

Biotronik Orsiro: Engineering Drives Performance

An exploration of the design elements that together achieved the clinical performance and success of the BIOTRONIK Orsiro biodegradable polymer drug-eluting stent.

BY PETER P. MONTELEONE, MD

System updates and technologic advances have consistently and dramatically driven forward the field of percutaneous coronary intervention (PCI). The rapid progression from angioplasty-alone therapies through multiple generations of scaffold-based technologies has led to dramatic improvement in the clinical outcomes associated with PCI.¹

INCREMENTAL EVALUATION VERSUS PERFORMANCE ASSESSMENT

Rigorous experimental testing of each engineering achievement has provided for the safe and effective development and adoption of contemporary PCI technologies. As PCI evolved, each novel device component and characteristic was assessed directly against its precursor. Stenting revolutionized outcomes when compared to angioplasty alone.² Novel alloys such as cobalt-chromium replaced stainless steel. Drug elution completely changed the clinical experience of patients after PCI.³ Other technologies “failed” to win the day when studied. Recently, the early enthusiasm behind bioabsorbable scaffolds lessened when direct comparison of the technology to a traditional scaffold underperformed in early analyses.⁴ Nonetheless, discrete technologies were sequentially developed and sequentially tested in a field that advanced by individual steps that together allowed for remarkable cumulative leaps. This was representative of the traditional “scientific method” as we compared one specific difference between experimental groups to decide whether to integrate that difference into our systems of care.

It is into this ecosystem of rigorous study of incremental change that the BIOTRONIK Orsiro stent emerged and rapidly became one of the best-studied coronary scaffolds in the world. Impressively, this was not accomplished via the traditional focused study of incremental engineer-

ing updates. The BIOTRONIK clinical trials did not ask if each novel component of the Orsiro scaffold “in isolation” improved outcomes. Rather, the device was developed in total and then studied in head-to-head competition against contemporary field leaders. The device succeeded in total PCI in BIOFLOW-V.⁵ It was demonstrated to be particularly successful in high-risk subgroups, including patients with long lesions and multivessel disease. Trials demonstrated a particularly robust subgroup improvement in ST-segment elevation myocardial infarction (the highest risk of cohorts). A resultant Bayesian analysis was thus developed that demonstrated Orsiro’s performance in these patients.⁶ In a field previously defined by incremental experimental assessment, this strategy was both novel and brave. Orsiro was not studied in tests of incremental value gained through single engineering variables. Orsiro was placed into, and succeeded in, pure head-to-head “performance” comparisons. As a result, the total body of Orsiro clinical trials does not provide the opportunity to reflect directly on the distinct engineering achievements underlying the device’s demonstrated performance. We therefore present descriptions of the “engineering underlying the performance” of the BIOTRONIK Orsiro stent.

SIROLIMUS

The impact of drug elution on PCI realized such a remarkable effect on the clinical outcomes of patients with coronary artery disease (CAD) that when a novel drug-eluting stent (DES) is introduced into the market the first question asked is often, “Which drug is eluted?”³ Because the field-leading devices prior to Orsiro used everolimus or zotarolimus, many may initially wonder if sirolimus drove the performance benefit of Orsiro in its trial evaluation. But the application of sirolimus to a scaffold in the treatment of CAD is certainly not new. Long ago, sirolimus

