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Interventional Cardiology

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Background—Treatment of in-stent restenosis with paclitaxel-coated balloon catheter as compared with plain balloon angioplasty has shown surprisingly low late lumen loss at 6 months and fewer major adverse cardiac events up to 2 years. We compared the efficacy and safety of a paclitaxel-coated balloon with a paclitaxel-eluting stent as the current standard of care.

Methods and Results—One hundred thirty-one patients with coronary in-stent restenosis were randomly assigned to treatment by a paclitaxel-coated balloon (3 μg/mm^2) or a paclitaxel-eluting stent. The main inclusion criteria encompassed diameter stenosis of $\geq$70% and $\leq$22 mm in length, with a vessel diameter of 2.5 to 3.5 mm. The primary end point was angiographic in-segment late lumen loss. Quantitative coronary angiography revealed no differences in baseline parameters. At 6 months follow-up, in-segment late lumen loss was 0.38 ± 0.61 mm in the drug-eluting stent group versus 0.17 ± 0.42 mm ($P=0.03$) in the drug-coated balloon group, resulting in a binary restenosis rate of 12 of 59 (20%) versus 4 of 57 (7%; $P=0.06$). At 12 months, the rate of major adverse cardiac events were 22% and 9%, respectively ($P=0.08$). This difference was primarily due to the need for target lesion revascularization in 4 patients (6%) in the coated-balloon group, compared with 10 patients (15%) in the stent group ($P=0.15$).

Conclusions—Treatment of coronary in-stent restenosis with the paclitaxel-coated balloon was at least as efficacious and as well tolerated as the paclitaxel-eluting stent. For the treatment of in-stent restenosis, inhibition of re-restenosis does not require a second stent implantation. (***Circulation***. 2009;119:2986-2994.)

Although drug-eluting stents are currently considered the best possible care in the treatment of in-stent restenosis,[1,2] they may further reduce the flexibility of the vessel and limit the repeatability of the procedure. Furthermore, concerns have been raised that such drug-eluting stents, although effective, require long-lasting antiplatelet therapy to avoid late thrombotic complications.[3–8]

Clinical Perspective on p 2994

Drug-coated balloon catheters may represent an alternative option for the treatment of coronary and peripheral arteries. Preclinical trials demonstrated the efficacy of a balloon coated with a paclitaxel-iopromide mixture in inhibiting neointimal proliferation.[9,10] These results were confirmed by first clinical evidence in patients with coronary in-stent restenosis[11,12] and peripheral artery disease.[13,14] However, these initial clinical studies compared treatment with paclitaxel-coated balloons with uncoated balloons either because drug-eluting stents were not yet approved for the treatment of in-stent restenosis when the studies began or because they were not efficacious in peripheral arteries.[15] Drug-eluting stents may now be considered the standard of treatment for coronary in-stent restenosis. Therefore, comparison of drug-coated balloon with an approved and recognized

drug-eluting stent is required to judge the potential benefit of this alternative treatment option.

The aim of the PEPCAD (Paclitaxel-Eluting PTCA-Balloon Catheter in Coronary Artery Disease) II trial was to compare the SeQuent Please balloon catheter (B. Braun Melsungen AG, Vascular Systems, Berlin, Germany), a second-generation paclitaxel-coated balloon, with the paclitaxel-eluting Taxus Liberté stent (Boston Scientific, Natick, Mass) in the treatment of coronary in-stent restenosis.

Methods

Study Design

The study was a randomized non-blinded trial performed at 10 German departments of cardiology in Rotenburg an der Fulda, Homburg/Saar, Dortmund, Regensburg, Bad Nauheim, Darmstadt, München, Berlin, and Esslingen. The study was sponsored by B.Braun Melsungen AG, the manufacturer of the drug-coated balloon catheter. The sponsor had a role in the design of the study but not in the analysis of the results, in the decision to publish, or in the preparation of the manuscript. An independent clinical research organization and core laboratory provided support for the accuracy and completeness of the data.

The study was performed according to the Declaration of Helsinki and World Health Organization guidelines. Requirements of sections 20 to 22 of the German Medical Device Law and of the European standard EN 540 were followed. Patients gave written informed consent. The study was approved by the responsible local ethics committees.

Eligible patients were ≥18 years of age, had clinical evidence of stable or unstable angina or abnormal functional study, and exhibited single restenosis in a bare-metal stent. Exclusion criteria comprised factors such as an acute myocardial infarction within the previous 48 hours; severe renal insufficiency (glomerular filtration rate <30 mL/min); known hypersensitivity or contraindication to the required medication; malignancies causing life expectancy of <2 years. Angiographic exclusion criteria encompassed stented segments >22 mm in length, vessel diameters of <2.5 mm, stenoses <70% of the luminal diameter, unprotected left main stenosis, or stents covering a major side branch (>2 mm).

