Clinical Cardiology: New Frontiers

New Frontiers in Cardiology
Drug-Eluting Stents: Part I

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Stents represent a major advance in the treatment of obstructive coronary artery disease since the advent of balloon angioplasty. The number of percutaneous coronary interventions performed each year has expanded considerably since the early days. Angioplasty procedures doubled in Europe between 1992 and 1996,1 while an estimated 601 000 procedures were performed each year has expanded considerably in the United States in 1997.2 Unfortunately, many of these patients develop an exaggerated vascular neointimal proliferation after stenting—namely, in-stent restenosis. Much research has been devoted to the pathophysiology and treatment of in-stent restenosis. As a result of many relentless “trial-and-error” endeavors, drug-eluting stents have emerged as a potential solution for restenosis. Drug-eluting stents are coated stents capable of releasing single or multiple bioactive agents into the bloodstream and surrounding tissues.

We have been commissioned to present an overview on drug-eluting stents. Acknowledging the challenge of examining such a dynamic and flourishing field, our goals in this 2-part article were to provide a broad perspective of the development of drug-eluting stent technology, to summarize the available clinical data, and to introduce emerging concepts for the understanding and application of this new device in clinical practice.

Why Drug-Eluting Stents?

In 1991, stent use was still facing skepticism because of an unacceptably high (20% to 25%) incidence of thrombotic complications.3 Systemic anticoagulation proved disappointing in reducing the catastrophic consequences of stent thrombosis, such as myocardial infarction and sudden death. Consequently, antithrombotic stent coatings were developed to decrease the inherent thrombogenicity of coronary metallic stents. Some heparin-coated stents have become available for clinical use: BX-Velocity Carmeda-coated stent (Johnson & Johnson), Wiktor Hepamed-coated stent (Medtronic, Inc), and the Jostent Corline-coated stent (Jomed International AB). Heparin-coated stents differ from drug-eluting stents because the medication is covalently bonded to the device and hence may remain attached long after deployment. However, these stents represented the first step toward loading medications onto stents. Fortunately, the incidence of subacute stent thrombosis has dropped significantly to \(<0.5\)% because of high-pressure stent deployment and the use of antiplatelet agents.

Although the success and safety of coronary stenting has dramatically increased, in-stent restenosis has persisted as a hindrance to stenting. The incidence of restenosis may vary from 8% to as high as 80% at 6 months, according to both anatomic and clinical risk factors.4 In-stent restenosis is primarily an exaggerated neointimal proliferation. Metallic stent struts activate platelets and macrophages. Cytokines and growth factors also contribute to smooth muscle cell proliferation. In addition, upregulation of genes and metalloproteinas leads to cell growth, remodeling of extracellular matrix, and smooth muscle cell migration.4 A combination of these factors may result in significant luminal narrowing several months after stent placement. Each of these processes is a potential target for antirestenosis therapy.

Mechanical approaches have proved too simplistic to prevent in-stent restenosis. Interfering with molecular cell division appears to be a much more effective manner of altering the healing process after stenting. The potential toxicity of systemic pharmacological therapy and the failure to achieve adequate drug concentrations at the injury site pose significant limitations to a systemic approach for restenosis. Local drug delivery systems were then developed to provide high concentrations of drug at the site of vascular injury. Although catheter-based local drug delivery has had mixed results in preventing in-stent restenosis in animal models, it has been largely unsuccessful in humans. These devices have been hampered by the rapid washout of the drug downstream into the coronary circulation and the potential flow- or pressure-mediated vessel wall injury.5 Recently, the emergence of drug-eluting stent technology offered a new perspective for the pharmacological prevention of restenosis.

The concept of using stents as vehicles for prolonged and sufficient intramural drug delivery is appealing. Stents represent an ideal platform for local drug delivery because of their permanent scaffolding properties, which prevent vessel recoil and negative remodeling. In addition, they represent drug reservoirs, inasmuch as medications are released from...
various coatings at different time intervals. The achievement of a hospitable relationship between stent, coating matrix, drug, and vessel wall is extremely challenging. In principle, most drug-eluting stent technologies face many potential limitations (Table). The scientific community, pharmaceutical and engineering industries, and clinicians have utilized a multidisciplinary approach to address these many issues in the formulation of a successful drug-eluting stent, which generally contains three basic components: stent, coating, and biological agent.