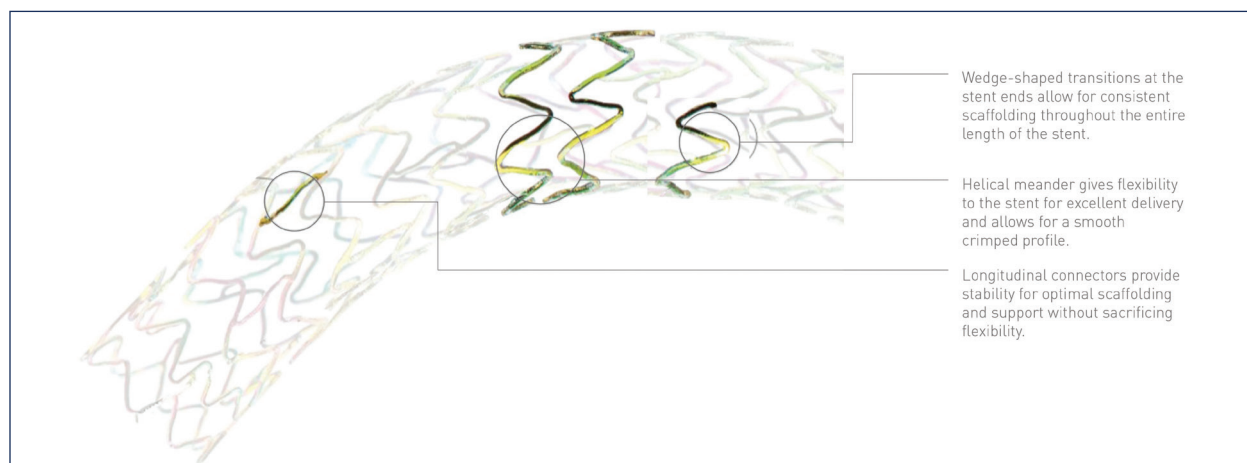


Figure 1. Engineering of the Orsiro scaffold. Image provided courtesy of BIOTRONIK, Inc. ©2020 BIOTRONIK, Inc. All rights reserved.

was demonstrated in vitro to inhibit the proliferation of T and B lymphocytes, mononuclear cells, and mast cells.⁷ It prohibited vascular smooth muscle cell proliferation, platelet-derived growth factor–stimulated cell migration, and endothelial cell growth. In animal models, sirolimus DESs compared with bare-metal stents (BMSs) resulted in less inflammation, less peri-stent inflammatory cell infiltration, and reduced expression of monocyte-released inflammatory markers.^{7,8}

In human clinical trials, sirolimus-eluting stents versus BMSs demonstrated improved rates of major adverse cardiovascular events (MACE), decreased clinically driven repeat target vessel revascularization, and improved mean late luminal loss in the stented segment and stent edges.⁸ In these studies, sirolimus elution resulted in improved frequency and severity of in-stent stenosis, volume obstruction, and late lumen loss.⁷ But there is nothing revolutionary about sirolimus in isolation, and it is unlikely that sirolimus alone affected the clinical improvements achieved by Orsiro. Previous generation stents utilized sirolimus technology. In 2016, the SORT-OUT IV study compared the historic sirolimus-eluting Cypher stent (Cordis, a Cardinal Health company) to the Xience everolimus-eluting stent (Abbott) and demonstrated superior clinical outcomes at 5 years with the everolimus device.⁹ The demonstrated clinical benefit seen in SORT-OUT IV likely represented the results of the many differences between these two scaffolds rather than simply a benefit of everolimus versus sirolimus alone. A preclinical study comparing different DESs with identical stent scaffolds but different drugs and drug loads demonstrated no significant difference among distinct drug groups.¹⁰ It is remarkable to comprehend that 2 years after SORT-OUT IV demonstrated the clinical benefits of everolimus-eluting Xience over the sirolimus-eluting Cypher, BIOFLOW-V demonstrated the clinical

benefits of sirolimus-eluting Orsiro over the everolimus-eluting Xience.⁵ There is very clearly much more driving a scaffold's performance than the drug it elutes.

ULTRATHIN STRUTS

The actual platform for the Orsiro stent is the PRO-Kinetic Energy BMS. This “ultrathin-strut” scaffold nominally measures 60 μm for stents ≤ 3 mm in diameter and 80 μm for stent diameters > 3 mm. This makes Orsiro the thinnest-strut stent available on the market (by comparison, Xience is 81 μm , Synergy [Boston Scientific Corporation] is 74 μm , and the Resolute Onyx [Medtronic] is 81 μm). Cobalt-chromium L605 is utilized in the design.¹¹ This allows for such thin struts to be achieved without compromising radial strength, radiopacity, or resistance to fatigue. The Orsiro design includes midstrut connectors and a double-helix design, including helical meanders that provide for improved flexibility and bending. Longitudinal connectors stabilize the double-helix structure and allow the scaffold to resist longitudinal compression and avoid foreshortening. The stent ends also include wedge-shaped transitions that provide for scaffolding and flexibility throughout the entire length of the stent (Figure 1).¹¹ Concern is sometimes raised that such thin-strut technology may be more sensitive to stent shortening or elongation on deployment. However, bench testing demonstrates that these risks are associated primarily with overall stent design rather than strut thickness alone.^{12,13} The design and engineering of the Orsiro scaffold resists these issues while achieving the benefits of ultrathin-strut technology.