Study Devices

Coronary angioplasty balloon catheters were coated with 3 μg of paclitaxel per square millimeter of balloon surface using iopromide as hydrophilic spacer (length 17 to 30 mm, diameter 2.5 to 3.5 mm; SeQuent Please, B. Braun Melsungen). Drug release is >90% on single balloon inflation.[9] Patients in the control group were treated with the paclitaxel-coated Taxus Liberté drug-eluting stent (length 16 to 28 mm, diameter 2.5 to 3.5 mm; Boston Scientific).

Interventional Procedure

Cardiac catheterization was performed through the femoral artery. Patients received 250 mg of aspirin intravenously, heparin as an initial bolus of 70 to 200 U/kg body weight adjusted according to the activated clotting time with a target of 200 to 250 seconds, and a loading dose of 300 mg of clopidogrel the day before the procedure or 600 mg immediately before the intervention. Glycoprotein IIb/IIIa antagonists were administered at the operator's discretion. After intracoronary injection of nitroglycerin (100 to 200 μg), baseline angiography of the target vessel was performed in at least 2 near-orthogonal views showing the target lesion free of foreshortening and vessel overlap. After assessment of the angiographic inclusion and exclusion criteria, each eligible patient was randomly assigned by envelope to undergo treatment of the target lesion with either the paclitaxel-coated balloon catheter or the drug-eluting stent.

Predilation of the target lesion was usually performed before using the study device. The diameter of the conventional nonstudy balloon

catheter was 0.5 mm smaller than that of the drug-coated study balloon or stent. The recommended inflation time for the drug-coated balloon was ≥30 seconds.[16] After the procedure, vascular sheaths were removed according to usual hospital practice.

Quantitative Coronary Angiography

Angiography was performed before and after all interventions, at 6 months, and at unscheduled angiography using identical projections. Quantitative analysis of the coronary angiographic images was performed by an independent core laboratory (Clinical Research Institute, Rotenburg an der Fulda, Germany). The CAAS II system (Pie Medical, Maastricht, the Netherlands) was used for automated contour detection and quantification. Measurements included the stented area, with measurement from shoulder to shoulder (in-stent), and the total treated area plus 5 mm of that area on either side (in-segment). Restenosis was defined as a diameter stenosis of ≥50%.

Follow-Up and End Points

All patients received ≥100 mg of aspirin daily lifelong. Clopidogrel (75 mg/day) was given for 3 months after drug-coated balloon angioplasty and for 6 months after drug-eluting stent implantation. Patients underwent clinical observation for a total of 12 months. All end points and adverse events were adjudicated by an independent clinical events committee.

Late lumen loss (the difference between the in-segment minimal lumen diameter after the procedure and at 6 months, as evaluated by quantitative coronary angiography) was the primary end point. Secondary end points included the rate of restenosis and the rate of the combined clinical events up to 12 months, including stent thrombosis, target-lesion revascularization, myocardial infarction, and death. Stent thrombosis was defined according to the Academic Research Consortium definition.[17] Target-lesion revascularization was defined as percutaneous reintervention or coronary-artery bypass grafting involving the target lesion. The decision to perform a revascularization procedure was based on symptoms, angiographic findings at follow-up, or both. Myocardial infarction was assumed to have occurred if 2 of the following 5 criteria were present: chest pain lasting longer than 30 minutes; substantial changes on ECG that were typical of acute myocardial infarction (an ST-segment elevation of 0.1 mV in at least 2 adjacent ECG leads or the new occurrence of a complete left bundle-branch block); a substantial increase in the level of creatine kinase or its myocardial band isoform (at least 3 times the upper normal value); new, clinically significant Q waves; and chest pain leading to angiography up to 6 hours after the onset of the pain, with angiographic evidence of a totally occluded vessel. Serious adverse events were defined according to international (International Conference on Harmonization) guidelines.[18]

Statistical Analysis

It was estimated that an enrollment of 130 patients would be needed for the study to achieve a statistical power of 90% to detect a reduction in late lumen loss from 0.4 ± 0.4 mm in the drug-eluting stent group to 0.15 ± 0.4 mm in the drug-coated balloon group, assuming a dropout rate of 15%. Estimates of late lumen loss for this power calculation were based on data from trials of paclitaxel-coated stents and drug-coated balloons for treatment of in-stent restenosis.[1,2,11,12]

Data were analyzed according to intention to treat. An as-treated analysis was performed for descriptive comparison only. Continuous data are expressed as means±SD. Categorical variables were compared with Fisher's exact test, and continuous variables were compared with the 2-sided Student t test or the Welch test for unequal variances. Confidence intervals for the difference between proportions were calculated with a normal approximation of the binomial distribution with correction for continuity (StatView 5.0 and BiAS 8.05). Event-free survival was compared using Kaplan–Meier analysis with the Mantel-Cox log-rank test constructed by

