Clinical Cardiology: New Frontiers

New Frontiers in Cardiology
Drug-Eluting Stents: Part II

J. Eduardo Sousa, MD, PhD; Patrick W. Serruys, MD, PhD; Marco A. Costa, MD, PhD

In this second part of the article, we will complete the review of drug-eluting stent technologies (Table 1) and discuss methodological and technical aspects of drug-eluting stents.

Biological Agents (Continued)

(1) Stents Eluting Antiproliferative Agents
A number of antineoplastic medications have been considered for the prevention of restenosis. Paclitaxel and its derivatives have been the most investigated compounds of this group.

(a) Paclitaxel-Eluting Stents
Paclitaxel (Taxol; Bristol-Myers Squibb) is a microtubule-stabilizing agent with potent antitumor activity. Many different platforms that use polymer coating or surface modifications to adhere paclitaxel onto the stents have been utilized over the past 2 years.

Preclinical Data
Unlike other antimitotic agents, paclitaxel shifts the cytoskeleton equilibrium toward assembly, leading to reduced vascular cell proliferation, migration, and signal transduction. Paclitaxel is highly lipophilic, resulting in a rapid cellular uptake and a long-lasting effect in the cell.

NIR stents (Boston Scientific Corp) coated with poly(lactide-co-ε-caprolactone) copolymer and paclitaxel (200 µg/stent) were placed in porcine coronary arteries. Paclitaxel-eluting stents showed a marked reduction in neointimal and medial cell proliferation at all time points (7, 28, 56, and 180 days). However, arteries treated with paclitaxel showed incomplete healing, late persistence of a large number of macrophages, and fibrin deposition. Similar findings were observed with a stent platform coated with cross-linked biodegradable polymer (chondroitin sulfate and gelatin) and 42.0, 20.2, 8.6, or 1.5 µg of paclitaxel in rabbit iliac arteries. These studies indicate the need for a more controlled drug release of paclitaxel due to the narrow toxic-therapeutic window and high hydrophobic character of this compound.

Clinical Data: De Novo Lesions
The QuaDS drug-eluting stent (Quanam Medical Corp) was the first drug-eluting stent implanted in human coronary arteries. This slotted tube stent has 50% of its surface area covered by multiple nonbiodegradable polyacrylate sleeves that release 7-hexanoyltxal (called QP2 or taxane). Approximately 800 µg of the drug was loaded per 2.4 mm of sleeve length, such that 13-mm-long stents have a total drug dose of 2400 µg, and 17-mm-long stents contained 3200 µg of taxane. This registry enrolled 26 patients randomly assigned to receive drug-loaded stents (n=13, 14 stents) or bare stents (n=13, 18 stents). At 18-month follow-up, there was no binary restenosis in the drug-eluting stent group. A 5-fold decrease in neointimal proliferation was detected by intravascular ultrasound (IVUS) in the paclitaxel group.

The SCORE trial (Study to COmpare REstenosis rate between QueST and QuaDS-QP2) was a randomized study conducted in 15 sites in Europe to test the effectiveness of the QuaDS-QP2 stent. The trial was interrupted prematurely after the enrollment of 266 patients because of a high incidence of stent thrombosis (9.4%) and myocardial infarction (14.5%) in the eluting stent group. These clinical events were probably related to poor stent design and extremely high concentrations of taxane.

The QuaDS-QP2 stent was further evaluated in 15 consecutive patients with in-stent restenosis. Combined antiplatelet therapy with aspirin (at least 100 mg/d) and ticlopidine 500 mg/d (or clopidogrel 75 mg/d) was continued for at least 6 months. Restenosis occurred in 2 lesions (13.3%) at 6 months and 8 lesions (61.5%) at 12 months, suggesting a late catch-up of restenosis.

Polymer-Based Paclitaxel-Eluting Stents
A series of clinical trials (TAXUS I through VI) have been designed to test the feasibility and effectiveness of polymer-based paclitaxel-eluting stents in a variety of clinical settings.

