Paclitaxel-eluting balloons, paclitaxel-eluting stents, and balloon angioplasty in patients with restenosis after implantation of a drug-eluting stent (ISAR-DESIRE 3): a randomised, open-label trial

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Summary

Background The best way to manage restenosis in patients who have previously received a drug-eluting stent is unknown. We investigated the efficacy of paclitaxel-eluting balloons (PEB), paclitaxel-eluting stents (PES), and balloon angioplasty in these patients.

Methods In this randomised, open-label trial, we enrolled patients older than 18 years with restenosis of at least 50% after implantation of any limus-eluting stent at three centres in Germany between Aug 3, 2009, and Oct 27, 2011. Patients were randomly assigned (1:1:1; stratified according to centre) to receive PEB, PES, or balloon angioplasty alone by means of sealed, opaque envelopes containing a computer-generated sequence. Patients and investigators were not masked to treatment allocation, but events and angiograms were assessed by individuals who were masked. The primary endpoint was diameter stenosis at follow-up angiography at 6–8 months. Primary analysis was done by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT00987324.

Findings We enrolled 402 patients, of whom 137 (34%) were assigned to PEB, 131 (33%) to PES, and 134 (33%) to balloon angioplasty. Follow-up angiography at 6-8 months was available for 338 (84%) patients. PEB was non-inferior to PES in terms of diameter stenosis (38·0% [SD 21·5] *vs* 37·4% [21·8]; difference 0·6%, one-sided 95% CI 4·9%; $p_{non\text{-}inferiority}$=0·007; non-inferiority margin of 7%). Findings were consistent in per-protocol analysis ($p_{non\text{-}inferiority}$=0·011). PEB and PES were superior to balloon angioplasty alone (54·1% [25·0]; $p_{superiority}$<0·0001 for both comparisons). Frequency of death, myocardial infarction, or target lesion thrombosis did not differ between groups.

Interpretation By obviating the need for additional stent implantation, PEB could be a useful treatment for patients with restenosis after implantation of a drug-eluting stent.

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Introduction

The introduction of the drug-eluting stent (DES) was an important milestone in the treatment of patients with obstructive coronary artery disease.[1] The high efficacy of these devices in prevention of restenosis compared with bare-metal stents has allowed percutaneous coronary intervention to be used in increasingly complex subsets of patients and lesions.[2] However, because likelihood of treatment failure increases with disease complexity,[3] the number of patients presenting with restenosis after implantation of DES is still fairly high.[4,5]

Although several treatment options are available for these patients—eg, repeat stenting with DES, drug-eluting balloons, or balloon angioplasty alone—management remains challenging, with no established best treatment strategy.[4–6] A previous randomised trial[7] showed that repeat stenting with a paclitaxel-eluting stent (PES) is efficacious and safe in patients with limus-stent restenosis, but there is concern about the long-term implication of several stent layers in the coronary vessel wall.[8] Moreover, although paclitaxel-eluting balloons (PEB) are effective in treatment of restenosis associated with bare-metal stents, their role in the management of restenosis after DES implantation has not been comprehensively assessed.[9] In the Intracoronary Stenting and Angiographic Results: Drug Eluting Stent In-Stent Restenosis: 3 Treatment Approaches (ISAR-DESIRE 3) trial, we investigated the efficacy of PEB, PES, and balloon angioplasty in patients with DES restenosis. The objectives of the study were to assess the non-inferiority of PEB compared with PES and the superiority of both PEB and PES compared with balloon angioplasty alone.

Methods

Study design and participants

In a randomised, open-label trial, we enrolled patients at three centres in Germany between Aug 3, 2009, and Oct 27, 2011. Eligible patients had to be older than 18 years and have ischaemic symptoms or evidence of myocardial ischaemia (inducible or spontaneous) in the presence of a

restenosis of at least 50% in a native vessel DES or proximal or distal margins. Patients with restenosis after implantation of any limus-eluting stent were eligible to participate. A limus-eluting stent was defined as a DES eluting sirolimus or its analogues (umirolimus [commonly known as biolimus], everolimus, and zotarolimus). Patients were excluded if they had a target lesion located in the left main stem or in a coronary bypass graft; acute ST-elevation myocardial infarction within the preceding 48 h; cardiogenic shock; severe renal insufficiency (defined as glomerular filtration rate ≤30 mL/min); tumours or other comorbid disorders with life expectancies of less than 12 months or that might result in protocol non-compliance; or contraindications or known allergy to antiplatelet therapy, paclitaxel, or stainless steel. Patients who were pregnant or suspected to be, or who were planning a pregnancy were also ineligible.

