Design of the Novel Tyrocore Polymer for the Next Generation of Thin Strut, Radiopaque Bioresorbable Scaffolds

INTRODUCTION

Drug-eluting bioresorbable scaffolds were developed as an alternative to metallic stents for the treatment of coronary artery disease. Scaffolds are designed to support the artery during healing following balloon angioplasty and then disappear (or "resorb") from the body over a period of time. This resorption is intended to avoid the long-term complications of a permanent implant including adverse events and limitations on retreatment and non-invasive diagnostic imaging.

BIORESORBABLE SCAFFOLDS

First Generation

The first bioresorbable scaffold, called Absorb from Abbott, became commercially available in Europe in 2012[1]. Absorb, made from high-molecular weight PLA, or polylactic acid, was quickly followed by a second PLA BRS (P-BRS) called DESolve from Elixir Medical and by a magnesium BRS (M-BRS) called Magmaris from Biotronik. Both P-BRS and M-BRS are designed with a PLA-based coating that incorporates an anti-proliferative drug. First generation BRS received an enthusiastic response but their limitations resulted in a decline in interest and utilization. Assessment of first generation BRS identified areas of improvement for future generations: strut thickness, radiopacity, and deliverability.

Second Generation

A second generation BRS, called Fantom from REVA Medical, was designed to overcome the limitations of first generation BRS. Fantom, made from Tyrocore (T-BRS), became commercially available in Europe in 2017. T-BRS are designed with an integrated Tyrocore coating that contains an anti-proliferative drug. T-BRS offer improvements needed to achieve broader adoption: thinner struts, full radiopacity, and ease-of-use.

Third Generation

The third generation BRS, Fantom Encore from REVA Medical, is the most advanced BRS. Like Fantom, it is made from Tyrocore with an integrated coating. Fantom Encore offers the thinnest struts of any commercially available BRS with 95 µm in the 2.5 mm diameter. The 3.0 and 3.5 mm diameter scaffolds have strut thicknesses of 105 µm and 115 µm, respectively.

Table 1: Improvements of 2nd and 3rd Generation Compared to 1st Generation BRS

1st Generation P-BRS, M-BRS	2nd Generation T-BRS	3rd Generation T-BRS
Strut thickness[2] ≥ 150 µm	Strut thickness 125 µm	Strut thickness 95-115 µm
Lack of radiopacity requiring metal markers	Full radiopacity without metal markers	Full radiopacity without metal markers
Distinct drug coating	Integrated drug coating	Integrated drug coating
Ease-of-use challenges	Ease-of-use features	Ease-of-use features

TYROCORE PROPERTIES

Tyrocore is a unique, proprietary polymer developed and manufactured by REVA Medical. It is designed to meet the requirements for vascular scaffold applications including radiopacity, strength, ductility, benign degradation with low lactic acid release, and storage stability. It is comprised of analogs of the amino acid tyrosine (desaminotyrosine) and biocompatible hydroxy-esters. Tyrocore consists of an iodinated diphenol and a low molecular weight oligomer of polylactic acid diol (Figure 1), with a significantly higher molar ratio of the iodinated diphenol.

The properties of Tyrocore and PLLA, as previously published, are shown in Table 2. The phenyl-ring of the iodinated diphenol is an inherently strong molecular structure, which contributes to Tyrocore's high tensile strength. The capability to retain ductility, while maintaining strength, is directly associated with Tyrocore's composition and high molecular weight. Tyrocore's radiopacity results from the iodine, which is covalently bound to the tyrosine analog to create the iodinated diphenol.

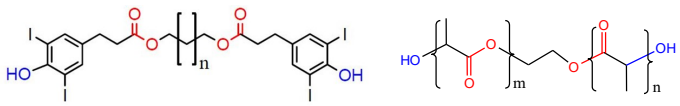


Figure 1: Iodinated diphenol (left) and polylactic acid diol (right)

Table 2: Properties of Tyrocore and PLLA

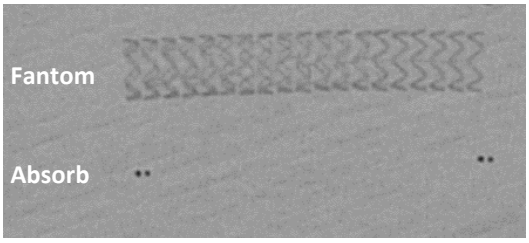
Attribute	Tyrocore[3]	PLLA[4]
Ultimate Tensile Strength	100-110 MPa	50-70 MPa
Elongation at Break (Ductility)	150-200%	2-10%
X-Ray Visible	Yes	No

FANTOM PERFORMANCE

Radiopacity

Fantom gets its radiopacity from the iodinated diphenol in Tyrocore. Iodine atoms scatter x-rays and impart radiopacity due to their high mass, allowing Fantom to be visualized using standard angiographic techniques (Figure 2). The amount of iodine in a Fantom scaffold is less than 1% of the iodine found in 1 mL of contrast media.

Figure 2: X-ray image demonstrating radiopacity of Fantom and Absorb[3]



Radial Strength and Recoil

Tyrocore's high tensile strength enables Fantom to have thin struts (125 µm) while improving strength and reducing recoil compared to P-BRS and M-BRS with strut thickness ≥ 150 µm (Table 3).

