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# Catheter-Based Delivery of Fluid Paclitaxel for Prevention of Restenosis in Native Coronary Artery Lesions After Stent Implantation

Christian Herdeg, MD; Katrin Göhring-Frischholz, MD; Karl K. Haase, MD; Tobias Geisler, MD; Christine Zürn, MD; Ulrike Hartmann, PhD; Jochen Wöhrle, MD; Thorsten Nusser, MD; Jürgen Dippon, PhD; Andreas E. May, MD; Meinrad Gawaz, MD

**Background**—Stents eluting antiproliferative drugs reduce the incidence of restenosis but delay healing of the vascular wall. We assessed the safety and efficacy of catheter-based local delivery of fluid paclitaxel in patients with coronary de novo stenoses after implantation of a bare metal stent.

**Methods and Results**—We conducted a prospective, randomized trial comparing the local delivery of fluid paclitaxel after bare metal stent implantation (group I) with the implantation of a bare metal stent (group II) and the implantation of a paclitaxel-eluting stent (group III) in 204 patients. The primary end point was in-stent late lumen loss. Secondary end points included binary restenosis rate >50%, minimal lumen diameter, diameter stenosis, and a composite clinical end point (major adverse cardiac events and revascularization of the target lesion) 6 months after intervention. At 6 months, angiography showed an in-stent late lumen loss of  $0.61 \pm 0.44$  mm in group I versus  $0.99 \pm 0.72$  mm in group II (I versus II,  $P=0.0006$ ) and  $0.44 \pm 0.48$  mm in group III (noninferiority of I versus III,  $P=0.023$ ). The 1-sided 95% CI for the true difference of the means of in-stent late lumen loss in groups I and III was  $-\infty$  to 0.3174188. The cumulative overall rate of major cardiac events was 13.4% in group I, 26.8% in group II, and 14.9% in group III. Target lesion revascularization rate was 13.4% (group I), 22.1% (group II), and 13.4% (group III).

**Conclusions**—Additional antiproliferative treatment of de novo lesions in native coronary arteries with catheter-based delivery of fluid paclitaxel after bare metal stenting was safe and significantly reduced neointimal proliferation, restenosis, and clinical events compared with bare metal stent implantation alone. (*Circ Cardiovasc Intervent.* 2009; 2:294-301.)

**Key Words:** local drug delivery ■ angioplasty ■ paclitaxel ■ drug-eluting stent ■ catheter

Drug-eluting stents have significantly reduced the incidence of restenosis after percutaneous coronary interventions, leading to an enthusiastic reception by interventional cardiologists and a rapid incorporation into daily clinical practice.<sup>1-6</sup> However, recent data on late and very late stent thrombosis after drug-eluting stent (DES) implantation have raised concerns about the long-term safety and have led to a decline in the worldwide use of DES.<sup>7-10</sup> Because inhibition of smooth muscle cell proliferation by currently available DES is inseparably connected with the inhibition of endothelial cell proliferation, delayed and incomplete healing is the result, the downside of restenosis reduction with DES. Local delivery of antiproliferative agents by means of special application catheters is an alternative approach for intracoronary pharmacotherapy. Besides the fact that no problematic

coating is needed as a drug carrier, catheter techniques for local delivery independent of the stent itself offer further advantages, including the ability to treat the whole vessel wall, stent edges, and adjacent vessel segments rather than just the area adjacent to the stent struts. However, experience with catheter-based local drug delivery has shown that this technique is hampered by a generally low drug-transfer rate to the vessel wall and a rapid wash out of the applied substance from the vasculature.<sup>11,12</sup> The antitumor drug paclitaxel may be able to compensate for this inherent problem because of its unique pharmacological properties.<sup>13-15</sup> It is highly lipophilic, which promotes rapid cellular uptake, and it has a long-lasting effect on the smooth muscle cell because of the irreversible structural alteration of the cytoskeleton. Along with other groups, we were able to show that paclitaxel

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exerts potent and sustained inhibitory effects on smooth muscle cell proliferation and migration, even after single dose applications, avoiding the need for sustained paclitaxel release such as it is supplied by DES.<sup>16–18</sup> To make use of this, we developed a new, catheter-based delivery system for local intracoronary pharmacotherapy, combining a passive application mode for lipophilic compounds with a simple, atraumatic delivery system. The catheter consists of a percutaneous balloon featuring a distal and proximal segment with occlusive function and a central segment that allows the transfer of paclitaxel to the vessel wall. Holes in the distal ramp of the catheter allow the drug depot to be filled without hydrojets because of an almost parallel flooding of the central segment. Our own experience with catheter-based delivery of paclitaxel, using a variety of animal models and species, has been quite promising.<sup>13,14,16,17,19</sup> Even more encouragingly, a recent trial in humans using a similar approach with paclitaxel-coated balloon catheters yielded very positive results.<sup>20</sup> Thus, the aim of this study, the “local intracoronary delivery of paclitaxel after stent implantation for prevention of restenosis in comparison with implantation of a bare metal stent (BMS) alone or with implantation of a paclitaxel-coated stent” (LOCAL TAX), was to evaluate the use of catheter-based local delivery of fluid paclitaxel for the treatment of de novo coronary lesions. The safety and efficacy of this new technique were evaluated in comparison with the use of a BMS or a paclitaxel-eluting TAXUS stent.

