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Use of paclitaxcel-coated balloons in clinical setting is not associated with increased mortality compared to plain balloon angioplasty in femoropopliteal lesions

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TITLE PAGE

Use of paclitaxcel-coated balloons in clinical setting is not associated with increased mortality compared to plain balloon angioplasty in femoropopliteal lesions

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Keywords: Paclitaxel; drug-coated balloon; Mortality; Endovascular intervention; Peripheral artery disease

ARTICLE HIGHLIGHTS

Type of Research: Single-center retrospective cohort study

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Key Findings: Of the 329 included patients with femoropopliteal artery occlusion or stenosis, 190 (58%) underwent percutaneous angioplasty without stenting using paclitaxel-coated balloon and 139 (42%) using plain balloon. The use of paclitaxel-coated balloon was associated with better survival compared to plain balloon at 1 year (83±3% vs 73±4%) and 5 years (56±5% vs 37±5%)(P=0.0001).

Take Home Message: The use of paclitaxel-coated balloon is safe and there is no concern of increased mortality at least up to five years after the procedure based on the survival estimates.

TABLE OF CONTENTS SUMMARY

Paclitaxel-coated balloon use was associated with better survival compared with plain balloon use in this retrospective single-center cohort study of 329 patients who underwent percutaneous femoropopliteal artery angioplasty without stenting. Informing patients about an increased risk of death associated with paclitaxel-coated balloon use may be unwarranted.

Abstract

Objective:

To investigate mortality and causes of death associated with the use of paclitaxel-coated balloon (PCB) compared to plain balloon (PB) angioplasty in the treatment of femoropopliteal artery lesions in real-world clinical setting.

Methods:

This retrospective single-center study included patients who underwent percutaneous femoropopliteal artery angioplasty without stenting between years 2014 and 2020. Patients were stratified into PCB and PB groups according to the index procedure. Those who had undergone any prior or subsequent intervention using drug-eluting technology were excluded from the PB

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group. Long-term survival was estimated up to 5 years using the Kaplan-Meier method and risk factors for all-cause mortality were assessed in a multivariable analysis. Causes of death were retrieved from a national registry.

Results:

The study included 139 patients treated with PB and 190 with PCB. Patients treated with PCB had higher prevalence of chronic pulmonary disease (27% vs 17%; P=0.02) and were less often on anticoagulant therapy (34% vs 48%; P=0.01) compared to patients in the PB group. Those treated with PB were more likely to have chronic limb-threatening ischemia (CLTI; 82% vs 72%; P=0.04). Ipsilateral perioperative amputation rate was significantly higher in the PB group (7% vs 1%; P=0.01). There were no major differences in other 30-day outcomes between the groups and no differences in the rates of reinterventions and ipsilateral amputations during a mean follow-up time of 2.7±1.9 years. Survival at 1-year in the PCB group was 83±3% compared to 73±4% in the PB group (P=0.0001). The 5-year survival estimates were 56±5% and 37±5%, respectively. PCB use was independently associated with decreased risk of mortality (hazard ratio [HR], 0.70; 95% confidence interval [CI] 0.50-0.97). Independent risk factors for increased mortality were age (HR 1.04 per year; 95% CI 1.02-1.06), cardiac insufficiency (HR 1.60; 95% CI 1.12-2.27), chronic renal insufficiency (HR 2.04; 95% CI 1.47-2.85), anticoagulation therapy (HR 1.65, 95% CI 1.16-2.34) and CLTI (HR 2.85; 95% CI 1.51-5.39). In the PCB group, 63% of deaths were due to cardiovascular causes compared to 42% in the PB group (P<0.01).

Conclusions:

The use of PCB is safe and there is no concern of increased mortality after the procedure based on the 5-year survival estimates.