Table 1. Baseline Clinical and Angiographic Data: Intention-to-Treat Analysis

	Drug-Coated Balloon	Drug-Eluting Stent
N	66	65
Age	64.6±9.7 years	65.1±8.7 years
Male gender	48 (72.7%)	50 (76.9%)
Diabetes mellitus	22 (33.3%)	17 (26.2%)
Hyperlipidemia	52 (74.8%)	46 (70.7%)
Smoking	16 (24.2%)	15 (23.1%)
Hypertension	53 (80.3%)	54 (83.1%)
Unstable angina	21 (31.8%)	12 (18.5%)
CAD		
Single-vessel disease	19 (28.8%)	23 (35.4%)
Two-vessel disease	27 (40.9%)	23 (35.4%)
Three-vessel disease	20 (30.3%)	19 (29.2%)
Vessel		1 saphenous venous graft
LAD	20 (30.3%)	28 (43.1%)
CX	24 (36.4%)	19 (29.2%)
RCA	22 (33.3%)	17 (26.2%)
Restenotic stent		
Length	17.4±5.8 mm	17.6±4.8 mm
Diameter	2.98±0.35 mm	2.98±0.34 mm
Patterns of in-stent restenosis*		
I	31 (47.0%)	25 (38.5%)
II	20 (30.3%)	26 (40.0%)
III	14 (21.2%)	12 (18.5%)
IV	1 (1.5%)	2 (3.1%)

All values are mean±SD or N (%). CAD indicates coronary artery disease; RCA, right coronary artery; CX, left circumflex coronary artery; and LAD, left anterior descending coronary artery.

*Patterns of in-stent restenosis according to the Mehran classification.[19]

SPSS software, version 15.0. A 2-sided *P* value of <0.05 was considered to indicate statistical significance.

Results

Patients
One hundred thirty-one patients were enrolled in the trial between January and December 2006. Sixty-five patients were randomly assigned to the drug-eluting stent group, and 66 patients were assigned to the coated-balloon group. Baseline characteristics of the patients were similar in the 2 groups (Table 1). The mean age of the patients in the study was 64.9±9.2 years; 75% were men. Most patients had multivessel coronary artery disease. The pattern of in-stent restenosis was predominantly diffuse.

Angioplasty
Procedural data were also similar in the 2 groups. In the drug-coated balloon group, 5 patients required additional bare-metal stent deployment as a result of dissections. Infla-

tion time was longer in those patients treated with the drug-coated balloon. The balloons and stents used in both treatment groups were similar in length and diameter owing to the same lengths and diameters of the lesions (Table 2).

Predilation was performed in 62 of 66 patients (93.9%) treated with the drug-coated balloon and in 49 of 65 patients (75.4%) in the Taxus group. One patient in the drug-coated balloon group was treated with 2 paclitaxel-eluting balloons. Every drug coated balloon was only used once. In the Taxus group, 2 patients were treated with an additional Taxus stent. In all patients in the drug-coated balloon group, crossing the lesion with the SeQuent Please balloon was successful, whereas passing the lesion with the Taxus stent failed in 5 patients despite predilation. Four of the crossing failure patients were successfully treated with the drug-coated balloon. In 1 patient, a conventional balloon catheter was used; this patient was excluded from the as-treated analysis. Target-lesion revascularization was driven by recurrent angina pectoris in 12 of 14 (85.7%) of the patients and in 1 each by a complete target vessel occlusion and a long (31.7 mm) 69% lesion in a diabetic patient.

Angiographic Follow-Up
A total of 116 patients (89%) underwent follow-up angiography after 6.1±1.1 months; 3 patients died before the scheduled follow-up angiography, and 12 patients declined to undergo angiographic follow-up because they had no clinical symptoms. The mean in-segment late lumen loss was 0.38±0.61 mm (median 0.24 mm, interquartile range 0.55 mm) in the drug-eluting stent group and 0.17±0.42 mm (median 0.09 mm, interquartile range 0.42 mm) in the drug-coated balloon group ($P=0.03$, Table 2 and Figure 1). Restenosis occurred in 12 of 59 patients (20%) in the drug-eluting stent group and in 4 of 57 patients (7%) in the drug-coated balloon group ($P=0.06$).

Clinical Follow-Up
All patients were eligible for clinical follow-up after 6 months. One myocardial infarction occurred in the drug-eluting stent group during the index procedure as a result of a side-branch occlusion. One patient in the drug-coated balloon group and 3 patients in the drug-eluting stent group died of noncardiac causes. One patient in the drug-coated balloon group suffered cardiac death as a result of chronic heart failure resulting in renal failure; there were no biomarkers or ECG changes indicating acute myocardial ischemia in this patient.

