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Long-Term Follow-Up After Treatment of Coronary In-Stent Restenosis With a Paclitaxel-Coated Balloon Catheter

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Objectives This study presents long-term clinical follow-up, including binary restenosis rate and major adverse cardiovascular events, of the PACCOCATH-ISR (Treatment of In-Stent Restenosis by Paclitaxel Coated PTCA Balloons) I and II trial.

Background The PACCOCATH-ISR trial was a first-in-human study with a drug-coated balloon catheter and the first study for the treatment of coronary ISR with a drug-coated balloon. So, far no long-term follow-up data have been presented.

Methods This study enrolled 108 patients in a randomized, double-blinded multicenter trial on the efficacy and safety of a paclitaxel-coated balloon (3 $\mu g/mm^2$ balloon surface; PACCOCATH [Bayer AG, Leverkusen, Germany]) compared with an uncoated balloon. The main inclusion criteria were a diameter stenosis of ≥70% and <30-mm length with a vessel diameter of 2.5 to 3.5 mm. The primary endpoint was angiographic late lumen loss in-segment after 6 months. Combined antiplatelet therapy was continued only for 1 month followed by treatment with aspirin alone.

Results During a follow-up of 5.4 ± 1.2 years, the clinical event rate was significantly reduced in patients treated with the drug-coated balloon (major adverse cardiovascular events: 59.3% vs. 27.8%, $p = 0.009$), which was mainly driven by the reduction of target lesion revascularization from 38.9% to 9.3% ($p = 0.004$).

Conclusions Treatment of coronary ISR with paclitaxel-coated balloon catheters is safe and persistently reduces repeat revascularization during long-term follow-up. The initial results were sustained over the 5-year period. (Treatment of In-Stent Restenosis by Paclitaxel Coated PTCA Balloons [PACCOCATH ISR I]; NCT00106587. Treatment of In-Stent Restenosis by Paclitaxel Coated PTCA Balloons [PACCOCATH ISR II]; NCT00409981) (J Am Coll Cardiol Intv 2012;5:323–30) © 2012 by the American College of Cardiology Foundation

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Coronary angioplasty was pioneered by Andreas Grüntzig in 1977 (1). A remarkable improvement of angioplasty has been achieved with the introduction of stents overcoming elastic recoil and dissections (2). However, restenosis due to neointimal proliferation was not affected. Local intravascular drug delivery by drug-eluting stents (DES) seemed to overcome the problem of restenosis (3). However, stents cannot be implanted at all sites where neointimal proliferation limits the long-term benefit of angioplasty. Furthermore, the need for long-term dual antiplatelet therapy due to delayed and incomplete endothelialization limits the use of this kind of therapy. The concept of intramural drug delivery independent from a stent platform became embodied in a drug-coated balloon (DCB) concept (4,5). By coating paclitaxel onto the surface of a conventional angioplasty balloon used to dilate the stenotic artery an exclusively local effect could theoretically be achieved, with the drug transferred to the dilated segment as the balloon is inflated. In this way, an effective local drug concentration was achieved with very low systemic exposure (4).

Paclitaxel is characterized by a high lipophilicity and tight binding to various cell constituents, resulting in effective local retention at the site of delivery (6–8). The addition of a contrast agent resulted in a solubility of paclitaxel far beyond the concentrations applied in previous investigations (9). In vitro and in vivo experiments identified a specific coating with paclitaxel in combination with the hydrophilic X-ray contrast medium iopromide (Ultravist, Bayer HealthCare Pharmaceuticals, Wayne, New Jersey) to be effective for restenosis prevention (PACCOCATH) (Bayer AG, Leverkusen, Germany) (4,10).