Thinner struts correlate with improved scaffold performance. Preclinical studies demonstrate a 1.5-fold increase in thrombogenicity of thick-strut stents (162 μm) versus identical thinner-strut stents (81 μm).^{11,14} In vivo, flow stagnation and neointimal fibrin deposition drive a 60% increase in thrombus formation and neointimal fibrin deposition at

3 days in thick- versus thin-strut stent systems.¹⁴ Stent endothelialization occurs faster with thin struts likely simply due to a smaller area requiring coverage.^{11,15} Thick-strut scaffolds induce greater inflammation, vessel injury, internal elastic lamina disruption, in-stent neointimal growth, and hyperplasia.^{11,16,17} Clinically, ISAR-STEREO-1 and 2 demonstrated that angiographic and clinical restenosis could be reduced with use of thin-strut stents.^{18,19} Ultrathin struts provide for decreased inflammation that corresponds to decreased restenotic and thrombotic disease. The Orsiro scaffold design and engineering allowed for achievement of these benefits of ultrathin-strut technology without sacrificing strength and scaffold integrity. If forced to predict a single element that best drove the performance benefit achieved by Orsiro in clinical evaluation, the achievement of a resilient ultrathin-strut scaffold design is a likely contender.

BIOLute ACTIVE COATING

Calling a scaffold a DES oversimplifies a device's engineering by limiting the technologic description to that of "drug" and "stent." The engineering of a DES is much more complicated than these two components. The outermost cover of the Orsiro stent is the BIOLute active coating, a thin drug carrier matrix that contains a highly biocompatible and biodegradable polymer. This polymer (and not the actual scaffold) is what elutes the antiproliferative agent sirolimus.¹¹ The BIOLute coating contains poly-L-lactic acid (PLLA). This polymer is solid and transparent, and it contains both a crystalline portion and amorphous random polymer chains. Controlled drug elution of sirolimus from the BIOLute coating occurs after the stent is deployed. Via the Krebs cycle, PLLA is metabolized into carbon dioxide and water.¹¹ It is this attribute that categorizes the Orsiro device as a biodegradable polymer DES. What remains after coating degradation is the inert stent backbone within the arterial wall.

The use of a PLLA sirolimus-eluting matrix has demonstrated in histopathology studies decreased inflammation, improved re-endothelialization, reduced neointimal growth, and adequate sirolimus drug tissue concentration in comparison with permanent polymer-based sirolimus-eluting platforms.²⁰ Direct comparative clinical studies remain to be performed, but these histopathologic data suggest that this technology assists the strong clinical performance of the Orsiro stent. The dynamic nature of the biodegradable polymer also drives conjecture about long-term benefits currently under evaluation. The eventual absence of polymer may suggest long-term clinical benefits from decreased inflammation. This analysis is ongoing.

proBIO™ PASSIVE COATING

The cobalt-chromium of the Orsiro stent is directly covered and sealed by the proBIO coating. This layer

is up to 200 nm thin and seals the scaffold surface and eliminates interaction between the metal and the surrounding tissue of the treated artery. The coating is composed of an amorphous hydrogen-rich silicon carbide that is deposited onto the stent through a plasma-enhanced chemical vapor deposition technique that bonds the inert coating to the metal surface.¹¹ The coating lowers the rate of corrosion of the stent and may decrease tissue inflammation, including from allergic reactions to the metal. The semiconductive silicon carbide coating has demonstrated up to a 96% reduction of allergenic metal ion release.^{11,21,22} The proBIO coating does not biodegrade and is thus considered "passive." However, the reduction of metal ion release and separation of the arterial wall from the scaffold's metal aim to further decrease inflammation characteristics and add to the cumulative clinical performance of Orsiro.

DELIVERING THE ENGINEERING

To demonstrate a clinical improvement at treating a lesion, a device has to be successfully delivered to the target area. In addition to the engineering elements that drive device performance that were mentioned previously, very tangible changes were integrated to provide for stent deliverability. The monorail catheter was redesigned to include a longer length than competitor devices. This redesign results in dramatic improvement in pushability by comparison to all leading competitors, including a 72% improvement in the transmission of force from the catheter hub to its tip with Orsiro compared to the Resolute Onyx platform.²³ Although designed for achieving the decreased inflammatory characteristics described previously, the ultrathin-strut technology also couples with the delivery catheter characteristics to dramatically impact the "crossing" of the Orsiro stent. Orsiro outperforms all leading competitors in crossing characteristics in benchtop models, requiring up to 79% less application of mean force (as measured by mean resistance) to achieve complete passage of the stent delivery system compared to Synergy.²³ The ultrathin-strut technology also results in a field-leading lower crossing profile with up to a 7% lower profile compared to Resolute Onyx (Figure 2).²³

