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Editor's Choice — Real World Study of Mortality After the Use of Paclitaxel Coated Devices in Peripheral Vascular Intervention

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WHAT THIS STUDY ADDS

In a cohort study of 11 452 patients, it was found that use of paclitaxel coated devices was not associated with an increased mortality rate. This finding was consistent across three cohorts: (A) patients with femoropopliteal and infrapopliteal disease with or without concurrent treatment of other lower extremity arteries; (B) patients with isolated superficial femoral or popliteal artery disease; and (C) patients with characteristics approximating randomised controlled trial populations. Results from cohort C closely aligned with the registry nested trial and updated meta-analysis, while results from cohort A were more in line with previous observational studies. This study provides robust and niche real world evidence on PCD safety and helps to understand and reconcile previously discrepant findings.

Objective: This observational cohort study examined outcomes after peripheral vascular intervention (PVI) with paclitaxel coated devices (PCD) and non-PCD, and evaluated heterogeneity of treatment effect in populations of interest.

Methods: The study included patients undergoing percutaneous transluminal angioplasty and or stent placement between 1 October 2015 and 31 December 2018 in the Vascular Quality Initiative Registry linked to Medicare claims. It determined differences in patient mortality and ipsilateral major amputation after PVI with PCD and non-PCD using Kaplan—Meier analyses and Cox regressions with inverse probability weighting in three cohorts: (A) patients treated for femoropopliteal or infrapopliteal occlusive disease with or without any other concurrent treatment (n = 11 452); (B) those treated for isolated superficial femoral or popliteal artery disease (n = 5 519); and (C) patients with inclusion criteria designed to approximate RCT populations (n = 2 278).

Results: The mean age of patients was 72.3 (SD = 10.9) years, and 40.6% were female. In cohort A, patients receiving PCD had a lower mortality rate (HR 0.88, 95% CI 0.79 — 0.98) than those receiving non-PCD. There was no significant difference in mortality between groups in cohort B (HR 0.91, 95% CI 0.80 — 1.04) and cohort C (HR 1.10, 95% CI 0.84 — 1.43). Patients receiving PCD did not have a significantly elevated risk of major amputation compared with those receiving non-PCD (cohort A: HR 0.84, 95% CI 0.70 — 1.00; cohort B: HR 0.84, 95% CI 0.67 — 1.06; and cohort C: HR 1.05, 95% CI 0.51 — 2.14).

Conclusion: No increased patient mortality or major amputation was found at three years after PVI with PCD *vs.* non-PCD in this large, linked registry claims study, after accounting for heterogeneity of treatment effect by population. The analysis and results from three cohorts intended to mirror the cohorts of previous studies provide robust and niche real world evidence on PCD safety and help to understand and reconcile previously discrepant findings.

Keywords: Device safety, Drug-coated balloon, Drug eluting stent, Paclitaxel, Peripheral arterial occlusive disease, Peripheral vascular intervention
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INTRODUCTION

Paclitaxel coated devices (PCD), including drug-coated balloons (DCB) and drug eluting stents (DES), are used in the treatment of peripheral artery disease (PAD) to improve clinical outcomes and reduce re-stenosis. A meta-analysis of 12 randomised controlled trials (RCTs) reported higher mortality in patients receiving PCD for the treatment of

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femoropopliteal disease at two years compared with those receiving non-PCD.[1] The safety signal was subsequently replicated by the US Food and Drug Administration (FDA) in an internal analysis using the same data[2] and confirmed by an individual patient data (IPD) meta-analysis of eight RCTs,[3] six of which were included in the original meta-analysis. A meta-analysis also recently showed that PCD use was associated with increased amputation. However, registry and claims based observational studies in the US [4-12] and Germany,[13-15] and a registry nested RCT (Swedish Drug Elution Trial in Peripheral Arterial Disease, SWEDEPAD),[16] with follow ups ranging one to 11 years, did not find increased mortality among patients receiving PCD compared with those receiving non-PCD. Some of these studies found a survival benefit among patients receiving PCD.[6-8,12-14] Thus far, there has been no plausible biological mechanism for increased mortality and amputation, or survival benefit related to PCD.

The inconsistencies in the findings from meta-analyses of RCTs, a large registry nested RCT, and observational studies illustrate the challenges in assessing paclitaxel safety in PAD treatment. The RCTs of PCD were single blinded or unblinded, not powered for mortality assessment, and had significant losses to follow up that might not have been random. For example, the IPD meta-analysis reported that 24% of mortality data were missing.[3] After obtaining some of the missing mortality data, the investigators reported reduced magnitude of the mortality signal. Meta-analyses were also subject to publication bias. A recently updated meta-analysis, incorporating 12 additional RCTs at two years follow up, found no difference in mortality following treatment with PCD and non-PCD.[17] In addition, RCTs enrolled a selected group of patients, predominantly those with intermittent claudication, with two year mortality (approximately 10%) much lower than that in real world data (RWD) (20 — 30%). While observational studies are often criticised for having unmeasured confounding and possible misclassifications of exposure, the results from RWD have been consistent. The interim analysis of SWEDEPAD, a hybrid of an RCT and RWD, and thus minimising unmeasured confounding and misclassification, also did not find increased mortality in patients receiving PCD.[16,18] This left the scientific community with an important question: Could the discrepancies between early meta-analyses and RWD be related to differences in patient populations?

Real world data can help to fill this gap by using a robust study design to investigate heterogeneities in the association between PCD and patient mortality across various populations and minimise unmeasured confounding and misclassifications. This study examined mortality and major amputation risks within three years after PAD treatment with PCD and non-PCD, using the most up to date linkage of the Vascular Quality Initiative (VQI) registry and Medicare claims data. Taking advantage of the granular clinical data, it evaluated heterogeneities in patient mortality following treatment with PCD *vs.* non-PCD in three cohorts: (A) patients treated for femoropopliteal or infrapopliteal occlusive disease with or without any other concurrent treatment; (B) patients treated for isolated superficial femoral or popliteal artery disease; and (C) patients with inclusion criteria designed to approximate RCT populations. These cohorts were designed to broadly match interested, indicated, and RCT approximate populations, respectively.

METHODS

Data sources

The Vascular Implant Surveillance and Interventional Outcomes Network (VISION) is a coordinated registry network that links the Society for Vascular Surgery (SVS) VQI registry and claims data to improve the evaluation of vascular devices.[19,20] VISION leverages the strengths of these two data sources by combining detailed device and clinical information from the VQI with longitudinal follow up from claims. The current study created a linked dataset of the VQI Registry and Medicare claims for the current observational cohort study. The VQI[21] Peripheral Vascular Intervention (PVI) Registry started collecting data in 2010 and currently collects patient demographics, comorbidities, PAD characteristics, and procedural and device details from 354 academic and community centres nationwide. It began capturing device identifiers in the autumn of 2016 with linkage to the Global Universal Device Identifier. Clinical outcomes are collected in the registry during the index hospitalisation and at 30 days and one year following the intervention. Medicare fee for service (FFS) data contain institutional and physician claims and vital status for all eligible Medicare beneficiaries. Medicare beneficiaries include the elderly (aged $\geq$ 65 years), patients with disabilities qualifying for Social Security Disability Insurance, and those with end stage renal disease. Medicare FFS currently covers two thirds of all Medicare beneficiaries. Characteristics of FFS and Medicare Advantage beneficiaries have been shown to be very similar.[22] The current linkage between VQI and Medicare used a combined direct and indirect linkage approach. The indirect linkage has a 93% matching rate and $>$ 99% accuracy.[23] The linkage between registry and Medicare claims allows longitudinal follow up of patients who use their Medicare FFS eligibility.

Study cohort

This study identified patients undergoing their first percutaneous transluminal angioplasty and/or stent placement (hereafter, index procedure) for femoropopliteal or infrapopliteal occlusive disease in inpatient and outpatient settings during October 2015 — December 2018 from the linked VQI-Medicare data (Fig. 1). The VQI began collecting device information in September 2016, and procedure codes to identify PCD became complete in October 2015. Therefore, patients with a prior infra-inguinal PVI were excluded to avoid misclassification of the exposure variable from possible prior PCD use. Patients undergoing emergency procedures, treated for acute limb ischaemia or

aneurysmal disease, having a concurrent aortic or foot procedure, or having a concomitant femoral endarterectomy were excluded because of the higher morbidity and mortality associated with these patients. Patients with missing comorbidities (< 1% of patients) were also excluded. To ensure complete follow up, the study was restricted to patients with Medicare FFS entitlement at the time of the index procedure.

To investigate the impact of the differences between RCT and RWD patient populations on the evaluation of PCD safety, three cohorts were established. Cohort A included all patients treated for femoropopliteal and infrapopliteal occlusive disease, with or without concurrent treatment in any lower extremity artery (iliac, common femoral, and profunda arteries); this cohort represented the population of broadest interest in studies using RWD. Cohort B included patients treated for isolated superficial femoral artery and or popliteal (SFA or POP) artery disease. Paclitaxel coated devices are currently approved in the US to treat femoropopliteal diseases only. Cohort C was a subgroup of cohort B, designed to approximate populations studied in RCTs; patients with haemodialysis, tissue loss, concurrent atherectomy, or prior ipsilateral amputation were excluded from this cohort.[24-27]

Paclitaxel coated device identification

The main comparison was between patients receiving PCD *vs.* non-PCD. A subgroup analysis compared DCB with plain balloon angioplasty and DES with bare metal stents (BMS). The VQI registry collects information on procedures performed and the specific devices used in each procedure. Paclitaxel coated devices were identified using device identifiers in the VQI registry. For those whose device information was not recorded by the registry, PCD were identified using procedure codes from inpatient and outpatient institutional claims (Supplementary Table S1). In cohort A of all patients, PCD exposure was determined by

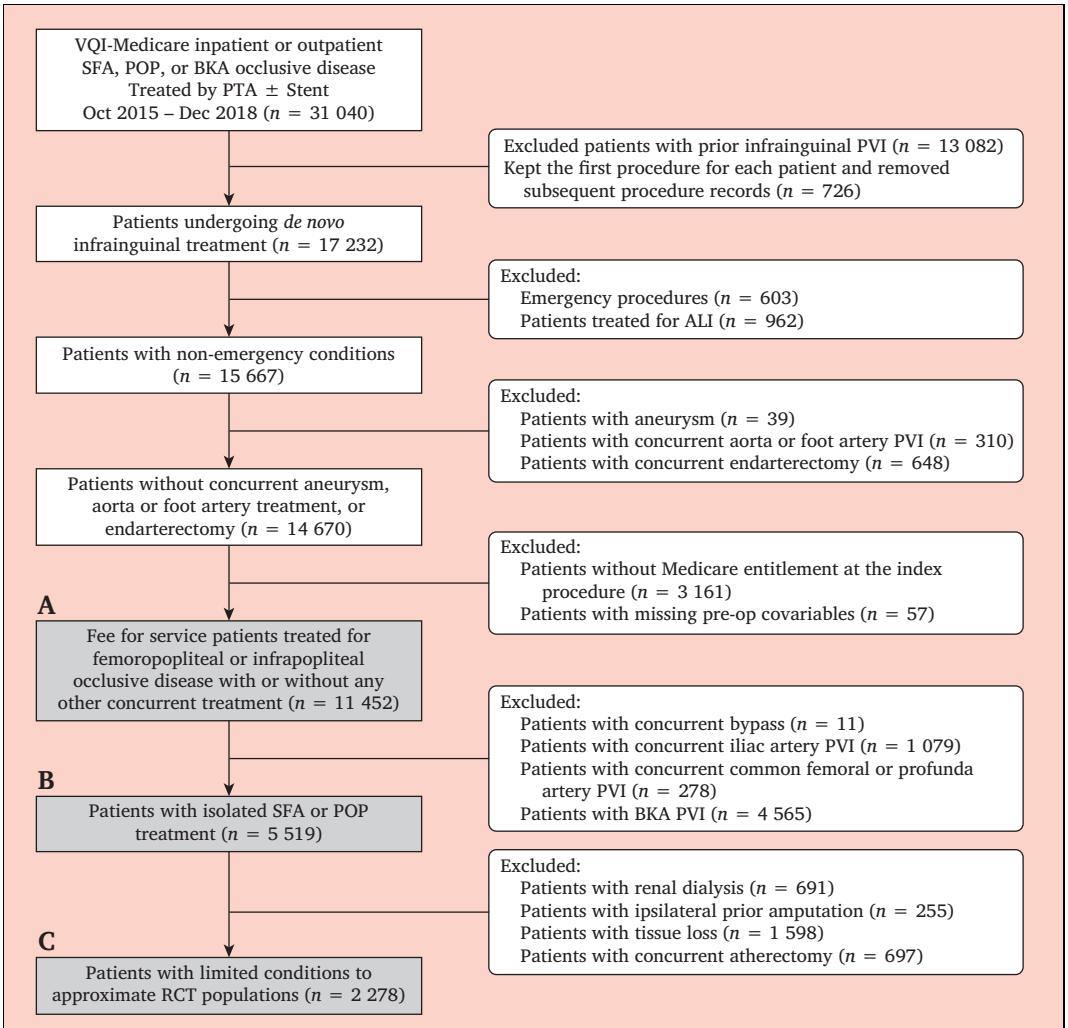

Figure 1. Flow diagram demonstrating inclusions and exclusions of patients undergoing peripheral vascular interventions with paclitaxel coated device (PCD) and non-PCD and the three cohorts of study patients: full cohort (A), isolated superficial femoral artery or popliteal artery (SFA or POP) cohort (B), and randomised controlled trial (RCT) approximate cohort (C). ALI = acute limb ischaemia; BKA = below knee artery; PTA = percutaneous angioplasty; PVI = peripheral vascular intervention; VQI = vascular quality initiative.

identifying the use of DCB or DES in the treatment of any of the lower extremity arteries.

Outcomes

The primary outcome was all cause mortality following the initial intervention. Mortality was identified from the Medicare Master Beneficiary Summary File. Overall, 99% of Medicare mortality data were validated. The secondary outcome was ipsilateral major amputation, defined as any above ankle amputation (above or below knee) in the same limb(s) treated in the index procedure. Major amputation was identified from Medicare claims using ICD-10 and CPT procedure codes. Laterality was determined by the side information in ICD-10 codes and CPT modifiers. In the current study, 95% of patients had follow up from Medicare claims until the end of the study or death. The 5% of patients who dropped out of Medicare FFS were censored in the survival analysis.

Important covariables

Covariables identified from VQI and Medicare data were patient demographics, BMI, smoking history, comorbidities, pre-operative ambulation, limb symptomatology, prior lower extremity amputations and interventions, procedural characteristics, stent placement, concurrent atherectomy or bypass, place of service, and pre-operative and discharge medication. Post-index paclitaxel exposures from additional PVI, treatment of dialysis fistula, or chemotherapy were identified from Medicare claims data using procedure codes. Post-index paclitaxel exposure was only considered among patients receiving non-PCD, assuming that the exposure to paclitaxel cannot be undone once it has occurred.

Statistical analysis

Descriptive analyses were performed to examine and compare characteristics between patients receiving PCD and non-PCD at the index PVI procedure. Student's *t* tests were used for BMI and Chi square tests for categorical variables. Because the distribution of length of follow up was skewed, it was reported in median and range.

Patient death and major amputations after PVIs with PCD *vs.* non-PCD were examined using inverse probability weighting. An inverse probability treatment weight was used to adjust for confounding and an inverse probability censoring weight (IPCW) to address post-index paclitaxel exposure (crossover). Inverse probability treatment weight was used to adjust for differences in patients' baseline characteristics between the PCD and non-PCD groups. A logistic regression model was used to obtain the probability of receiving PCD. The covariables that were used were pre-operative or procedural variables that were hypothesised confounders or potential confounders (i.e., variables associated with death but not necessarily treatment).[28] These included patient demographics, smoking status, comorbidities, disease characteristics and severity, procedure characteristics, and pre-operative medication. The treatment weight for each individual was the inverse of the probability of receiving the device that they actually received. The stabilised treatment weight was calculated by using the marginal probability of the actual treatment as the numerator. Patients who had a crossover in the non-PCD group were then artificially censored to create a selection bias and it was adjusted using IPCW.[29] A logistic regression model was used to obtain the probability of being censored for crossover. Covariables used in the logistic regression model were variables that could affect patients' subsequent likelihood of re-interventions, including patient demographics, lifestyle factors, comorbidities, pre-operative ambulation, disease characteristics and severity variables, procedure urgency, concurrent procedures, and pre-operative and discharge medication. The censoring weight for each individual was the inverse of the probability of being censored for crossover given their characteristics. Using IPCW, censored patients would be represented by uncensored ones who had similar probabilities of having a crossover. The censoring weight for patients in the PCD group was 1, as no crossover occurred. The assumption of this approach was that patients' baseline conditions directly or indirectly gave rise to the crossover. The final weight was the stabilised treatment weight multiplied by the censoring weight. Balances in patient characteristics before and after weighting were examined using standardised mean differences (Supplementary Fig. S1).

This study analysed all cause mortality and major amputation using a time to event analysis. Patients were censored at the end of study (31 December 2018) or the end of FFS entitlement, whichever was earlier. Patient death and the risk of major amputation following index PVIs at one, two, and three years were estimated using a Kaplan—Meier analysis and then compared between those receiving PCD and non-PCD using a Cox regression model. For the weighted analysis, a marginal Cox regression with a robust sandwich variance estimator was used. The hazard ratio (HR) for mortality from the weighted analysis was interpreted as the difference in mortality had all patients received PCD at the initial procedure *vs.* had all patients received non-PCD at the initial procedure and never switched groups. A sensitivity analysis was performed using propensity score matching among patients who did not have crossover; one was also performed for major amputation using Fine and Gray competing risk analysis.[30]

Subgroup analyses were based on the SFA or POP cohort B because this cohort was more homogeneous than the full cohort A, and had more power than the RCT approximate cohort C. They were stratified by patient sex, limb symptoms (claudication and critical limb threatening ischaemia [CLTI]), and device type (balloon or stent). Drug coated balloons were compared with plain balloon angioplasty among patients who received angioplasty without stent placement. Drug eluting stents were compared with BMS among patients who had stent placement without DCB. All analyses were performed using SAS 9.4 (Cary, NC).

Ethical approval

The Weill Cornell Medicine Institutional Review Board approved using the linked database for research purposes and did not require written informed consent.

RESULTS

There were 11 452 patients who underwent PVI between October 2015 and December 2018 and who met the inclusion criteria for the broadest cohort (cohort A). The mean age of patients was 72.3 (SD 10.9) years, and 40.6% were female. Among these patients, 5 519 (48.2%) were treated for isolated femoropopliteal disease (cohort B), and 2 278 (19.9%) were included in the RCT approximate cohort (cohort C). Paclitaxel coated devices were used in 4 982 (43.5%), 2 895 (52.5%), and 1 184 (52.0%) patients in cohorts A, B, and C, respectively. Patients receiving PCD were more likely to be female and white race, and less likely to have comorbidities such as diabetes, congestive heart failure, and haemodialysis than those receiving non-PCD (Table 1, Supplementary Table S2). Patients receiving PCD were more likely to have CLTI, urgent procedures, adjunctive atherectomy, and be inpatients than those receiving non-PCD.

In the full cohort (A), patients receiving PCD were more likely to have stents than those receiving non-PCD. When limiting to patients treated for isolated femoropopliteal diseases (cohorts B and C), those receiving PCD were less likely to undergo stent placement than those receiving non-

Table 1. Selected characteristics of 11 452 patients undergoing peripheral vascular interventions with a paclitaxel coated device (PCD) and non-PCD during 2015 – 2018, identified in the Vascular Quality Initiative Registry linked to Medicare claims

	Non-PCD	PCD	*p* value
Full cohort (A) – n	6 470	4 982	
Age at index – y	71 (65–80)	72 (66–80)	<.001
Female sex	2 459 (38)	2 189 (44)	<.001
White race	4 744 (73)	4 046 (81)	<.001
*Limb symptom**			<.001
Asymptomatic	184 (2.8)	113 (2.3)	
Claudication	1 431 (22)	2 000 (40)	
Rest pain	896 (14)	621 (12)	
Tissue loss	3 959 (61)	2 248 (45)	
Urgent procedure	1 282 (20)	623 (13)	<.001
Stent placement	2 463 (38)	2 306 (46)	<.001
Concurrent atherectomy	1 090 (17)	1 477 (30)	<.001
Inpatient procedure	3 458 (53)	1 815 (36)	<.001
Follow up paclitaxel exposure	698 (11)	NA	
Isolated SFA or POP cohort (B) – n	2 624	2 895	
Age at index – y	72 (65–80)	72 (66–79)	.66
Female sex	1 161 (44)	1 347 (47)	.090
White race	2 018 (77)	2 391 (83)	<.001
*Limb symptom**			<.001
Asymptomatic	81 (3.1)	73 (2.5)	
Claudication	876 (33)	1 392 (48)	
Rest pain	441 (17)	343 (12)	
Tissue loss	1 226 (47)	1 087 (38)	
Urgent procedure	452 (17)	309 (11)	<.001
Stent placement	1 491 (57)	1 219 (42)	<.001
Concurrent atherectomy	336 (13)	813 (28)	<.001
Inpatient procedure	1 208 (46)	911 (31)	<.001
Follow up paclitaxel exposure	326 (12)	NA	
RCT approximate cohort (C) – n	1 094	2 895	
Age at index – y	72 (67–80)	72 (67–79)	.47
Female sex	460 (42)	559 (47)	.010
White race	903 (83)	1 029 (87)	.009
*Limb symptom**			<.001
Asymptomatic	67 (6.1)	42 (3.5)	
Claudication	704 (64)	920 (78)	
Rest pain	323 (30)	222 (19)	
Tissue loss	0 (0)	0 (0)	
Urgent procedure	123 (11)	57 (4.8)	<.001
Stent placement	692 (63)	632 (53)	<.001
Concurrent atherectomy	0 (0)	0 (0)	–
Inpatient procedure	328 (30)	200 (17)	<.001
Follow up paclitaxel exposure	150 (14)	NA	

Data are presented as *n* (%) or median (interquartile range). "NR, not reportable" or "<11" or ">xx": cannot disclose N <11 per Data Use Agreement requirement

* If bilateral procedures were performed, used the symptom of the more severe side.

Table 2. Cox regression analyses for patient mortality and major amputation rates following paclitaxel coated device (PCD) vs. non-PCD, primary and subgroup analyses of total 11 452 patients undergoing peripheral vascular interventions during 2015 –2018, identified in the Vascular Quality Initiative Registry linked to Medicare claims

	Mortality		Major amputation	
	Crude analysis HR (95% CI)	Weighted analysis HR (95% CI)	Crude analysis HR (95% CI)	Weighted analysis HR (95% CI)
Primary analysis				
Full cohort (A)	0.68 (0.63–0.74)	0.88 (0.79–0.98)*	0.51 (0.45–0.58)	0.84 (0.70–1.00)*
Isolated SFA/POP cohort (B)	0.68 (0.61–0.77)	0.91 (0.80–1.04)	0.59 (0.48–0.71)	0.84 (0.67–1.06)
RCT approximate cohort (C)	0.81 (0.64–1.04)	1.10 (0.84–1.43)	0.55 (0.30–1.03)	1.05 (0.51–2.14)
Subgroup analyses within isolated SFA or POP cohort (B)				
By sex				
Male	0.66 (0.57–0.77)	0.91 (0.74–1.13)	0.65 (0.51–0.84)	1.03 (0.70–1.50)
Female	0.71 (0.60–0.84)	0.97 (0.81–1.16)	0.49 (0.36–0.69)	0.71 (0.50–1.01)
By limb symptom				
Claudication	0.91 (0.68–1.20)	1.06 (0.77–1.47)	0.54 (0.26–1.12)	1.03 (0.42–2.56)
CLTI	0.81 (0.72–0.93)	0.90 (0.78–1.04)	0.77 (0.63–0.95)	0.85 (0.67–1.08)
By device				
Angioplasty DCB *vs.* plain balloon	0.68 (0.58–0.79)	1.02 (0.84–1.24)	0.47 (0.36–0.61)	0.80 (0.56–1.15)
Stent placement DES *vs.* BMS	0.67 (0.55–0.82)	0.86 (0.68–1.08)	0.66 (0.45–0.95)	0.93 (0.62–1.39)

SFA = superficial femoral artery; POP = popliteal artery; CLTI = chronic limb threatening ischaemia; DCB = drug coated balloon; DES = drug eluting stent; BMS = bare metal stent; HR = hazard ratio; CI = confidence interval.
* Additionally adjusted for stent placement, which was not well balanced in the weighted full cohort.

PCD. Patients receiving PCD were more likely to use statin and antiplatelet medication pre-operatively and at discharge than those receiving non-PCD. The difference in medication use between device groups became smaller in the RCT approximate cohort (C).

Main analysis

The median length of follow up was 1.0 year, with a range of 0 — 3.3 years. In the unadjusted analysis, patients receiving PCD had a lower mortality rate than those receiving non-PCD in the full cohort (A: HR 0.68, 95% CI 0.63 — 0.74) and the isolated SFA or POP cohort (B: HR 0.68, 95% CI 0.61 — 0.77) (Table 2, Supplementary Fig. S2). No difference was observed in mortality between groups in the RCT approximate cohort (C: HR 0.81, 95% CI 0.64 — 1.04). After weighting, patients receiving PCD had a 12% lower risk of death than those receiving non-PCD in cohort A (HR 0.88, 95% CI 0.79 — 0.98) (Table 2, Fig. 2). There was no statistically significant difference in mortality between groups in cohorts B (HR 0.91, 95% CI 0.80 — 1.04) and C (HR 1.10, 95% CI 0.84 — 1.43). Sensitivity analysis using propensity score matching showed consistent results that there was no difference in mortality between groups after limiting to the RCT approximate cohort (Supplementary Table S3).

In the unadjusted analysis, patients receiving PCD had a lower risk of major amputation than those receiving non-PCD in all three cohorts (Supplementary Fig. S3). After weighting, no statistically significant difference in the risk of major amputation was observed among patients treated with PCD compared with those treated with non-PCD in cohorts A (HR 0.84, 95% CI 0.70 — 1.00) and B (HR 0.84, 95% CI 0.67 — 1.06). No difference in amputation risk was observed between groups in cohort C (HR 1.05, 95% CI 0.51 — 2.14) (Fig. 2, Table 2). Results from the competing risk analysis were consistent with those from the main analysis (Supplementary Table S4).

Subgroup analyses

Within the isolated SFA or POP cohort B, there was no difference in mortality or major amputation rates between the PCD and non-PCD groups for males, females, and patients with claudication or CLTI (Supplementary Fig. S4 — S6, Table 2). Among patients undergoing angioplasty without stent placement, there was no difference in mortality or major amputation rate between patients treated with DCB *vs.* plain balloons. Among patients undergoing stent placement without DCB, there was no difference in mortality or major amputation rate between patients treated with DES *vs.* BMS.

DISCUSSION

This study used a national vascular registry linked to Medicare and obtained comprehensive long term follow up for patients undergoing PVI. It did not find increased mortality or amputation rates among patients receiving PCD compared with those receiving non-PCD in any cohort, including the population that approximated RCTs. In the entire cohort of patients undergoing PVI for femoropopliteal and infrapopliteal disease with concurrent treatment in any lower extremity artery (A), those receiving PCD had slightly lower risks of death than those receiving non-PCD. But the reduction in mortality associated with

PCD was numerically lower in the isolated SFA or POP cohort (B), absent in the RCT approximate cohort (C), and not statistically significant in either population.

The linkage of a national registry and claims database combined granular baseline patient, disease, anatomic, and procedural characteristics with longitudinal follow up and included a large, representative patient population. The validity and value of claims based mortality assessment have been demonstrated in previous RCTs.[31] Compared with previous studies relying on claims data alone, the linked data more accurately captured device and disease information; this helped to minimise exposure misclassification from prior PCD use and unmeasured confounding. It was also able to consider real world situations such as off label device use and post-index paclitaxel exposure. Additionally, the linked data enabled investigation as to whether

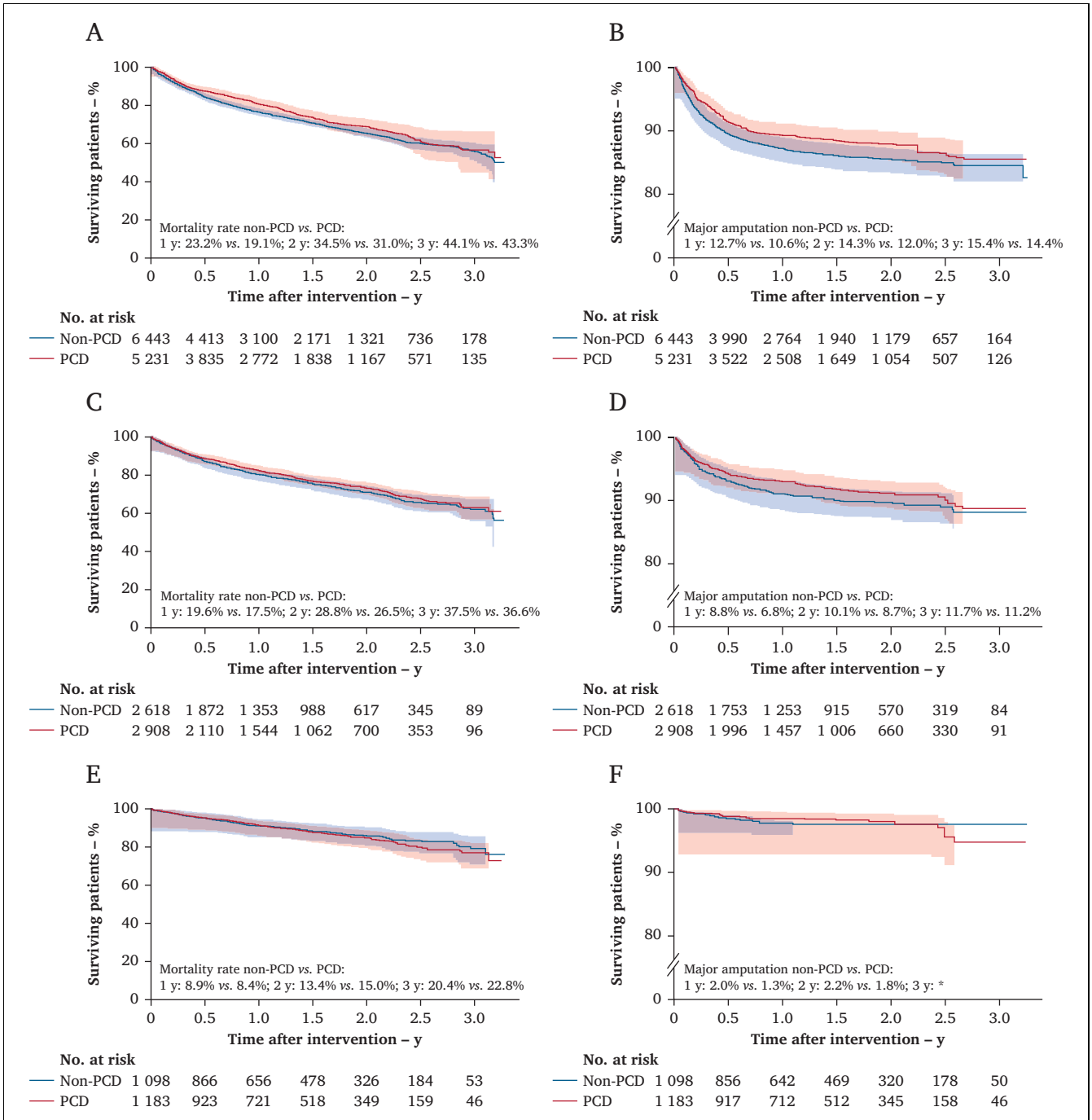

Figure 2. Cumulative Kaplan–Meier estimates of (A, C, E) patient survival and (B, D, F) ipsilateral major amputation for patients undergoing peripheral vascular interventions with paclitaxel coated device (PCD) *vs.* non-PCD in the full cohort (A – B), the isolated superficial femoral artery or popliteal artery (SFA/POP) cohort (C – D), and the randomised controlled trial (RCT) approximate cohort (E – F), weighted analysis. Note the adapted scale for y axis in B, D and F. *No amputation event in the third year for the non-PCD group in the RCT approximate cohort to provide Kaplan–Meier estimate.

the difference in the mortality findings from meta-analyses of RCTs and RWD had been related to the different patient populations enrolled in RCTs. Previous studies have examined the effect of PCD in subgroups stratified by sex, disease symptom, procedure location, or comorbidities.[8,11,12,32] The current study used rich linked data and a holistic approach to design a cohort approximating RCT participants; this approach improved the effect modifier assessment and made the results more interpretable within the context of previous studies.

The current results indicated that the hazard ratio for PCD *vs.* non-PCD treatment became less positive as the included analytical population became more similar to those enrolled in RCTs. This trend could have been due to many factors. Cohort A captured patients undergoing PVI for femoropopliteal and infrapopliteal disease with/without concurrent treatment in any lower extremity artery and represented the population of broadest interest in previous RWD research. The effect measure for mortality from this cohort was in line with most observational studies (Fig. 3), whereas the absolute risk and effect measure for mortality from the RCT approximate cohort (C) more closely aligned with those from SWEDEPAD[16] and the updated meta-analysis.[17] Cohort A included patients with increased disease burden, who were progressively more likely to be excluded from cohorts B and C. Thus, for cohort A, PCD related mortality or amputation, if any, would be relatively small compared with the risks posed by their existing comorbidities. Paclitaxel coated devices were used among healthier patients who were less likely to have comorbidities and CLTI, undergo urgent procedures, and receive care in inpatient settings. Hence, there may have been residual confounding in observational studies, even with the most rigorous statistical adjustments. Additional restrictions were used in cohort C to achieve a more homogeneous population.

Additionally, discrepancies in results from the current study and earlier meta-analyses need to be interpreted in the context of the limitations of meta-analyses. Meta-analyses are constrained by the availability of published evidence and heterogeneities between studies. Only some of the existing RCTs of PCD had two year and five year follow ups at the time of earlier meta-analyses of mortality.[1-3] A recent meta-analysis reported a higher risk of major amputation at two years among those receiving PCD than those receiving non-PCD.[33] However, this study included a mixture of heterogeneous RCTs, pooling together patients receiving treatment for femoropopliteal and or infrapopliteal disease and those receiving *de novo* treatment or treatment for in stent stenosis. These patient groups have very different risks of amputation after treatment.

The late mortality signal associated with the use of peripheral PCD has been subject to intense investigations and debate over the past three years and had significant regulatory implications. After reviewing the initial evidence, the FDA issued a communication recommending consideration of alternative devices and patient preferences in PAD treatment while leaving PCD available for clinical use.[34] The European regulators requested

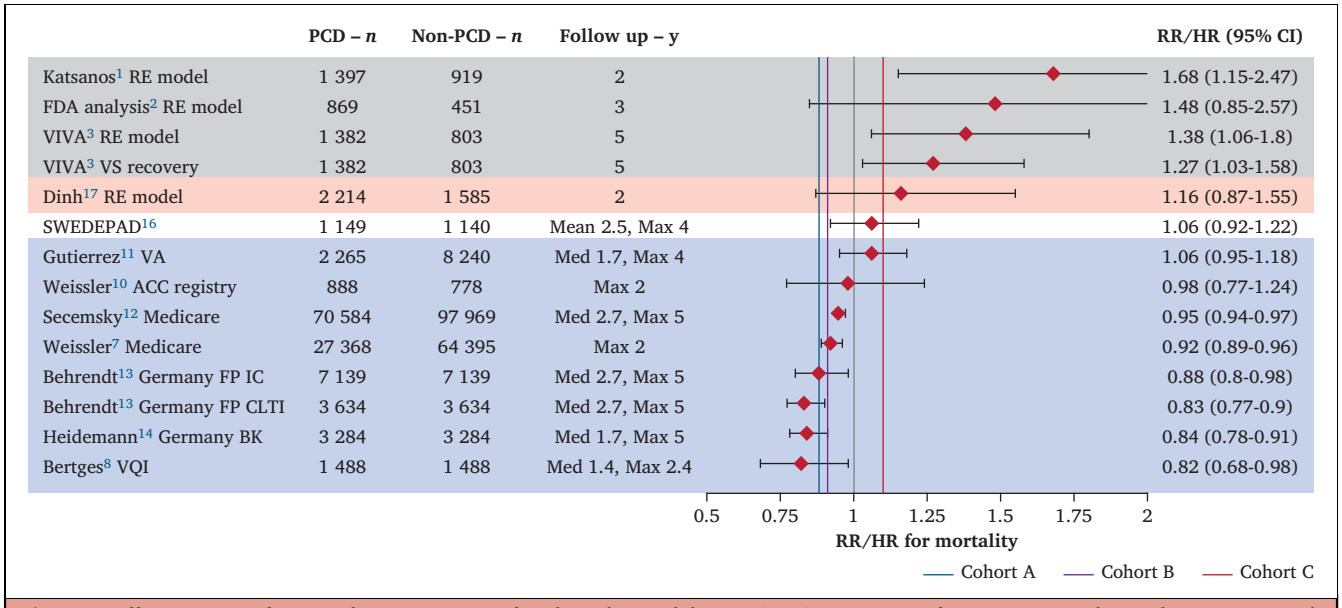

Figure 3. Effect measures for mortality comparison of paclitaxel coated devices (PCD) *vs.* non-PCD from existing studies and current research in patients undergoing peripheral vascular interventions. Gray shading indicates early meta-analyses of randomised controlled trials (RCTs), red shading indicates updated meta-analysis of RCTs, white indicates registry nested RCT, and blue shading indicates observational studies. Vertical lines indicate hazard ratio for death from the current study for full cohort, isolated femoral artery or popliteal artery (SFA or POP) cohort and RCT approximate cohort. Katsanos *et al.*, FDA analysis, and Dinh *et al.* also presented five year outcomes but included fewer RCTs and were thus not shown. RE = random effect; VA = Veterans Administration; ACC = American College of Cardiology; FP = femoropopliteal; IC = intermittent claudication; CLTI = chronic limb threatening ischaemia; BK = below knee; VQI = Vascular Quality Initiative; Med = median; Max = maximum.

manufacturers to add a warning to the indications for use for PCD and encouraged the physicians to discuss benefits and risks of PAD treatment with patients.[35] When paclitaxel DES was embroiled in the controversy in the context of coronary artery disease over 15 years ago,[36] RWD had a minor role in helping clarify the question. Today, clinical and scientific communities are able to deploy RWD and RCTs in a complementary way to address the uncertainties surrounding peripheral PCD. The effective use of robust RWD highlights its value in the evaluation of controversial signals, particularly when multiple stakeholder groups collaborate to proactively design a study that can optimally meet their mutual needs. Randomised controlled trials are often underpowered for long term safety assessments due to costs and difficulties in enrolment. When designed with sufficient scientific rigor and conducted with robust follow up compliance, RWD research can help balance the potential limitations associated with evidence from RCTs.

The current study had some limitations. It was restricted to Medicare beneficiaries in the US. Most Medicare beneficiaries are aged $\geq$ 65 years and the results may not be entirely generalisable to younger patients. The linked data included only centres participating in the VQI and caution should be exercised when generalising results to centres not participating in registries. Device information was not collected for 33% of patients in the registry and was determined based on procedure codes, which may have been subject to coding errors. The current data were used to validate the procedure codes, and the sensitivity and specificity were found to be 80% and 95%, respectively. The sensitivity and specificity of procedure codes in identifying PCD were consistent with those reported in a recent study.[37] Due to logistic difficulties, paclitaxel use in dialysis fistula treatment and chemotherapy could not be ascertained before the index procedure. Although uncommon, these may have resulted in some misclassification of the paclitaxel exposure. The attempt to construct a cohort similar to the RCT population was imperfect and could not account for all inclusion and exclusion criteria used in previous RCTs. There might also have been residual confounding, such as socio-economic status. The analyses of cohorts B and C were subject to lower power due to the smaller sample sizes, and the non-significant results may be a potential type II statistical error. Laterality was missing for 2.9% of the major amputations in the full cohort and was imputed as the index side. Due to the lack of availability of patient data at longer time points, only three year mortality was assessed in the current study. Further monitoring of PCD performance is warranted to ensure patient safety.

To conclude, this study did not find an increased patient mortality or major amputation rate at three years after PVI with PCD *vs.* non-PCD in this large, linked registry claims study. The analysis and results from three cohorts intended to mirror the cohorts of previous studies to provide robust and niche real world evidence on PCD safety and help understand and reconcile previously discrepant findings.

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DISCLOSURES

None.

AUTHOR CONTRIBUTIONS

Conception and design of the study: Mao, Sedrakyan, Bertges; acquisition of data: Mao, Sedrakyan, Goodney; statistical analysis: Mao; analysis and interpretation of data: all authors; drafting the manuscript: Mao, Sedrakyan, Bertges; critical revising the manuscript for important intellectual content: all authors; supervision: Sedrakyan, Bertges; final approval of the article: all authors.

APPENDIX A. SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejvs.2022.08.014.

REFERENCES

1 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**:e011245.

2 U.S. Food and Drug Administration. *FDA Executive Summary. Paclitaxel-Coated Drug Coated Balloon and Drug-Eluting Stent Late Mortality Panel*. U.S. Food and Drug Administration; 2019. Available at: https://www.fda.gov/media/127698/download [Accessed 25 June 2021].

3 Rocha-Singh KJ, Duval S, Jaff MR, Schneider PA, Ansel GM, Lyden SP, et al. Mortality and paclitaxel-coated devices: an individual patient data meta-analysis. *Circulation* 2020;**141**:1859–69.

4 Secemsky EA, Kundi H, Weinberg I, Jaff MR, Krawisz A, Parikh SA, et al. Association of survival with femoropopliteal artery revascularization with drug-coated devices. *JAMA Cardiol* 2019;**4**:332–40.

5 Secemsky EA, Kundi H, Weinberg I, Schermerhorn M, Beckman JA, Parikh SA, et al. Drug-eluting stent implantation and long-term survival following peripheral artery revascularization. *J Am Coll Cardiol* 2019;**73**:2636–8.

6 Long CA, Zepel L, Greiner MA, Hammill BG, Patel MR, Jones WS. Use and 1-year outcomes with conventional and drug-coated balloon angioplasty in patients with lower extremity peripheral artery disease. *Am Heart J* 2019;**217**:42–51.

7 Weissler EH, Zepel L, Greiner M, Hammill BG, Long CA, Patel MR, et al. No increase in all-cause mortality at 2 years among patients undergoing drug-coated balloon angioplasty. *JACC Cardiovasc Int* 2020;**13**:902–4.

8 Bertges DJ, Sedrakyan A, Sun T, Eslami MH, Schermerhorn M, Goodney PP, et al. Mortality after paclitaxel coated balloon angioplasty and stenting of superficial femoral and popliteal artery in the vascular quality initiative. *Circ Cardiovasc Interv* 2020;**13**:e008528.

9 Secemsky EA, Barrette E, Bockstedt L, Bonaca MP, Hess CN, Hanson T, et al. Long-term safety of drug-coated devices for peripheral revascularisation. *EuroIntervention* 2020.
10 Weissler EH, Annapureddy A, Wang Y, Secemsky EA, Shishehbor MH, Mena-Hurtado C, et al. Paclitaxel-coated devices in the treatment of femoropopliteal stenosis among patients ≥65 years old: An ACC PVI Registry Analysis. *Am Heart J* 2021;**233**:59–67.
11 Gutierrez JA, Rao SV, Jones WS, Secemsky EA, Aday AW, Gu L, et al. Survival and causes of death among veterans with lower extremity revascularization with paclitaxel-coated devices: insights from the Veterans Health Administration. *J Am Heart Assoc* 2021;**10**:e018149.
12 Secemsky EA, Shen C, Schermerhorn M, Yeh RW. Longitudinal Assessment of safety of femoropopliteal endovascular treatment with paclitaxel-coated devices among Medicare beneficiaries: The SAFE-PAD Study. *JAMA Intern Med* 2021.
13 Behrendt CA, Sedrakyan A, Peters F, Kreutzburg T, Schermerhorn M, Bertges DJ, et al. Editor's Choice - long term survival after femoropopliteal artery revascularisation with paclitaxel coated devices: a propensity score matched cohort analysis. *Eur J Vasc Endovasc Surg* 2020;**59**:587–96.
14 Heidemann F, Peters F, Kuchenbecker J, Kreutzburg T, Sedrakyan A, Marschall U, et al. Long-term outcomes after revascularisations below the knee with paclitaxel coated devices: a propensity score matched cohort analysis. *Eur J Vasc Endovasc Surg* 2020;**60**:549–58.
15 Freisinger E, Koeppe J, Gerss J, Goerlich D, Malyar NM, Marschall U, et al. Mortality after use of paclitaxel-based devices in peripheral arteries: a real-world safety analysis. *Eur Heart J* 2020;**41**:3732–9.
16 Nordanstig J, James S, Andersson M, Andersson M, Danielsson P, Gillgren P, et al. Mortality with paclitaxel-coated devices in peripheral artery disease. *N Engl J Med* 2020;**383**:2538–46.
17 Dinh K, Limmer AM, Chen AZL, Thomas SD, Holden A, Schneider PA, et al. Mortality rates after paclitaxel-coated device use in patients with occlusive femoropopliteal disease: an updated systematic review and meta-analysis of randomized controlled trials. *J Endovasc Ther* 2021. 15266028211023505.
18 Bjorck M, Dick F. No Increased mortality risk following paclitaxel treatment in a large Swedish registry based randomised controlled trial - reassuring patient safety. *Eur J Vasc Endovasc* 2021;**61**:5–6.
19 Tsougranis G, Eldrup-Jorgensen J, Bertges D, Schermerhorn M, Morales P, Williams S, et al. The Vascular Implant Surveillance and Interventional Outcomes (VISION) Coordinated Registry Network: An effort to advance evidence evaluation for vascular devices. *J Vasc Surg* 2020;**72**:2153–60.
20 Hoel AW, Faerber AE, Moore KO, Ramkumar N, Brooke BS, Scali ST, et al. A pilot study for long-term outcome assessment after aortic aneurysm repair using Vascular Quality Initiative data matched to Medicare claims. *J Vasc Surg* 2017;**66**:751–9.
21 Cronenwett JL, Kraiss LW, Cambria RP. The Society for Vascular Surgery Vascular Quality Initiative. *J Vasc Surg* 2012;**55**:1529–37.
22 Jacobson G, Cicchiello A, Sutton J, Shah A. Medicare Advantage vs. traditional Medicare: how do beneficiaries' characteristics and experiences differ? *CMWF* 2021.
23 Mao J, Moore KO, Columbo JA, Mehta KS, Goodney PP, Sedrakyan A. Validation of an indirect linkage algorithm to combine registry data with Medicare claims. *J Vasc Surg* 2022.
24 Laird JR, Schneider PA, Tepe G, Brodmann M, Zeller T, Metzger C, et al. Durability of treatment effect using a drug-coated balloon for femoropopliteal lesions: 24-month results of IN.PACT SFA. *J Am Coll Cardiol* 2015;**66**:2329–38.
25 Rosenfield K, Jaff MR, White CJ, Rocha-Singh K, Mena-Hurtado C, Metzger DC, et al. Trial of a paclitaxel-coated balloon for femoropopliteal artery disease. *N Engl J Med* 2015;**373**:145–53.
26 Schroeder H, Werner M, Meyer DR, Reimer P, Kruger K, Jaff MR, et al. Low-dose paclitaxel-coated versus uncoated percutaneous transluminal balloon angioplasty for femoropopliteal peripheral artery disease: one-year results of the ILLUMENATE European randomized clinical trial (randomized trial of a novel paclitaxel-coated percutaneous angioplasty balloon). *Circulation* 2017;**135**:2227–36.
27 Krishnan P, Faries P, Niazi K, Jain A, Sachar R, Bachinsky WB, et al. Stellarex drug-coated balloon for treatment of femoropopliteal disease: twelve-month outcomes from the randomized ILLUMENATE pivotal and pharmacokinetic studies. *Circulation* 2017;**136**:1102–13.
28 Austin PC. An Introduction to propensity score methods for reducing the effects of confounding in observational studies. *Multivariate Behav Res* 2011;**46**:399–424.
29 Seaman SR, White IR. Review of inverse probability weighting for dealing with missing data. *Stat Methods Med Res* 2013;**22**:278–95.
30 Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc* 1999;**94**:496–509.
31 Sweeting MJ, Patel R, Powell JT, Greenhalgh RM, Investigators ET. Endovascular repair of abdominal aortic aneurysm in patients physically ineligible for open repair: very long-term follow-up in the EVAR-2 randomized controlled trial. *Ann Surg* 2017;**266**:713–9.
32 Behrendt CA, Sedrakyan A, Katsanos K, Nordanstig J, Kuchenbecker J, Kreutzburg T, et al. Sex disparities in long-term mortality after paclitaxel exposure in patients with peripheral artery disease: a nationwide claims-based cohort study. *J Clin Med* 2021:10.
33 Katsanos K, Spiliopoulos S, Teichgraber U, Kitrou P, Del Giudice C, Bjorkman P, et al. Risk of major amputation following application of paclitaxel coated balloons in the lower limb arteries: a systematic review and meta-analysis of randomised controlled trials. *Eur J Vasc Endovasc Surg* 2021.
34 U.S. Food and Drug Administration. *August 7, 2019 UPDATE: Treatment of peripheral arterial disease with paclitaxel-coated balloons and paclitaxel-eluting stents potentially associated with increased mortality*. 2019. Available at: https://www.fda.gov/medical-devices/letters-health-care-providers/august-7-2019-update-treatment-peripheral-arterial-disease-paclitaxel-coated-balloons-and-paclitaxel [Accessed 15 June 2021].
35 Agence Nationale de Sécurité du Médicament (ANSM). *Ballons recouverts de paclitaxel et stents à élution de paclitaxel*. 2020. Available at: https://ansm.sante.fr/informations-de-securite/ballons-recouverts-de-paclitaxel-et-stents-a-elution-de-paclitaxel [Accessed 15 June 2021].
36 Stettler C, Wandel S, Allemann S, Kastrati A, Morice MC, Schomig A, et al. Outcomes associated with drug-eluting and bare-metal stents: a collaborative network meta-analysis. *Lancet* 2007;**370**:937–48.
37 Raja A, Dicks A, Sardar P, Schermerhorn ML, Yeh RW, Secemsky EA. Accuracy of administrative claims codes for identifying devices used in endovascular femoropopliteal artery revascularisation: a retrospective observational study at two tertiary centres in the United States. *Eur J Vasc Endovasc Surg* 2022;**63**:769–70.