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## Clinical Perspective on p 301

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### Methods

#### Patients and Study Protocol

The study was a prospective, randomized, single-blinded 3-armed trial performed at the Department of Cardiology of the Tübingen University Hospital. The study was sponsored by the University Hospital of Tübingen and by Acrostak Corp (Winterthur, Switzerland), which manufactured and supplied the drug delivery catheters used in the study. The sponsors had no role in the design and conduct of the study, the analysis of the results, the decision to publish, or the drafting of the manuscript. The authors collected and evaluated the data. The authors vouch for the accuracy and completeness of the data presented.

All subjects provided written informed consent. The study protocol was approved by the independent ethics committee of the University Hospital Tübingen and authorized by the German Federal Institute for Drugs and Medical Devices. The study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization Guidelines for Good Clinical Practice. The project was registered in the public trials registry sponsored by the US Library of Medicine ([www.clinicaltrials.gov](http://www.clinicaltrials.gov), NCT 00396929).

Patients who were at least 18 years of age, had clinical evidence of ischemia or a positive function test, and were undergoing percutaneous coronary intervention for a single de novo lesion in a native coronary artery were considered for enrollment. Major clinical criteria for exclusion were acute myocardial infarction within 72 hours before enrollment, a left ventricular ejection fraction of <30%, hemorrhagic diatheses, contraindications or allergy to aspirin, clopidogrel, heparin, paclitaxel, or stainless steel, a serum creatinine level of >1.5 mg/dL (133  $\mu$ mol/L), a leukocyte count of <3000 per cubic millimeter, or a platelet count of <100 000 per cubic millimeter, pregnancy, breastfeeding or possibility of pregnancy during the study period, and coexisting conditions that limited life expectancy to <12 months or that could affect a patient's compliance with the

protocol. We also excluded patients with concomitant illness that required cytostatic therapy. Current participation in other investigational trials was an exclusion criterion. Angiographic exclusion criteria were a stented segment of 20 mm or longer, a vessel diameter >4.0 mm, left main or ostial target lesion stenosis, severe calcification, an occluded target vessel, or thrombus. Enrollment was permitted after the successful treatment of nonstudy lesions before randomization.

#### Randomization, Interventional Procedure, and Adjunct Drug Therapy

After identification of a target lesion that met all eligibility criteria, patients were randomly assigned to treatment with the polymer-based paclitaxel-eluting TAXUS stent (Boston Scientific), a BMS (Multi-Link Zeta, Guidant), or a BMS (Multi-Link Zeta, Guidant), followed by catheter-based local delivery of fluid paclitaxel. Sealed, opaque envelopes containing a computer-generated random sequence were supplied by the local study coordination center CenTrial and used for randomization. Patients received 500 mg of aspirin intravenously and a loading dose of 600 mg clopidogrel before the procedure. Heparin was given as an initial bolus according to standard practice. Glycoprotein IIb/IIIa antagonists were administered at the operator's discretion. After intracoronary injection of nitroglycerin at a dose of 100  $\mu$ g, baseline angiography of the target vessel was performed in at least 2 orthogonal views. After predilatation, the target lesion was stented. Stent size was chosen to be 2 to 4 mm longer than the lesion, with a ratio of stent diameter to reference vessel diameter (RVD) of 1.1 to 1.2:1. In patients allocated to subsequent paclitaxel delivery, the catheter (GENIE, Acrostak, Winterthur, Switzerland) (supplemental Figure I) was introduced in the stented segment in the same fashion as a conventional balloon catheter and inflated with a constant pressure of maximal 2 atm, allowing the blockage of the vessel and simultaneous release of paclitaxel into the inner segment of the balloon. The length of the GENIE catheter was 20 mm in all patients, securing complete coverage of the shorter stent. The recommended time of inflation was 120 seconds. After the procedure, heparin was discontinued, and vascular sheaths were removed according to standard practice. A postprocedural ECG was obtained immediately after intervention and after 4 and 24 hours. Routine laboratory tests, including differential blood count, electrolytes, and cardiac enzymes, were obtained at the same time points. Patients took 100 mg of aspirin daily indefinitely and 75 mg of clopidogrel daily for 6 months in all study groups. Clinical follow-up was scheduled at 1, 6, and 12 months and yearly thereafter for 5 years.