The study was done in accordance with the provisions of the Declaration of Helsinki and with the International Conference on Harmonization Good Clinical Practices. The trial protocol was approved by the institutional ethics committee responsible for the participating centres (Deutsches Herzzentrum, Munich, Germany; Universitäts-Herzzentrum, Freiburg-Bad Krozingen, Germany; and 1. Medizinische Klinik, Klinikum rechts der Isar, Munich, Germany). Participants or legally authorised representatives provided written informed consent.

Randomisation and masking

In each participating centre, patients were allocated to one of three treatments by means of sealed, opaque envelopes containing a computer-generated sequence. Randomisation was done after the decision was made to proceed with percutaneous coronary intervention and after crossing of the lesion with a guidewire. Eligible patients were randomly assigned (1:1:1) in the order that they qualified. Randomisation was stratified according to participating centre. Patients and investigators were not masked to treatment assignment. All events were adjudicated and classified by an event adjudication committee masked to the treatment groups. Angiograms were assessed by operators masked to treatment assignment.

	Paclitaxel-eluting balloon (n=137)	Paclitaxel-eluting stent (n=131)	Balloon angioplasty (n=134)
Age (years)	67·7 (10·4)	68·8 (10·0)	67·1 (9·3)
Women	32 (23%)	43 (33%)	39 (29%)
Diabetes mellitus	56 (41%)	61 (47%)	50 (37%)
Insulin-dependent	21 (15%)	27 (21%)	19 (14%)
Hypertension	105 (77%)	101 (77%)	90 (67%)
Hyperlipidaemia	108 (79%)	103 (79%)	102 (76%)
Present smoker	19 (14%)	15 (11%)	22 (16%)
Previous myocardial infarction	53 (39%)	50 (38%)	57 (43%)
Previous bypass surgery	15 (11%)	32 (24%)	24 (18%)
Multivessel disease	129 (94%)	122 (93%)	127 (95%)
Clinical presentation of acute coronary syndrome	26 (19%)	22 (17%)	31 (23%)
Ejection fraction*	53·6 (9·8)	54·5 (9·9)	53·2 (9·9)

Data are mean (SD) or n (%). *Data available for 297 (74%) patients.

Table 1: **Baseline characteristics**

Procedures

Patients were assigned to receive PEB (SeQuent Please, B Braun, Melsungen, Germany), PES (Taxus Liberté, Boston Scientific, Natick, MA, USA), or balloon angioplasty. PEB catheters were coated with 3 μg of paclitaxel per mm² of balloon surface with iopromide as hydrophilic spacer (length 10–30 mm; diameter 2·5–4·0 mm). Time zero was defined as the time of randomisation and patients were judged to be enrolled in the study at this timepoint. After treatment allocations, patients immediately underwent their assigned procedure.

We gave all patients an oral loading dose of platelet ADP-receptor antagonist before the intervention. During the procedure, patients were given intravenous aspirin and heparin with or without glycoprotein inhibitors or bivalirudin. The same randomly assigned treatment approach had to be used for all restenotic lesions in patients requiring intervention for several restenotic lesions. The use of more than one balloon or stent per lesion was allowed. Stenting was strongly discouraged in the groups assigned to PEB or balloon angioplasty. Stenting could be done in these groups when large dissections particularly with flow limitation were present, or when residual stenosis of more than 50% was present after several balloon dilations.

