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Long Term Survival after Femoropopliteal Artery Revascularisation with Paclitaxel Coated Devices: A Propensity Score Matched Cohort Analysis

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WHAT THIS PAPER ADDS

In this retrospective cohort study of 37 914 patients and 21 546 propensity score matched patients having index revascularisation between 1 January 2010 and 31 December 2018, rapid adoption of paclitaxel coated devices and higher long term survival at five years was observed after their use for the treatment of symptomatic peripheral arterial occlusive disease. Among BARMER patients, no sign of increased all cause mortality following use of paclitaxel coated devices was found, emphasising differences between population based evidence and randomised trials.

Objective: The aim of this study was to determine the survival of patients after use of paclitaxel coated devices (PCX), as a recent meta-analysis of randomised trials reported higher mortality in patients treated with PCX balloons and stents

Methods: A retrospective health insurance claims analysis of patients covered by the second largest insurance fund in Germany, BARMER, was used to identify index femoropopliteal arterial interventions between 1 January 2010 and 31 December 2018. To ensure first PCX exposure, patients with prior deployment of PCX were excluded. The study cohort was stratified into patients with chronic limb threatening ischaemia (CLTI) and intermittent claudication (IC), then into balloons *vs.* stents cohorts. Within each stratum PCX were compared with uncoated devices. Propensity score matching was used to balance the study groups. Survival was evaluated using the Kaplan—Meier method and Cox regression.

Results: There were 37 914 patients (mean age 73.3 years; 48.8% female) included in the study. The annual proportion of PCX use increased from 3% to 39% during the study period for CLTI and from 4% to 48% for IC (both $p < .001$). Paclitaxel coated balloons and stents were associated with improved overall survival (hazard ratio [HR] 0.83, 95% confidence interval [CI] 0.77—0.90), amputation free survival (HR 0.85, 95% CI 0.78—0.91), and freedom from major cardiovascular events (HR 0.82, 95% CI 0.77—0.89) *vs.* uncoated devices at five years for CLTI. In IC cohort, mortality was significantly lower after using drug coated balloons (DCB) (HR 0.87, 95% CI 0.76—0.99) or combined DCB and drug eluting stents (HR 0.88, 95% CI 0.80—0.98).

Conclusion: In this large health insurance claims analysis, rapid adoption of PCX, higher long term survival, better amputation free survival, and lower rates of major cardiovascular events were seen after their use for the treatment of CLTI.

Keywords: Chronic limb threatening ischaemia, Drug coated balloon, Drug eluting stent, Intermittent claudication, Paclitaxel, Peripheral arterial occlusive disease

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INTRODUCTION

Peripheral arterial occlusive disease (PAOD) affects more than 200 million patients worldwide.[1] Over 3.7 million patients worldwide underwent endovascular interventions in 2017, with the number expected to exceed 4.5 million by 2022.[2] Paclitaxel coated technology has become increasingly popular in the past decade for the treatment of PAOD

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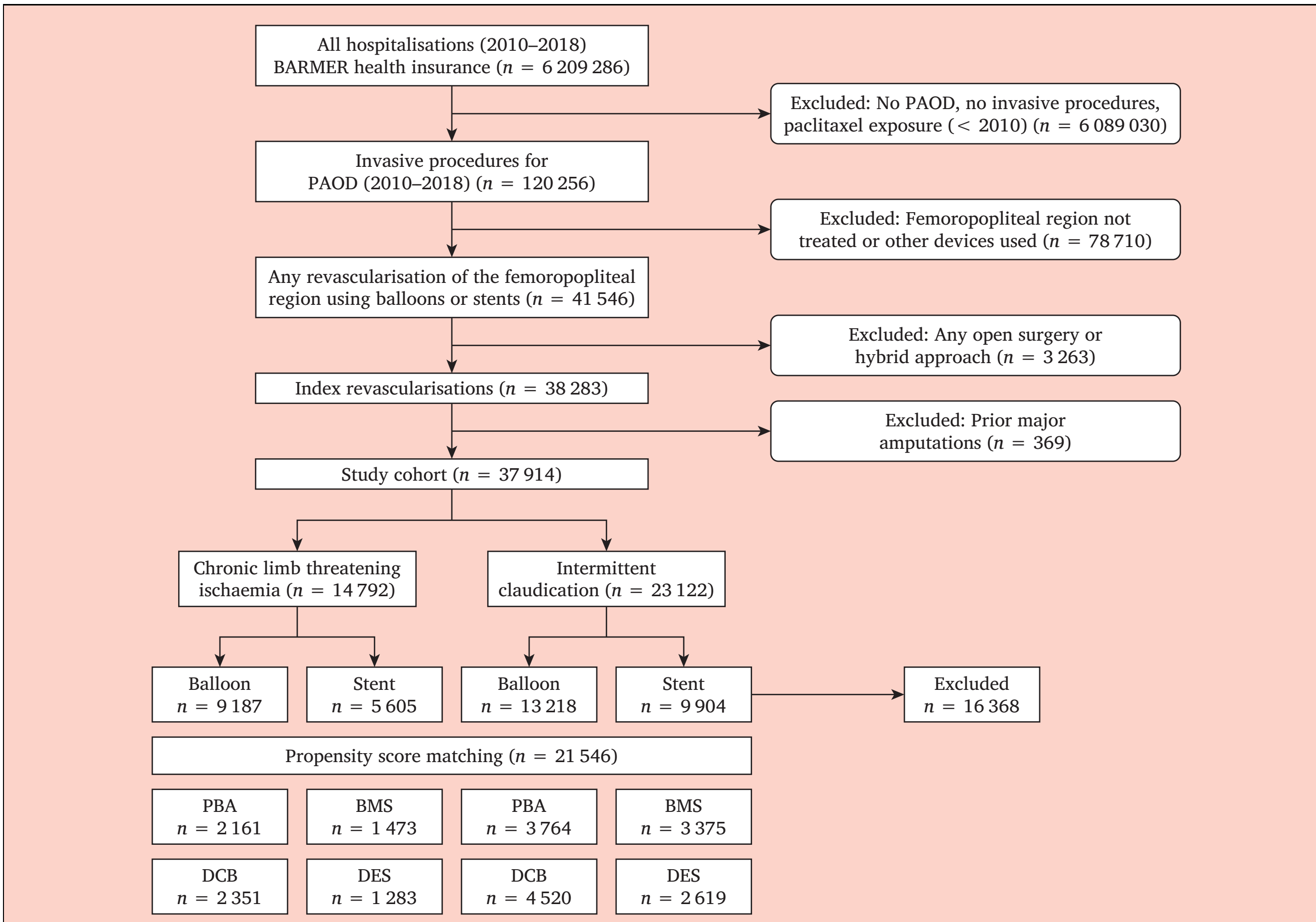

Figure 1. Flow chart of this propensity score matched retrospective analysis of health insurance claims. PAOD = peripheral arterial occlusive disease; PBA = plain balloon angioplasty; BMS = bare metal stent; DCB = drug coated balloon; DES = drug eluting stent.

in an effort to reduce the notoriously high restenosis rate. Practice guidelines from societies in the USA and Europe have recommended the use of drug eluting devices.[3,4] Moreover, the 2018 SCAI consensus guidelines recommended drug eluting stents (DES) or drug coated balloons (DCB) as first line treatments in the femoropopliteal segment, because of their perceived greater efficacy.[5,6] Recently, these recommendations have been heavily scrutinised after a systematic review and meta-analysis was published that involved data from 28 randomised controlled trials (RCTs) that enrolled 4663 patients with 12 different devices.[7] The authors found a higher risk of death at two and five years following the use of paclitaxel coated balloons and stents in the femoropopliteal artery. Following this report, a study in the USA using Medicare fee for service claims data to evaluate outcomes found no differences between paclitaxel coated and uncoated devices. The study was limited owing to its short follow up duration and inclusion of only patients aged >65 years.[8] The US Food and Drug Administration (FDA) conducted an independent review of trial data submitted to the FDA for device approval and confirmed the presence of a safety signal associated with paclitaxel coated devices (https://www.fda.gov/media/127698/download). These inconsistent findings between RCT and real world data have since been debated by physicians and regulators, highlighting the need for longer term patient level data, and device surveillance studies using population based data from registries and/or health insurance claims.[9–12] The aim of this study was to address concerns related to long term survival after treatment of the femoropopliteal artery with paclitaxel coated devices using a propensity score matched retrospective analysis of health insurance claims from Germany.

PATIENTS AND METHODS

BARMER cohort

The longitudinal data of Germany's second largest insurance fund, BARMER, includes the outpatient and inpatient medical care provided to approximately 9.4 million German citizens (13.2% of Germany's population) involving 6.2 million hospitalisations between 2010 and 2018. The BARMER cohort includes nationally generalisable data with comparable sex and age distribution to the entire German population, and has been widely used for cardiovascular research.[13,14] A regular random sample validation of internal and external validity is performed by the Medical

Service of the Health Funds in Germany, and various validation studies have been published previously.[15–18]

The International Classification of Diseases in its German Modification (ICD-10-GM) was used to identify diagnoses and Operations and Procedures Codes (OPS) to identify procedures. The German OPS coding is adapted to the International Classification of Procedures in Medicine. To identify medical prescriptions, the German version of the international Anatomical Therapeutic Chemical classification was used.

Study population

A cohort of patients with symptomatic PAOD (intermittent claudication [IC], Fontaine stage II or chronic limb threatening ischaemia [CLTI], Fontaine stages III–IV) in the femoropopliteal segment was created. All patients aged $\geq$40 years with endovascular peripheral vascular intervention (PVI) stent/balloon revascularisation in the femoropopliteal artery were included. The index hospitalisation for PVI was from 1 January 2010 to 31 December 2018, with follow up until 31 December 2018. To create relevant comorbidities (available ICD-10-GM data going back to 2005) and to ensure first paclitaxel exposure (available procedure codes for drug coated devices going back to 2008), five year lookback in the BARMER data set was used.

In the analyses, separate cohorts for IC and CLTI were created (Fig. 1).[19] The primary diagnoses for inclusion were IC (I70.21 until 2014 and I70.21–22 since 2015) or CLTI (I70.22–24 until 2014 and I70.23–25 since 2015) with or without diabetic foot syndrome (E10.50–51, E10.7, E11.50–51, E11.7), other peripheral vascular diseases (I73), arterial embolism and thrombosis (I74), cellulitis of finger and toe, including acute lymphangitis (L03.01–02, L03.11), or chronic ulcer of skin and gangrene (L98.4, R02) using the ICD-10-GM.[20]

Patients who received at least one index DCB/DES during the study period were assigned to the paclitaxel group. If a patient received a stent and balloon at the same time, it was defined as a stent procedure. Additional information and coding criteria for DES or DCB can be found in Table S1 (see Supplementary Material). Patients with hybrid interventions (open surgical repair and PVI) exposed to paclitaxel before 2010 or patients who received a major amputation prior to the paclitaxel treatment and missing information on age, sex, and follow up ($\sim$0.48%) were excluded using complete case deletion from the analyses. The non-paclitaxel group included plain balloon angioplasty and bare metal stent. Patients with plain balloon angioplasty or bare metal stent at index stay, but exposed to paclitaxel (e.g., DCB or DES) at a later revascularisation in the femoropopliteal artery of the lower limbs, were assigned to the paclitaxel group according to the date of the second procedure. If patients were exposed to consecutive treatments using paclitaxel coated devices during the study period, the initial application of paclitaxel (first exposure) was used as the index treatment.

For the baseline characteristics the comorbidity groups categorised by ICD-10 codes, separated into 30 Elixhauser comorbidity groups[21,22] for five years before the first PAOD diagnosis (lookback), were used. The linear van Walraven score is a validated weighted sum score ranging from -19 to $+89$ based on the Elixhauser groups; high scores represent a higher in hospital mortality risk.[23]

Statistical analysis

Baseline patient characteristics were summarised as mean $\pm$ standard deviation for normally distributed variables and as median (interquartile range [IQR]) for non-normally distributed variables. For discrete variables, percentages and risk differences, including 95% Wald confidence interval (CI; significant if 0 outside the interval), were used.

The Student's *t*-test and Wilcoxon rank sum test were used to test for differences between exposure groups. The Cochrane Armitage trend test was used for the trend test of proportion of paclitaxel use. The discharge year; age; sex; number of prior hospital admissions and PAOD related outpatient admissions; number of different prescriptions during the prior year; prescription for antithrombotics, antihypertensives, lipid lowering drugs, antihypertensives, antidiabetics, analgesics, hypnotics and sedatives, antidementives, and antidepressives during the prior year; all the Elixhauser coding groups (except acquired immunodeficiency syndrome/human immunodeficiency virus); and prior stroke or transient ischaemic attack (TIA), dyslipidaemia, coronary artery disease, smoking, and prior myocardial infarction were used as variables for propensity score matching stratified by CLTI and IC.[21–23]

The primary outcome was all cause mortality; the end of follow up was in December 2018. Secondary outcomes were the composite end points of amputation free survival (AFS; major amputation or all cause mortality) and major cardiovascular events (myocardial infarction, stroke or TIA, and all cause mortality). Follow up times were censored after five years to compute robust five year rates. All outcomes were estimated using Cox proportional hazard models stratified by CLTI and IC for the full sample, and by subgroup stent and balloon. All Cox models were additionally adjusted for age; sex; Fontaine stage; prior myocardial infarction; van Walraven score; congestive heart failure; cardiac arrhythmias; valvular disease; hypertension; neurogenerative disorders; chronic pulmonary disease; hypothyroidism; renal failure; liver disease; metastatic cancer; solid tumour without metastasis; obesity; fluid and electrolyte disorders; deficiency anaemia; psychosis; depression; lipid lowering drugs in the year before admission; antithrombotics in the year before admission; antihypertensives in the year before admission; antidementives in the year before admission; number of different prescriptions in the year before admission; number of previous inpatient admissions total (including the index admission); and number of prior PAOD outpatient admissions entered into the matching algorithm to account for residual confounding.

In the sensitivity analysis, patients experiencing events within 30 days after hospital discharge (landmark analysis) were excluded and Cox proportional hazards (PH) models without adjustment for residual confounding were computed (Table S2; see Supplementary Material). As an additional sensitivity analysis long term survival, including patients with IC and CLTI (unstratified), was calculated.

The primary exposure of interest was any index (first) paclitaxel coated device application. Disease severity specific propensity score matching (greedy 1:1 matching) was applied to adjust for observed confounding allowing for differences in confounding effects between IC and CLTI. To measure the validity of the matching algorithm, standardised differences (values > 0.1 or < -0.1 deemed to indicate meaningful differences) were used. Details of the logistic regression model and a comparison of quality for propensity score matching are reported in Tables S3 and S4 (see Supplementary Material).

All analyses were performed with SAS version 9.04 (SAS Institute, Cary, NC, USA). Results were reported using the REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) statement,[24] the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) statement,[25] and following international recommendations on medical device evaluation studies.[24]

Cox regression models and visualisations were performed with R version 3.3.3 (R Foundation for Statistical Computing, Vienna, Austria).

The trial was registered on the ClinicalTrials.gov website (NCT03909022).

RESULTS

This study included a total of 37 914 patients hospitalised during the study period (mean age 73.33 ± 10.36 years; 48.8% females) and 21 546 propensity score matched patients undergoing PVI from 1 January 2010 to 31 December 2018. The cohort was stratified by CLTI *vs.* IC and then by balloon *vs.* stent use. Within each cohort, drug eluting device use was evaluated. The annual proportion of paclitaxel coated devices for CLTI increased from 3% in 2010 to 39% in 2018, ($p<.001$), and for IC from 4% in 2010 to 48% in 2018 ($p<0.001$).

Unmatched analyses for demographics and comorbidities

The median length of follow up was 983 days (IQR 412—1777 days [4.9 years]). The longest follow up was eight years.

In the CLTI group, patients treated with paclitaxel coated devices were younger (75.8 *vs.* 77.4 years; $p < .001$), received a larger mean number of medications (13.6 *vs.* 13.0; $p < .001$), were hospitalised more often prior to their index revascularisation (5.9 *vs.* 5.0; $p < .001$), and had a shorter length of follow up (median 567 *vs.* 764 days) (Table 1). Furthermore, they were more likely to be smokers (15.8% *vs.* 12.7%), to have dyslipidaemia (62.1% *vs.* 51.5%), obesity (19.5% *vs.* 17.6%), hypertension (90.1% *vs.* 88.5%), and liver disease (6.9% *vs.* 5.5%). At the same time, patients treated with paclitaxel coated devices had less often had a prior stroke/TIA (11.3% *vs.* 12.9%).

In the IC group, patients treated with paclitaxel coated devices received a larger mean number of medications (9.9 *vs.* 9.2; $p < .001$), were hospitalised more often prior to their index revascularisation (4.1 *vs.* 3.5; $p < .001$), had a shorter follow up time (median 805 *vs.* 1398 days), were more often females (47.7% *vs.* 45.1%), and exhibited multiple comorbidities with a van Walraven score >9 (27.1% *vs.* 25.2%). They were also more likely to be smokers (21.0% *vs.* 19.7%), have dyslipidaemia (65.1% *vs.* 55.9%), hypertension (86.3% *vs.* 82.9%), coronary artery disease (37.4% *vs.* 35.0%), cardiac arrhythmias (20.2% *vs.* 18.9%), complicated diabetes (19.3% *vs.* 18.1%), and renal failure (27.3% *vs.* 23.6%).

Outcomes in matched cohorts

Demographics and comorbidities of the comparison groups after propensity score matching are given in Table 2.

In the CLTI group, patients treated with paclitaxel coated devices less often experienced acute respiratory failure (0.6% *vs.* 1.1%), pneumonia (0.6% *vs.* 1.0%), and had a shorter length of stay (median 7.0 *vs.* 9.0 days) (Table 3).

The proportion of patients discharged to rehabilitation (0.6% *vs.* 1.0%) was lower in the paclitaxel coated devices group, when compared with uncoated devices for CLTI (Table 3).

A total of 2454 deaths occurred within five years of follow up. After treatment for CLTI, a lower mortality rate was observed in the paclitaxel coated device group at five years (31.8% *vs.* 35.8%) (Table 3).

In the IC group, patients treated with paclitaxel coated devices less often experienced stroke/TIA (0.1% *vs.* 0.2%), had a shorter length of stay (median 3.0 *vs.* 3.0 days, 8 + days: 6.5% *vs.* 8.9%), and died less often within five years of hospital discharge (9.4% *vs.* 10.5%).

Cox proportional hazards analyses in matched cohorts

The results of the Cox proportional hazards models for survival after five years are given in Fig. 3. In propensity score matched cohorts, a paclitaxel related survival benefit was observed for patients with CLTI treated with DCB (hazard ratio [HR] 0.82, 95% CI 0.74—0.91), for those treated with a DES (HR 0.84, 95% CI 0.73—0.96), and in the combined DCB and DES analysis (HR 0.83, 95% CI 0.77—0.90).

For AFS and major cardiovascular events after treatment of patients with CLTI, there was also a benefit of paclitaxel coated devices (HR 0.85 [95% CI 0.78—0.91] and HR 0.82 [95% CI 0.77—0.88], respectively) (data not shown).

For the subgroup of patients with IC, survival was better for DCB (HR 0.87, 95% CI 0.76—0.99) and combining DCB and DES (HR 0.88, 95% CI 0.80—0.98), but similar for DES (HR 0.91, 95% CI 0.77—1.08) (Fig. 3).

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For AFS and major cardiovascular events following treatment of patients with IC, no benefit of paclitaxel coated devices was detected (HR 0.91 [95% CI 0.82—1.00] and HR 0.93 [95% CI 0.87—1.00], respectively) (data not shown).

Additional sensitivity analysis using cox proportional hazards in the unstratified matched cohort

Sensitivity analyses estimated the Cox proportional hazards for the unstratified matched cohort including both patients with CLTI and IC. DCB (HR 0.83, 95% CI 0.77—0.90), DES (HR 0.86, 95% CI 0.77—0.96), and combined DCB/DES (HR 0.85, 95% CI 0.80—0.90) added significantly to the model.

DISCUSSION

In this propensity score matched retrospective analysis of health insurance claims, comprising a rapidly increasing proportion of paclitaxel coated devices in the treatment of PAOD, higher long term survival, AFS, and adverse cardiovascular event free survival after the treatment of CLTI with paclitaxel coated devices (both balloon and stent) was found, when compared with the uncoated control group. In patients with IC, paclitaxel coated devices were associated with higher long term survival only, visible in the group where balloons and stents were combined and for balloons but not for stents. Unlike any other prior analysis, a persistent, robust, and positive association of paclitaxel exposure and survival is documented for a wide range of subgroups.

Table 1. Baseline characteristics of the entire unmatched study cohort of patients treated endovascularly with a paclitaxel coated device (PCX) or other device protocol (control) for chronic limb threatening ischaemia (CLTI) or intermittent claudication (IC)

	CLTI				IC			
Unmatched characteristics	PCX (n = 3 634)	Control (n = 11 158)	p value	RD (95% CI)	PCX (n = 7 139)	Control (n = 15 983)	p value	RD (95% CI)
Age – years	75.8 ± 10.5	77.4 (±10.5)	<.001*		70.93 ± 9.5	71.03 ± 9.6	.47	
No. of prescriptions prior to admission†	13.61 ± 6.8	13.0 ± 6.8	<.001*		9.9 ± 5.6	9.2 ± 5.4	<.001*	
No. of prior hospitalisations	5.9 ± 4.5	5.0 ± 4.0	<.001*		4.1 ± 3.3	3.5 ± 3.0	.001*	
Follow up time – d	567 (236–1094)	763.5 (255–1531)	<.001*		805 (383–1383)	1398 (708–2205)	.001*	
Female sex	1 969 (54.2)	5 918 (53.0)		1.14 (−0.72 to 3.01)	3 407 (47.7)	7 210 (45.1)		2.61 (1.22–4.01)*
vWS > 9	2 064 (56.8)	6 274 (56.2)		0.57 (−1.29 to 2.42)	1 936 (27.1)	4 024 (25.2)		1.94 (0.71–3.17)*
Prior stroke or TIA	411 (11.3)	1 441 (12.9)		−1.6 (−2.81 to −0.40)*	478 (6.7)	1 092 (6.8)		−0.14 (−0.84 to 0.56)
Smoking	574 (15.8)	1 417 (12.7)		3.1 (1.76–4.43)*	1 498 (21.0)	3 144 (19.7)		1.31 (0.18–2.44)*
Dyslipidaemia	2 257 (62.1)	5 744 (51.5)		10.63 (8.8–12.46)*	4 649 (65.1)	8 936 (55.9)		9.21 (7.86–10.56)*
Obesity	707 (19.5)	1 961 (17.6)		1.88 (0.41–3.35)*	970 (13.6)	2 121 (13.3)		0.32 (−0.64 to 1.27)
Prescription of lipid lowering drugs prior to admission†	1 986 (54.7)	4 908 (44.0)		10.66 (8.80–12.53)*	4 570 (64.0)	8 883 (55.6)		8.44 (7.08–9.79)*
Hypertension	3 273 (90.1)	9 879 (88.5)		1.53 (0.39–2.67)*	6 159 (86.3)	13 252 (82.9)		3.36 (2.37–4.35)*
CAD	1 654 (45.5)	4 889 (43.8)		1.7 (−0.16 to 3.56)	2 668 (37.4)	5 588 (35.0)		2.41 (1.07–3.75)*
Prior MI	566 (15.6)	1 695 (15.2)		0.38 (−0.97 to 1.74)	834 (11.7)	1 771 (11.1)		0.6 (−0.29 to 1.49)
CHF	1 529 (42.1)	4 652 (41.7)		0.38 (−1.46 to 2.23)	1 339 (18.8)	2 867 (17.9)		0.82 (−0.27 to 1.90)
Valvular disease	683 (18.8)	2 064 (18.5)		0.3 (−1.16 to 1.76)	621 (8.7)	1 345 (8.4)		0.28 (−0.50 to 1.07)
Cardiac arrhythmias	1 419 (39.0)	4 433 (39.7)		−0.68 (−2.51 to 1.15)	1 445 (20.2)	3 024 (18.9)		1.32 (0.21–2.43)*
Prescription of antithrombotics prior to admission†	2 206 (60.7)	5 845 (52.4)		8.32 (6.48–10.16)*	3 784 (53.0)	6 973 (43.6)		9.38 (7.99–10.77)*
Prescription of antiplatelets prior to admission†	1 656 (45.6)	3 920 (35.1)		10.44 (8.59–12.28)*	3 270 (45.8)	5 610 (35.1)		10.7 (9.33–12.08)*
Prescription of oral anticoagulation prior to admission†	962 (26.5)	2 599 (23.3)		3.18 (1.54–4.81)*	885 (12.4)	1 698 (10.6)		1.77 (0.87–2.67)*
Prescription of antiplatelets and of oral anticoagulation prior to admission†	365 (10.0)	699 (6.3)		3.78 (2.70–4.86)*	355 (5.0)	471 (2.9)		2.03 (1.46–2.59)*
Chronic pulmonary disease	712 (19.6)	2 147 (19.2)		0.35 (−1.13 to 1.83)	1 072 (15.0)	2 263 (14.2)		0.86 (−0.13 to 1.85)
Diabetes, complicated	1 607 (44.2)	4 766 (42.7)		1.51 (−0.35 to 3.36)	1 376 (19.3)	2 893 (18.1)		1.17 (0.08–2.27)*
Prescription of antidiabetics prior to admission†	1 608 (44.2)	4 630 (41.5)		2.75 (0.90–4.61)*	2 074 (29.1)	4 391 (27.5)		1.58 (0.32–2.84)*
Renal failure	1 825 (50.2)	5 434 (48.7)		1.52 (−0.35 to 3.39)	1 952 (27.3)	3 768 (23.6)		3.77 (2.54–4.99)*
Liver disease	251 (6.9)	610 (5.5)		1.44 (0.51–2.37)*	293 (4.1)	601 (3.8)		0.34 (−0.20 to 0.89)

Data are mean ± standard deviation, n (%), or median (interquartile range). RD = risk difference; CI = confidence interval; vWS = van Walraven score; TIA = transient ischaemic attack; CAD = coronary artery disease; MI = myocardial infarction; CHF = congestive heart failure.
* Denotes significant result.
† Within one year prior to admission.

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The cohort was population based and comparable to current European populations. To date, 15 DCBs and two DESs have been approved for the European market; three DCBs and two DES have been approved by the FDA in the USA.[9] In the midst of the widespread adoption of this new technology, a recent meta-analysis led to a global debate concerning possible harms of paclitaxel coated devices, which has led to regulatory actions in the USA and Europe.[7] The most recent 2019 Global Vascular Guidelines for the treatment of CLTI contain a distinct statement concerning the indeterminate risk and efficacy of these devices, emphasising the need to exercise appropriate caution until data from controlled prospective studies are available.[26] Moreover, ongoing trials, such as BASIL-3 (Balloon *vs.* Stenting in Severe Ischaemia of the Leg 3) or SWEDEPAD (Swedish Drug Elution Trial in Peripheral Arterial Disease), have temporarily stopped recruitment until this critical issue is resolved.[27] Meanwhile, several arguments have been raised by the proponents of the meta-analysis, mostly concerning the lack of patient level data available to the authors, and insufficient stratification of non-homogeneous subgroups (e.g., CLTI *vs.* IC, stent *vs.* balloon angioplasty).[9,28] Most importantly, several RCTs included in the recently published meta-analyses did not have a long enough follow up to determine long term survival, and most were underpowered. Only three of 28 RCTs reported mortality rates at least three years after inclusion.[10,29–31] The five year all cause mortality rates in the Zilver Paclitaxel (PTX)[10,29] and THUNDER (Local Taxan With Short Time Contact for Reduction of Restenosis in Distal Arteries)[30] trials were 16.9% (25.0%) for the paclitaxel group and 10.2% (14.8%) for the PTA group.[10,29] At three years after

Table 2. Baseline characteristics of the matched study cohort of patients treated endovascularly with a paclitaxel coated device (PCX) or other device (control) for chronic limb threatening ischaemia (CLTI) or intermittent claudication (IC)

Matched characteristics	CLTI PCX (n = 3 634)	CLTI Control (n = 3 634)	CLTI p value	CLTI RD (95% CI)	IC PCX (n = 7 139)	IC Control (n = 7 139)	IC p value	IC RD (95% CI)
Age – years	75.7 ± 10.5	76.0 ± 10.3	.27		70.93 ± 9.48	71.19 ± 9.51	.10	
No. prescriptions prior to admission†	13.61 ± 6.8	13.6 ± 6.8	.81		9.85 ± 5.56	9.63 ± 5.45	.02*	
No. of prior hospitalisations	5.9 ± 4.5	5.6 ± 4.6	.02*		4.13 ± 3.28	3.88 ± 3.35	<.001*	
Follow up time	567 (236–1 094)	508 (193–1 026)	<.001*		805 (383–1 383)	839 (406–1 377)	.01*	
Female sex	1 969 (54.2)	1 968 (54.2)		0.03 (–2.26 to 2.32)	3 407 (47.7)	3 325 (46.6)		1.15 (–0.49 to 2.79)
vWS > 9	2 064 (56.8)	2 035 (56.0)		0.80 (–1.48 to 3.08)	1 936 (27.1)	1 918 (26.9)		0.25 (–1.2 to 1.71)
Prior stroke or TIA	411 (11.3)	409 (11.3)		0.06 (–1.4 to 1.51)	4 78 (6.7)	501 (7.0)		–0.32 (–1.15 to 0.51)
Smoking	574 (15.8)	552 (15.2)		0.61 (–1.06 to 2.27)	1 498 (21.0)	1 432 (20.1)		0.92 (–0.4 to 2.25)
Dyslipidaemia	2 257 (62.1)	2 256 (62.1)		0.03 (–2.2 to 2.26)	4 649 (65.1)	4 522 (63.3)		1.78 (0.21–3.35)*
Obesity	707 (19.5)	708 (19.5)		–0.03 (–1.85 to 1.79)	970 (13.6)	950 (13.3)		0.28 (–0.84 to 1.4)
Prescription of lipid lowering drugs prior to admission†	1 986 (54.7)	1 956 (53.8)		0.83 (–1.47 to 3.12)	4 570 (64.0)	4 447 (62.3)		1.72 (0.14–3.31)*
Hypertension	3 273 (90.1)	3 264 (89.8)		0.25 (–1.14 to 1.63)	6 159 (86.3)	6 104 (85.5)		0.77 (–0.37 to 1.91)
CAD	1 654 (45.5)	1 689 (46.5)		–0.96 (–3.25 to 1.33)	2 668 (37.4)	2 663 (37.3)		0.07 (–1.52 to 1.66)
Prior MI	566 (15.6)	578 (15.9)		–0.33 (–2.00 to 1.34)	834 (11.7)	841 (11.8)		–0.10 (–1.15 to 0.96)
CHF	1 529 (42.1)	1 535 (42.2)		–0.17 (–2.44 to 2.11)	1 339 (18.8)	1 342 (18.8)		–0.04 (–1.32 to 1.24)
Valvular disease	683 (18.8)	689 (19.0)		–0.17 (–1.96 to 1.63)	621 (8.7)	621 (8.7)		0 (–0.92 to 0.92)
Cardiac arrhythmias	1 419 (39.0)	1 444 (39.7)		–0.69 (–2.93 to 1.56)	1 445 (20.2)	1 455 (20.4)		–0.14 (–1.46 to 1.18)
Prescription of antithrombotics prior to admission†	2 206 (60.7)	2 189 (60.2)		0.47 (–1.78 to 2.72)	3 784 (53.0)	3 668 (51.4)		1.62 (–0.01 to 3.26)
Prescription of antiplatelets prior to admission†	1 656 (45.6)	1 469 (40.4)		5.15 (2.87–7.42)*	3 270 (45.8)	2 942 (41.2)		4.59 (2.97–6.22)*
Prescription of oral anticoagulation prior to admission†	962 (26.5)	1 007 (27.7)		–1.24 (–3.28 to 0.81)	885 (12.4)	934 (13.1)		–0.69 (–1.78 to 0.41)
Prescription of antiplatelets and of oral anticoagulation prior to admission†	365 (10.0)	293 (8.1)		1.98 (0.66–3.30)*	355 (5.0)	275 (3.9)		1.12 (0.45–1.79)*
Chronic pulmonary disease	712 (19.6)	728 (20.0)		–0.44 (–2.27 to 1.39)	1 072 (15.0)	1 044 (14.6)		0.39 (–0.77 to 1.56)
Diabetes, complicated	1 607 (44.2)	1 579 (43.5)		0.77 (–1.51 to 3.05)	1 376 (19.3)	1 339 (18.8)		0.52 (–0.77 to 1.81)
Prescription of antidiabetics prior to admission†	1 608 (44.2)	1 586 (43.6)		0.61 (–1.68 to 2.89)	2 074 (29.1)	2 048 (28.7)		0.36 (–1.12 to 1.85)
Renal failure	1 825 (50.2)	1 812 (49.9)		0.36 (–1.94 to 2.66)	1 952 (27.3)	1 909 (26.7)		0.60 (–0.85 to 2.06)
Liver disease	251 (6.9)	240 (6.6)		0.30 (–0.85 to 1.46)	293 (4.1)	296 (4.1)		–0.04 (–0.69 to 0.61)

Data are mean ± standard deviation, n (%), or median (interquartile range). RD = risk difference; CI = confidence interval; vWS = van Walraven score; TIA = transient ischaemic attack; CAD = coronary artery disease; MI = myocardial infarction; CHF = congestive heart failure.
* Denotes significant result.
† Within one year prior to admission.

Table 3. Peri-operative (in hospital) outcomes and long term survival of the matched study group of patients treated endovascularly with a paclitaxel coated device (PCX) or other device (control) for chronic limb threatening ischaemia (CLTI) or intermittent claudication (IC)

Matched outcomes	CLTI PCX (n = 3 634)	CLTI Control (n = 3 634)	CLTI p value	CLTI RD (95% CI)	IC PCX (n = 7 139)	IC Control (n = 7 139)	IC p value	IC RD (95% CI)
Length of stay	7.0 (4.0–14.0)	9.0 (4.0–17.0)	<.001*		3.0 (2.0–4.0)	3 (2.0–4.0)	<.001*	
Length of stay ≥ 8 d	1 767 (48.6)	2 089 (57.5)		−8.86 (−11.15 to −6.58)*	462 (6.5)	637 (8.9)		−2.45 (−3.32 to −1.58)*
ALI	253 (7.0)	251 (6.9)		0.06 (−1.11 to 1.22)	346 (4.8)	349 (4.9)		−0.04 (−0.75 to 0.66)
Bleeding	123 (3.4)	142 (3.9)		−0.52 (−1.38 to 0.34)	51 (0.7)	59 (0.8)		−0.11 (−0.4 to 0.17)
Acute MI	18 (0.5)	29 (0.8)		−0.30 (−0.67 to 0.07)	17 (0.2)	19 (0.3)		−0.03 (−0.19 to 0.14)
Acute renal failure	105 (2.9)	106 (2.9)		−0.03 (−0.8 to 0.74)	24 (0.3)	23 (0.3)		0.01 (−0.17 to 0.20)
Acute respiratory failure	20 (0.6)	41 (1.1)		−0.58 (−1 to −0.16)*	11 (0.2)	13 (0.2)		−0.03 (−0.16 to 0.11)
Post-operative delirium	31 (0.9)	46 (1.3)		−0.41 (−0.88 to 0.06)	7 (0.1)	13 (0.2)		−0.08 (−0.21 to 0.04)
Pneumonia	20 (0.6)	37 (1.0)		−0.47 (−0.87 to −0.06)*	3 (0.0)	3 (0.0)		0.0 (−0.07 to 0.07)
Stroke or TIA	6 (0.2)	6 (0.2)		0 (−0.19 to 0.19)	5 (0.1)	14 (0.2)		−0.13 (−0.25 to −0.01)*
Sepsis or SIRS	18 (0.5)	18 (0.5)		0 (−0.32 to 0.32)	2 (0.0)	1 (0.0)		0.01 (−0.03 to 0.06)
In hospital death	65 (1.8)	82 (2.3)		−0.47 (−1.11 to 0.18)	5 (0.1)	7 (0.1)		−0.03 (−0.12 to 0.07)
Discharged to rehabilitation	20 (0.6)	36 (1.0)		−0.44 (−0.84 to −0.04)*	4 (0.1)	8 (0.1)		−0.06 (−0.15 to 0.04)
Discharged to nursing home	78 (2.1)	98 (2.7)		−0.55 (−1.26 to 0.16)	6 (0.1)	10 (0.1)		−0.06 (−0.17 to 0.05)
Death within 30 days	108 (3.0)	130 (3.6)		−0.61 (−1.42 to 0.21)	10 (0.1)	16 (0.2)		−0.08 (−0.22 to 0.06)
Death within five years	1 154 (31.8)	1 300 (35.8)		−4.02 (−6.19 to −1.85)*	673 (9.4)	753 (10.5)		−1.12 (−2.1 to −0.14)*
Amputation after five years	226 (6.2)	226 (6.2)		0 (−1.11 to 1.11)	70 (1.0)	57 (0.8)		0.18 (−0.13 to 0.49)
MI after five years	318 (8.8)	348 (9.6)		−0.83 (−2.15 to 0.5)	593 (8.3)	602 (8.4)		−0.13 (−1.03 to 0.78)
Stroke/TIA after five years	275 (7.6)	301 (8.3)		−0.72 (−1.96 to 0.53)	429 (6.0)	433 (6.1)		−0.06 (−0.84 to 0.73)

Data are median (interquartile range) or n (%). RD = risk difference; CI = confidence interval; ALI = acute limb ischaemia; MI = myocardial infarction; TIA = transient ischaemic attack; SIRS = systemic inflammatory response syndrome.
* Denotes significant result.

inclusion in the IN.PACT SFA (IN.PACT Admiral® Drug Coated Balloon *vs.* Standard PTA for the Treatment of SFA and Proximal Popliteal Arterial Disease) trial, deaths were reported in 10.7% of the paclitaxel group *vs.* 1.9% of the PTA group.[31] For the latter, the authors discussed the significantly higher all cause death rate among patients receiving DCB *vs.* uncoated balloons, underlining that all events occurred late after therapy and none of the deaths was determined to be related to the balloon treatment.[31] The updated meta-analysis recently reported no differences in mortality, which also illuminates possible problems with RCT data pooling, with a fine line between methodological validity and possible selection bias.[28] Owing to a large sample size and high internal and external validity of death ascertainment, longitudinal data from the present study can complement the evidence base and at least partially fill the knowledge gap.[32]

Interestingly, the results of the current study are inconsistent with the central findings and conclusions of a meta-analysis in 2018.[7] Higher rates of amputations following the application of paclitaxel coated devices possibly responsible for survival differences could not be confirmed. In addition, a delayed effect leading to long term differences was not observed. In fact, the differences in survival were immediately noticeable one year after the index procedure (Fig. 2).

Recently, a German health insurance claims analysis using the same database was published concerning a similar research question. The authors used a heterogeneous sample using a relatively flexible model with multiple collinearities and only moderate adjustment for confounding (Table S5; see Supplementary Material).[32] Interestingly, differences in the median length of follow up are explained by the fact that the present study included more up to date treatments with short term follow up lowering this estimate. Correspondingly, the study by Freisinger *et al.*[32] included only 177 DESs and 61 DCBs implanted before 2010 (0.5% of all devices). The authors concluded that no evidence for increased mortality after drug eluting devices was found over a follow up of 11 years. The present study confirmed the findings using a more robust model. Aiming to add to the existing evidence, the current approach rested on a rigorous study design involving a more homogeneous study population (only femoropopliteal segment, no prior major amputation), with a lookback period of up to five years and follow up periods (left and right censoring) of five years, stratified propensity score matching and adjustment

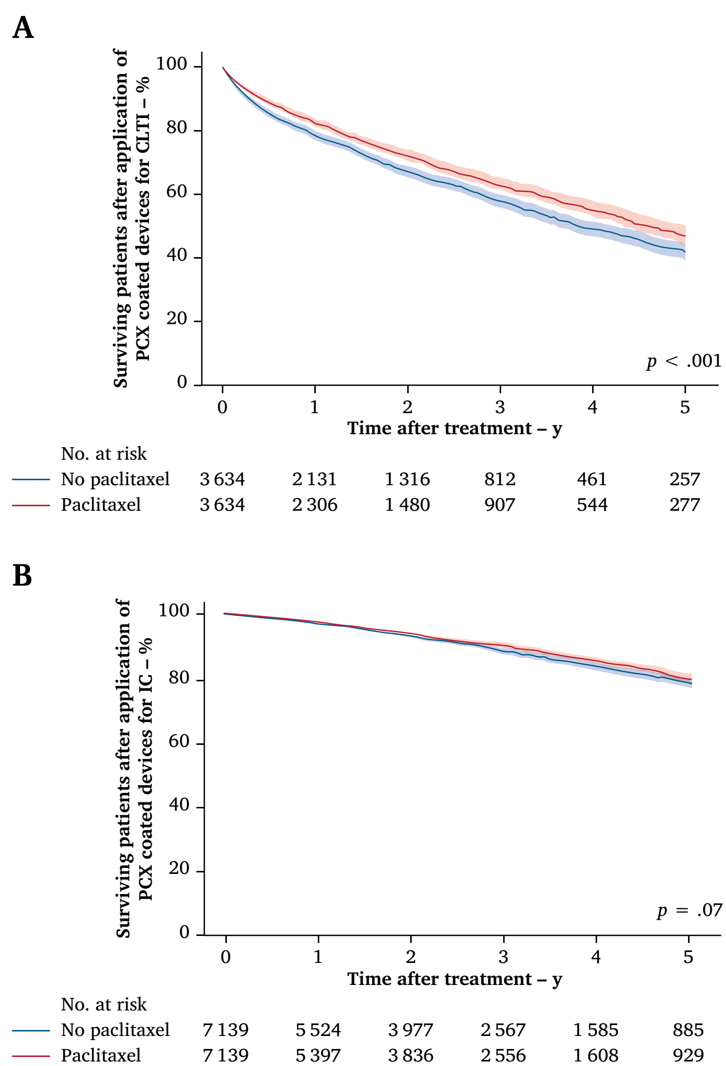

Figure 2. Cumulative Kaplan–Meier estimate of five year survival by treatment approach using propensity score matched cohorts, including 95% Wald confidence intervals and log rank test (*p* value). All analyses were stratified into (A) chronic limb threatening ischaemia (CLTI) and (B) intermittent claudication (IC). PCX= paclitaxel-coated devices.

for residual confounding based on the most up to date information, and extensive sensitivity analyses to ensure the robustness of the findings.

The present study has limitations. It is possible that the experience of the centre performing the procedures and the follow up of those patients play a major role increasing the overall survival of the target population. Follow up studies can determine the impact of optimal medical treatment, especially the effect of statins, and a possible clustering of patients in high volume paclitaxel trial centres. Furthermore, information on specific devices, doses of paclitaxel delivered, or paclitaxel applied during coronary or cancer treatment could not be collected validly. There is a very small proportion of coatings other than paclitaxel, making some of the codings used, less specific. In addition, the primary purpose of the data collection should be considered when using the data for secondary purposes, and all research data should undergo validation. Health insurance funds in Germany perform random cross checks with patient files on a regular basis. Prior validation studies revealed high major outcomes validity such as mortality in health insurance claims data.[15–18] Patients with CLTI have competing risks for mortality that may mask the mortality effects of devices. Known confounders were controlled for in an effort to minimise this possibility. However, there are probably remaining confounders not available in health insurance claims data. It must be highlighted that retrospective observational studies are merely hypothesis generating. Only a properly powered RCT would be suitable to confirm or refute the signal identified in the recently published meta-analysis. Lastly, although the fee for service reimbursement system in Germany probably motivates interventionalists to perform inpatient procedures rather than outpatient procedures, there might be another target

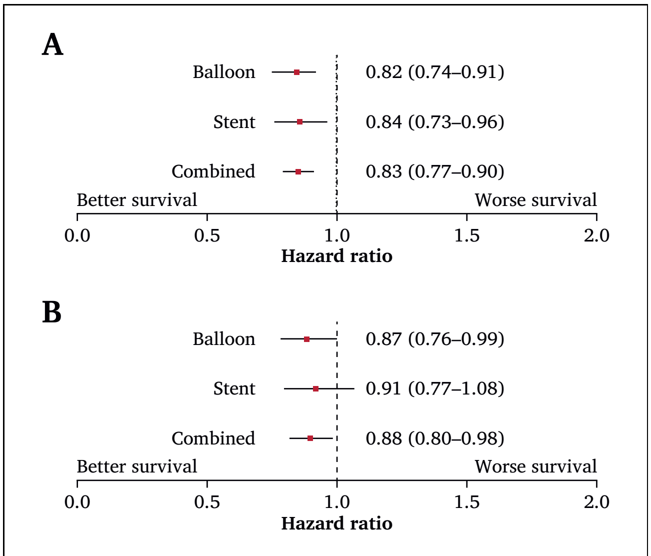

Figure 3. Forest plots of five year survival by treatment approach using propensity score matched cohorts with hazard ratios and 95% confidence intervals (balloon *vs.* stent *vs.* both approaches merged together). All analyses were stratified in (A) chronic limb threatening ischaemia and (B) intermittent claudication.

population not included in this study. The same limitation is valid for patients insured by other insurance providers or patients changing their health insurance company during the study period, although this is known to occur seldomly in the target population. However, it is believed that paclitaxel distribution is comparable and that there is no relevant selection bias limiting the results of this study.

The current results significantly differ between CLTI and IC, and between balloons and stents, indicating that studies should stratify their analyses accordingly. However, it remains unclear if there is a varying effect in different subgroups, or if these differences are caused by a longer time delay between index treatment for IC until major adverse outcomes.

As patients with paclitaxel coated devices were fundamentally different from those without paclitaxel coated devices in the unmatched cohort, the possibility that unmeasured confounding may partly explain the findings should be considered. A possible explanation may be that patients revascularised with DCB or DES are more likely to be treated in highly experienced trial centres with a clear follow up protocol. A higher proportion of statin prescriptions and strict surveillance for cardiac diseases might explain some of the differences observed in the current study. Further studies should exploit quasi-experimental research designs, for example randomised blinded studies or instrumental variables, to explore this in greater detail.[16,33–35]

The results of this study provide important information for physicians caring for patients with PAOD, which should be considered in addition to data from RCTs. It also adds significantly to the knowledge base by including patients with CLTI *vs.* IC who were not sufficiently covered by the recently published meta-analysis.

CONCLUSIONS

Using a propensity score matched retrospective analysis of paclitaxel coated devices in the treatment of PAOD, higher long term survival, AFS, and freedom from major cardiovascular events after treatment of CLTI and IC with paclitaxel coated devices was found when compared with the uncoated control group. These results emphasise the differences between population based evidence and meta-analyses of trials, prompting future research and reflection by policy makers.

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CONFLICTS OF INTEREST

MS has done consultancy work (medical advisory board) for Abbott, Cook, and Medtronic. TiK received travel and research grants, speaking fees, IP, royalties, and proctoring with Cook Medical. He is shareholder of Mokita Medical GmbH. ESD has received funding from Bayer and Terumo. The other authors declare no conflicts of interest.

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APPENDIX A. SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejvs.2019.12.034.

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