Four patients in the coated-balloon group and 10 patients in the drug-eluting stent group underwent repeated target-lesion revascularization during the first 6 months or during follow-up angiography (Table 2). Between 6 and 12 months, 2 third-repeat target-lesion reinterventions occurred in the drug-eluting stent group, whereas 2 patients in the drug-coated balloon group underwent percutaneous coronary intervention in a non-target vessel.

The Kaplan–Meier estimates of survival free from clinical events during 12 months are shown in Figure 2. The difference in event rates (22% in the drug-eluting stent group

Table 2. Procedural Data, Angiographic Findings at Intervention and 6-Month Angiographic Follow-Up, Clinical Follow-Up up to 12 Months: Intention-to-Treat Analysis
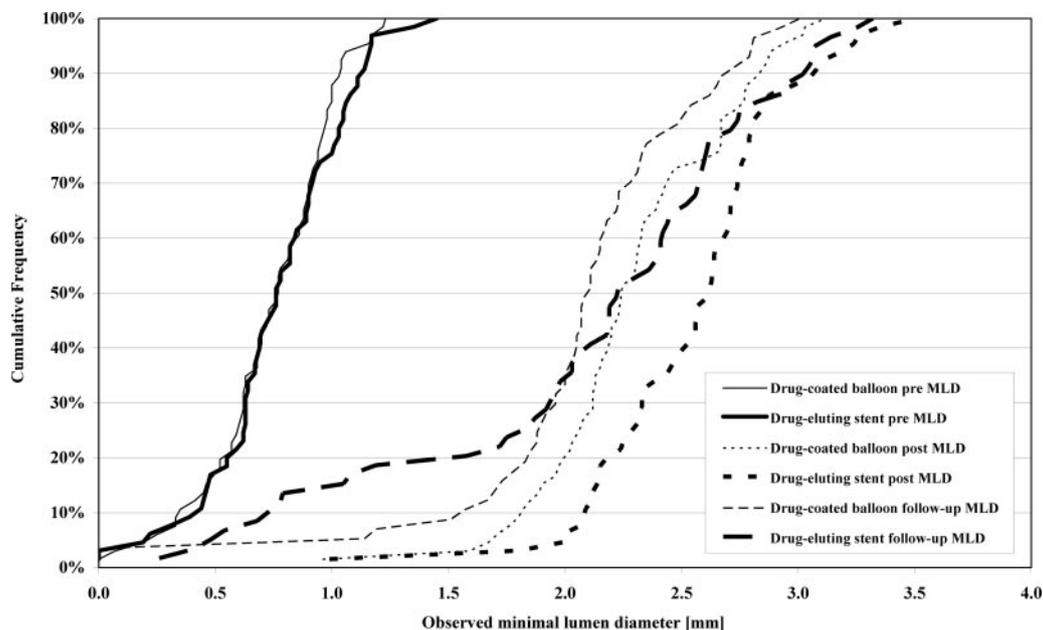
	Drug-Coated Balloon	Drug-Eluting Stent	Difference (95% CI)	*P*
Procedural data				
n	66	65		
Study device, mm				0.51
Length	22.2±4.6	21.6±4.7	−0.54 (−1.08 to 2.16)	
Diameter	2.99±0.33	2.97±0.33	0.03 (−0.09 to 0.14)	
Mean pressure, bar	13.18±2.51	13.94±2.19	−0.76 (−1.57 to 0.06)	0.07
Balloon/stent inflation time, sec	40.42±13.06	24.92±11.92	15.50 (11.14 to 19.87)	<0.0001
Additional stents, n (%)	6 (9.1)	2 (3.1)	0.06 (−0.04 to 0.16)	0.28
GP IIb/IIIa antagonists, n (%)	2 (3.0)	2 (3.1)	0.001 (−0.07 to 0.07)	0.62
Lesion length, mm	15.7±6.6	15.4±6.6	0.22 (−2.07 to 2.51)	0.85
Reference diameter, mm	2.85±0.39	2.83±0.36	0.02 (−0.11 to 0.15)	0.74
Diameter stenosis before intervention, %	73.9±8.8	72.8±9.4	1.1 (−2.1 to 4.2)	0.51
Diameter stenosis postintervention, %	19.5±9.9	11.2±8.1	8.3 (5.1 to 11.4)	<0.0001
Minimal lumen diameter before intervention, mm	0.74±0.27	0.77±0.30	−0.28 (−0.13 to 0.07)	0.57
Minimal lumen diameter postintervention, mm	2.30±0.40	2.56±0.41	−0.26 (−0.40 to −0.12)	0.0003
Angiographic follow-up at 6 months				
Angiographic follow-up, n (%)	57 (86.4)	59 (90.8)	−0.04 (−0.15 to 0.05)	0.43
Minimal lumen diameter				
In-stent, mm	2.08±0.56	2.11±0.78	−0.04 (−0.29 to 0.21)	0.77
In-segment, mm	2.03±0.56	1.96±0.82	0.07 (−0.19 to 0.33)	0.60
Diameter stenosis, %	29.4±17.5	34.2±24.3	−4.7 (−12.5 to 3.1)	0.23
Late lumen loss, mm				
In-stent	0.19±0.39	0.45±0.68	−0.26 (−0.47 to −0.06)	0.01
In-segment	0.17±0.42	0.38±0.61	−0.21 (−0.40 to −0.02)	0.03
Late lumen loss index, mm				
In-stent	0.12±0.26	0.28±0.48	−0.16 (−0.30 to −0.02)	0.03
In-segment	0.11±0.29	0.30±0.53	−0.19 (−0.35 to −0.03)	0.02
Binary restenosis rate, n (%)				
In-stent	4 (7)	10 (16.9)	−0.10 (−0.23 to 0.03)	0.17
In-segment	4 (7)	12 (20.3)	−0.13 (−0.27 to 0.01)	0.06
Patterns of restenosis, n/N (%)*				0.10
I	1/4 (25)	7/12 (58.3)		
II	0/4 (0)	1/12 (8.3)		
III	1/4 (25)	2/12 (16.7)		
IV	2/4 (50)	0/12 (0)		
Proximal in-segment	0/4 (0)	2/12 (16.7)		
Clinical follow-up up to 12 months, n (%)				
Target-lesion revascularization	4 (6.3)	10 (15.4)	−0.09 (−0.21 to 0.03)	0.15
Myocardial infarction	0	1 (1.5)†	−0.02 (−0.06 to 0.03)	0.99
Death	2 (3.0)	3 (4.6%)	−0.02 (−0.10 to 0.07)	0.98
Cardiac	1 (1.5)‡	0	0.02 (−0.03 to 0.06)	0.99
Noncardiac	1 (1.5)	3 (4.6)	−0.03 (−0.11 to 0.04)	0.60
Stent thrombosis	0	0		
Target-lesion revascularization, myocardial infarction, stent thrombosis, or cardiac death	5 (7.6)	11 (16.9)	−0.09 (−0.22 to 0.03)	0.17
Target-lesion revascularization, myocardial infarction, stent thrombosis, or all-cause death	6 (9.1)	14 (21.5)	−0.12 (−0.26 to 0.01)	0.08

