Drug-eluting stents (DES) were primarily conceived to reduce in-stent neointimal formation and therefore minimize the occurrence of restenosis, the major drawback of percutaneous coronary interventions with bare-metal stents (BMS).

The development of DES has been pioneered through a combination of the increased understanding of the biology of restenosis, the selection of drugs that target 1 or more pathways in the restenotic process, controlled-release drug delivery strategies, and the use of the stent as a delivery platform.

Although first-generation DES Cypher (sirolimus-eluting stent; Cordis Corporation, Johnson & Johnson, Warren, NJ) and Taxus (paclitaxel-eluting stent; Boston Scientific Corporation, Natick, Mass) have effectively achieved their main goal, reducing restenosis across virtually all lesion and patient subsets, their safety has been limited by suboptimal polymer biocompatibility, delayed stent endothelialization leading to late and very late thrombosis, and local drug toxicity.1–9

Both Cypher and Taxus use durable thick polymers to carry and control the release of their antiproliferative agents. The permanent presence of these polymers has been correlated to inflammatory responses and local toxicity in preclinical analysis.10–13 Furthermore, durable polymers used in first-generation DES have been associated with mechanical complications (eg, polymer delamination and “webbed” polymer surface leading to stent expansion issues)14 and nonuniform coating resulting in erratic drug distribution. As a consequence, in recent years, the focus of clinical research has been on the development of novel drug carrier systems including absorbable (or biodegradable) polymers and nonpolymeric stent surfaces. Additional improvements include the development of more modern platforms (eg, better deliverability, radiopacity, flexibility, and radial strength) as well as the use of novel antiproliferative agents or reduced doses of current approved antiproliferative drugs.

This review focuses on describing next-generation drug-eluting stent systems based on the use of novel coatings and carrier systems developed to enhance DES safety. Initially, we will address the issue of how to plan and conduct first-in-man studies to evaluate efficacy of novel devices for coronary intervention. After this brief introduction, we will discuss the next-generation DES systems and for didactic purpose the text will be divided into 2 parts, focusing on programs with biodegradable polymers and finally moving to nonpolymeric DES.

First-in-Man Studies

A lot has changed since our institution conducted the first-ever successful in-human DES evaluation, the Cypher-Sirolimus-eluting stent first-in-man (FIM) trial. At that time, 10 years ago, with 15 patients receiving the slow-release formulation and 15 patients receiving the moderate-release version, we were able to show the impressive power of the novel technology in reducing neointimal proliferation by means of surrogate end points: in-stent late luminal loss and intravascular ultrasound (IVUS) percent stent obstruction.

FIM studies are aimed at demonstrating the feasibility and acute safety of novel devices. These studies are frequently carried out with few patients and many times include a control group treated with a FDA approved DES. Because these studies are underpowered to show differences in clinical outcomes, they use surrogate end points to demonstrate their noninferiority. In terms of efficacy, quantitative coronary angiography in-stent late loss and IVUS percent stent obstruction remain the most widespread tools to accomplish this task.

Regarding safety, new technologies and procedures have been incorporated into recent FIM studies. In particular, 2 deserve more emphasis: optical coherence tomography (OCT) and coronary vessel reactive tests, with acetylcholine, pacemaker, physical stress, and so forth.

With its superior (at least in vivo) high resolution, OCT has been able to evaluate the amount of DES strut coverage in the follow-up procedure, a potential marker of stent vulnerability. Furthermore, this technology allows investigating in more details the occurrence of strut incomplete apposition, intraluminal thrombus formation, presence of different types of tissues covering the struts, and so forth.

Vessel reactive tests allow assessing whether the neointimal tissue covering the DES struts as well as the adjacent segment are properly responding to pharmacological agents to assess the physiological endothelium responsiveness. Whether these novel surrogates will correlate with late clinical events is also being investigated. Also, they will...
Table 1. Main DES Systems With Bioabsorbable Polymers

