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*Clinical Investigation*

# Effect of Paclitaxel Drug-Coated Balloon Angioplasty of Infrapopliteal Lesions on Mortality

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***Background:*** *Meta-analyses of randomized controlled trials have suggested an increased long-term mortality risk following femoropopliteal and infrapopliteal angioplasty using paclitaxel-coated devices. This study was conducted to evaluate long-term mortality after paclitaxel drug-coated balloon (DCB) and plain old balloon angioplasty (POBA) of infrapopliteal lesions in real-world practice.*

***Methods:*** *A retrospective mortality analysis of patients with at least 3 years of follow-up who underwent balloon-based endovascular therapy of infrapopliteal lesions was performed.*

***Results:*** *Overall, 2,424 patients with infrapopliteal lesions were treated within the study period. Five hundred seventy-six patients fulfilled the study criteria. Of those, 269 patients were treated with uncoated devices without crossover to a paclitaxel-coated device during follow-up and 307 patients with DCB angioplasty. Mean (SD) follow-up was 46.48 (32.77) months. The mortality rate was 66.9% after POBA and 46.9% after DCB (*P < .001*). In the matched-pair cohort, 164 patients died after uncoated treatment (66.7%), and 119 in the DCB group died (48.4%;* P < .001*). There was no correlation between DCB length and mortality rate (*P = .357*). For the entire cohort, multivariate logistic regression analysis showed type of treatment (uncoated device vs DCB;* P = .002*), age (*P < .001*), stroke (*P = .005*), renal insufficiency (*P = .014*), and critical limb ischemia (*P = .001*) to be independent predictors of all-cause mortality. There was no significant difference in mortality among the paclitaxel exposure groups.*

***Conclusion:*** *In this real-world retrospective analysis, the long-term mortality rate was lower after DCB angioplasty than after POBA of infrapopliteal lesions.* ***(Tex Heart Inst J. 2022;49(6):e217560)***

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Endovascular therapy is the therapy of choice for treating femoropopliteal lesions.[1] In cases of critical limb ischemia (CLI) and infrapopliteal vascular lesions, an endovascular approach is also primarily recommended.[2] An important development in endovascular therapy was the combination of balloon dilation and local administration of an antiproliferative drug in the form of drug-coated balloons (DCBs). In recent years, impressive results have been achieved after femoropopliteal interventions using DCB technology.[3-5]

For the treatment of infrapopliteal lesions, the results after DCB angioplasty are more controversial than are those after femoropopliteal interventions. Regarding the patency rates, 2 pilot studies showed positive results after DCB angioplasty compared with uncoated balloon angioplasty.[6,7] In contrast, multicenter randomized controlled trials (RCTs) have not shown any substantial benefit of DCB angioplasty compared with uncoated balloon angioplasty.[8,9]

In cases of recurrent stenosis, the coated devices are still routinely used in clinical settings. Recently, a meta-analysis of RCTs showed an increased mortality risk within 5 years after application of paclitaxel-coated balloons or stents in femoropopliteal lesions.[10]

A further meta-analysis of 8 RCTs (N = 1,420 patients) showed a nonsignificant increase in all-cause death after paclitaxel-coated balloon angioplasty for the treatment of infrapopliteal lesions in patients with CLI during a follow-up of 6 months to

1 year.[11] However, the recently published 5-year follow-up analysis of the IN.PACT Deep trial did not confirm this mortality signal.[12]

Although the benefit of DCB angioplasty of infrapopliteal lesions has not been adequately assessed, it is crucial that patients undergoing treatment are not exposed to excess procedure- or device-related risks. It is therefore of great clinical relevance to investigate mortality rates after infrapopliteal interventions with DCBs.

The aim of the present retrospective single-center study is to evaluate mortality after treatment of infrapopliteal lesions using DCB angioplasty and plain old balloon angioplasty (POBA).

## Patients and Methods

### Patient Population

From a prospectively collected database, patients who received POBA or DCB in de novo and restenotic infrapopliteal atherosclerotic artery lesions were retrospectively selected. This analysis included patients treated between January 1, 2009, and February 28, 2017. The ethics committee of Albert-Ludwigs-Universität Freiburg approved the study on February 2, 2020. Only patients with lifestyle-limiting claudication, rest pain, or ulcerations (Rutherford-Becker class [RBC]) 1-5) were included. Patients were treated with different brands of DCB.

Patients undergoing treatment for inflow lesions were included into the analysis as long as this treatment was performed using uncoated devices. Those who received multiple interventions during the study period and those treated with a sirolimus-eluting stent were excluded from the study.

It was essential for the control group not to have been in contact with a drug-coated device either before the index procedure or during follow-up, resulting in a paclitaxel exposure–naive control cohort. A minimum follow-up of 36 months was required for study inclusion.

### Study End Points

The primary end point of the study was all-cause mortality. The primary analysis was to examine the difference in the cumulative all-cause mortality rates between the groups using the log-rank test. Secondary analyses examined the relationships between DCB length and mortality and paclitaxel dosage and mortality. A multivariate logistic regression analysis was conducted to identify predictors of mortality. Type of treatment (POBA vs DCB), age, sex, hyperlipidemia, diabetes mellitus, renal insufficiency, cerebral artery disease, coronary heart disease, and CLI (RBC 1-3 vs 4 and 5) were investigated. These analyses were performed for the entire study population. To achieve a better balance of the groups regarding their major baseline characteristics, a matched-pair analysis was performed. In this propensity analysis, all variables that were significantly different in the baseline characteristics of the entire cohort were included.

A further secondary analysis used Kaplan–Meier curves and the log-rank test to examine the relationship between paclitaxel dosage and mortality. The electronic patient database was checked to determine patient survival, and if no information was available, this information was requested from every patient and/or family clinician.

The total paclitaxel dosage was calculated by obtaining dosage information of different devices listed in the summary of safety and effectiveness of the Food and Drug Administration (available for Eluvia [Boston Scientific],[13] IN.PACT Admiral [Medtronic],[14] Lutonix [BD],[15] and Stellarex [Philips][16]) or in the instructions for use (Zilver PTX [Cook Medical][17]).

For the non–Food and Drug Administration-approved devices, it was necessary to calculate the paclitaxel dosage with the known density, device length, and diameter using the formula for a cylinder surface. With these data, the paclitaxel dosage for every coated device used in the index and all subsequent interventions could be calculated. In this way, a total paclitaxel exposure from leg interventions could be determined, and a Kaplan–Meier survival analysis stratified according to cumulative paclitaxel dosage could be performed.

### Statistical Analysis

Analyses were performed using the SPSS software (versions 20.0 and 23.0; SPSS). Survival graphs with 95% CIs were created in Stata Statistical Software Release 15 (StataCorp). Continuous data are given as mean (SD) or, if there is no normal distribution, as median with interquartile range; categorical data are presented as counts (percentages). The $\chi^2$ test or, in cases of cell size less than 5, the Fisher exact test, were used to compare the variables. Kaplan–Meier analysis was used to evaluate survival, and the survival curves were compared using the log-rank test.

