

37. THE BOSTON SCIENTIFIC ANTIPROLIFERATIVE, PACLITAXEL ELUTING STENTS (TAXUS)

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Background and rationale

Restenosis in general, especially in-stent restenosis, is still the major limitation of percutaneous coronary interventions (PCI) and predominantly responsible for major adverse cardiac events (MACE) in follow-up studies and registries [Hoffmann and Mintz 2000]. Since in-stent restenosis is due to cell proliferation, stents coated with antiproliferative drugs promise to be the next revolution in the field of interventional cardiology [Gunn and Cumberland 1999]. The hope is that these drug-coated stents will overcome the problem of restenosis by providing lesion-directed intravascular delivery of drugs that interrupt the molecular cascade leading to in-stent restenosis. These drug-coated stents provide a perfect opportunity for local vascular drug delivery without prolonging the procedure. Potential advantages of drug-coated stents include:

- a) targeted drug delivery to precise area requiring treatment
- b) delivery at the time of implant injury
- c) ongoing delivery through phases of healing
- d) no additional materials or procedures required

Four interactive parameters may contribute to the success of a drug-coated stent in reducing restenosis: stent platform, selected drug(s), drug delivery vehicle or carrier, and the underlying vascular tissue. Stent implantation is associated with endovascular injury followed by a healing response. High degrees of injury appear to translate into more restenosis in the long term presumably because of more robust fibrotic healing responses. Ideally, the selected drug should interrupt multiple steps in the pathway that leads to restenosis, providing an effective anti-restenotic activity. For drug-eluting stents, the delivery vehicle must release the drug into the vessel in a manner that is consistent with the drug's mode of action. The drug and carrier must be compatible and together control drug release kinetics. Finally, the carrier and the drug individually or together have the potential to alter the tissue characteristics in the vessel. The cumulative effects of all these drug-coated

stent parameters should interrupt the cascade associated with the healing response that culminates in restenosis.

The stent platform

The NIRx™ stent

The design of the NIRx™ stent is identical with the well-known stainless steel NIR™ stent (Figure 37.1). The NIRx™ stent is a premounted monorail (single operator exchange) system and combines the mechanical advantages of the NIR™ stent with a drug coating system (see below). Currently, the NIRx™ is available for clinical evaluation premounted on Boston Scientific's Advance catheter system (Figure 37.2). The distal section of the catheter has a dual lumen; the outer lumen is used for balloon inflation and the inner accepts a 0.014 inch guidewire. The Advance system is a monorail style stent delivery system (Figure 37.2). The proximal section is a single lumen stainless steel hypotube with a single luer port for inflation. The tip is tapered to facilitate advancement. The catheter will deliver 15 mm length stents with 3.0 mm and 3.5 mm diameter options. Only in TAXUS-I the stent had to be manually crimped.

Description of eluting coating

The carrier polymer encapsulating the NIR™ Conformer stent (Figure 37.1) is a proprietary formulation and impregnated with the antiproliferative drug paclitaxel (Figures 37.3 and 37.4).

The NIRx™ paclitaxel-coated stent uses a proprietary copolymer system as a carrier. Combining paclitaxel with the carrier system provides controlled release of the drug into the vessel wall. The technical development has included assessment of the effects of copolymer carrier system with and without various dose formulations of paclitaxel at various times in porcine stent implantation models. These studies have identified and refined the safe dose ranges for human trials and have provided insight into how paclitaxel alters the post-implant injury responses. The copolymer carrier system has been developed to provide homogeneous coverage of the stent platform after deployment (Figure 37.3) and deliver reproducible amounts of paclitaxel to the target area in the vessel. The carrier polymer is inert without effects on vascular healing up to 6 months after implantation [Rogers *et al* 2000]. The 15 mm NIRx™ stent holds 85 µg or 171 µg paclitaxel.

