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The Paclitaxel-Eluting Coroflex™ Please Stent Pilot Study (PECOPS I): Acute and 6-Month Clinical and Angiographic Follow-Up

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Background and Objectives: Various active stent coatings significantly reduce restenosis rates and target lesion revascularization compared to bare metal stents. Therefore, the procedural and 6-month performance of the new paclitaxel-eluting Coroflex™. Please stent was investigated. Methods: Ninety-seven patients (66 ± 7.6 years, 34/97(35.1%) diabetics, 11/97(11.3%) unstable angina) were enrolled per protocol for elective single stent deployment into native coronary de-novo or post-PTCA restenotic lesions (stenosis: ≥70%, <100%; reference diameter ≥2.25 mm and <3.3 mm; lesion length ≤16 mm) with 13/97(13.4%) lesion type A, 64/97(66%) type B1, 20/97(20.6%) type B2). The mean reference diameter was 2.88 ± 0.42 mm, the lesion length 10.03 ± 2.93 mm, and the minimal lumen diameter 0.64 ± 0.22 mm. Results: The success rates of procedure and study stent deployment were 100% and 94.8%, respectively. In 5/97(5.2%) two stents were implanted. Follow-up was performed clinically in 86/87(98.9%) and angiographically in 77/87(88.5%) patients after 6.1 ± 0.7 months. Major adverse cardiac events occurred in 7/87(8%) 1/87(1.2%) subacute thrombosis 10.3hrs post procedure, 1/87(1.2%) myocardial infarction, 5/87(5.7%) target lesion revascularizations. The in-segment stenosis declined from 78 ± 7.2% to 9.4 ± 6.2% after stenting increasing to 31.9 ± 18.6% at follow-up. The in-segment late loss and the late loss index were 0.47 ± 0.6 mm and 0.23 ± 0.29 resulting in 6/77(7.8%) in-segment restenoses three each of which were located either within or beyond the stent structure. The outcome was neither influenced by the prevalence of diabetes ($p = 0.4$), hypercholesterolemia ($p = 1$), hypertension ($p = 1$), overweight ($p = 1$), nor by the family history of coronary artery disease ($p = 0.7$). Conclusion: The data of the paclitaxel-eluting Coroflex™. Please stent tested in PECOPS I are within the range other available paclitaxel-eluting stent.

Key words: restenosis; stents; paclitaxel; drug eluting stents; active coating; PECOPS I

INTRODUCTION

Stents with passive and active coatings have emerged as the standard device used to treat atherosclerotic coronary artery lesions [1–3]. Paclitaxel has proven its efficacy after elution from stents by reducing intimal proliferation in the animal model [4–7] as well as in man [8]. The clinical and angiographic outcome in humans after deployment of stents coated with paclitaxel into de-novo coronary artery lesions [9,10] and into in-stent restenoses [11] was significantly superior in comparison to bare stents of the otherwise same design.

Therefore, PECOPS I was launched to evaluate the procedural and 6-month results of the new paclitaxel-eluting Coroflex™ Please stent in coronary artery lesions at low-to-high risk for recurrence such as small vessels, restenoses, in diabetics, and others.