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Introduction

Endovascular interventions are commonly used as the primary revascularization method in patients with peripheral artery disease (PAD) of the femoropopliteal region. However, restenosis due to intimal hyperplasia may jeopardize the long-term patency of the intervention. Paclitaxel is an antiproliferative agent that is used in drug-coated balloons and to reduce the risk of restenosis[1]. The recent development of paclitaxel-coated devices, including both paclitaxel-coated balloons and drug-eluting stents, have expanded the use of endovascular interventions and increased their durability[2]. However, in December 2018, a meta-analysis by Katsanos et al[3] suggested a mortality signal at 2 and 5 years after treatment with paclitaxel-coated devices. The U.S. Food and Drug Administration (FDA) subsequently issued a warning regarding the use of these devices[4]. This lead to cessation of PCB use in many institutions. Also, there was plenty of discussion among vascular surgeons whether patients should be warned before treatment about the increased risk of death associated with the use of PCB.

One major point of criticism concerning the meta-analysis by Katsanos, besides an insufficient involvement of patients with chronic limb-threatening ischemia (CLTI) and patients treated below the knee, was that several of the included randomized controlled trials (RCTs) were underpowered and had no adequate long-term follow up. After publication of the meta-analysis, several "real-world" studies investigating the outcomes of paclitaxel-coated devices emerged[5]. Patient-level data from these studies demonstrated no association with mortality[6]. Thus, the subject has remained controversial. Moreover, it is unclear, whether the causes of death in patients treated with paclitaxel-coated devices differ from those treated with non-paclitaxel-coated devices[7]. The aim of the present study was to investigate long-term mortality and causes

of deaths in patients treated with PCBs without stenting in femoropopliteal artery compared with to those treated with plain balloon angioplasty in the real-world clinical setting.

Methods

Study patients and definitions

This was a retrospective single-center study based on a prospectively collected database of adult patients undergoing endovascular revascularization of femoropopliteal lesions between years 2014 and 2020. The study was approved by the local institutional review board. Because of the register-based set-up, no formal informed consent was needed. Patients treated with PCB without stenting were included in the study group and those treated with PB without stenting were included in the control group. Patients who had undergone endovascular revascularization of only iliac or tibial arteries alone were excluded. Altogether, 375 patients were stratified into PCB and PB groups according to index procedure registered in a local vascular database. Fifteen patients in the PB group had undergone a prior or subsequent endovascular upper or lower extremity revascularization with drug-coated devices and were excluded from the analysis. In addition, 30 patients who had been treated with prior or subsequent coronary artery intervention using drug-eluting technology were excluded from the PB group. Thus, the patients that were ultimately included in the PB control group had not been exposed to paclitaxel before or after the index procedure. One patient in the PCB group was lost to follow-up (**Figure 1**).

Comorbidities and early outcomes were retrieved from the electronic medical records retrospectively. Survival status and causes of death were retrieved from a national population registry in September 2021. Chronic pulmonary disease was defined as chronic

obstructive pulmonary disease or asthma with continuous medication. An active malignancy or a history of cancer included any type of malignancy. Chronic renal insufficiency was defined as calculated glomerular filtration rate <60 ml/min/1.73m^2 and end-stage renal disease was defined as need for regular dialysis. Smoking was categorized as current smoker or nonsmoker. Antiplatelet agents included aspirin and clopidogrel, anticoagulation therapy included any kind of anticoagulants and lipid-lowering drugs were defined as statin treatment with or without adjuncts. The indication for revascularization was classified as claudication (Fontaine II), rest pain (Fontaine III) or tissue loss (Fontaine IV). The radiologic severity of the disease was determined by a single vascular surgeon and classified as TASC A-B (femoropopliteal artery multiple stenosis or occlusion totaling <15cm) and TASC C-D (femoropopliteal artery multiple stenosis or occlusion totaling >15cm). The level of intervention was classified as femoropopliteal intervention alone or femoropopliteal angioplasty with adjunctive infrapopliteal angioplasty. The target lesion was predilated with PB and if stenting was not required due to dissection or recoil, the use of PCB was based on operator decision. On some occasions, the possible use of PCB had been discussed in a multidisciplinary team with vascular surgeons and interventional radiologists prior to the procedure, but most decisions were made on-the-table.