• TAXUS I. This study evaluated the safety of the slow-release polymer-coated NIRx Conformer stent (Boston Scientific Corp) loaded with 85 µg of paclitaxel (1.0 µg/mm²). About 80% of the drug is released within the first 1 to 3 days. Sixty-one patients with short (<15 mm), de novo coronary lesions were randomized to either drug-eluting or bare stent. In-stent late loss was 0.36 mm in the drug-eluting stent group versus 0.71 mm in control group.

From the Institute Dante Pazzanese of Cardiology, São Paulo, Brazil (J.E.S.); Thoraxcenter, Dijkzigt University Hospital, Rotterdam, the Netherlands (P.W.S.); and University of Florida Health Science Center, Shands Jacksonville, Jacksonville, Fla (M.A.C.).


Correspondence to Prof. J. Eduardo Sousa, MD, PhD, Director of the Institute Dante Pazzanese of Cardiology, Av. Dr Dante Pazzanese, 500 – Ibirapuera, 04012180, São Paulo, Brazil. E-mail jesousa@uol.com.br

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At 1 year, incidence of major adverse cardiac events (MACE) was 3% in the eluting stent group versus 10% in the uncoated stent group. There were no reports of death, stent thrombosis, target lesion revascularization, or binary restenosis in the drug-eluting stent group.

**TAXUS II.** This triple-blinded, randomized, multicenter trial tested the efficacy of 2 formulations of paclitaxel-eluting NIRx Conformer stent to treat patients with short, de novo coronary lesions. The study included 536 patients divided into 4 groups: 267 were treated with either bare (n=136) or slow-release (SR, n=131) eluting stents, whereas 269 were treated with bare (n=134) or moderate-release (MR) eluting stents (n=135). All cohorts were treated with a 15-mm NIRx Conformer Stent. All eluting stents were coated with the translute polymer loaded with 0.1 g of paclitaxel/mm². Clopidogrel (75 mg QID) was administered for 6 months. The primary end point was percent in-stent volume neointimal hyperplasia (by IVUS) at 6 months. Binary in-stent restenosis rates were 2.3% (SR) and 4.7% (MR) versus 17.9% and 20.2% in the control groups, respectively. Late loss was 0.31 mm (SR) and 0.30 mm (MR) in the eluting stent groups. Percent neointimal hyperplasia volume was markedly reduced in the eluting groups (SR = 7.85% and MR = 7.84%) versus control (23.17% and 20.54%, re-
There were no late stent thromboses or aneurysms up to 6 months (Antonio Colombo, MD, Columbus Hospital, Milan, Italy, unpublished data, 2002). This stent is currently available for clinical use in Europe.

**In-Stent Restenosis**

- **TAXUS III.** This feasibility study utilized SR paclitaxel-eluting NIRx Conformer platform for the treatment of patients with in-stent restenosis and was conducted at 2 sites in Europe, enrolling 30 patients. The protocol allowed the implantation of up to 2 (15-mm) eluting stents. In-stent late loss averaged 0.44 mm after 6 months. Overall binary restenosis rate was 16% (4 of 25), but 2 restenoses occurred at the gap between eluting stents and another within a bare stent implanted adjacent to the eluting stent. There were no deaths, and repeat revascularizations occurred in 21.4% of the patients (Kengo Tanabe, MD, Thoraxcenter, Rotterdam, the Netherlands, unpublished data, 2002).

**Upcoming Studies**

- **TAXUS IV and TAXUS V** are pivotal, large, randomized US trials testing the efficacy of MR paclitaxel-eluting Express stents (Boston Scientific Corp) in patients with de novo lesions. TAXUS IV included 1326 patients with de novo coronary lesions varying from 10 to 28 mm in length, treated with a single stent. TAXUS V will include a more complex population with longer lesions (up to 40 mm) and allow the implantation of multiple MR stents. TAXUS VI is the European counterpart of the TAXUS V trial. Results are expected in 2003.

