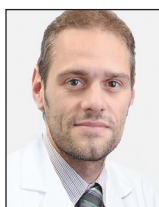


A Novel, Radiopaque, Bioresorbable Tyrosine-Derived Polymer for Cardiovascular Scaffolds

BY GREGOR LEIBUNDGUT, MD



First-generation, drug-eluting, bioresorbable coronary scaffolds utilized polylactic acid (PLA) due to its known biocompatibility, degradation, and resorption profile. However, visualizing these devices under x-ray is a challenge. PLA is radiolucent, which requires the scaffolds to have small

metal markers embedded in each end so that the physician can identify the location of the scaffold under fluoroscopy. Additionally, first-generation PLA bioresorbable scaffolds (P-BRS) were designed with thick struts (150 μm) in order to accommodate the material strength of PLA. The thick struts resulted in reduced flexibility, which can make it more difficult to deliver the scaffold through a guide catheter and navigate the coronary arteries. Additionally, thick struts can slow down the reendothelialization and healing processes that take place after a scaffold is implanted in a coronary artery.¹

Subsequently, a magnesium alloy was developed as an alternative to PLA, but radiopacity and a reduction in strut thickness were not achieved, and rapid resorption resulted in early scaffold failures.² A PLA-based coating appeared to be the solution, but cases of early scaffold failure continued to persist in routine clinical practice.³

The ISAR-STEREO-2 trial demonstrated the advantage of stents with thinner struts when they resulted in lower restenosis rates compared to stents with thicker struts.⁴ With thinner struts associated with better procedural and clinical results, bioresorbable scaffold development focused on reducing strut thickness.

In the search for improvements in strength and biocompatibility, combined with radiopacity, a new bioresorbable polymer was specifically developed with scaffold applica-

tions in mind. This polymer is based on the tyrosine amino acid, which is bound with iodine for radiopacity and combined with short-chain polylactic acid for flexibility and ductility. This article summarizes the polymer design, as well as the mechanical and biological performance of this new polymer material in the coronary vasculature.

POLYMER DESIGN AND PROPERTIES

A thorough search for bioresorbable materials was conducted to identify a polymer family appropriate for scaffold development. A group of materials based on the naturally occurring amino acid tyrosine and its derivatives developed at Rutgers University (New Jersey, USA) was selected. An extensive literature review and series of tests confirmed that these tyrosine-derived polycarbonates had the characteristics that would be important in the coronary scaffold application: appropriate mechanical properties, potential for radiopacity, biocompatible degradation and resorption profile, and compatibility with thermoprocessing for manufacturing.

Development of a specific polymer for a coronary bioresorbable scaffold commenced with the design goals of radiopacity, strength, ductility, benign degradation with low lactic acid release, and storage stability. Multiple formulations were evaluated. The final polymer selected for coronary scaffolds is a copolymer of short-chain polylactic acid and tyrosine analogs, which are iodinated for visibility under standard fluoroscopy. This polymer is manufactured by REVA Medical (San Diego, California, USA) under the trade name Tyrocore™ and is used to make REVA's Fantom® bioresorbable scaffold.

Tyrocore is composed of analogs of the amino acid tyrosine (desaminotyrosine) and biocompatible hydroxy esters.

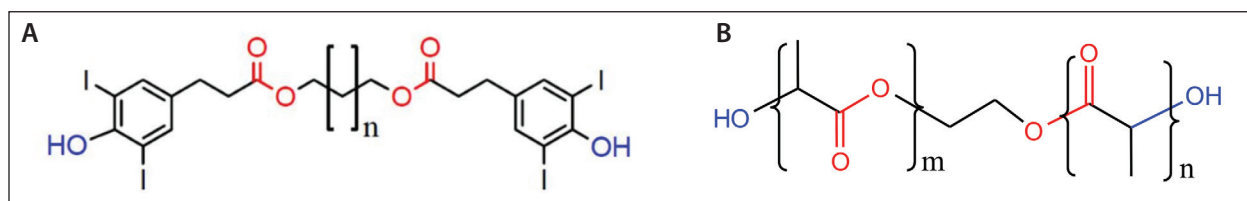


Figure 1. Molecular structure of Tyrocore components: iodinated diphenol (A) and polylactic acid diol (B).