**Step I: The Carrier Stent**

Endovascular stents were initially designed as scaffolding structures, not medication-delivery devices. Consequently, stent design has been altered to afford more flexibility, greater radial strength, and minimal metallic coverage. These alterations are unfavorable for housing a drug-eluting vehicle. Efforts are now directed at coating a stent with a sufficient amount of medication that can be delivered uniformly to the underlying tissue. Uniform drug distribution in human, diseased coronary arteries is unrealistic, however. Besides stent design, other factors govern drug diffusion, such as vessel wall morphology, drug physicochemical characteristics, and the multifaceted milieu of the underlying atherosclerotic plaque.

Compared with current stents, the ideal drug-delivery stent might have a much larger surface area, minimal gaps between cells, and minimal strut deformation after deployment. Yet these new stents would need to maintain their low profile, conformability, radial support, and flexibility to reach complex anatomies. All clinical trials to date have tested conventional stent designs as drug carriers. The optimal outcomes observed in some of these studies may obviate such specific design requirements for the success of drug-eluting stents. However, compounds with narrow toxic-therapeutic windows or different physicochemical properties may require a customized stent platform. Stent designs dedicated for drug-elution kinetics during deployment and modulates drug-elution kinetics. By altering the release kinetics of different drugs in the same coating matrix, distinct phases of the restenotic process may be targeted. In theory, a sustained release of antirestenotic drugs for at least 3 weeks after deployment is required to prevent smooth muscle cell migration and proliferation.

Drugs may be held by covalent bonds (eg, C-C bonds, sulfur bridges) or noncovalent bonds (eg, ionic, hydrogen bonds). The blended matrix may then be attached to the stent surface by dipping or spraying the stent.

Drugs are released by particle dissolution or diffusion when nonbioerodable matrices are used, or during polymer breakdown when incorporated (absorbed) into a biodegradable substance. Drug-elution kinetics from coating matrices are influenced by a variety of factors (Table).

The coating material should act as a biologically inert barrier. This has only been achieved with a few polymers. The selection of a noninflammatory, inert coating matrix has been a major obstacle to the development of drug-eluting stents. van der Giessen and coworkers tested 8 different polymers attached longitudinally across 90° of the circumferential surface of coil wire stents (Medtronic, Inc). These biological agents (Figure 1). The coating ensures drug retention during deployment and modulates drug-elution kinetics. By altering the release kinetics of different drugs in the same coating matrix, distinct phases of the restenotic process may be targeted. In theory, a sustained release of antirestenotic drugs for at least 3 weeks after deployment is required to prevent smooth muscle cell migration and proliferation.

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**Step II: The Coating Matrix—A Double-Edged Sword?**

Several approaches to coating stents with medications exist (Figure 1). Some drugs can be loaded directly onto metallic surfaces (eg, prostacyclin, paclitaxel), but a coating matrix, which contains the medication, is required for most of the
coated stents were implanted in porcine coronary arteries, but none of these proved to be physiologically inert.\(^8\)

Coating materials must maintain their physicochemical characteristics after sterilization and after stent expansion. The list of candidate substances for stent coatings is long and ever expanding.\(^7\) These substances may be categorized as organic, inorganic, bioerodable, nonbioerodable, synthetic, or naturally occurring substances.

**Synthetic Polymers**

To date, the most successfully tested drug-eluting stents have been coated with synthetic polymers: poly-n-butyl methacrylate and polyethylene-vinyl acetate with sirolimus,\(^9\) and a poly(lactide-co-\(\Sigma\)-caprolactone) copolymer with a paclitaxel-eluting platform.\(^10\)

Polymers are long-chain molecules consisting of small repeating units. Because they form a reservoir of medications and facilitate prolonged drug delivery, they serve an important role as coating matrices. Polymer toxicity results in enhanced neointimal hyperplasia.\(^8\) This type of response is influenced by the molecular weight and thickness of the coating layer. Slowly degrading coatings may elicit less inflammatory reaction. In addition, the metabolites of biodegradable polymers also play a role in inflammation.