#### Data Management

Independent study monitors from The Coordination Centre for Clinical Trials at the University clinics of Tübingen and Ulm (CenTrial) verified the data onsite from case report files. Major adverse events were reviewed and adjudicated by an independent data and safety committee, whose members were unaware of patients' treatment allocation. An interim safety report with data from the first 60 patients was reviewed by the safety committee. Angiography was performed before and after all interventions and at 6 months. Identical projections and analyses were used in each case. The contrast-filled injection catheter was used as the calibration source. Quantitative analysis of coronary angiograms was performed at an independent angiographic core laboratory (Cardiology Department of the University of Ulm) by investigators blinded to the study protocol. The CAAS II research system (Pie Medical Imaging) was used for quantification and automated contour detection. Measurements were reported separately for plaque maximum, within the stent from shoulder to shoulder (in-stent) and within 5 mm proximal and distal to each edge (in-segment).

#### End Points and Follow-Up

The primary end point was the in-stent late lumen loss (LLL) at the 6-month follow-up. Secondary end points included binary restenosis rate >50%, minimal luminal diameter (MLD), and diameter steno-

**Table 1. Baseline Clinical and Angiographic Characteristics**

Characteristic	BMS + Paclitaxel (N=67)	BMS (N=68)	Paclitaxel-Eluting Stent (N=67)	<i>P</i>
Age, y	64.8±9.4	64.7±8.8	65.7±8.4	0.829
Male sex, n (%)	53 (79)	59 (87)	45 (67)	0.023
Other conditions, n (%)				
Diabetes mellitus	23 (34)	23 (33)	26 (40)	0.910
Hyperlipidemia	46 (69)	48 (71)	52 (78)	0.464
Current smoker	11 (16)	5 (7)	11 (16)	0.326
Hypertension	57 (85)	59 (87)	60 (90)	0.754
Unstable angina	6 (9)	9 (13)	9 (13)	0.736
Previous myocardial infarction	25 (37)	25 (37)	16 (24)	0.159
Previous percutaneous coronary intervention	36 (54)	34 (50)	24 (36)	0.087
Previous CABG surgery	6 (9)	7 (10)	9 (13)	0.722
Coronary artery disease, n (%)				
Single-vessel disease	9 (13)	14 (21)	16 (25)	0.289
Two-vessel disease	24 (36)	24 (35)	19 (28)	0.610
Three-vessel disease	34 (51)	30 (44)	32 (48)	0.758
Vessels affected, n (%)				
Right coronary artery	25 (35)	23 (34)	23 (34)	0.948
Left anterior descending coronary artery	17 (25)	19 (28)	21 (31)	0.741
Left circumflex artery	25 (37)	24 (35)	23 (34)	0.948
Left ventricular ejection fraction, %	54.7±9.7	54.9±9.6	57.1±10.3	0.149

CABG indicates coronary artery bypass graft.

sis. We also analyzed a composite clinical end point consisting of cardiac death, myocardial infarction, acute or subacute closure of the vessel, and target lesion revascularization (TLR) 6 months after intervention. If the cause of death was undetermined, it was categorized as cardiac. Occurrence of myocardial infarction after the intervention was assumed when 2 of the following criteria were present: chest pain lasting longer than 30 minutes; new, clinically significant pathological Q waves in at least 2 contiguous leads; new changes on the ECG that were typical for myocardial infarction (ST elevation of >0.1 mV in at least 2 adjacent leads or new occurrence of a complete left bundle branch block); or a significant increase in the level of creatine kinase to at least 3 times the upper limit of normal, with an elevated creatine kinase MB level. Acute closure was defined as the occurrence of new, persistent severely reduced flow (grade 0 or 1 according to the Thrombolysis in Myocardial Infarction classification) within the target vessel during intervention, resulting in a nonassigned treatment strategy or myocardial infarction or death. Subacute closure was defined as closure occurring during follow-up. TLR was defined as percutaneous or surgical revascularization involving the target lesion. LLL was defined as the MLD immediately after the procedure minus the MLD at the 6-month follow-up. Acute gain was defined as the MLD immediately after the procedure minus the MLD before the procedure. Percent diameter stenosis was defined as  $(1 - (\text{MLD}/\text{RVD}) \times 100)$ . Binary angiographic restenosis was defined as >50% diameter stenosis at follow-up.