<table>
<thead>
<tr>
<th>DES System</th>
<th>Platform</th>
<th>Antiproliferative Agent</th>
<th>Polymer</th>
</tr>
</thead>
<tbody>
<tr>
<td>BioMatrix (Biosensors Inc)</td>
<td>S-Stent (316 L) stainless steel stent with a strut thickness of 0.0054 inches (137 ( \mu m ))</td>
<td>Biolimus A9 (~15.6 ( \mu g/mm ) of stent length)</td>
<td>Polylactic acid (PLA) applied to the abluminal surface</td>
</tr>
<tr>
<td>Cardiomind 0.014 inches Sparrow (Cardiomind, Inc)</td>
<td>CardioMind self-expandable Nitinol stent platform with strut thickness of 0.0024 inches (61 ( \mu m ))</td>
<td>Sirolimus (~5.2 ( \mu g/mm ) of stent length)</td>
<td>Polyactic acid (PLA)/Polyactic-co-glycolic acid (PLGA) block copolymer matrix</td>
</tr>
<tr>
<td>ELIXIR-DES program (Elixir Medical Corp)</td>
<td>Cobalt-chromium (Co-Cr) stent with strut thickness of 0.0032 inches (81 ( \mu m ))</td>
<td>Novolimus (~5 ( \mu g/mm ) of stent length)</td>
<td>Polyester-based or polylactide-based</td>
</tr>
<tr>
<td>JACTAX (Boston Scientific Corp)</td>
<td>Liberté (316 L) stainless steel stent with a strut thickness of 0.0038 inches (96.5 ( \mu m ))</td>
<td>Paclitaxel (~0.6 ( \mu g/mm ) of stent length)</td>
<td>D-lactic polylactic acid (DLPLA) applied to the abluminal surface on premounted stent (no postcoating crimping distortion)</td>
</tr>
<tr>
<td>NEVO (Cordis Corporation, Johnson &amp; Johnson)</td>
<td>Cobalt chromium (Co-Cr) stent with strut thickness of 0.0039 inches (99 ( \mu m ))</td>
<td>Sirolimus (~7.4 ( \mu g/mm ) of stent length)</td>
<td>Polyactic-co-glycolic acid (PLGA) exclusively housed in reservoirs</td>
</tr>
<tr>
<td>Sirolimus+ EPC capture (OrbusNeich Medical Inc)</td>
<td>OrbusNeich R stent (316L) stainless steel stent with a strut thickness of 0.0040 inches (101 ( \mu m ))</td>
<td>Sirolimus (~5 ( \mu g/mm ) of stent length)</td>
<td>Synbiosys polymer (2 bioabsorbable urethane-linked poly(ether ester) multiblock copolymers composed of glycolide (GA), lactide (LA), ( \varepsilon )-caprolactone (CL), and polyethylene glycol (PEG) pre-polymer blocks)</td>
</tr>
<tr>
<td>Supralimus and Supralimus-Core (Sahajanand Medical Technologies Pvt Ltd)</td>
<td>Millennium Matrix (316L) stainless steel stent with a strut thickness of 0.0032 inches (81 ( \mu m ))</td>
<td>Sirolimus (~4.7 ( \mu g/mm ) of stent length)</td>
<td>Poly L-Lactide, 50/50 Poly DL-Lactide-co-Glycolide and Polyvinyl Pyrrolidone</td>
</tr>
<tr>
<td></td>
<td>Coronium (L605) cobalt-chromium stent with a strut thickness of 0.0023 inches (60 ( \mu m ))</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

never be a replacement for studies with clinical end points, but surely they can avoid larger trials with ineffective novel devices.

**DES Systems With Bioabsorbable (Biodegradable) Polymers**

Since durable, thick polymers of first-generation DES seem to have a central role in perpetuating local vascular inflammatory reaction and potentially inducing the occurrence of late and very late stent thrombosis, the concept of a polymer that carries and controls the drug release during an proper period of time and after that erodes and vanishes from the vascular surface seems to be very attractive. Most of the systems presented in this section utilize poly-l-lactic acid (PLLA) and poly-d,l-lactide (PDLA), which are progressively erode by shortened as ester bonds and ultimately will degrade into lactic acid.

Table 1 contains a brief description of the main components of the DES systems reviewed in this section.

**BioMatrix (Biosensors Inc)**

The BioMatrix (Biosensors Inc, Newport Beach, Calif) stent is a novel DES that incorporates the S-Stent platform, a thin, stainless steel, laser-cut, tubular stent with 16.3% to 18.4% metal surface area. The antiproliferative drug is biolimus A9, a highly lipophilic, semisynthetic sirolimus analogue with an alkoxy-alkyl group replacing hydrogen at position 42-O. At a cellular level, biolimus A9 forms a complex with intracellular FKBP-12, which binds to the mammalian target of rapamycin and reversibly inhibits cell-cycle transition of proliferating smooth muscle cells with a similar potency to sirolimus. On the basis of in vivo studies, the biodegradable polymer fully converted to lactic acid at 6 to 9 months (data on file at Biosensors).