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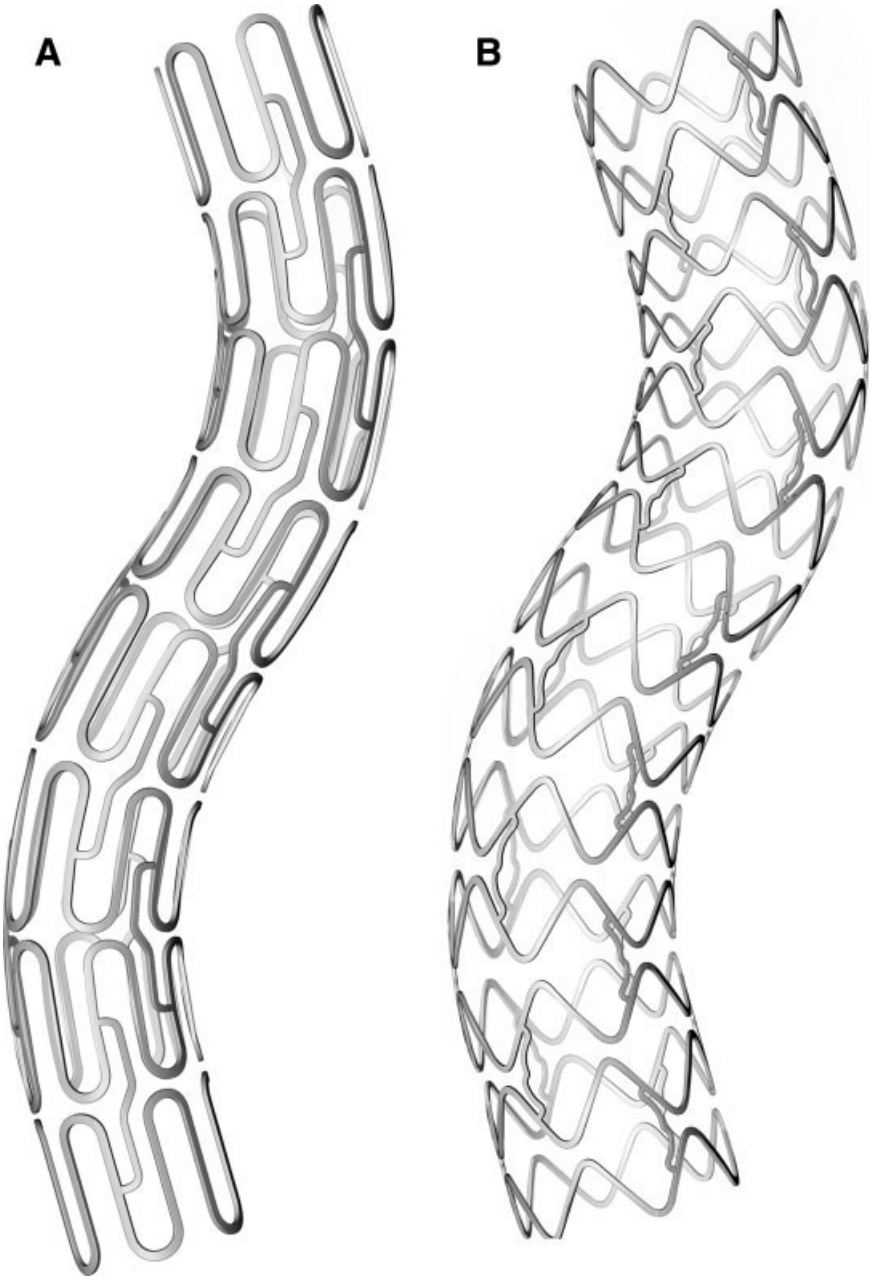

Fig. 1. The Coroflex™ Please stent before (a) and after (b) expansion.

METHODS

Design

This multicenter, prospective, nonrandomized trial was conducted in accordance with ICH-GCP (International Commission on Harmonization – Good Clinical Practice) guidelines [12]. The protocol was approved by an independent ethics committee. The patients provided written informed consent at least 1 day prior to the procedure.

The primary endpoint was the binary restenosis rate at 6 months. Secondary endpoints encompassed acute procedural success, target lesion revascularization, acute ischemic, vascular and hemorrhagic complications, as well as follow-up minimal lumen diameter, percent diameter stenosis, late loss, and late loss index [13]. Clinical endpoints comprised combined major cardiac events (death, myocardial infarction, and premature target vessel revascularization).

Quantitative coronary angiography (QCA) was performed by an independent core laboratory (Clinical Research Institute at the Center of Cardiovascular Diseases, Rotenburg an der Fulda, Germany).

The stents were provided by the manufacturer free of charge (B. Braun, Melsungen, Germany).

Study Device Description and Study Rationale

The new Coroflex™ Please stent features 0.120-mm thick 316L stainless steel struts covered by a 7.3 ± 1 μm layer of paclitaxel with a dose of 1 μg per mm^2 of stent surface (Fig. 1a and b). At the nominal pressure of 6 bars, the metal coverage areas for the 2.5, 3.0, and 3.5 mm devices are reported as 17.4, 14.5, and 12.8%, respectively. The overall properties include a crossing profile of 1.2 mm, an elastic recoil of 4.6%, a foreshortening of 1–3%, and a radial strength of 1.5 bars. The rate burst pressure is 15 bars for the stents deployed.

Pharmacologic Properties of Paclitaxel

Since its approval to fight ovarian cancer in 1993 paclitaxel has become an undisputed drug in tumor therapy [14]. The substance is highly lipophilic with a molecular weight of 853.9 Da that stabilizes cellular microtubules essential to cell function, migration, and replication, [14,15] thereby impairing arterial vascular wall contraction, retarding the migration of and reducing the mitosis rate of vascular wall cells in vitro and in vivo [7,16–18] through a sustained mitotic block at the metaphase–anaphase boundary [19].

In vitro, the maximal inhibitory concentration of paclitaxel for vascular smooth muscle cell growth was reported to be 1 μmol/l whereas the 50% inhibitory value is 2.1 nmol/l [15]. The vascular endothelium requires concentrations of the drug on the order of 1–10 nmol/l for complete growth inhibition [15].

Systemic side effects, such as neutropenia, peripheral neuropathy, severe hypersensitivity reactions, and asymptomatic bradycardia have been reported in systemic therapy for cancer with high-plasma levels in the order of 100–1,000 times higher as determined after the local intraarterial application [15].

For local intraarterial application, the release of the drug seems to be independent from such factors as pressure of delivery [20].

Study Population

One hundred and twenty five patients (Table I) were enrolled in the study. Subjects had to present with objective myocardial ischemia requiring therapeutic intervention to treat a de-novo or restenotic lesion after stand alone balloon angioplasty in a native coronary artery (reference diameter from ≥2.25 to ≤3.3 mm, length ≤16 mm, severity of stenosis ≥70%, (100%). Exclusion criteria encompassed contraindications for both aspirin and clopidogrel, or known intolerance to stainless steel, unprotected left main stenosis, single lesion within 2 mm of the origin of the left anterior descending or the left circumflex, lesion covering a major side branch (>2 mm), myocardial infarction within 72 hr preceding the intervention, planned multiple lesion PCI within the same vessel, left ventricular ejection fraction <30%, transient cerebral ischemic attacks within the past 12 months, contraindications to blood transfusions, and life expectancy of less than 1 year for any reason.

TABLE I. Patient Characteristics

Variables	
Number of patients	97
Age (years)	66.5 ± 7.5
Male	70 (72.2%)
Severity of coronary artery disease	
1-Vessel disease	42 (43.3%)
2-Vessel disease	27 (27.8%)
3-Vessel disease	28 (28.9%)
Risk factors	
Hypertension	59 (60.8%)
Hypercholesterolemia	53 (54.6%)
Total cholesterol (mg/dl)	194.7 ± 46.5
Diabetes mellitus	34 (35.1%)
Diet solely ($n = 34$)	2 (5.9%)
Oral medication ($n = 34$)	17 (50.0%)
Insulin ($n = 34$)	15 (44.1%)
Current smokers	17 (17.5%)
Family history of coronary artery disease (CAD)[a]	27 (27.8%)
Body mass index	28.2 ± 4.1
Medication	
ACE-inhibitors/AT_1-antagonists	67 (69.1%)
Aspirin	79 (81.4%)
β-blockers	72 (74.2%)
Ca^{++}-channel antagonists	19 (19.6%)
Diuretics	34 (35.1%)
NO-donors	21 (21.6%)
Statins	61 (62.9%)
Cardiac glycosides	7 (7.2%)

[a]Male relatives ≤55 years; female relatives ≤65 years.

Twenty-eight of 125 (22.4%) patients did not meet the above criteria. In one patient (1%), a major side branch (diameter: >2mm) originated from the lesion. In 24 subjects (19.2%), the lesion length exceeded 16 mm and was therefore not completely covered by the stent, while in three subjects (2.4%), the reference diameter of the target vessel was smaller than 2 mm.

Operator Technique

Assessment of lesion severity and lesion length, and, therefore, choice of stent, was based on visual estimation.

Heparin was administered in doses of 100–200 IU/kg of body weight after introduction of the sheath and was supplemented as needed throughout the procedure. Following intracoronary injection of nitroglycerin (100–200 μg), baseline angiography of the culprit vessel was performed in at least two near-orthogonal views showing the target lesion free of foreshortening or vessel overlap. The stenotic lesion was crossed with a 0.014″

exchange-length guide wire before the Coroflex™ Please stent was deployed according to the manufacturer's instructions for use. The procedure was deemed successful with a remaining stenosis of ≤30%.

