Use and 1-year outcomes with conventional and drug-coated balloon angioplasty in patients with lower extremity peripheral artery disease

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Abstract Background With the growing use of drug-coated balloons for the treatment of peripheral artery disease, information regarding the safety and effectiveness of drug-coated balloons in current practice is needed. We examined patient, physician, and procedural characteristics as well as cardiovascular and limb events in patients who underwent peripheral vascular intervention with drug-coated balloons.

Methods This is a retrospective cohort analysis utilizing Medicare data for 100% of fee-for-service beneficiaries from 2015 to 2016 who had a claim for femoropopliteal intervention. The use of drug-coated balloons was identified via specific transitional pass-through codes. All-cause mortality, all-cause hospitalization, repeat femoropopliteal intervention, and major lower extremity amputation at 1 year were the clinical outcomes of interest.

Results In total, 83,225 patients underwent femoropopliteal intervention, and drug-coated balloons were utilized in 29% of all procedures. Patients treated with drug-coated balloons had a lower cumulative incidence of all-cause hospitalization, all-cause mortality, and major lower extremity amputation, but were more likely to undergo repeat femoropopliteal intervention when compared with patients treated with conventional balloon angioplasty. After adjustment for measured confounders, patients treated with drug-coated balloons had lower rates of hospitalization (HR 0.91 (0.88, 0.93), $P < .001$), all-cause mortality (HR 0.89 [0.84, 0.94], $P < .001$), and major amputation (HR 0.93 [0.88, 0.99], $P = .017$).

Conclusions Patients who underwent femoropopliteal intervention with drug-coated balloons had lower observed rates of all-cause mortality, all-cause hospitalization, and major amputation at 1 year. Interestingly, there was not a reduction in rates of repeat revascularization, and further work is required to understand this finding. Nevertheless, the use of drug-coated balloons appears to be safe in this large study of contemporary patients in the United States. (Am Heart J 2019;217:42-51.)

"What is known"

- The use of drug-coated balloons in peripheral endovascular intervention has grown over the last 5 years.
- Recently, a meta-analysis by Katsanos et al has reported a significantly higher hazard of all-cause mortality in patients treated with drug-coated balloons.
- Despite the meta-analysis findings, clinicians and researchers have had difficulty with understanding the biologic plausibility of paclitaxel-associated mortality events in PAD patients and little real-world evidence exists to confirm or refute the findings from Katsanos et al.

"What the study adds"

- This is a study of all comers undergoing femoropopliteal peripheral endovascular intervention in Medicare patients, and the unadjusted risks of all-cause mortality following index revascularization are significantly lower in patients treated with DCB.

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- After adjustment for differences in baseline characteristics and medication use, the risks of all-cause mortality were attenuated; however, those patients treated with DCB had lower risks of all-cause hospitalization and amputation.

Peripheral artery disease (PAD) affects more than 200 million people worldwide, with a prevalence that increases substantially after 50 years of age.[1-3] Despite medical therapy and lifestyle modification (including exercise training), many patients remain symptomatic and require peripheral endovascular intervention (PVI). Stenosis and/or occlusion of the femoropopliteal segment is frequently encountered in the treatment of these patients, and multiple endovascular strategies exist (eg, conventional balloon angioplasty (PTA), drug-coated balloon (DCB) angioplasty, atherectomy, stenting). Recently, a tremendous amount of research and development has been leveraged towards DCB and drug-eluting stent technology (mostly centered on paclitaxel) that can ameliorate the inflammatory response following PVI and result in improved treatment outcomes for patients with PAD.[4-12]

Early clinical investigation has delivered promising results suggesting an improved efficacy and safety profile of DCB angioplasty when compared with conventional PTA, and while long-term outcomes have not been available or consistently reported, the U.S. Food and Drug Administration has approved the use of these devices for femoropopliteal PVI.[9-11,13-19] Recently, a meta-analysis of all studies of paclitaxel-coated balloons and paclitaxel-eluting stents reported an increased hazard of all-cause death at 2 years in those patients treated with paclitaxel when compared with conventional balloons and stents.[20] With the explosion of PVI over the last decade and the resultant higher costs associated with newer devices, there remains concern that the exuberance around DCB use should be tempered until the effectiveness and safety of DCB have been demonstrated in a real-world cohort that is reflective of the actual PAD population undergoing these interventions.