### Statistical Analysis

The objective of the study was to assess whether the outcome of treatment with catheter-based local delivery of fluid paclitaxel after BMS implantation is superior to BMS implantation alone. If superiority was established, the study would go on to assess whether the outcome of treatment with catheter-based local delivery of fluid paclitaxel after stenting was not inferior to the outcome of paclitaxel-eluting stent. Calculation of the sample size was based on the margin of superiority (local delivery of fluid paclitaxel after BMS versus BMS) and of noninferiority (local delivery of fluid paclitaxel after

BMS versus paclitaxel-eluting stent) for in-stent late luminal loss of 0.35 mm. Estimates of LLL were based on data from trials of paclitaxel- and rapamycin-eluting stents.<sup>2-6,21</sup> Furthermore, the standard deviation of LLL was assumed to be 0.6 mm. By using a 1-sided significance level of 0.025, we estimated that 64 patients per group were sufficient to demonstrate superiority or noninferiority of the local delivery of fluid paclitaxel after BMS, with a statistical power of 90% (total study group 192 patients). Expecting a dropout rate of up to 5% of the patients, we included 204 patients (68 patients per group). Analyses related to angiographic measures were conducted according to the number of patients available for each analysis. All other analyses were conducted according to the intention-to-treat principle. Statistical analysis was performed with the statistical software package R (version 2.4.1, [www.r-project.org](http://www.r-project.org)) and SPSS (version 15 for Windows, SPSS Inc, Chicago, Ill). Fisher exact test for categorical data was applied to compare the relative frequency of events between groups. If there was no strong evidence against normality, 2 groups of continuous data were compared by Student *t* test, allowing for unequal variances; otherwise Wilcoxon's test was applied. The Kruskal-Wallis test was chosen to analyze 3 groups of continuous data. All *P* values were 2 sided unless stated otherwise, and a *P* value of <0.05 (0.025 in the case of a 1-sided *P* value) was considered to indicate statistical significance.

## Results

### Baseline Characteristics and Procedural Results

Between August 19, 2005, and February 15, 2007, 204 patients were assigned to receive a BMS with catheter-based paclitaxel delivery (group I), a BMS (group II), or a paclitaxel-eluting stent (group III, 68 patients each). Two patients were withdrawn after randomization because they did not receive the assigned therapy (in 1 case because initial percutaneous coronary intervention failed due to a heavily calcified lesion, in the other because of a too large vessel diameter). The final

**Table 2. Procedural Data and Angiographic Findings During Intervention**

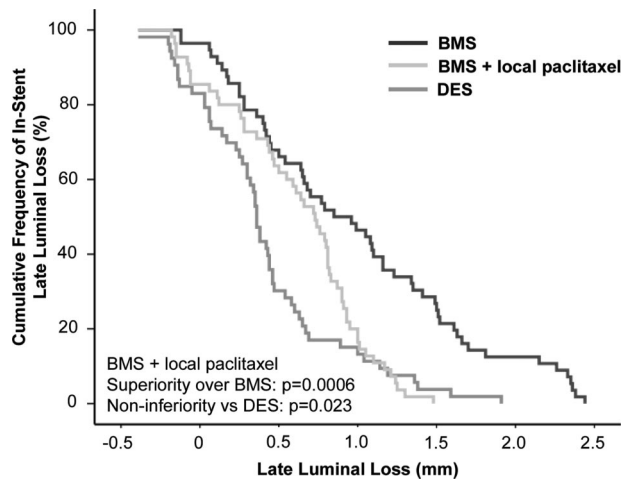
Variable	BMS+Paclitaxel, (N=67)	BMS (N=68)	Paclitaxel-Eluting Stent (N=67)	P
Stent diameter, n (%)				
2.5 mm	13 (19)	17 (25)	13 (19)	0.530
3.0 mm	38 (57)	29 (43)	36 (54)	0.147
3.5 mm	16 (24)	19 (28)	14 (21)	0.631
4.0 mm	0 (0)	3 (4)	4 (6)	0.076
Length of stented segment, mm	14.1±3.6	14.4±3.7	14.5±3.4	0.899
Ratio of balloon to vessel	1.14±0.36	1.12±0.45	1.16±0.39	0.860
Maximal balloon pressure, atm	12.3±2.8	12.2±2.6	12.1±2.3	0.668
Local delivery of fluid paclitaxel				
Device inflation time, s	113.8±14.2	...	...	
Amount of paclitaxel delivered, ml	13.4±4.1	...	...	
Complex (type B or C) lesions, n (%)	60 (90)	61 (90)	61 (91)	1.000
Vessel size, mm	2.43±0.48	2.50±0.53	2.49±0.46	0.860
Lesion length, mm	11.1±5.7	10.9±4.8	10.3±4.9	0.636
Minimal luminal diameter before procedure, mm	0.84±0.33	0.81±0.34	0.78±0.35	0.375
Final minimal luminal diameter after procedure, mm				
In segment	2.08±0.42	2.15±0.52	2.07±0.48	0.748
In stent	2.47±0.37	2.49±0.50	2.53±0.44	0.741
Proximal margin	2.46±0.48	2.54±0.60	2.44±0.51	0.621
Distal margin	2.18±0.47	2.26±0.60	2.15±0.55	0.685
Diameter stenosis before procedure, % of luminal diameter	65.8±11.3	67.60±11.71	68.68±12.23	0.234
Final stenosis after procedure, % of luminal diameter				
In segment	20.88±10.52	22.40±9.11	23.26±11.67	0.426
In stent	9.25±8.28	12.45±7.55	10.17±7.37	0.069
Proximal margin	16.25±9.55	15.52±13.84	18.12±11.41	0.381
Distal margin	16.64±12.15	16.76±10.99	19.50±12.16	0.259
Net luminal gain, mm				
In segment	1.23±0.44	1.35±0.54	1.29±0.49	0.615
In stent	1.64±0.34	1.68±0.48	1.73±0.52	0.396
Proximal margin	0.14±0.38	0.20±0.47	0.15±0.44	0.618
Distal margin	0.21±0.39	0.31±0.48	0.22±0.44	0.243
Final reference diameter	2.75±0.41	2.83±0.50	2.83±0.45	0.728