All values are mean±SD or n (%). GP indicates glycoprotein.

*Patterns of in-stent restenosis in patients with repeated restenosis at follow-up angiography according to the Mehran classification.[19]

†Myocardial infarction due to occlusion of a small side branch.

‡Death due to heart failure, renal failure but no creatine kinase elevation and no ECG change.

Figure 1. Angiographic patency: cumulative frequency distribution of in-segment minimal lumen diameters (MLD) determined by quantitative coronary angiography (n=131). Drug-eluting stent versus drug-coated balloon catheter: preprocedure (pre), postprocedure (post), and at 6 months (follow-up). Intention-to-treat analysis: although drug-eluting stent treatment results in larger MLD immediately after the intervention due to a significantly greater late lumen loss, restenosis rate is greater than in patients treated with the coated balloon.

versus 9% in the drug-coated balloon group; $P=0.08$) was primarily a consequence of target-lesion revascularization.

A total of 58 serious adverse events occurred in 41 patients; 33 of these occurred in 22 patients treated with drug-eluting stents, and 25 occurred in 19 patients treated with drug-coated balloons (Table 3).

Antiplatelet Therapy Adherence During Follow-Up

After 6 months, 65 of 66 (98.5%) of the patients in the drug-coated balloon group and 64 of 65 (98.5%) of those treated with the Taxus stent were using aspirin ($P=1$), whereas after 12 months, the usage declined to 57 of 66 (86.4%) and 58 of 65 (89.2%), respectively ($P=0.79$). For clopidogrel, the respective numbers were 19 of 66 (28.8%) and 42 of 65 (64.6%) after 6 months ($P<0.0001$) and 12 of 66 (18.1%) and 27 of 65 (41.5%) after 12 months ($P<0.01$).

As-Treated Analysis

In the as-treated analysis, 4 crossing failures in the drug-eluting stent group were counted in the drug-coated balloon group. In the drug-eluting stent group, the mean in-segment late lumen loss was 0.39 ± 0.63 mm, as compared with 0.18 ± 0.41 mm in the drug-coated balloon group ($P=0.04$). The advantage of the drug-coated balloon was also seen with respect to the binary in-segment restenosis rate (6.7% versus 20.4%; $P=0.05$), target-lesion revascularization (5.7% versus 16.7%; $P=0.08$), and major adverse cardiac events (7.1% versus 18.3%; $P=0.06$).