Study outcomes

The perioperative 30-day outcomes included bleeding, pseudoaneurysm, wound infection, thrombosis, deep vein thrombosis, myocardial infarction, stroke, acute renal failure, a return to operating room, any complication, major amputation and 30-day all-cause mortality. The long-term outcomes included ipsilateral major amputation, any ipsilateral reintervention and all-cause mortality during the follow up. The medical records of all patients who had died during

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the follow-up period were reviewed by the main investigator. The causes of death were retrieved from the Finnish national database (Statistics Finland).

Statistical analysis

The primary end point was all-cause mortality during the follow up. Secondary end points were 30-day outcomes. The X^2 test and Fisher's exact test were used for comparison of categorical variables and Mann-Whitney U test was utilized for continuous variables. The Kaplan-Meier method was used for survival estimates and the Log-rank test was used to compare long-term survival between the groups. All preoperative variables were first tested in univariable analysis and those with $P<0.05$ were included in a multivariable Cox regression analysis to determine independent risk factors for mortality during the follow up. Statistical significance was defined as $P<0.05$. All analyses were performed using IBM SPSS Statistics, Version 26.

Results

Patient characteristics

Of the 329 included patients, 139 (42%) had undergone femoropopliteal intervention with PB and 190 (58%) femoropopliteal intervention with PCB (**Table I**). Patients, who were treated with PCB, had higher rates of chronic pulmonary disease (27% vs 17%; P=0.02) and were less often on anticoagulant therapy (34% vs 48%; P=0.01). Patients treated with PB were more likely to have CLTI (82% vs 72%; P=0.04). No differences were found in mean body mass index, other comorbidities, history of smoking, or in the use of antiplatelet and lipid-lowering medications between the two groups.

Procedural characteristics

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Among those treated with PCB, 111 (58%) revascularizations were performed on femoropopliteal segment alone and 79 (42%) patients underwent simultaneous adjunctive infrapopliteal intervention of the same leg (**Table II**). There was a significant difference in the femoropopliteal artery lesion severity between the two groups. Patients treated with PB were more likely to have longer TASC C-D lesions compared with patients treated with PCB; 23% vs 13% (P=0.02), respectively.

Perioperative and 30-day outcomes

No major differences were found in the perioperative complications between patients treated with PCB and PB (**Table III**). There was no difference in 30-day mortality either (2% vs 2%; P=1.00). However, the incidence of perioperative ipsilateral amputations rate was higher in the PB group compared to the PCB group; 7% versus 1% (P=0.01), respectively.

Long-term outcomes and causes of death

The mean follow-up time for all patients was 2.7±1.9 years. The mean follow-up times for PCB and PB groups were 2.9 ± 1.7 years and 2.3 ± 2.1 years, respectively (P<0.001). During the follow-up time, PCB use was associated with lower ipsilateral major amputation rate of borderline significance (8% vs 14%; P=0.07) and higher ipsilateral reintervention rate of borderline significance (32% vs 23%; P=0.08) compared with PB use (**Table III**). Mortality was significantly lower among patients treated with PCB (37% vs 55%, P=0.002). Kaplan–Meier curves comparing mortality also demonstrated clear differences between the two groups (**Figure II**). Survival at 1-year in the PCB group was 83±3% compared to 73±4% in the PB group (P=0.0001). The 2-year survival estimates were 75±3% and 59±5% and 5-year survival estimates were 56±5% and 37±5%, respectively. Few statistically significant differences were found in the causes of death between the two groups; 44 out of 70 deaths (63%) in PCB group occurred due

to cardiovascular causes in comparison to 32 out of 76 deaths (42%) in the PB group (p=0.01); 3 out of 70 deaths (4%) in PCB group occurred due to respiratory causes in comparison to 16 out of 76 (16%) in the PB group (p=0.03). There was no difference in cardiovascular mortality during the follow up between the groups whereas mortality due to respiratory disease was higher in the PB group (**Table IV**).