Differences in baseline characteristics between the POBA and the DCB group were adjusted using propensity-score matching. A propensity-matched analysis using python-based extensions for SPSS 20.0 (FUZZY and PSM) was performed. Patients were matched according to all baseline characteristics in a 1:1 fashion (POBA:DCB), with a maximum difference of 0.05 for the propensity variable.

Adjusted between-group comparison was made for all-cause mortality with Cox proportional hazards analysis. Proportionality was tested using the log [-log(survival)] vs log (time) graph and the time-dependent Cox model. Cox proportional hazards analysis was performed for the risk factors that were significantly dif-

ferent between the groups (ie, age and renal insufficiency). Logistic binary regression analysis was performed to detect predictors of death. Univariate analyses were performed first, and the factors that were significant in the univariate analysis were included in the multivariate analysis. Statistical significance was defined as $P < .05$.

## Results

From January 1, 2009, to February 28, 2017, a total of 2,424 patients with infrapopliteal lesions underwent an infrapopliteal artery intervention. Of these patients, 269 were treated using uncoated devices and 307 using DCB angioplasty. A study flowchart is shown in Figure 1. Table I reports patient characteristics. With regard to cardiovascular risk factors, the 2 groups were not balanced. Patients treated with DCBs were significantly more often male ($P = .025$) and significantly more often had hypertension ($P = .026$), hyperlipidemia ($P = .001$), diabetes mellitus ($P = .027$), and coronary heart disease ($P = .002$).

In the matched analysis (POBA, n = 246; DCB, n = 246), baseline variables were balanced (Table II). Most patients had CLI (RBC 4 and 5, n = 474 [82.3%]). The procedure details are given in Table III, and details about the DCB brands used are shown in Table IV.

The mean (SD) follow-up time of the entire cohort was 46.48 (32.77) months and ranged from 0 to 129 months. The mean (SD) follow-up time of the DCB group was 48.5 (29.43) months and that of the POBA group was 44.5 (36.40) months.

During follow-up, 324 patients died. Thus, the overall all-cause mortality incidence was 56.3%. One hundred eighty patients died in the POBA group and 144 patients died in the DCB group, resulting in overall all-cause mortality rates of 66.9% and 46.9%, respectively ($P < .001$).

The overall all-cause mortality incidence of the matched cohort was 57.5% (n = 283). One hundred sixty-four patients died after uncoated balloon treatment (66.7%), and 119 patients in the DCB group died (48.4%; $P < .001$).

The survival by Kaplan–Meier analysis for the entire cohort is shown in Figure 2 and for the matched patients in Figure 3. Figure 4 shows the Kaplan–Meier curve regarding mortality for the group with claudication and patients with CLI. Amputation-free survival data are given in Supplemental Figure 1.

Table V reports causes of death. In many cases, the cause of death could not be determined. The most common known cause of death was a cardiovascular event. A death cluster could not be detected.

Univariate logistic regression analysis identified type of treatment (uncoated device vs DCB; $P < .001$), age ($P < .001$), stroke ($P = .003$), renal insufficiency ($P = .001$), hyperlipidemia ($P = .019$), and CLI ($P < .001$) as predictors of all-cause mortality (Table VI, Supplemental Table I, and Supplemental Table II).

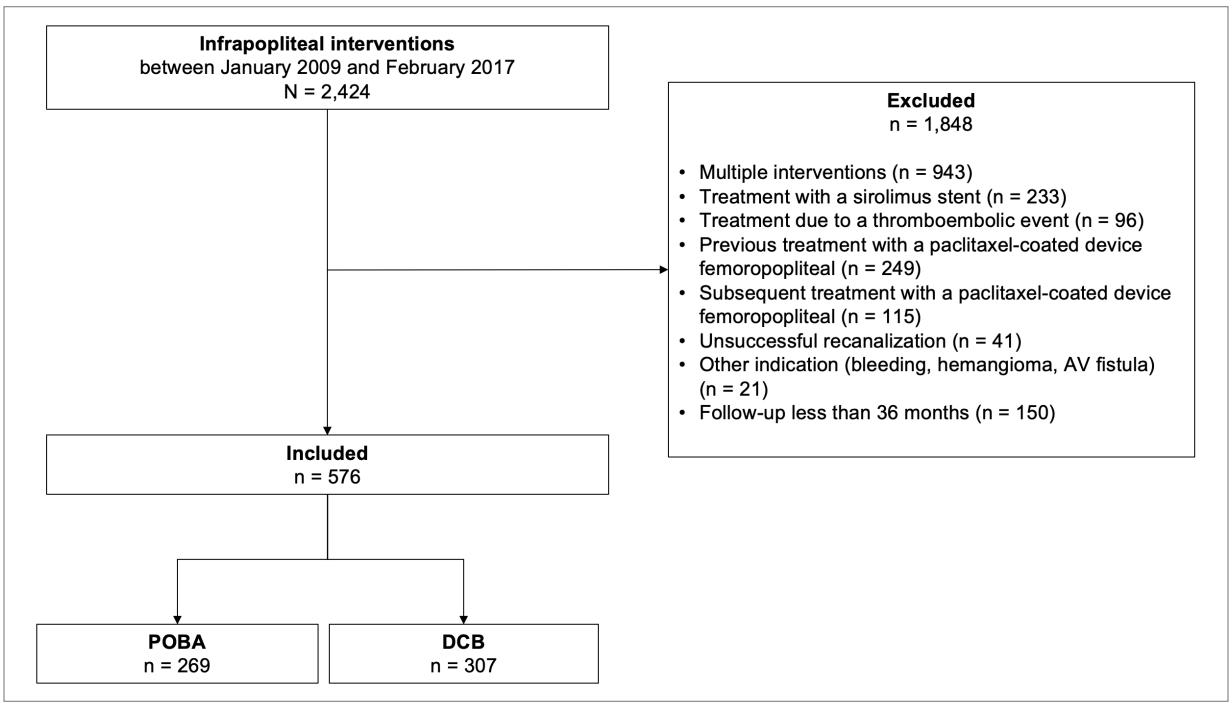



***Fig. 1*** *Flowchart shows selection of patients included in the study.*

*AV, arteriovenous; DCB, drug-coated balloon; POBA, plain old balloon angioplasty.*

**TABLE I. Baseline Characteristics of the Entire Cohort**

| | DCB (n = 307) | POBA (n = 269) | *P* value[a] |
|---|---|---|---|
| Age, median (IQR), y | 75 (12) | 76 (13) | .051 |
| Male, No. (%) | 244 (79.5) | 192 (71.4) | .025 |
| Hypertension, No. (%) | 276 (89.9) | 224 (83.3) | .026 |
| Diabetes mellitus, No. (%) | 198 (64.5) | 149 (55.4) | .027 |
| Hyperlipidemia, No. (%) | 228 (74.3) | 164 (61.0) | .001 |
| Smoker, No. (%) | 90 (29.3) | 74 (27.5) | .645 |
| Coronary heart disease, No. (%) | 145 (47.2) | 92 (34.2) | .002 |
| Cerebrovascular disease, No. (%) | 43 (14.0) | 26 (9.7) | .123 |
| Stroke, No. (%) | 50 (16.3) | 39 (14.5) | .566 |
| Renal insufficiency,[b] No. (%) | 169 (55.0) | 142 (52.8) | .616 |
| CLI, No. (%) | 245 (79.8) | 229 (85.1) | .102 |

CLI, critical limb ischemia; DCB, drug-coated balloon; IQR, interquartile range; IQR, interquartile range; POBA, plain old balloon angioplasty.