With the assignment of transitional pass-through codes by the Centers for Medicare and Medicaid Services (CMS), DCB usage can be evaluated in a real-world population using administrative claims codes. We examined CMS administrative claims data for femoropopliteal PVI in order to provide much-needed insight into characteristics associated with DCB utilization, effectiveness, and safety in this contemporary US population.

Methods

The authors declare that all supporting data are available within the article [and its online supplementary files].

Data sources

We obtained 100% Medicare data from the Centers for Medicare and Medicaid Services for patients with a qualifying claim for a lower extremity PVI. The data included inpatient, outpatient, and carrier claims, Part D prescription drug claims, and the corresponding Master Beneficiary Summary Files (MBSF) from 2014 to 2016. The inpatient files contain institutional claims for hospital inpatient services. The outpatient files contain institutional claims for hospital outpatient services. The carrier files contain noninstitutional provider claims for services rendered in any setting. Each of these files includes, among other things, dates of service, diagnosis codes, procedure codes, and other institution- or physician-specific information. The MBSF contains information on demographics, birth and death dates, and program eligibility and enrollment.

Study population

Using the carrier files, we identified patients with a lower extremity PVI on the femoropopliteal segment and a diagnosis of PAD (in any position) listed on the same claim during the time period when DCB was approved and could be identified in the outpatient setting (starting April 1, 2015) or the inpatient setting (starting October 1, 2015). Supplemental Table 1 lists all procedural and diagnosis codes. If a patient had multiple PVI procedures, the date of the earliest was used as the index PVI. The PVI was identified as a DCB if the index claim linked to a corresponding outpatient claim with HCPCS C2623 or inpatient claim with ICD-10-PCS 047Kxx1, 047Lxx1, 047Mxx1, or 047Nxx1 procedural code. Given the nature of the data, the specific type and brand of DCB was not able to be studied; however, only the Bard Lutonix.

and Medtronic IN.PACT Admiral DCBs were available during the study period. The study population was restricted to Medicare beneficiaries ≥40 years old at the index PVI who were enrolled in Medicare fee-for-service (FFS) at the index PVI and for at least the 12 months prior. PVI procedures performed in an office setting were excluded since DCB use cannot be identified in this setting.

Study variables

Information on age, sex, race, and region were derived from the MBSF. We searched inpatient, outpatient, and carrier claims between the index date and 1 year prior for comorbid conditions using validated algorithms.[21,22] The Charlson comorbidity score was calculated using comorbidities defined based on an established algorithm.[23] Physician specialty was defined using the specialty codes from the index PVI carrier claim. Disease severity was derived using the PAD diagnosis codes on the index PVI claim

and classified into three groups (1) critical limb ischemia, (2) intermittent claudication, and (3) other. If a patient had multiple PAD diagnosis codes, they were assigned to the most severe classification (critical limb ischemia > claudication > other). Anatomic burden and lesion severity data are not included in the CMS files.

Outcomes

The primary outcomes of interest were all-cause mortality, all-cause hospitalization, repeat femoropopliteal revascularization, and major lower extremity amputation 1 year after the index PVI. All-cause mortality was identified using death dates in the MBSF. All-cause hospitalization was determined using the earliest admission date in the inpatient file after the index PVI. Transfers and admissions for rehabilitation were excluded. Repeat femoropopliteal revascularization and major lower extremity amputation were based on the earliest procedure date on a carrier claim (see codes, Supplemental Table 1) with a qualifying diagnosis for PAD in any position on the same claim. At least 1 day between the index PVI and the repeat revascularization procedure date was required. For patients without an event of interest, follow up time was censored at the earliest of (a) 1 year following the index date, (b) the end of claims data availability (December 31, 2016), (c) the date when enrollment in FFS Medicare ended, or (d) death date for non-mortality outcomes.

Statistical analysis

Summary statistics for patient and physician characteristics by DCB PVI are presented as percentages for categorical variables and medians with interquartile ranges for continuous variables. To test for differences between groups, we used chi-squared tests for categorical variables and Kruskal-Wallis tests for continuous variables. The 1-year event rate for all-cause mortality was calculated using Kaplan–Meier estimates and group differences were tested using the log-rank test. For all other outcomes, the 1-year event rates were calculated using the cumulative incidence function to account for the competing risk of mortality and group differences were tested using Gray's test.