**Biological Materials**

The surfaces of a vascular prosthesis must be both bio- and hemo-compatible.\(^11\) Fibrin, cellulose, and albumin, all naturally occurring, have been tested to improve the quality of stent surfaces, with promising results from the animal studies. Phosphorylcholine is a neutral, zwitterionic, naturally occurring phospholipid polymer. In vivo experiments have shown that phosphorylcholine does not interfere with stent reendothelization and elicits a similar amount of neointimal hyperplasia compared with uncoated stents. Phosphorylcholine-coated BiodivYSio stents are currently available for clinical use and can be loaded with variety of compounds.

**Inorganic Coatings**

Inorganic substances have been placed on stent surfaces to improve their electromechanical properties. Recently, pilot clinical investigations have been initiated with stents coated with a nonporous 300-\(\mu\)m ceramic layer containing tacrolimus-loaded nanocavities. In addition, other ongoing studies involve stents designed with a deep reservoir for drug loading coated with a thin layer of pyrolytic carbon (Carbofilm).

**Step III: The Biological Agent**

The ideal antirestenotic agent for local delivery should have potent antiproliferative effects yet preserve vascular healing. Such a compound should contain hydrophobic elements to ensure high local concentrations, as well as hydrophilic properties to allow homogeneous drug diffusion. In addition, the drug should have a wide therapeutic to toxic ratio and should not incite thrombosis or inflammation. Other factors such as molecular weight, charge, and degree of protein binding\(^12\) may also affect drug kinetics and ultimately influence the biological success.

Figure 2. The leading processes of restenosis (solid lines) and correspondent inhibitory (dashed lines) effects of different biological agents. MMP indicates matrix metalloproteinase; VEGF, vascular endothelial growth factor.

The search for an effective biological agent to prevent restenosis has extended beyond the realm of cardiology. Anticancer and anti–transplant rejection agents are now being considered in the fight against restenosis. Only a few agents have demonstrated clinical efficacy, but the search is still ongoing. Drugs that interfere earlier in the cell cycle (G\(_1\) phase) are generally considered cytostatic and potentially elicit less cellular necrosis and inflammation compared with agents that affect the cell cycle in a later stage (beyond the S phase)\(^13\) (Figure 2). On the basis of the mechanism of action of the biological compound and its target in the restenotic process, drug-eluting stents may be generally classified as immunosuppressive, antiproliferative, antiinflammatory, antithrombotic, and prohealing. Some agents, such as sirolimus, may affect multiple targets in the restenotic process but will be discussed under a single category.

The next section summarizes the clinical data available for the different classes of drug-eluting stents.

(1) Stents Eluting Antiinflammatory Agents

Because of the role of inflammatory cells in restenosis, these cells seemed to be an optimal target in the fight against restenosis. Indeed, corticosteroids have long been shown to reduce the influx of mononuclear cells, to inhibit monocyte and macrophage function, and to influence smooth muscle cell proliferation.\(^14\) Nonetheless, clinical trials have failed to demonstrate any benefit of systemic steroid therapy.\(^15\)

(a) Corticosteroid-Eluting Stents

**Preclinical Data**

The effectiveness of stents coated with steroid agents is unclear. Methylprednisolone (300 mg)–eluting tantalum stents coated with poly(organophosphazene were utilized in a porcine model. Although 96% of the drug was released within 24 hours, a reduction in neointimal proliferation resulted, compared with a severe intimal hyperplasia promoted by the polymer alone.\(^16\) Others did not observe the
antirestenotic effect of stents loaded with 0.8 mg of dexamethasone in a similar model. 17