After the intervention, all patients—irrespective of treatment allocation—were prescribed 200 mg aspirin every day for an indefinite period and oral platelet ADP-receptor antagonist for at least 6 months. Other cardiac drugs (eg, β blockers, angiotensin-converting enzyme inhibitors, and statins) were prescribed according to the judgment of the patient's physician. After their procedure (ie, enrolment), patients remained in hospital for at least 48 h. Blood samples were taken every 8 h for the first 24 h after enrolment and daily afterwards to identify cardiac markers (creatine kinase, creatine kinase-MB, and troponin T). We did daily electrocardiograms (ECGs) until discharge. All patients were assessed at 1 and 12 months by phone or office visit. Repeat coronary angiography was scheduled for all patients at 6–8 months. Angiographic follow-up data from patients who returned before 6–8 months and underwent angiography and target lesion revascularisation were included in analyses of the primary endpoint. Patients who returned for angiography before 4 months and did not undergo target lesion revascularisation were rescheduled for angiography at the time defined in the protocol.

Personnel of the Clinical Data Management Centre (ISAResearch Centre, Munich, Germany) entered relevant data into a computer database. Baseline, post-procedural,

and follow-up coronary angiograms were digitally recorded and assessed offline in the quantitative coronary angiographic core laboratory (ISAResearch Centre, Munich, Germany) with an automated edge-detection system (QAngio XA, version 7.1; Medis Medical Imaging Systems, Leiden, Netherlands) by experienced operators. Measurements were taken on cineangiograms recorded after intracoronary nitroglycerine. Baseline measurements of quantitative coronary angiography were taken with the single worst view projection for the index lesion; the same view projection was used for the measurements after stent implantation. In the follow-up angiogram, the measurements of quantitative coronary angiography were done with the single worst-view projection at that timepoint. The contrast-filled non-tapered catheter tip was used for calibration. In the follow-up angiogram, the in-segment area was defined as the balloon-treated or stent-treated area and 5 mm margins proximal and distal to the treated area. Restenosis morphology was adjudicated according to criteria modified from Mehran and colleagues.[10]

The primary endpoint was diameter stenosis in the in-segment area at follow-up angiography. Secondary endpoints were in-segment minimum lumen diameter and in-segment binary angiographic restenosis (defined as stenosis of at least 50% diameter in the in-segment area at follow-up angiography); the need for target lesion revascularisation (defined as any revascularisation procedure involving the target lesion because of luminal renarrowing with symptoms or objective signs of ischaemia at 1 year of follow-up); combined incidence of death or myocardial infarction at 1 year; and incidence of target lesion thrombosis at 1 year. Myocardial infarction was adjudicated on the basis of clinical symptoms, ECG, and cardiac biomarkers. Detailed definition of myocardial infarction adjudication has been previously described.[11] Acute coronary syndrome was defined as unstable angina pectoris or ST-segment or non-ST-segment elevation myocardial infarction. We applied Academic Research Consortium criteria for definite stent thrombosis for adjudication of target lesion thrombosis.[12]

Statistical analysis

For assessment of the non-inferiority of PEB compared with PES, the null hypothesis was that PEB would be inferior to PES. Sample size calculation for this non-inferiority analysis was based on several assumptions: stenosis diameter of 35% after PEB and PES,[7,13,14] common SD of 20%, a non-inferiority margin of 7% absolute (20% relative) difference in stenosis diameter, an α of 0·05, and a power of 80%. Evidence to reject the null hypothesis would be considered significant if the one-sided 95% CI of the difference between the treatments was less than 7%. Accordingly, 102 patients with angiographic follow-up were necessary in each group.

For the second assessment of the superiority of PEB and PES to balloon angioplasty alone, the null hypothesis was that no difference between either PEB or PES and balloon angioplasty alone would be recorded. Sample size calculation for the superiority analysis was based on several assumptions: stenosis diameter of 35% after PEB or PES versus 45% after balloon angioplasty,[7,13,14] common SD of 20%, a two-sided α of 0·025 (because two comparisons), and a power of 90%. Accordingly, 101 patients with angiographic follow-up were necessary in each group.