Table 3: BRS Performance Characteristics[2,3]

	Fantom	Absorb	Magmaris
Strut Thickness (µm)	125	157	166
Radial Strength (N/mm)	0.22	0.14	0.17
Recoil	2.0%	2.3%	7.7%

FANTOM PERFORMANCE, continued

Ease of Use

Tyrocore's inherent strength and ductility result in ease-of-use features for Fantom (Table 4). Fantom has thinner struts than first generation scaffolds as well as a smaller crossing profile to facilitate deliverability. Once the scaffold is delivered to the target lesion, Fantom's single-step inflation and higher expansion over nominal make it easier to achieve full scaffold expansion and apposition.

Table 4: Scaffold Deliverability Features (3.0 mm diameter)[5]

Feature	Fantom	Absorb	DESolve	Magmaris
Crossing Profile (mm)	1.35	1.43	1.44	1.50
Expansion Over Nominal (mm)	0.75	0.5	0.5	0.6

FANTOM HEALING ADVANTAGES

Computer modeling and animal studies were used to investigate the characteristics that may contribute to late scaffold events observed with P-BRS and compare them to T-BRS. To study the time course of polylactic acid degradation for both P-BRS and T-BRS, a computational model was developed capable of predicting lactic acid accumulation in local arterial tissue from 0 to 42 months following implantation in the coronary arteries (Figure 3)[3]. P-BRS is represented by Absorb based on a previously published analysis[6], which was modified to account for its two-step degradation of coating followed by the scaffold.

The model predicts two peaks of lactic acid tissue concentration for Absorb. The first is between 0 and 6 months associated with coating degradation. The second, larger peak, falls between 18 and 42 months associated with scaffold degradation. For Fantom, there is no coating-related early peak because of the integrated drug coating and a very low and broad peak around 28 months associated with scaffold degradation. The maximum lactic acid tissue concentration for Fantom is two orders of magnitude lower than for Absorb.

The difference in late stage lactic acid release likely results from the lesser amount and substantially shorter segment polylactic acid diol (<10,000 Da) contained in Tyrocore compared to the high molecular weight poly-L-lactic acid (>100,000 Da) in Absorb. The short chain segment poly-L-lactic acid diol in Tyrocore can break down more quickly and over a sufficiently long time to better match elimination of lactic acid by natural biologic processes, whereby lactic acid does not accumulate in the arterial wall.

The effect of early stage lactic acid release from polymer degradation can be observed in animal studies. During this time, the antiproliferative drug elutes from the scaffold and, in the case of P-BRS, the PLA-based polymer coating completely degrades. The difference in tissue response between T-BRS and P-BRS can be seen in a direct comparison of Fantom and Absorb. Endothelialization of the Fantom scaffold was significantly better than Absorb at 3 months after implant in a rabbit artery model (Figure 4)[3]. Additionally, increased irritation exists for Absorb compared to Fantom as evidenced by the calcium present at the interface between the tissue and scaffold struts in a porcine artery at 6 months (Figure 4)[3].

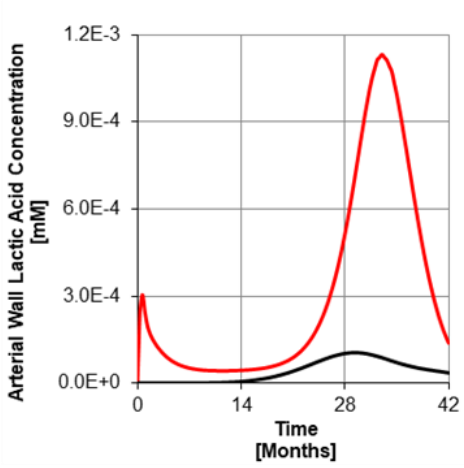


Figure 3: Computational model of lactic acid concentration in the arterial wall during BRS degradation. Absorb (red) and Fantom (black).

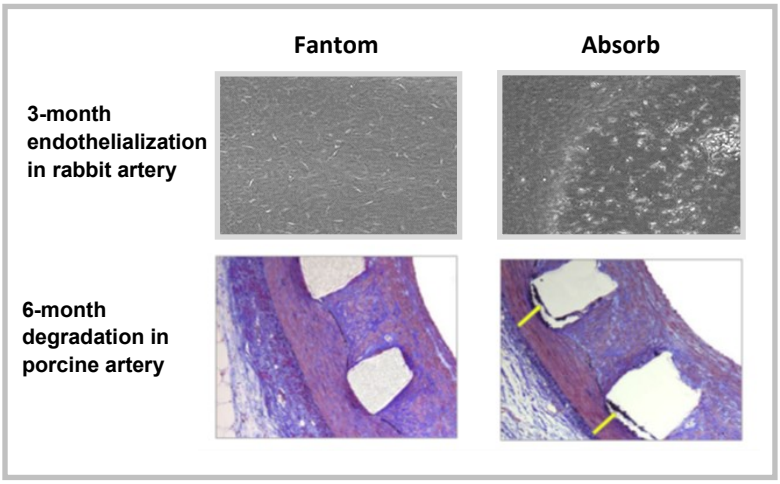


Figure 4: Top: 6-month degradation in porcine artery of Fantom (left) and Absorb (right). Bottom: 3-month endothelialization in rabbit artery of Fantom (left) and Absorb (right).

CONCLUSION

T-BRS is differentiated from P-BRS and M-BRS based on improvements achieved through the development of the novel Tyrocore polymer: strut thickness ≤ 125 µm, full scaffold radiopacity without metal markers, an integrated coating, and ease-of-use features. These attributes contribute to improved ease-of-use during the implant procedure and better vessel healing. Complete scaffold healing into the vessel wall ensures that the scaffold is secure during the degradation and resorption process. The long-term goal is complete resorption and absence of a permanent implant in order to reduce long term adverse events and improve options for retreatment and non-invasive diagnostic imaging.

References

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