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The Effect of Variable Dose and Release Kinetics on Neointimal Hyperplasia Using a Novel Paclitaxel-Eluting Stent Platform

The Paclitaxel In-Stent Controlled Elution Study (PISCES)

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OBJECTIVES The aim of this study was to evaluate the effect of variable dose and release kinetics of paclitaxel on neointimal hyperplasia.

BACKGROUND Conventional paclitaxel-eluting stents use a durable polymer coating as a vehicle for drug delivery. The Conor stent (Conor Medsystems, Menlo Park, California) with intra-strut wells and erodable polymer is specifically designed for drug delivery with programmable pharmacokinetics.

METHODS Two hundred and forty-four patients with single vessel disease received either a bare metal Conor stent (n = 53) or one of six different release formulations that varied in dose (10 or 30 μg) and elution release kinetics (first order, zero order), direction (abluminal, luminal), and duration (5, 10, and 30 days). End points at six months (bare stent group) and at four months (eluting stent groups) were angiographic late loss and neointimal tissue volume by intravascular ultrasound and the rate of major adverse cardiac events (MACE).

RESULTS The lowest in-stent late loss (0.38 mm, $p < 0.01$, and 0.30 mm, $p < 0.01$) and volume obstruction (8%, $p < 0.01$, and 5%, $p < 0.01$) were observed with the 10-μg and 30-μg doses in the 30-day release groups respectively, whereas the highest in-stent late loss (0.88 mm), volume obstruction (26%), and restenosis rate (11.6%) were observed in the bare stent group. The overall MACE rate of the eluting stent group was 8.6%: death 0.5%, myocardial infarction 2.7%, and target lesion revascularization (TLR) 5.3%. Sub-acute thrombosis was 0.5%. The TLR rates in the two 30-day release groups were 0% and 3.4%.

CONCLUSIONS This novel eluting stent platform, using an erodable polymer with complete elution of low doses of paclitaxel, is safe. The inhibition of the in-stent neointimal hyperplasia was best in the long release groups. (J Am Coll Cardiol 2005;46:253–60) © 2005 by the American College of Cardiology Foundation

Drug-eluting stents (DES) have recently been introduced to clinical practice and have revolutionized the treatment of coronary artery disease. Several randomized clinical studies have demonstrated significant reduction of restenosis and revascularization rates, into the single digits, compared with bare stents (1–4).

Each DES comprises three components: the stent platform, the active pharmacologic compound, and a drug carrier vehicle, usually a polymer, that controls drug elution. Conventional research for development of new and more effective DES has focused on the use of new drugs and advanced biocompatible polymers coated on stent struts. This approach has limitations, including limited control of kinetic profiles and drug-loading capacity.

A novel metallic stent has been engineered specifically as a coronary drug delivery system. It is designed to permit precise and programmable control over spatial and temporal release profiles and to enhance the drug-loading capacity (5).

The present study evaluates this new stent platform without drug and with six different pharmacokinetic release formulations of paclitaxel. These formulations have previously been investigated for their safety and efficacy in animal models (6). The objective of the Paclitaxel In-Stent Controlled Elution Study (PISCES) trial is to compare the safety and performance of different doses and release rates from the Conor paclitaxel-eluting stent for reducing clinical events and angiographic late loss at four months when used in native coronary vessels.

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Abbreviations and Acronyms

DES	= drug-eluting stent(s)
IVUS	= intravascular ultrasound
LV	= lumen volume
MACE	= major adverse cardiac events
MI	= myocardial infarction
MLD	= minimal luminal diameter
PISCES	= Paclitaxel In-Stent Controlled Elution Study
QCA	= quantitative coronary angiography
SV	= stroke volume
TLR	= target lesion revascularization
TVR	= target vessel revascularization

METHODS

Study design. The PISCES trial was preceded by the registry phase of the bare Conor stent so as to establish safety and for use as a historical control. Angiographic and intravascular ultrasound (IVUS) follow-up was planned at six months in the bare stent registry. Fifty-three patients were included in this cohort.

The PISCES trial was a prospective, multi-center, sequentially enrolled, non-randomized, open-label trial in which the patient data collected from six release formulations were compared with one another and to the historical bare stent cohort.

One hundred and ninety-one subjects from the ten participating sites were enrolled in the PISCES trial and received a paclitaxel-eluting stent with one of the six release formulations. At least one study stent was implanted in each subject. When additional stents were required for treatment of edge dissection, stents from the same formulation type were used.