patient cohort included 202 patients (67 patients in group I, 68 in group II, and 67 in group III). Clinical follow-up was performed in 201 patients (99.5%), and angiographic follow-up could be performed in 164 patients (81.2%, 54 in group I, 56 in group II, and 54 in group III). There were more women in group III, all other baseline characteristics were well matched (Table 1). Among all patients, the mean age was 65 years, 78% were men, 33% had had a previous myocardial infarction, 47% had undergone previous percutaneous coronary intervention, 11% had undergone previous coronary artery bypass grafting surgery, and 36% had diabetes. The majority of treated coronary arteries (90%) were class B or C according to the American College–American Heart Association classification. The average reference vessel diameter was 2.48 mm, and the mean lesion length was 10.8 mm. In patients receiving catheter-based paclitaxel delivery, the mean application time was 113.8 seconds, and the delivered volume was 13.4 mL (equaling 110  $\mu$ g pacli-

taxel). The procedural variables and initial angiographic results are listed in Table 2.

### Angiographic Results

Follow-up angiography was performed in 54 patients (80.6%) in the local paclitaxel group, 56 patients (82.4%) in the BMS group, and 54 patients (80.6%) in the paclitaxel-eluting stent group. Patients who did not undergo follow-up angiography did not differ significantly from those who did with respect to the baseline characteristics. The median duration of angiographic follow-up was 184 days (25th and 75th percentiles, 181 and 195 days) in the local paclitaxel group, 182 days (25th and 75th percentiles, 179 and 191 days) in the paclitaxel-eluting stent group, and 183 days (25th and 75th percentiles, 180 and 188 days) in the BMS group. The primary end point mean in-stent LLL was significantly reduced after catheter-based paclitaxel delivery compared with the BMS arm ( $0.61\pm0.44$  versus  $0.98\pm0.72$  mm,



**Figure.** Cumulative frequency distribution curve of in-stent LLL on quantitative coronary angiography.

$P=0.0006$  in the 1-sided  $t$  test). Compared with paclitaxel-eluting stent, catheter-based paclitaxel delivery after stenting was not significantly inferior in respect to in-stent LLL ( $0.61 \pm 0.44$  versus  $0.44 \pm 0.49$  mm,  $P=0.023$  in the 1-sided  $t$  test). The 1-sided 95% CI for the true difference of the means of in-stent LLL in groups I and III was  $-\infty$  to 0.3174188. The cumulative frequency distribution curve of in-stent LLL is shown in the Figure. All secondary angiographic end points (binary restenosis rate, percent diameter stenosis, MLD) were also significantly improved after local paclitaxel delivery compared with the BMS arm (1-sided  $P$  values of 0.0012, 0.018, and 0.0026, respectively). Angiographic data are listed in Table 3 (with  $P$  values related to global comparisons).

## Clinical Results

Major adverse cardiac events are listed in Table 4. There were no deaths, myocardial infarctions, or TLR during the index hospitalization. At 30 days, 1 patient in the paclitaxel-eluting stent arm had undergone TLR because of subacute closure of the target lesion. There was a lower rate of cumulative out-of-hospital events during follow-up in patients who were treated with paclitaxel than in patients who received a BMS alone. At 6 months, there was no death in the local paclitaxel arm, no death in the DES arm, but 2 deaths in the BMS group. No myocardial infarction occurred after local paclitaxel delivery, 1 myocardial infarction was seen in the DES arm, and 3 in the BMS arm. Nine patients underwent TLR after local paclitaxel delivery (13.4%), 15 patients in the BMS arm (22.1%) and 8 in the DES arm (11.9%). Altogether, the combined rate of major adverse cardiac events and TLR was identical in both arms receiving paclitaxel therapy (either after DES or after catheter-based delivery) but halved compared with the BMS arm (13.4% versus 26.8%).