Discussion

Restenosis caused by neointimal proliferation is a slow and continuous process, suggesting that prolonged local drug administration is necessary for its effective inhibition. Drug-eluting stents are characterized by sustained drug delivery. Possibly, sustained drug release is essential because drug distribution from a drug-eluting stent to the arterial wall is inhomogeneous.[20] Approximately 85% of the stented vessel wall area is not covered by the stent struts, resulting in low tissue concentrations of the antiproliferative agent in these areas. To achieve antirestenotic efficacy in these areas, high drug concentrations on the stent struts are mandatory for stent-based local drug delivery,[21] with the consequence of delayed and incomplete endothelialization of the stent struts.[22] Furthermore, the polymeric matrixes on the stent embedding the antiproliferative drug could induce inflammation and thrombosis.[23]

A variety of catheter-based local drug delivery approaches for restenosis inhibition have been studied before, for example, double-balloon catheters,[24,25] porous balloons,[26,27] or, more recently, balloons that have the drug coated on their surface.[9,10,16,28] Reliable clinical experience, however, is still limited. The Treatment of In-Stent Restenosis by Paclitaxel-Coated Balloon Catheters (PACCOCATH) ISR I trial was a controlled, randomized, blinded first-in-human study that investigated the use of paclitaxel-coated balloon catheters for treatment of coronary in-stent restenosis. Patients who were treated with the coated PACCOCATH balloon had significantly superior angiographic results associated with improved 12-month clinical outcomes compared with the patients treated with an uncoated balloon.[11] The results of this trial were confirmed by longer follow-up and the subsequent PACCOATH ISR II trial.[12] Further evidence of the efficacy and tolerance of the device is available from the treatment of peripheral arteries with balloon catheters coated in an identical way.[13,14]

The present study compares the SeQuent Please (B. Braun Melsungen), a second-generation balloon with the same coating
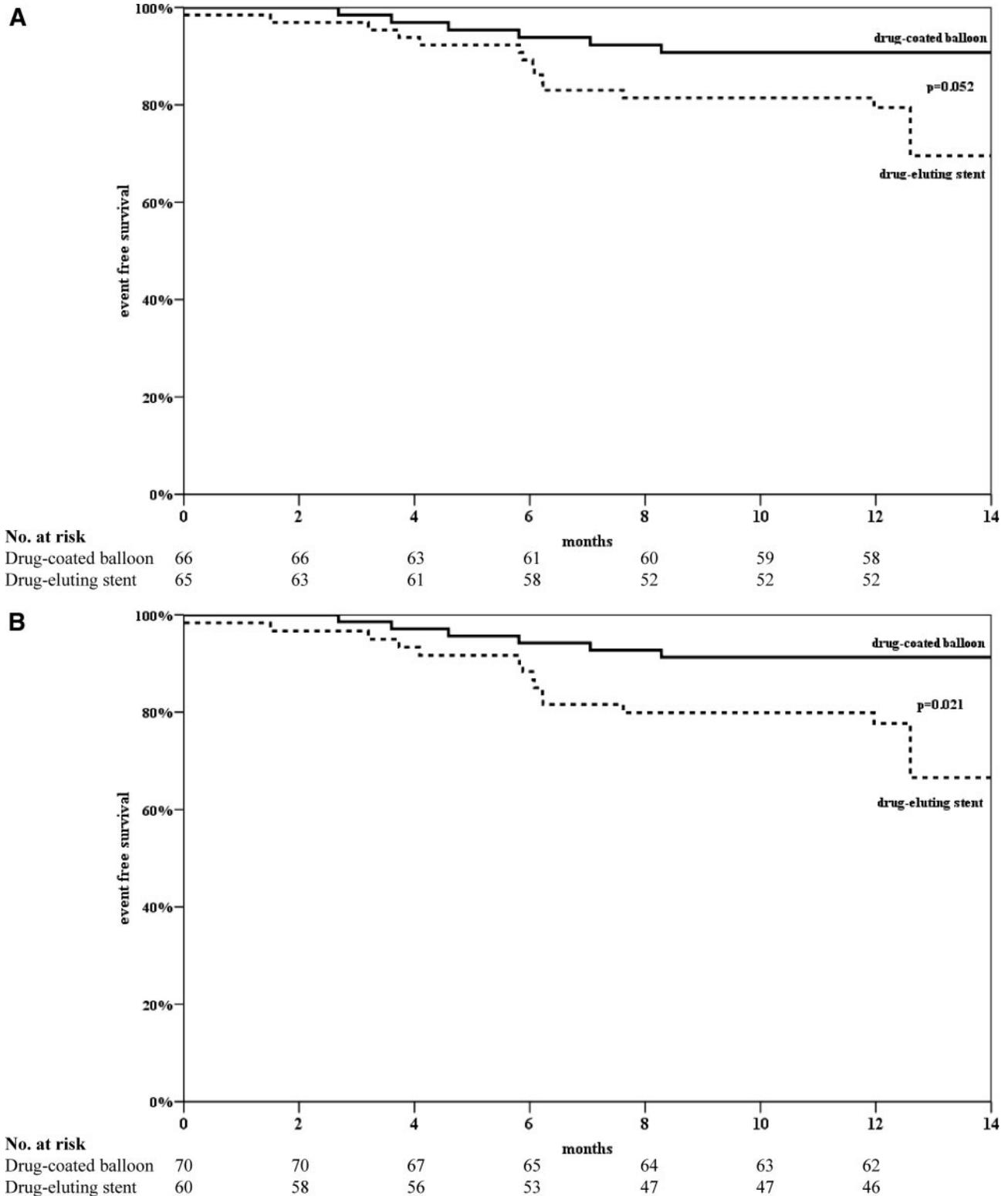
Figure 2. Freedom from stent thrombosis, target-lesion revascularization, myocardial infarction, and death. Log-rank (Mantel-Cox). A, Intention-to-treat analysis (n=131); B, as-treated analysis (n=130).