The FIM assessment of the efficacy of BioMatrix was conducted in 3 centers (2 in Germany and 1 in Brazil) comparing 80 patients treated with this device with 40 patients who received its bare-metal equivalent. At 6-month follow-up, late lumen loss was significantly decreased with BioMatrix, both in the stent (0.26±0.43 versus 0.74±0.45 mm, \( P<0.001 \)) and in the segment (0.14±0.45 versus 0.40±0.41 mm, \( P=0.004 \)). In-stent restenosis was 3.9% in the BioMatrix group versus 7.7% in the control group (\( P=0.40 \)). By IVUS evaluation, the use of the BioMatrix stent was associated with a 10-fold reduction in the percent stent obstruction (3.2±2.5% versus 32±18%, \( P<0.001 \)).

More recently, the LEADERS trial compared this novel DES system with Cypher in a larger, randomized clinical trial designed to assess noninferiority of the novel DES versus the first generation sirolimus-eluting stent. A total of 1707 real-world patients were randomly assigned in a 1:1 fashion and the primary end point of the study was a composite of cardiac death, myocardial infarction, or clinically driven target vessel revascularization within 9 months. Biolimus-eluting stents were noninferior to sirolimus-eluting stents for the primary end point at 9 months (9% patients versus 11%; rate ratio; 0.88 [95% confidence interval (CI), 0.64 to 1.19];
P for noninferiority = 0.003). Frequency of cardiac death (1.6% versus 2.5%, P = 0.22), myocardial infarction (5.7% versus 4.6%, P = 0.30), and clinically driven target vessel revascularization (4.4% versus 5.5%, P = 0.29) were similar for both stent types. A prespecified cohort of patients underwent repeated angiography at 9 months showing equivalence regarding in-stent late-luminal loss between the stents (0.13 ± 0.46 mm in the BioMatrix cohort versus 0.19 ± 0.50 mm for Cypher, P = 0.34). Rates of stent thrombosis were similar at all time points (acute, subacute, late, and very late) and according to any ARC definition.

More recently, Prof Klauss presented the 2-year results of this trial (21st Annual Transcatheter Cardiovascular Therapeutics meeting, San Francisco, 2009). Overall, there was no statistically significant difference between Cypher and BioMatrix in regard to major adverse cardiac events (MACE) (13% for BioMatrix versus 15.4% for Cypher, P = 0.18) and combined cardiac death/myocardial infarction (8.3% for BioMatrix versus 9.1% for Cypher, P = 0.59), although the numeric difference in favor of the novel DES has increased when compared with previous 9-month assessment. In the prespecified subset of patients with ST-elevation MI, MACE difference was markedly significant in favor of the novel device (8.1% for BioMatrix versus 19.3% for Cypher, P < 0.01). Notably, there were no cases of very late stent thrombosis in BioMatrix cohort after discontinuation of dual antiplatelet therapy (versus 2 cases in the Cypher group). It is important to note that the number of events, especially stent thrombosis, was relatively low in both cohorts and the study was not primarily designed to address the thrombosis issue.

Cardiomind 0.014-Inch Sparrow (CardioMind, Inc)
The Sparrow Coronary Stent System (CardioMind, Inc, Sunnyvale, Calif) is a 0.014-inch guide wire–based stent delivery platform combining a limus drug in a biodegradable polymer matrix on the Cardiomind nitinol stent platform with a novel release mechanism that uses a principle of electrochemical dissolution for stent release (Figure 1).

The delivery system has a 2- to 3-cm flexible radiopaque guide wire tip at the distal end to enable positioning within the vessel. The distal end of the stent is located at the proximal end of the guide wire tip and a second radiopaque marker indicates the proximal end of the stent. The Cardiomind Stent is deployed through an electronic mechanism within the Sparrow delivery system, which enables the electrolysis of mechanical latches holding down each end of the Cardiomind Stent. Stent release is via an electric actuation mechanism which incorporates a removable, reusable handheld power supply that delivers a maximum of 0.2 mA to dissolve latches holding the mechanical restraints on the stent. The DES version incorporates sirolimus in a biodegradable copolymer matrix.