To assess differences in outcomes between treatment groups, we used inverse probability-weighted (IPW) estimates based on the probability of a patient receiving a DCB PVI conditional on observed covariates.[24] A logistic regression model with DCB (yes/no) as the outcome was used to examine the association between patient and procedure-related characteristics with a DCB PVI and to calculate the weights. We calculated weighted standardized differences to compare baseline characteristics between treatment groups after weighting.[25]

Cox regression models were used to estimate the association between DCB PVI and outcomes. First, we estimated the unadjusted relationship between DCB PVI and each outcome. Next, we estimated the adjusted relationship between DCB PVI and all outcomes by applying the weights described above. All models included robust sandwich estimators to account for clustering of patients within hospitals.

Part D sensitivity analysis

A sensitivity analysis in a subset of patients with part D eligibility was performed to adjust for prior medication therapy (anticoagulant, antiplatelet, statin, and other) in the Cox proportional hazards model. Prescription information from 90 days prior to 180 days after the PVI index date was obtained from the Part D drug files. Prescription drug analyses were performed in the subgroup of the population with Part D enrollment for this entire periprocedure period (See Supplemental Table 2).

Several additional analyses were performed, including adding a 90-day blanking period to account for staged PVI and analyses designed to determine laterality of repeat PVI procedures (see Supplemental Methods).

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The institutional review board of the Duke University Health System reviewed and approved this study. We used SAS 9.4 (SAS Institute, Cary, North Carolina) for all analyses.

Results

Patient characteristics

A total of 83,225 patients underwent index femoropopliteal PVI with balloon angioplasty (DCB or conventional PTA) during the study period. DCB angioplasty was performed in 24,361 patients (29.3%), whereas 58,864 patients (70.7%) underwent conventional PTA. Table 1 illustrates the baseline characteristics of the study groups according to DCB or PTA use (Part D subgroup baseline characteristics, Supplemental Table 2). Patients treated with DCB were more likely to be white, younger, and female when compared with patients treated with conventional PTA. Despite differences in comorbidities between the two groups, the median Charlson comorbidity index score was 5 for both groups. Dual Medicare–Medicaid eligibility differed slightly with the DCB group representing 21.7% versus 24.4% in the non-DCB group.

The ICD-9 or ICD-10 diagnosis code (eg, symptom severity) for the index procedure differed between the two groups. Intermittent claudication was identified in 46.7% of patients treated with DCB and in only 36.4% of the patients treated with conventional PTA, and critical

Table 1. Baseline characteristics of PAD patients from 2015–2016, by DCB

	DCB PVI	Non-DCB PVI	Std diff	*P*
N	24,361	58,864		
Age, years	73.0 (68.0, 80.0)	74.0 (67.0, 81.0)	2.1%	.003
Age group, %			8.0%	<.001
<65	3573 (14.7)	9336 (15.9)		
65-<75	9869 (40.5)	22,342 (38.0)		
75-<85	7887 (32.4)	18,574 (31.6)		
85+	3032 (12.4)	8612 (14.6)		
Female, %	11,067 (45.4)	25,738 (43.7)	3.4%	<.001
Race, %			6.5%	<.001
White	20,049 (82.3)	47,000 (79.8)		
Black	3175 (13.0)	8933 (15.2)		
Other	1137 (4.7)	2931 (5.0)		
Comorbidities, %				
Cancer	3638 (14.9)	9087 (15.4)	1.4%	.07
Cerebrovascular disease	10,647 (43.7)	26,295 (44.7)	1.9%	.01
Chronic obstructive pulmonary disease	11,158 (45.8)	27,812 (47.2)	2.9%	<.001
Congestive heart failure	8715 (35.8)	22,979 (39.0)	6.7%	<.001
Dementia	1530 (6.3)	4694 (8.0)	6.6%	<.001
Diabetes mellitus	14,739 (60.5)	36,603 (62.2)	3.5%	<.001
Hypertension	23,356 (95.9)	56,342 (95.7)	0.8%	.30
Ischemic heart disease	17,322 (71.1)	41,069 (69.8)	2.9%	<.001
Renal disease	9194 (37.7)	23,900 (40.6)	5.9%	<.001
Myocardial infarction	5740 (23.6)	14,988 (25.5)	4.4%	<.001
Stroke/TIA	4335 (17.8)	12,149 (20.6)	7.2%	<.001
Charlson Comorbidity Index	5.0 (3.0, 7.0)	5.0 (3.0, 8.0)	8.7%	<.001
Region, %			11.5%	<.001
Midwest	7308 (30.0)	14,899 (25.3)		
Northeast	3628 (14.9)	9591 (16.3)		
South	10,237 (42.0)	26,923 (45.7)		
West	3168 (13.0)	7352 (12.5)		
Other	20 (0.1)	99 (0.2)		
Physician Specialty, %			34.7%	<.001
Cardiologist	12,381 (50.8)	20,468 (34.8)		
Surgeon	8865 (36.4)	30,569 (51.9)		
Radiologist	2384 (9.8)	6368 (10.8)		
Other	731 (3.0)	1459 (2.5)		
Dual Medicaid eligibility, %	5285 (21.7)	14,367 (24.4)	6.4%	<.001
Inpatient PVI setting, %	4281 (17.6)	17,489 (29.7)	28.9%	<.001
Index PVI diagnosis severity			21.3%	<.001
Intermittent claudication	11,374 (46.7)	21,454 (36.4)		
Critical limb ischemia	7842 (32.2)	23,624 (40.1)		
Other	5145 (21.1)	13,786 (23.4)		