Abbreviations and Acronyms

BMS = bare-metal stent(s)
DCB = drug-coated balloon(s)
DES = drug-eluting stent(s)
ISR = in-stent restenosis
TIMI = Thrombolysis In Myocardial Infarction

The first accepted coronary indication for DCB was the treatment of in-stent restenosis (ISR). Based on the results of the PACCOCATH ISR (Treatment of In-Stent Restenosis by Paclitaxel Coated PTCA Balloons) (5,11) and PEPCAD (Paclitaxel-Eluting PTCA-Balloon Catheter in Coronary Artery Disease) II (12) trials, the European Society of Cardiology/European Association for Cardio-Thoracic Surgery guidelines for coronary revascularization gave a class IIa recommendation for this treatment modality. The first-in-human PACCOCATH ISR trial compared the efficacy and tolerance of the PACCOCATH prototype DCB (Bayer AG) with conventional uncoated catheters for the treatment of coronary ISR (5). The longest available clinical follow-up was 2 years (11). In this paper, we present the clinical long-term follow-up data of these first-in-human patients enrolled in the PACCOCATH ISR trial after treatment of coronary ISR with a paclitaxel-coated balloon or an uncoated balloon.

Methods

Study design. A total of 108 patients were enrolled in 2 separately randomized study blocks (PACCOCATH ISR I (5) and ISR II (11)) investigating the efficacy and safety of a paclitaxel-coated balloon (3 $\mu g/mm^2$ balloon surface; PACCOCATH) (Bayer AG). The study was conducted at

Table 1. Baseline Clinical and Angiographic Data, Procedural Data (Intention-to-Treat Analysis)

	Uncoated Balloon (n = 54)	Drug-Coated Balloon (n = 54)	p Value
Age, yrs	66.3 ± 9.8	65.4 ± 10.3	0.805
Male	31 (57)	42 (78)	0.125
Diabetes mellitus	17 (31)	12 (17)	0.313
Insulin-dependent	6 (11)	3 (6)	
Hyperlipidemia	39 (72)	42 (78)	0.485
Smoking	26 (48)	23 (43)	0.772
Hypertension	44 (82)	44 (82)	0.866
Unstable angina	22 (41)	20 (37)	1.000
No. of diseased vessels			0.495
1	13 (24)	9 (17)	
2	19 (35)	24 (44)	
3	22 (41)	21 (39)	
Treated vessel			0.611
RCA	17 (32)	18 (33)	
LCX	12 (22)	13 (24)	
LAD	25 (46)	23 (43)	
Patterns of ISR*			0.377
IA	0	0	
IB	3 (6)	0	
IC	8 (15)	11 (20)	
ID	2 (4)	0	
II	25 (46)	26 (48)	
III	14 (26)	11 (20)	
IV	2 (4)	6 (11)	
Study balloon			
Diameter, mm	3.0 ± 0.3	3.0 ± 0.3	1.000
Length, mm	24.3 ± 5.0	24.1 ± 4.9	0.592
Mean pressure, atm	12.7 ± 2.7	12.5 ± 2.6	0.819
Balloon inflation time, s	68.9 ± 37.7	77.2 ± 42.2	0.063
Restenotic stent type			1.000
BMS	52 (96)	52 (96)	
DES	2 (4)	2 (4)	
Restenotic stent			
Diameter, mm	3.0 ± 0.3	3.0 ± 0.3	0.910
Length, mm	18.4 ± 4.9	20.8 ± 7.3	0.058
Additional stents	2 (4)	3 (6)	1.000
GP IIb/IIIa antagonists	7 (13)	5 (9)	1.000

Values are mean ± SD or n (%). *Patterns of in-stent restenosis according to the Mehran classification (13). The p values were adjusted according to the Fisher method of combining independent tests.

BMS = bare-metal stent(s); DES = drug-eluting stent(s); GP = glycoprotein; ISR = in-stent restenosis; LAD = left anterior descending coronary artery; LCX = left circumflex coronary artery; RC = right coronary artery.

5 departments of cardiology at the medical schools of the universities of Berlin, Freiburg, Homburg/Saar, and Mannheim/Heidelberg in Germany. Financial support was provided by Bavaria Medizintechnik GmbH, Oberpfaffenhoven, Germany, the manufacturer of the balloon catheters used in this study. The sponsor had no role in the design or conduct of the study, in the analysis of the results, in the decision to publish, or in the drafting of the manuscript. The long-term follow-up data were obtained by the authors without external financial support. The authors vouch for the accuracy and completeness of the data presented.

The study was performed according to the Declaration of Helsinki and World Health Organization guidelines. Furthermore, the requirements of sections 20 to 22 of the German Medical Device Law as well as the European standard EN 540 were followed. All patients gave written informed consent. The study was approved by the local ethics committees.