A DIFFERENT PATH

BIOTRONIK Orsiro has taken a very different path to the American market from contemporary stent technologies. Even geographically, Orsiro market share grew first within the European and Asian markets, achieving European CE Mark approval in 2011 and being used to treat more than a million patients worldwide prior to FDA approval in February 2019. As described, the clini-

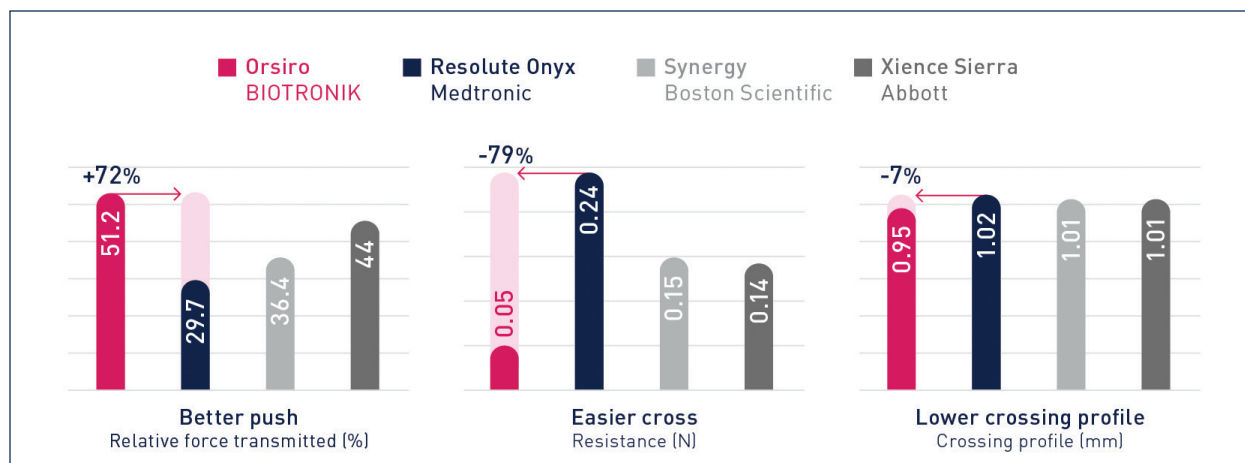


Figure 2. Push, crossing, and profile characteristics of contemporary coronary stent platforms. Image provided courtesy of BIOTRONIK, Inc. ©2020 BIOTRONIK, Inc. All rights reserved.

cal trial evaluation of Orsiro has been as distinct as its geographic path. Coronary stenting technology prior to Orsiro had improved incrementally through serial demonstration of advancing scaffold characteristics. But in the world immediately preceding the BIOFLOW analyses, DES had improved to the point where negative clinical outcomes were so rare that decisions between contemporary DES were driven primarily by price rather than variant clinical performance.

With Orsiro came a renewed focus for the field on performance analysis. The multiple novel and upgraded characteristics described previously were developed together, and a scientific risk was taken. Rather than testing one scaffold characteristic at a time, the total performance of the features was assessed. Failure would have meant not just failure of a characteristic but failure of the device on the whole. But success was achieved and changed the market forever, demonstrating that the assembled device characteristics had ushered in a new phase in “performance” evaluation of our scaffold therapies for the treatment of CAD. BIOFLOW-VII is a postapproval study now enrolling to further assess the performance of Orsiro in the real-world American market, and we look forward to continued evaluation of performance of this exciting device. ■