Angiographic images were acquired at pre-procedure, post-procedure, and at scheduled follow-up after 6 months, or driven either by suspected or proven recurrence of stenosis.

Concomitant Medical Therapy

All patients received aspirin 100 mg/day pre-procedure and throughout the follow-up period. Clopidogrel with a loading dose of 300 mg followed by 75 mg/day for 6 months was added.

Quantitative Coronary Analysis

The angiograms were reviewed by two observers, using qualitative morphologic and quantitative angiographic methods by means of the CAAS II-System (Pie-Medical, Maastricht, The Netherlands) at the Clinical Research Institute's Angiographic Core Lab at Rotenburg an der Fulda.

The contrast filled catheters served as the calibration standard, while the reference and minimal lumen diameters were determined using an automated edge-detection algorithm. Reference contours were calculated by using a linear regression algorithm with assessment of the reference diameter at the site of the minimal lumen diameter [21]. The minimal lesion diameter was given as absolute (mm) and relative (%) figures. The diameters were taken from the view exhibiting the most severe degree of stenosis preprocedure, after stent deployment, and at follow-up. In case of obvious false assessment of the vessel by CAAS, operator adjustment was permitted.

Follow-up

Follow-up procedures included resting ECG, white blood cell count, hematocrit, hemoglobin, creatinine, creatine kinase and CK-MB, and catheterization at 6 months unless clinically indicated earlier.

Definitions

A thrombus is a noncalcified filling defect within the vascular lumen, which is visible in several views and which may migrate into the peripheral artery. An acute thrombosis is defined by a total occlusion (TIMI grade 0) occurring within 24 hr after stent deployment whereas subacute thrombosis occurs >24 hr and <1 month after stent deployment.

Q-wave infarction was diagnosed with the occurrence of new Q-waves (>0.04 sec) in the ECG and rise of creatinine kinase twice the upper limit of normal with significant CK-MB whereas in non-Q-wave-infarctions pathologic Q-waves were absent.

Acute complications occurred within 24 hr after stent deployment, early complications after hospital discharge until <2 months after the intervention, and late complications could occur any time thereafter.

Statistical Analysis

All analyses were performed and reported in compliance with the August 1998 FDA device reporting guidelines for coronary stents.

All endpoints were analyzed on an intention-to-treat basis. Patients were therefore analyzed regardless of the subsequent sequence of events. Those patients who met eligibility requirements for primary endpoint ascertainment included all patients who were enrolled.

Statistical Tests

The Kolmogoroff-Smirnoff-test was used to prove Gaussian distribution allowing for calculation of the mean and standard deviation. Non-Gaussian samples were described by the median and the maximal and minimal value. Categorical variables were evaluated with the two-sided exact Fisher test. For all tests the significance level α was 0.05.

RESULTS

All procedures were successful, 94.8% by deployment of the study stent, 4.1% by means of a noncoated stent, and 1.1% by long-term dilatation with a balloon catheter only. Twenty-nine out of 97 (29.9%) stents were placed without predilation. In 5/97 (5.2%) patients, additional stents were deployed for the treatment of type A dissection in 1/97 (1%) subject and for type B dissections to 4/97 (4.1%) patients. Glycoprotein IIb/IIIa receptor antagonists were not administered to any patient.

The most common stent diameter used was 3.0 mm in 36/97 (37.1%) of the per protocol patients. Larger sizes were less frequently deployed: 3.5 mm in 31/97 (32.0%) and 2.5 mm stents were used in 30/97 (30.9%). The length of stents implanted were 44/97 (45.4%) of 13 mm and 53/97 of 16 mm (Table II).

The lesion characteristics preprocedure are given in Table III.

Of the 97 patients included per protocol, five (5.2%) subjects each had to be excluded for deployment failure of the study stent and for the need to place an additional stent to treat dissections. In 86 (98.9%) of the remaining 87 patients, clinical follow-up was completed after 6.1 ± 0.7 months since one patient moved to an unknown location. For angiographic follow-up, 77/87 (88.5%) participants were eligible.

