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.

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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 engineering 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?” 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
was demonstrated in vitro to inhibit the proliferation of T and B lymphocytes, mononuclear cells, and mast cells. 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. 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. In these studies, sirolimus elution resulted in improved frequency and severity of in-stent stenosis, volume obstruction, and late lumen loss. 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. 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. 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. 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. 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).

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. 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). 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. Stent endo-
thelialization occurs faster with thin struts likely simply due
to a smaller area requiring coverage. Thick-strut scaffolds
induce greater inflammation, vessel injury, internal elastic
lamina disruption, in-stent neointimal growth, and hyper-
plasia. Clinically, ISAR-STEREO-1 and 2 demonstrated
that angiographic and clinical restenosis could be reduced
with use of thin-strut stents. Ultrathin struts provide
degraded 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 resil-
ient ultrathin-strut scaffold design is a likely contender.

**BIOlute ACTIVE COATING**

Calling a scaffold a DES oversimplifies a device’s engineer-
ing by limiting the technological description to that of “drug”
and “stent.” The engineering of a DES is much more com-
plicated 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 bio-
degradable polymer. This polymer (and not the actual scaf-
dfold) is what elutes the antiproliferative agent sirolimus. 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 coat-
ing occurs after the stent is deployed. Via the Krebs cycle,
PLLA is metabolized into carbon dioxide and water. It is
this attribute that categorizes the Orsiro device as a biode-
gradable polymer DES. What remains after coating degrada-
tion is the inert stent backbone within the arterial wall.

The use of a PLLA sirolimus-eluting matrix has dem-
onstrated in histopathology studies decreased inflamma-
tion, improved re-endothelialization, reduced neointimal
growth, and adequate sirolimus drug tissue concentration
in comparison with permanent polymer-based sirolimus-
eluting platforms. Direct comparative clinical studies
remain to be performed, but these histopathologic data
suggest that this technology assists the strong clinical per-
formance 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 sur-
rounding 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. 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 car-
bide coating has demonstrated up to a 96% reduction of
alлерgic metal ion release. The proBIO coating does not biodegrade and is thus considered “passive.”
However, the reduction of metal ion release and separa-
tion 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 previ-
ously, 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 competi-
tors, including a 72% improvement in the transmission
of force from the catheter hub to its tip with Orsiro
compared to the Resolute Onyx platform. Although
designed for achieving the decreased inflammatory
characteristics described previously, the ultrathin-strut
technology also couples with the delivery catheter char-
acteristics 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
sten delivery system compared to Synergy. The ultra-
thin-strut technology also results in a field-leading lower
crossing profile with up to a 7% lower profile compared
to Resolute Onyx (Figure 2).

**A DIFFERENT PATH**

BIOTRONIK Orsiro has taken a very different path to
the American market from contemporary stent tech-
nologies. 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-
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.

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