Paclitaxel-Eluting Stents: Are They All Equal? An Analysis of Six Randomized Controlled Trials in De Novo Lesions of 3,319 Patients

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In Germany, four different drug eluting stents (DES) systems are currently commercially available. Whereas sirolimus has been clinically tested in only a single type of stent with a single type of coating in only a single dose, paclitaxel has been tested on various stent designs, in various dose densities, and in various relase formulations with or without a polymer carrier. Therefore, the question arises: are all paclitaxel stents equally safe and effective? Six clinical randomized trials investigated the safety and efficacy of paclitaxel-eluting stents in patients with de-novo lesions: TAXUS-I (61 pats), TAXUS-II (536 pats), ASPECT (177 pats), ELUTES (190 pats), DELIVER-I (1041 pats) and TAXUS-IV (1314 pats). In the TAXUS-series, paclitaxel released from the stent was controlled by the Translute™ polymer. In the other studies, however, no polymer carrier was used. In TAXUS-I, II & IV, the dose density of 1 $\mu g/mm^2$ significantly reduced angiographic parameters of restenosis and improved clinical outcomes. In ASPECT and ELUTES there was a dose-dependent effect on angiographic parameters of restenosis with the best results for a paclitaxel dose density of apprimately 3.0 $\mu g/mm^2$. Clinical outcomes at 6 and 12 months, however, were not improved in these studies without coating. The studies unanimously show that the paclitaxel-eluting stents are safe, if clopidogrel is added to ASA for 3 to 6 months. The safety of paclitaxel-eluting stents is independent of the stent design, the dose density and the presence or absence of a polymer carrier system. For paclitaxel-eluting stents using a polymer carrier, the dose density of 1 $\mu g/mm^2$ is highly effective, whereas for paclitaxel-eluting stents without a polymer carrier, the minimal effective dose density is much higher (3 $\mu g/mm^2$). Despite their improvement of angiographic parameters, paclitaxel-eluting stents without a polymer carrier did not demonstrate a positive effect on clinical outcome. In contrast, polymer-based paclitaxel elution produced significant clinical benefit. (J Interven Cardiol 2003;16:485–490)

Introduction

Since their clinical introduction in 2002,[1] drug-eluting stents (DES) have become widely accepted for the majority of coronary lesions in patients with stable angina[2–11]—and are even used in acute coronary syndromes.[12] DES are considered as first-line therapy for de novo lesions. For in-stent restenosis, however, brachytherapy is still the only evidence-based intervention, since no randomized, controlled trials comparing DES to either bare stents or brachytherapy have yet been presented.[13–15]

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In Germany, four different DES systems are commercially available: the sirolimus (rapamycin)-eluting Cypher™-stent (based on the BX™ stent, J&J/Cordis), the paclitaxel-eluting TAXUS™ stent (based on the Express™ stent, Boston-Scientific), the paclitaxel-eluting Logic™ PTx™ stent (based on the V-Flex Plus™ stent, Cook), and the dexamethasone-eluting Dexamet™ stent (0.5 $\mu g/mm^2$, based on the phosphorylcholine stent, BiodivYsio/Biocompatible/Abott). Whereby no randomized clinical trials exist for dexamethasone, which is regarded as an anti-inflammatory drug, the cytostatic drugs sirolimus and paclitaxel have been investigated in various randomized, controlled trials. Sirolimus has been clinically tested on only a single type of stent (BX™, Cordis) with a single type of coating and a single type of release formulation (2 polymer layers: basecoat +

topcoat) in predominantly a single dose (1.4 μg/mm^2, RAVEL[1] and SIRIUS-studies). In contrast, paclitaxel has been investigated on various stent designs, such as on the NIR™ Conformer stent (Medinol/Boston Scientific), the Express™ stent (Boston Scientific), the V-Flex Plus™ and Supra-G™ stents (Cook) and on the Multi-Link Penta™ stent (Guidant). Paclitaxel has furthermore been tested in various dose densities (from 0.2 to 3.1 μg/mm^2). In addition, the release of paclitaxel was controlled by a polymer carrier (Translute™, Boston Scientific) in various release formulations (slow and moderate release) or released without a polymer carrier (Cook, Guidant). The question therefore arises: are all paclitaxel stents equally safe and effective?