We planned intention-to-treat analyses of primary and secondary endpoints. We also planned per-protocol analysis in line with preference of some authorities in trials with non-inferiority testing.[15] We prespecified analyses of subsets of interest (old and young patients, men and women, patients with and without diabetes, and small and large vessels) and a comparison of late lumen loss at follow-up angiography for patients

	PEB	PES	Balloon angioplasty
Lesions	172	168	160
Target vessel			
Left anterior descending	59 (34%)	50 (30%)	52 (33%)
Left circumflex	54 (31%)	61 (36%)	56 (35%)
Right coronary artery	59 (34%)	56 (33%)	52 (33%)
Left main	0	1 (1%)	0
Restenosis morphology			
Focal margin	31 (18%)	25 (15%)	23 (14%)
Focal body	70 (41%)	70 (42%)	70 (44%)
Multifocal	18 (10%)	15 (9%)	12 (8%)
Diffuse	44 (26%)	49 (29%)	45 (28%)
Proliferative	3 (2%)	3 (2%)	1 (1%)
Occlusive	6 (3%)	6 (4%)	9 (6%)
Index stent type			
Biolimus-eluting	6 (3%)	4 (2%)	8 (5%)
Everolimus-eluting	53 (31%)	48 (29%)	42 (26%)
Sirolimus-eluting	82 (48%)	94 (56%)	90 (56%)
Zotarolimus-eluting	31 (18%)	22 (13%)	20 (13%)
Bifurcation	47 (27%)	40 (24%)	37 (23%)
Vessel size (mm)	2·75 (0·50)	2·80 (0·49)	2·72 (0·45)
Diameter stenosis (%)	64·4% (16·8)	66·7% (16·5)	67·7% (15·7)
Minimum lumen diameter (mm)	0·97 (0·48)	0·93 (0·50)	0·88 (0·49)
Procedures*			
Treated per protocol	161 (94%)	156 (93%)	150 (94%)
Predilation	139 (81%)	145 (86%)	NA
Cutting balloon	2 (1%)	2 (1%)	0
Maximum balloon pressure (atm)†	13·7 (4·1)	15·9 (3·1)	15·4 (3·9)
Minimum lumen diameter after procedure (mm)‡	2·29 (0·44)	2·53 (0·48)	2·10 (0·49)
Diameter stenosis after procedure (%)§	18·5% (8·3)	12·8% (7·8)	23·3% (12·6)

Data are n (%) or mean (SD). PEB=paclitaxel-eluting balloon. PES=paclitaxel-eluting stent. NA=not applicable. *No significant differences recorded between groups unless otherwise indicated; measurements based on in-stent analysis. †Maximum balloon pressure for PEB was significantly lower than for PES (p<0·0001) and than for balloon angioplasty (p=0·00018). ‡Minimum lumen diameter after PEB was significantly lower than after PES (p<0·0001) but significantly higher than after balloon angioplasty (p=0·00079), and was significantly higher after PES than after balloon angioplasty (p<0·0001). §Stenosis after PEB was significantly higher than after PES (p<0·0001) but was significantly lower than after balloon angioplasty (p=0·00024), and was significantly lower after PES than after balloon angioplasty (p<0·0001).

Table 2: **Characteristics of lesions at baseline and of procedures**

	PEB	PES	Balloon angioplasty	p values*		
				PEB *vs* PES	PEB *vs* balloon angioplasty	PES *vs* balloon angioplasty
Lesions	147	142	127	..	..	..
Minimum luminal diameter (mm)	1·79 (0·74)	1·82 (0·74)	1·26 (0·75)	0·71	<0·0001	<0·0001
Diameter stenosis (%)	38·0% (21·5)	37·4% (21·8)	54·1% (25·0)	0·80	<0·0001	<0·0001
Recurrent binary restenosis	39 (27%)	34 (24%)	72 (57%)	0·61	<0·0001	<0·0001
Late lumen loss (mm)	0·37 (0·59)	0·34 (0·61)	0·70 (0·69)	NA†	<0·0001	NA†
Recurrent restenotic lesions	39	34	72	..	..	..
Diameter stenosis (%)	68·3% (15·9)	69·9% (16·7)	72·7% (14·2)	0·69	0·14	0·37
Lesion length (mm)	9·6 (5·9)	10·6 (6·3)	13·3 (7·3)	0·51	0·016	0·09
Restenosis morphology	..	..	..	0·86	0·41	0·41
Focal margin	3 (8%)	5 (15%)	7 (10%)	..	..	..
Focal body	18 (46%)	14 (41%)	22 (31%)	..	..	..
Multifocal	3 (8%%)	2 (6%)	6 (8%)	..	..	..
Diffuse	8 (21%)	7 (21%)	28 (39%)	..	..	..
Proliferative	1 (3%)	0	1 (1%)	..	..	..
Occlusive	6 (15%)	6 (18%)	8 (11%)	..	..	..