Details of the methods and results up to 2 years have been previously published (5,11). Patients at least 18 years of age with clinical evidence of stable or unstable angina or a positive functional study and a single restenotic lesion in a stented coronary artery with bare-metal stents (BMS) or DES, were considered for enrollment. Major clinical exclusion criteria were: acute myocardial infarction within the past 72 h; chronic renal insufficiency with serum creatinine levels >2.0 mg/dl; known hypersensitivity or contraindications to aspirin, heparin, clopidogrel, abciximab, or paclitaxel; and sensitivity to contrast media not amenable to pre-medication. Cardiac catheterization pre-medication and medication during the intervention was carried out according to hospital practice. Glycoprotein IIb/IIIa antagonists were administered at operator's discretion.

After assessment for angiographic exclusion criteria, each suitable patient was randomly assigned to undergo balloon angioplasty of the target lesion with either a paclitaxel-coated or an uncoated balloon catheter. Standard angioplasty catheters (Orbus X, Bavaria Medizin Technologie GmbH, Oberpfaffenhofen, Germany) were supplied either uncoated or coated with a paclitaxel dose of 3 $\mu g/mm^2$ on the balloon surface.

Pre-dilation of the target lesion was usually performed before the study intervention, using a nonstudy balloon catheter with a diameter 0.5 mm smaller than the study balloon. Study balloon inflation was performed in the same fashion as the inflation of a conventional balloon catheter. Recommended balloon inflation time was 60 s. Immediately following the procedure, heparin was discontinued. Vascular sheaths were removed according to usual hospital practice.

Quantitative coronary angiography. Angiography was performed before and after all interventions and at angiographic follow-up using identical projections and analyses. Quantitative analysis of the coronary angiographic images was performed by an independent, blinded core laboratory. The CAAS II Research System (Pie Medical Imaging, Maastricht, the Netherlands) was used for automated contour detection and quantification. Measurements were obtained in the inner stenotic area, in the stented area with

Table 2. Angiographic Findings at Treatment and 6-Month Follow-Up (Intention-to-Treat Analysis)

	Uncoated Balloon (n = 54)	Drug-Coated Balloon (n = 54)	Difference (95% CI)	p Value
Angiographic measurements at treatment				
Left ventricular function, %	60.3 ± 13.9	60.8 ± 14.5	−0.49 (−6.2 to 5.2)	0.862
Lesion length, mm	18.6 ± 8.3	18.3 ± 9.7	0.28 (−3.41 to 3.97)	0.845
Reference diameter, mm	2.94 ± 0.37	2.94 ± 0.35	−0.05 (−0.25 to 0.14)	0.731
Minimal lumen diameter initial, mm	0.70 ± 0.35	0.63 ± 0.29	0.07 (−0.06 to 0.21)	0.015
Minimal lumen diameter after angioplasty, mm	2.34 ± 0.44	2.43 ± 0.47	−0.09 (−0.27 to 0.09)	0.955
Findings at follow-up angiography (6 months)				
Follow-up angiography	49 (91)	48 (87)		0.944
Left ventricular function, %	61.1 ± 14.1	60.1 ± 14.7	1.0 (−5.2 to 7.2)	0.816
Minimal lumen diameter at follow-up, mm				
In-stent	1.53 ± 0.81	2.30 ± 0.62	−0.77 (−1.06 to 0.47)	0.003
In-segment	1.50 ± 0.79	2.23 ± 0.57	−0.72 (−1.01 to 0.44)	0.004
Late lumen loss, mm				
In-stent	0.81 ± 0.79	0.14 ± 0.46	0.67 (0.41 to 0.93)	0.001
In-segment	0.80 ± 0.79	0.11 ± 0.44	0.69 (0.44 to 0.96)	0.001
Binary restenosis rate				
In-stent	24 (49)	3 (6)	0.39 (0.24 to 0.54]	0.001
In-segment	25 (51)	3 (6)	0.41 (0.26 to 0.56)	0.001

Values are mean ± SD or n (%). The p values were adjusted according to the Fisher method of combining independent tests.
CI = confidence interval.

measurement shoulder to shoulder (in-stent), and in the total stented area plus 5 mm proximally and distally (in-segment). Restenosis was defined as ≥50% diameter stenosis at angiographic follow-up. Patterns of ISR were defined according to the Mehran classification (13).

