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Orsiro - The First Hybrid Drug-eluting Stent, Opening Up a New Class of Drug-eluting Stents for Superior Patient Outcomes

Michael Tittelbach, Tobias Diener

Abstract

The Orsiro device is a hybrid drug-eluting stent that represents a new strategy in the treatment of coronary artery stenosis. Orsiro features a hybrid coating of passive and active components: the PROBIO passive coating seals the metal surface of the stent and prevents interaction with the surrounding blood and tissue, while the BIOlute active coating contains a highly biocompatible polymer that delivers a -limus drug over 12–14 weeks and degrades gently over one to two years, thereby avoiding increased inflammation. The stent backbone is the PRO-Kinetic Energy platform, which has a double-helix stent design and thin struts, bringing flexibility and ease of deliverability.

Keywords

Orsiro, hybrid, drug-eluting stent, coronary artery stenosis, PROBIO passive coating, BIOlute active coating, PRO-Kinetic Energy platform

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Since the introduction of drug-eluting stents (DES), physicians have tried to find a delicate balance between achieving a highly effective result without compromising the safety of the patient. Various concepts have been introduced into the marketplace in the attempt to identify the optimal combination of characteristics; however, until now very little attention has been paid to combining a temporary drug therapy with passivation of the metallic stent that is left in the coronary artery. The Orsiro DES (Biotronik AG, Bülach, Switzerland) is the first hybrid DES, offering a unique hybrid coating consisting of passive and active components. The PROBIO passive coating encapsulates the stent and eliminates interaction between the metal stent and the surrounding tissue.

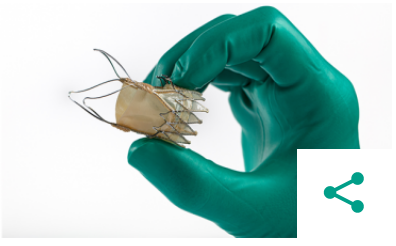
The BIOlute active component is a bioabsorbable polymer matrix combined with a -limus drug that is released in a controlled manner, leaving only the PROBIO-coated stent in the long term. The hybrid solution with the PROBIO and BIOlute coatings is delivered using the underlying PRO-Kinetic Energy™ stent system with its thin strut design. This combination of effortless deliverability with a hybrid structure opens up a new generation of devices for improved patient outcomes.

PROBIO Passive Coating

The PROBIO passive coating[1] seals the stent surface and greatly reduces interaction between the metal stent and the surrounding tissue and blood by acting as a diffusion barrier (see *Figure 1*). This thin-layer, amorphous silicon carbide coating is deposited onto the surface of the stent through a plasma-enhanced chemical vapour deposition technique.[2] This process covalently bonds the inert coating to the metallic surface.

Surface passivation aims to improve the biocompatibility of the material by reducing thrombogenicity and encouraging re-endothelialisation. The PROBIO coating achieves this passivation through its semi-conductive properties by reducing the interactions of protein/cell constituents with the stent surface. Lower diffusion of ions also leads to a lower rate of corrosion and a lower risk of tissue inflammation response as a result of allergic reactions.*In vitro* studies have shown up to a 96 % reduction of allergenic metal ion release when the stent surface is coated with silicon carbide.[1,2] PROBIO is well known as it has been used for more than 15 years on all Biotronik-manufactured stents and has been implanted in more than one million patients.

In the short term the passive PROBIO coating is covered by the active absorbable polymer coating, but nevertheless PROBIO serves a purpose since ion release can take place through the degrading polymer. After the active



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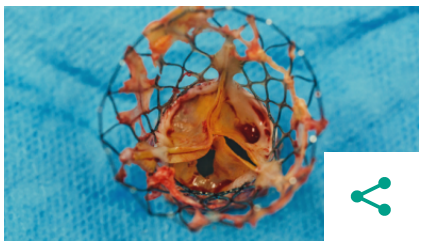

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polymer coating has been absorbed, PROBIO keeps the stent surface sealed indefinitely and thereby minimises the risk of late adverse events.

BIOlute Active Coating

The BIOlute polymer base is made of poly-L-lactide (PLLA), a well-characterised bioabsorbable polymer that has been approved for medical use in a multitude of applications since the 1960s. The selection of this polymer was made after thorough screening of various polymer materials, both permanent and biodegradable. There are four essential requirements for a carrier polymer:[3]

- biocompatibility;
- controlled release of the drug;
- mechanical stability able to withstand the plastic deformation during stent expansion; and
- ability to protect the drug from degradation during processes such as sterilisation and during shelf life.

Essentially, the desired polymer is one that can provide safe transport of the drug through the vasculature without drug loss and ensure controlled drug release. Release can be controlled by such factors as polymer identity, formulation (drug:polymer ratio) and coating processes. The formulation and coating developed with the desired release properties have to show mechanical properties capable of withstanding implantation. In the development of BIOlute, from those polymers meeting the initial screening parameters, the selection was narrowed to focus on the criteria of biocompatibility as measured by local tissue responses in pig coronaries; this led to the selection of Poly- L-Lactidde (PLLA)[4] as the polymer matrix of BIOlute. Another benefit of PLLA is that its slow degradation allows for full control of release kinetics since the polymer degradation is limited during the drug-elution period, which is not the case with polymers that degrade more quickly. The controlled release kinetics obtained with the homogeneous PLLA polymer matrix also means that Orsiro does not need to have any additional base or top coat, which is often required for other DES coatings. Another advantage of the prolonged gentle degradation seen with PLLA is that it minimises the inflammatory response (see *Figure 2*).