The FIM study with the noneluted version of the Cardiomind Stent was the CARE I trial that demonstrated the feasibility of the stent releasing system with no concerns regarding safety of the system. Currently ongoing, the CARE II trial is randomizing the DES version of the Cardiomind Stent versus its BMS equivalent.

ELIXIR-DES Program (Elixir Medical Corporation)
Elixir Medical Corporation is currently working with 2 pharmaceutical agents, Novolimus, a metabolite of sirolimus, and Myolimus, a sirolimus analog. Both drugs belong to the family of macrocyclic lactones with immunosuppressive and antiproliferative properties and have a similar mechanism of action to other macrocyclic lactones such as rapamycin. The Elixir Medical Drug-Eluting Coronary Stent Systems (Elixir...
diovascular Therapeutics, 2008, Washington, DC). Among the 72 patients who underwent 9-month invasive follow-up, in-stent late loss was 0.32±0.43, with 4.2% of binary restenosis. By IVUS, the percent stent obstruction was 9.6±10.3. No stent thrombosis was observed through 12 months Among patients submitted to OCT evaluation (n=13), complete coverage was detected in more than 96% of the examined struts.

**Nevo (Cordis, Johnson & Johnson)**

Nevo (Cordis Corporation, Johnson & Johnson, Warren, NJ) is a cobalt-chromium stent dotted with “reservoirs” that can be loaded with 1 or more drugs and polymers to release drug more specifically, potentially in various doses or formulations. In the case of the Nevo, the reservoirs are filled with a biodegradable polymer impregnated with sirolimus. As a potential advantage, the stent reduces tissue-polymer contact by more than 75% and total polymer load by approximately 80%.

Although this novel DES system has been built from the Costar stent, in the current version it uses a different stent structure, a different bioresorbable polymer, and the antiproliferative agent paclitaxel was replaced by sirolimus.

The current platform is an open-cell design, cobalt-chromium very thin strut stent with increased number of rings aimed to improve drug distribution and scaffolding.

The sculpted reservoirs on the Nevo stent are filled with sirolimus in a dose similar to the Cypher stent and the release of the drug is controlled by the biodegradable polymer. In the first 10 to 15 days, the release of sirolimus is somewhat slower than in the Cypher stent; however, similar to Cypher, 100% of the drug is released by the 90th day after the procedure. The polymer degrades in a similar time course so that by the third month there is a complete reversion of Nevo to a bare metal chromium-cobalt stent (Figure 3).

The FIM assessment of the efficacy and safety of this novel device was the RESELUTION I Trial, a multicenter (40 sites in Europe, Brazil, Australia, and New Zealand) randomized (1:1) comparison of Nevo to Taxus Liberté stent. The study was designed to show noninferiority or superiority of Nevo for the primary end point of 6-month in-stent loss. A total of 394 patients with RAVEL-like lesions were enrolled and the preliminary results were recently presented by Dr Spauding (EuroPCR, Barcelona, 2009). At 6 months, late lumen loss (the trial’s primary end point) was markedly and significantly lower in the Nevo-treated patients as compared with the Liberté, both in-stent and in-segment (0.13±0.31 mm versus 0.36±0.46 mm in-stent and 0.06±0.32 mm versus 0.20±0.39 mm in-segment, with \( P<0.001 \) for both comparisons). The difference surpassed the margin for noninferiority (defined as a difference of 0.20 mm or more), meaning that the Nevo emerged as statistically superior to the Liberté for the trial’s primary end point. Angiographic measurements of in-stent binary restenosis (1.1 versus 8.0, \( P=0.002 \)), as well as IVUS neointimal volume (5.82±11.68 mm³ versus 19.45±24.66 mm³, \( P=0.004 \)), were also significantly lower in the Nevo group. Up to 6 months, there was no case of stent thrombosis in the Nevo cohort versus 1.1% in the Taxus Liberté group (all types of thrombosis included, \( P=0.24 \)).

**Figure 2. JACTAX DES system: Microscopic detail of the novel technology for coating DES that uses precisely metered droplets of a biodegradable polymer (DLPLA) and paclitaxel formulation to create a thin (<1 µm) coating solely on the abluminal surface of the coronary stent.**

Medical Corp, Sunnyvale, Calif) are designed to optimize safety and efficacy through the combination of a cobalt chromium stent platform, a low polymer loading with controlled release and a low pharmacological drug dose.

