyalkanoates (PHA), thermoplastic starch, poly(glycolic acid) (PGA), poly(lactic-glycolic acid) (PLGA), tyrosine polycarbonate, and PLA.

Although CA has the appropriate mechanical and biodegradation properties, it has marginal sterilizability with radiation and poor sterilizability with ethylene oxide and steam autoclave [20], which precludes it from use in a BVS.

PHA have excellent sterilizability with ethylene oxide [20] and poly 3-hydroxybutyrate and poly 4-hydroxybutyrate, members of the PHA family, do not have systemic toxicity concerns for their degradation products [22]. However, the degradation products of poly 3-hydroxybutyrate were associated with a persistent foreign-body response [22]. When poly 3-hydroxybutyrate was tested in a biodegradable stent implanted in the iliac arteries of rabbits, it caused intense inflammatory vascular reactions, destroying the elastic membranes of the artery and causing thrombosis and lumen narrowing [23]. As a result, I would not recommend exploring clinical applications of PHA.

Starch composites show promise in biomedical applications, especially due to their ability to completely biodegrade with no toxic byproducts [24], and the local non-toxicity of their degradation products [22]. However, polymers formulated using starch have far inferior mechanical properties compared to synthetic polymers, restricting their use [22]. Thermoplastic starch also has the lowest tensile strength and Young's modulus out of the materials that passed the material refinement (Fig. 2). As a result, it's unlikely that a BVS could be constructed predominantly of a thermoplastic starch polymer, and I would recommend against further exploration.

PGA's sterilizability with ethylene oxide is good [20]. There is no systemic toxicity predicted for PGA's degradation products, however for local toxicity, an inflammatory response involving mononuclear cells and multinucleated giant cells as well as decreased differentiation of smooth muscle cells has been observed in response to PGA's degradation products [22]. PGA's time to complete resorption is 6-12 months, the ideal range for this value. Additionally PGA has the higher Young's modulus and tensile strength of the materials that passed the biodegradability limit (Fig. 2). Due to PGA's superior mechanical properties and favorable resorption time, I would still recommend further research into its use, despite the issues raised with the local toxicity of the degradation products.

PLGA can be suitably sterilized by ethylene oxide [22]. Additionally, its degradation products are naturally occurring and do not raise any concerns for systemic toxicity [22]. Similar to PGA, as PLGA is a copolymer of PGA, there's significant local inflammation due to its degradation products, however this can be modulated by changing the ratio of PLA to PGA [22]. PLGA has a degradation time to complete resorption of 1-6 months [22], which may be insufficient to prevent restenosis after angioplasty. Additionally, the Young's modulus and tensile strength of PLGA are lower than both PLA and PGA (Fig. 2). For these reasons, I would not recommend development of a PLGA-based BVS, as it has the unfavorable inflammatory features of PGA without the mechanical advantage.

As only polycarbonate, not tyrosine polycarbonate, is listed in both EduPack and the ASM Medical Materials database, I relied on mechanical data presented by REVA Medical for its

proprietary tyrosine polymer at a conference [25]. Tyrosine-derived polycarbonates degrade by hydrolysis, but don't release bursts of acidic degradation products like PLA does [22, 23]. Tyrosine polycarbonate has been characterized as slowly degrading, high strength, and easily processed [26]. Despite its slow time to degrade completely (3-4 years) [25], REVA Medical's BVS using Tyrocore is very promising, and I would recommend further exploration of tyrosine polycarbonate as a material for BVS.

Finally, PLA has excellent sterilizability for ethylene oxide [20], but radiation and steam are unsuitable for use with it [22]. PLA's degradation product is lactic acid, which doesn't result in systemic toxicity, but can result in a local inflammatory response if lactic acid accumulates [22]. PLA takes more than 18 months to completely resorb [22], but I would still recommend further development of PLA-based BVS. Its Young's modulus and tensile modulus were among the highest of the biodegradable materials, and Abbott's PLA-based BVS has already been approved by the FDA, both of which are favorable for further research.

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Authors

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