Factors independently associated with long-term mortality

Multivariable Cox regression analysis showed that PCB use was independently associated with a decreased risk of mortality during the follow up (hazard ratio [HR], 0.70; 95% confidence interval [CI] 0.50-0.97). The independent risk factors for increased mortality risk were age (HR, 1.04 per one year; 95% CI, 1.02-1.06), cardiac insufficiency (HR, 1.60; 95% CI, 1.12-2.27), chronic renal insufficiency (HR, 2.04; 95% CI, 1.47-2.85), anticoagulation therapy (HR, 1.65, 95% CI, 1.16-2.34) and CLTI (HR, 2.85; 95% CI, 1.51-5.39). A subgroup analysis of patients without anticoagulation showed significantly lower mortality (HR, 0.40; 95% CI, 0.24-0.65) in the PCB group, whereas no difference in mortality risk was observed between PCB and PB use for those who were on anticoagulation therapy during the index procedure (HR, 0.91; 95% CI, 0.59-1.41). Another subgroup analysis of patients with claudication showed significantly lower mortality in the PCB group (HR, 0.17; 95% CI, 0.05-0.57) as well as in patients with CLTI (HR, 0.70; 95% CI 0.50-0.99).

Discussion

In the present study, PCB use was associated with better survival compared with PB use and this trend persisted up to five years after the index procedure. This finding contradicts the recently published data that raised concerns regarding the long-term safety of

paclitaxel-coated devices[3]. The findings of the meta-analysis by Katsanos and colleagues had a major impact on the management of patients with lower extremity PAD. The FDA recommended taking increased long-term mortality signal into consideration as part of informed consent process in patients treated with paclitaxel-coated devices and discussing the risks and benefits of all available PAD treatment options with the patients[4]. Although ideal, this is impractical in the clinical setting, and as our study suggests, may be unnecessary. It is often uncertain before treatment, whether a femoropopliteal lesion is going to require PCB treatment or not. The decision to use PCB is often made "on-the-table" after predilatation of the lesion. Nonetheless, results similar to the Katsanos paper were reported later in other meta-analyses based on patient-level data from the same randomized trials[8,9] whereas several other meta-analyses and randomized controlled trials have not been able to demonstrate higher mortality rates associated with drug-coated devices[6,7,10,11,12,13]. Analyses of real-world registry data across several countries have not shown any association with drug-coated device usage and mortality[5,7, 14,15,16,17]. The present study adds to this evidence, and interestingly, showed better survival for those treated with PCB compared to those treated with PB even when adjusted with preoperative characteristics in the multivariable model.

There are no known obvious biological mechanisms how PCBs might influence mortality. The dose of paclitaxel delivered by drug-coated devices is very small compared with doses used in other applications such as cancer treatment[19]. Some authors have suggested that the extended half-life of the crystalline paclitaxel formulation used for drug-coated balloons and drug-eluting stents may cause negative long-term effects and that an unknown amount of the drug compound may embolize downstream of the target lesion[1].

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In the present study, there were some notable differences in the causes of deaths between the study groups. A larger proportion of deaths in the PCB group were caused by cardiovascular diseases (63%) in comparison with the PB group (42%) whereas more deaths were caused by respiratory diseases in the PB group (16%) compared to the PCB group (4%). However, the same percentage (23%) of all patients died from cardiovascular causes during the follow-up in both groups. Thus, no difference in cardiovascular mortality was observed between the groups. A larger percentage of patients died from respiratory disease in the PB group even though chronic pulmonary disease was more prevalent at baseline in the PCB group; these differences are small and likely coincidental.

Studies, that have included patients treated for both claudication and CLTI, have not shown any differences in mortality with the use of paclitaxel-coated devices in either population [1,16]. The present study included patients treated for both claudication and CLTI with the majority of patients treated for CLTI. In the Katsanos meta-analysis, all-cause death at one year was similar between paclitaxel-coated devices and control arms; the signal of increased mortality in paclitaxel group began to emerge after two years (7.2 % versus 3.8%)[3]. The overall mortality at two years reported in the current study is remarkably higher in both groups compared to the Katsanos study and probably results from advanced age, multiple comorbidities including severe PAD and CLTI in our population. This reflects the inherent differences in the patient populations between real-world setting and prospective studies including the lack of CLTI patients in randomized trials.