Elixir Medical Corporation has also developed both durable and polylactide-based bioabsorbable polymers, which are being evaluated in FIM studies. The durable polymer is from the methacrylate family of polymers and provides a sustained release of the drugs for 4 to 6 weeks.

Two bioabsorbable polymers allow release of the drug in 2 to 4 weeks and biodereod over a period of 3 to 9 months.

Recently presented, 6-month data on the Myolimus (3 µg/mm) bioabsorbable polymer (3 month degradation) showed 0.37±0.44 mm of in-stent late-luminal loss and 14.2±7.7 mm³ of neointimal hyperplasia (IVUS), with a MACE rate of 6.9% (2/29) [unpublished data]. Clinical results with the bioabsorbable polymer (6- to 9-month deg- radation) will be available soon.

**JACTAX (Boston Scientific Corporation)**

Labcoat has developed a novel technology for coating DES that uses precisely metered droplets of a biodegradable polymer and drug formulation to create an ultrathin coating confined to the abluminal surface of a coronary stent. Once the drug has been delivered, the biodegradable coating resorbs, leaving behind only the BMS. After the acquisition of Labcoat, Boston Scientific has recently developed the JACTAX DES system (Boston Scientific Corp, Natick, Mass) comprising the market approved stainless steel (316 L) Liberté premounted stent (Boston Scientific), the antiproliferative agent, paclitaxel, in a reduced dose coupled with the ultrathin polymer delivery system (Figure 2). Labcoat technology can be applied to any stent and is presently under investigation for both paclitaxel and everolimus drug delivery. Compared with the first-generation Taxus DES in which less than 10% of the total amount of paclitaxel is released in the coronary artery, 100% of the drug in the JACTAX DES system is released within 4 months of implantation.

Preliminary results of the FIM assessment of this novel technology were presented by Dr Grube (Transcatheter Car-
Sirolimus/EPC Capture (OrbusNeich Medical, Inc)
The DES comprises the OrbusNeich R stent (OrbusNeich Medical, Inc, Ft Lauderdale, Fla), with an abluminal coating of a bioabsorbable polymer matrix formulated with sirolimus (60% of the dose used in the Cypher stent with similar release profile) for sustained release, and an anti-CD34 antibody cell capture coating on the luminal surface (Figure 4).

Furthermore, the Genous Bio-engineered Surface Technology serves as a surface modification for anti-CD34 antibody capture of EPCs from circulating blood onto the surface of the stent, which may potentially speed up the reendothelialization process. Circulating EPCs are attracted to the surface through CD34+ transmembrane proteins on the EPC cell surface interacting with the immobilized anti-CD34 antibodies on the Genous-treated surfaces.

The clinical program of the Sirolimus/EPC capture DES is yet to be initiated.

Supralimus and Supralimus-Core (Sahajanand Medical Technologies Pvt Ltd)
Supralimus and Supralimus-Core sirolimus-eluting stent (Sahajanand Medical Technologies Pvt Ltd, India) are new generation DES that combine a thin stainless-steel platform (Supralimus) or cobalt-chromium platform (Supralimus-Core), a potent immunosuppressant agent (Sirolimus), and biodegradable drug-carrier components (Figure 5). The stents are coated in a multiple layer system using biodegradable polymers as a carrier which gives control release of Sirolimus drug up to the predicted time period. After the removal of this protective layer, an early burst phase releases 50% of the drug within 7 days to inhibit inflammatory response and smooth cell migration and proliferation. The remaining 50% of sirolimus is released within 41 days.

The FIM assessment of this technology was the SERIES trial, which enrolled 100 patients (126 Supralimus) stents deployed. At 30-month clinical follow-up, there was a cumulative incidence of MACE of 7% with only 4% of target vessel revascularization. Of note, there was no definite stent thrombosis and 1 case of probable and 1 of possible stent thrombosis after the ARC definition. A subgroup of 59 patients underwent angiographic follow-up at 6 months showing an in-stent late lumen loss of only 0.09±0.28 mm, with no case of binary angiographic restenosis.
Polymer-Free DES Systems

Better than having a biodegradable polymer would be having no polymer. However, polymers in DES systems are intended not only to carry antiproliferative drugs but also to control their release. In this section, we will briefly discuss some alternative to polymers that are being current tested. Most of the time, modifications in the surface of the platform are necessary to carry the antiproliferative drug. It is important to notice that this is an incipient field in interventional cardiology and long-term data as well as larger controlled trials should not be expected soon.

Table 2 contains a brief description of the main components of the DES systems reviewed in this section.