Clinical Experience
The data utilizing antiinflammatory-eluting stents is limited. The Study of anti-Restenoses with BiodivY’sio Dexamethasone-Eluting stent (STRIDE) was a phase II, multicenter registry conducted in Europe. Stents were immersed on-site in a solution of dexamethasone. Sixty patients with de novo lesions were treated with these dexamethasone-eluting stents. At 6-month follow-up, angiographic binary restenosis (>50% diameter stenosis at follow-up) was 13.3%, and late loss (the difference between the minimal luminal diameter immediately after the procedure and the minimal luminal diameter at follow-up) was 0.45 mm (Ivan De Scheerder, MD, University Hospitals, Leuven, Belgium, unpublished data, 2002). Another registry, the DEXamethasone Loaded stents In small coronary VEssels to prevent Restenosis (DELIVER) study, will enroll 30 patients to test the feasibility of dexamethasone-eluting stents (average dose of 0.27 μg/mm² of stent) for the treatment of small coronary arteries. A dose-finding, multicenter study using the BiodivY’sio stent preloaded with dexamethasone is currently ongoing in Germany. This stent has been approved for clinical use in Europe.

(b) Tranilast-Eluting Stent
Tranilast, N-(3,4-dimethoxycinnamoyl) anthranilic acid, has been shown to inhibit proliferation and migration of vascular smooth muscle cells in experimental models. Systemic use of this agent for prevention of restenosis was tested in a large multicenter trial, but results were disappointing. 18 Initial experiments with the biodegradable Igaki-Tamai stent loaded with 184 μg of tranilast per stent have been initiated, but results are still pending.

(2) Stents Eluting Immunosuppressive Agents
Encouraged by the early experience with ionizing radiation therapy, researchers have proposed sophisticated pharmacological strategies interfering with cell cycle division. 13 Xenobiotic molecules (rapamycin, FK506, cyclosporine, and analogues) and antimetabolites (mycophenolate mofetil) have been utilized.

(a) Sirolimus-Eluting Stents
Sirolimus is a macrolide antibiotic with potent antifungal, immunosuppressive, and antimitotic properties. 19 The drug is produced by cultured Streptomyces hygroscopicus. Rapamune (Wyeth-Ayerst Laboratories) was approved by the US Food and Drug Administration for the prophylaxis of renal transplant rejection in 1999. Shortly after this approval, the first sirolimus-eluting stents were implanted in human coronary arteries. 20

Preclinical Data
The sirolimus-eluting stent is composed of a tubular stainless steel stent, the BX Velocity stent (Cordis), coated with a 5-μm-thick layer of nonerodable polymer blended with sirolimus in a concentration of 140 μg sirolimus/cm² of stent. 9

The release kinetics can be modulated in such a way that both fast-release (<15-day drug release) and slow-release formulations (~28-day drug release) are obtained. Only slow-release formulations were tested in randomized studies and consequently became commercially available. In vivo studies demonstrated that sirolimus levels in whole blood peaked at 1 hour (0.9±0.2 ng/mL) after stent implantation and fell below the lower limit of quantification by 72 hours (0.4 ng/mL). 21

Sirolimus binds to specific cytosolic proteins. The mechanism of action of sirolimus is distinct from other immunosuppressive agents that act solely by inhibiting DNA synthesis. Upregulation of FK506-binding protein 12 (FKBP12) has been observed in human neointimal smooth muscle cells. The sirolimus FKBP complex binds to a specific cell cycle–regulatory protein, the mammalian target of rapamycin (mTOR), and inhibits its activation. The inhibition of mTOR ultimately induces cell-cycle arrest in late G1 phase 13,19 and consequently arrests smooth muscle cell growth.