[a] Statistical significance was set at $P < .05$.

[b] Defined as creatinine clearance <60 mL/min.

**TABLE II. Baseline Characteristics of the Matched Cohort, All Variables**

| | DCB (n = 246) | POBA (n = 246) | Standardized mean difference | *P* value[a] |
|---|---|---|---|---|
| Age, median (IQR), y | 75 (13) | 75 (13) | −0.003 | .809 |
| Male, No. (%) | 186 (76.2) | 182 (74.6) | 0.04 | .753 |
| Hypertension, No. (%) | 214 (87.7) | 208 (85.2) | 0.07 | .508 |
| Diabetes mellitus, No. (%) | 150 (61.5) | 142 (58.2) | 0.07 | .518 |
| Hyperlipidemia, No. (%) | 171 (70.1) | 162 (66.4) | 0.08 | .437 |
| Smoker, No. (%) | 68 (27.9) | 70 (28.9) | −0.02 | .920 |
| Coronary heart disease, No. (%) | 110 (45.1) | 91 (37.3) | 0.16 | .098 |
| Cerebrovascular disease, No. (%) | 31 (12.7) | 25 (10.2) | 0.08 | .478 |
| Stroke, No. (%) | 37 (15.2) | 35 (14.3) | 0.03 | .899 |
| Renal insufficiency,[b] No. (%) | 133 (54.5) | 132 (54.1) | 0.01 | .999 |
| CLI, No. (%) | 202 (82.8) | 204 (83.6) | −0.02 | .904 |

CLI, critical limb ischemia; IQR, interquartile range; POBA, plain old balloon angioplasty.

[a] Statistical significance was set at $P < .05$.

[b] Defined as creatinine clearance <60 mL/min.

Multivariate logistic regression analysis showed type of treatment (uncoated device vs DCB; $P = .002$), age ($P < .001$), renal insufficiency ($P = .014$), stroke ($P = .005$), and CLI ($P = .001$) as independent predictors of all-cause mortality (Table VI).

The mean length of DCB used was greater in the group of patients who did not die during follow-up. A correlation between DCB length and mortality could not be shown ($P = .357$; Table VII).

The applied paclitaxel dosages during the index procedure and follow-up interventions, and the total dosage are given in Table VIII. In a comparison of low-dose and high-dose index procedure paclitaxel exposure ($P = .844$) and the total paclitaxel exposure groups ($P = .228$), there was no significant difference between the group of deceased patients and the surviving patients (Table VII).

For low– and high–index procedure paclitaxel dose groups, the survival by Kaplan–Meier analysis is shown in Figure 5. Kaplan–Meier mortality curves stratified to total paclitaxel dose groups are shown in Figure 6. Even after adjustment of the significantly different risk factor (age) between the groups, there was no significant difference in mortality for the different paclitaxel dosage groups (Fig. 7 and Fig. 8).

**TABLE III. Index Procedure Characteristics for the Entire Cohort**

| | DCB, No. (%) | POBA, No. (%) | *P* value[a] |
|---|---|---|---|
| Right-side intervention | 144 (46.9) | 140 (52.0) | .242 |
| Reintervention | 118 (38.4) | 29 (10.8) | <.001 |
| Multivessel intervention | 152 (49.5) | 151 (56.1) | .132 |

DCB, drug-coated balloon; POBA, plain old balloon angioplasty.

[a] Statistical significance was set at $P < .05$.

**TABLE IV. Drug-Coated Balloon Characteristics for the DCB Group**

| Characteristic | Value |
|---|---|
| No. of DCBs, median (IQR) | 2 (2) |
| Length of DCB, median (IQR), mm | 200 (240) |
| DCB brand, No. (%) | |
| Amphirion IN.PACT (Medtronic) | 202 (65.8) |
| Lutonix (BD) | 93 (30.3) |
| Other | 12 (3.9) |

DCB, drug-coated balloon; IQR, interquartile range.

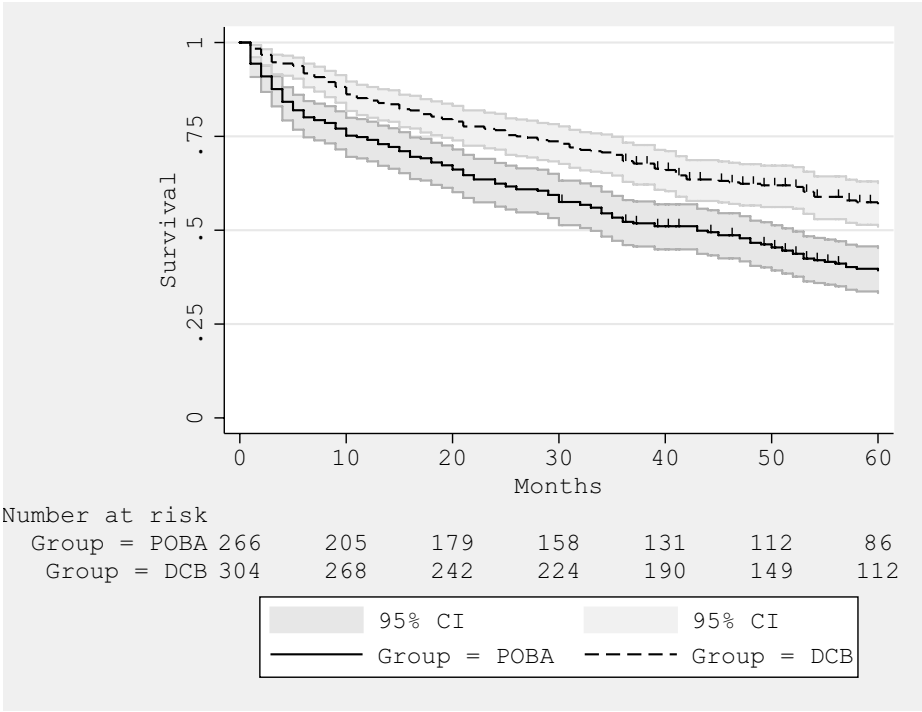



***Fig. 2*** *Kaplan–Meier plot shows survival for all patients in the POBA group and in the DCB group.*

P *from log-rank test <.001.* P < *.05 was considered statistically significant.*