## Discussion

The aim of our study was to evaluate the use of a novel system for catheter-based local delivery of fluid paclitaxel for the treatment of de novo coronary lesions. The LOCAL TAX trial was the first to apply fluid paclitaxel to human coronary arteries, therefore, special attention was focused on the feasibility and safety of this new procedure. Because the handling of the catheter is identical to that of a standard percutaneous transluminal coronary angioplasty catheter, the intervention was technically easy and successful in 100% of cases. No periprocedural problems or adverse events during

**Table 3. Results of Quantitative Angiographic Analysis at Follow-Up**

Variable	BMS+Paclitaxel (N=54)	Bare Metal Stent (N=56)	Paclitaxel-Eluting Stent (N=54)	$P$
Reference diameter, mm	$2.63 \pm 0.54$	$2.58 \pm 0.44$	$2.59 \pm 0.45$	0.536
Late luminal loss, mm				
In segment	$0.62 \pm 0.45$	$0.95 \pm 0.77$	$0.44 \pm 0.58$	0.001
In stent	$0.61 \pm 0.44$	$0.98 \pm 0.72$	$0.44 \pm 0.49$	<0.0001
Proximal margin	$0.18 \pm 0.39$	$0.31 \pm 0.62$	$0.22 \pm 0.51$	0.758
Distal margin	$0.13 \pm 0.37$	$0.27 \pm 0.53$	$0.14 \pm 0.42$	0.387
Minimal luminal diameter, mm				
In segment	$1.71 \pm 0.55$	$1.41 \pm 0.66$	$1.77 \pm 0.60$	0.015
In stent	$1.84 \pm 0.59$	$1.46 \pm 0.69$	$2.04 \pm 0.59$	<0.0001
Proximal margin	$2.30 \pm 0.65$	$2.14 \pm 0.75$	$2.19 \pm 0.64$	0.629
Distal margin	$2.06 \pm 0.50$	$1.94 \pm 0.57$	$1.95 \pm 0.59$	0.641
Stenosis, % of luminal diameter				
In segment	$34.02 \pm 15.61$	$43.19 \pm 24.89$	$31.23 \pm 18.93$	0.011
In stent	$30.49 \pm 16.53$	$42.07 \pm 24.88$	$21.85 \pm 19.18$	<0.0001
Proximal margin	$17.02 \pm 14.32$	$20.19 \pm 22.25$	$21.54 \pm 15.87$	0.355
Distal margin	$15.14 \pm 14.16$	$16.70 \pm 18.19$	$22.01 \pm 17.43$	0.019
Angiographic restenosis, n (%)				
In segment	8 (14.8)	22 (39.3)	8 (14.8)	0.003
In stent	6 (11.1)	21 (37.5)	3 (5.6)	<0.0001
Proximal margin	2 (3.7)	5 (8.9)	4 (7.4)	0.678
Distal margin	1 (1.9)	3 (5.4)	4 (7.4)	0.446

**Table 4. Results of Clinical Follow-Up**

Variable	BMS+Paclitaxel (N=67)	BMS (N=67)	Paclitaxel-Eluting Stent (N=67)	P
<b>In hospital</b>				
Death	0	0	0	...
Myocardial infarction	0	0	0	...
Acute or subacute closure	0	0	0	...
TLR	0	0	0	...
TLR, myocardial infarction, acute or subacute closure, or death	0	0	0	...
<b>At 30 d</b>				
Death	0	0	0	...
Myocardial infarction	0	0	0	
Subacute closure	0	0	1 (1.5)	0.663
TLR	0	0	1 (1.5)	0.663
TLR, myocardial infarction, subacute closure, or death	0	0	1 (1.5)	0.663
<b>At 6 mo</b>				
Death	0	2 (3.0)	0	0.330
Myocardial infarction	0	3 (4.5)	1 (1.5)	0.130
Subacute closure	0	0	0	...
TLR	9 (13.4)	15 (22.1)	8 (11.9)	0.203
TLR, myocardial infarction, subacute closure, or death	9 (13.4)	18 (26.8)	9 (13.4)	0.078