**Non–Polymer-Based Paclitaxel-Eluting Stents**

- **ELUTES (European Evaluation of Paclitaxel-Eluting Stent).** This study compared the V-Flex stent (Cook, Inc) loaded with 4 different doses of paclitaxel (0.2, 0.7, 1.4, and 2.7 μg/mm²) versus bare metal stents for the treatment of de novo coronary lesions. Stents were directly impregnated with paclitaxel without a polymer. Patients (n=180) were randomized evenly among the 5 groups. A dose-dependent effect on in-stent late loss was observed: 0.1 mm in the high-dose group, 0.47 and 0.5 mm in intermediate-dose groups, and 0.7 mm in both low-dose and control groups. One-year MACE incidence was similar among groups. There were no reports of death or stent thromboses (Ivan De Scheerder, MD, University Hospitals Leuven, Leuven, the Netherlands, unpublished data, 2002).

- **ASPECT (Asian Paclitaxel-Eluting Clinical Trial).** This randomized study compared Supra-G stents (Cook, Inc) directly impregnated with 2 different doses of paclitaxel (1.3 and 3.1 μg/mm²) versus bare metal stents. Patients (n=180) with de novo coronary lesions were treated with single stents. Antiplatelet therapy was administered for 6 months. In 37 patients, cilostazol was used in place of clopidogrel or ticlopidine. In-stent late loss was 0.29 mm in the high-dose group, compared with 0.57 in low-dose group and 1.04 mm in the bare stent group. Neointimal hyperplasia volume was 12, 18, and 31 mm³, and restenosis rates were 4%, 12%, and 27% for the high-dose, low-dose, and control groups, respectively. Overall, 1-year MACE incidence and target lesion revascularization rates were similar among all groups. However, 4 of the 12 patients receiving the high-dose eluting stents, who were also receiving cilostazol, had stent thromboses (Seung-Jung Park, MD, Asan Medical Center, Seoul, Korea, unpublished data, 2002).

**Drug-Eluting Stents: Part II**

- **PATENCY (Paclitaxel-Eluting Stent for Cytostatic Prevention of Restenosis).** This study compared Logic PTX (Cook, Inc) paclitaxel-eluting stents (2.0 μg/mm²) with bare stents in de novo coronary lesions. A total of 50 patients were enrolled at 2 US sites. Clopidogrel was administered for 3 months. There were no stent thromboses up to 9 months, but restenosis rates were similar in the 2 groups (38% in the eluting stent group and 35% in the control arm) (Alan Heldman, MD, Johns Hopkins University, Baltimore, Md, unpublished data, 2002).

**Upcoming Studies**

- **DELIVER.** This randomized study compared Multilink Penta stents (Guidant) directly impregnated with 3 μg/mm² of paclitaxel using surface modification with bare stents. Patients with de novo coronary lesions (n=1043) have been enrolled at 50 US sites.

**(b) Angiopeptin-Eluting Stents**

Somatostatin, an angiopeptin analogue, has been shown to reduce tissue response to several growth factors, including platelet-derived growth factor, basic fibroblast, and insulin-like growth factors. In humans, systemic administration of angiopeptin has improved the clinical outcome after angioplasty but showed no effect in restenosis.10 Angiopeptin-loaded phosphorylcholine-coated BiodivYsio stents (Biocompatibles Cardiovascular, Inc) decreased neointimal proliferation compared with bare stents in pig coronary models.11 The SWAN study (First Human Experience With Angiopeptin-Eluting Stent), an open-label registry, tested the feasibility of angiopeptin-eluting BiodivYsio stents in 13 patients with coronary de novo lesions. Thirteen stents were loaded with 22 μg of angiopeptin, and 1 stent was loaded with 126 μg of the drug. There were no in-hospital or 30-day MACE (Vincent On-Hing Kwok, MD, Grantham Hospital, Hong Kong, China, unpublished data, 2002). Long-term follow-up data are pending.

**(c) Tyrosine Kinase Inhibitor–Eluting Stents**

Tyrosine kinases are both transmembrane and intracellular protein kinases that are fundamental to a number of extracellular signals that regulate proliferation, differentiation, and specific functions of differentiated cells.12 Poly-L-lactic acid (185 kDa) biodegradable stents loaded with ST638 (0.8 mg), a specific tyrosine kinase inhibitor, were implanted in pig coronary arteries. After 3 weeks, the amount of neointimal proliferation was significantly decreased in the ST638 stents compared with its inactive metabolite (ST494).13 Clinical studies are still pending.