Background

Molecular Action of Paclitaxel. Paclitaxel is a trace compound found in the bark of the pacific yew tree in the northwestern America (*Taxus brevifolia*). Today, synthetically produced Taxol® has become a standard medication in oncology. Paclitaxel specifically inhibits microtubules by inhibiting their depolymerization resulting in an inhibition of cellular replication at the G0/G1 and G1/M phases.[16] Paclitaxel exerts its pharmacological effects through formation of numerous decentralized and unorganized microtubules,[17,18] stopping inflammation mediators and interrupting cell migration and proliferation.[19–21] For chemotherapeutic purposes, it is administered systemically at concentrations greater than 3,000-fold higher than are being used for local stent delivery.[22] The distribution of paclitaxel in the arterial wall has been investigated thoroughly.[23–27]

The Stent Platforms

The Boston Scientific Studies. The stent platform used in TAXUS I, II (de novo lesions) and TAXUS-III (in-stent restenosis) was the NIR™ Conformer stent[28]; in TAXUS-IV and later trials, it is the Express™ Stent[29] (Table 1).

Elution profile. The copolymer carrier system of the TAXUS stent was developed to provide homogeneous coverage of the stent platform after deployment 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. The Translute™ polymer provides controlled biphasic release, with an initial burst of paclitaxel release in the first two days followed by lower-level release sustained through 10 days. Although the slow release (SR) and moderate release (MR) formulations carry the same total loaded dose of 1.0 μg/mm^2, the MR is characterized by an 8-fold higher 10-day release.

The Cook Studies. The Supra-G Stent was used as the platform in the ASPECT study (Table 1[30]). It is a stainless-steel slotted tube design with high radial strength, low recoil, and a large surface area. The diameters of the stents used were 2.5, 3.0, and 3.5 mm in 15 mm length. In ELUTES, the V-Flex Plus Stent was used as the platform for the Logic™ PTx™ stent. It is also a stainless-steel slotted tube design with high radial strength and low recoil. The stent diameters used were 3.0 and 3.5 mm in 16 mm length.

In contrast to the Boston Scientific approach, the stents used in the Cook and Guidant studies had no polymer as a carrier—the paclitaxel was directly applied to the abluminal surface of the stents using a proprietary process. In the ASPECT study, the total amount of paclitaxel in the 1.3 μg/mm^2 stents was 54–60 μg and in the 3.1 μg/mm^2 stents 130–146 μg.[30]

The Guidant Studies. The ACHIEVE™ paclitaxel-eluting stent was a Guidant Multi-Link Penta™ coated with Cook's paclitaxel coating. Under the terms of its agreement with Cook, Guidant would manufacture bare-metal stents, ship those stents to Cook for coating, who would then ship the product back

Table 1. Comparison of Stent Platforms, Coating Characteristics and Dose Densities of Paclitaxel-eluting Stents Used in Clinical Trials

	Boston Scientific				Cook		Guidant/Cook
	TAXUS-I	TAXUS-II	TAXUS-III	TAXUS-IV	ASPECT	ELUTES	DELIVER I+II
Stent platform	NIR™	NIR™	NIR™	Express™	Supra G™	VflexPlus™	Multi-Link Penta™
Coating	Translute™	Translute™	Translute™	Translute™	proprietary	proprietary	proprietary
Polymer carrier	Yes	Yes	Yes	Yes	No	No	No
Dose density (μg/mm^2)	1.0	1.0	1.0	1.0	1.3/3.1	0.2/0.7, 1.4/2.7	3.0

to Guidant for marketing. In the DELIVER trials, the ACHIEVE™ stent was coated with 3.0 μg/mm^2 paclitaxel (Table 1).

The Trials

The Boston Scientific Trials. TAXUS I evaluated the safety and feasibility of using the slow-release formulation TAXUS™ stent (TAXUS-SR) in the treatment of de novo coronary lesions.[31,32] TAXUS I was a randomized, double-blinded, controlled trial comparing the safety and feasibility of the slow-release TAXUS NIRx™ stent with the uncoated NIR™ Conformer stent.