follow-up occurred that could be indicative of an intervention-related safety issue. The primary end point was significantly reduced in patients treated with local paclitaxel delivery compared with patients who received a BMS only. LLL after this new catheter-based technique was in the same range as that reported for DES,<sup>22</sup> but late loss was further reduced in this trial by the use of a paclitaxel-eluting stent. This angiographic difference did not translate into a difference in the clinical outcome, with identical rates of the combined clinical end point in both paclitaxel-treated groups during follow-up. This discrepancy between clinical events and angiographic measures was also noted in the ENDEAVOR study program with zotarolimus-eluting stents and supports the suggestion that it may be sufficient to reduce neointimal proliferation below a critical threshold to ensure a good clinical outcome.<sup>22-25</sup> Significantly, more clinical events occurred in patients who received a BMS only. Other angiographic measures, ie, MLD, percent diameter stenosis, and binary restenosis, revealed an interesting pattern, with better results for the DES than for the catheter technique when the in-stent zone only was evaluated, but virtually no differences when the entire in-segment zone was included. Angiographic restenosis after DES implantation was even higher within the proximal and distal segments adjacent to the stent edges, suggesting a positive effect of the antiproliferative coverage beyond the stent edges when using catheter techniques.

Because there is no prolonged release from a polymer after catheter-based delivery, 1 additional conceivable advantage is unhampered re-endothelialization. In different animal models, this could be shown histologically, but the clinical study provides no additional information because the combined antithrombotic treatment with aspirin and clopidogrel was

upheld in all 3 arms for 6 months, and no direct visualization of the vascular wall was performed using angiography.<sup>16,19</sup>

Excellent clinical data obtained recently with paclitaxel-eluting balloons may serve as a further proof of principle that a short, single-dose administration is sufficient to effectively reduce neointima formation.<sup>20,23</sup> The catheter technique used in this study shares important features with drug-eluting balloons, most important of which is the even distribution of the applied drug on the vascular wall and the independence from stent struts as drug carriers. An additional similarity is the need for a certain application time to allow for cellular uptake of the lipophilic paclitaxel. Application time was reported to be 60 seconds with drug-eluting balloons; in our study, 120 seconds were attempted and maintained in most, but not all, patients. This led to the suggestion of performing a fractionated delivery of 2 times 60 seconds in further trials. In contrast to the drug-eluting balloon, which is a paclitaxel-coated medical device like the DES, the catheter technique used in this study delivers paclitaxel in a fluid solution. On the basis of our preclinical studies, we believe that it could be an advantage that even deeper layers of the injured vascular wall, like dissections, are easily reached by the pharmacological agent. Another fundamental difference to drug-eluting balloons is the concept of delivering paclitaxel independent of the coronary intervention itself by using low, less traumatic pressures (just enough to block the blood stream and to enable delivery) in contrast to the drug-eluting balloons that require percutaneous transluminal coronary angioplasty as a prerequisite for drug delivery. The concept of delivering drugs in fluid solution with atraumatic catheters provides major flexibility in 2 crucial aspects: first, the possibility to deliver various compounds or even a combination of different pharmacological principles; in fact, preliminary preclinical

data with an antithrombotic compound were promising.<sup>26</sup> Second, the possibility to treat longer or more complex vessel segments medically without mechanical trauma. Consequently, a number of patients with chronic total occlusions, bifurcation restenoses, or in-stent stenoses have been treated so far in our institution and are included in registers.<sup>27–29</sup>

A number of limitations of this study should be addressed. Although great efforts were made to avoid any bias and an independent Coordination Centre for Clinical Trials organized and supervised all phases of the study from planning to monitoring, it is still a single-center experience. Although the independent core laboratory that analyzed quantitative coronary angiography was unaware of the assigned treatment, it was possible to identify patients receiving catheter-based paclitaxel delivery simply because it involves an additional step in the procedure after stent implantation. Furthermore, a patient cohort of 202 patients is far too small to test for crucial clinical questions such as differences in the rate of stent thrombosis between the differing methods of paclitaxel delivery. Finally, concomitant medical treatment, especially dose and duration of the combined antiplatelet therapy, were similar in all 3 study arms, making it impossible to test for important questions such as the optimal duration of clopidogrel treatment in the 2 paclitaxel groups.

In conclusion, treatment of native coronary lesions with catheter-based paclitaxel delivery significantly lowered the incidence of clinical events and restenosis compared with BMSs and showed similar effectivity in most parameters compared with paclitaxel-eluting stents.

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### Disclosures

Dr Herdeg reports serving as a consultant for Cordis and Boston Scientific. Dr Gawaz has received a research grant from Boston Scientific for the Department of Cardiology. Drs Göhring-Frischholz, Haase, Geisler, Zürn, Hartmann, Wöhrle, Nusser, Dippon, and May have no disclosures. The sponsors had no role in the design and conduct of the study, the analysis of the results, the decision to publish, or the drafting of the manuscript.