- McKeage K, Murdoch D, Goa KL. The sirolimus-eluting stent: a review of its use in the treatment of coronary artery disease. *Am J Cardiovasc Drugs*. 2003;3:211-230.
- Curfman GD. Sirolimus-eluting coronary stents. *N Engl J Med*. 2002;346:1770-1771.
- Jensen LO, Thaysen P, Christiansen EH, et al. Safety and efficacy of everolimus- versus sirolimus-eluting stents: 5-year results from SORT OUT IV. *J Am Coll Cardiol*. 2016;67:751-762.
- Steigerwald K, Ballke S, Quee SC, et al. Vascular healing in drug-eluting stents: differential drug-associated response of limus-eluting stents in a preclinical model of stent implantation. *EuroIntervention*. 2012;8:752-759.
- Iglesias JF, Roffi M, Degrauwe S, et al. Orsiro cobalt-chromium sirolimus-eluting stent: present and future perspectives. *Expert Rev Med Devices*. 2017;14:773-788.
- Prabhu S, Schikorr T, Mahmoud T, et al. Engineering assessment of the longitudinal compression behaviour of contemporary coronary stents. *EuroIntervention*. 2012;8:275-281.
- Barragan P, Garitey V, Mouneimne K, Rieu R. Longitudinal compression behaviour of coronary stents: a bench-top comparative study. *EuroIntervention*. 2014;9:1454-1462.
- Kolandaivelu K, Swaminathan R, Gibson WJ, et al. Stent thrombogenicity early in high-risk interventional settings is driven by stent design and deployment and protected by polymer-drug coatings. *Circulation*. 2011;123:1400-1409.
- Soucy NV, Feygin JM, Tunstall R, et al. Strut tissue coverage and endothelial cell coverage: a comparison between bare metal stent platforms and platinum chromium stents with and without everolimus-eluting coating. *EuroIntervention*. 2010;6:630-637.
- Farb A, Weber DK, Kolodgie FD, et al. Morphological predictors of restenosis after coronary stenting in humans. *Circulation*. 2002;105:2974-2980.
- Timmins LH, Miller MW, Clubb FJ Jr, Moore JE Jr. Increased artery wall stress post-stenting leads to greater intimal thickening. *Lab Invest*. 2011;91:955-967.
- Kastrati A, Mehilli J, Dirschinger J, et al. [Intracoronary stenting and angiographic results strut thickness effect on restenosis outcome (ISAR-STREDE) Trial]. *Vestn Rentgenol Radiol*. 2012;52:60.
- Pache J, Kastrati A, Mehilli J, et al. Intracoronary stenting and angiographic results: strut thickness effect on restenosis outcome (ISAR-STREDE-2) trial. *J Am Coll Cardiol*. 2003;41:1283-1288.
- Koppa T, Joner M, Bayer G, et al. Histopathological comparison of biodegradable polymer and permanent polymer based sirolimus eluting stents in a porcine model of coronary stent implantation. *Thromb Haemostasis*. 2012;107:1161-1171.
- Dahm JB, Willems T, Wolpers HG, et al. Clinical investigation into the observation that silicon carbide coating on cobalt chromium stents leads to early differentiating functional endothelial layer, increased safety and DES-like recurrent stenosis rates: results of the PRO-Heal Registry (PRO-Kinetic enhancing rapid in-stent endothelialisation). *EuroIntervention*. 2009;4:502-508.
- Kalnins U, Englis A, Dinne I, et al. Clinical outcomes of silicon carbide coated stents in patients with coronary artery disease. *Med Sci Monit*. 2002;8:P16-20.
- BIOTRONIK data on file. IIB (P) 24/2018.

Peter P. Monteleone, MD

Director, Ascension Seton Heart Institute
The University of Texas at Austin Dell School of Medicine
Seton Heart Institute
Austin, Texas
(512) 324-3440; peter.monteleone@austin.utexas.edu
Disclosure: Receives consulting fees from BIOTRONIK and Medtronic and institutional research grant support from Medtronic and Abbott.

- Stefanini GG, Holmes DR Jr. Drug-eluting coronary-artery stents. *N Engl J Med*. 2013;368:254-265.
- Fischman DL, Leon MB, Baim DS, et al. A randomized comparison of coronary-stent placement and balloon angioplasty in the treatment of coronary artery disease. Stent Restenosis Study Investigators. *N Engl J Med*. 1994;331:496-501.
- Iqbal J, Gunn J, Semmings PW. Coronary stents: historical development, current status and future directions. *Br Med Bull*. 2013;106:193-211.
- Ali ZA, Gao R, Kimura T, et al. Three-year outcomes with the Absorb bioresorbable scaffold: individual-patient-data meta-analysis from the ABSORB randomized trials. *Circulation*. 2018;137:464-479.
- Kandzari DE, Koolen JJ, Doros G, et al. Ultrathin bioresorbable polymer sirolimus-eluting stents versus thin durable polymer everolimus-eluting stents. *J Am Coll Cardiol*. 2018;72:3287-3297.
- Iglesias JF, Muller O, Heg D, et al. Biodegradable polymer sirolimus-eluting stents versus durable polymer everolimus-eluting stents in patients with ST-segment elevation myocardial infarction (BIOSTEMI): a single-blind, prospective, randomised superiority trial. *Lancet*. 2019;394:1243-1253.