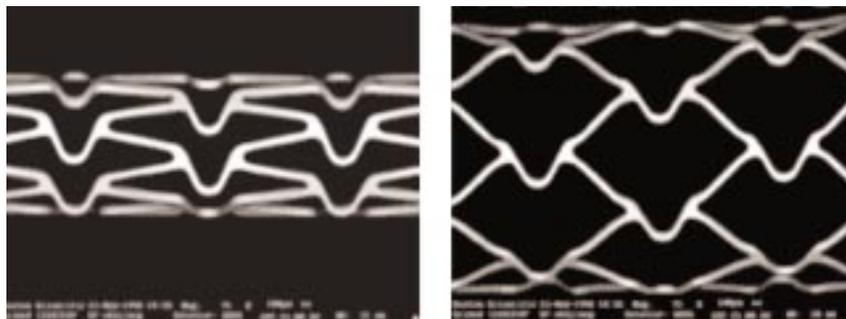


Figure 37.1: The NIR™ Conformer stent: Geometry before (left) and after (right) expansion.

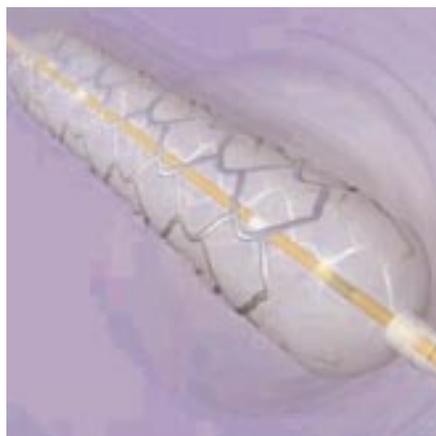


Figure 37.2: The Advance catheter delivery system for the NIR™ and NIRx™ Conformer stent.

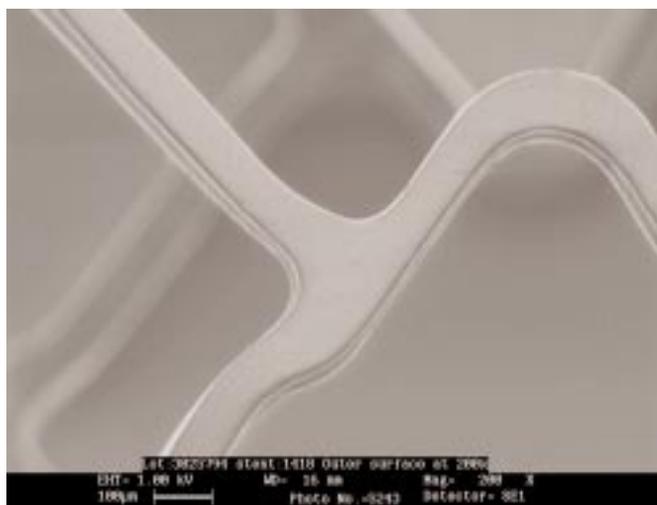


Figure 37.3: Electron microscopic view of the expanded NIRx™ Stent (with coating).

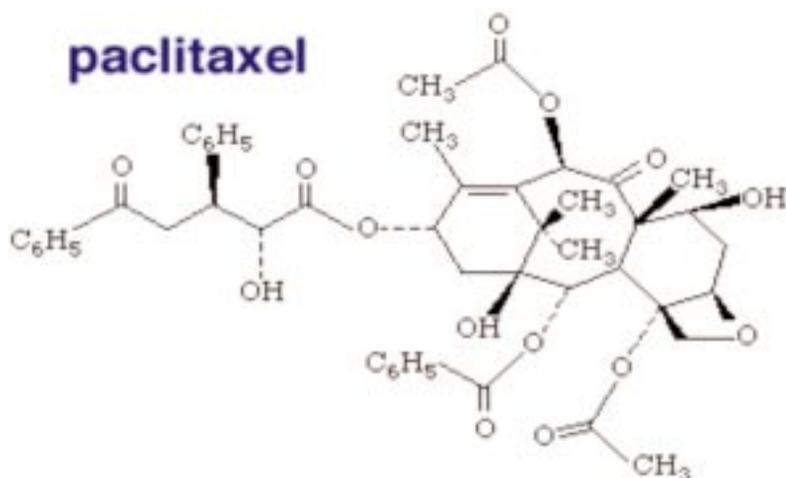


Figure 37.4: Structural formula of paclitaxel. It was originally isolated from the bark of the Pacific Yew. It is a diterpenoid with a characteristic taxane-skeleton of 20 carbon atoms and has a molecular weight of 853.9 Daltons [Herdeg *et al.* 1998].

