Advantages of Novel BioMime™ Sirolimus Eluting Coronary Stent System. Moving towards biomimicry

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Since the first reported use of percutaneous transluminal coronary angioplasty (PTCA), advancements in interventional cardiology arena have been fast paced. Within the last ten years, these developments have been exponential. Developers & clinicians are fast adapting from the learning curve awarded by the time course of DES evolution. In that light BioMime™ Sirolimus Eluting Coronary Stent comes as a fresh thought in taking stents towards a biomimicry concept. The stent is built on an ultra-low strut thickness (65 μm) cobalt chromium stent platform, using an intelligent hybrid of close and open cells allowing for morphology mediated expansion, employs a well known anti-proliferative – Sirolimus that elutes from a biodegradable co-polymer formulation in 30days and ensures high coating integrity and low coating thickness of 2 μm. The resultant stent demonstrates almost 100% endothelialization at 30days in preclinical model and zero percent MACE >18 months in the primary efficacy and safety clinical study.

Key words: Drug-eluting stents - Thrombosis - Restenosis.

Advancements in PCI – An overview

Over the last ten years the interventional cardiology field has evolved tremendously. From the ground breaking work of Forssmann in 1960s and to Andreas Gruentzig’s successful procedure with a percutaneous transluminal coronary angioplasty (PTCA) balloon catheter in 1977, the application of devices used to open up clogged coronary arteries have expanded manifold. As soon as PTCA balloon angioplasty became popular, problems surrounding the use of POBA technique emerged in form of dissections and abrupt vessel closures.

These were soon tackled using metal scaffoldling designed by Palmaz and Schatzt and others and soon the concerns surrounding POBA technique were virtually eliminated by stenting.

However while stenting emerged as a sound technique to hold dissected vessel flaps and the thus expanded vessel, it caused injury and thus gave rise to a ubiquitous problem known as restenosis, “the exuberance of neo intimal proliferation” which again in-turn threatened to narrow or close down the vessel in the mid-term period.

While “restenosis” remained the Achilles’ heel of Interventional Cardiology for a while, stent thrombosis also emerged as an
important safety parameter that threatened the success of the procedure.\textsuperscript{5}

On a parallel front this development saw the rise of antiplatelet therapy in form of aspirin, ticlopidine and then clopidogrel which significantly reduced the thrombosis issue.\textsuperscript{6-10}

While two novel forms of treatment for curbing of the "restenosis" came into existence - brachytherapy was the first which was quickly abandoned due to its technological problems; second the science of releasing an antiproliferative agent directly at the site of stent implantation which would work in-situ and have a control over "restenosis". This came to be known as drug eluting stent (DES) therapy.

Soon the DES therapy caught on to the fast developmental pace and today more than 5 million PTCAs and stenting procedures are performed worldwide in which more than 70% stents consumed are DES.

DES efficacies brought high degree of treatment satisfaction and world over interventional cardiologists observed with contentment that perhaps an era of complete control over neointimal proliferation has arrived.\textsuperscript{11-15} Event free survival comparable or even superior to Coronary Artery Bypass Graft surgery \textsuperscript{11} (CABG) can be considered.

**DES in the eye of the storm**

The well-charted time course of evolution of novel technologies (Figure 1) flows as follows - Unbridled enthusiasm follows innovations, which find high acceptance since they promise new ways to encounter existing problems. After a period of time with expanding usage, new problems like late and very late stent thrombosis issue surfaced. Consequently the usage came down. This shaken confidence prompted developers to bring about thoughtful adaptations. The problems of the first generation stents were identified and technology was improved giving rise to its ultimate applicability.

**First generation DES to newer DES**

Prompted by excellent first in-man results with first generation DES,\textsuperscript{11-15} larger randomized clinical trials were conducted which showed a small increment in late loss, restenosis and MACE yet,\textsuperscript{15-19} this was still significantly lower than its bare metal counterpart truly cementing the DES therapy as gold standard.