Clinical follow-up was conducted at one and four months after the index procedure. Quantitative angiography and IVUS were performed at four months. Provisional angiographic and IVUS follow-up is planned at 12 months in the dose treatment groups showing efficacy.

End points. The safety end point of the study is a composite of major adverse cardiac events (MACE), defined as death, Q-wave or non–Q-wave myocardial infarction (MI), and target lesion revascularization (TLR; coronary artery bypass grafting or percutaneous coronary intervention) at four months. All deaths were considered cardiac unless they were unequivocally documented to be non-cardiac. Myocardial infarction was diagnosed by a rise in the creatine kinase level to more than twice the upper normal limit with an increased creatine kinase-MB accompanied by new abnormal Q-waves in the surface electrocardiogram (Q-wave MI) or not (non–Q-wave MI). Target lesion revascularization was defined as revascularization of the stented and the peri-stent segments (5 mm proximal and distal). Target vessel revascularization (TVR) was defined as revascularization due to narrowing (>50% diameter stenosis) of any portion of the target vessel outside the peri-stent segment, but was not included as an event in the MACE rate. Both TLR and TVR are reported as actual rates without adjudication for clinical indication.

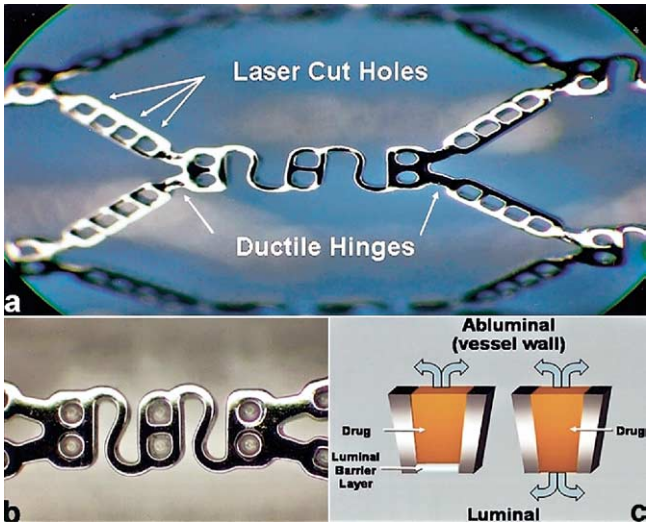

Figure 1. Single cell of the Conor stent showing the intra-strut wells **(a)** filled with erodable polymer **(b)**. The ductile hinge allows full deployment of the stent without deformation of the wells containing the drug. The release of the drug **(c)** can be either uni-directional toward the vessel wall (abluminal) or bidirectional toward the lumen of the vessel (luminal) and the vessel wall.

The efficacy end points included the in-stent and peri-stent angiographic late loss and binary restenosis rate as well as percent volume obstruction of the stent and neointimal hyperplasia of the stented and peri-stent segments, as determined by quantitative IVUS.

Patient selection. Subjects were eligible for the study if they were 18 to 80 years of age, had single de novo lesions with a reference diameter of 2.5 to 3.5 mm and a lesion length that could be covered by a single 17-mm stent, and if they had stable or unstable angina pectoris or documented silent ischemia.

Subjects were excluded from the study if they had an acute MI 72 h before the procedure, an ejection fraction <30%, stroke/gastro-intestinal bleeding within six months, severe hepatic disease or renal insufficiency with a serum creatinine level >2.5 mg/dl, or known intolerance or contraindication to aspirin and/or clopidogrel. Further angioplasty exclusion criteria included total occlusions (Thrombolysis In Myocardial Infarction flow grade 0), bifurcational (adjacent branch >2 mm) and ostial lesions, left main disease, and tortuous target vessel. Written informed consent was obtained from all patients.

The inclusion and exclusion criteria for both the bare metal registry phase and the PISCES trial were identical.