TABLE II. Deployment Data

Variables	
Deployment pressure (mm Hg)	13.5 ± 3.3
Inflation time (sec)	24.5 ± 7.8
Stent length (mm)	14.7 ± 1.5
Number of stents	
13.0 mm in length	44/97 (45.4)
16.0 mm in length	53/97 (54.6)
Stent diameter (mm)	3.0 ± 0.4
Ø 2.5 mm	30/97 (30.9)
Ø 3.0 mm	36/97 (37.1)
Ø 3.5 mm	31/97 (32.0)
Glycoprotein IIb/IIIa antagonists	0

Values in parentheses indicate percentage values.

TABLE III. Vessels Stented and Type of Lesion

Location of lesion	
Left anterior descending (LAD)	42/97 (43.3%)
Right coronary artery (RCA)	28/97 (28.9%)
Left circumflex (LCx)	27/97 (27.8%)
Type of lesion[a]	
Type A	13/97 (13.4%)
Type B1	64/97 (66.0%)
Type B2	20/97 (20.6%)
Type C	0/97 (0)
Reference diameter (mm)	2.88 ± 0.42
Lesion diameter (mm)	0.64 ± 0.22
Lesion length (mm)	10.03 ± 2.93

Values in parentheses indicate percentage values.
[a]Modified American College of Cardiology/American Heart Association scores.

Stent deployment increased the minimal in-segment lumen diameter from 0.64 ± 0.22 mm to 2.62 ± 0.40 mm. At follow-up the minimal in-segment diameter decreased to 1.92. ± 0.71 mm translating into a late loss and late loss index of 0.47 ± 0.6 mm and 0.23 ± 0.2, respectively. The percent stenosis decreased from 78 ± 7.2% to 9.4 ± 6.2% immediately post stent implantation, and increased to 31.9 ± 18.6% at follow-up (Fig. 2). The binary recurrence rates were located in-stent in 3/77 (3.9%) and in-segment in 6/77 (7.8%) of the lesions, five of which (6.5%) required target lesion revascularization. According to the Mehran classification, two of the recurrences were IB and one was II, while the remaining three lesions occurred beyond the stent within the segment of 5 mm on either side of the device.

With respect to clinical events, one acute stent thrombosis occurred 10 hr after stent deployment and was treated by reintervention immediately. One myocardial infarction was reflected by creatine kinase elevation 3.3 times the upper normal 22 hr after stent deployment. No interventional measures were taken by the operator. None of the patients required coronary artery bypass operation during the 6 month follow-up period and no deaths were recorded during this period.

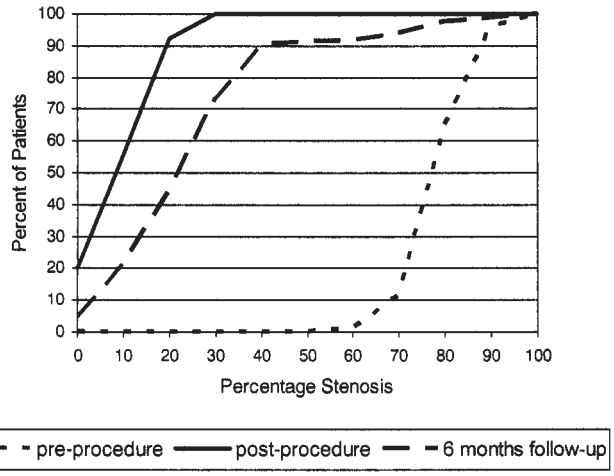

Fig. 2. Cumulative frequency distribution of percent in-segment diameter stenosis.

None of the cardiovascular risk factors such as diabetes ($P = 0.4$), hypercholesterolemia ($P = 1$), arterial hypertension ($P = 1$), overweight ($P = 1$), actual smoking or history of smoking ($P = 0.7$), or family history of coronary artery disease ($P = 0.7$) showed a statistical significant relationship neither to the angiographic nor to the clinical outcome.

DISCUSSION

All of the procedures in PECOPS I were successful with a 94.8% success rate of study stent deployment. The latter is at the lower end in comparison to recently published interventional trials with 95% and 96% [22], 98.6% [23], 99% [3], 99.4% [10], and 100% [24] respectively (for comparison of the studies discussed further refer to Table IV). Among those studies, the TAXUS II trials [24] included low-risk lesions as opposed to PECOPS I, since also lesions more likely prone to restenosis with diameters ranging from 2.25 to ≤3.3 mm of up to 16 mm in length were enrolled. In PECOPS I, 86.6% of the stenoses were type B1 or B2 lesions [25–27]. Moreover, the average stenosis pre-procedure was 78 ± 7.2% in PECOPS I and, therefore, more severe than in both of the TAXUS II studies with 64.9 ± 10.3% (medium release, MR) and 63.3 ± 9.6% (slow release, SR), respectively. In the two recently published studies [23,24], however, the lesions were more complex than in PECOPS I.

In all deployment failures in PECOPS I, scrutiny of the devices unveiled a thicker crossing profile on the order of up to 1.9 mm secondary to remarkable curling of the balloon at the distal part of the catheter. Although those changes may be secondary to extensive manipulation during the deployment procedure, this

TABLE IV. Angiographic Characteristics of Studies with Paclitaxel-Eluting Coronary Stents

	TAXUS II [22]	TAXUS II [22]	TAXUS IV [10]	ISAR-DIABETES [24]	SIRTAX [23]	PECOPS I
Type of stent	Taxus SR	Taxus MR	Taxus SR	Taxus	Taxus	Coroflex PLEASE
Number of patients	131	135	662	125	509	125
Age (years)	61.5 ± 10.5	58.3 ± 10.1	62.8 ± 11.2	68.3 ± 9.6	62 ± 12	66.0 ± 7.6
Male	70%	76%	72%	71.2%	78.4%	76%
Diabetics	11%	17%	23%	100%	18.3%	35.2%
1-Vessel disease	100%	100%	100%	NP	NP	41.6%
2-Vessel disease	–	–	–			28.8%
3-Vessel disease	–	–	–			29.6%
Lesion characteristics	De novo	De novo	De novo		A 21.6%	A 11.2%
				B2 and C 73.6%	B1 43.4%	B1 68.0%
					B2 21.9%	B2 20.8%
					C 13.1%	
Lesion length (mm)	10.6 ± 3.9	10.2 ± 4.8	13.4 ± 6.3	12.4 ± 7.7	12.4 ± 7.2	10.16 ± 2.91
Reference diameter (mm)	2.8 ± 0.4	2.7 ± 0.5	2.75 ± 0.47	2.75 ± 0.56	2.82 ± 0.43	2.89 ± 0.41
MLD preprocedure	1.02 ± 0.30	0.95 ± 0.32	0.92 ± 0.33	1.12 ± 0.4	0.53 ± 0.43	0.64 ± 0.23
MLD postprocedure	IS 2.53 ± 0.29	IS 2.53 ± 0.36	AS 2.26 ± 0.48	AS 2.65 ± 0.52	AS 2.60 ± 0.44	IS 2.63 ± 0.40
			IS 2.66 ± 0.43	IS 2.67 ± 0.52	IS 2.68 ± 0.39	
Relative stenosis	63.3 ± 9.6	64.9 ± 10.3	66.5 ± 10.7%	59.4 ± 11.9%	81.5 ± 14.5%	77.98 ± 7.16%
Binary restenosis rate (%)	IS 2.3	IS 4.7	IS 5.5	IS 13.6	IS 7.5	IS (3/77)3.9
	AS 5.5	AS 8.6	AS 7.9	AS 16.5	AS 11.7	AS (6/77)7.8
Late loss (mm)	IS 0.31 ± 0.38	IS 0.30 ± 0.39	0.39 ± 0.50	IS 0.46 ± 0.64	IS 0.13 ± 0.28	IS 0.47 ± 0.60
				AS 0.67 ± 0.62	AS 0.17 ± 0.32	
MACE 30 days	2.3%	4.4%	2.9%	NP	2.3%	(2/87) 3.1%
MACE 6–9 months	8.5%	7.8%	8.5%	19.2%	10.8%	(7/87) 8.0%
Target lesion revascularization	4.6%	3.7%	3.0%	12%	8.3%	(5/87) 5.7%

MLD, Minimal lumen diameter; MACE, major adverse cardiac event; IS, in-stent; AS, analyzed segment; NP, not yet published in the paper.

result is in line with the operators' observations who reported an increased friction/resistance when initially advancing the systems within the guiding catheters also in successful cases.