Values are median (IQR) or N (%). The study population includes patients with a qualifying carrier claim for lower extremity PVI applied on the femoral/popliteal segment during the time when DCB was approved and could be identified in the outpatient setting (between 4/1/2015 and 12/31/2016) or the inpatient setting (between 10/1/2015 and 12/31/2016).

limb ischemia was lower in the DCB group (32.2%) compared to the non-DCB group (40.1%). With regard to delivery of care, cardiologists accounted for the highest utilization of DCB at 50.8%, followed by surgeons (36.4%) and radiologists (9.8%). After weighting by the inverse probability of treatment with DCB, all baseline characteristics were balanced with the standardized differences <10% between treatment groups.

Factors associated with DCB use

The characteristics associated with DCB usage are shown in Table 2 (Part D subgroup seen in Supplemental Table 3). Female and white patients were more likely to be treated with DCB. Compared to PVI patients in the South, patients in the Midwest (OR 1.24, 95% CI 1.19–1.29, $P < .001$), West (OR 1.19, 95% CI 1.14–1.26, $P < .001$) and Northeast (OR 1.13, 95% CI 1.08–1.19, $P < .001$) were more likely to be treated with DCB intervention vs conventional PTA. Several patient characteristics were associated with a lower likelihood of DCB utilization, including chronic obstructive pulmonary disease (OR 0.97, 95% CI 0.94–1.00, $P = .04$), prior myocardial infarction (OR 0.92, 95% CI 0.89–0.96, $P < .001$), and prior stroke (OR 0.90, 95% CI 0.86–0.94, $P < .001$). Furthermore, patients with a procedural diagnosis code for critical limb ischemia (OR 0.86, 95%

Table 2. Factors associated with any DCB use.