It consists of an iodinated diphenol and a low-molecular-weight oligomer of polylactic acid diol (Figure 1), in an 8:1 ratio, respectively. The properties of Tyrocore and poly-L-lactic acid (PLLA), as previously published,⁵ are shown in Table 1. 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 unique composition and high molecular weight. Tyrocore's radiopacity results from the iodine, which is covalently bonded to the tyrosine analog to create the iodinated diphenol.

SCAFFOLD CHARACTERISTICS AND PERFORMANCE

Manufacturing

The Fantom device is a Tyrocore bioresorbable scaffold (T-BRS). The process begins when the iodinated diphenol and polylactic acid diol monomers are combined in a polymerization reaction. The resulting Tyrocore polymer is then formed into a tube. Once the tubes are formed to the desired diameter, they are laser cut to achieve the final scaffold design (Figure 2). The laser-cut scaffolds are coated with a mixture of Tyrocore and sirolimus, resulting in a drug dose of 1.97 $\mu\text{g}/\text{mm}^2$, which is equivalent to a 115 μg dose on a 3.0 x 18 mm scaffold; > 60% of the drug is eluted within the first 30 days. The coated scaffold is crimped onto a rapid-exchange balloon catheter with a semicompliant balloon. The nominal pressure for all sizes of the Fantom device is 7 atm with a balloon-rated burst pressure of 18 atm.

Fantom is coated with the same Tyrocore polymer as the scaffold; therefore, there is no discernible coating layer. The

TABLE 1. PROPERTIES OF TYROCORE AND PLLA		
	Tyrocore	PLLA
Ultimate tensile strength (MPa)	100–110	50–70
Elongation at break (ductility)	150%–200%	2%–10%
X-ray visibility	Yes	No

result is an integrated coating with the same mechanical properties, degradation, and resorption profile as the underlying scaffold. This differs substantially from first-generation PLA and magnesium alloy scaffolds, which are coated with a distinct drug-containing polymer that is not the same as the underlying scaffold material.

Radiopacity

Fantom gets its radiopacity from the iodinated diphenol in Tyrocore. Due to their high mass, iodine atoms scatter x-rays and impart radiopacity, allowing Fantom to be visualized using standard angiographic techniques (Figure 3). The visibility allows for accurate scaffold placement and expansion, which reduces the risk of geographic miss and malapposition. The amount of iodine in a Fantom scaffold is < 1% of the iodine found in 1 mL of contrast media.

Thin Struts and Radial Strength

Tyrocore's high tensile strength enables Fantom to have thin struts (125 μm) while improving strength and reducing recoil compared to first-generation bioresorbable scaffolds with strut thickness $\geq 150 \mu\text{m}$ (Table 2).⁶ Thin struts



Figure 2. Laser-cutting of Fantom from a Tyrocore tube.

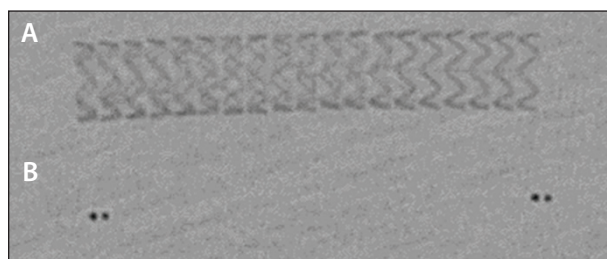


Figure 3. Radiopacity of the Fantom bioresorbable scaffold (A) compared to the Absorb bioresorbable scaffold (B).

TABLE 2. PERFORMANCE CHARACTERISTICS OF THE FANTOM BIORESORBABLE SCAFFOLD COMPARED TO THE ABSORB BIORESORBABLE SCAFFOLD AND THE MAGMARIS BIORESORBABLE SCAFFOLD

	Fantom	Absorb (Abbott Vascular)	Magmaris (Biotronik)
Strut thickness (µm)	125	157	166
Radial strength (N/mm)	0.22	0.14	0.17
Recoil	2.0%	2.3%	7.7%

are one of the most important technical improvements in bioresorbable scaffolds owing to their effect on improving outcomes and procedural performance. High radial strength and low recoil are important to ensure complete apposition of the scaffold during implantation, as well as to provide structural support to the vessel during healing.