Suzuki and colleagues 9 tested sirolimus-eluting stents in porcine restenosis models. A similar degree of reendothelialization was observed in both drug-eluting and bare stents. However, both neointimal proliferation and inflammation were markedly reduced in the treatment group. 9 Sirolimus-eluting stents also reduced neointimal proliferation compared with both bare and polymer-coated stents in rabbit iliac arteries. 21

Clinical Data: De Novo Lesion
The first clinical experience with sirolimus-eluting stent, the First-In-Man (FIM) study, was initiated in 1999 and involved 45 patients with native coronary artery disease and angina pectoris. 20,22 Two different formulations of sirolimus-eluting stents were used (slow release, n = 30; fast release, n = 15). Virtual absence of neointimal proliferation was documented by serial intravascular ultrasound and angiography at all time points (4, 6, 12, and 24 months) in both groups. One patient had target vessel thrombosis at 14 months. There was no in-stent restenosis up to 2 years, and the overall major adverse cardiac event rate was 11.1%, including procedural complications. No death occurred after hospital discharge. 23 This pioneer investigation provides unique long-term data on sirolimus-eluting stents (Figure 3) and allays some of the concerns about a potential late “catch-up” of restenosis or late side effects.

The RAndomized study with the sirolimus-eluting Bx VElocity balloon-expandable stent (RAVEL) was the first randomized trial to compare slow-release sirolimus-eluting stents with bare BX Velocity stents (Cordis, a Johnson & Johnson Company) for revascularization of single, de novo lesions in native coronary arteries. 24 The trial included 238 patients at 19 medical centers in Europe and Latin America. The primary end point was in-stent late luminal loss. Patients received clopidogrel or ticlopidine for 2 months. In-stent late loss was significantly lower in the sirolimus stent group (−0.01 mm) than in the standard stent group (0.80 mm, P<0.001). None of the patients in the sirolimus-stent group had binary restenosis, and the incidence of major adverse cardiac events was 5.8% in the sirolimus-stent group after 1 year. Notably, no episodes of stent thrombosis occurred. This study uniquely reported zero percent restenosis after coronary
stenting. The Cypher stent (Cordis, a Johnson & Johnson Company) is currently approved for clinical use in Europe.

Data from the multicenter, randomized, double-blind study of the SIRIUS-coated Bx Velocity stent in the treatment of patients with de novo coronary artery lesions (SIRIUS) have recently been presented (Martin B. Leon, MD, Lenox Hill Hospital, New York, NY, unpublished data, 2002). Patients (n = 1100) with de novo coronary disease were randomized to receive sirolimus-eluting stents or bare BX Velocity stents at 53 US sites. The inclusion criteria were more liberal than the previous studies and allowed the implantation of >1 stent per lesion, which could vary from 15 to 30 mm in length. The primary end point was target vessel failure, which included cardiac death, myocardial infarction, or target vessel revascularization at 9 months’ follow-up. Multiple stents were implanted in 27.4% of the patients (mean of 1.4 stents/patient). In-stent late loss was 0.17 mm, and in-lesion late loss was 0.25 mm. After 9 months, 10.5% of the patients receiving the Cypher stent reached the primary end point of target vessel failure, compared with 19.5% in the control group. In the sirolimus group, in-stent restenosis was 2.0%, and in-lesion restenosis was 9.1%. This large-scale randomized trial confirmed the potent antirestenotic effects of Cypher stents.

In-Stent Restenosis Studies
The In-Stent Restenosis Registry involved 41 patients treated in Brazil (n = 25) and in the Netherlands (n = 16). This was an open-label safety study involving only patients with single-vessel in-stent restenotic lesions. The protocol allowed the implantation of up to 2 Cypher stents. In the Brazilian cohort, all vessels were patent at the time of 12-month follow-up angiography.25 Late loss averaged 0.36 ± 0.46 mm in-stent and 0.16 ± 0.42 mm in-lesion. One of the 25 patients developed in-stent restenosis by 1-year follow-up. There were no deaths, stent thromboses, or repeat revascularizations. The Rotterdam cohort included a more complex group of patients.

In this group, 19% of the patients had previous brachytherapy failure, and 1 heart transplantation patient was treated. There were 2 deaths, 1 late thrombosis, 1 vessel occlusion, and 2 in-lesion restenoses.

Upcoming Studies
The European-Canadian SIRIUS trial (EC-SIRIUS) randomized 350 patients with similar baseline characteristics of the US SIRIUS study. Eight-month angiographic results are expected in 2003. In the United States, the US Food and Drug Administration approved the SECURE (Compassionate Use of Sirolimus-Eluting stents) protocol for patients with in-stent restenosis who have failed other approved therapies, such as radiation therapy and coronary artery bypass surgery. SECURE data will provide unique information on the applicability of the Cypher stent in highly complex situations.

