CARDIOLOGY Rounds®

AS PRESENTED IN THE ROUNDS OF THE DIVISION OF CARDIOLOGY, ST. MICHAEL'S HOSPITAL, UNIVERSITY OF TORONTO

# Drug-eluting stents for the treatment of coronary artery disease

## Part 1: Background and trials with paclitaxel

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**The acceptance and widespread clinical application of coronary stents is the most important advance in interventional cardiology since the introduction of balloon angioplasty 20 years ago. This issue and the August/September issue of *Cardiology Rounds* will examine the concerns surrounding the use of coronary stents and the various stent systems that are available. This issue (Part 1) will review the background and rationale for using coronary stents, as well as the results of earlier trials that form the basis for subsequent and ongoing trials.**

The rapid escalation of the use of coronary stents began with the simultaneous publication of the landmark BElgian NEtherlands Stent Study (BENESTENT) and the STent REStenosis Study (STRESS) trials demonstrating that the elective placement of intracoronary stents significantly reduced the incidence of angiographic restenosis in patients with discrete, *de novo* lesions in large target vessels.[1,2] Paradoxically, the BENESTENT and STRESS trials were accepted by clinicians as being positive overall, despite a subacute occlusion rate of 3.7% that was higher than with balloon angioplasty alone, as well as longer hospitalization times and more vascular and bleeding complications. The reasons for the routine clinical implementation of coronary stents include:

- stents provide favourable and predictable acute angiographic results;
- stents improve the safety of angioplasty by successfully treating acute and threatened closure;
- stents improve long-term clinical outcomes by reducing restenosis;
- stents are easy to use;
- the use of stents often decreases total procedure time;
- stents provide favourable angiographic and clinical results in most complex lesion morphologies that are poorly treated using conventional balloon angioplasty techniques (ie, saphenous vein graft lesions, ostial stenosis, eccentric lesions and total occlusions).

The long-term success of coronary stenting procedures is still limited by in-stent restenosis. The angiographic restenosis rate (> 50% diameter stenosis) in stented arteries is 10% to 20% in short lesions and large vessels,[3] however, restenosis occurs in 30% to 60% of patients with diabetes, diffuse lesions, or lesions that occur in small vessels or are located at a bifurcation,[4] with long lesions being at the highest risk.[5] Currently, the only effective treatment for in-stent restenosis is brachytherapy and this still has a target lesion revascularization rate of 11% and a target vessel revascularization rate of 20%.[6]

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The disappointing results of trials employing systemic strategies designed to prevent in-stent restenosis led to an interest in the development of local delivery techniques for the administration of anti-restenotic compounds. The combination of mechanical scaffolding to prevent negative arterial remodelling, and sustained high-dose local drug delivery of an agent that effectively inhibits neointimal hyperplasia offers a powerful method to improve patency.

Although early results of the use of the endovascular stent as a platform for the delivery of pharmacological therapies showed limited success, recently, there has been renewed interest in their use for the prevention of both (sub)acute stent thrombosis and restenosis. Drug delivery can be accomplished by coating metallic stents with controlled-release matrices, or incorporating a pharmacologically active compound into a polymeric stent or a polymer-metal composite stent. Controlled-release matrices are formulated by uniform dispersion or dissolution of the drug of interest in a polymeric preparation. Drug release occurs by means of particle dissolution and diffusion through the base polymer or by matrix breakdown and biodegradation of a hydrolysable (biodegradable) polymer. Stents can also be formulated with a synthetic biodegradable or non-biodegradable polymeric matrix system, or a biological polymer with a dispersed pharmacologic agent. Some general considerations about the choice of agents are important in formulating drug-polymer systems. For example, if nondegradable polymers are to be used for stent coatings, only water-soluble agents should be considered for incorporation because insoluble agents could be entrapped in the polymer. Non-water-soluble agents can be easily incorporated into a biodegradable stent structure since matrix breakdown will release these compounds.