composition as catheters used in the ISR trial, with the clinically established drug-eluting Taxus stent in the treatment of coronary in-stent restenosis. Compared with the drug-eluting stent, the drug-coated balloon induced significantly less late lumen loss and improved event-free survival. This benefit was observed

although clopidogrel administration was shortened to 3 months. However, in the PACCOCATH ISR trials, clopidogrel was administered for 4 weeks only after drug-coated balloon angioplasty, and no thrombotic complications occurred during the 2-year follow-up period.[12]

Table 3.   Overall Numbers* of Serious Adverse Events (as Defined by the ICH Guidelines) According to Clinical Investigators' Classification

Type of Serious Adverse Event	Drug-Coated Balloon (n=66)	Drug-Eluting Stent (n=65)	P
Total	25	33	0.16
SAEs due to coronary artery disease other than target-lesion revascularization and myocardial infarction listed in Table 2			
Unscheduled angiography, unstable angina pectoris, dyspnea, or chest discomfort (hospitalization)	8	13	0.34
PCI of a nontarget lesion	8	2	0.09
Bypass (nontarget lesion)	1	0	1.00
Cardiac death	1	0	1.00
Noncardiac death	1	3	0.62
Other (hospitalization due to pacemaker implantation, pulmonary edema, or hypertensive crisis)	1	4	0.37
Other SAEs (not related to coronary artery disease)			
Cancer	0	2	0.50
PAVD	1	2	1.00
Other (eg, orthopedic surgery)	4	7	0.53

ICH indicates International Conference on Harmonisation; SAE, serious adverse event; PCI, percutaneous coronary intervention; and PAVD, peripheral arterial vascular disease.

*No. of patients with SAEs (multiple mentions possible).

The results of the current study are in good agreement with both the PACCOCATH ISR I study and a randomized controlled study comparing a sirolimus- and a paclitaxel-eluting stent with plain balloon angioplasty in the treatment of coronary in-stent restenosis.[2] The patient populations were comparable with respect to age and gender: the proportion of patients with diabetes was slightly higher in this study than in PACCOCATH ISR I, and the proportion of current smokers and patients suffering from hyperlipidemia and hypertension was somewhat higher than in the study comparing the 2 drug-eluting stents. In the current study, mean balloon inflation time was only 40 seconds, compared with 80 seconds in the ISR I trial. The patterns of restenosis and lesion lengths in the current study were more favorable than in the ISR I study and less favorable than in the study comparing the drug-eluting stents. Reference diameters and minimal lumen diameters before the intervention were similar in the 3 studies. Immediately after the intervention, the minimal lumen diameter was ≈10% larger if a stent was implanted than in the group treated with the coated balloon.

In-segment late lumen loss and binary restenosis rates in the current study (0.17±0.42 mm and 7%) are slightly higher than those of the PACCOCATH ISR I study (0.03±0.48 mm and 5%). For the paclitaxel-eluting stent group, the 6-month binary restenosis rate in the current study is identical to that of the Intracoronary Stenting and Angiographic Results: Drug-Eluting Stents for In-Stent Restenosis (ISAR-DESIRE) study (20%).[2] Twelve-month target-lesion revascularization rates in the coated-balloon groups of the current study and the PACCOCATH ISR I study were similar and very low (6% and 0%) compared with 15% in the stent group of this study, which is in good agreement with the 19% stated for target-vessel revascularization in the corresponding group of ISAR-DESIRE. Therefore, there is growing evidence that the drug-eluting balloon used in the current study and in the previously published PACCOCATH ISR studies is equally effective as a drug-eluting stent in treating in-stent restenosis.[2,11,12] Furthermore, promising results are available from patients with de novo lesions in peripheral arteries[13,14] and de novo lesions in small coronary arteries (M Unverdorben, MD, PhD, unpublished data, 2009).