Data are n, mean (SD), or n (%). Measurements based on in-segment analysis. PEB=paclitaxel-eluting balloon. PES=paclitaxel-eluting stent. NA=not applicable. *From generalised estimating equations for no=mally distributed data. †Comparison of late lumen loss between angioplasty and stenting not done.

Table 3: **Angiographic follow-up at 6–8 months**

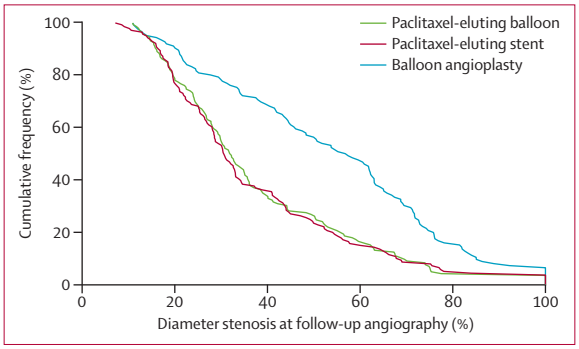

Figure 1: **Cumulative frequency distribution curves for diameter stenosis by treatment group**

treated with PEB compared with those who underwent balloon angioplasty.

Continuous data are presented as mean (SD) or median (IQR). Categorical data are presented as counts or proportions. We checked differences between groups for significance with the Student's *t* test for continuous data and the χ^2 test (or Fisher's exact test when the expected cell value was less than five) for categorical variables. For lesion-level data, we checked differences between groups for significance with generalised estimating equations for non-normally distributed data to address intrapatient correlation in patients who underwent multilesion interventions.[16] We assessed survival with Kaplan-Meier analyses and did comparisons with the log-rank test. We did sample size calculation with nQuery Advisor (version 7.0; Statistical Solutions, Cork, Ireland) and tested the non-inferiority hypothesis with EquivTest (version 1.0; Statistical Solutions, Cork, Ireland). We used S-PLUS (version 4.5; Insightful Corp, Seattle, WA, USA) for all other analyses.

This trial is registered with ClinicalTrials.gov, number NCT00987324.

Role of the funding source

The trial was sponsored by the Deutsches Herzzentrum, which is where most authors work. Data collection and monitoring were done by the ISAResearch Centre, which is affiliated with the Deutsches Herzzentrum. No extramural funding was used for this trial. RAB and AK had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

We enrolled 402 patients, of whom 137 (34%) were assigned to PEB, 131 (33%) to PES, and 134 (33%) to balloon angioplasty. Overall, 167 (42%) patients had diabetes mellitus (table 1). 500 lesions were treated during the study (table 2). At enrolment, a focal pattern of in-stent restenosis was present in 334 (67%) lesions (table 2). The proportion of patients who were treated per protocol did not differ between groups (table 2). 11 lesions in the PEB group were treated with stent implantation (six with PES, one with a bare-metal stent, and four with everolimus-eluting stents); 12 lesions in the PES group were treated with balloon dilatation only (two with PEB and ten with balloon angioplasty); ten lesions in the balloon angioplasty group were treated with stent implantation (seven with PES, two with sirolimus-eluting stents, and one with biolimus-eluting stent).

Overall, angiographic follow-up data were available for 338 (84%) of 402 patients, with no significant differences

between treatment groups (p=0·35). Median time to follow-up angiography was 198 days (IQR 183–210) in patients treated with PEB, 196 days (178–205) in patients treated with PES, and 197 days (169–204) in patients treated with balloon angioplasty (p=0·58). PEB was non-inferior to PES in terms of diameter stenosis at follow-up angiography in intention-to-treat analysis (difference 0·6%, one-sided 95% CI 4·9%; $p_{non\text{-}inferiority}$=0·007; table 3, figure 1). We recorded similar results when data were analysed according to per-protocol analysis (difference 1·0%, one-sided 95% CI 5·3%, $p_{non\text{-}inferiority}$ =0·011). PEB and PES treatment were superior to balloon angioplasty alone (table 3, figure 1).