Drug-polymer composites are referred to as monolithic matrices. When nondegradable matrices are utilized, drug delivery is achieved through sustained release by way of particle dissolution and diffusion through the cavitating network of the matrix. Extended drug release is possible through this approach, and formulations have been reported with a release duration from hours to decades. Examples of nonbiodegradable polymers include polyurethane,[7] poly(dimethyl)-siloxane (SIL),[8] and polyethene terephthalate.[9] Biodegradable polymer systems have also been used to formulate drug-delivery matrices. Biodegradable polymer matrices provide sustained delivery of pharmacologic agents both by drug dissolution and by matrix degradation in vivo, leading to the release of entrapped agents. Examples of some of the more widely investigated biodegradable polymers include polylactic-polyglycolic acid,[10-17] high-molecular-weight polyanhydrides,[18-20] pluronics,[21,22] chitosan,[23-26] polycaprolactone,[27,28] polyhydroxybutyrate/valerate copolymer (78:22),[29,30] polyorthoester,[31,32] and polyethyleneoxide/polybutylene terephthalate copolymer (30:70).[33,34] The coating of a pharmaceutic stent with a biodegradable polymer also offers the attractive possibility that the drug-polymer system could disappear after a desired period of drug release.

The potency of the incorporated drug is also of crucial importance in view of the limited space available on the strut structure of the stent. Therefore, many of the conventionally available pharmaceuticals may not be the best available agents. Of the conventional drugs, very potent compounds with a relatively low systemic dose compared to others, offer the best possibilities. In addition, drugs rejected for human use because of systemic side effects may, in fact, be the most suitable candidates for incorporation into pharmaceutic stents.

## Drug-eluting stents to prevent thrombosis

Several candidate drugs for release by coated stents to prevent subacute stent thrombosis have been considered. A stainless steel stent (InFlow stent, InFlow Dynamics AG, Munich, Germany) coated with a polylactic acid (PLA) carrier containing 5% polyethylene glycol-hirudin and 1% prostaglandin $I_2$ ($PGI_2$)-analog (Iloprost) has shown promise both in vitro and in pre-clinical assessment. In vitro analysis demonstrated favourable degradation properties of the carrier and time-release characteristics of the incorporated antithrombotic and platelet inhibiting drug.[35] Analysis of the hirudin- and Iloprost-eluting stents tested during stasis in a human shunt model demonstrated a significant effect on both platelet activation and blood coagulation,[36] and when implanted in sheep coronaries they exhibited a favourable effect on neointimal formation.[37,38]

Another carrier/active agent system that appears promising is a cellulose polymer with passively adsorbed glycoprotein IIb/IIIa receptor antibody.[39-41] Preparation of these devices is relatively simple. GR II stents, no longer commercially available, were supplied with a proprietary cellulose polymer coating. Immersion of these devices into a solution of anti-GP IIb/IIIa antibody caused the coating to swell and passively adsorb the Fab fragment as a function of the concentration of protein and the time of

immersion. The active compound elutes from the stents in an exponential manner, and when studied in vitro, 48% of the bound agent eluted at 12 days.[42,43] When investigated in a rabbit iliac-artery model, antibody to GP IIb/IIIa eluted from cellulose-polymer coated stents significantly reduced platelet aggregation in the stent micro-environment, reduced thrombus formation, improved blood flow and arterial patency rates, and inhibited cyclic blood flow variation.[41]

## Drug-eluting stents to inhibit neointimal hyperplasia

There has been considerable effort engaged in developing a drug-eluting stent to inhibit in-stent restenosis. Early animal studies have shown limited success for the inhibition of neointimal hyperplasia with stents coated with dexamethasone/polylactide/(dl-PLA),[44] dexamethasone/polylactide copolymer (PLA-co-TMC),[44] methylprednisolone/polyorganophosphazene,[45] and angiopeptin/phosphorylcholine.[46] There has been a recent revival of interest in drug-eluting stents with the demonstration of possible benefits from the use of cytostatic and cytotoxic agents.