*DCB, drug-coated balloon; POBA, plain old balloon angioplasty.*

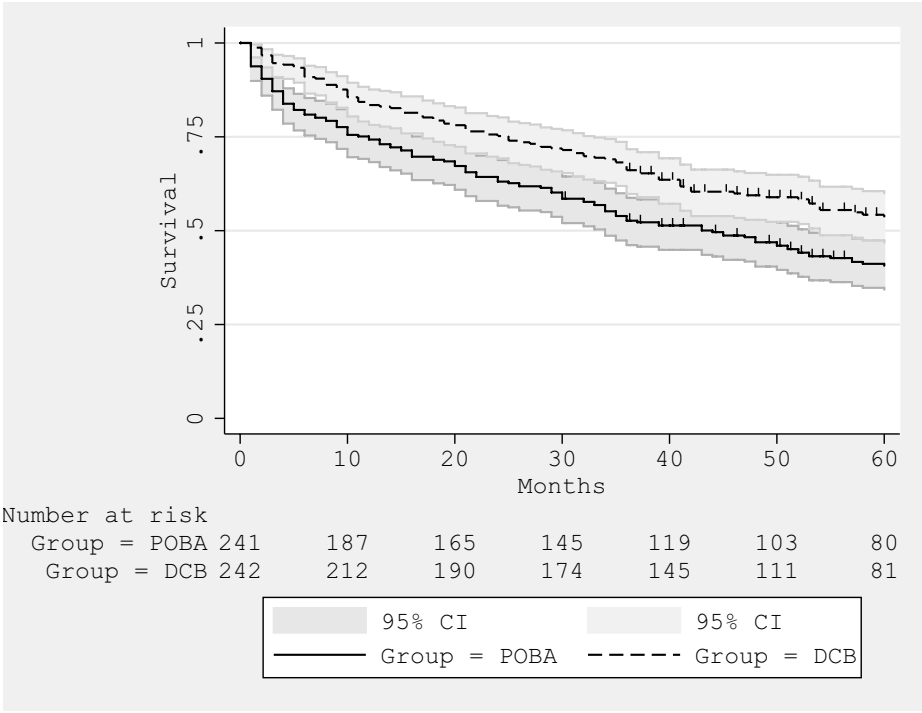
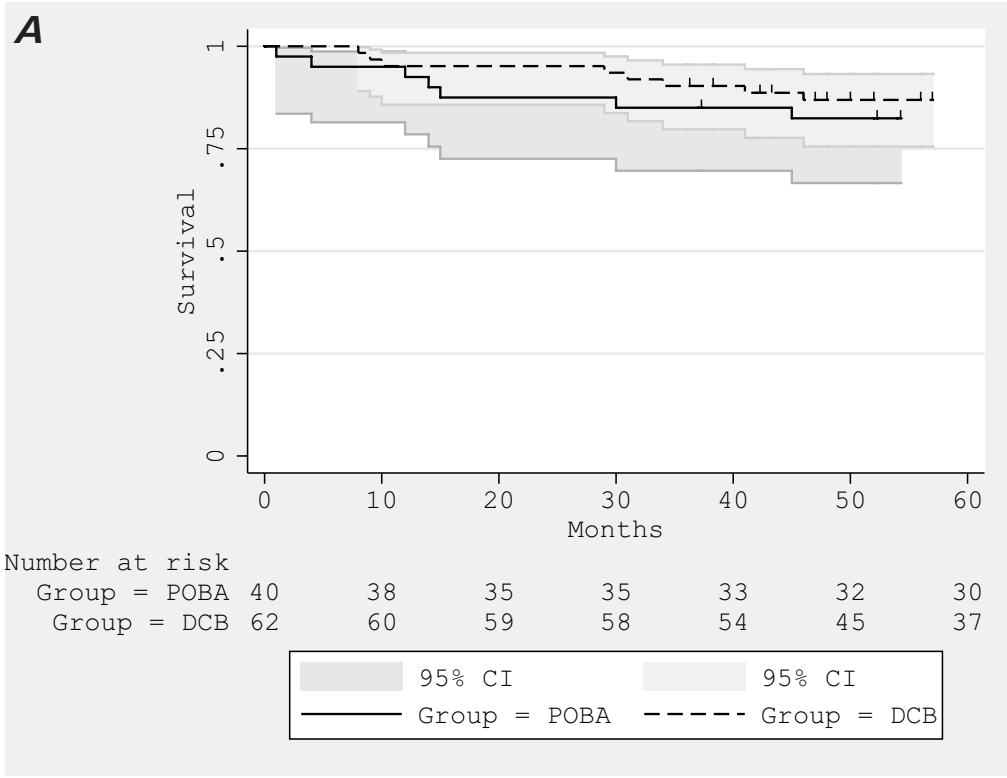



***Fig. 3*** *Kaplan–Meier plot shows survival for the matched patients in the POBA group and in the DCB group.*

P *from log-rank test = .002.* P < *.05 was considered statistically significant.*