The present study demonstrated a lower rate of ipsilateral major amputation during the same hospitalization or within 30 days among patients treated with PCB compared with PB. This together with the fact that there were slightly more CLTI and longer lesions in the PB group

suggest that patients in the PB group had more severe PAD than patients in the PCB group. Although more severe disease likely contributes to the higher mortality in the PB group, a significant difference in favor of the PCB group remained after adjusting for these factors in the multivariable analysis. A registry-based propensity-matched study from South Korea demonstrated the same phenomenon of better amputation-free survival associated with paclitaxel coated devices in patients with PAD, but the same effect was not seen in overall survival[15]. A new meta-analysis based on randomized controlled trials by the Katsanos' study group comparing amputation risk following the application of PCBs in the lower limb arteries observed higher amputation risk for those treated with PCB at 2 years[19]. Downstream embolization of cytotoxic paclitaxel particulate material was proposed to be the most likely explanation. Considering the widespread use of paclitaxel-coated devices in high-risk cardiovascular patients, further investigations are needed. The present study was not specifically designed to assess long-term patency or amputation rates.

There were some statistically significant differences between the study groups at baseline. The prevalence of respiratory disease was higher in the PCB group, but this difference was relatively small and did not affect the results as chronic pulmonary disease was not a risk factor for mortality in this study. Patients in the PB group were more often on anticoagulation at baseline. This could reflect higher occurrence of atrial fibrillation, history of deep venous thrombosis or other cardiovascular comorbidities in the group. Interestingly, when stratified by the use of anticoagulation at baseline, the risk of mortality was significantly lower in the PCB group in the subgroup of patients without anticoagulation whereas no difference in mortality was observed between PCB and PB group patients who were on anticoagulation. Although anticoagulation was found to be an independent risk factor for mortality, it was not a major

driving factor for the higher mortality in the PB group. As discussed earlier, a higher proportion of CLTI patients were treated in the PB group. Overall, the proportion of CLTI patients treated in this study was high and the absolute difference between the groups was small (82% in PB group, 72% in PCB group, P=0.04). Although CLTI was associated with almost three times higher mortality in the multivariable analysis, it is unlikely that CLTI was a major driving factor for the higher mortality in the PB group. All confounding factors were included in a multivariable model, and PCB use remained as an independent predictor in the model. There may be some factors that contribute to the survival differences between the groups, for example, longer lesions and slightly more amputations in the PB group, and some that remain unseen in this retrospective study. Therefore, the conclusion of this study is not that PCB would protect patients from mortality, but rather, that there is no signal of increased mortality contributed to PCB use in the treatment of the femoropopliteal segment.

There are some limitations in our study: 1) The present study included very heterogeneous group of patients with all categories of PAD, including tissue lost, rest pain and intermittent claudication; 2) The mortality sample size was small and it is possible that a larger sample size might have shown more apparent differences in the causes of deaths; 3) The device selection between PCD and PB was not based on randomization but on operator preference, which can lead to variability between the patient groups; 4) It was not possible to determine the cumulative paclitaxel dose each patient received in the PCB group. All types of drug-coated balloons were grouped together as a single PCB group despite their different paclitaxel doses and properties; 5) The median length of follow up was only 3 years although the 5-year survival estimates presented in this study are statistically reliable; 6) Patients in the PB group were more likely to have CLTI and had slightly higher rate of amputiations which may contribute to the

higher mortality rate in the PB group. The strengths of this study are: 1) It is based on real-world population with 2) consecutive patients treated in a single institution and 3) with minimal loss to follow-up.

Conclusion

The use of PCB is safe and there seems to be no concern of increased mortality after the procedure based on the 5-year survival estimates. Informing patients about an increased risk of death associated with PCB use may be intimidating and unwarranted.