Follow-up and endpoints. Aspirin (100 mg) and clopidogrel (75 mg) were continued orally for 1 month, followed by treatment with aspirin alone. Patients underwent follow-up angiography after 6 months (up to 9 months) and were followed up for 6 months, 12 months, 2 years, and 5 years (maximum 6.4 years) by clinical observation. All endpoints and adverse events were evaluated in consensus by the investigators. The investigators and the core laboratory remained blinded until the database was closed.

Long-term clinical follow-up after 5 years was defined in the study protocol. Patient's medical history was evaluated by: telephone interviews; a questionnaire on their actual health status and clinical events in the period between 2 and 5 years after randomization; patient's records reviews; and contacting patients' treating physicians.

Angiographic late lumen loss (difference between the post-procedural and 6-month follow-up in-segment minimal lumen diameter; evaluated by quantitative coronary angiography) was the primary endpoint. Secondary end-

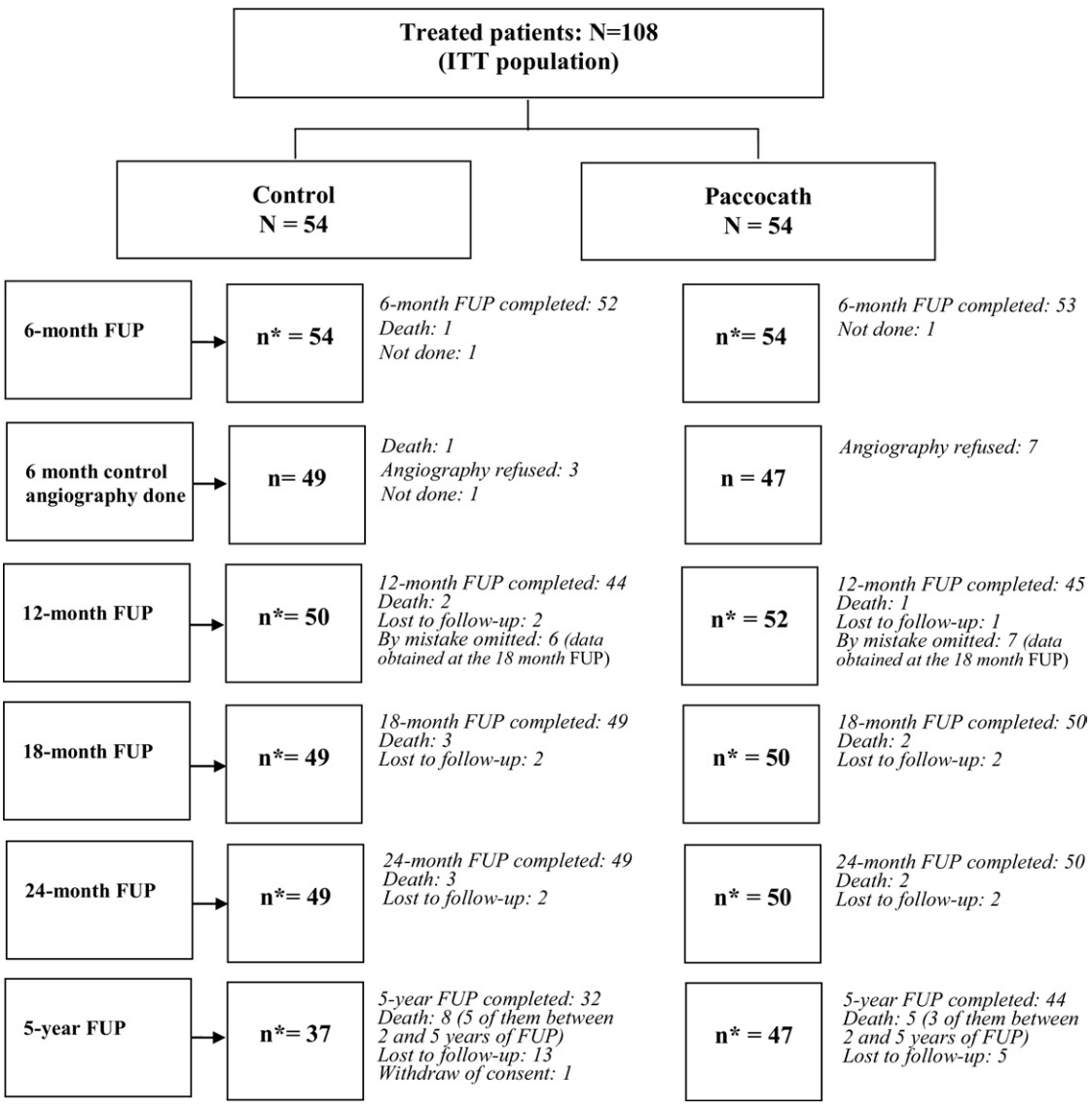

Figure 1. Study Flow Charts

Disposition of patients (n* = number of patients for whom information about their health condition was available). FUP = follow-up; ITT = intention-to-treat.

points included binary angiographic restenosis rate (diameter stenosis of at least 50% assessed by quantitative coronary angiography at 6-month follow-up) and combined clinical endpoints with a follow-up up to 5 years, including acute and subacute stent thrombosis, target lesion revascularization, myocardial infarction, cerebral stroke, and death. The results of the primary angiographic endpoint have been published before (5,11).