*DCB, drug-coated balloon; POBA, plain old balloon angioplasty.*



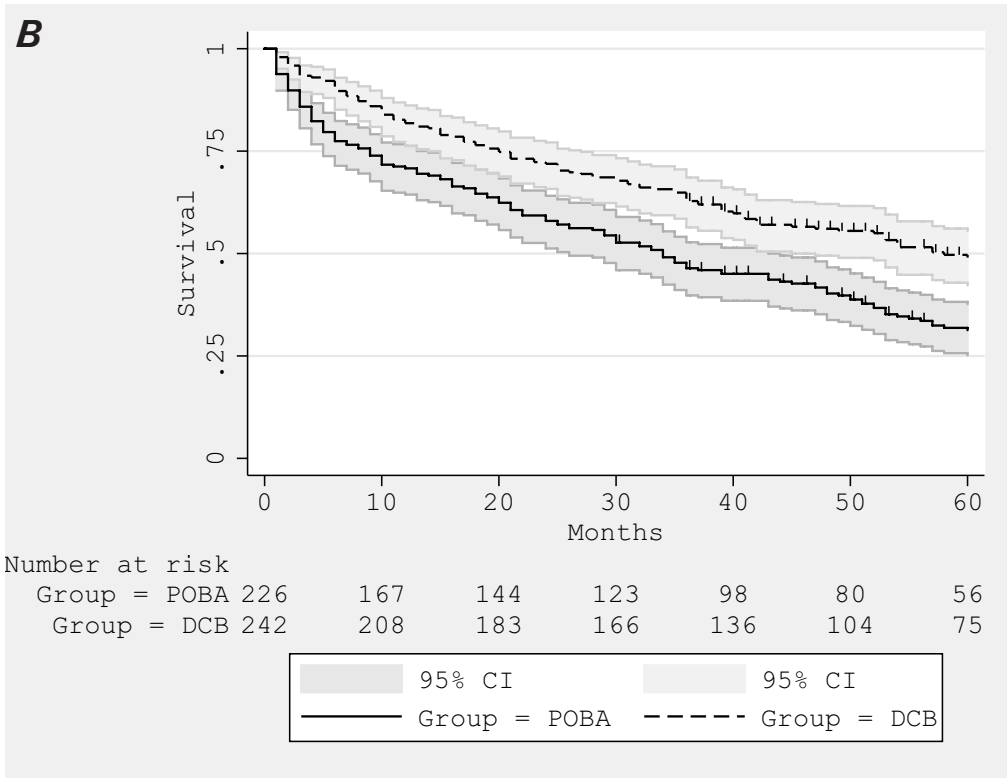




***Fig. 4*** *Kaplan–Meier plot shows survival in the patients* ***A****) with claudication (*P *from log-rank test = .599) and in those with* ***B****) critical limb ischemia (*P *from log-rank test <.001).* P < .05 *was considered statistically significant.*

*POBA, plain old balloon angioplasty; DCB, drug-coated balloon.*

## Discussion

A meta-analysis of 8 RCTs showed a nonsignificantly lower short-term all-cause mortality after uncoated balloon treatment of infrapopliteal arteries in patients with CLI compared with treatment with paclitaxel-coated DCBs.[11] The present retrospective analysis with a follow-up over a period of at least 3 years cannot confirm these findings. This real-world analysis shows a mortality benefit after using paclitaxel-coated balloons for the treatment of infrapopliteal lesions. The mortality benefit favoring DCB treatment persisted after propensity-score matching (66.9% vs 48.4%; $P < .001$). These results are in line with the recently published 5-year outcome of the IN.PACT Deep study. This study evaluated the safety and efficacy of the IN.PACT Amphirion DCB (Medtronic), and no increase in mortality was found in the DCB group. By trend, mortality was lower in the DCB group. Seventy-four patients (39.4%) in the DCB group died, and 45 patients (45%) in the POBA group died ($P = .727$).[12] In line with these results, an analysis of German health insurance data over 11 years showed no association between paclitaxel-based treatment and increased long-term mortality.[18]

In addition, no increased all-cause mortality was shown in a large nationwide US Centers for Medicare & Medicaid Services claims data analysis in a real-world setting following femoropopliteal interventions with drug-coated devices.[19]

The meta-analysis was limited by incomplete access to original data and the lack of an analysis of cofounding variables.[11] In the present study, the multivariate analysis showed—both in the entire cohort and after the matched analysis—type of treatment, age, renal insufficiency, coronary heart disease, and CLI to be predictors of mortality. In the unmatched cohort, hyperlipidemia, diabetes mellitus, and hypertension were additional mortality predictors, whereas stroke became a predictor after propensity-score matching.

In the IN.PACT Deep study, age, RBC greater than 4 and previous peripheral revascularization were predictors of increased mortality. However, increasing dosage of paclitaxel was not a predictor of all-cause mortality.[17]

Both meta-analyses suggesting an increase in all-cause mortality risk after treatment of femoropopliteal and infrapopliteal artery lesions with paclitaxel-coated devices with increasing paclitaxel dose only considered the paclitaxel dose applied during the index procedure.[10,11] The authors had no information about additional paclitaxel exposure during follow-up in the DCB cohort or in the control group. In contrast, the present study included

**TABLE V. Causes of Death for the Entire Cohort**

| | DCB, No. (%) | POBA, No. (%) | *P* value[a] |
|---|---|---|---|
| Cardiovascular | 19 (5.9) | 12 (3.7) | .460 |
| Stroke | 0 (0) | 1 (0.3) | .467 |
| Carcinoma | 3 (0.9) | 9 (2.8) | .076 |
| Other | 28 (8.6) | 29 (9.0) | .576 |
| Unknown | 94 (29) | 129 (39.8) | <.001 |

DCB, drug-coated balloon; POBA, plain old balloon angioplasty.

[a] Statistical significance was set at $P < .05$.

**TABLE VI. Predictors of Death for the Entire Cohort**

| | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|
| **Predictor** | **OR** | **95% CI** | ***P* value[a]** | **OR** | **95% CI** | ***P* value[a]** |
| Treatment type | 0.332 | 0.182-0.607 | <.001 | 0.318 | 0.154-0.655 | .002 |
| Age (per year) | 1.065 | 1.033-1.099 | <.001 | 1.071 | 1.031-1.112 | <0.001 |
| Sex | 0.932 | 0.489-1.779 | .832 | | | |
| Cerebrovascular disease | 1.358 | 0.523-3.525 | .530 | | | |
| Coronary heart disease | 1.582 | 0.886-2.824 | .121 | | | |
| Stroke | 4.032 | 1.594-10.197 | .003 | 4.597 | 1.576-13.405 | .005 |
| Smoker | 0.808 | 0.439-1.489 | .495 | | | |
| Renal insufficiency | 2.654 | 1.490-4.727 | .001 | 2.422 | 1.196-4.906 | .014 |
| Hypertension | 0.973 | 0.400-2.367 | .973 | | | |
| Hyperlipidemia | 0.460 | 0.241-0.881 | .019 | 0.518 | 0.232-1.155 | .108 |
| Diabetes mellitus | 0.986 | 0.556-1.750 | .962 | | | |
| CLI | 6.417 | 2.722-15.132 | <.001 | 4.956 | 1.859-13.209 | .001 |

CLI, critical limb ischemia; OR, odds ratio.

[a] Statistical significance was set at $P < .05$.

**TABLE VII. Total Length of DCB, Index Procedure Paclitaxel Dosage, and Cumulative Total Paclitaxel Dosage in the DCB Group**

| | Death | No. | Mean (SD), mm/μg | *P* value[a] |
|---|---|---|---|---|
| Total length | 0 | 163 | 232.12 (132.62) | .357 |
| | 1 | 144 | 224.65 (147.61) | |
| Initial paclitaxel dosage | 0 | 163 | 5,016 (3,039) | .844 |
| | 1 | 144 | 5,070 (3,453) | |
| Total paclitaxel dosage | 0 | 163 | 12,569 (14,563) | .228 |
| | 1 | 144 | 11,143 (13,628) | |

DCB, drug-coated balloon; 0, patients who survived; 1, patients who died.

[a] Statistical significance was set at $P < .05$.