Delivery and Deployment

Tyrocore's composition and high molecular weight allow it to maintain ductility while sustaining high radial strength. These attributes provide critical deliverability features for Fantom, including a smaller crossing profile and a larger expansion range (Table 3).⁷⁻⁹ 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 diameter make it easier to achieve full scaffold expansion and apposition (Figure 4).⁹

BIOCOMPATIBILITY, DEGRADATION, AND RESORPTION

Degradation and Resorption

Tyrocore degrades through a bulk erosion process. Once in the body, water enters the scaffold and breaks the molecular bonds in the polymer. This hydrolysis reaction occurs evenly throughout the entire structure of the scaffold, which differs from the surface-based corrosion reaction associated with degradation of magnesium alloy-based scaffolds. Once the polymer is degraded into individual monomers, the resorption process begins. The final degradants of Tyrocore are the iodinated tyrosine analog, carbon dioxide, and water. Radiolabeled studies have shown that the iodinated tyrosine analog is safely excreted from the body.

Tyrocore degradation takes approximately 1 year for the polymer to lose 80% of its molecular weight. Figure 5 shows the radial strength of the scaffold during degradation as measured *in vitro*. During the first month following implantation, polymer hydration results in an increase in radial

TABLE 3. DELIVERABILITY FEATURES OF THE FANTOM BIORESORBABLE SCAFFOLD COMPARED TO THE ABSORB BIORESORBABLE SCAFFOLD AND THE MAGMARIS BIORESORBABLE SCAFFOLD (3.0 MM DIAMETER)

	Fantom	Absorb	Magmaris
Crossing profile (mm)	1.35	1.44	1.50
Expansion over nominal pressure (mm)	0.75	0.50	0.60

strength. Structural support is sustained at this level during the critical 3-month vessel healing period. By 12 months, the scaffold is no longer providing structural support to the vessel, although the material is still present and visible using fluoroscopy or intravascular imaging.

Complete resorption of the Tyrocore polymer takes approximately 4 years. During this time, mass loss occurs as the polymer degradants are cleared from the vessel and body, resulting in reduced radiopacity of the scaffold over time.

Biocompatibility

Computer modeling, animal studies, and clinical 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 PLA degradation for both P-BRS and T-BRS, a computational model was developed that is capable of predicting lactic acid accumulation in local arterial tissue from 0 to 42 months following implantation in the coronary arteries (Figure 6). The P-BRS is represented by the Absorb bioresorbable vascular scaffold system (Abbott Vascular) based on a previously published analysis,¹⁰ which was modified to account for its two-step degradation of the coating followed by the scaffold.

The model predicts two peaks of lactic acid tissue con-

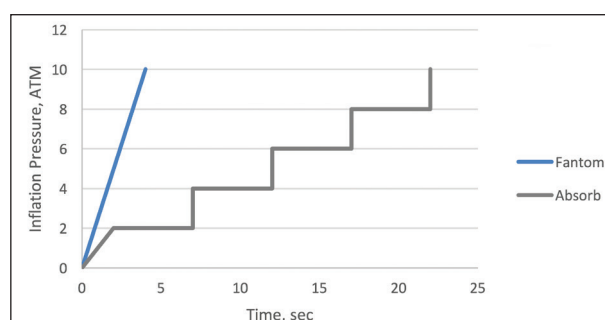


Figure 4. Deployment procedure of the Fantom bioresorbable scaffold compared to the Absorb bioresorbable scaffold.

TYROCORE AND THE FANTOM BIORESORBABLE SCAFFOLD

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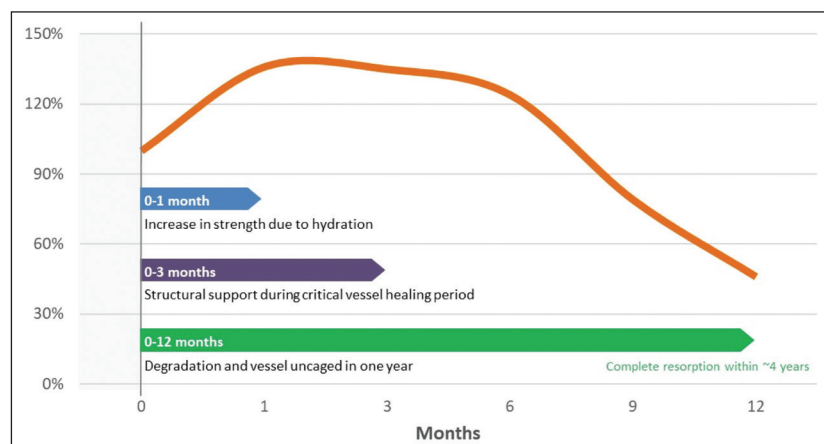