In patients treated with PEB or PES, diameter stenosis did not differ between the groups according to restenosis morphology at baseline: patients who had focal restenosis and had PEB had stenosis of 35·1% (SD 18·4) versus 33·1% (18·0) in those who had PES (p=0·46); patients who had non-focal restenosis and PEB had stenosis of 44·5% (SD 26·1) versus 45·3% (25·8) in those who had PES (p=0·87). We recorded no interaction between treatment with PEB or PES and age, sex, diabetes, and vessel size (p for interaction >0·34 in all cases). Late lumen loss at 6–8 months was significantly lower in patients treated with PEB than in those treated with balloon angioplasty (table 3).

392 (98%) patients completed clinical follow-up. One (1%) patient in the PEB group, four (3%) in the PES group, and five (4%) in the balloon angioplasty group had incomplete follow-up. Frequency of clinical events did not differ in the PEB and PES groups (table 4). However, frequency of target lesion revascularisation was significantly lower with PEB or PES than with balloon angiography (table 4, figure 2). Additionally, the frequency of the composite of death, myocardial infarction, or target lesion revascularisation was significantly lower with PEB or PES than with balloon angiography (table 4). Frequency of target lesion thrombosis and the composite of death or myocardial infarction did not differ significantly between groups (table 4).

	PEB	PES	Balloon angioplasty	p values		
				PEB *vs* PES	PEB *vs* balloon angioplasty	PES *vs* balloon angioplasty
Death	3 (2·2%)	6 (4·6%)	7 (5·3%)	0·27	0·17	0·80
Myocardial infarction	3 (2·1%)	3 (2·4%)	2 (1·5%)	0·92	0·70	0·63
Q wave myocardial infarction	1 (0·7%)	1 (0·8%)	0	0·95	0·34	0·32
Target lesion thrombosis	1 (0·7%)	1 (0·8%)	0	0·97	0·33	0·31
Target lesion revascularisation	30 (22·1%)	17 (13·5%)	56 (43·5%)	0·09	<0·0001	<0·0001
Target vessel revascularisation	33 (24·2%)	21 (16·6%)	58 (45·1%)	0·18	0·0001	<0·0001
Death or myocardial infarction	6 (4·4%)	9 (6·9%)	9 (6·8%)	0·35	0·36	0·97
Death, myocardial infarction, or target lesion revascularisation	32 (23·5%)	25 (19·3%)	61 (46·2%)	0·50	<0·0001	<0·0001

Data are n (%). Percentages are Kaplan-Meier estimates. PEB=paclitaxel-eluting balloon. PES=paclitaxel-eluting stent.

Table 4: **Clinical results at 1 year by treatment group**

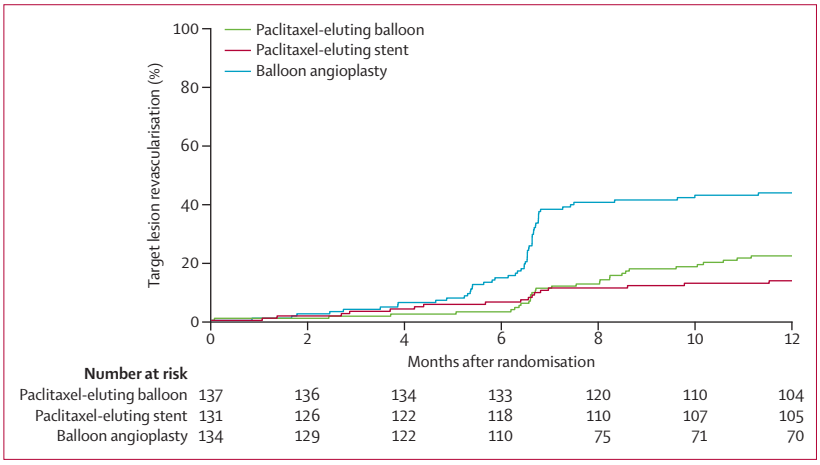

Figure 2: **Survival analysis curves for target lesion revascularisation by treatment group**