One of the most intensely studied agents considered for local stent delivery in the prevention of restenosis is paclitaxel (Taxol). Paclitaxel is a potent antiproliferative agent that inhibits the disassembly of microtubules. The stabilized microtubules are dysfunctional, and cell replication is inhibited in the G0/G1 and G2/M phases.[47] Also microtubular stabilization affects cell motility, shape, and intracellular transport. Paclitaxel is highly lipophilic; this enables it to pass easily through cell membranes, resulting in a long-lasting antiproliferative action. The efficacy of paclitaxel-loaded, coated stainless steel stents for reducing in-stent restenosis has been shown in several animal models, including the rat,[48] rabbit,[49] and pig.[50-51]

Based on the promising results of animal studies, clinical evaluation of coronary stents coated with a cytostatic dose of paclitaxel is currently underway. Paclitaxel-eluting stainless steel Cook stents (V-Flex-Plus, Logic PTX, Supra G; Cook Inc., Bloomington, IN, USA), coated with paclitaxel using a proprietary polymer-free technology, have been examined in several clinical trials. The ELUTES (European Evaluation of Paclitaxel Eluting Stent) trial examined the safety, efficacy, and dosing of a paclitaxel-coated stent in patients implanted with paclitaxel-coated V-Flex-Plus stents.[52] The trial divided 192 patients into five groups; four groups received a 16 mm long V-Flex Plus paclitaxel-coated stent at 4 different doses of paclitaxel (0.2 μg/mm$^2$, 0.7 μg/mm$^2$, 1.4 μg/mm$^2$, 2.7 μg/mm$^2$) and the fifth received a non-coated stent as control. All patients had a single, *de novo* lesion in one artery. The primary endpoint of the study was effectiveness, assessed by the percent diameter stenosis and late loss at follow-up, 6 months after implantation. Safety was determined by assessing major adverse cardiac events at 1 and 6 months. The high-dose paclitaxel group showed significant reductions in diameter stenosis (14% vs 34%; $P < 0.01$). Although there was no difference between the treated groups in terms of benefit, a dose-response curve was seen. Late loss was also significantly lower in the high-dose group, compared to controls (0.10 mm vs 0.73 mm, $P < 0.005$), with no difference between treated groups. Only 3% of high-dose patients versus 31% of controls experienced binary in-stent restenosis (> 50% diameter stenosis, $P = 0.055$). There were no significant adverse events at 1 month, with a nearly 100% event-free rate in all arms. At 6 months, event rates were still low among all treated groups, with between 89% to 97% of patients remaining event-free.

Paclitaxel-eluting V-Flex Plus stents have also been shown to be effective for the prevention of recurrent in-stent restenosis. De Scheerder's group from Belgium have reported their results on the implantation of V-Flex Plus eluting stents in patients with in-stent restenosis.[53] In their study, 21 patients who had been treated a minimum of 4 times for recurring in stent restenosis, received a 16 mm Cook V-Flex Plus coronary stent coated with a cytostatic dose of paclitaxel. After 6 months, no patients in the study exhibited restenosis in the portion of the target vessel where the paclitaxel-coated stent was placed.

The double-blind ASPECT (Asian Paclitaxel-Coated Stent Clinical Trial) randomized 177 patients to control or to 1 of 2 paclitaxel-dose groups, high-dose (3.1 μg/mm$^2$) and low-dose (1.3 μg/mm$^2$) delivered using Cook's coated Supra-G stent system.[54] At 6-month follow-up (Figure 1), a significant, dose-dependent reduction in binary restenosis rates was seen in the paclitaxel arms, compared to the control group (high-dose: 3%, low-dose: 12%, control: 27%).

The PATENCY trial has begun, and enrollment of the first 50 patients is complete. The first 50-patient cohort is a safety and feasibility study, and enrollment of the other 1600 patients will begin soon. Of the 1600 patients, 450 will have in-stent restenosis and the remainder will be *de*

*novo* lesions. The PATENCY trial will use the Cook Logic PTX stent that is not approved currently for use in the United States.