Acute stent thrombosis was defined as the occurrence of new severely reduced flow (TIMI [Thrombolysis In Myocardial Infarction] flow grade 0 or 1) within the target vessel during the intervention that persisted and required rescue by a nonassigned treatment strategy or resulted in myocardial infarction or death. Subacute stent thrombosis was defined as vessel closure occurring during follow-up. Target lesion revascularization was defined as percutaneous reintervention or coronary artery bypass graft surgery involving the target lesion. The decision to perform a reintervention procedure was based on symptoms, anatomic findings at follow-up angiography, or both.

Myocardial infarction was assumed if 2 of the following 5 criteria applied: 1) chest pain lasting longer than 30 min; 2) significant electrocardiographic changes typical of acute myocardial infarction (0.1-mV ST-segment elevation in at least 2 adjacent electrocardiogram leads or new occurrence of a complete left bundle branch block); 3) significant increase (3× above normal) of creatinine kinase or its myocardial band isoform; 4) new significant Q waves; or 5) chest pain leading to angiography up to 6 h after the onset of symptoms and showing a totally occluded vessel compared with the previous angiogram. Deaths were documented and confirmed from hospital records or by contacting the patient's relatives or the treating physician.

Statistical analysis. Analysis of the data for all endpoints was performed according to intention-to-treat. Continuous data are expressed as mean ± SD. Categorical variables were compared using the 2-sided chi-square test, and continuous variables were compared using 2-sided Student *t* test. Confidence intervals for the difference of proportions were calculated using normal approximation of the binominal distribution without correction for continuity. Event-free survival was compared by Kaplan-Meier analysis using a log-rank test (Mantel-Cox) (SPSS, version 19.0, SPSS Inc., Chicago, Illinois). The p values were adjusted accord-

Table 3. Clinical Follow-Up (Intention-to-Treat Analysis)