Amazonia Pax (MINVASYS)
The Amazonia PAX (MINVASYS, Paris, France) integrates a Cobalt Chromium coronary stent, Amazonia CroCo, a well-tested antiproliferative agent (paclitaxel) and the polymer-free PAX technology (Figure 6).

The kinetics of paclitaxel in the Amazonia PAX stent includes a burst release and a 100% drug elution within 30 days of the procedure.

Notably, paclitaxel is carried into the vessel by an abluminal coating, so that drug and eventual polymer are not exposed to the flowing blood in the arterial lumen. Conversely, the absence of stent intraluminal coating preserves future reendothelialization, and makes Amazonia PAX stent retention toward delivery catheter unchanged when compared to predicate BMS behavior.

To date, no clinical data on the Amazonia Pax has been presented.

BioFreedom (Biosensors Inc)
The BioFreedom Drug-Eluting Coronary Stent Delivery System (Biosensors Inc, Newport Beach, Calif) is composed of 3 key components, including a 316 L stainless steel platform that has been modified with a proprietary surface treatment resulting in a selectively microstructured, abluminal surface. The selectively microstructured surface allows Biolimus A9 (drug) adhesion to the abluminal surface of the stent without the use of a polymer or binder (Figure 7).

To render the BioFreedom Stent, the abluminal surface of the stent is texturized by displacing the metal using a micro abrasion process resulting in a selectively microstructured surface. The resulting crevices of this selectively microstructured surface allow a significant portion of the drug biofilm A9 to wick into the stent surface thereby providing a means for anchoring the drug.

Biolimus A9 antiproliferative properties have been previously addressed on this review. The ideal dose of biolimus A9 to be used in the BioFreedom stent is still a subject of research. This question is being currently addressed in the BioFreedom FIM trial. A total of 180 patients will be enrolled in this prospective, multicenter study and randomly assigned

Table 2. Main Polymer-Free DES Systems

<table>
<thead>
<tr>
<th>DES System</th>
<th>Platform</th>
<th>Antiproliferative Agent</th>
<th>Drug Carrier</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amazon Pax (MINVASYS)</td>
<td>Amazonia CroCo (L605) cobalt chromiuim (Co-Cr) stent with strut thickness of 0.0028 inches (73 μm)</td>
<td>Paclitaxel (~2.5 μg/mm of stent length)</td>
<td>Abluminal coating (5 μm) applied on cramped stent</td>
</tr>
<tr>
<td>BioFreedom (Biosensors Inc)</td>
<td>BioFlex II Stent (316 L) stainless steel stent with a strut thickness of 0.0047 inches (119 μm)</td>
<td>Biolimus A9 (dose under investigation)</td>
<td>Modified microstructured, abluminal stent surface</td>
</tr>
<tr>
<td>Optima (CID S.r.l.)</td>
<td>316 L stainless steel stent with strut thickness of 0.0054 inches (137 μm)</td>
<td>Tacrolimus (~2.3 μg/mm of stent length)</td>
<td>Integrated turbostratic carbon coating (Carbofilm) with multiple grooves (reservoirs) on its external surface</td>
</tr>
<tr>
<td>VESTAsync (MIV Therapeutics)</td>
<td>GenX Stainless Steel (316 L) stent with strut thickness of 0.0026 inches (65 μm)</td>
<td>Sirolimus (~2.9 μg/mm of stent length)</td>
<td>Microporous hydroxyapatite coating</td>
</tr>
<tr>
<td>YUKON ChoiceDES (Translumina)</td>
<td>YUKON Choice 316 L stainless steel stent with strut thickness of 0.0034 inches (87 μm)</td>
<td>Translumina has licensed the technology for several companies and therefore different anti-proliferative and antiinflammatory agents have been tested. To the present, the largest successful experience was with a combination of sirolimus (120 μg/cm²) and pravastatin (100 μg/cm²)</td>
<td>Modified microporous stent surface</td>
</tr>
</tbody>
</table>
(1:1:1) to receive the low dose (LD) BioFreedom (112 μg of biolimus A9), the standard dose (SD) BioFreedom (225 μg of biolimus A9), or Taxus Liberté.

In the recently completed first cohort of the BioFreedom FIM trial, results demonstrated a significant reduction of in-stent late loss at 4 months in the 2 BioFreedom groups (SD and LD) when compared with the TAXUS Liberté group (BioFreedom SD = 0.08 mm versus BioFreedom LD = 0.12 mm versus TAXUS Liberté = 0.37 mm, P < 0.0001 and P = 0.002, respectively).