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Figure legends

Figure 1. Study flowchart. PB, plain balloon; DCB, drug-coated balloon; DES, drug-coated stent

Figure 2. Cumulative Kaplan–Meier estimate of all-cause mortality in patients treated with plain balloon and paclitaxel-coated balloon. PCB, paclitaxel-coated balloon; PB, plain balloon.

Table I. Demographics, comorbidities and medication stratified by device type

Table II. Procedural characteristics stratified by device type

Table III. Perioperative complications and long-term outcomes stratified by device type

Table IV. Causes of death stratified by device type

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Table I. Demographics, comorbidities and medication stratified by device type

Variable	PB (n=139)	PCB (n=190)	*P* value
Demographics			
Age, years	77 ± 11	75 ± 11	0.07
Male sex	61 (44)	90 (47)	0.58
Body mass index, kg/m2	26.8 ± 5.6	26.8 ± 4.5	0.54
Comorbidity			
Diabetes	72 (52)	91 (48)	0.51
Hypertension	120 (86)	152 (80)	0.14
Hyperlipidemia	76 (55)	104 (55)	1.00
Coronary artery disease	64 (46)	81 (43)	0.58
Cardiac insufficiency	38 (27)	44 (23)	0.44
Stroke	21 (15)	22 (12)	0.41
Chronic pulmonary disease	23 (17)	52 (27)	0.02
Chronic renal insufficiency	44 (32)	52 (27)	0.46
Plasma creatinine (µmol/l)	115	105	0.16
End-stage renal disease	5 (4)	7 (4)	0.77
Active malignancy	6 (4)	8 (4)	1.00
History of malignancy	16 (12)	32 (17)	0.21
Smoking	18 (13)	23 (12)	0.87
Medication			
Antiplatelet drugs	86 (62)	119 (63)	0.91
Anticoagulation therapy	67 (48)	65 (34)	0.01
Lipid-lowering drugs	84 (60)	123 (63)	0.42

PB, plain balloon; PCB, paclitaxel-coated balloon.

Data presented as mean ± standard deviation or number (%).

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Table II. Procedural characteristics stratified by device type

Variable	PB (n=139)	PCB (n=190)	*P* value
Indication			0.04
Claudication	25 (18)	54 (28)	
Critical ischemia	114 (82)	136 (72)	
Laterality			
Right	63 (45)	98 (52)	0.27
Left	71 (51)	90 (47)	0.58
Bilateral	5 (4)	2 (1)	0.14
Level			0.18
Femoro-popliteal angioplasty alone	70 (50)	111 (58)	
Adjunctive infrapopliteal angioplasty	69 (50)	79 (42)	
TASC classification			0.02
TASC A-B	107 (77)	166 (87)	
TASC C-D	32 (23)	24 (13)	

PB, plain balloon; PCB, paclitaxel-coated balloon.

Data presented as number (%)

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Table III. Perioperative complications and long-term outcomes stratified by device type

Variable	PB(n=139)	PCB (n=190)	*P* value
Perioperative outcomes			
Bleeding	5 (4)	2 (1)	0.14
Pseudoaneurysm	1 (1)	5 (3)	0.41
Thrombosis	1 (1)	2 (1)	1.00
Deep vein thrombosis	0 (0)	0 (0)	1.00
Myocardial infarction	0 (0)	1 (1)	1.00
Stroke	1 (1)	0 (0)	0.42
Acute renal failure	2 (1)	3 (2)	1.00
Return to operating room	0 (0)	1 (1)	1.00
Major amputation	10 (7)	2 (1)	0.01
Any complication	3 (2)	5 (3)	1.00
30-day mortality	3(2)	4(2)	1.00
Long-term outcomes			
Long-term follow-up, years	2.3 ± 2.1	2.9 ± 1.7	<0.001
Mortality	76 (55)	70 (37)	0.002
Ipsilateral major amputations	20 (14)	15 (8)	0.07
Any ipsilateral reintervention	32(23)	61(32)	0.08
Ipsilateral interventions, no.	1.6 ± 1.0	1.8 ± 1.2	0.21