This study enrolled a total of 61 subjects at three sites in Germany (Siegburg, Munich, and Trier; Table 2). Inclusion criteria were: lesion lengths $\leq$12 mm, diameter stenosis between 50% and 99%, and vessel diameter between 3.0 and 3.5 mm.[31] Clinical evaluation was conducted 1, 6, and 12 months after stent implantation; annual follow-up will be continued until 5 years post implantation.

Mean patient age (control vs TAXUS) was 63.8 $\pm$ 7.8 versus 66 $\pm$ 6.8 year (83% vs 94% male) with 13% versus 23% diabetic patients. The 6-month quantitative angiographic indices of minimum lumen diameter, percent diameter stenosis, late lumen loss, and loss index were significantly improved in the TAXUS group compared with the control group (Table 2[31]). Binary restenosis was 0% in the TAXUS group and 10% in the control group (P = 0.11) Angiographic analysis of the vessel 5 mm proximal and distal to the stent showed no statistically significant difference in percent diameter stenosis at the edges between TAXUS-treated and control patients.

At 6 months, the MACE rate was 0% for the TAXUS group compared with 7% in the control group. Due to the small number of patients, this difference was not statistically significant (Table 3). The two MACE in the control group were target lesions revascularizations (TLR) due to diffuse in-stent restenosis. One year after stent implantation, MACE rates were 3% in the TAXUS group and 10% in the control group (Table 3). The single MACE in the TAXUS group was due to target vessel revascularization in a lesion remote from the target lesion. MACE in the control group was attributed to four target vessel revascularizations in three patients–three percutaneous target lesion re-interventions and one coronary artery bypass grafting that included the target lesion. No stent thromboses were reported at any time during the first year after implantation in either treatment group.

After 2 years, angiographic results in TAXUS stents were still impressive.[33] As compared to 6 months, IVUS-determined neointimal hyperplasia was not statistically different after 2 years (8.3 vs 9.7 mm^3). The 2-year MACE rates in both groups were identical to the 1-year MACE rates (Table 3) demonstrating sustained clinical advantage of the TAXUS stents.

TAXUS II trial was a randomized, double-blind, multicenter trial comparing the safety and efficacy of the TAXUS slow-release (TAXUS-SR) and moderate-release (TAXUS-MR) stents with uncoated control stents (Tables 1–3[34]). Two sequential cohorts were randomized 1:1 to either the TAXUS stent (SR or MR) or uncoated control stent. The primary endpoint was percent in-stent net volume obstruction measured by intravascular ultrasound.

A total of 536 patients were enrolled into two consecutive but independent cohorts: Cohort 1 consisted

Table 2. Key Characteristics of Randomized, Controlled Trials Investigating Paclitaxel-eluting Stents in Patients with de novo Lesions

	TAXUS-I	TAXUS-II	TAXUS-IV	ASPECT‡	ELUTES‡	DELIVER-I
Primary endpoint	Clinical	IVUS	Clinical	Angiographic	Angiographic	Clinical
Release formula	SR	SR/MR	SR	n/a	n/a	n/a
Patients (number)	31/30	266/270	662/652	60/59	37/38	522/519
Lesion length (mm)	10.7/11.9	10.6/10.2/10.6	13.4/13.4	10.9/10.5	11.1/10.9	11.7/11.1
Ref. vessel (mm)	2.99/2.94	2.8/2.7/2.8	2.75/2.75	2.94/2.88	2.95/2.99	2.85/2.77
Late lumen loss (mm)	0.36/0.71*	0.3/0.3/0.78*	0.23/0.61*	0.29/1.04*	0.11/0.73*	0.81/0.98*

‡Only the highest of the tested dosages are listed (for dosage see Table 1); SR: slow release, MR: moderate release; n/a: not applicable.
In the numbers of patients the latter number represents the control (bare stent) group. The listed measurements are mean values for their groups with the latter number representing the control (bare stent) group.
In TAXUS-II the first two numbers reflect the results for SR and MR respectively, the latter number represents the control (bare stent) group.
*Statistically significant (P < 0.05) as compared to the bare stent.