**TABLE VIII. Paclitaxel Dosage Initial Procedure and During Follow-Up, and Cumulative Total for the DCB Group**

| | No. | Dose, μg Minimum | Maximum | Mean (SD) |
|---|---|---|---|---|
| Initial | 307 | 516 | 24,897 | 5,041 (3,235) |
| Follow-up | 122 | 642 | 91,841 | 17,261 (17,296) |
| Total | 307 | 516 | 93,218 | 11,901 (14,127) |

DCB, drug-coated balloon.

exclusively paclitaxel-naive patients in the control cohort and was able to calculate the live time paclitaxel dose of patients who underwent additional paclitaxel-coated device interventions after the index procedure. In the present analysis, 122 patients of the DCB cohort (39.7%) had at least 1 follow-up intervention using a paclitaxel-coated device. In this patient cohort, the mean dosage of paclitaxel applied by using paclitaxel-coated devices during the follow-up interventions was about 3 times as high as that applied in the index procedure. Only the knowledge of the real cumulative paclitaxel dosage allows the establishment of a potential link between the drug exposure and mortality.

The log-rank analysis of the present cohort showed no significant difference in mortality between the different paclitaxel dosage ranges. Nevertheless, mortality was shown to be lower for the higher total paclitaxel dose.

Overall, the mortality rates in both study groups are high. This is consistent with findings from other studies investigating mortality rates for patients with peripheral artery disease (PAD) showing an increase in mortality rate with increasing RBC.[20,21] In a meta-analysis, the mortality for patients with CLI was 46.2% at 5 years.[22]

An analysis of German health insurance data showed the highest mortality in the patient group with diabetic foot syndrome, followed by patients with diabetes mellitus and PAD.[23] The mortality rates at 1- and 4-year follow-up were 16.8% and 39.2% for patients with PAD and diabetes, and those rates were 17.7% and

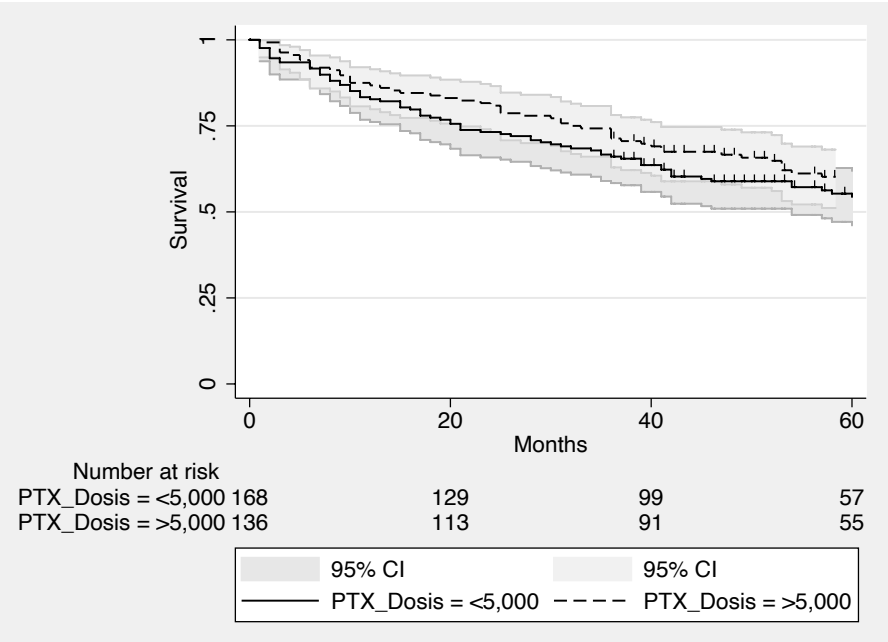



***Fig. 5*** *Kaplan–Meier plot shows survival in patients receiving a drug-coated balloon at the index procedure, stratified according to low (<5,000 μg) and high (>5,000 μg) PTX dosage.* P *from log-rank test = .554.* P < .05 *was considered statistically significant.*

*PTX, paclitaxel.*

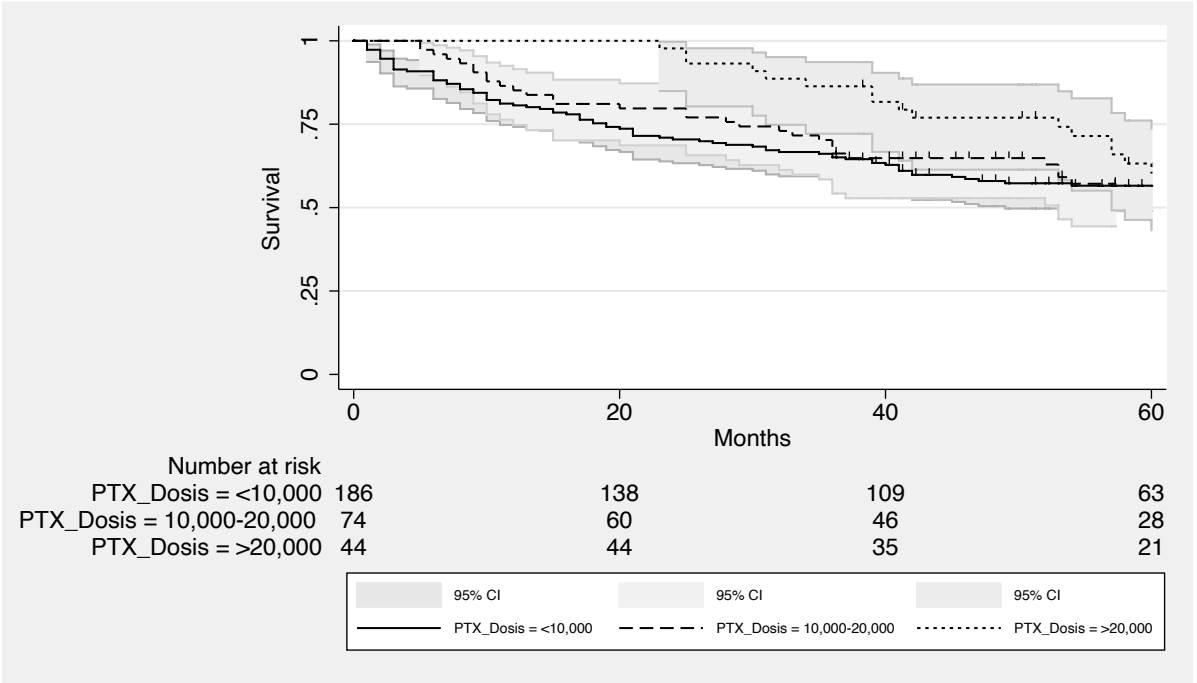



***Fig. 6*** *Kaplan–Meier plot of survival for all patients treated with a drug-coated balloon, stratified according to cumulative PTX dosage: <10,000 µg, 10,000-20,000 µg, or >20,000 µg).* P *from log-rank test = .208.* P < *.05 was considered statistically significant.*