OPTIMA (Carbostent and Implantable Devices [CID] S.r.l.)

The CID OPTIMA new-generation DES system offers the combination of patented polymer-free drug reservoir and the proven antithrombotic and potentially pothealing integral Carbofilm coating. The OPTIMA (CID S.r.l., Saluggia, Italy) key features are the absence of any polymer to carry the drug (Tacrolimus, a cytostatic drug produced by Astellas), the proprietary drug-release system with reservoirs on the stent outer surface, ensuring targeted release only toward the vessel wall, and the integral Carbofilm coating that favors early endothelialization of the deployed stent minimizing the risk of stent thrombosis (Figure 8).

The platform for the OPTIMA is a slotted tubular multicellular architecture stainless steel (L-316) stent with an integrated carbon coating (Carbofilm) that confers its thrombus-resistant properties.

The antiproliferative agent used in the OPTIMA is the tacrolimus (FK 506), a lipophilic macrolid immunosuppressant known to lower the incidence and severity of organ rejection after transplantation and to inhibit the formation of neointimal tissue, an effect that was associated with a decreased inflammation around the struts. Tacrolimus concentration in the artery wall peaks a few days after implantation and then declines to steady values over the following weeks. About 50% of the drug is released from the stent 1 month after implantation, and no drug is released into the blood stream.

VESTAsync (MIV Therapeutics)

The VestaSync Hydroxyapatite Non-Polymer-Based Sirolimus-Eluting Stent System (MIV Therapeutics, Atlanta, Ga) comprises 3 basic components: a platform, an antiproliferative agent, and a drug carrier (Figure 9).
The GenX Stainless Steel Coronary Stent (MIV Therapeutics, Inc) is a new-generation, variable-geometry stent designed to minimize stent-induced arterial injury. Regarding the sirolimus kinetics in the VestaSync stent, in vitro testing on crimped and expanded stents demonstrates a drug release rate that is almost the same as Cypher for the first hour. Thereafter, the release rate slows down to less than half the rate of Cypher. By in vitro experimentation, it is calculated that 100% of the drug will be released from the stent in approximately 3 to 4 weeks.

The coating is composed of a microporous hydroxyapatite \([\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2]\) underlying coating. Sirolimus in a bio-compatible oil-based formulation is loaded into the microporous hydroxyapatite coating. Hydroxyapatite constitutes 70% of natural bone composition and therefore has excellent biocompatibility. The in vivo expected lifetime of hydroxyapatite coating is between 9 months and 1 year. After that period, it is expected to disappear (100% according to preclinical data).

FIM evaluation of this DES system was conducted at Instituto Dante Pazzanese. Fifteen patients were successfully treated with the VestaSync stent and underwent angiography and IVUS at 4 and 9 months’ follow-up. The main findings of this study consisted of an in-stent late-loss (quantitative coronary angiography) and percent stent obstruction (IVUS) of 0.30±0.25 mm and 2.6±2.2% at 4 months. There was a mild, nonsignificant increase in both surrogates at 9 months (0.36±0.23 mm and 4.0±2.2%). Of note, there was no case of late incomplete stent apposition. Up to 24 months of clinical follow-up, none of these patients presented any MACE, including death, myocardial infarction, and target lesion revascularization.

**YUKON ChoiceDES (Translumina)**

The YUKON ChoiceDES (Translumina, German) is a stent especially designed for nonpolymeric application of antiproliferative, anti-inflammatory, and/or antithrombotic drugs.

The surface of the YUKON ChoiceDES contains micropores to enable the adsorption of different organic substances. The coating solution fills the pores completely and creates a uniform layer after evaporation of the solvent. After the drug is fully released, the microporous PEARL Surface favors the adhesion of endothelial cells (Figure 10).

One potential advantage of this system lays on the possibility of using different drug concentrations and combinations of different agents. The drug is applied to the surface of the stent in the catheterization laboratory using a dedicated stent-coating machine. Thus, the operator may increase (or decrease) the amount of antiproliferative drug according to patient and lesion complexity. Translumina has tested different drug formulations in its DES system, including sirolimus and trapidil. More recently, a combination of sirolimus and probucol (the Dual-DES stent) has been tested with enthusiastic initial results.