Parameter	Unadjusted OR (95% CI)	Unadjusted *P* value	Adjusted OR (95% CI)	Adjusted *P*
Age				
<65	0.87 (0.83, 0.91)	<.001	1.00 (0.95, 1.05)	.98
65-<75	1.00 [Reference]	-	1.00 [Reference]	-
75-<85	0.96 (0.93, 1.00)	.03	0.96 (0.92, 0.99)	.01
85+	0.80 (0.76, 0.84)	<.001	0.85 (0.81, 0.90)	<.001
Female	1.07 (1.04, 1.10)	<.001	1.12 (1.09, 1.16)	<.001
Race				
White	1.00 [Reference]	-	1.00 [Reference]	-
Black	0.83 (0.80, 0.87)	<.001	0.91 (0.87, 0.96)	<.001
Other	0.91 (0.85, 0.98)	.008	0.99 (0.92, 1.06)	.73
Medicaid dual eligibility	0.86 (0.83, 0.89)	<.001	0.92 (0.88, 0.96)	<.001
Region				
Midwest	1.29 (1.24, 1.34)	<.001	1.24 (1.19, 1.29)	<.001
Northeast	0.99 (0.95, 1.04)	.82	1.13 (1.08, 1.19)	<.001
Other	0.53 (0.33, 0.86)	.01	0.52 (0.32, 0.85)	.009
South	1.00 [Reference]	-	1.00 [Reference]	-
West	1.13 (1.08, 1.19)	<.001	1.19 (1.14, 1.26)	<.001
Cancer	0.96 (0.92, 1.00)	.07	0.98 (0.94, 1.02)	.30
Cerebrovascular disease	0.96 (0.93, 0.99)	.01	1.00 (0.97, 1.04)	.80
Chronic obstructive pulmonary disease	0.94 (0.92, 0.97)	<.001	0.97 (0.94, 1.00)	.04
Congestive heart failure	0.87 (0.84, 0.90)	<.001	0.97 (0.93, 1.00)	.06
Dementia	0.77 (0.73, 0.82)	<.001	1.00 (0.94, 1.07)	.95
Diabetes Mellitus	0.93 (0.90, 0.96)	<.001	1.02 (0.99, 1.06)	.21
Hypertension	1.04 (0.97, 1.12)	.30	1.04 (0.96, 1.13)	.32
Ischemic heart disease	1.07 (1.03, 1.10)	<.001	1.02 (0.98, 1.06)	.42
Renal disease	0.89 (0.86, 0.91)	<.001	1.03 (1.00, 1.07)	.06
Myocardial infarction	0.90 (0.87, 0.93)	<.001	0.92 (0.89, 0.96)	<.001
Stroke/TIA	0.83 (0.80, 0.86)	<.001	0.90 (0.86, 0.94)	<.001
Physician specialty				
Cardiologist	1.00 [Reference]	-	1.00 [Reference]	-
Other	0.83 (0.76, 0.91)	<.001	0.86 (0.79, 0.95)	.002
Radiologist	0.62 (0.59, 0.65)	<.001	0.69 (0.65, 0.72)	<.001
Surgeon	0.48 (0.46, 0.50)	<.001	0.54 (0.52, 0.56)	<.001
Index PVI diagnosis severity				
Claudication	1.00 [Reference]	-	1.00 [Reference]	-
Critical limb ischemia	0.63 (0.61, 0.65)	<.001	0.86 (0.83, 0.90)	<.001
Other severity	0.70 (0.68, 0.73)	<.001	0.84 (0.80, 0.87)	<.001
Inpatient setting	0.50 (0.49, 0.52)	<.001	0.61 (0.59, 0.63)	<.001

OR: odds ratio.
Unadjusted: Univariate logistic model.
Adjusted: logistic model adjusted for age, sex, race, Medicaid dual eligibility, region, baseline comorbidities, physician specialty, PVI severity, and inpatient setting.

CI 0.83–0.90, $P < .001$) and those treated as an inpatient (OR 0.61, 95% CI 0.59–0.63, $P < .001$) were significantly less likely to be treated with DCB.