*PTX, paclitaxel.*

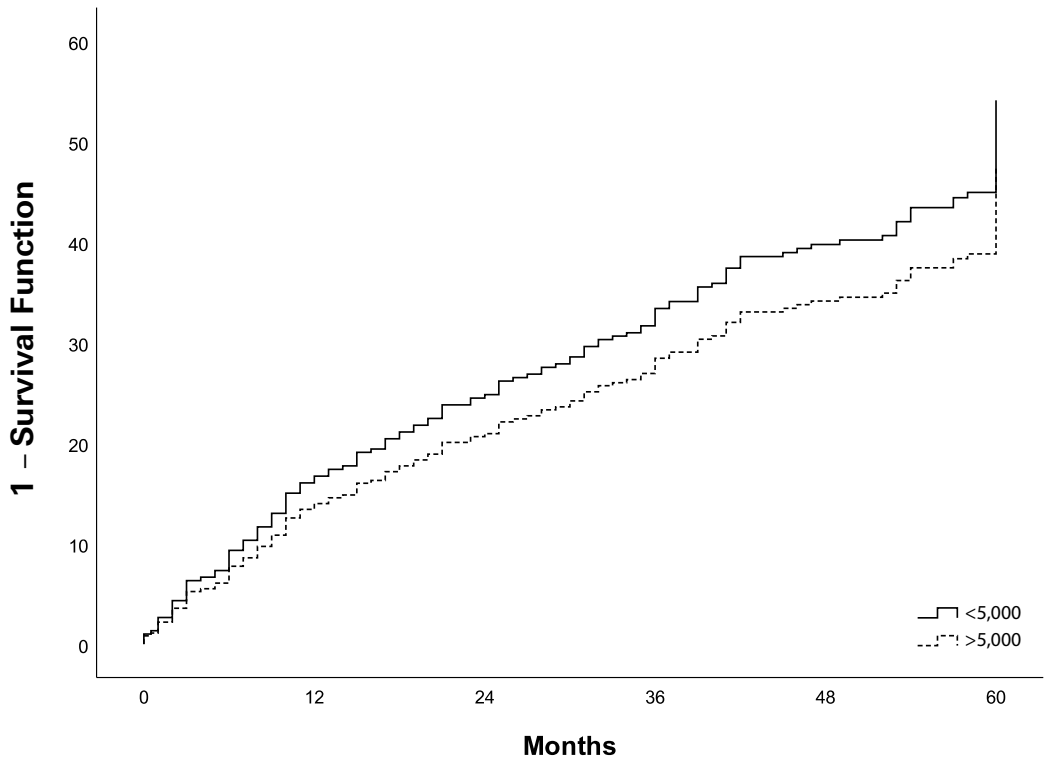



***Fig. 7*** *Survival function plot after adjustment of the significantly different risk factors between the groups (age and renal insufficiency), stratified according to paclitaxel exposure during the index procedure (entire cohort, divided into dosage group <5,000 µg vs >5,000 µg).*

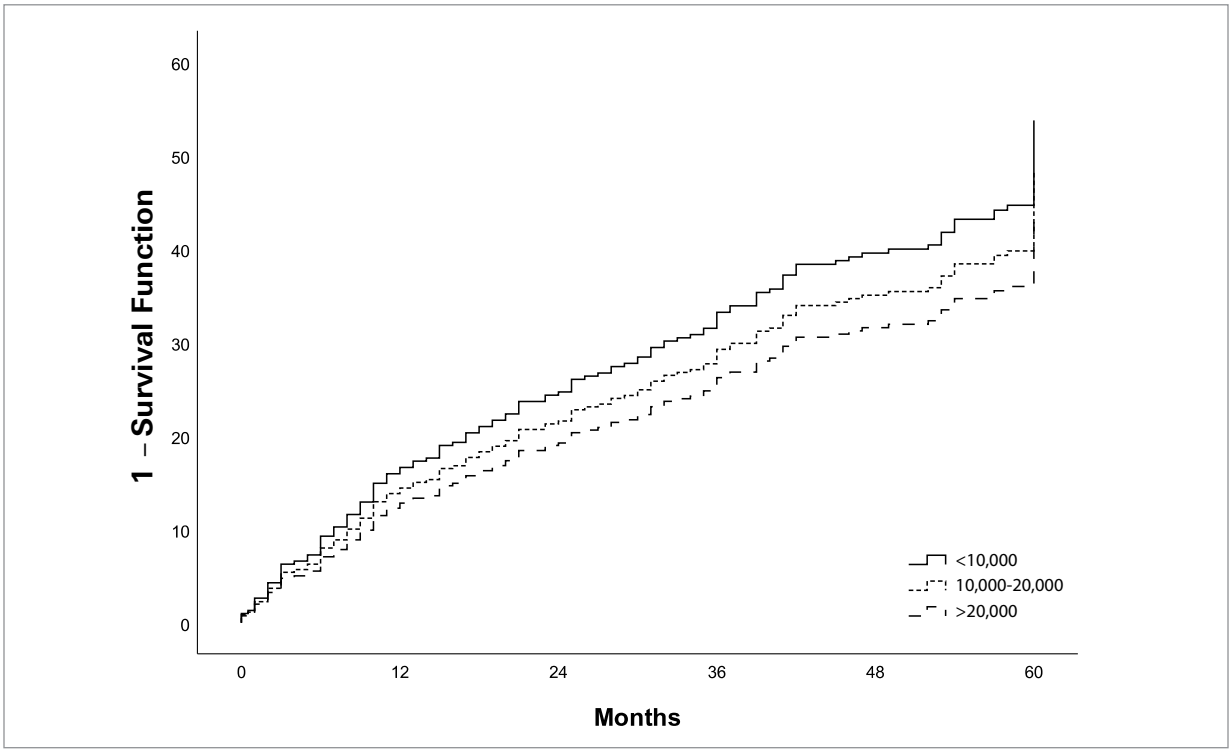



***Fig. 8*** *Survival function after adjustment of the significantly different risk factors between the groups (age and renal insufficiency), stratified according to paclitaxel exposure during the index procedure and follow-up interventions (entire cohort, divided into dosage groups <10,000 µg, 10,000-20,000 µg, and >20,000 µg).*

42.6%, respectively, for patients with diabetic foot syndrome. In the cohort in this study, the proportions of patients with diabetes (60.2%) and patients with diabetes in RBC 5 (70.8%) were also high.

Patients with PAD but without diabetes had the best chance of survival. However, even in this group, the mortality rate was 12.4% after 1 year. The 4-year mortality rate in this group was 30%.

## Limitations

The single-center observational study design could be discussed as a limitation because of potentially confounding variables. This analysis only focuses on all-cause mortality; amputation-free survival could not be adequately investigated in this retrospective analysis because part of the information was obtained via official death notifications, and thus no information on the amputation status was provided.

## Conclusion

This real-world cohort showed a lower mortality risk after using DCB for the treatment of infrapopliteal lesions than after using noncoated devices. There was no correlation between the paclitaxel dosage and mortality. Indeed, a lower mortality rate was shown for the higher total paclitaxel dosage. Large, prospective real-world studies are necessary to confirm this potential benefit.

