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CLINICAL RESEARCH

CORONARY

Long-Term Efficacy and Safety of Paclitaxel-Eluting Balloon for the Treatment of Drug-Eluting Stent Restenosis

3-Year Results of a Randomized Controlled Trial

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ABSTRACT

OBJECTIVES This study sought to investigate the long-term comparative efficacy and safety of paclitaxel-eluting balloon (PEB), paclitaxel-eluting stent (PES), or balloon angioplasty (BA) for the treatment of drug-eluting stent restenosis.

BACKGROUND The optimal treatment of drug-eluting stent restenosis remains unknown. Although PEB has shown encouraging results, the long-term clinical efficacy and safety of PEB remains poorly defined.

METHODS A total of 402 patients with clinically significant restenosis in limus-eluting stents were randomly assigned to receive PEB (n = 137), PES (n = 131), or BA (n = 134). For this analysis, PEB versus PES and PEB versus BA were compared. The primary efficacy and safety endpoints were target lesion revascularization and the composite of death or myocardial infarction.

RESULTS At a median follow-up of 3 years, the risk of target lesion revascularization was comparable with PEB versus PES (hazard ratio [HR]: 1.46, 95% confidence interval [CI]: 0.91 to 2.33; p = 0.11) and lower with PEB versus BA (HR: 0.51, 95% CI: 0.34 to 0.74; p < 0.001). The risk of death/myocardial infarction tended to be lower with PEB versus PES (HR: 0.55, 95% CI: 0.28 to 1.07; p = 0.08), due to a lower risk of death (HR: 0.38, 95% CI: 0.17 to 0.87; p = 0.02). The risk of death/myocardial infarction was similar with PEB versus BA (HR: 0.96, 95% CI: 0.46 to 2.0; p = 0.91).

CONCLUSIONS At 3 years, the use of PEB as compared with PES to treat patients with limus-eluting stent restenosis has similar efficacy and safety. PEB remains superior to BA. The sustained efficacy without trade-off in safety supports the role of PEB as treatment option for patients with drug-eluting stent restenosis. (Intracoronary Stenting and Angiographic Results: Drug Eluting Stent In-Stent Restenosis: 3 Treatment Approaches [ISAR-DESIRE 3]; NCT00987324) (J Am Coll Cardiol Intv 2015;8:877–84) © 2015 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

BA = balloon angioplasty

CI = confidence interval

DES = drug-eluting stent(s)

HR = hazard ratio

MI = myocardial infarction

PEB = paclitaxel-eluting balloon

PES = paclitaxel-eluting stent(s)

TLR = target lesion revascularization

In patients with coronary artery disease requiring percutaneous coronary intervention, the implantation of drug-eluting stents (DES) has superior antirestenotic efficacy as compared with that of bare metal stents (1,2). However, owing to the overall increase in the use of DES and the growing number of complex clinical and lesion subsets treated, the absolute number of patients with DES restenosis remains considerable (3). Moreover, the optimal treatment strategy for these patients is not clearly established. Repeat stenting with DES is widely practiced and previous studies have supported this approach (4,5). Nevertheless, concerns exist about the long-term sequelae of multiple stent layers in the coronary vessel wall (6).

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The use of balloon catheters coated with antiproliferative drugs has emerged as a promising technology (7). In particular, the use of paclitaxel-eluting balloon (PEB) therapy for the treatment of restenosis after DES has demonstrated encouraging angiographic and short-term clinical results as compared with DES or balloon angioplasty (BA) alone (8,9). However, the long-term clinical efficacy and safety of PEB therapy in cases of restenosis after DES has not been well evaluated. In the present report, we evaluate the efficacy and safety of PEB as compared with paclitaxel-eluting stent (PES) or BA alone 3 years after the treatment of DES restenosis in the setting of the randomized ISAR-DESIRE 3 (Intracoronary Stenting and Angiographic Results: Drug Eluting Stent In-Stent Restenosis: 3 Treatment Approaches) trial.