Figure 5. Radial strength of the Fantom bioresorbable scaffold during degradation.

centration for Absorb. The first, between 0 and 6 months, is associated with degradation of the PLA-based drug and polymer coating. The second, larger peak falls between 18 and 42 months and is associated with PLA scaffold degradation. For Fantom, there is no coating-related early peak because the Tyrocore-based drug and polymer coating integrates into the Tyrocore scaffold without creating a separate layer. A very low and broad peak of lactic acid tissue concentration around 28 months is associated with the Tyrocore scaffold resorption. 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 PLLA

(> 100,000 Da) in Absorb. The short-chain segment polylactic acid diol in Tyrocore can break down quicker and over a sufficiently longer time to better match the 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 the Fantom and Absorb devices. Endothelialization of the Fantom scaffold was significantly better than Absorb at 3 months after implantation in a rabbit artery model (Figure 7). Additionally, increased irritation exists for Absorb compared to Fantom as evidenced by the presence of calcium at the interface between the tissue and scaffold struts in a porcine artery at 6 months (Figure 7).

The effect of the low, late-stage lactic acid release from Fantom can be seen in imaging follow-up from the FANTOM II clinical trial. Of the 240 patients enrolled, 36 patients returned for angiographic follow-up at 24 months. From these 36 patients, serial (baseline, 6-month, and 24-month) optical coherence tomography (OCT) imaging was available for analysis in 25 patients. The stability and biocompatibility of the scaffold during resorption can be seen in the OCT images (Figure 8).¹¹ The OCT

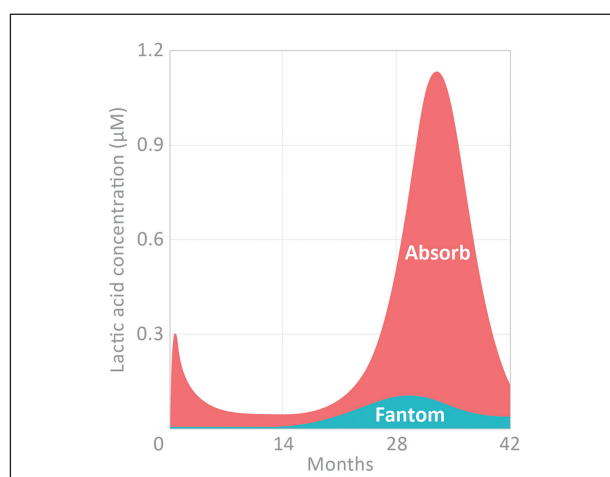


Figure 6. Lactic acid concentration in the arterial wall during degradation and resorption of the Fantom bioresorbable scaffold compared to the Absorb bioresorbable scaffold based on a computational model.

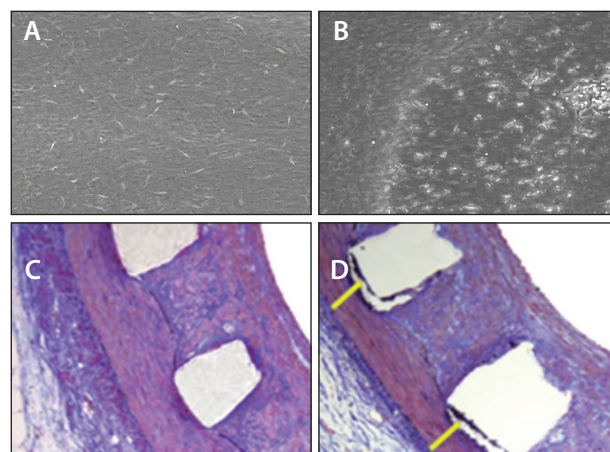


Figure 7. Biocompatibility analysis of the Fantom bioresorbable scaffold compared to the Absorb bioresorbable scaffold. Three-month endothelialization in a rabbit artery using the Fantom (A) and Absorb (B) devices. Six-month degradation in a porcine artery using the Fantom (C) and Absorb (D) devices.