Molecular action of drug

Paclitaxel is a trace compound found in the bark of the Pacific yew tree in the northwestern USA (*Taxus brevifolia*). Today, synthetically produced Taxol[®] (Figure 37.4) has become a standard medication in oncology.

The antitumor activity of paclitaxel has been documented *in vitro* and *in vivo*. In 1992 the FDA approved it for solid tumors and in 1993 for ovarian cancer [Kristensen *et al.*, 1997]. Paclitaxel specifically inhibits microtubules by inhibiting their depolymerization resulting in an inhibition of cellular replication at the G₀/G₁ and G₁/M phases [Wu *et al.* 2001]. Paclitaxel exerts its pharmacological effects through formation of numerous decentralized and unorganized microtubules [Schiff *et al.* 1979, Rowinsky *et al.* 1995]. Substantial experience has been gathered with paclitaxel as it is the active ingredient in Taxol¹¹ (Bristol Myers Squibb). For chemotherapeutic purposes, it is administered systemically at concentrations greater than 3,000 fold higher than are being used for local stent delivery. Due to its specific inhibition of microtubules, it offers promise in preventing restenosis, stopping inflammation mediators and interrupting cell migration and proliferation [Sollott *et al.* 1995, Axel *et al.* 1997].

Elution profile

Paclitaxel interacts with arterial tissue elements as it moves under the forces of diffusion and convection and can establish substantial partitioning and spatial gradients across the tissue [Creel *et al* 2000].

In a bilateral rabbit iliac model two types of coated stents were investigated: the 7 cell/9 mm length containing 200 μg paclitaxel/stent ($4.09 \mu\text{g}/\text{mm}^2$, fast release, FR) or 50 μg paclitaxel/stent ($1.02 \mu\text{g}/\text{mm}^2$, slow release, SR). At day 1, the FR released approximately 70 μg and the SR appr. 2.4 μg . At the time of writing, the exact dose and release rates of the drug to be tested in humans based on pre-clinical in vivo and in vitro studies, will likely fall between $1.0 \mu\text{g}/\text{mm}^2$ and $2.0 \mu\text{g}/\text{mm}^2$ (loaded drug/stent surface area). For clinical studies, the SR stent will probably be as described above with 7 cell/15 mm containing $1.02 \mu\text{g}/\text{mm}^2$ and therefore a total dose of 85 $\mu\text{g}/\text{stent}$. The FR will probably contain $2.04 \mu\text{g}/\text{mm}^2$ and therefore a total dose of 171 $\mu\text{g}/\text{stent}$. Higher doses delivered in a sustained fashion seem likely to offer the best trade off between safety and efficacy [Rogers *et al* 2000].

Preclinical data

In vitro and in vivo data show that paclitaxel inhibits smooth muscle cell proliferation and migration in a dose-dependent manner in monocultures and co-cultures even in the presence of mitogens. The long-lasting effect after just several minutes' exposure time made this lipophilic substance a promising candidate for local antiproliferative therapy of restenosis [Axel *et al* 1997]. Local delivery of paclitaxel resulted in reduced neointimal stenosis and enlargement in vessel size. Both these effects contributed to a preservation of vessel shape and were likely to be caused by a structural alteration of the cytoskeleton [Herdeg *et al* 2000]. In rat carotid arteries, perivascular slow release of paclitaxel totally inhibited intimal hyperplasia [Signore *et al* 2001]. In a porcine model, paclitaxel-coated coronary stents produced a significant dose-dependent inhibition of neointimal hyperplasia in the LAD 28 days after implantation [Heldman *et al* 2001]. Delivery of paclitaxel into the intrapericardial space significantly reduced vessel narrowing in a balloon-overstretch model. This effect was mediated by a reduction of neointimal mass as well as a positive vascular remodeling [Hou *et al* 2000]. In the rabbit, neointimal hyperplasia is abolished for months after stent implantation, long after completion of drug delivery and polymer degradation [Drachman *et al* 2001].

Clinical data

The goals in the first human use feasibility studies in Europe are divided into two stages: first to evaluate safety of the triblock copolymer carrier system with low dose formulations of paclitaxel (TAXUS I). The second stage is an evaluation of two dose formulations of paclitaxel focusing on safety and estimates of efficacy for pivotal studies (TAXUS II–IV).