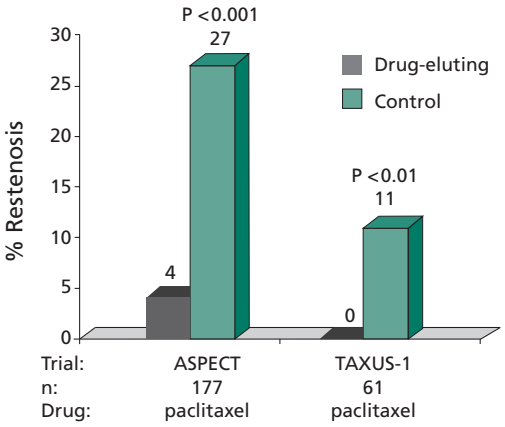
Cook Inc. has partnered with Guidant to develop and distribute a paclitaxel-coated stent. Under the partnering agreement, Guidant will supply the bare stents and catheters, while Cook will coat the stent and mount it on the catheter system. Guidant will also act as the exclusive worldwide distributor of the final product. FDA approval has been obtained to begin the 1000 patient DELIVER trial that will examine the ability of the Cook proprietary stent coating containing paclitaxel on a MULTI-LINK stent platform to inhibit in-stent restenosis.

Boston Scientific (Natick, MA, USA) has initiated several clinical trials to evaluate its proprietary copolymer system containing paclitaxel on two of its stent platforms, the NIR stent (NIRx) and the EXPRESS stent. The paclitaxel stents developed by Guidant/Cook and Boston Scientific are different; Boston Scientific uses a polymer coating to hold and release the drug, while the Cook system involves direct application to the stent without a polymeric coating.

The TAXUS program is a series of studies designed to evaluate the safety of the copolymer carrier system with low-dose formulations of paclitaxel (TAXUS I), and to compare 2 dose formulations of paclitaxel focusing on safety and estimates of efficacy in the reduction of coronary restenosis.

The TAXUS-I study was a prospective, randomized, double-blind, clinical trial designed to evaluate the feasibility and safety of low-dose paclitaxel-eluting stents (NIRx) used for the treatment of *de novo* and restenotic lesions.[55] The coated stents were 7 cell, 15 mm long NIR stents containing 1 μg paclitaxel/mm$^2$ (85 μg/ stent) and uncoated NIR stents served as control. The trial was performed at 3 centres in Germany, and included 31 patients in the experimental arm and 30 in the control arm. The primary endpoint was the incidence of major adverse cardiac events (MACE) at 30 days. Angiographic and IVUS was performed on all patients at 6 months, and clinical follow-up is planned to 5 years. There were no adverse events reported in either group at 30 days. The binary restenosis rate (>50% diameter stenosis) in the bare-stent control group was 11% compared with zero restenosis in the paclitaxel-coated stent group

**Figure 1: Restenosis rates at six months in two randomized trials of drug-eluting stents**




($P = 0.1062$). The angiographic analysis also demonstrated the absence of any edge effect at the proximal and distal edges in both the paclitaxel-eluting and bare-stent control groups. Six-month angiographic binary restenosis rates (>50% diameter stenosis) in 2 randomized clinical trials are compared in Figure 1.

The TAXUS II trial is a 536-patient, randomized, double-blind, multicentre, international study designed to assess safety and efficacy of a slow-release and a moderate-release paclitaxel formulation. The trial is being carried out in 30 European centres. One group of 134 patients was randomized to NIRx and the other 134 patients to uncoated control NIR stents in each of the two cohorts. The primary endpoint of the trial is the reduction of mean percent in-stent net volume obstruction at 6 months, as measured by IVUS. Secondary endpoints are MACE, assessed at 30 days, 6, and 12 months after stent placement and annually to 5 years after the index procedure, target lesion revascularization, target vessel revascularization, and 6-month angiographic findings. Enrollment is complete, and results will soon be available.

TAXUS III is a 30-patient registry study examining the feasibility of the slow-release formulation on a NIRx platform for treatment of in-stent restenosis. Follow-up data at 6 months has been completed in 28 patients. Clinical follow-up showed one non-Q wave myocardial infarction (3.6%) and 5 (18%) clinically driven repeat angioplasties (target lesion revascularization rate). The angiographic restenosis rate was 16% (4/25).

TAXUS IV will enroll more than 1,600 patients and is a randomized, double-blind trial designed to study the safety and efficacy of a moderate-release formulation, using an EXPRESS stent platform, on both de novo lesions and in-stent restenosis.

In conclusion, drug-eluting stents hold promise to prevent thrombosis and inhibit neointimal hyperplasia. Data thus far with the use of paclitaxel are encouraging. In the next issue (Part 2), trials with use of other coating agents such as rapamycin, resten-NG and dexamethasone will be examined.

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