PB, plain balloon; PCB, paclitaxel-coated balloon

Data presented as mean ± standard deviation or number (%)

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Table IV. Causes of death stratified by device type

Cause of death % out of all deaths	**PB (n=76)**	**PCB (n=70)**	***P* value**
Cardiovascular	32 (42)	44 (63)	0.01
Cancer	4 (5)	7 (10)	0.35
Infectious	6 (8)	6 (9)	1.00
Neurologic	5 (7)	2 (3)	0.44
Respiratory	12 (16)	3 (4)	0.03
Renal	3 (4)	1 (1)	0.62
Gastrointestinal	3 (4)	3 (4)	1.00
Other/unknown	11 (14)	4 (6)	0.10
Cause of death % out of all patients	**PB (n=139)**	**PCB (n=190)**	***P* value**
Cardiovascular	32 (23)	44 (23)	1.00
Cancer	4 (3)	7 (4)	0.77
Infectious	6 (4)	6 (3)	0.77
Neurologic	5 (4)	2 (1)	0.14
Respiratory	12 (9)	3 (2)	0.003
Renal	3 (2)	1 (1)	0.31
Gastrointestinal	3 (2)	3 (2)	0.70
Other/unknown	11 (8)	4 (2)	0.02
All deaths	76 (55)	70 (37)	0.002

PB, plain balloon; PCB, paclitaxel-coated balloon

Data presented as number (%)

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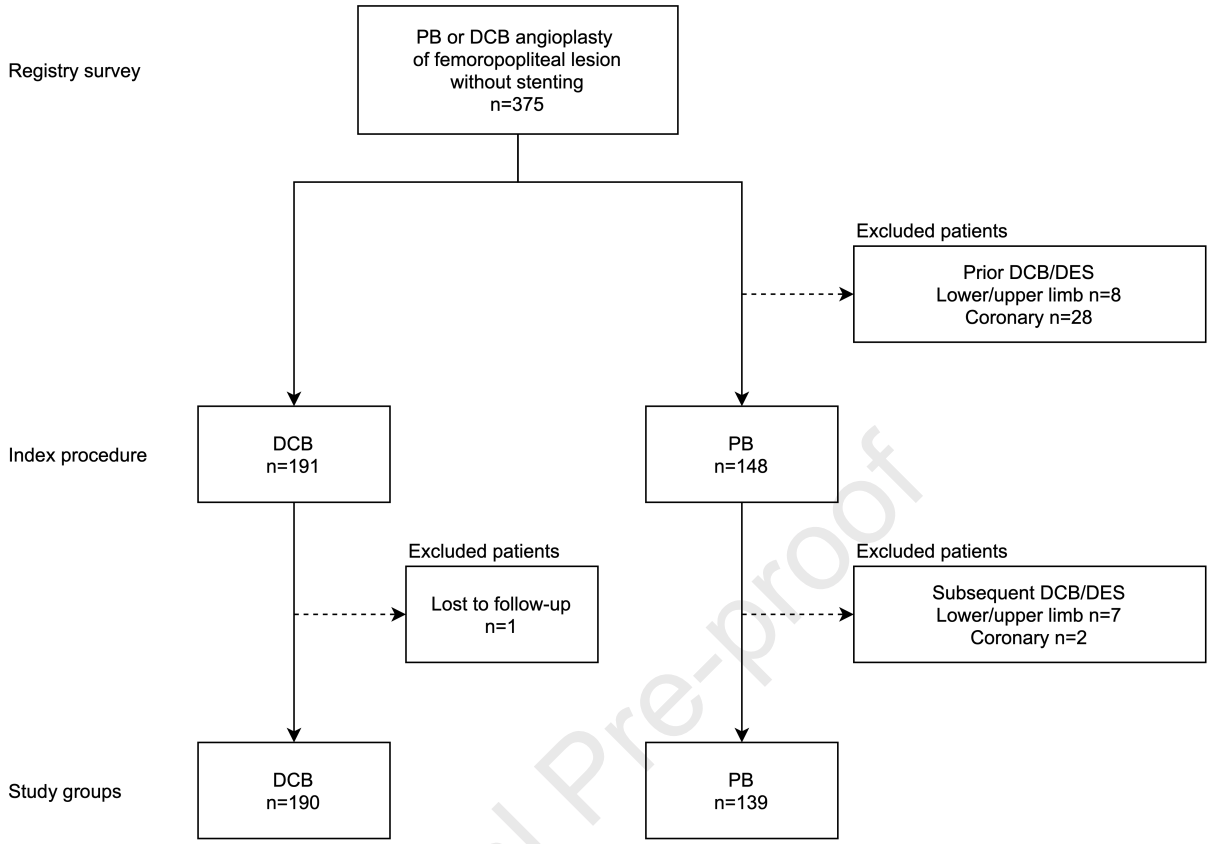

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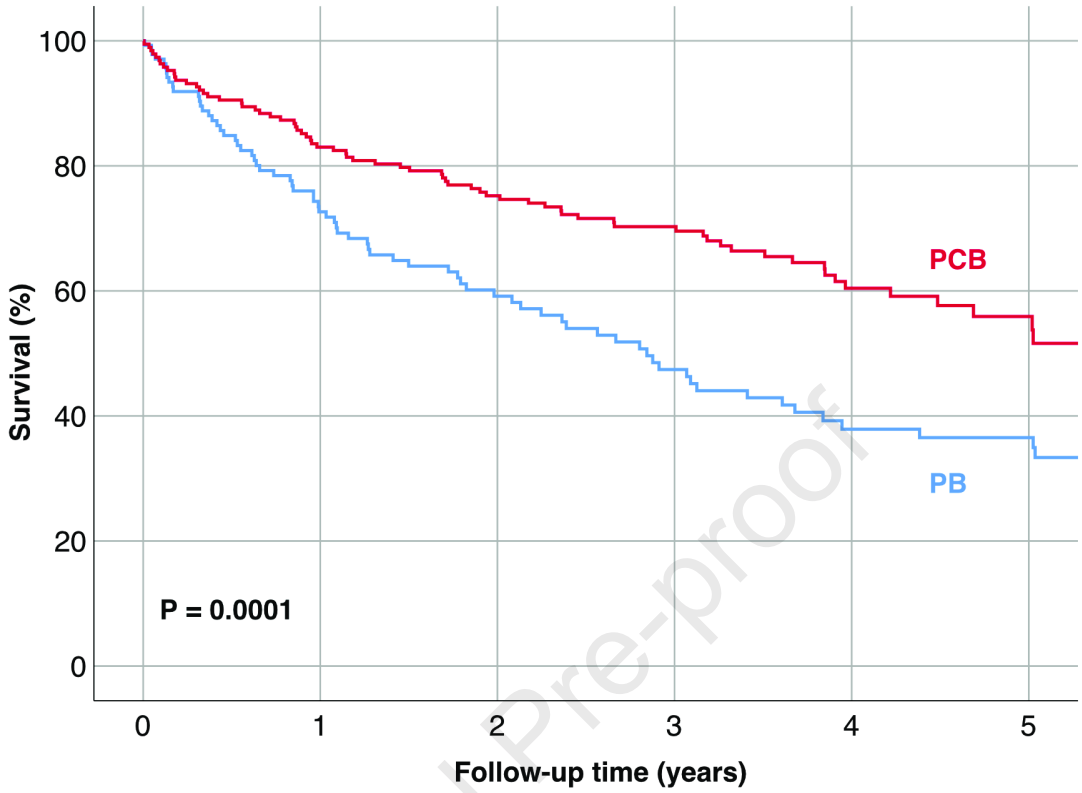

No. at risk

PCB	190	153	128	97	53	26
PB	139	86	58	41	27	22

Std. error (%)

PCB	0	2.7	3.2	3.4	4.1	4.5
PB	0	4.0	4.5	4.8	4.9	4.9

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