Discussion

We have shown that PEB in patients presenting with restenosis after implantation of limus-eluting DES is non-inferior to repeat stenting with PES and that PEB or PES is superior to balloon angioplasty alone. Randomised trials[14,17–19] in which patients with restenosis after implantation of bare-metal stent were enrolled have shown that DES implantation is the best treatment option. Acute gain is maximised and late loss is minimised, providing superior outcomes in comparison with balloon angioplasty alone and vascular brachytherapy. However, concerns exist about the long-term effect of many stent layers in the coronary vasculature; therefore, treatment with drug-eluting balloons is a potentially attractive approach for patients with in-stent restenosis. Two small randomised trials[13,20] provided encouraging results with drug-eluting balloons in patients with restenosis after bare-metal stenting when compared with angioplasty alone and repeat stenting with DES.

The widespread adoption of DES treatment in the past decade means that, despite high efficacy, restenosis in clinical practice is most often restenosis after DES. Moreover, an emerging body of data suggests that important differences exist in the processes of restenosis after implantation of bare-metal stents and DES.[21] So far, one randomised trial[7] has focused on the role of repeat DES in patients with restenosis and established that such an approach is efficacious and safe. This study[7] showed that a PES in patients with restenosis after treatment with a limus-eluting DES was associated with similar outcomes to a sirolimus-eluting stent. Additionally, although second-generation limus-eluting stents have had better results than have PES in de-novo coronary disease,[22] their role in the treatment of restenosis after implantation of DES has not been investigated. For these reasons—as well as the mechanistic advantages of a comparison of stents and balloons eluting the same

drug—we chose PES as the stent comparator in our trial. Finally, data from the previous randomised trial[7] and other registry studies[23,24] show that restenosis after DES implantation is more challenging to treat than is restenosis after bare-metal stenting, which suggests that alternative treatment strategies should be sought.

Our study is the first randomised controlled trial to investigate the role of drug-eluting balloons in patients with restenosis after DES implantation, examining comparative efficacy across the range of available treatments (panel). As far as we are aware, it is also the largest reported randomised trial of drug-eluting balloons. Although larger studies with a longer follow-up are necessary to establish whether there are clinically meaningful differences between PEB and PES, the overall effect of DES treatment on the frequency of restenosis has greatly reduced the feasibility of restenosis trials powered for clinical endpoints. Additionally, the superiority of both PEB and PES to balloon angioplasty in our study suggests that angioplasty alone has a restricted role, at least as a default treatment strategy for these patients. The lower late loss with PEB than with balloon angioplasty is consistent with data from other randomised trials[25,26] (panel) and provides further evidence to support the validity of the notion that a brief (typically 60 s) dilation with a drug-eluting balloon results in sustained suppression of neointimal hyperplasia in the medium term.

Despite similar rates of recurrent binary restenosis, the number of patients undergoing target lesion revascularisation was higher in patients treated with PEB than with PES. To explore reasons for this difference, we compared characteristics of the recurrent restenotic lesion and recorded no differences between the two groups. In the absence of significant differences in angiographic characteristics, the most likely explanation for this finding is that the presence of an existing additional stent layer in the PES group might have discouraged the operator from repeat intervention (typically in the form of further stent implantation).

Our study is a clinical trial with protocol-mandated follow-up angiography and a primary angiographic endpoint. Several issues of trial conduct and design arise as a result. First, the choice of endpoint affects the validity of between-group comparison in trials comparing different percutaneous intervention strategies (ie, stenting *vs* angioplasty). Specifically, an endpoint such as late loss—which is commonly used in stent trials—is not suitable, because modalities with fairly high acute gain—eg, stenting—tend to incur increased late loss. For this reason, diameter stenosis at follow-up is preferred as the primary endpoint for such comparative efficacy analyses. Second, although analysis of the primary endpoint is based on incomplete observations (84%), this issue is an inherent feature of large angiographic follow-up studies and the reliability of such data has been shown to be high when angiographic follow-up exceeds 80%.[27] Moreover, angiographic endpoints are robust markers of clinical efficacy.[28,29] Third, interpretation of secondary clinical endpoints should be undertaken with caution, because trials with angiographic follow-up tend to inflate frequency of revascularisation.[30] Although absolute differences in repeat revascularisation between groups could be higher than in routine practice, relative differences between treatments are expected to be real. Additionally, this trial was not powered to detect differences in clinical endpoints across the treatment groups. Fourth, in relation to baseline analysis, although technicians in the quantitative coronary angiography laboratory were masked to treatment allocation, to mask treatment with a balloon or a stent is difficult in trials comparing different treatment modalities. This factor is another reason to prefer diameter stenosis at follow-up as a primary endpoint.