TAXUS-I

Purpose of TAXUS-I was to evaluate safety & feasibility of low-dose paclitaxel in the treatment of de novo and restenotic lesions in a prospective, controlled, randomized and double-blind study. The coated stents tested were seven cells/15 mm length (either 3.0 or 3.5 mm diameter) containing 1 µg paclitaxel/mm² (85 µg/stent). The corresponding uncoated NIRTM stents served as control. Inclusion criteria were lesions ≥ 50% and ≤ 99% and ≤ 12 mm in length with a reference vessel diameter of ≥ 3.0 and ≤ 3.5 mm (visual estimate). Patients with a LV-EF < 30%, an MI within the past 72 hours, in-stent restenosis and patients with another planned coronary intervention within 90 days after study procedure were excluded. Post-procedure, 75 mg q.d. clopidogrel or 250 mg b.i.d. ticlopidine in addition to ASA was prescribed for 6 months. IVUS was part of the protocol in all patients at procedure and at 6 months. Clinical follow-up is planned at 12 months and up to 5 years. Enrolment into TAXUS-I is now complete. Sixty-one patients have been included at three German sites with 31 active and 30 controls (40 in Siegburg, 13 in Munich 8 and in Trier). Data for 30-day MACE (still blinded) is summarized in Table 37.1. The 6-month data will be available by November 2001.

Upcoming clinical trials

With the NIRxTM stent, several more studies have been initiated or are being planned:

TAXUS II

The primary objective of this study is to evaluate the safety and performance of the NIRxTM paclitaxel-coated stent compared with the uncoated NIRTM stent (PI: Antonio Colombo, Milan, Italy). Secondary objectives include

Table 37.1 TAXUS-I study: MACE after 30 days (Grube, Silber Hauptmann)

Event	Combined active and control arms
Death	0
Q-wave myocardial infarction	0
Target vessel revascularization	0
Stent thrombosis	0
Total	0

evaluation of MACE. In this multicenter, prospective, randomized and controlled study 532 patients should be enrolled in approximately 30 European centres. (133 patients randomized to NIRxTM and 133 to uncoated NIRTM control stent in each of the two cohorts = 4 × 133). In cohort 1, the slow-release formulation NIRxTM will be studied. If the safety profile is acceptable, the moderate-release formulation NIRxTM will be studied in cohort 2. All patients are to return for clinical follow-up 1 month and 6 months after stent placement. Telephone interviews are scheduled annually for 5 years. Angiography and intravascular ultrasound (IVUS) are required for all patients. The study is considered complete with regard to the primary endpoint after all patients have completed the 12-month follow-up.

Primary endpoint is the reduction of mean percent in-stent net volume obstruction at 6 months as measured by IVUS. Secondary endpoints are MACE as assessed 30 days, 6 and 12 months after stent placement and annually for 4 more years (i.e. 5 years after stent placement) and target lesion revascularization (TLR) as well as target vessel revascularization (TVR). Binary angiographic restenosis after 6 months is also considered a secondary endpoint. Inclusion criteria are similar to TAXUS-I.

TAXUS-III will investigate patients with in-stent restenosis. Finally TAXUS IV will be the pivotal study focusing on the paclitaxel eluting EXPRESS stent.

Future aspects

The TAXUS studies are designed to explore safety and utility of the Boston Scientific paclitaxel eluting stent. These studies will address the hypothesis that low levels of paclitaxel can blunt the initial response to injury and therefore prevent restenosis while still allowing vascular healing with endothelialization. Antiproliferative stents have clear advantages over radiation therapy: there is

Table 37.2 Brachytherapy vs. antiproliferative stents: similarities regarding smooth muscle cell (SMC) inhibition, reduction of restenosis and differences of low dose effects

	Brachytherapy	Antiproliferative stents
SMC inhibition	++	++
Restenosis reduction	+ (ISR)	+ (de novo)
Late thrombosis	+	+
Effects of low dose	Negative	None
Easy access	–	+

no low-dose stimulation in injured coronary segments [Serruys *et al*, 2001] and — of course — handling is much easier (Table 37.2). Long-term results of the paclitaxel stents according to various dosages [Rogers *et al*, 2000] and the experience with other antiproliferative stents [Sousa *et al*, 2001] will define the ultimate role of antiproliferative stents in interventional cardiology.

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