	Uncoated Balloon (n = 54)	Drug-Coated Balloon (n = 54)	Risk Estimate OR (95% CI)	p Value
12-month clinical follow-up (total event rate from baseline to 12 months)				
Target lesion revascularization	20 (37)	2 (4)	0.07 (0.01–0.30)	0.001
Myocardial infarction	5 (9)	1 (2)	0.19 (0.02–1.64)	0.577
Death	3 (6)	2 (4)	0.65 (0.11–4.08)	0.912
Stroke	2 (4)	2 (4)	1.00 (0.14–7.37)	1.000
Stent thrombosis	0	0		1.000
MACE	24 (44)	5 (9)	0.13 (0.04–0.37)	0.001
2-yr clinical follow-up (total event rate from baseline to 24 months)				
Target lesion revascularization	20 (37)	3 (6)	0.10 (0.03–0.36)	0.001
Myocardial infarction	5 (9)	1 (2)	0.19 (0.02–1.64)	0.577
Death	3 (6)	2 (4)	0.65 (0.11–4.08)	0.912
Stroke	3 (6)	2 (4)	0.65 (0.11–4.08)	0.840
Stent thrombosis	0	0		1.000
MACE	25 (46)	6 (11)	0.15 (0.05–0.40)	0.001
5-yr clinical follow-up (total event rate from baseline to 5.4 ± 1.2 yrs)				
Follow-up, yrs	5.2 ± 1.5	5.6 ± 0.9		0.222
Target lesion revascularization	21 (38.9)	5 (9.3)	0.16 (0.055–0.468)	0.004
Myocardial infarction	8 (14.8)	5 (9.3)	0.59 (0.179–1.924)	0.510
Death	8 (14.8)	5 (9.3)	0.59 (0.179–1.924)	0.938
Stroke	5 (9.3)	5 (9.3)	1.00 (0.272–3.674)	1.000
Stent thrombosis	0	0		1.000
MACE	32 (59.3)	15 (27.8)	0.26 (0.118–0.592)	0.009

Values are n (%) or mean ± SD. The p values were adjusted according to the Fisher method of combining independent tests. MACE includes target lesion revascularization, myocardial infarction, stroke, and death.

CI = confidence interval; MACE = major adverse cardiac events; OR = odds ratio.

ing to the Fisher method of combining independent tests. A 2-sided p value of <0.05 was considered significant.

Results

A total of 108 patients were enrolled and were randomly assigned to the uncoated-balloon group (n = 54) and to the coated-balloon group (n = 54). Baseline parameters were similar in both groups (Tables 1 and 2). The mean age of the study population was 66 years at the time of enrollment in the study. Most patients had multivessel coronary artery disease. The pattern of ISR was predominantly diffuse. One patient assigned to the uncoated-balloon group was erroneously treated with a DCB catheter taken from a nonassigned set but was analyzed by intention-to-treat with the uncoated-balloon group.

Angiographic follow-up at 6 months was available in 49 of 54 patients (91%) in the uncoated-balloon group and in 47 of 54 patients (87%) in the DCB group. After 6 months, in-segment late lumen loss was reduced from 0.80 ± 0.79 mm with the uncoated balloon to 0.11 ± 0.44 mm in the paclitaxel-coated balloon group (p = 0.001) (Table 2).

Clinical follow-up was available after 5.4 ± 1.2 years on average (maximum 6.4 years) (Fig. 1). Eight patients from the uncoated-balloon group and 5 from the coated-balloon group died during this period. Furthermore, 8 myocardial infarctions occurred in the uncoated-balloon group and 5 in the coated-balloon group. The incidence of major adverse cardiac events was significantly reduced from 59% in the uncoated group to 28% in patients treated with the drug-coated balloon (p = 0.002). This difference was mainly driven by the reduction of target lesion revascularization from 39% to 9% (Table 3). No stent thrombosis occurred in both groups. Between 2 and 5 years, 5 target lesion revascularizations occurred. It was the first target lesion revascularization for 1 patient in the uncoated-balloon group and 2 patients in the coated-balloon group. Two further patients had their second target lesion revascularizations (1 patient from the uncoated-balloon and 1 patient from the coated-balloon groups). Table 4 summarizes the number of patients with major adverse cardiovascular events between 2 and 5 years. The Kaplan-Meier curves of major adverse cardiovascular events for the 2 groups over up to 6.4 years are shown in Figure 2.

Four patients presenting with DES-ISR were included. In 2 cases, they were randomized to treatment with uncoated balloons and in 2 cases with DCBs. Both patients treated with uncoated balloons underwent target lesion revascularization, whereas no major adverse cardiovascular events occurred in the 2 patients treated with the DCB.