Study device. Figure 1 shows the balloon-expandable, 316L stainless steel Conor stent. The unique design features include struts with holes along their length, linked to flexible sinusoidal bridges by specially contoured features called ductile hinges. Unlike conventional stents consisting of repeating units wherein the entire structure is deformed by expansion forces placed on it, the Conor stent differs in

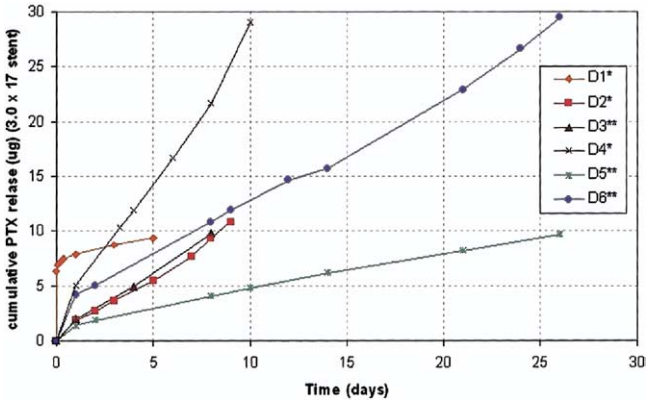

Figure 2. The six kinetic elution profiles, with their respective duration of elution (days, x axis), kinetic release (zero or first order; see slope of curve), cumulative dose (μg, y axis), and direction of elution (*bidirectional release, **abluminal (mural) release only). PTX = paclitaxel.

that deformation is confined to the 10% of the stent comprising the ductile hinges, rendering the struts as passive elements. This allows the struts to be cored with holes or reservoirs for drug delivery with no effect on the strength or crush resistance of the struts. The holes can be inlaid with polymer/drug that will not deform or separate from the stent during stent expansion, and bench testing shows no extrusion of polymer (5). The strut thickness is 127 μm (range 122 to 132 μm).

Each stent is loaded with paclitaxel within a bioresorbable polylactide-co-glycolide matrix. An automated micro-jet system is used to evenly load the polymer/drug combination by depositing individual drops within each hole. The amount of polymer and the surface area of polymer in contact with the vessel wall are minimized, offering a lower chance of polymer-related effects. The drug is released by erosion of the polymer and by diffusion. Predetermined release kinetics can be "programmed" by varying the method and concentration of drug deposition in the holes. At the end of the release period, neither polymer nor drug is retained on the stent.

Dose and kinetic release profiles. The drug under evaluation in the PISCES study was paclitaxel. The Conor stent is designed to deliver a similar dose density (measured in μg/mm^2 of vessel surface area) to all vessels treated; stents comprise varying numbers of stent cells. As the stents increase in diameter, more stent cells are used to complete the structure. In this way, the total contained dose on the stent will increase in proportion to the vessel diameter, thereby maintaining approximately a consistent dose per unit of vessel surface area (6). The PISCES trial evaluated one of six different release formulations that varied in dose (10 or 30 μg) and elution release kinetics (first order, zero order), direction (abluminal, luminal), and duration (5, 10, and 30 days). The release profiles for the formulations are shown in Figure 2 and Table 1.

Antiplatelet therapy. Double antiplatelet therapy (aspirin $\geq$80 mg daily and clopidogrel 75 mg daily) was prescribed for at least six months after procedure. A loading dose of 300 mg clopidogrel was given before the procedure.

Quantitative coronary angiography evaluation. Quantitative coronary angiography (QCA) was performed by means of the CAAS II analysis system (Pie Medical BV, Maastricht, the Netherlands). In each patient, the following segments were analyzed:

A. *Stented segment*: defined by the radiopacity of the Conor stent.
B. *Peri-stent segments*: defined by a length of 5 mm proximal and distal to the stent edge.

The following QCA parameters were computed: computer-defined minimal luminal diameter (MLD), reference diameter obtained by an interpolated method, and percentage diameter stenosis. *Binary restenosis* was defined in every segment as diameter stenosis >50% at follow-up. Late loss was defined as the difference between MLD after procedure and MLD at follow-up.

Quantitative IVUS. Post-procedure and follow-up stented vessel segments were examined with mechanical IVUS (Cardio Vascular Imaging System, CVIS, Sunnyvale, California) with automated pullback at 0.5 mm/s. A coronary segment beginning 5 mm distal to and extending 5 mm proximal to the stented segment was also examined. A computer-based contour detection program was used for automated three-dimensional reconstruction of the stented and adjacent segments. The lumen, stent boundaries, and external elastic membrane (vessel boundaries) were detected with a minimum cost algorithm. The stent volume (SV) and lumen volume (LV) were calculated according to Simpson's rule. The intra-stent neointimal volume was calculated as "SV-LV." The percentage obstruction of the SV was calculated as intra-stent neointimal volume/SV $\times$ 100. Feasibility, reproducibility, and inter- and intra-observer variability of this system have been validated in vitro and in vivo (7,8). The IVUS data of the proximal and distal peri-stent segments are expressed in mean area (vessel and lumen area) instead of volume, because the analyzable lengths of these segments were variable, owing to anatomical (side branch)

Table 1. Release Formulations

	D1	D2	D3	D4	D5	D6
Dose (μg/17-mm stent)	10	10	10	30	10	30
Duration of elution (days)	5	10	10	10	30	30
Direction of elution	Abluminal and luminal (bidirectional)	Abluminal and luminal (bidirectional)	Abluminal (mural)	Abluminal and luminal (bidirectional)	Abluminal (mural)	Abluminal (mural)
Key	10/5/b	10/10/b	10/10/m	30/10/b	10/30/m	30/30/m

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Table 2. Baseline Patient Characteristics

	Total Population n = 244
Age in yrs (mean ± SD)	59.2 ± 9.2
Gender (% male)	70.5% (172/244)
History of smoking	70.5% (172/244)
Diabetes mellitus	18.0% (44/244)
Hypertension	51.2% (125/244)
Dyslipidemia	66.8% (163/244)
Prior MI	39.8% (97/244)
Prior CABG	4.1% (10/244)
*Prior PCI	13.5% (33/244)
Angina class	88.9% (217/244)
I	96.8% (21/217)
II	33.2% (72/217)
III	33.2% (72/217)
IV	23.5% (51/217)
Unknown	0.92% (2/217)

*Prior angioplasty and/or prior stent implantation.
CABG = coronary artery bypass graft; MI = myocardial infarction; PCI = percutaneous coronary intervention.

and/or technical limitations. The "plaque" behind the stent struts was also expressed in mean area.

Statistical analysis. Continuous parameters were presented as mean values and standard deviations, and discontinuous parameters as percentages. For lesion characteristics and procedural outcomes, the following tests were applied to calculate the differences among the seven groups (one bare stent and six paclitaxel-eluting stent groups): F test from an analysis of variance (ANOVA), two-sample *t* test, likelihood ratio chi-square test, Fisher exact test, and Cochran-Mantel-Haenszel test. Overall QCA and IVUS parameters were compared using general linear models (i.e., one-way ANOVA) for unbalanced data. As per protocol, the Student *t* test was performed between each release formulation and the bare stent group when ANOVA was positive, and, hence, no correction for multiple comparisons was performed. The statistical significance of all tests was defined at the $p < 0.05$ level.

RESULTS

Baseline characteristics and acute procedural outcome. Two hundred and forty-four patients (53 in the bare stent group and 191 in the six paclitaxel-eluting stent groups) were enrolled. The baseline patient characteristics and the procedural outcomes are presented in Tables 2 and 3. A significant difference among the seven groups was only found in the mean age, which varied between 56.7 ± 7.6 years and 62.6 ± 8.5 years, and in the history of smoking, which varied between 50.9% and 89.7%. Direct stenting was performed in 54% of the patients, and a total of 272 stents (1.1 stent per patient) were implanted. In six patients (bare n = 3; eluting stent n = 3), failure to cross the lesion resulted in inability to implant the investigational device. These patients were not followed past the primary 30-day safety end point. There were no MACE in these patients at 30 days. The remaining 50 patients in the bare stent group and 187 in the eluting stent group received the investigational devices and completed clinical follow-up (Table 4).

MACE. The clinical events are presented in Table 4. The lowest cumulative MACE and TLR rates were observed in groups D5 (2.6% and 0%, respectively) and D6 (3.4% and 3.4%, respectively). One patient in group D5 was readmitted to the catheterization laboratory on the day of the procedure for an unrecognized dissection of the main stem, underwent bail-out stenting of the main stem, the left circumflex artery, the left anterior descending artery (target vessel), and sustained a major MI (CPK 6,634 U/l), dying four days later resultant to cardiac rupture. One patient in D6 interrupted his aspirin and clopidogrel treatment three days after stent implantation and presented with subacute occlusion and MI six days after the index procedure. At angiographic follow-up, 22 days after stent implantation, the stented vessel was occluded. Attempt at percutaneous revascularization was unsuccessful. As such, this patient was not included in the four-month angiographic follow-up analysis.

Serial QCA analyses. Table 5 shows the serial QCA analyses. Each QCA parameter is the average of multiple angiographic views. Angiographic follow-up was available in 93% of the patients. Groups D5 and D6 show the lowest in-stent late loss, which is reduced approximately by 57% and 66%, respectively, when compared with the loss in the bare stent group. In D5 and D6, there were no cases of edge restenosis. The overall restenosis rates in the stented and peri-stent segments in D5 and D6 are 0% and 3.8%, respectively, compared with 14% in the bare stent.

IVUS. Follow-up IVUS was available in 85% of the patients. The lowest percent volume obstruction was observed in groups D5 and D6 and was reduced by 69% and 81%,

Table 3. Baseline Lesion Characteristics and Procedural Outcomes

	Total Population n = 244
Target lesion location	
LAD	44.7% (106/237)
LCX	21.5% (51/237)
RCA	33.8% (80/237)
RVD (mm)	2.74 ± 0.43
Lesion length (mm)	10.3 ± 3.7
Percent stenosis (%)	63 ± 10
ACC class	
A/B1/B2	98.3% (233/237)
C	1.7% (4/237)
Patients receiving treatment device	97.1% (237/244)
Technical success*	95.1% (232/244)
Procedural success†	93.0% (227/244)
Final diameter stenosis (%)	13 ± 6
Unable to cross lesion	2.5% (6/244)
Device malfunctions	2.0% (5/244)

*Technical success is defined as the ability of the stent system to dilate the lesion with <20% residual stenosis (visual assessment) in the absence of a device-related failure or complications. †Procedural success is defined as technical success in the absence of any in-hospital major adverse cardiac events (MACE).
ACC = American College of Cardiology; LAD = left arterior descending; LCX = left circumflex; RCA = right coronary atery; RVD = reference vessel diameter.

Table 4. Clinical Events and MACE

Event	Event Type	D0 Bare Stent n = 50	D1 10/5/b* n = 30	D2 10/10/b* n = 29	D3 10/10/m* n = 30	D4 30/10/b* n = 30	D5 10/30/m* n = 39	D6 30/30/m* n = 29
Duration of follow-up (months)		6	4	4	4	4	4	4
Death	—	0	0	0	0	0	1	0
MI	Q-MI	0	1	0	0	1	1	1
	Non–Q-MI	1	1	1	0	0	0	0
Death or MI		1	2	1	0	1	1	1
Revascularization	TLR	3	5	4	2	1	0	1
	TVR	1	0	0	1	0	2*	1
	TVR-CABG	0	0	1	0	0	0	0
Any MACE		4 (8.0%)	5 (16.7%)	5 (17.2%)	2 (6.7%)	2 (6.7%)	1 (2.6%)	1 (3.4%)

*See Table 1 (release formulations): dose/duration/direction.
CABG = coronary artery bypass graft surgery; MACE = major adverse cardiac events and is a composite of death, myocardial infarction (MI), target lesion revascularization (TVR) (clinically justified or not), or emergent CABG; TVR = target vessel revascularization and is not included as an event in the MACE rate; QM = Q-wave MI.

Table 5. Serial QCA Analyses

	D0 Bare Stent n = 43	D1 10/5/b* n = 29	D2 10/10/b* n = 28	D3 10/10/m* n = 28	D4 30/10/b* n = 29	D5 10/30/m* n = 38	D6 30/30/m* n = 26	ANOVA
In stent								
MLD post (mm)	2.66 ± 0.37	2.60 ± 0.31	2.57 ± 0.33	2.70 ± 0.38	2.49 ± 0.33	2.68 ± 0.36	2.52 ± 0.35	0.11
MLD follow-up (mm)	1.79 ± 0.44	1.87 ± 0.52	1.90 ± 0.63	2.02 ± 0.51	2.02 ± 0.49†	2.30 ± 0.32‡	2.26 ± 0.47‡	<0.0001
Late loss (mm)	0.88 ± 0.41	0.72 ± 0.39	0.70 ± 0.56	0.67 ± 0.52	0.48 ± 0.47‡	0.38 ± 0.34‡	0.30 ± 0.35‡	<0.0001
Restenosis rate %	11.6	10.3	10.7	3.6	6.9	0.0	3.8	0.38
Proximal stent edge								
MLD post (mm)	2.77 ± 0.49	2.66 ± 0.53	2.63 ± 0.53	2.85 ± 0.44	2.55 ± 0.50	2.69 ± 0.53	2.60 ± 0.45	0.21
MLD follow-up (mm)	2.23 ± 0.5	2.38 ± 0.52	2.32 ± 0.68	2.51 ± 0.39	2.38 ± 0.49	2.47 ± 0.52	2.48 ± 0.54	0.28
Late loss (mm)	0.47 ± 0.39	0.27 ± 0.48	0.32 ± 0.54	0.30 ± 0.33	0.17 ± 0.32‡	0.23 ± 0.39‡	0.13 ± 0.33‡	0.01
Restenosis rate %	2.3	0.0	3.6	0.0	0.0	0.0	0.0	0.61
Distal stent edge								
MLD post (mm)	2.38 ± 0.45	2.32 ± 0.41	2.30 ± 0.50	2.32 ± 0.51	2.14 ± 0.54	2.37 ± 0.42	2.27 ± 0.48	0.46
MLD follow-up (mm)	2.17 ± 0.45	2.15 ± 0.34	2.21 ± 0.52	2.09 ± 0.52	2.03 ± 0.47	2.30 ± 0.38	2.23 ± 0.39	0.27
Late loss (mm)	0.23 ± 0.39	0.15 ± 0.31	0.11 ± 0.36	0.22 ± 0.52	0.13 ± 0.30	0.08 ± 0.29	0.09 ± 0.34	0.47
Restenosis rate %	0.0	0.0	0.0	0.0	3.4	0.0	0.0	0.58
Stent and peri-stent segments								
Restenosis rate %	14	10.3	14.3	3.6	10.3	0.0	3.8	0.39

*See Table 1 (release formulations): dose/duration/direction; †p <0.05 compared with the bare stent group; ‡p <0.01 compared with the bare stent group.
ANOVA = analysis of variance; MLD = minimal luminal diameter; QCA = quantitative coronary angiography.

respectively, when compared with the volume observed in the bare stent group (D0). Although an ANOVA showed an overall significant difference in SVs among the seven groups, no significant difference in SV between group D5 or D6 and the bare stent (D0) could be specifically demonstrated in an unpaired Student *t* test. The sequential analysis of the proximal edge area of the bare stent showed a significant reduction of the lumen due to constrictive remodeling associated with an increase in plaque media. There was a trend toward similar findings in group D1, whereas no significant reduction in the lumen area of the proximal or distal edge was observed in the other groups (D2 to D6). Significant increments in plaque area behind the struts were observed in D2 to D6 as opposed to D0 and D1. The IVUS results are presented in Table 6.

DISCUSSION

This multi-center registry with the bare metal and paclitaxel-eluting Conor stent is the first clinical application of this novel stent technology. The results of this trial may be summarized as follows: First, the bare stent, with intra-strut wells and relatively thick struts (127 μm), yields comparable acute and follow-up results and a safety profile to that previously reported with conventional stainless steel stents (9,10). Specifically, there was no undue incidence of thrombotic episodes or unusual pattern of neointimal hyperplasia. Second, this novel eluting stent platform, with an erodable polymer with complete elution of low doses of paclitaxel, is safe. Third, the duration of release had greater impact on the inhibition of the in-stent neointimal hyperplasia than did dose. Despite application of approximately 10% to 30% of the dose of the commercially available polymer-controlled paclitaxel-eluting stent, the inhibition of neointimal hyperplasia was comparable. The principal finding of this study is that, for paclitaxel, differing release kinetic profiles at similar doses seem to have profound impact on efficacy. Specifically, at the 10-μg dose, the <10-day release formulations did not reduce the intra-stent neointima observed in the bare metal stent group (31 mm^3 vs. 44 mm^3, p = NS). In marked contrast, the 30-day release formulation of the same dose was highly efficacious with a 57% reduction in late loss and a 69% reduction in percent volume obstruction with IVUS when compared with the bare Conor stent. Furthermore, the 30-μg/10-day release was less effective than one-third the dose released over a longer duration.

The precise reasons for these observations are unclear but may be related to several factors. First, molecular biology studies have demonstrated activation of genes potentially responsible for proliferation for periods up to 21 days (11). As such, the inhibitory compound may need to be present for some minimum period of time. Second, animal studies with the Conor drug delivery system have demonstrated that, at 30 days, all the doses used in the PISCES trial were effective, but slightly higher indexes of injury (e.g., fibrin deposition, eosinophilic deposits) were observed with the shorter release formulations (6). There were no significant differences in the balloon-to-artery ratios between the different groups, suggesting that the histologic variability was pharmacologic rather than mechanical. In these same studies, at 90 days, there was durability of the 30-day results in the longer release formulations that was not seen in the shorter release formulations. One may speculate that the anti-proliferative effects of the drug may be blunted by a secondary injury, induced either by the drug itself or by the bio-absorbable polymer, an effect which is not seen in the longer releases. Our data may help explain some of the discordant data found in other paclitaxel clinical trials (3,4,12–14).

The TAXUS II study, a blinded, randomized trial with two paclitaxel treatment arms and two control arms, enrolled over 500 patients. At drug concentrations of 1 $\mu g/mm^2$ (equivalent to a total drug loading of 108 μg/16-mm stent), delivered in either moderate or slow release formulations, restenosis rates of <5% and reductions in late loss of 60% versus bare-metal control stent were reported. Although there were no reported toxic side-effects related to the use of paclitaxel after 6 or 12 months, concern has been raised about the long-term biological effect of the non-erodable polymer used as well as persistence of significant quantities of drug still present in the polymer at 30 days; 92.5% for the slow release formulation or 78.1% for the moderate release (personal communication from Mary Russell, June 2004).

The DELIVER trial also used paclitaxel—without a polymer carrier—and failed, at a dose density of 3.04 $\mu g/mm^2$, to demonstrate significant improvement versus the bare stent. The reasons for such discordant results with the same drug are unclear, but suggest that release rates may impact efficacy (12). The present observation may therefore have relevance for optimizing paclitaxel efficacy and, potentially, even have implications for other therapeutic compounds.

A further finding of our study was that in dose 3, which had abluminal release only, and dose 2, which had bi-directional release, there was no differential efficacy either on the in-stent segment or edges of the stent.

The IVUS observations made with the TAXUS polymer-coated DES have been duplicated in these limited populations. First, a significant tissue growth behind the struts of the stent has been observed, accompanied by expansive remodeling of the external elastic membrane (15). Second, lumen reductions at the edge of the stent—predominantly at the proximal edge—are usually seen after bare metal stent implantation, owing to constrictive remodeling combined with plaque growth. This phenomenon is prevented by the paclitaxel-eluting stent, because the plaque growth is partially accommodated by expansive remodeling (16).

Study limitations. This study is subject to several limitations. It was not designed as a pivotal efficacy study but rather as a first-in-man study and, therefore, was not