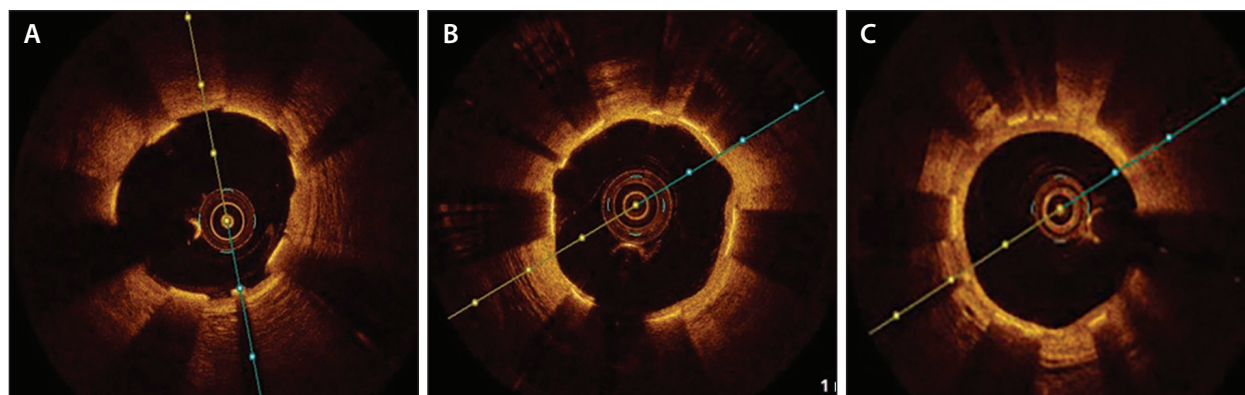


Figure 8. OCT healing analysis of the Fantom bioresorbable scaffold. Matched images from the FANTOM II study of Fantom at baseline (A), at 6 months (B), and at 24 months (C).

TABLE 4. RESULTS FROM THE FANTOM II OCT HEALING ANALYSIS SHOWING MEAN LUMEN AREA AND MEAN SCAFFOLD AREA AT BASELINE, AT 6 MONTHS, AND AT 24 MONTHS (N = 25)

	Baseline	6 Months	24 Months
Mean lumen area (mm ²)	7.1	6.0	5.9
Mean scaffold area (mm ²)	7.3	7.4	7.5

analysis demonstrated that the mean scaffold area was maintained through 24 months and that the mean vessel lumen area was sustained from 6 to 24 months (Table 4).¹¹ Additionally, the OCT analysis showed that 100% of Fantom struts were covered with tissue at 24 months (Figure 9).¹¹

CONCLUSION

The properties and biocompatibility of this radiopaque, tyrosine-derived polymer compare favorably to PLA polymers for use in the coronary scaffold application. To achieve these properties, a new polymer family of tyrosine-derived polymers was identified, and the unique Tyrocore

polymer was developed. This enables a bioresorbable scaffold with thin struts, high radial strength, and radiopacity. Additionally, the Tyrocore-based Fantom bioresorbable scaffold has demonstrated biocompatibility in preclinical and clinical studies. These attributes contribute to improved ease-of-use during the implantation procedure and enhanced 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 restore natural vessel function. ■

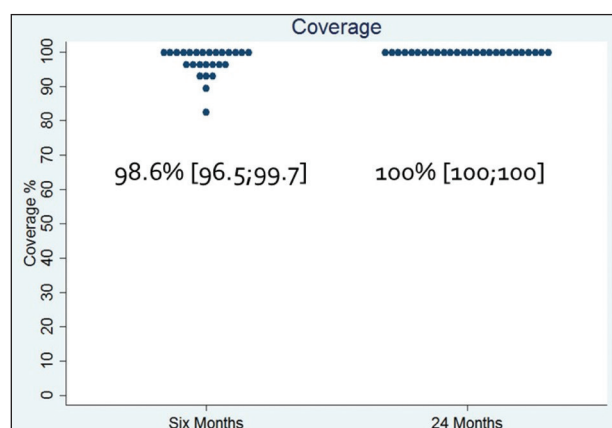


Figure 9. Results from the FANTOM II OCT healing analysis showing strut coverage at 6 months and 24 months (n = 25).

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