Table 4. Number of Patients With TLR, MI, Stroke, Death, and Other Cardiovascular Events Observed Between 2 and 5 Years

	Uncoated Balloon	Drug-Coated Balloon	p Value
MACE			
Patients with available data at 5 yrs	37	47	
Target lesion revascularization*	2 (3.7)	3 (5.6)	1.00
First TLR	1	2	
Second TLR	1	1	
Myocardial infarction*	4 (7.4)	4 (7.4)	0.89
NSTEMI non-TV/TV/TL	1/0/2	2/0/0	
STEMI non-TV/TV/TL	1/0/0	1/1/0	
Death*	5 (9.3)	3 (5.6)	0.43
Cardiac death	2	1	
Noncardiac death	1	1	
Death of unknown cause	2	1	
Stent thrombosis*	0 (0)	0 (0)	1.00
Stroke*	3 (5.6)	3 (5.6)	1.00
MACE*	12 (22.2)	10 (18.6)	0.71
Other cardiovascular events			
PCI of a nontarget lesion	10	5	
Unscheduled angiography, unstable angina pectoris, dyspnea, or chest discomfort (hospitalization)	20	18	

Values are n or n(%). *% refers to total number of included patients.

MACE = major adverse cardiac event(s); MI = myocardial infarction; non-TV = non-target vessel related; NSTEMI = non–ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction; TL = target lesion related; TLR = target lesion revascularization; TV = target vessel related.

Discussion

Treatment of coronary ISR remains a challenge. Despite increasing DES use, the expansion of indications for percutaneous coronary intervention to high-risk patients and complex lesions leads to an increasing total number of patients suffering from ISR (14). Conventional balloon angioplasty as treatment modality for BMS-ISR is limited by high restenosis rates of about 40% to 60% (15,16). Other approaches, such as the implantation of a second, uncoated stent or mechanical debulking have not been associated with a significant reduction in recurrent in-stent restenosis. Intracoronary radiation (brachytherapy) was the first effective treatment in this setting, with recurrence rates of 16% to 23% (17). Meanwhile, the implantation of a DES in a restenotic BMS has become the most accepted approach. Repeated restenosis rates after implantation of a DES for the treatment of BMS-ISR vary between 16% and 21% (12,15) and are about 20% for the treatment of DES-ISR independent from the antiproliferative drug used (18).

DCBs offer a new therapeutic option in such high-risk patients suffering from ISR. The concept of DCB avoids the implantation of a second layer of metal. Furthermore, a significant reduction in dual antiplatelet therapy compared