Table 6. IVUS Analyses

	D0 Bare Stent n = 39	D1 10/5/b n = 28	D2 10/10/b n = 23	D3 10/10/m n = 27	D4 30/10/b n = 26	D5 10/30/m n = 37	D6 30/30/m n = 21	ANOVA D0-D6	ANOVA D1-D6
Stent length (mm)	19.0 ± 6.6	18.3 ± 4.2	18.8 ± 5.2	17.7 ± 2.8	18.0 ± 2.2	17.9 ± 2.7	17.0 ± 1.0	0.63	0.57
Stent volume follow-up (mm^3)	175 ± 89	136 ± 44†	150 ± 73	141 ± 32†	125 ± 28‡	146 ± 34	144 ± 30	0.01	0.32
Neointimal volume follow-up (mm^3)	44 ± 31	31 ± 24	31 ± 31	25 ± 20‡	16 ± 21‡	11 ± 12‡	8 ± 10‡	<0.0001	<0.0001
Obstruction volume follow-up %	26 ± 13	22 ± 13	20 ± 17	17 ± 13†	12 ± 13‡	8 ± 7‡	5 ± 7‡	<0.0001	<0.0001
Proximal (area mm^2)	n = 28	n = 21	n = 15	n = 20	n = 16	n = 22	n = 17		
Mean vessel post	17.4 ± 4.2	15.5 ± 5.0	14.6 ± 4.7	17.1 ± 3.6	15.3 ± 4.4	15.9 ± 4.5	15.5 ± 3.7		
Mean vessel follow-up	16.7 ± 4.3	14.9 ± 4.9	14.8 ± 5.6	17.0 ± 3.9	15.5 ± 3.7	16.4 ± 4.9	16.4 ± 3.6		
p value	0.03	0.34	0.83	0.95	0.68	0.15	0.2		
Plaque post	7.9 ± 2.8	7.5 ± 2.7	7.0 ± 3.3	7.7 ± 2.9	6.8 ± 2.5	7.2 ± 2.5	7.1 ± 2.8		
Plaque follow-up	8.9 ± 2.9	7.7 ± 2.9	7.6 ± 3.6	8.6 ± 3.0	7.5 ± 1.8	8.0 ± 2.6	8.1 ± 3.1		
p value	0.004	0.75	0.09	0.08	0.11	0.0003	0.009		
Mean lumen post	9.6 ± 2.5	7.9 ± 3.6	7.6 ± 2.5	9.4 ± 3.0	8.5 ± 2.6	8.7 ± 3.3	8.5 ± 2.5		
Mean lumen follow-up	7.8 ± 2.9	7.2 ± 2.9	7.2 ± 3.2	8.5 ± 3.2	8.0 ± 3.1	8.4 ± 3.6	8.3 ± 2.7		
p value	<0.0001	0.047	0.45	0.08	0.23	0.39	0.77		
Distal (area mm^2)	n = 30	n = 21	n = 16	n = 20	n = 16	n = 27	n = 16		
Mean vessel post	14.3 ± 4.6	13.1 ± 4.9	13.8 ± 5.7	13.6 ± 3.8	12.5 ± 2.8	13.6 ± 3.6	15.3 ± 4.7		
Mean vessel follow-up	14.6 ± 4.8	13.1 ± 4.3	13.6 ± 4.9	13.6 ± 3.6	13.3 ± 2.5	13.9 ± 3.3	15.6 ± 4.3		
p value	0.48	0.91	0.73	0.91	0.07	0.39	0.60		
Plaque post	5.7 ± 2.5	5.9 ± 2.7	6.3 ± 3.4	6.0 ± 2.6	5.8 ± 2.0	5.7 ± 2.5	7.2 ± 2.4		
Plaque follow-up	6.6 ± 2.7	6.6 ± 2.9	7.0 ± 4.0	6.3 ± 2.6	6.5 ± 1.8	6.4 ± 2.3	7.9 ± 2.5		
p value	0.0001	0.09	0.08	0.19	0.04	0.003	0.01		
Mean lumen post	8.6 ± 3.3	7.2 ± 2.7	7.5 ± 3.5	7.6 ± 2.6	6.7 ± 2.2	7.9 ± 2.3	8.2 ± 2.8		
Mean lumen follow-up	8.0 ± 3.3	6.5 ± 1.9	6.5 ± 2.0	7.3 ± 2.5	6.7 ± 2.3	7.5 ± 2.0	7.7 ± 2.4		
p value	0.13	0.09	0.19	0.48	0.88	0.12	0.22		
PBS (area mm^2)	n = 33	n = 25	n = 21	n = 24	n = 23	n = 34	n = 20		
Post	9.6 ± 3.0	7.8 ± 2.8	7.8 ± 2.4	8.6 ± 2.1	7.7 ± 2.1	7.7 ± 2.0	8.2 ± 1.7		
Follow-up	9.5 ± 2.5	8.2 ± 2.6	8.6 ± 2.6	9.3 ± 2.4	8.7 ± 2.1	9.1 ± 2.2	9.3 ± 1.8		
p value	0.8	0.21	0.002	0.02	0.0004	<0.0001	<0.0001		

*See Table 1 (release formulations): dose/duration/direction; †p <0.05 compared with the bare stent group; ‡p <0.01 compared with the bare stent group.
ANOVA = analysis of variance; IVUS = intravascular ultrasound; PBS = plaque behind the stent struts.

blinded or randomized. As a pilot study, the primary follow-up was conducted at four months for safety reasons similar to other first-in-man studies. Comparison of the neointimal hyperplasia at four months in the paclitaxel-eluting stent with the neointimal hyperplasia at six months in the bare stent was not aimed to show superiority, but to demonstrate that the novel platform itself was not providing unusual results compared with conventional stainless steel stents. Consequently, the study was not statistically modeled to demonstrate efficacy but rather to develop insight into how to optimize the pharmacokinetics and to understand the relative importance of different doses versus duration of elution for paclitaxel.

Conclusions. The PISCES trial demonstrates for the first time that kinetic variations play a key role in the efficacy of DES systems. These findings may have significant implications for future research and development. Ongoing research activities with this reservoir-based technology involve the ultra-thin cobalt-chromium stent in place of stainless steel and long-release paclitaxel formulations. Evaluation of other compounds for indications other than restenosis is also underway. Future studies with respect to restenosis will be larger and include longer-term follow-up, randomized cohorts, and non-inferiority trials with other DES.

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