This enthused the operators world over to expand DES usage to the so called "off-label" indications. Interestingly the real world usage of DES failed to replicate the results of RCTs and the results showed a late stent thrombosis of 0.53% per year with a continued increase to 3% over four years.\textsuperscript{20, 21} In patients with complex multivessel disease (ARTS II), the rate of combined definite, probable and possible stent thrombosis was as high as 9.4% at five years accounting for 32% of MACE events.\textsuperscript{22}

While these late ST episodes continued to bother the operators, one of initial suspects was non-compliance of thienopyrine therapy.\textsuperscript{23} The research thus turned around to investigate anti-platelet therapy compliance related benefits. However, analysis of the timing of late stent thrombosis events in the BASKET-LATE study showed that events continued to occur over 6-18 months after stopping clopidogrel, an observation that would not be expected if the withdrawal of clopidogrel were the single trigger of thrombosis.\textsuperscript{24}

Interestingly, the two-year follow-up of diabetic patients included in the RESEARCH
registry showed that very late DES thrombosis may still occur in diabetic patients with antiplatelet treatment and the analysis of multiple registries has shown a lack of noticeable increase in the rate of thrombosis and thrombosis related events immediately after stopping clopidogrel.25, 26

These findings suggest that “dual antiplatelet” treatment is not the only factor associated with late stent thrombosis. Multiple factors involved, related to the procedure; the patient; lesion morphology and even the entire device – stent, drug and polymer are thought to be responsible in isolation or conjunction for late ST.

From the above observations the criteria of DES safety have emerged as: reducing vessel injury, ensuring complete stent apposition, use of thrombo-resistant polymers, ensuring optimal anti-platelet treatment for reduction of acute events and encouraging re-endothelialization, resolving local inflammation and finally facilitating generation of functional endothelium for reduction of late events.

Considering the above safety parameters, criteria for sound DES construction thus are:

1. a thin strut stent platform design:
   - that minimizes injury;
   - ensures complete apposition;
   - endothelializes well due to conformability against the vessel wall;

2. a drug that ensures antiproliferative/anti-inflammatory effect:
   - is not cytotoxic;
   - has a broad therapeutic window;
   - has been tested in similar clinical situations;

3. a polymeric coating:
   - is non-thrombogenic;
   - has elastic properties to allow for thin coating and to withstand mechanical trauma;
   - is biodegradable.

The Penrose triangle of DES development

Having identified the classical triads of an “ideal DES” construction; the challenge of creating one is like creation of the Penrose’s impossible triangle.

The Penrose triangle (Figure 2) is a typical combination of properties which cannot be realized by any 3-dimensional object in ordinary Euclidean space and is a demonstration in the current challenges during design and development of an ideal DES. All the classical parameters of a DES construction are polarized and offer little homogeneity when put together.

Any compromise in the stent architecture and the drug formulation would lead to incomplete healing, likewise inappropriate polymer usage would cause inflammation and the formulation itself can lend sub-optimal drug release kinetics.

Moving towards biomimicry and development of BioMime™ Sirolimus Eluting Coronary Stent System

Derived from the clinical and the technological need gaps in the existing coronary stents and DES, the BioMime™ Sirolimus Eluting Coronary Stent System has been developed on simple yet fundamentally sound principles. The resultant DES has the ability to be arterially biocompatible leading to its predictably safe and efficacious profile.

BioMime™ Sirolimus Eluting Stent (SES) – Primary device description

The BioMime™ SES is made of the following three components:
— stent — NexGen™ Cobalt Chromium Coronary Stent System;
— drug — Sirolimus (Rapamycin) 1.25 μg/mm²;
— Polymer — BioPoly™ the biodegradable co-polymer combination of Poly-L-Lactic Acid (PLLA) and Poly-L-Glycolic Acid (PLGA).

**The right stent architecture**

The BioMime™ SES (Figure 3) employs the CE marked NexGen™ Cobalt Chromium Coronary Stent System — a novel concept conceived to minimize intra-arterial injury.

The design stretches the boundaries of structural engineering with ultra-low strut thickness (65 μm) stent maintained across all dimensions without any loss in radial strength. On bench testing, NexGen™ demonstrates a high radial strength of 1.1 bar with a mean recoil of <3% and a foreshortening of 0.29%.²⁷

The novel stent design and a modified balloon expanding characteristic results in a morphology mediated expansion ²⁷ (Figure 4) due to a hybrid cell design structure (open cell configurations in the centre and closed at the edges). This unique method of expansion eliminates the classical dogboning seen in conventional designs and also ensures minimal edge injury.²⁷

Further the struts have unique strut width variability (Figure 5) which ensures flexibility while retaining high radial strength.

Evidently due to these features the stent demonstrates superior acute gain (Figure 6) and complete wall apposition.

Thus it appears to endothelialize quickly (Figure 7) in porcine coronary artery model at 28 days.²⁷

The stent delivery system also ensures minimal arterial injury. The semi-compliant rapid exchange balloon catheter shoulders are carefully constructed short-taper and abrupt with a marginal over-hang (Figure 8). This allows for high trackability and deliverability at the same time minimizing any chance of balloon related edge injury.²⁷

The resultant stent system has a predict-
ably low injury profile. Simons et al. have proven through their experimental work that topography of the stent as measured by its strut thickness has a direct impact on the endothelialization and Kastrati et al. have proven through ISAR STERE0 and ISAR STERE0 that low strut thickness stents irrespective of the stent designs are associated with a significant reduction of angiographic and clinical restenosis after coronary stenting.

In an interesting preclinical evaluation work undertaken in porcine coronary artery model, low strut thickness (65 μm) NexGen™ stents were compared versus high strut thickness (91 μm) Driver stent (Medtronic, USA). Piglets were sacrificed at 28 and 90 days to appraise the biocompatibility. The primary endpoint was mid in-stent neo-intimal thickness. Histomorphometric analysis at 28 days showed significant differences in mid-stent neo-intimal thickness 0.18+0.08 mm for NexGen™ segments versus 0.30+0.41 mm for Driver segments, P=0.03 favoring thinner strut cobalt chromium stents (Figure 9).

This beneficial result was maintained at 90 days, 0.09+0.04 mm for NexGen™ segments versus 0.25+0.03 mm for Driver segments.

This study corroborates with earlier stated results obtained in humans by Kastrati et al. which allows for predictability in lowering restenosis and TVR incidence versus high strut thickness.

The right antiproliferative drug – Sirolimus

BioMime™ stent releases the tried and tested sirolimus. In this context sirolimus is the right candidate for DES application since it targets the “final common pathway” to prevent vascular smooth muscle cell proliferation.

The efficacy of sirolimus eluting stents in animals has long been established and
a large volume of published data in human coronaries is available.

In a preclinical model involving porcine coronary arteries, piglets were randomized to receive either BioMime\textsuperscript{TM} or NexGen\textsuperscript{TM} with Polymer (control stent) or Cypher (Cordis, USA) and arteries were explanted at 28 and 90 days.\textsuperscript{27}

At both 28 and 90 days, BioMime\textsuperscript{TM} stented segments appear to be as safe as corresponding control stents or Cypher while demonstrating a superior trend in reducing neo-intimal thickness as compared to either the control stent or Cypher.\textsuperscript{27}

The control stent which was NexGen\textsuperscript{TM} coated with biodegradable polymer was found to be equivalent in terms of biocompatibility to NexGen\textsuperscript{TM} bare stent itself suggestive of non-inflammatory nature of the polymer.\textsuperscript{27}

In terms of its drug release kinetics, BioMime\textsuperscript{TM} demonstrates a release kinetics that is similar to that of Cypher \textsuperscript{27} (Figure 10).

The Right polymer - BioPoly\textsuperscript{TM}

BioPoly\textsuperscript{TM} is a biodegradable polymeric base in BioMime\textsuperscript{TM} comprising of a proprietary co-polymer formulation mix consisting of Poly-L-Lactide (PLLA) and Poly-L-co-Glycolide (PLGA). The principle mode of degradation BioPoly\textsuperscript{TM} is \textit{via} hydrolysis. Degradation first proceeds by diffusion of water into the material; followed by random hydrolysis; fragmentation of the material and finally a more extensive hydrolysis accompanied by phagocytosis, diffusion and metabolism. Once hydrolysed the products are either metabolized or excreted. The lactic acid thus generated becomes incorporated into the tricarboxylic acid cycle (Kreb's cycle) and is excreted as carbon dioxide and water.

BioPoly\textsuperscript{TM} has been found to have a short degradation time and has been tested non-inflammatory in the pre-clinical model. The composition offers a uniform stent coating and does not crack, web, lump or stick to the balloon surface.\textsuperscript{27}

On BioMime\textsuperscript{TM} the drug plus BioPoly\textsuperscript{TM} coating thickness is maintained at $2 \mu m$ which is lowest amongst the available DES on the market (Figure 11).

Achieving biomimicry behavior
- Endothelialization

BioMime\textsuperscript{TM} in preclinical model

In preclinical model, BioMime\textsuperscript{TM} demonstrates almost 100\% endothelialization at the end of one month as is noticed from the SEM picture below. A uniform endothelial coating over and between the struts on edges (close cell configuration) and in mid-segment (open cell configuration) are observed \textsuperscript{11} (Figure 12).
BioMime™ clinical update

Based on the encouraging preclinical results and predictable design configuration, BioMime™ was studied in a phase IV prospective, single arm, primary efficacy and safety study involving 30-patients – meriT-1. All patients represented with a single, discrete de-novo lesion and were stented with BioMime™ ranging from diameters 2.5, 3.0 and 3.5 mm and lengths from 13 to 24 mm. Primary end point was MACE defined as death, myocardial infarction (MI) or any ischemia driven target lesion revascularization (TLR).

Zero percent MACE was noted beyond 18 months’ clinical follow-up. No case of death – cardiac or non-cardiac, no MI (Q-wave or non-Q-wave), no ischemia driven TLR was reported.31

Eight-month angiographic follow-up and subsequent QCA analysis (Quantitative Coronary Angiography) reveals a highly satisfactory late lumen loss of 0.15 mm demonstrating high efficacy.

RAVEL study reported a MACE of 5.8% in Cypher arm at one-year follow-up 11 and so far with zero percent MACE/ST in BioMime™ stented patients the results are encouraging.

In a larger multicentric, non-randomized all comers trial known as meriT-2 trial, BioMime™ is being studied in 250 patients present in a real world scenario and the only exclusion criteria are saphenous vein grafts (SVGs), acute myocardial infarction (AMIs), left main disease and a left ventricular ejection fraction (LVEF) of <30%.

Primary safety and efficacy end points are defined as MACE which is a composite of death, MI (Q-wave and non-Q-wave), emergent CABG and clinically driven TLR. In-stent and in-segment late loss will be calculated via QCA. Secondary end-points will be MACE at 1 year and device related serious adverse events until 12 months, angiographic stent thrombosis (acute, subacute and late). Angiographic and device success and procedural success will be additional parameters in the secondary point.

Currently 4.7% MACE and three cases of ST are observed up to one year of follow-up. QCA of first 132 segments reveals an in-stent late loss of 0.15 mm.32

Insights and conclusions

The first generations DES were laced with late stent thrombosis and were created on bulky stent platforms with questionable deliverability and polymer biocompatibility. BioMime™ Sirolimus Eluting stent comes as a fresh approach in designing of DES, keeping in mind that eventually the DES should endothelialize in a few months.

Hence all the ingredients that allow for optimal endothelialization have been incorporated in BioMime™ development:
— the stent (CE marked) cobalt chromium, ultralow strut thickness (65 μm) with variable strut width and a novel geometry involving an intelligent hybrid of open and close cells which allows for morphology mediated expansion of the stent while retaining high radial strength and conformability;
— the drug employed is sirolimus which is an ideal choice considering that it acts on the common final pathway of cell division cycle without exceptional risk of necrosis induction;
— the BioPoly™ is a co-polymer formulation of well known biodegradable polymers PLLA and PLGA which are non-inflammatory and allow for a 2-μm stable coating.
The resultant SES has drug elution kinetics of 30 days and a polymer degradation which is short and well documented.

BioMime™ has been found to be safe and efficacious in preclinical models and in the primary safety and efficacy study. Notable at 18 months is the zero percent MACE. Data from the large multicentric trial involving 250 real world patients has further established its credibility in routine clinical practice.

Hence based on the available, preclinical and initial clinical reports, it can be predicted that this third generation DES has adapted itself from the learning curve of the past DES and will rightfully set path for the biomimicry concept in DES design for future.
Riassunto

Vantaggi del nuovo sistema di stent coronarico medicato con sirolimus BioMime™. Un passo avanti verso la biomimetica

Sin dal primo utilizzo riportato di angioplastia coronarica percutanea (percutaneous transluminal coronary angioplasty, PTCA), i progressi nell'area della cardiologia intervenzionale si sono succeduti a ritmo elevato. Nell'ultimo decennio, tali sviluppi sono stati esponenziali. Sviluppatori e medici si stanno adattando in fretta alla curva di apprendimento conferita dal decurso temporale dell'evo-

luzione degli stent medici. Da questo punto di vista, lo stent coronarico medicato con sirolimus BioMime™ rappresenta un passo in avanti degli stenti verso un concetto di biomimetica. Lo stent è costruito su una piattaforma in lega di crono-co-

baltico, di spessore su due sottile (65 μm), utilizzando un ibrido intelligente di celle aperte e chiuse che permettono l'espansione mediata dalla morfologia, e utilizza un ben noto agente antiproliferativo, il sirolimus, il quale elusce da una formulazione di copolimeri biodegradabile in 30 giorni, garantendo un'elevata integrità del rivestimento e un sottile spessore di rivestimento pari a 2 μm. Lo stent risulta offrendo un endotelizzazione di quasi il 100% a 30 giorni in un modello preclinico e 0% MACES>18 mesi nello studio clinico su sicurezza ed efficacia primaria.

Parecchi chiave: Stent medicati - Trombosi - Restenosi.

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