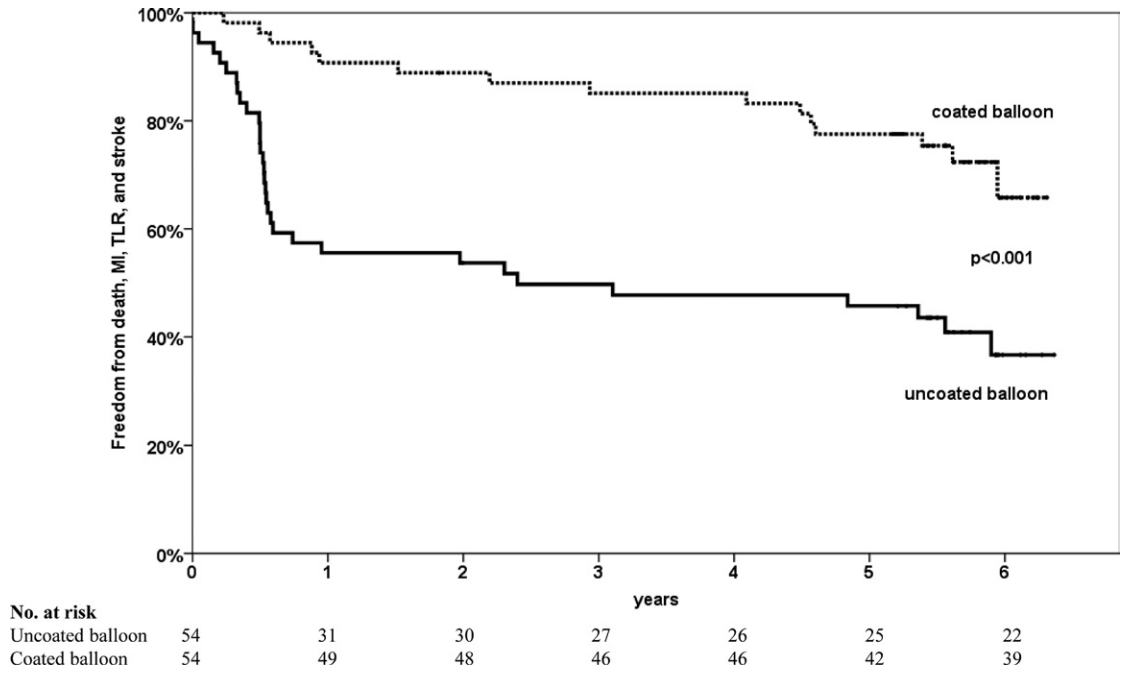

Figure 2. Event-Free Survival From TLR

Event-free survival from target lesion revascularization (TLR), myocardial infarction (MI), stroke, and death (n = 108). Log-rank (Mantel-Cox, intention-to-treat analysis).

with the implantation of a second stent is possible (19). In the clinical trials with paclitaxel-iopromide–coated balloon catheters, the duration of dual antiplatelet therapy after treatment of BMS-ISR varied between 4 weeks (5,11) and 3 months (12). The PEPCAD II ISR study in 131 patients compared a commercially available DCB (SeQuent Please, B. Braun, Melsungen, Germany) using the paclitaxel-iopromide coating with the Taxus stent (Boston Scientific, Natick, Massachusetts) in the treatment of coronary BMS-ISR. Compared with the DES, the DCB induced statistically significantly less in-segment late lumen loss (0.17 ± 0.42 mm vs. 0.38 ± 0.61 mm; p = 0.03), resulting in a lower binary restenosis rate (7% vs. 20%; p = 0.06) at 6-month follow-up (12). In this trial, dual antiplatelet therapy was extended to 3 months to minimize the effect of clopidogrel treatment on clinical events. The results of PEPCAD II compare well with the first-in-human data seen in this trial with the PACCOCATH prototype balloon (Bayer AG) (in-segment late lumen loss 0.11 ± 0.44 mm, binary restenosis rate 6%) (11). Dual antiplatelet therapy was limited to 4 weeks in both groups. Even during long-term follow-up, no cases of stent thrombosis occurred.

The results of PACCOCATH ISR (5,11) and PEPCAD II (12) led to a class IIa recommendation in the European guidelines for revascularization on the treatment of BMS-ISR (20). Both trials studied paclitaxel-iopromide–coated balloon catheters. Therefore, this recommendation is limited to the respective lesion characteristics of the studies and DCB based on the paclitaxel-iopromide coating (20). So far, the longest available clinical follow-up was 2 years (11).

Meanwhile, a randomized study in 50 patients with sirolimus DES-ISR demonstrated a significant reduction of in-segment late lumen loss with SeQuent Please DCB compared with conventional angioplasty (0.18 ± 0.45 mm vs. 0.72 ± 0.55 mm; p = 0.001). Furthermore, recurrent restenosis (8.7% vs. 62.5%; p = 0.0001) and survival free of major adverse cardiovascular events were significantly better in the DCB group (96% vs. 60%; p = 0.005) (16).

Concerns have been raised that a short-term local drug application may not result in a long-lasting inhibition of restenosis. Delayed restenosis of sirolimus- and paclitaxel-eluting stents was found (21–23), but this is not the case after BMS implantation (23). In contrast to these findings, the long-term clinical follow-up of this first-in-human study on the prototype paclitaxel-iopromide–coated balloon on BMS-ISR revealed no evidence for delayed restenosis or other potential local or systemic adverse events. The initial benefit seen by the reduced target lesion revascularization rates was maintained during a mean follow-up of more than 5 years.

Study limitations. The limited number of patients and the selection of conventional angioplasty as comparison are limitations of this study. However, when starting the trial in

2003, DES were not accepted as a valuable treatment option for BMS-ISR.

Conclusions

In a more than 5-year period after treatment of coronary BMS-ISR with a paclitaxel-iopromide–coated balloon, the initial results were sustained compared with an identical uncoated balloon. In contrast to DES, DCB allow a local intravascular drug delivery without the need for stent implantation. Furthermore, dual antiplatelet therapy was given for only 4 weeks.

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