The active compounds of the Dual-DES stent are sirolimus (0.7%) and probucol (0.7%), which are dissolved in solution in a 1:1 ratio, combined with a shellac resin (0.07%) and applied to the stent surface in a single coating process; no polymer is used. The coating process is fully sterile and takes between 3 and 8 minutes, depending on stent length. The distribution concentration of rapamycin is 120 mg/cm² stent and of probucol is 100 mg/cm². Shellac resin is a biocompatible resin widely used in the coating of medical tablets; its release kinetics is similar to those of both active drugs. The inclusion of resin allows for improved adherence of the drug mixture to the stent surface and enhances the structural integrity of the coating. No traces of sirolimus, probucol, or resin have been observed beyond 6 to 8 weeks.

In the ISAR-test 2, 1007 patients were randomly assigned to receive Cypher (n=335), Endeavor (n=339), or the Translumina Dual-DES (n=333). The primary end point was binary angiographic restenosis at 6- to 8-month follow-up angiography. Follow-up angiographic data were available for 828 (82.2%) patients. There was a significant difference in both binary restenosis and target lesion revascularization.
across treatment groups ($P=0.003$ and $P=0.001$, respectively). Binary restenosis in the Dual-DES group (11.0%) was significantly lower than that in the Endeavor group (19.3%; $P=0.002$) but comparable with that in the Cypher group (12.0%; $P=0.68$). Similarly, target lesion revascularization with Dual-DES (6.8%) was significantly lower than Endeavor (13.6%; $P=0.001$) but not different from that of Cypher (7.2%; $P=0.83$). In-stent late lumen loss after the deployment of Cypher and Dual-DES was similar (0.24±0.51 0.23±0.50, respectively) and significantly lower than in the Endeavor group (0.58±0.55, $P<0.001$ for both comparisons). Stent thrombosis rates were very low and equivalent among the 3 cohorts.

More recently, the same group presented a systematic report of 1331 treated with Cypher, Taxus, and the Translumina Dual-DES and submitted to 2 invasive follow-ups (at 6 to 8 months and 2 years). In that analysis, they observed a mild but significant increase in the late lumen loss between the early and late follow-ups in patients treated with both durable-polymer first-generation DES (increase of 0.17±0.50 mm for Cypher and of 0.13±0.50 mm for Taxus); conversely, in patients receiving the Translumina Dual-DES, this increase was not observed (late lumen loss variation of 0.01±0.42 mm).23

Moore et al24 evaluated with OCT 24 patients treated with either Cypher or the Translumina YUKON to examine neointimal thickness, stent strut coverage, and protrusion at 90 days. Mean neointimal thickness for the polymer-coated sirolimus-eluting stent was significantly less than the non-polymer sirolimus-eluting stent, but as a result, coverage was not homogenous, with >10% of struts being uncovered in the Cypher cohort (versus <3% with YUKON, $P=0.03$). Also, >25% of struts protruded into the vessel lumen with Cypher compared with <5% YUKON.

**Conclusion**

After several years involved in the task of “bringing to life” novel devices to treat coronary disease, we feel comfortable to make a few predictions:

1. First-generation DES systems with thick, durable polymer loading will be gradually replaced to more advanced technology.
2. Bioabsorbable polymers with abluminal release and reservoir technology as well as modified polymer-free stent surfaces represent an attractive alternative in this transition process.
3. However, despite the very promising initial results of most of next-generation programs presented in this review, for different reasons (economic crisis included here), a few of them will probably never get into clinical practice.
4. For the ones who survive the long journey toward market approval, there will be the final task to demonstrate meaningful safety superiority (with at least equivalent efficacy) over the current approved drug-eluting devices. Because the incidence of hard end points (death and myocardial infarction) does not markedly differ among the so far tested drug-eluting stents, we should expect that large controlled studies, real-world registries and/or meta analysis will be required to prove (or not) the superiority hypothesis, and this process may take a few years.

Despite all these remarks, we still believe the future is bright for these technologies, and much is expected for the coming years.

**Disclosures**

Dr Abizaid has served as consultant for Abbott Vascular and Boston Scientific. Dr Costa has no conflict of interest to state. Instituto Dante Pazzanese has received research grant from Abbott Vascular, Boston Scientific, Cordis, Sahajanand, Minvasys, Cardiomind, Elixir, MIV e Biosensors in the recent years to conduct research related to some of the devices discussed in the text.

**References**


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