Limitations of this study concern the number and selection of patients. Furthermore, most patients had simple (type I or II) patterns of in-stent restenosis that are associated with favorable outcome. Treatment of some patients in the drug-eluting stent group with the coated balloon resulted in an advantage for the stent group. In the as-treated analysis, the coated-balloon group suffered from a systematic shift of difficult-to-treat patients from the drug-eluting stent group to the coated-balloon group.

Conclusions

Compared with drug-eluting stents, the drug-coated balloon avoids the stent-in-stent approach with a second layer of metal in the treatment of coronary in-stent restenosis. The present study confirms the findings of the PACCOCATH ISR I and II trials. Furthermore, the drug-coated balloon was superior to the drug-eluting stent with respect to the primary angiographic end point and was associated with fewer adverse clinical events. This advantage was observed despite a shorter period of combined antiplatelet therapy.

Appendix

PEPCAD II Study Group

Principal Investigator: Martin Unverdorben, Institut für Klinische Forschung, Herz- und Kreislaufzentrum, Rotenburg an der Fulda, Germany. Clinical Research Organisation and Angiographic Core Laboratory: Ralf Degenhardt, Institut für Klinische Forschung, Herz- und Kreislaufzentrum, Rotenburg an der Fulda, Germany. Staff: Tina Iffland, Melanie Häußler. Statistical Advisor: Hanns Ackermann, Zentrum für medizinische Informatik, Abteilung für Biomathematik, Universität Frankfurt/Main, Germany. Kardiologische Klinik, Herz- und Kreislaufzentrum, Rotenburg an der Fulda, Germany: Christian Vallbracht, Manfred Scholz, Henning Köhler, Bernd Abt, Eberhard Wagner (40 patients); Klinik für Innere Medizin III, Universitätsklinikum des Saarlandes, Homburg/Saar, Germany: Bruno Scheller, Bodo Cremers, Michael Kindermann, Michael Böhm; Nicole Hollinger, Bianca Werner (37 patients); Medizinische Klinik, Kardiologie, St. Johannes Hospital, Dortmund, Germany: Hubertus Heuer, Norbert Schulze Waltrup, Joachim Weber-Albers, Maritta Marks, Axel Bünemann, Dietmar Schmitz, Mathias Stratmann; Martin Schulz, Claudia Rosendahl, Birgit Laschewski, Alexandra

Thrun, Kathrin Euler, Ute Dieckheuer (17 patients); Klinik und Poliklinik für Innere Medizin II, Universitätsklinikum Regensburg, Germany: Christian Hengstenberg, Andreas Jeron, Andreas Luchner, Daniel Griese, Kurt Debl, Stefan Weber, Roland Wensel; Katrin Pietzsch (11 patients); Kerckhoff Klinik, Bad Nauheim, Germany: Christian Maikowski, Matthias Rau, Christian Hamm (9 patients); Medizinische Klinik I, Klinikum Darmstadt, Germany: Gerald Werner, Werner Jung (5 patients); I. Medizinische Abteilung, Krankenhaus Bogenhausen, München, Germany: Diethmar Antoni, M. Kasel (4 patients); Klinik für Innere Medizin, Unfallkrankenhaus Berlin, Berlin, Germany: Franz. X. Kleber, Sascha Rux, Daniel Grund; Heike Bull (4 patients); Medizinische Klinik mit Schwerpunkt Kardiologie, Campus Virchow-Klinikum, Universitätsklinikum Charité, Berlin, Germany: Wolfgang Bocksch, Martin Steeg; Katrin Dittkrist (3 patients); Klinik für Kardiologie, Pneumologie und Angiologie, Klinikum Esslingen, Germany: Matthias Leschke, Jean Rieber; Birgit Blaich (1 patient).

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CLINICAL PERSPECTIVE

Drug-eluting stents are currently considered the best possible care in the treatment of in-stent restenosis. However, they include the presence of 2 layers of metal and may further reduce the flexibility of the vessel and limit the repeatability of the procedure. First-in-human trials with short-time local drug delivery using a paclitaxel-coated balloon catheter as compared with plain balloon angioplasty have shown beneficial effects in the treatment of coronary in-stent restenosis and in peripheral arteries. The PEPCAD (Paclitaxel-Eluting PTCA-Balloon Catheter in Coronary Artery Disease) II trial compares the drug-coated SeQuent Please balloon with the approved and recognized drug-eluting Taxus Liberté stent. Angiographic late lumen loss was significantly lower with the coated balloon as compared with the drug-eluting stent. Furthermore, there was a trend toward a reduction of clinical events. Treatment of coronary in-stent restenosis with the paclitaxel-coated balloon was at least as efficacious and as well tolerated as the paclitaxel-eluting stent. For the treatment of in-stent restenosis, inhibition of re-restenosis does not require a second stent implantation.

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