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## References


1. Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FGR; TASC II Working Group. Inter-society consensus for the management of peripheral arterial disease (TASC II). *J Vasc Surg.* 2007;45(suppl S):S5-S67. doi:10.1016/j.jvs.2006.12.037
2. Lawall H, Huppert P, Rümenapf G. S3-Leitlinie zur Diagnostik, Therapie und Nachsorge der peripheren arteriellen Verschlusskrankheit. Deutsche Gesellschaft für Angiologie und Deutsche Gesellschaft für Gefäßmedizin 2015;30.
3. Tepe G, Zeller T, Albrecht T, et al. Local delivery of paclitaxel to inhibit restenosis during angioplasty of the leg. *N Engl J Med.* 2008;358(7):689-699. doi:10.1056/NEJMoa0706356
4. Werk M, Langner S, Reinkensmeier B, et al. Inhibition of restenosis in femoropopliteal arteries: paclitaxel-coated versus uncoated balloon: femoral paclitaxel randomized pilot trial. *Circulation.* 2008;118(1):1358-1365. doi:10.1161/CIRCULATIONAHA.107.735985
5. Tepe G, Laird J, Schneider P, et al. Drug-coated balloon versus standard percutaneous transluminal angioplasty for the treatment of superficial femoral and popliteal peripheral artery disease: 12-month results from the IN.PACT SFA randomized trial. *Circulation.* 2015;131(5):495-502. doi:10.1161/CIRCULATIONAHA.114.011004
6. Fanelli F, Cannavale A, Boatta E, et al. Lower limb multilevel treatment with drug-eluting balloons: 6-month results from the DEBELLUM randomized trial. *J Endovasc Ther.* 2012;19(5):571-580. doi:10.1583/JEVT-12-3926MR.1
7. Liistro F, Porto I, Angioli P, et al. Drug-eluting balloon in peripheral intervention for below the knee angioplasty evaluation (DEBATE-BTK): a randomized trial in diabetic patients with critical limb ischemia. *Circulation.* 2013;128(6):615-621. doi:10.1161/CIRCULATIONAHA.113.001811
8. Zeller T, Baumgartner I, Scheinert D, et al. Drug-eluting balloon versus standard balloon angioplasty for infrapopliteal arterial revascularization in critical limb ischemia: 12-month results from the IN.PACT DEEP randomized trial. *J Am Coll Cardiol.* 2014;64(15):1568-1576. doi:10.1016/j.jacc.2014.06.1198
9. Zeller T, Beschorner U, Pilger E, et al. Paclitaxel-coated balloon in infrapopliteal arteries: 12-month results from the BIOLUX P-II randomized trial (BIOTRONIK'S-first in man study of the Passeo-18 LUX drug releasing PTA balloon catheter vs. the uncoated Passeo-18 PTA balloon catheter in subjects requiring revascularization of infrapopliteal arteries). *JACC Cardiovasc Interv.* 2015;8(12):1614-1622. doi:10.1016/j.jcin.2015.07.011
10. Katsanos K, Spiliopoulos S, Kitrou P, Krokidis M, Karnabatidis D. Risk of death following application of paclitaxel-coated balloons and stents in the femoropopliteal artery of the leg: a systematic review and meta-analysis of randomized controlled trials. *J Am Heart Assoc.* 2018:7(24):e011245. doi:10.1161/JAHA.118.011245
11. Katsanos K, Spiliopoulos S, Kitrou P, Krokidis M, Paraskevopoulos I, Karnabatidis D. Risk of death and amputation with use of paclitaxel-coated balloons in the infrapopliteal arteries for treatment of critical limb ischemia: a systematic review and meta-analysis of randomized controlled trials. *J Vasc Interv Radiol.* 2020;31(2):202-212. doi:10.1016/j.jvir.2019.11.015
12. Zeller T, Micari, A, Scheinert D, et al. The IN.PACT DEEP clinical drug-coated balloon trial: 5-year outcomes. *JACC Cardiovasc Interv.* 2020;13(4):431-443. doi:10.1016/j.jcin.2019.10.059
13. US Food and Drug Administration. ELUVIA drug-eluting vascular stent system. 2018. Accessed May 7, 2021. https://www.accessdata.fda.gov/cdrh_docs/pdf18/P180011B.pdf
14. US Food and Drug Administration. IN.PACT Admiral paclitaxel-coated PTA balloon catheter summary of safety and effectiveness data. 2014. Accessed May 7, 2021. https://www.accessdata.fda.gov/cdrh_docs/pdf14/P140010B.pdf
15. US Food and Drug Administration. LUTONIX 035 drug coated balloon PTA catheter: summary of safety and effectiveness data. 2017. Accessed May 7, 2021. https://www.accessdata.fda.gov/cdrh_docs/pdf13/P130024S009B.pdf
16. US Food and Drug Administration. Stellarex 0.035" OTW drug-cated angioplasty balloon summary of safety and effectiveness data. 2017. Accessed May 7, 2021. https://www.accessdata.fda.gov/cdrh_docs/pdf16/P160049B.pdf
17. Zilver PTX Drug-eluting peripheral stent, instructions for use, IFU 0118-6. Cook Medical . Published July 2020. https://www.cookmedical.com/data/resources/PI-D56387-EN-F_M3_1602699734616.pdf
18. Freisinger E, Koeppe J, Gerss J, et al. Mortality after use of paclitaxel-based devices in peripheral arteries: a real-world safety analysis. *Eur Heart J.* 2020;41(38):3732-3739. doi:10.1093/eurheartj/ehz698
19. Secemsky EA, Kundi H, Weinberg I, et al. Association of survival with femoropopliteal artery revascularization with drug-coated devices. *JAMA Cardiol.* 2019;4(4):332-340. doi:10.1001/jamacardio.2019.0325
20. Taylor SM, Cull DL, Kalbaugh CA, et al. Comparison of interventional outcomes according to preoperative indication: a single center analysis of 2,240 limb revascularizations. *J Am Coll Surg.* 2009;208(5):770-778. doi:10.1016/j.jamcollsurg.2009.01.025
21. Reinecke H, Unrath M, Freisinger E, et al. Peripheral arterial disease and critical limb ischaemia: still poor outcomes and lack of guideline adherence. *Eur Heart J.* 2015;36(15):932-938. doi:10.1093/eurheartj/ehv006
22. Rollins KE, Jackson D, Coughlin PA. Meta-analysis of contemporary short-and long-term mortality rates in patients diagnosed with critical leg ischaemia. *Br J Surg.* 2013;100(8):1002-1008. doi:10.1002/bjs.9127
23. Malyar NM, Freisinger E, Meyborg M, et al. Amputations and mortality in in-hospital treated patients with peripheral artery disease and diabetic foot syndrome. *J Diabetes Complications.* 2016;30(6):1117-1122. doi:10.1016/j.jdiacomp.2016.03.03