(b) Rapamycin Analogue–Eluting Stents
Everolimus, [40-O-(2-hydroxyethyl)-rapamycin], is also an inhibitor of mTOR. It has been shown to inhibit proliferation of hematopoietic and nonhematopoietic cells. Although the immunosuppressive activity of everolimus is 2- to 3-fold lower than sirolimus in vitro, animal studies have shown a potent antirestenotic effect of everolimus given orally or via a drug-eluting stent.26 The S-Stent (Biosensor) has been impregnated with a blend of everolimus and slowly biodegradable hydroxyacid polylactic acid polymer. Low- (180 μg/stent) and high-dose (360 μg/stent) everolimus-eluting stents were implanted in pig coronary arteries. Percent area stenosis by histomorphometric analysis was 62% in bare stents, 70% in polymer-coated stents, 39% in low-dose everolimus-eluting S-stents, and 38% in high-dose everolimus-eluting S-stents (H. Honda, MD, UCLA School of Medicine, Los Angeles, Calif, unpublished data, 2002).

ABT-578, methyl rapamycin, is another synthetic analogue of sirolimus. Preliminary animal studies have shown significant inhibition of intimal proliferation after stenting. The BiodivYsio stent has been loaded with ABT-578, and clinical studies have been initiated in Australia.

Upcoming Studies
The First Use To Underscore REduction in restenosis with everolimus (FUTURE) study completed the enrollment of 36 patients in July 2002. The FUTURE II study has just started in 3 German sites and will randomize 90 patients with de novo lesions, treated either with eluting or bare stents. A US multicenter randomized study (PREFER) will compare the ABT-578–eluting stent versus standard BiodivYsio stent in 950 patients with de novo coronary lesions (Richard Kuntz, MD, Brigham and Women’s Hospital, Boston, Mass, unpublished data, 2002).

(c) FK506 (Tacrolimus)
Tacrolimus is a hydrophobic immunosuppressive agent that has been used clinically to prevent renal transplant rejection. It binds to the FKBP12 protein, but its mechanism of action differs from sirolimus. Tacrolimus has been shown to inhibit the release of proinflammatory cytokines and activation of T cells. Initial in vitro and in vivo studies have failed to demonstrate the inhibition of smooth muscle cell proliferation with tacrolimus.27
Upcoming Studies
The EndoVascular Investigation Determining the safety of New Tacrolimus-eluting stent grafts (EVIDENT) registry will include 15 patients with saphenous vein graft disease treated with tacrolimus-eluting stent grafts. In the PREliminary Safety Evaluation of Nanoporous Tacrolimus-eluting stent (PRESENT) study, 30 patients with de novo lesions will be treated with nanoporous ceramic-coated stents (Jomed) loaded with tacrolimus.

(d) Mycophenolic Acid–Eluting Stent
Mycophenolic acid (MPA) is the active metabolite of mycophenolate mofetil, an antibiotic derived from cultures of the *Penicillium* species, and has both antiinflammatory and immunosuppressive properties. The Duraflex stent (AvanTec Vascular Devices), coated with a 5-μm layer of polyhydrocarbon polymer loaded with MPA, showed a 40% reduction in neointimal proliferation compared with control in a porcine coronary model (Guy Leclerc, MD, Montreal Heart Institute, Montreal, Canada, personal communication, 2002). The Inhibition with MPA of Coronary restenosis Trial (IMPACT) is a multicenter study that included 150 patients with de novo coronary lesions. Slow-release (45 days) and fast-release (15 days) eluting stents coated with 4.5 μg of MPA/mm² were compared with bare Duraflex stents. Preliminary results suggest no differences in angiographic outcomes between groups, but final data are still pending.

Additional drug-eluting stent technologies will be described in the next part of this article, which will also discuss some methodological and technical aspects of drug-eluting stents.

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References

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