**(d) Actinomycin D–Eluting Stents**

Actinomycin D is an anticancer drug that selectively inhibits RNA synthesis. Little information about the use of actinomycin D for the prevention of smooth muscle cell proliferation and restenosis is available. The ACTION (Actinomycin
Eluting Stents Improve Outcomes by Reducing Neointimal Hyperplasia) study was a large randomized trial designed to test the safety, feasibility, and effectiveness of 2 different doses of actinomycin-eluting Tetra stents (Guidant) for the treatment of de novo coronary lesions. The study was interrupted prematurely because of a high incidence of repeat revascularization in the treated arms.

(e) **C-myc Antisense–Eluting Stent**
Upregulation of genes such as c-myc, which regulates cell division, leads to cellular proliferation. Antisense oligonucleotides have the ability to block critical phases of the smooth muscle cell growth cycle. Inhibition of several cellular proto-oncogenes have been shown to inhibit smooth muscle cell proliferation in vitro and to reduce neointimal thickening in vivo. C-myc antisense oligonucleotides have also been shown to inhibit inflammation and extracellular matrix production. However, the first clinical experience using catheter-based local delivery of c-myc antisense oligonucleotides was disappointing.

(2) **Stents Eluting Antithrombosis Agents**
Vessel injury with resulting platelet aggregation and thrombus formation plays a prominent role in the development of restenosis. Antithrombotic pharmacological approaches to inhibit restenosis, however, have proven ineffective. Nitric oxide and glycoprotein IIb/IIIa inhibitors have been used as stent coatings, but their efficacy has yet to be demonstrated. A combination of hirudin and iloprost were blended with a polylactic acid polymer in a homogeneous thin layer and loaded onto a stent. While iloprost was slowly released by the breakdown of the polymer, about 60% of the hirudin was eluted in the first 24 hours. Decreased neointimal formation was observed in sheep and pig injury models treated with this antithrombotic-eluting stent, but clinical data are still pending.

(3) **Stents Eluting Extracellular Matrix Modulators**
Extracellular matrix constitutes a major component of the restenotic lesion and therefore represents a potential target for antirestenosis therapy. Matrix metalloproteinases (MMP), particularly MMP-2 (72-kDa type IV collagenase) and MMP-9 (92-kDa type IV collagenase), have the ability to digest collagen and facilitate smooth muscle cell migration. Batimastat, a nonspecific MMP inhibitor, and other MMP inhibitors have been shown to inhibit neointimal hyperplasia in animal models. The BRILLIANT-I (Batimastat Anti-Restenosis Trial Utilizing the Biodivysio Local Delivery PC-Stent) was a multicenter registry designed to test the feasibility of a batimastat-eluting stent to treat de novo coronary lesions in 173 patients. Although safety was demonstrated, late loss was 0.88 mm, and 21% of the patients developed binary restenosis. The EASTER study is ongoing in Italy.

(4) **Stents Eluting Prohealing Agents**
The promotion of healing in the vascular endothelium may be a more natural and consequently safer approach to the prevention of restenosis. Endothelial denudation and dysfunc-

...tion are common at the site of endovascular interventions and have been associated with vessel thrombosis and restenosis. In addition, delayed reendothelialization has been associated with late side effects of potent antiproliferative therapies, such as with radiation therapy.

Immediate restoration of endothelial function might abort the initiation of restenosis. Endothelial cell seeding has been proposed as the ultimate method to assure immediate stent endothelialization, but cell viability has been a limitation. Stents may be used to attract circulating endothelial cells. R stents (Orbus Medical Technologies) coated with antibodies to CD34 receptors on progenitor circulating endothelial cells have been implanted in pig coronary arteries. Preliminary results suggested the feasibility of capturing endothelial cells in situ (Michael Kutryk, MD, St Michael’s Hospital, Toronto, Canada, unpublished data, 2002). These non–drug-based stents would ultimately promote elution of biological active substances through a functioning endothelium monolayer. The effects of these ingenious stents on restenosis remain to be demonstrated.