METHODS

STUDY POPULATION AND PROTOCOL. Patients were enrolled between August 3, 2009, and October 27, 2011 in 3 German centers. Full details of the study population, methods, endpoints, and primary analysis have been previously reported (10). In brief, patients were included if they met the following criteria: were >18 years old; had ischemic symptoms or evidence of myocardial ischemia (inducible or spontaneous) in the presence of a restenosis ≥50% located in a native vessel DES or proximal or distal margins; and had provided written, informed consent. Patients with restenosis occurring in any limus-eluting stent were considered eligible for participation in the study. Patients were excluded if they met any of the following criteria: had a target lesion located in the left main stem or in a coronary bypass graft; presented with acute ST-segment elevation myocardial infarction within the preceding 48 h, cardiogenic shock, severe renal insufficiency (defined as glomerular filtration rate ≤30 ml/min), malignancies, or other comorbid conditions with life expectancy <12 months or that may result in protocol noncompliance; or had contraindications or known allergy to antiplatelet therapy, paclitaxel, stainless steel, or pregnancy (present, suspected or planned).

Patients were randomly assigned to receive open-label PEB (SeQuent Please, B. Braun, Melsungen, Germany), PES (Taxus Liberté, Boston Scientific, Natick, Massachusetts), or BA alone. Detailed descriptions of devices, drugs, and elution characteristics have been reported previously (10). Patient allocation to each of the 3 treatment groups was in equal proportions. All patients were evaluated at 1, 12, and 36 months by phone contact or office visit. An angiographic follow-up was scheduled for all patients at 6 to 8 months.

The study was conducted 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 centers.

ENDPOINTS AND DEFINITIONS. The primary efficacy and safety endpoints of interest in the current analysis were the need for target lesion revascularization (TLR) and the composite of death or myocardial infarction (MI), respectively. Other outcomes of interest were death, MI, target lesion thrombosis, and major adverse cardiac event (the composite of TLR, death, or MI).

Study definitions have been previously described in detail (10).

STATISTICAL ANALYSIS. The results of the primary analysis have already been published, and this additional analysis is exploratory in nature. Baseline descriptive statistics are presented as mean ± SD for continuous variables and as counts or proportions (%) for categorical variables. Differences across groups were checked for significance using analysis of variance for continuous data and chi-squared test (or Fisher exact test where the expected cell value was <5) for categorical variables. Survival was analyzed according to Kaplan-Meier methods and hazard ratio (HR) with pertinent 95% confidence interval (95% CI) was calculated using Cox proportional hazards methods. The proportional hazards assumption was checked by the method of Grambsch and Therneau and was fulfilled in all cases in which we

used Cox proportional hazards models (11). A landmark analysis explored the occurrence of primary endpoints between 1- and 3-year follow-ups. Summary statistics were derived for comparisons of PEB versus PES as well as of PEB versus BA alone, respectively. Analysis of the primary efficacy and safety outcomes was also performed for the comparison PEB versus PES according to pre-specified subsets of interest (age [median value], sex, diabetic status, and vessel size [median diameter]), and interaction between treatment effect and these covariates was assessed with Cox proportional hazards models. All endpoints of interest for the current analysis were analyzed on an intention-to-treat basis. Statistical software S-PLUS (version 4.5, S-PLUS, Insightful Corp, Seattle, Washington) was used for analysis.

RESULTS

As previously reported, a total of 402 patients with 500 treated lesions were enrolled in this study: 137 patients (172 lesions) were treated with PEB; 131 patients (168 lesions) with PES; and 134 patients (160 lesions) with BA. Baseline clinical, angiographic, and procedural characteristics were similar across treatment groups (Table 1). Clinical follow-up was available for 363 patients (90.3%, median 3.0 years [2.8 to 3.0 years]). Of patients with incomplete 3-year clinical follow-up 13 (3.2%) had clinical follow-up ≤2 years (median 1.4 years [1.0 to 1.7 years]).

PEB VERSUS PES FOR RESTENOSIS AFTER DES IMPLANTATION. Regarding the primary efficacy outcome, TLR at 3 years occurred in 44 cases (33.3%) with PEB and in 29 cases (24.2%) with PES (HR: 1.46, 95% CI: 0.91 to 2.33; p = 0.11) (Figure 1A). TLR between 1 and 3 years occurred in 14 cases (14.5%) with PEB and in 12 cases (12.4%) with PES (HR: 1.17, 95% CI: 0.54 to 2.53; p = 0.69) (Figure 1B).

Regarding the primary safety outcome, the composite of death or MI at 3 years occurred in 14 cases (10.4%) with PEB and in 23 cases (18.3%) with PES (HR: 0.55, 95% CI: 0.28 to 1.07; p = 0.08) (Figure 2A). Death or MI between 1 and 3 years occurred in 8 cases (6.3%) with PEB and in 14 cases (12.3%) with PES (HR: 0.51, 95% CI: 0.21 to 1.22; p = 0.12) (Figure 2B). PEB as compared with PES showed a significant lower risk of death (6% vs. 15.3%, HR: 0.38, 95% CI: 0.17 to 0.87; p = 0.02). At 3-year follow-up, the risk of MI (5.4% vs. 3.2%, HR: 1.60, 95% CI: 0.47 to 5.48; p = 0.45), target lesion thrombosis (0.8% vs. 1.6%, HR: 0.46, 95% CI: 0.04 to 5.10; p = 0.53), or major adverse cardiac events (38.0% vs. 37.7%, HR: 1.02, 95% CI: 0.69 to 1.52; p = 0.91) was comparable between PEB and PES (Table 2).

No significant interaction was found between PEB versus PES and the pre-specified subgroups in terms of efficacy and safety (Figure 3).

PEB VERSUS BA FOR RESTENOSIS AFTER DES IMPLANTATION. Regarding the primary efficacy outcome, TLR at 3 years occurred in 44 cases (33.3%) with PEB and in 65 cases (50.8%) with BA (HR: 0.51, 95% CI: 0.34 to 0.74; p < 0.001) (Figure 1A). TLR between 1 and 3 years occurred in 14 cases (14.5%)

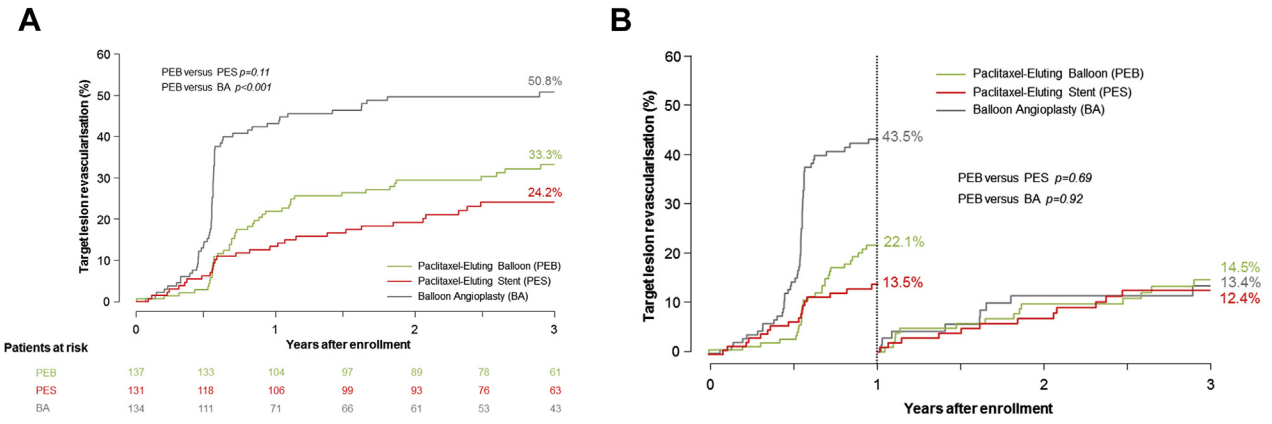
TABLE 1 Baseline Clinical and Angiographic Characteristics According to Treatment Group

	PEB	PES	BA
Clinical Characteristics			
	(n = 137)	**(n = 131)**	**(n = 134)**
Age, yrs	67.7 ± 10.4	68.8 ± 10.0	67.1 ± 9.3
Female	32 (23.4)	43 (32.8)	39 (29.1)
Diabetes mellitus	56 (40.9)	61 (46.6)	50 (37.3)
Insulin-dependent	21 (15.3)	27 (20.6)	19 (14.2)
Hypertension	105 (76.6)	101 (77.1)	90 (67.2)
Hyperlipidemia	108 (78.8)	103 (78.6)	102 (76.1)
Current smoker	19 (13.9)	15 (11.5)	22 (16.4)
Previous MI	53 (38.7)	50 (38.2)	57 (42.5)
Previous CABG*	15 (11.0)	32 (24.4)	24 (17.9)
Multivessel disease	129 (94.2)	122 (93.1)	127 (94.8)
Clinical presentation			
Acute coronary syndrome	26 (19.0)	22 (16.8)	31 (23.1)
Ejection fraction†	53.6 ± 9.8	54.5 ± 9.9	53.2 ± 9.9
Lesion and Procedural Characteristics			
	(172 Lesions)	**(168 Lesions)**	**(160 Lesions)**
Target vessel			
LAD	59 (34.3)	50 (29.8)	52 (32.5)
LCX	54 (31.4)	61 (36.3)	56 (35.0)
RCA	59 (34.3)	56 (33.3)	52 (32.5)
LM	0 (0.0)	1 (0.6)	0 (0.0)
Index stent type			
Biolimus-eluting	6 (3.5)	4 (2.4)	8 (5.0)
Everolimus-eluting	53 (30.8)	48 (28.6)	42 (26.3)
Sirolimus-eluting	82 (47.7)	94 (56.0)	90 (56.3)
Zotarolimus-eluting	31 (18.0)	22 (13.1)	20 (12.5)
Bifurcation	47 (27.3)	40 (23.8)	37 (23.1)
Vessel size, mm	2.75 ± 0.50	2.80 ± 0.49	2.72 ± 0.45
Diameter stenosis, pre, %	64.4 ± 16.8	66.7 ± 16.5	67.7 ± 15.7
MLD, pre, mm	0.97 ± 0.48	0.93 ± 0.50	0.88 ± 0.49
MLD, post, mm‡	2.29 ± 0.44	2.53 ± 0.48	2.10 ± 0.49
Diameter stenosis, post, %§	18.5 ± 8.3	12.8 ± 7.8	23.3 ± 12.6

Values are mean ± SD or n (%) unless otherwise indicated. Lesion characteristics are based on in-stent analysis. *There were no significant differences across the groups at baseline with the exception of previous CABG (p = 0.015). †Data available for 279 patients (73.9%). ‡The MLD post-procedure was significantly lower for PEB versus PES (p < 0.001) and significantly higher for PEB versus BA (p < 0.001) and PES versus BA (p < 0.001). §Diameter stenosis post-procedure was significantly higher for PEB versus PES (p < 0.001) and significantly lower for PEB versus BA (p < 0.001) and PES versus BA (p < 0.001).

BA = balloon angioplasty; CABG = coronary artery bypass graft; LAD = left anterior descending artery; LCX = left circumflex artery; LM = left main; MI = myocardial infarction; MLD = minimum lumen diameter; PEB = paclitaxel-eluting balloon; PES = paclitaxel-eluting stent(s); RCA = right coronary artery.

FIGURE 1 Cumulative Survival Analysis Curves and Landmark Analysis for TLR



Cumulative survival analysis curves at 3 years **(A)** and landmark analysis from 1 to 3 years **(B)** for target lesion revascularization (TLR) by treatment group. BA = balloon angioplasty; PEB = paclitaxel-eluting balloon; PES = paclitaxel-eluting stent(s).

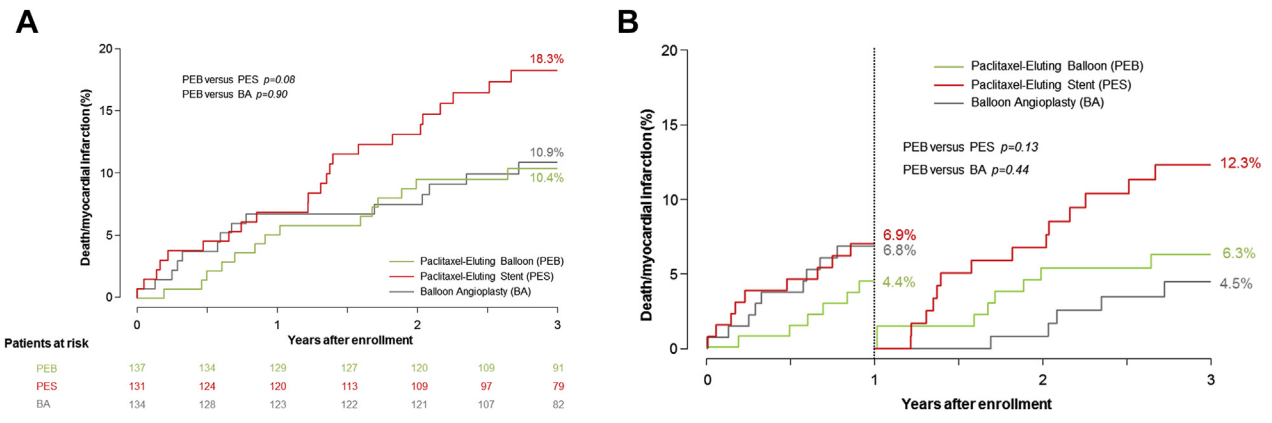
with PEB and in 9 cases (13.4%) with BA (HR: 1.04, 95% CI: 0.45 to 2.41; p = 0.92) (Figure 1B).

Regarding the primary safety outcome, the composite of death or MI at 3 years occurred in 14 cases (10.4%) with PEB and in 14 cases (10.9%) with BA (HR: 0.96, 95% CI: 0.46 to 2.00; p = 0.90) (Figure 2A). Death or MI between 1 and 3 years occurred in 8 cases (6.3%) with PEB and in 5 cases (4.5%) with BA (HR: 1.55, 95% CI: 0.51 to 4.75; p = 0.44) (Figure 2B). At 3-year follow-up, the risk of death (6% vs. 9.4%, HR: 0.63, 95% CI: 0.26 to 1.54; p = 0.31) or MI (5.4% vs. 1.5%, HR: 3.34, 95% CI: 0.69 to 16.06; p = 0.11) was comparable with PEB versus BA. Conversely, PEB was associated with a significantly lower risk of major adverse cardiac events than BA was (38.0% vs. 55.7%, HR: 0.52, 95% CI: 0.37 to 0.75; p < 0.001) mainly driven by the lower risk of TLR. There was no target lesion thrombosis in the BA group (p = 0.33 for PEB vs. BA) (Table 2).

DISCUSSION

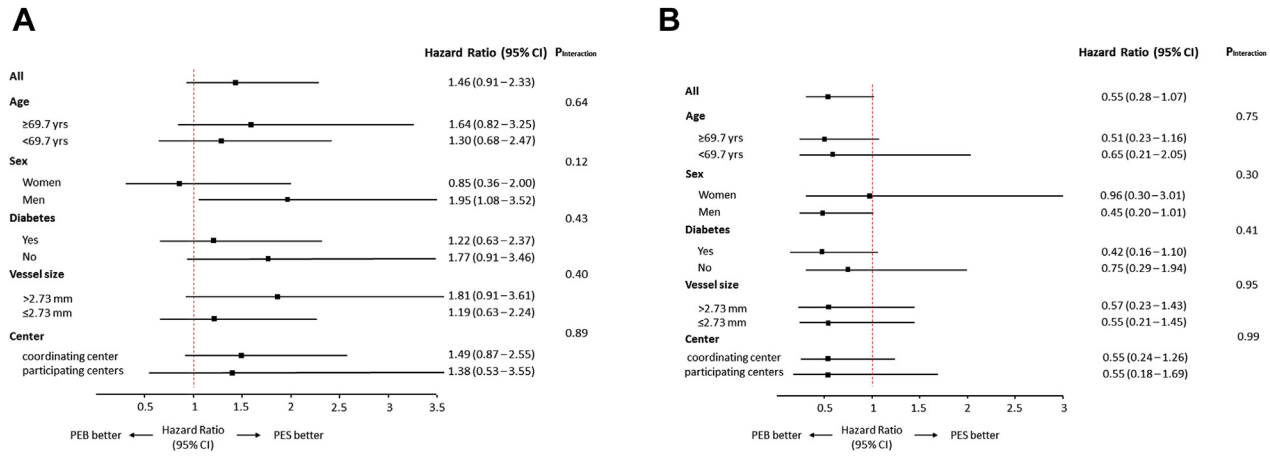
The ISAR-DESIRE 3 study was a randomized trial comparing PEB versus PES or BA for the treatment of

FIGURE 2 Cumulative Survival Analysis Curves and Landmark Analysis for Death or MI



Cumulative survival analysis curves at 3 years **(A)** and landmark analysis from 1 to 3 years **(B)** for death or myocardial infarction (MI) by treatment group. Abbreviations as in Figure 1.

FIGURE 3 Comparison of Incidence of TLR and Death or MI According to Pre-Specified Subgroups



Comparison of incidence of TLR **(A)** and death or MI **(B)** according to pre-specified subgroups in patients treated with PEB versus PES. CI = confidence interval; other abbreviations as in Figures 1 and 2.

patients with restenosis after DES implantation. The current analysis is the first report of long-term outcomes of PEB in patients presenting with DES restenosis. The principal findings are that at 3-year follow-up, PEB as compared to PES shows overall similar efficacy and safety, and that PEB as compared to BA shows sustained superior efficacy.

Patients with restenosis after stenting represent a high-risk cohort with increased risk of adverse events in comparison with patients who remain restenosis free (12). In particular, the treatment of patients with DES restenosis is associated with poorer outcomes in comparison with patients with bare-metal stent restenosis (3,13). In the setting of DES restenosis, a treatment strategy of repeat drug-eluting stenting has been demonstrated to be effective and safe at short- to mid-term follow-up even in high-risk subgroups (4,14). However, concerns exist about the long-term implications of multiple stent layers—the so-called onion-skin phenomenon (3). By offering the possibility to locally deliver sufficient quantities of an antiproliferative drug and obviating the need for another stent layer, PEB is a potentially attractive treatment option for these patients (7).

In the particular setting of restenosis after DES implantation, PEB has demonstrated encouraging short-term results as compared with repeat DES or BA alone (8,9). However, although a report of long-term outcomes after PEB use in patients with bare-metal stent restenosis showed maintained efficacy out to 5 years (15), long-term outcomes after PEB for DES restenosis are not known. Indeed data suggest that there may be important pathophysiological differences between restenosis after bare metal and drug-eluting stenting (16). Moreover, pre-clinical reports suggest that signs of delayed arterial healing can be observed after PEB (17) and case reports have documented the occurrence of de novo atherosclerosis after PEB for the treatment of in-stent restenosis (18). Therefore, the evaluation of long-term outcomes in these patients remains a matter of broad clinical relevance.

The current analysis of 3-year outcome data demonstrates the durable antirestenotic efficacy of PEB as compared with PES or BA. These data should be interpreted in light of some recently reported results from other randomized trials. First, the sustained superiority of PEB in comparison with BA is in line with the recently presented 3-year results of the PEPCAD-DES (Treatment of DES-In-Stent Restenosis With SeQuent Please Paclitaxel Eluting PTCA Catheter) randomized trial in which no signs of late "catch-up" phenomenon were observed with PEB (19). Indeed the low incidence of revascularization with PEB between 1 and 3 years underscores that the significant difference in terms of efficacy between PEB and BA is achieved during the first year after treatment and suggests that a brief (typically 60 s) dilation with a drug-eluting balloon results in long-term sustained suppression of neointimal hyperplasia. In view of the lower efficacy, BA as a routine treatment approach for DES restenosis in clinical

TABLE 2 Clinical Results at 3 Years and Landmark Analysis From 0 to 1 and 1 to 3 Years by Treatment Group

	PEB	PES	BA	HR (95% CI) PEB vs. PES	p Value PEB vs. PES	HR (95% CI) PEB vs. BA	p Value PEB vs. BA
TLR							
0–1 yr	30 (22.1)	17 (13.5)	56 (43.5)	1.65 (0.91–3.0)	0.09	0.41 (026–0.64)	<0.001
1–3 yrs	14 (14.5)	12 (12.4)	9 (13.4)	1.17 (0.54–2.53)	0.69	1.04 (0.45–2.41)	0.92
0–3 yrs	44 (33.3)	29 (24.2)	65 (50.8)	1.46 (0.91–2.33)	0.11	0.51 (0.34–0.74)	<0.001
Clinically driven TLR							
0–1 yr	25 (18.5)	15 (11.9)	47 (36.5)	1.54 (0.81–2.93)	0.18	0.43 (0.26–0.69)	<0.001
1–3 yrs	12 (12.0)	8 (8.2)	4 (5.1)	1.42 (0.58–3.48)	0.44	2.22 (0.72–6.89)	0.16
0–3 yrs	37 (28.1)	23 (19.1)	51 (39.5)	1.50 (0.89–2.53)	0.12	0.58 (0.38–0.88)	0.01
Death or MI							
0–1 yr	6 (4.4)	9 (6.9)	9 (6.8)	0.62 (0.22–1.73)	0.35	0.62 (0.22–1.75)	0.36
1–3 yrs	8 (6.3)	14 (12.3)	5 (4.5)	0.51 (0.21–1.22)	0.12	1.55 (0.51–4.75)	0.44
0–3 yrs	14 (10.4)	23 (18.3)	14 (10.9)	0.55 (0.28–1.07)	0.08	0.96 (0.46–2.00)	0.90
Death							
0–1 yr	3 (2.2)	6 (4.6)	7 (5.3)	0.46 (0.12–1.85)	0.27	0.40 (0.10–1.54)	0.17
1–3 yrs	5 (3.9)	13 (11.2)	5 (4.4)	0.34 (0.12–0.96)	0.03	0.95 (0.28–3.30)	0.94
0–3 yrs	8 (6.0)	19 (15.3)	12 (9.4)	0.38 (0.17–0.87)	0.02	0.63 (0.26–1.54)	0.31
Cardiac death							
0–1 yr	2 (1.5)	5 (3.8)	4 (3.0)	0.37 (0.07–1.92)	0.22	0.47 (0.09–2.59)	0.38
1–3 yrs	1 (0.9)	5 (4.4)	2 (1.8)	0.18 (0.02–1.52)	0.07	0.48 (0.04–5.25)	0.54
0–3 yrs	3 (2.4)	10 (8.1)	6 (4.7)	0.27 (0.08–0.99)	0.03	0.48 (0.12–1.90)	0.28
MI							
0–1 yr	3 (2.1)	3 (2.4)	2 (1.5)	0.92 (0.19–4.58)	0.92	1.42 (0.24–8.50)	0.63
1–3 yrs	4 (3.2)	1 (0.9)	0 (0.0)	3.63 (0.41–32.45)	0.22	NA	0.05
0–3 yrs	7 (5.4)	4 (3.2)	2 (1.5)	1.60 (0.47–5.48)	0.45	3.34 (0.69–16.06)	0.11
Q-wave MI							
0–1 yr	1 (0.7)	1 (0.8)	0 (0.0)	0.92 (0.06–14.64)	0.95	NA	0.34
1–3 yrs	0 (0.0)	0 (0.0)	0 (0.0)	NA	0.18	NA	0.69
0–3 yrs	1 (0.7)	1 (0.8)	0 (0.0)	0.92 (0.06–14.75)	0.96	NA	0.34
Target vessel–related MI							
0–1 yr	0 (0.0)	2 (1.6)	1 (0.8)	NA	0.14	NA	0.31
1–3 yrs	3 (2.3)	0 (0.0)	0 (0.0)	NA	0.10	NA	0.09
0–3 yrs	3 (2.3)	2 (1.6)	1 (0.8)	1.36 (0.23–8.17)	0.73	2.84 (0.29–27.26)	0.35
Target lesion thrombosis							
0–1 yr	1 (0.8)	1 (0.8)	0 (0.0)	0.94 (0.06–15.11)	0.97	NA	0.33
1–3 yrs	0 (0.0)	1 (0.8)	0 (0.0)	NA	0.29	NA	0.69
0–3 yrs	1 (0.8)	2 (1.6)	0 (0.0)	0.46 (0.04–5.10)	0.53	NA	0.33
Death, MI, or TLR							
0–1 yr	32 (23.5)	25 (19.3)	61 (46.2)	1.20 (0.71–2.02)	0.50	0.40 (0.26–0.62)	<0.0001
1–3 yrs	19 (19.2)	23 (22.9)	12 (18.0)	0.83 (0.45–1.52)	0.54	1.08 (0.52–2.23)	0.83
0–3 yrs	51 (38.0)	48 (37.7)	73 (55.7)	1.02 (0.69–1.52)	0.91	0.52 (0.37–0.75)	<0.001

Values are n (%) unless otherwise indicated. The percentages are Kaplan-Meier estimates. The p values were determined by log-rank test. Hazard ratios with pertinent 95% confidence intervals are derived from Cox proportional hazard models.

CI = confidence interval; HR = hazard ratio; NA = not applicable; TLR = target lesion revascularization; other abbreviations as in Table 1.

practice should be discouraged. In this study, in patients treated with PEB, thorough pre-treatment of the restenotic lesion was first performed with conventional BA; this is the recommended approach for using PEB in clinical practice. Second, the comparable results observed with PEB in comparison with repeat stenting with DES is encouraging and lends support to the concept that by avoiding further stent layers, a strategy based on PEB may be the preferred treatment for these patients. Importantly, however, it should be acknowledged that the comparator stent in ISAR-DESIRE 3 was the early generation PES. Nevertheless, although PES has been superseded by newer generation DES for the treatment of de novo coronary disease, it has shown comparable efficacy to leading DES in the treatment DES restenosis (4,14). At the same time, a randomized trial comparing new generation DES with PEB in patients with bare-metal stent restenosis showed some evidence of higher angiographic antirestenotic

efficacy with newer generation DES, although this did not translate into significant differences in terms of clinical efficacy (20). In addition, a recently presented randomized trial in patients with DES restenosis suggests that a strategy of everolimus-eluting stenting might offer superior efficacy as compared with a treatment with PEB, although the long-term clinical impact of such strategy remains unstudied (21).

Interestingly, in relation to safety outcomes in terms of the composite of death or MI the current analysis shows some evidence of higher safety with PEB therapy compared with repeat stenting with PES as well as comparable overall late safety versus BA alone. In particular, the treatment of DES restenosis with PEB versus PES seems to be associated with a lower risk of death and cardiac death; this difference is mainly driven by events occurring after 1 year. Whereas analysis of late outcomes should be regarded as post hoc, and this difference may represent a chance finding, it is interesting to note that similar observations have recently been presented in the 2-year follow-up of the PEPCAD China ISR (Prospective, Multicenter, Randomized Trial of Paclitaxel-Coated Balloon versus Paclitaxel-Eluting Stent for the Treatment of DES In-Stent Restenosis) trial (22). Moreover, although a clear mechanistic link is not apparent - despite a numerically lower risk of target lesion thrombosis with PEB versus PES – this issue warrants further investigation.

STUDY LIMITATIONS. First, the design of the ISAR-DESIRE 3 trial was based on primary comparative efficacy between the treatment groups in relation to angiographic endpoints at 6 to 8 months. Accordingly, the trial was not specifically powered for the detection of differences in clinical outcomes and these findings should be verified in larger trials powered for clinical endpoints. Second, as efficacy and safety among different paclitaxel-eluting balloons may vary (7,23), the results observed in this analysis might not be generalizable to other devices. Third, the study protocol included angiographic follow-up and the influence of planned invasive surveillance on the rates of TLR must be considered. Fourth, although all treatment groups received the same recommendation for duration of treatment after index PCI (minimum of 6 months), complete 3-year data relating to compliance or actual duration of dual antiplatelet therapy received was not available. Fifth, in patients with DES restenosis, the results of a repeat stenting treatment strategy might be improved with the use of newer generation DES (21).

CONCLUSIONS

At 3-year follow-up, the use of PEB as compared with PES to treat restenosis in patients who have previously received a limus-eluting stent has similar efficacy and safety. In addition, PEB remains superior to BA. The sustained efficacy without trade-off in safety supports the role of PEB as a treatment option for patients with DES restenosis.

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PERSPECTIVES

WHAT IS KNOWN? Although PEB angioplasty has shown encouraging results for the treatment of DES restenosis, the long-term clinical efficacy and safety of this therapy remains poorly defined.

WHAT IS NEW? In this study, the use of PEB as compared with PES implantation to treat DES in-stent restenosis has similar efficacy and safety out to 3 years. In addition, PEB remains superior to BA alone.

WHAT IS NEXT? The sustained efficacy without trade-off in safety supports the role of PEB as a treatment option for patients with DES restenosis. These findings should be verified in larger trials powered for clinical endpoints.

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