After selection of the appropriate polymer, the next critical step in terms of elution kinetics was ensuring a uniform coating of the polymer and drug.[5] The homogenous coating of the stent was realised using a unique coating technique.

The mechanical stability is crucial for carrier systems of DES and BIOLute, due to the high strength of PLLA, is providing very good properties. The polymer thickness on the abluminal side of the Osiro device is 7.4 µm, one of the lowest among available DES (see *Figure 3*). On Orsiro, a circumferential coating rather than an abluminal coating was chosen to ensure that the polymer adheres to the stent platform even in the areas that face high stress during stent expansion. This, together with the strong mechanical properties of the polymer matrix itself, means that the risk of tearing off the coating as a result of stress during implantation and balloon dilatation is avoided. The highly biocompatible polymer gently degrades over one to two years, avoiding increased inflammation and ultimately metabolises into CO_2 and H_2O via the Krebs cycle. Studies in minipigs have shown no residual PLLA and benign histology at 24 and 36 months. The biocompatible and gentle degradation is believed to lead to better patient outcomes.

The sirolimus drug load is 1.4 µg/mm^2 and the elution is optimised for clinical benefit to 12–14 weeks. (see *Figure 4*). In vivo studies have demonstrated that 50 % of the drug is released within 30 days and 80 % within three months (see *Figure 5*). The elution curve is adapted to the therapeutic window of the drug and is in line with that of other -limusbased stents. While studies have noted that -limus drugs as well as paclitaxel are effective in clinical use, -limus drugs have proved to be clinically superior with no significant difference between the different - limus derivatives.[6,7]

Expert Panel Discussion

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PRO-Kinetic Energy Stent Platform

The deliverability and mechanical properties of the underlying stent backbone are known to be key success factor for any DES. To achieve this we use the highly deliverable PRO-Kinetic Energy bare metal stent as a platform for Orsiro. The PRO-Kinetic Energy cobalt–chromium stent platform has a double-helix stent design that allows for increased flexibility without compromising scaffolding or fatigue resistance. The helical meanders give flexibility to the stent for excellent delivery and allow for a smooth crimped surface without fish scaling. The longitudinal connectors provide stability to the double-helical structure for optimal scaffolding and support without sacrificing flexibility.

The wedge-shaped transitions at the stent ends allow for scaffolding and flexibility throughout the entire length of the stent. All of these features of the double-helix stent design translate into increased trackability, crossability and ability to conform to the vessel wall. The cobalt– chromium stent material allows for thin struts while maintaining optimal radial strength and radiopacity. Orsiro is noted to have the thinnest struts compared with other DES, specifically down to 60 µm, varying with the available stent diameters of 2.25–4.0 mm and lengths of 9– 30 mm. This ensures minimal wall injury, leading to better patient outcomes. Adding the polymer to the thin struts of the PRO-Kinetic Energy stent platform, the total thickness of the stent struts of stents with a nominal diameter of up to 3.0 mm is 71 µm – significantly lower than the thickness of competitors, including Xience (Abbott Vascular, Abbott Park, IL, US) at 95 µm and Endeavor Resolute (Medtronic, Minneapolis, MN, US) at 99 µm. The advanced stent crimping technology provides a low crossing profile (0.99 mm) and the optimised delivery system allows for higher-pressure inflations (mean burst pressure 24–30 atm depending on diameter; rated burst pressure 16 atm).

Pre-clinical Results

The safety of Orsiro was demonstrated in animal studies. A safety study of both the Orsiro and Cypher (Cordis Corporation, Bridgewater, NJ, US) stents looking specifically at histology and quantitative coronary angiography at four, 12 and 26 weeks in pig coronaries demonstrated that Orsiro with PLLA + sirolimus had a better safety profile than Cypher; the same was seen with an overdose model. Furthermore, an overlap safety study looking at four-week quantitative coronary angiography and histology showed that there was no difference in safety profile and drug effect in the overlapping region of Orsiro. A pharmacokinetic study up to three months showed comparable blood levels and coronary tissue concentrations to a -limus-based DES together with low organ tissue concentrations. A long-term polymer degradation study evaluating histology and histomorphometry up to three years was performed, demonstrating excellent biocompatibility and a lack of late increase in inflammation (data on file, BIOTRONIK AG, under publication).

Clinical Programme

Orsiro is supported by a comprehensive clinical programme consisting of a series of trials sharing the family name BIOFLOW. BIOFLOW-I is the first-in-man trial with 30 patients conducted in 2009 under the leadership of Professor Martial Hamon (University Hospital of Caen, France). The excellent results[8] of the BIOFLOW-I study (ClinicalTrials.gov Identifier: NCT01214148) are on par with other first-in-man trials of contemporary DES and was used for the CE-mark application. The results also served as input to the design of BIOFLOW-II (ClinicalTrials.gov Identifier: NCT01356888), a pan-European randomised controlled trial with 440 patients comparing the Orsiro with the Xience Prime stent that started enrolment in July 2011. BIOFLOW-III is a global, open-label registry that will enrol 1,000+ patients and will also look at pre-specified subgroups including diabetes, small vessels, acute myocardial infarction and chronic total occlusion. Enrolment is scheduled to start in 2011.

Conclusion

In conclusion, Orsiro brings a new strategy to the treatment of coronary artery disease with a hybrid solution of active and passive components. The PROBIO passive coating provides a seal on the metal surface of the stent and the BIOlute active coating provides controlled drug release, with both components preventing an increased inflammatory response. The stent backbone is the PRO-Kinetic Energy platform, which provides flexibility with a double-helix stent design and thin struts. The clinical performance, which has been assessed in initial *in vitro* and *in vivo* studies, will be further demonstrated in forthcoming publications.

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