Nitric oxide, vascular endothelial growth factor, and 17b-estradiol have all been tested as prohealing, antirestenotic agents, as well. Local delivery of vascular endothelial growth factor to prevent restenosis has been evaluated in animal models, but results are conflicting.

**Estradiol-Eluting Stents**
Estradiol may improve vascular healing, reduce smooth muscle cell migration and proliferation, and promote local angiogenesis. Recently, estradiol-eluting phosphorylcholine-coated stents (Abbott/Biocompatibles) implanted in porcine coronary arteries reduced neointimal hyperplasia by 40% compared with control stents.

EASTER (Estrogen and Stent to Eliminate Restenosis) was a single-center feasibility study testing 17β-estradiol–eluting BiodivYsio stents in 50 patients with de novo coronary lesions. Stents were loaded on-site by immersion in a solution of estradiol. The average concentration was 2.54 µg/mm² of stent. Late loss was 0.32 mm in lesion and 0.57 mm in stent. IVUS-detected neointimal hyperplasia was 23.5%. At 6 months, there were no deaths or stent thromboses, and only 1 patient underwent repeat revascularization. A second phase of the EASTER study is ongoing in Italy.

What Have We Learned?

**Methodological Considerations**
Interpretation and comparison of different investigations have been complicated by the lack of a standard format to report study findings. Angiographic and clinical data have been compiled at different time points (4, 6, 8, 9, or 12 months). Defining the most appropriate study end point has also been a dilemma. The classical binary restenosis rate has limited value in determining whether a device had restraining or inhibitory effects on neointimal proliferation, particularly in small clinical studies. Angiographic late lumen loss and neointimal hyperplasia volume detected by IVUS are the most appropriate parameters to evaluate the performance of drug-eluting stents. IVUS imaging should become an integral component of clinical investigations testing new agents, in

...
order to identify arterial wall reactions that would be unappreciated by conventional angiography. IVUS and angiographic analysis should involve both stented and edge segments, commonly defined as the stent plus at least 5 mm proximal and distal to the stent borders (Figure 1). Clinically, target lesion revascularization represents the best surrogate for restenosis. However, the incidence of late thrombosis (>30 days) and repeat target vessel revascularization should be reported among traditional end points, given the clinical implications of these events.

Clinical Considerations
Although some drug-eluting stents demonstrate efficacy in animal models, they have not always yielded similar results in humans. The experience with paclitaxel illustrates the importance of correct drug dosing and stent design in order to produce a successful drug-eluting stent. Variations in pharmacological mechanisms and stent-coating technologies elicited different vascular reactions. Many of these studies have demonstrated that not all stents are equal. Currently, only 2 drug-eluting stent platforms have proven effective in large randomized trials: sirolimus-eluting stents and polymer-based paclitaxel-eluting stents.

The sirolimus experience further demonstrates that not all patients are equal. High-risk anatomic features such as diffuse disease, in-stent restenosis, and failed brachytherapy also impact clinical outcomes of patients treated with drug-eluting stents. Differences in angiographic outcomes between RAVEL (Randomized study with the sirolimus-eluting Bx VElocity balloon-expandable stent) and SIRIUS (A U.S. multicenter, randomized, double-blind study of the SIrolimus-eluting stent in de novo native coronary lesions) have been attributed to the treatment of a higher-risk population in the US trial. Subanalyses of these studies, however, demonstrated a larger benefit in terms of absolute reduction in restenosis among high-risk patients.

A high incidence of incomplete stent apposition was observed in the sirolimus-eluting stent arm of the RAVEL study. Although intriguing, these IVUS findings were not associated with any clinical event up to 1-year follow-up. Late thrombosis and aneurysmal formation have not been associated with the use of sirolimus-eluting stents so far. The high incidence of stent thrombosis observed in the early paclitaxel23 studies may be due to high drug concentrations, poor stent design (SCORE), and inadequate antiplatelet therapy (ASPECT). No late thrombosis has been reported in the randomized TAXUS II trial, but patients were still taking clopidogrel at 6-month follow-up.

Patient Selection
Patient selection for drug-eluting stent is an evolving issue. On the basis of published randomized data, drug-eluting stents should only be utilized in patients with short, de novo coronary lesions. Long-term follow-up as well as experience in more complex lesions is now accumulating. Thus, indications for drug-eluting stents are expected to expand considerably in the near future, while future studies may further broaden clinical indications. The financial burden of drug-eluting stents will have a major impact on patient selection. Substantial costs may limit utilization of such a device to patients at high risk for restenosis. Unfortunately, these patients may require multiple stents, which ultimately increase the cost of the procedure. On the other hand, patients with large vessels or those with short lesions actually had the greater relative risk reduction in the SIRIUS trial. Considering that these patients usually require the implantation of a single stent, the drug-eluting stent strategy may prove more cost-effective in a low-risk population. A more detailed discussion on the cost-effectiveness of drug-eluting stents will be provided in a future article.

Technical Considerations
The application of this new therapeutic modality does not require vast changes in the arena of interventional cardiology.
**TABLE 2. Technical Aspects of Drug-Eluting Stent Deployment**

<table>
<thead>
<tr>
<th>Problems</th>
<th>Potential Solutions</th>
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<tbody>
<tr>
<td>Coating disruption</td>
<td>Careful device handling</td>
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<tr>
<td>“Geographic miss” and secondary in-lesion restenosis</td>
<td>If pre- or post-dilatation required, always use a balloon shorter than the stent length</td>
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<tr>
<td></td>
<td>Complete cover of the atherosclerotic segment</td>
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<tr>
<td></td>
<td>Avoid trauma (wire, balloon, debulking) outside the stented segment</td>
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<tr>
<td></td>
<td>Avoid gap between stents</td>
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<tr>
<td>Select appropriate stent size (IVUS guidance?), particularly in small vessels and long lesions</td>
<td>Appropriate patient selection</td>
</tr>
<tr>
<td>Non–target lesion repeat revascularization</td>
<td>If a second stent is required, use another drug-eluting stent*</td>
</tr>
<tr>
<td>Restenosis in adjacent bare metal stents</td>
<td>Appropriate drug-eluting stent selection</td>
</tr>
<tr>
<td>In-stent restenosis</td>
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*Overlapping may not be safe for all drug-eluting stents.

(Table 2). However, diligent stent placement in various plaque morphologies may be more important than ever. The new drug-eluting stents abolish neointimal proliferation within the stent, and any tissue growth in segments adjacent to the stents becomes unmasked. Incomplete lesion coverage, arterial trauma outside the stented segment, and gap between stents, generally operator-dependent factors, represent the new face of “geographic miss” in the drug-eluting stent era and have been linked to treatment failures.

Proper stent sizing is also a critical stage of the drug-eluting stent procedure. Oversized stents may produce extensive trauma to the media, adventitia, and surrounding tissues, with enhanced proliferative reaction that cannot be counteracted by usual drug concentrations. Conversely, placing a too-small stent in a large vessel may lead to underdosing at the tissue level due to a lack of contact between the stent and vessel wall secondary to incomplete stent apposition, or because the struts are expanded beyond the limit for optimal vessel wall secondary to incomplete stent apposition, or because the struts are expanded beyond the limit for optimal vessel wall function. Insufficient local drug concentration or disproportionate vessel trauma rather than a failure of the drug itself may lead to inadequate inhibition of intimal hyperplasia, namely “axial geographic miss.”

Although overlapping sirolimus-eluting stents seem to be safe, it is unclear if overlapping other drug-eluting devices will have similar profiles, due to the risk of toxic local concentration with certain agents. Careful handling of the stent before stent deployment should be undertaken to avoid potential disruption of the coating surface. Operator- and technical-related factors will become the ultimate determinants of clinical outcomes.

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**References**


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