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### CLINICAL PERSPECTIVE

Catheter-based local delivery of fluid paclitaxel is a stent-independent, new strategy of intracoronary pharmacotherapy. It offers the advantages of atraumatic homogenous drug delivery to the whole vessel wall, even beyond stent edges, while avoiding the use of polymer as a drug carrier and allowing for rapid reendothelialization. Deeper layers of the injured vascular wall, like dissections, are easily reached by the fluid pharmacological agent. Another fundamental difference to drug-eluting stents or balloons is the concept of delivering paclitaxel independent of the coronary intervention itself by using low, less traumatic pressures. We assessed the safety and efficacy of this new technique in patients with coronary de novo stenoses after implantation of a bare metal stent. The 3-armed LOCAL TAX study compared, for the first time, catheter-based local delivery of fluid paclitaxel to implantation of a drug-eluting stent or a bare metal stent in 204 patients. The results of the LOCAL TAX study showed that local delivery of fluid paclitaxel was safe and significantly reduced neointimal proliferation, restenosis, and clinical events compared with bare metal stent implantation alone. Compared with paclitaxel-eluting stent, catheter-based paclitaxel delivery was not significantly inferior in respect to the primary end point. We believe the concept of delivering drugs in fluid solution with atraumatic catheters to be very promising because it provides major flexibility in 2 crucial aspects: first, the possibility to deliver various compounds or even a combination of different pharmacological principles; and second, the possibility to treat longer or more complex vessel segments medically without mechanical trauma.

## **SUPPLEMENTAL MATERIAL**

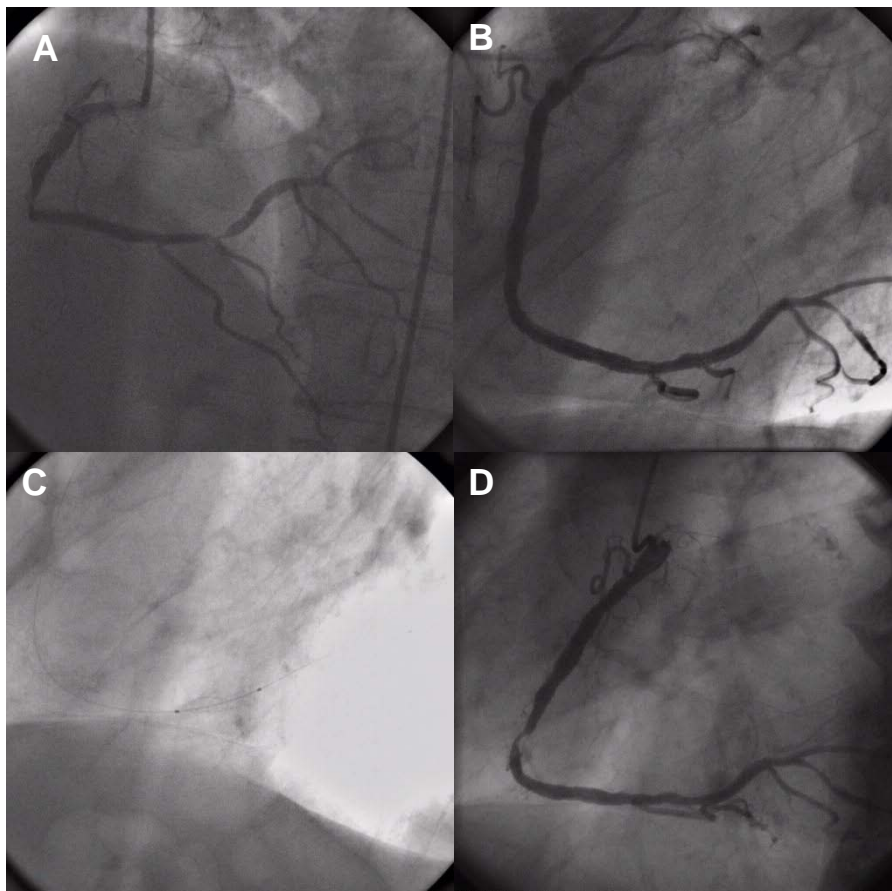
### **Supplemental Figure 1:**

Angiograms of patient Nr. 5, who was treated with local paclitaxel delivery following bare metal stent implantation. Panel A shows the initial angiogram with 2 significant stenoses of the RCA, Panel B the postprocedure angiogram after placement of two identical bare metal stents, Panel C the markers of the application catheter for paclitaxel delivery bordering the distal lesion, and Panel D the 6-month follow-up angiogram showing restenosis of the proximal lesion after bare metal stent implantation and no restenosis of the distal, paclitaxel-treated lesion.

### **Supplemental Figure 2:**

Schematic drawing: function and aspect of the GENIE™ application device (Acrostak, Winterthur, Switzerland) for local drug delivery.

Supplemental Figure 1:



Supplemental Figure 2:

