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RESEARCH ARTICLE

Long-term clinical outcome and mortality risks after paclitaxel-coated balloon angioplasty in patients with peripheral artery disease: An observational clinical study

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Abstract

Background and aims: Drug-eluting devices (DEDs) are usually used as a standard therapy for revascularization in femoropopliteal artery disease. Randomized controlled trails have found that DEDs with paclitaxel result in superior patency rates and decreased target lesion revascularization. A meta-analysis by Katsanos et al indicated an increased long-term mortality in patients treated with paclitaxel-coated devices. The aim of this observational clinical study was to assess the long-term clinical outcomes and mortality risk after paclitaxel-coated balloon angioplasty in patients with symptomatic peripheral artery disease.

Methods: We retrospectively evaluated 287 patients with peripheral interventions, including 173 drug-coated balloon (DCB) angioplasties and 114 plain old balloon angioplasties (POBA), performed at our center between 2015 and 2018.

Results: There were no significant differences in mortality rates between patients who received DCB angioplasty and those who received POBA. In the first year, the hazard ratio (HR) for DCB angioplasty was 0.59 (95% confidence interval [CI] 0.31 to 1.12, P = .104). After 2 years, this HR was 0.64 (95% CI 0.36-1.17, P = .145), while the 3-year and 4-year HR increased to 0.71 and 1.30 (3-year: 95% CI 0.37-1.33, P = ,283; 4-year: 95% CI 0.55-3.08, P = .546). No paclitaxel dose-response relationship with mortality rate was identified when adjusted for key predictors of mortality.

Conclusions: Analyses of patient level data identified no significant mortality differences between DCB angioplasty and POBA after 4 years of follow-up. Furthermore, there was no dose-response relationship between paclitaxel and mortality. These findings demonstrate that paclitaxel DCB is safe. Further long-term multicenter studies are needed to determine the risk of late mortality.

KEYWORDS

drug-eluting devices, lower extremity artery disease, plain old angioplasty balloon, re-intervention, revascularization

Nadjib Schahab and Ann-Kathrin Prengel contributed equally to this work.

1 | INTRODUCTION

Drug-eluting devices (DEDs) such as drug-coated balloons (DCBs) or drug-eluting stents (DESs) are applied for peripheral-arterial revascularization in patients with obstructive peripheral arterial disease (PAD). They are specially used to prevent restenosis in these patients.[1-3] The THUNDER study published in 2008 was the first to show less target lesion revascularization in patients who were treated with paclitaxel[3] than in those who received plain old balloon angioplasty (POBA). Paclitaxel is an anti-proliferative drug applied to the inner side of the artery during balloon inflation. Due to its effect on β-tubulin, stabilizing the microtubule assembly, it protects from disassembly and thus from complete cell division and restenosis.[4]

The THUNDER study was followed by several randomized studies, which demonstrated the superiority of paclitaxel-coated balloons vs non-paclitaxel-coated devices in revascularization of peripheral arteries.[5-7] Thus, paclitaxel balloons were rapidly accepted into clinical practice and regularly used in the United States since 2012,[8,9] without concerns, until the meta-analysis by Katsanos et al was published with new surprising outcomes. In this systematic review and meta-analysis of 28 randomized controlled trials, including 4663 patients, Katsanos et al reported an "increased risk of death following the application of paclitaxel-coated balloon and stents in the femoropopliteal artery."[10] They also identified a "highly significant association between paclitaxel dose-time product and the absolute risk of death."[10] Once these results were published, there were many controversial studies that confirmed or disproved this thesis,[11-13] leading to a safety alert in January 2019 and further details on the implications of these devices in future clinical use by the Food and Drug Administration (FDA) in March 2019 and the Federal Institute for Drugs and Medical Devices in Germany (BfArm) in June 2019, in order to appraise the benefits and risks more carefully and to increase transparency regarding possible side-effects, such as increased mortality.[14,15]

Therefore, this observational clinical study aimed to evaluate the long-term clinical outcomes and mortality risk after paclitaxel-coated balloon angioplasty in patients with symptomatic PAD, using patient-level data from the clinical database of the Department of Cardiology and Angiology of University Hospital Bonn in Germany.

2 | MATERIALS AND METHODS

2.1 | Study design and population

Between January 2015 and December 2018, 746 peripheral vascular interventions (n = 555 patients) performed at the University Hospital Bonn in Germany were, retrospectively, analyzed using the clinical database (Orbis, AGFA Healthcare) of the Department of Cardiology and Angiology.

We excluded 268 of the 555 patients (335/746 interventions): 15 who received DESs (15/746 interventions), 119 subjected to peripheral diagnostic procedures (162/746 interventions) without requiring any further intervention, and 134 (158/746 interventions) subjected to other procedures, such as peripheral vascular bed other than that of the lower limbs.

Patients with an iliaco-femoropopliteal and infrapopliteal intervention and at least a 12-month follow-up period (n = 287 patients, 411 interventions) were included in this observational clinical study. Patients were assigned to two groups based on the use of DCB (n = 173/287) and POBA (n = 114/287). All included patients were diagnosed with symptomatic PAD. Patients were included in the DCB group irrespective of having formerly received POBA or bare metal stent (BMS) at the time of their first DCB angioplasty. Moreover, 58/287 patients (124 interventions) had a recurrent stenosis and re-interventions after POBA (n = 15) or DCB (n = 43; Figure 1).

PAD was confirmed based on an ankle-brachial index (ABI) score ≤0.9, duplex sonography findings, and/or clinical symptoms (Fontaine stage), all of which were assessed as part of the standard procedure for patients with PAD who are scheduled to undergo percutaneous transluminal angioplasty (PTA). ABI is defined as the ratio of the highest systolic blood pressure of the ankle (*A. dorsalis* pedis or *A. tibialis* posterior) to the highest systolic blood pressure of the upper arms (*A. brachialis*).[16]

Patients in the DCB group received four types of DCBs with different paclitaxel dose/mm^2: IN.PACT (3.5 μg/mm^2; IN.PACT Admiral, Medtronic Inc, Dublin, Ireland), Biopath (3.0 μg/mm^2; Biopath 035, Biosensors international, Singapore, Republic of Singapore), Lutonix (2.0 μg/mm^2; Lutonix 035, BARD Peripheral Vascular Inc., Tempe, Arizona), and Ranger (2.0 μg/mm^2; Ranger, Boston Scientific, Marlborough, Massachusetts).[17-20] The used paclitaxel dose was estimated on the base of the used DCB and diameter/length of the lesion.

All patients were followed for all-cause death and restenosis after DCB and POBA. In total, 18 patients (6.27%) were lost to follow-up. Data analyzed included age, body mass index, diabetes mellitus, and renal insufficiency, as well as the correlation of paclitaxel DCB with higher mortality risk.

2.2 | Statistical analyses

Data were retrospectively analyzed using Microsoft Excel for Office 365 (Redmond, Washington) and IBMSPSS software, version 26.0 (IBM Corporation, Armonk, New York). Metric variables are described as mean ± standard deviation (SD) and compared with a *t*-test when normally distributed. For categorical variables, we used cross tables to present the absolute and relative frequency and verified independency using the Chi-square-test. Cox regression analyses were performed to measure the time-dependent association between the usage of DCB, the localization of the index lesion, the used paclitaxel dose, general comorbidities, and long-term mortality. For the cox regression, we defined the risk ratio and the associated 95% confidence interval (CI). We performed Kaplan-Meier survival analysis to estimate the survival curve of both the paclitaxel DCB and POBA group. The level of statistical significance was set at $P < .05$. We also run a sensitivity analysis using propensity score matching and

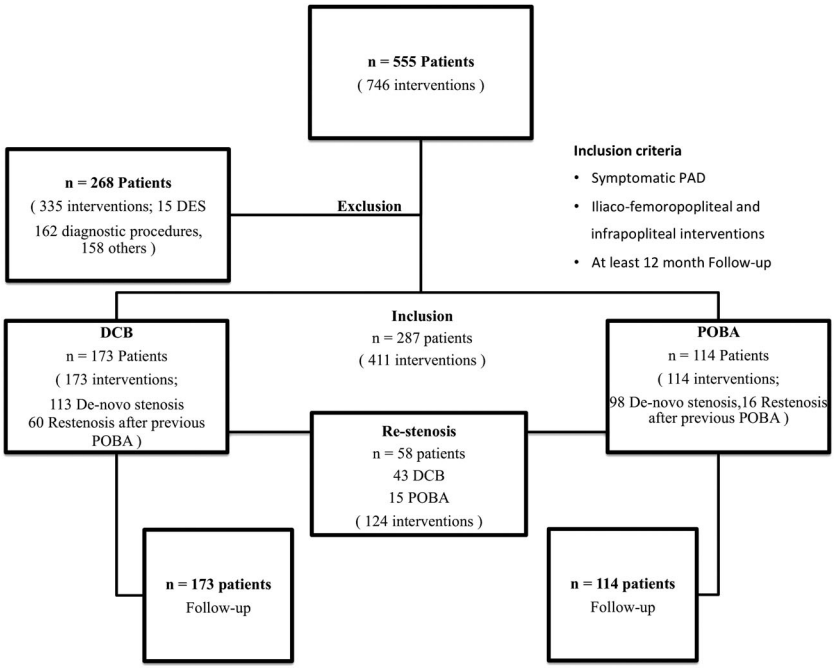

FIGURE 1 Flow chart of study design. DCB, drug-coated balloon; DES, drug-eluting stent; PAD, peripheral arterial disease; POBA, plain old balloon angioplasty

propensity score weighted cox-analysis. For analytical purposes, we created composite of death, amputation, or re-intervention for both group.

2.3 | Ethical considerations

All data were fully anonymized before access and analysis. The study was approved by the Ethics committee of the Faculty of Medicine at University Hospital Bonn and was done in accordance with the Declaration of Helsinki. All patients signed written informed consent before study inclusion.

3 | RESULTS

3.1 | Baseline characteristic and intervention

Table 1 presents the patients' baseline characteristics. From 2015 to 2018, we analyzed the data of 287 patients who received an index-PTA (DCB: n = 173 and POBA: n = 114), including 84 women (29.3%). The patients' mean ± SD age was 71.30 ± 10.35 years. There was a high prevalence for arterial hypertension and dyslipidemia in both groups.

Patients who received DCB angioplasty were more likely to be staged as Fontaine IV than those who received POBA (31.8% in DCB group vs 23.7% in POBA group). In total, there was no significant difference in the distribution of patients according to Fontaine stages between groups (P = .078).

There was also no statistically significant difference in the diagnosed comorbidities and daily medication intake between the two patient groups. The mean C-reactive protein (CRP) value was higher in the POBA group (30.38 ± 53.51 mg/L) than in the DCB group (17.50 ± 28.85 mg/L; P = .001). Calculating the logarithm of the CRP value reduced the statistical significance of this difference.

Table 2 shows the procedure characteristics according to usage of DCB or POBA. Significantly more patients with iliac artery stenosis and infrapopliteal arterial segment stenosis received POBA than DCB angioplasty (iliac: 38.6% POBA vs 17.5% DCB, P < .001; infrapopliteal: 24.3% POBA vs 14.0% DCB, P = .034). The use of BMS at the iliac artery and femoropopliteal segment was higher in patients who received POBA than DCB angioplasty (iliac: 16.7% vs 3.5%, P < .001; femoropopliteal: 49.1% vs 26.0%, P < .001). Moreover, 34.7% (60/173) of the patients in the DCB group had a previous POBA and were classified as having recurrent stenosis at the index event; in contrast, only 14.0% (16/114) of the patients in the POBA group had a previous angioplasty, with the difference between groups being statistically significant (P < .001). The lesion length was statistically significantly longer in the DCB than in the POBA group (115.79 ± 6.22 mm in DCB vs 82.38 ± 3.22 mm in POBA, P < .001; Table 2).

3.2 | Clinical follow-up (Fontaine stage and ABI)

The patients' distribution according to Fontaine stage and ABI before and 24 months after the intervention is presented in Figures 2 and 3. There was no statistically significant difference between the two groups in terms of Fontaine stage after 24 months (P = .091). Twenty-four months after the intervention, the ABI improved by 0.85 ± 0.30 units in the DCB group (Figure 3) and by 0.72 ± 0.34 units in the POBA group (Figure 2), with no significant difference between groups (P = .472).

TABLE 1 Baseline characteristics

Characteristics	DCB (n = 173)	POBA (n = 114)	*P*-value
Mean age (±SD), years	71.49 ± 10.37	71.02 ± 10.34	.787
Sex, female, % (n)	29.5 (51)	28.9 (33)	.923
BMI (mean ± SD), kg/m^2	26.70 ± 4.56	27.00 ± 5.20	.258
ABI (mean ± SD)	0.62 ± 0.38	0.67 ± 0.41	.973
Stenosis in duplex, % (n)	87.3 (137)	76.7 (79)	.026
Fontaine stage			
Fontaine stages I-IV	n = 172	n = 110	.078
Fontaine stage I, % (n)	0 (0)	0 (0)	
Fontaine stage IIa, % (n)	0 (0)	0 (0)	
Fontaine stage IIb, % (n)	63.6 (110)	64.9 (74)	
Fontaine stage III, % (n)	4.0 (7)	7.9 (9)	
Fontaine stage IV, % (n)	31.8 (55)	23.7 (27)	
Diagnosed comorbidities			
Sleep apnea, % (n)	10.4 (18)	8.8 (10)	.648
Renal insufficiency, % (n)	26.0 (45)	29.8 (34)	.479
Arterial hypertension, % (n)	90.2 (156)	87.7 (100)	.512
Diabetes mellitus, % (n)	41.0 (71)	38.6 (44)	.679
Dyslipidemia, % (n)	83.2 (144)	84.2 (96)	.827
Active smoker, % (n)	27.2 (47)	33.3 (38)	.263
Ex-smoker, % (n)	28.9 (50)	22.8 (26)	.252
Coronary heart disease, % (n)	52.6 (91)	60.5 (69)	.186
Previous myocardial infarction, % (n)	20.2 (35)	23.7 (27)	.487
Cerebrovascular disease, % (n)	26.6 (46)	26.3 (30)	.959
Previous stroke, % (n)	12.1 (21)	13.2 (15)	.799
COPD, % (n)	15.0 (26)	18.4 (21)	.447
Medication intake			
Acetylsalicylic acid, % (n)	71.1 (123)	77.2 (88)	.252
Phenprocoumon or other oral anticoagulant, % (n)	34.1 (59)	23.7 (27)	.059
Statin, % (n)	83.2 (144)	84.2 (96)	.827
Antihypertensive drug, % (n)	90.2 (156)	87.7 (100)	.512
Lab results			
CRP, mean ± SD, mg/L	17.50 ± 28.85	30.38 ± 53.51	.001
Log (CRP), mean ± SD	0.79 ± 0.66	1.02 ± 0.64	.511
HbA1c, mean ± SD, %	6.77 ± 1.54	6.90 ± 1.90	.831
Cholesterol, mean ± SD, mg/dL	173.75 ± 50.11	173.42 ± 44.89	.625
HDL, mean ± SD, mg/dL	52.08 ± 20.52	48.30 ± 17.16	.218
LDL, mean ± SD, mg/dL	98.03 ± 37.64	97.56 ± 36.08	.665
Triglycerides, mean ± SD, mg/dL	195.28 ± 166.06	194.80 ± 156.32	.715
Thrombocytes, mean ± SD, cells/nL	254.49 ± 88.80	250.70 ± 93.01	.326
Prothrombin time, mean ± SD, %	95.73 ± 22.95	95.18 ± 26.72	.049
aPTT, mean ± SD, seconds	28.47 ± 13.67	27.49 ± 7.35	.087
Creatinine, mean ± SD, mg/dL	1.45 ± 1.21	1.63 ± 1.40	.153

Abbreviations: ABI, ankle-brachial index; aPTT, activated partial thromboplastin time; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein; Log, logarithm.

TABLE 2 Procedure characteristics according to usage of DCB or POBA

Characteristic	DCB (n = 173)	POBA (n = 114)	*P*-value
Multi-stenosis % (n)	58.4 (101)	51.8 (59)	.269
De-novo stenosis % (n)	65.3 (113)	86.0 (98)	<.001
Residual-stenosis % (n)	34.7 (60)	14.0 (16)	<.001
Lesion length, mean ± SD, mm	115.79 ± 82.49	82.38 ± 34.48	<.001
Localization of stenosis			
Iliac artery, % (n)	17.5 (30)	38.6 (44)	<.001
Femoropopliteal segment, % (n)	71.1 (123)	65.8 (75)	.341
Infrapopliteal segment, % (n)	24.3 (42)	14.0 (16)	.034
Type of DCB			
Biopath, % (n)	37.6 (65)		
Inpact, % (n)	38.2 (66)		
Lutonix, % (n)	26.0 (45)		
Ranger, % (n)	8.7 (15)		
Dose of paclitaxel, mean ± SD, μg	10 184.01 ± 9166.40		
BMS localization			
Iliac artery, % (n)	3.5 (6)	16.7 (19)	<.001
Femoropopliteal segment % (n)	26.0 (45)	49.1 (56)	<.001
Infrapopliteal segment % (n)	1.2 (2)	0.9 (1)	.820

Abbreviations: BMS, bare metal stent; DCB, drug-coated balloon; POBA, plain old balloon angioplasty.

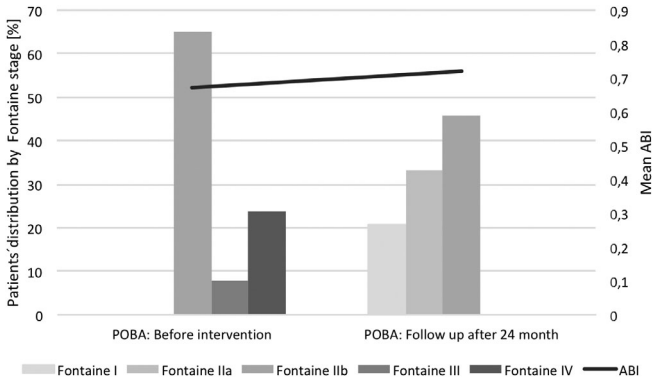

FIGURE 2 Changes in the patients' distribution by Fontaine stage and in the mean Ankle-brachial index between the time of the index event and after 24 months of follow-up in patients subjected to POBA. ABI, ankle-brachial index; POBA, plain old balloon angioplasty

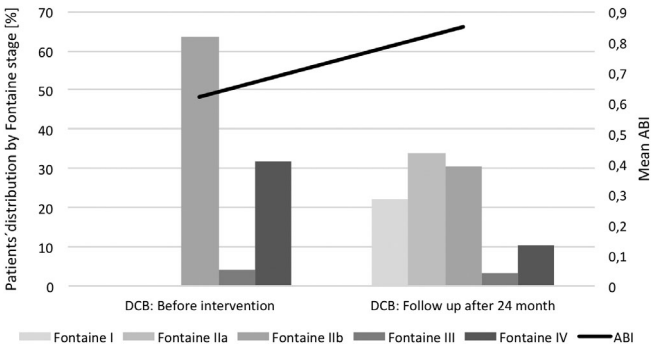

FIGURE 3 Changes in the patients' distribution by Fontaine stage and in the mean ankle-brachial index between the time of the index event and after 24 months of follow-up in patients subjected to DCB angioplasty. ABI, ankle-brachial index; DCB, drug-coated balloon

3.3 | Long-term outcomes

The median follow-up time until death or the last known date alive was 2.11 ± 1.44 years in patients subjected to POBA and 2.11 ± 1.22 years in those subjected to DCB angioplasty. In the analysis of all patients over the entire study time (2.11 ± 1.31 years), the rate of all-time mortality was 25.28% and was comparably higher in patients subjected to POBA than to DCB angioplasty (33.7% vs 20.0%, *P* = .012). We no longer found a statistically significant difference between the two groups when analyzing the time-related mortality per year. To test the impact of different basic and intervention characteristics on time-dependent mortality after the intervention, we performed cox regression analysis (Figure 4). Compared to the use of POBA, the use of DCB was associated with a lower mortality rate in the first 3 years (first year: hazard ratio [HR] 0.59, 95% CI 0.31-1.12, *P* = .104; second year: HR 0.64, 95% CI 0.36-1.17, *P* = .145; third year: HR 0.71, 95% CI 0.37-1.33, *P* = .283) but with a higher mortality risk in the fourth year (HR 1.30, 95% CI 0.55-3.08, *P* = .546), although these differences were not statistically significant. On the contrary, Kaplan-Meier survival analysis indicated a significantly lower mortality in patients who received DCB angioplasty (*P* = .031; Figure 5).

Furthermore, we ascertained that older age (HR: 1.05, 95% CI 1.01-1.10, *P* = .026), diabetes mellitus (HR: 2.42, 95% CI 1.38-4.24, *P* = .002), and renal insufficiency (HR: 2.99, 95% CI 1.66-5.38, *P* < .001) significantly correlated with a higher mortality risk. Between

	HR	CI	p-value
DCB after 1 year	0.59	(0.31,1.12)	0.104
DCB after 2 years	0.64	(0.36,1.17)	0.145
DCB after 3 years	0.71	(0.37,1.33)	0.283
DCB after 4 years	1.30	(0.55,3.08)	0.546
POBA after 1 year	1.71	(0.89,3.27)	0.104
POBA after 2 years	1.55	(0.86,2.82)	0.145
POBA after 3 years	1.42	(0.75,2.68)	0.283
POBA after 4 years	0.77	(0.32,1.82)	0.546
Age at index	1.05	(1.01,1.10)	0.026
BMI	0.91	(0.82,1.01)	0.079
Localization: iliacal	1.41	(0.76,2.58)	0.272
Localization: femoropopliteal	0.91	(0.50,1.64)	0.757
Localization: infrapopliteal	1.53	(0.79,2.95)	0.204
Dose of paclitaxel	1.00	(1.00,1.00)	0.088
Arterial hypertension	1.34	(0.52,3.43)	0.547
CVD	0.70	(0.36,1.34)	0.276
COPD	0.70	(0.32,1.54)	0.372
Coronary Heart Disease	1.31	(0.75,2.30)	0.346
Diabetes mellitus	2.42	(1.38,4.24)	0.002
Dyslipidemia	0.68	(0.33,1.41)	0.304
Nicotin abuse: active	0.79	(0.43,1.46)	0.449
Nicotin abuse: Ex-	0.82	(0.43,1.55)	0.535
Previous myocardial infarction	1.61	(0.85,3.04)	0.139
Previous stroke	1.74	(0.81,3.75)	0.151
Renal insufficiency	2.99	(1.66,5.38)	<0.001
Sleep apnea	0.48	(0.16,1.45)	0.187

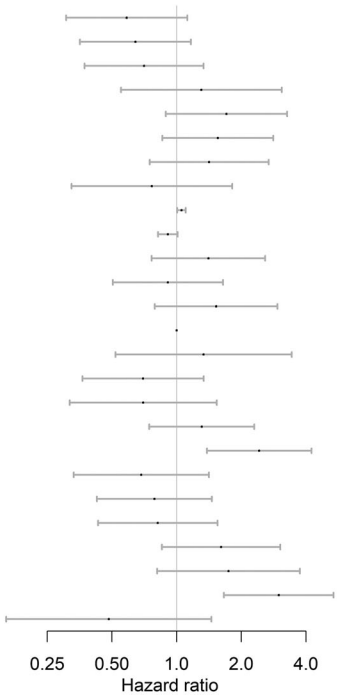

FIGURE 4 Cox regression analysis: mortality risk as hazard ratio in patients who received DCB and POBA in relation to baseline and intervention characteristics. One- to four-year mortality risk: all-time mortality did not differ significantly between DCB and POBA groups. Among the included baseline and intervention characteristics, age, diabetes mellitus, and renal insufficiency were significant prevalent risk factors. There was no association between the mortality risk and other baseline and intervention-related variables. BMI, body mass index; COPD, chronic obstructive pulmonary disease; CVD, cerebrovascular disease; DCB, drug-coated balloon; POBA, plain old balloon angioplasty

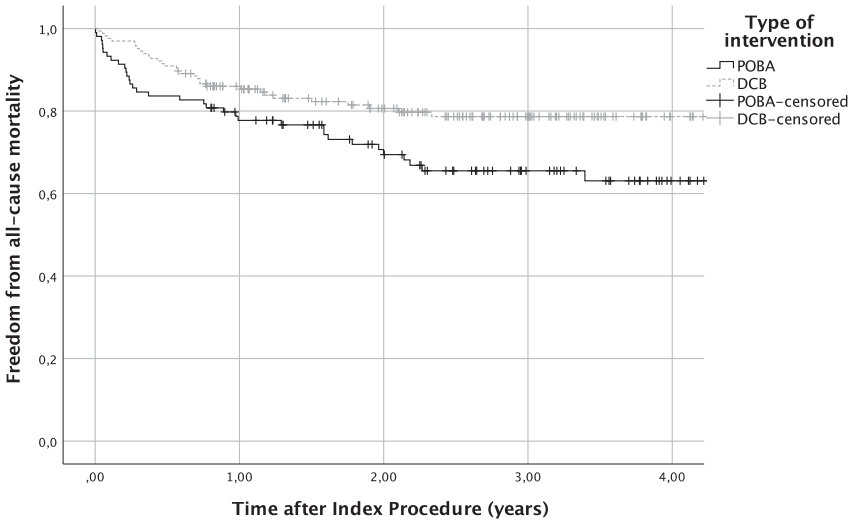

FIGURE 5 Kaplan-Meier curves for freedom from all-cause mortality after DCB and POBA. Kaplan-Meier survival analysis over a maximum of 4 years shows a lower mortality risk in patients subjected to DCB angioplasty (grey) than in those subjected to POBA (black; P = .031). DCB, drug-coated balloon; POBA, plain old balloon angioplasty

the dose-response relationship of paclitaxel and mortality, we could not find a statistically significant correlation (HR 1.00, 95% CI 1.00-1.00, P = .088).

Considering the long-term outcome, 20.21% (58/287 patients) of the patients had to undergo re-intervention. In our study, patients subjected to DCB angioplasty (n = 173) were more likely to show restenosis; 43/173 (24.9%) of these patients had a restenosis during the follow-up time. In contrast 15/114 (13.2%) of patients subjected to POBA had a re-intervention because of a restenosis (P = .016). However, we could not find a statically significant correlation regarding lesion length, lesion localization, and the applied paclitaxel dose with the occurrence of restenosis.

There were also statistically no significant differences between the different DCBs regarding clinical outcomes re-intervention and mortality (Tables 3 and 4).

We also performed cox regression analysis for Fontaine stage III or IV, amputation, re-intervention and composite of death, amputation, and re-intervention as HR in all patients (Figures S1-S4). In cox regression analysis for re-intervention, the risk for re-intervention was significantly higher in the DCB than the POBA group (Figure S3) and renal insufficiency was a significant predictor of a higher risk for combination of death, amputation, and re-intervention (Figure S4). The other analysis showed no significant correlations except some trends (Figures S1-S3). Kaplan-Meier analysis for Fontaine III/IV, amputation,

TABLE 3 Outcome regarding re-intervention in correlation with different DCB

	HR	CI lower	CI upper	*P*
IN.PACT	0.784	0.257	2.393	.669
Biopath	1.144	0.386	3.394	.808
Lutonix	1.327	0.432	4.075	.621
Ranger	0.812	0.147	4.494	.812

TABLE 4 Outcome regarding mortality in correlation with different DCBs

	HR	CI lower	CI upper	*P*-value
IN.PACT	1.230	0.414	3.653	0.710
Biopath	1.373	0.456	4.132	0.573
Lutonix	1.087	0.337	3.509	0.889
Ranger	2.402	0.627	9.203	0.201

re-intervention and composite of death, amputation, and re-intervention in DCB and POBA indicated also a significantly higher freedom of re-intervention in POBA than DCB group ($P = .028$), slight tendency but not significant that DCB patients are more likely to have an amputation ($P = .199$) and to be classified in Fontaine stage III/IV ($P = .136$; Figures S5-S7). However, we could not find a statically significant risk in Kaplan-Meier curves for freedom from composite of death, amputation, and re-intervention in DCB and POBA group ($P = .613$; Figure S8).

Given the small sample, and to exclude any bias, therefore we run a sensitivity analysis using propensity scores. The propensity score was based on the variables: age, sex, body mass index, ABI, Fontaine-Stadium, arterial hypertension, coronary heart disease, diabetes mellitus, dyslipidemia, nicotin abuse, renal insufficiency, and cerebrovascular disease.

There was very similar distribution of the propensity score variables of the two groups with no significant differences between the two groups. The propensity scores were included in the mortality analysis using cox regression. After 1 year, we see a significant difference in mortality. Patients who received DCB have a significantly lower mortality risk in the first year (HR: 0.41, CI 0.17-0.96, $P = .040$). Thereafter, there were no significant differences in the mortality rate between patients who received DCB angioplasty and those who received POBA (Table 5).

TABLE 5 Propensity score weighted Cox-analysis

	HR	CI lower	CI upper	*P*-value
DCB after 1 year	0.409	0.174	0.961	.040
DCB after 2 years	0.517	0.254	1.055	.070
DCB after 3 years	0.563	0.274	1.155	.117
DCB after 4 years	0.784	0.403	1.527	.475

4 | DISCUSSION

This retrospective single-center observational clinical study was designed to examine whether the usage of DCBs increases mortality in patients with PAD. Real-world data of 287 patients, who were divided into two nearly homogeneous groups based on the usage of DCB or POBA, were analyzed. The long-term mortality was not significantly higher in patients who received DCB angioplasty compared to that in patients who received POBA. Instead, the mortality risk was lower in the first 3 years of follow-up after DCB than after POBA; in the fourth year, the risk increased but not statistically significantly.

In their systematic review and meta-analysis, Katsanos et al showed that patients subjected to DCB angioplasty have a higher mortality risk than those subjected to POBA. The authors hypothesized that this was due to late paclitaxel toxicity.[10] The studies included in this meta-analysis focused on the efficacy of DCB in preventing restenosis, not on the mortality. This explains why the number of patients lost to follow-up was higher than that in our study (4.6% in the DCB group and 8.8% in the POBA group). Moreover, it might explain the lower total mortality rates reported by Katsanos et al (14.7% after DCB and 8.1% after POBA)[10] compared to those found in our study (20.0% after DCB and 33.7% after POBA). Furthermore, we evaluated nearly homogenous treatment arms, with a comparable prevalence of comorbidities, in contrast to the meta-analysis by Katsanos et al,[10] where, for example, the prevalence of smoking, hyperlipidemia, arterial hypertension, and diabetes differed in favor of the POBA group. In our study, we excluded patients treated with DES to avoid falsification in the outcome of efficiency.[21] In the meta-analysis,[10] the exposure to paclitaxel was calculated by the dose-time product, and a significant correlation was found with mortality. Considering that paclitaxel has a half-life time of 45 days,[22] the inclusion of time could have influenced this result. In addition, long-term outcomes were reported only in three randomized controlled studies included in the meta-analysis, with follow-ups of 4 to 5 years. Thus, in order to definitely confirm the correlation between paclitaxel devices and increased mortality, further studies on long-term outcomes are required.

During our study period, patients subjected to DCB angioplasty were more likely to show restenosis ($P = .016$), which contradicts previous evidence-based studies.[1-3] This might be explained by the inclusion criteria and by the fact that patients who received DCB once were assigned to the DCB group regardless of previous POBA interventions. Additionally, it might be explained by the number of existing restenosis events at the index event, which was significantly higher in patients who received DCB. Also, the better compliance with follow-up and lower all-time mortality in patients who received paclitaxel DCB in our study may have also influenced the rate of treated restenosis.

4.1 | Study limitations

The present study has certain limitations. First, due to the retrospective, single-center design of the study, we can only conclude on the

safety and efficiency of DCB in patients treated in our center. Second, the sample size was small, the study was statistically underpowered, and the follow-up time was rather short; thus, we could only make conclusions within this limited time period and can just testify on the safety and efficiency of DCB during this period. The median follow-up time until death or the last known date alive was 2.11 ± 1.22 years in those subjected to DCB angioplasty and 2.11 ± 1.44 years in patients subjected to POBA due to poor compliance and high mortality rates.

5 | CONCLUSIONS

Collectively, our findings do not show a higher mortality rate after DCB angioplasty than after POBA in our population during the study follow-up period. The lack of dose-response relationship argues against a causal relationship between paclitaxel and mortality. DCB was found to be safe and can be used in everyday clinical practice. Randomized controlled multicenter studies are needed to estimate the mortality risk of paclitaxel DCB. In patients with high risk of restenosis and complex lesions, the usage of DCB should be considered for avoiding restenosis and re-interventions.

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CONFLICT OF INTEREST

Nadjib Schahab reports grants from Medtronic, BARD, and Boston Scientific outside the submitted work. All other authors declare no conflicts of interest regarding this study.

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All authors have read and approved the final version of the manuscript.

The corresponding author Nadjib Schahab confirms that he had full access to all of the data in the study and takes complete responsibility for the integrity of the data and the accuracy of the data analysis.

TRANSPARENCY STATEMENT

Nadjib Schahab affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

DATA AVAILABILITY STATEMENT

The authors confirm that the data supporting the findings of this study are available within the article. The data that support the findings of this study are available for the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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