The angiographic follow-up after 6.1 ± 0.7 months revealed a binary in-segment recurrence rate of 7.8% in PECOPS I. After 6 months, the corresponding rate for the paclitaxel-eluting Taxus™ Express stent was 8.6% [22]. With the same dose per square millimeter of stent, this device also exhibits a similar MR kinetics of paclitaxel in comparison to the paclitaxel-eluting Coroflex™ Please stent. In PECOPS I, the patients included were at higher risk for coronary events as opposed to TAXUS II. Despite rather identical values for the mean reference diameter and average lesion length, 71.1% of the subjects in PECOPS I exhibited multivessel diseases while in TAXUS II all patients had single vessel coronary artery disease. The patients in PECOPS I were more likely diabetic (35.2 vs 17%). In the SR arm of TAXUS II in subjects with single vessel coronary disease only similar data for lesion length and reference diameter and a share of 11% diabetics, a 5.5% in-segment recurrence rate was reported [22]. The distribution of the recurrences along the device starting with the 5 mm proximal to the stent, the stent itself, and then the 5 mm adjacent distal to the device was 3.9/3.9/0% for PECOPS I, 1.6/2.3/1.6% for TAXUS II MR, and 2.3/4.7/2.3% for TAXUS II SR. The relative high incidence of stenoses outside the stent body is different in comparison to bare metal devices, in which in-stent restenoses are clearly more frequent accounting for about 70% of the in-segment recurrences [22].

In TAXUS IV, the de-novo lesions of 662 patients tended to be longer (13.4 ± 6.3 mm) but less severe (66.5 ± 10.7%) than in PECOPS I. The 9-month follow-up after paclitaxel-eluting stent deployment revealed a binary in-segment recurrence in 7.9% (proximal edge: 2.7%, in-stent: 5.5%, distal edge: 0.7%) on the basis of a late lumen loss of 0.39 ± 0.5 mm. The late lumen loss in PECOPS I of 0.47 ± 0.6 mm was higher than in TAXUS II MR (0.30 ± 0.39 mm) and SR (0.31 ± 0.38 mm) [22], respectively. While the late lumen loss was also more pronounced than in SIRTAX (0.32 ± 0.55 mm) [23], the interpretation of which being limited by the angiographic follow-up rate of 53.4%, the ISAR-DIABETES Investigators reported 0.67 ± 0.62 mm of in-segment lumen loss in a high-risk population encompassing only diabetics with 73.6% type B2 and C lesions [24]. In this context, it is worth mentioning that the application of glycoprotein IIb/IIIa-receptor antagonists differed markedly between the various trials, while in PECOPS I, none of patients received the drug the proportion was higher in the remainder ranging from 11.5% [10], 19.2% [24],28.9% [23], to 55.7% [22].

The 2.3% rate of major adverse events observed in PECOPS I after 30 days following single study stent deployment is within the range of other trials with stents eluting paclitaxel [10,22,28].

In TAXUS II, enrolling patients with single vessel disease and low-risk stenoses (diameter: 3.0–3.5 mm, length: <12 mm), the combined event rate of death, myocardial infarction, target lesion revascularization, and stent thrombosis was also 2.3% [22]. In TAXUS IV, still including patients with single vessel disease, with increasing complexity of the lesions (diameter: 2.5–3.75 mm, length:10–28 mm), the MACE rate encompassing death, myocardial infarction, and target vessel revascularization climbed to 2.9% for the paclitaxel-eluting stent [10,28].

The 6-month MACE rates for PECOPS I were 8.0% and for TAXUS II MR and SR 8.5 and 7.8%, respectively. While in TAXUS IV, including low-risk lesions, the 9-month follow-up revealed a MACE rate of 5.7%, the more complex lesions as treated in the paclitaxel-eluting stent arms of SIRTAX and ISAR-DIABETES were associated with MACE rates of 10.8 and 19.2% [23,24].

Limitations of PECOPS I include the design as a one-arm observational study and the considerable number of major protocol violations at enrollment primarily due to visual underestimation of the lesion length by the operators. Since it is reasonable to assume that curling of the balloon tip might have contributed to the rate of deployment failures, these failures do not seem to reflect the properties of the stent as such.

In summary, the data of the paclitaxel-eluting Coroflex™ Please stent tested in PECOPS I are within the range of the other currently available Paclitaxel-eluting stents.

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