Our study has some important additional limitations. We enrolled only patients with restenosis occurring after implantation of DES that elute sirolimus or its analogues. Therefore, these data cannot be applied to patients with restenosis after implantation of stents eluting paclitaxel, although the use of these stents for de-novo disease has decreased substantially in the past 5 years. We systematically excluded patients with restenosis after implantation of DES in the left main stent and those who presented with ST-elevation myocardial infarction. Additionally, we used a PEB based on an iopromide excipient to enable drug loading and release. Because significant differences exist between different drug-eluting balloon catheters, the results of our study might not be generalisable to other devices.[31,32] Furthermore, preclinical data suggest a delay in vascular healing after drug-eluting balloon treatment,[31] so the optimum duration of dual antiplatelet treatment remains unknown; we recommended a minimum of 6 months of such treatment. Planned follow-up for a longer period than in this report

***Panel:* Research in context**

Systematic review

We searched PubMed from Jan 1, 2006, to Oct 30, 2012, for published reports of randomised trials comparing drug-eluting balloons, drug-eluting stents, or balloon angioplasty in patients with restenosis solely within drug-eluting stents. We used a combination of several search terms: "randomised" (or "randomized"), "coronary", "in≈nt restenosis", "drug-eluting stent", "drug-eluting balloon" (or "drug-coated balloon"), and "balloon angioplasty". We used no language restrictions. We identified only the study of Habara and colleagues (n=50)[25] and the PEPCAD-DES trial (n=110),[26] both of which compared paclitaxel-eluting balloons with balloon angioplasty alone. Both studies[25,26] showed that paclitaxel-eluting balloons were superior to balloon angioplasty.

Interpretation

We confirmed the previous findings, with paclitaxel-eluting balloons proving to be superior to balloon angioplasty alone in terms of diameter stenosis at follow-up angiography. However, we also showed that paclitaxel-eluting balloons were not inferior to repeat stenting with paclitaxel-eluting stents. Therefore, by obviating the need for further stent scaffold implantation, treatment with drug-eluting balloons might be recommended as the default approach for patients presenting with restenosis after implantation of a drug-eluting stent.

will be necessary to confirm the safety of this approach. Finally, the efficacy of drug-eluting balloons could be further improved by lesion preparation with cutting or scoring balloon dilation before deployment of the drug-eluting balloon. This hypothesis is the subject of a randomised trial (ISAR-DESIRE 4; NCT01632371).

In conclusion, we have established that treatment of patients presenting with DES restenosis with PEB is non-inferior to repeat stenting with PES. Moreover, both treatments are superior to balloon angioplasty alone. By obviating the need for additional stent implantation, treatment with a drug-eluting balloon could be a useful treatment strategy for these patients.

Contributors

RAB and AK did the data analysis and wrote the first draft of the report. RAB, JM, KT, and AK were involved in study conception and design. RAB, SP, BW, KT, SS, and CV were involved in data acquisition. F-JN, JM, SP, BW, KT, SS, MF, IO, TI, JH, CV, JP, K-LL, and SM revised the report for important intellectual content. All authors approved the report for final submission.

Study committees

Steering committee: A Kastrati (chairman), J Mehilli (principal investigator), and K Tiroch. Clinical Event Adjudication Committee: C Schmitt (chairman), D Poci, and P Barthel. Patient follow-up and data coordination at the ISAResearch Centre: J Mehilli, R A Byrne, S Schulz, K A Fiedler, H Holle, K Hösl, S Kufner, F Maimer-Rodrigues, H Paul, N Rifatov, G Schömig, B Wolff, B von Merzljak, and I Zenullahi. Angiographic and Intravascular Imaging Core Laboratory at the ISAResearch Centre: R A Byrne, S Pinieck, D Blersch, S Cassese, S Hurt, L King, and T Tada.

Conflicts of interest

We declare that we have no conflicts of interest.

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