Table 3. Clinical Outcome (MACE) in Randomized, Controlled Trials after Paclitaxel-eluting Stents for de novo Lesions

MACE	TAXUS-I	TAXUS-II	TAXUS-IV	ASPECT‡	ELUTES‡	DELIVER-I
MACE at 6 months (%)						
Control	7	19.5/20.0		4/10	13	
Paclitaxel	0	8.5/7.8*		4/33	11	
MACE at 9 months (%)						
Control			15.0			13.3
Paclitaxel			8.5*			10.3
MACE at 12 months (%)						
Control	10	22.0/21.4		10/10	18	
Paclitaxel	3	10.9/9.9*		10/42	13	

‡Only the highest of the tested dosages are listed (for dosage see Table 1).
In TAXUS-II the two number for MACE in the paclitaxel groups reflect the results for SR and MR respectively.
In ASPECT, the first number depicts the MACE for ASS+clopidogrel/ticlopidine, the second number for ASS + cilostazol.
*Statistically significant positive effects ($P < 0.05$) as compared to the bare stent.

of patients randomized to the TAXUS-SR stent (n = 131) or control stent (n = 136). Cohort 1 was enrolled from patients at 28 centers in 12 countries including European nations, Canada, and Australia. After review of Cohort I 30-day safety data by a safety data monitoring board, enrollment of Cohort II began. Cohort II randomized patients to the TAXUS-MR stent (n = 135) or uncoated control stent (n = 134). Angiographic inclusion criteria were: diameter stenosis between 50% and 99%, lesion length ≤12 mm in a vessel between 3.0 and 3.5 mm in diameter.

Mean patient age (control vs TAXUS-SR/MR) was 59.8 ± 9.7 versus 61.5 ± 10.5/59.3 ± 10.5 year (78% vs 70/76% male) with 15% versus 11/17% diabetic patients. At 6 months, all quantitative angiographic indices were significantly improved in the TAXUS-SR and TAXUS-MR groups compared with the control group: The binary restenosis rate in the stented segment was significantly lower in the TAXUS-SR (5.5%; P = 0.0001) and TAXUS-MR (8.6%; P = 0.001) groups compared with the control group (22%). Additionally, binary restenosis in the analysis segment, which includes the proximal and distal edges, was significantly lower for TAXUS-SR (2.3%; P = 0.0001) and TAXUS-MR (4.7%; P = 0.0001) groups as compared with the control group (19%). In addition, IVUS showed no significant difference in late-acquired incomplete stent apposition between the two groups. No clinical events were attributed to aneurysm or incomplete stent apposition.[34]

MACE rates at 6 months were significantly lower in the TAXUS-SR (8.5%; P = 0.0035) and TAXUS-MR (7.8%; P = 0.0019) groups than in the control group (19.8%, Table 3). This reduction was predominantly due to reductions in target vessel revascularizations. Specifically, the target lesion revascularization rate was significantly lower in the TAXUS-SR (4.6%; P = 0.008) and TAXUS-MR (3.1%; P = 0.001) groups than in the control group (13.3%). Only one of the 10 target lesion revascularizations in the TAXUS-treated patients was performed for restenosis occurring within the study stent segment. At 12 months, the MACE rates in the TAXUS groups (SR: 10.9% and MR: 9.9%) continued to be significantly lower than in the control group (21.7%; Table 3). This difference was largely attributable to significantly lower target lesion revascularization rates in the TAXUS groups (SR: 4.7% and MR: 3.8%) compared with the control group (14.4%).[34]

TAXUS-IV was recently presented.[35] It is the USA pivotal study (73 sites, 1314 patients) with 9 months' TVR as the primary endpoint. Main inclusion criteria were de-novo lesions in a native coronary artery with a reference vessel diameter of 2.5–3.75 mm and a lesion length of 10–28 mm. Mean patient age was 62.8 ± 11.3 years (72% male) with 24% diabetic patients. The primary endpoint was reached and the results are listed in tables 2 and 3.

The Cook Trials. ASPECT was a three-arm, randomized, double-blind, controlled, Asian study (three sites) with the Supra-G™ stent.[30] The mean patient age was 60 ± 10 year (76% male) with 20% diabetic and 40% multivessel disease patients. In contrast to the other studies, patients not only received clopidogrel or ticopidine (in addition to ASA), they were allowed to get cilostazol instead (37 patients). Two doses were investigated: 1.3 and 3.1 μg paclitaxel/mm^2.[30]

In the higher-dose group, the reduction of binary restenosis from 27% to 4% was significant ($P < 0.001$).[30] Binary restenosis rate for the lower dose was 12%.

Although restenosis was significantly reduced, even the higher dose of paclitaxel did not result in an improved clinical outcome at 6 months and 1 year (Table 3). If cilostazol was used instead of clopidogrel/ticlopidine, clinical outcome with the DES was even worse (Table 3).

ELUTES was a European five-arm study (nine sites) with the V-Flex plus™ stent.[36] A total of 190 patients were enrolled: the mean patient age was 60 ± 11 years (82% male) with 16% diabetic and 43% multi-vessel disease patients. In contrast to ASPECT, all patients received clopidogrel and ASA (for three months). Four dose densities were investigated: 0.2, 0.7, 1.4, and 2.7 μg paclitaxel/mm^2.[36] The reduction of binary restenosis in the highest dose group (2.7 μg) from 20.6% to 3.1% was significant ($P < 0.001$).[36] Binary restenosis rates for the 0.2, 0.7, and 1.4 μg were 20.0%, 11.8%, and 13.5%, respectively, and not statistically different from the control rate.

Clinical outcome in ELUTES as determined by MACE showed the same pattern as in ASPECT: no significant improvement even after 1 year (Table 3).

PATENCY was originally a US pivotal clinical trial with the Logic™ PTx™ stent holding a dose density of 2.0 μg/mm^2 paclitaxel (total loaded dose of 60 μg). Patients with de novo lesions from 2.7 to 4.0 mm were enrolled; 24% were diabetics.[37] Due to its poor efficacy with a 38% restenosis rate in the Logic™ PTx arm as compared to 35% in the Logic™ control arm, the study was prematurely terminated. There were no safety-identified concerns after 9 months.

The Guidant Trials. DELIVER-I was a prospective, randomized, single-blinded, parallel-group (two-arm), multicenter clinical trial in the United States designed to show a 40% reduction in target vessel failure (TVF) at 9 months.[38] Inclusion criteria were de-novo lesions $\leq$25 mm in length in vessels $\geq$2.5 mm and $\leq$4.0 mm in diameter. Stent sizes were 2.5 mm—4.0 mm in 15 mm—28 mm lengths (8 and 13 mm stents were solely for bail-out). A total of 1,041 patients were enrolled (Table 2). The primary endpoint TVF was reduced from 14.5% to 11.9%, but this did not reach statistical significance ($P = 0.128$). Accordingly, the reduction in the angiographic restenosis rate, from 22.4% in the control group to 16.7% in the ACHIEVE group as well as the reduction in MACE (Table 3) were not statistically significant ($P = 0.149$ and $P = 0.147$). Also the trend for a decrease in target vessel revascularization from 10% to 7% was not significant.

Conclusions

Together, these studies unanimously show that paclitaxel-eluting stents are safe, if clopidogrel is added to ASA for 3–6 months. Due to their antiproliferative effects, all drug-eluting stents need prolonged antiplatelet therapy, as is the case after brachytherapy.[15,39] The safety of paclitaxel-eluting stents is independent of the stent design, the dose density and the presence or absence of a polymer carrier system. For paclitaxel-eluting stents using a polymer carrier, the dose density of 1 μg/mm^2 is highly effective, whereas for paclitaxel-eluting stents without a polymer carrier, the minimal effective dose density is 3 μg/mm^2. Despite their significant improvement of angiographic parameters, paclitaxel-eluting stents without a polymer carrier were not able to demonstrate a positive effect on clinical outcome in patients with de novo lesions. In contrast, 1-year MACE rates for TAXUS SR and MR stents in TAXUS-II are significantly lower than control rates. Most importantly, the reduction in MACE is exclusively due to fewer revascularization procedures on the target lesion. In addition, 2-year MACE in TAXUS I is identical to 1-year MACE, demonstrating sustained clinical advantage of the TAXUS stents. The safety and clinical efficacy of the TAXUS-stent has been recently confirmed by the TAXUS-IV trial.

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