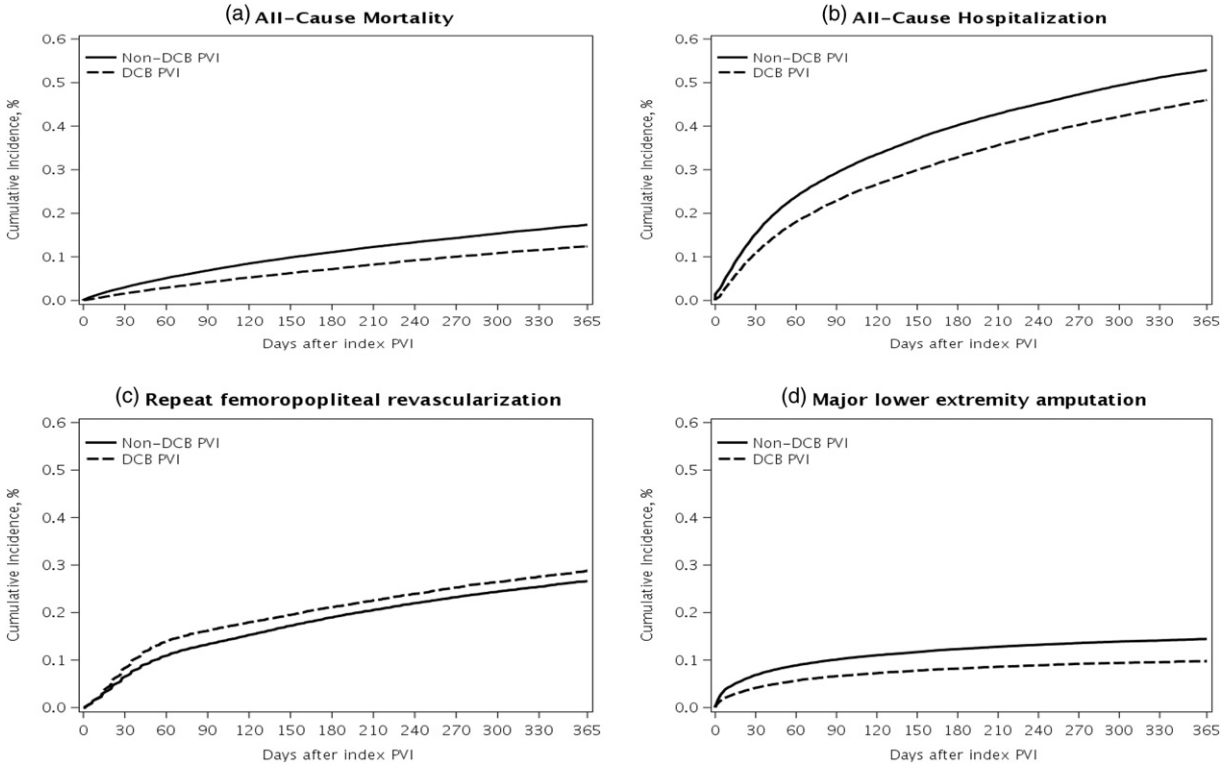
Outcomes at 1 year

Figure 1 graphically represents the 1-year clinical outcomes following index PVI between DCB and conventional PTA. Patients treated with DCB had a lower cumulative incidence of all-cause mortality (12.4% versus 17.4%, $P < .001$), all-cause hospitalization (46.0% versus 52.9%, $P < .001$) and major amputation (9.8% versus 14.4%, $P < .001$) at 1 year (Supplemental Table 4). Repeat revascularization occurred more frequently in patients undergoing index PVI with DCB when compared with conventional PVI at 1 year (28.8% vs 26.6%, $P < .001$). However, after requiring a 90-day blanking period for possible staged, repeat revascularization, patients treated with DCB had a lower cumulative incidence of repeat revascularization at 1 year (15.9% vs 16.5%, $P = .002$) (Supplemental methods and Supplemental Table 4).

After adjustment with inverse probability weighting, the hazard was lower for all-cause mortality (HR 0.89, 95% CI 0.84–0.94, $P < .001$), all-cause hospitalization (HR 0.91, 95% CI 0.88–0.93, $P < .001$) and major amputation (HR 0.93, 95%CI 0.99–0.99, $P = .017$) for patients treated with DCB compared with conventional PTA (Table 3). The hazard of repeat revascularization with DCB and conventional PTA was not statistically different following adjustment (HR 1.03, 95% CI 0.99–1.07, $P = .09$).

After adjustment with inverse probability weighting in the Part D subgroup, the differences in clinical outcomes

Figure 1



Observed 1-year clinical outcomes following index PVI date, by any DCB useFigure 1 demonstrated the cumulative incidence in all-cause mortality (a), all-cause hospitalization (b), repeat revascularization (c), and major amputation (d) at 1-year. All figures demonstrate a significant difference between the groups at 1-year ($P < .001$).

between index treatment with DCB and conventional PTA were attenuated and all-cause mortality was not statistically different (Table 4).

Table 3. Cardiovascular and limb outcomes and all-cause hospitalizations for patients treated with DCB versus conventional PTA during index PVI

Outcome	Unadjusted HR (95% CI)	*P*	Weighted HR (95% CI)	Weighted *P*
All-cause mortality	0.67 (0.64, 0.71)	<.001	0.89 (0.84, 0.94)	<.001
All-cause hospitalization	0.77 (0.75, 0.79)	<.001	0.91 (0.88, 0.93)	<.001
Repeat femoropopliteal revascularization	1.10 (1.06, 1.14)	<.001	1.03 (0.99, 1.07)	.09
Major lower extremity amputation	0.64 (0.61, 0.68)	<.001	0.93 (0.88, 0.99)	.02

DCB = drug-coated balloon.
PTA = percutaneous transluminal balloon angioplasty.
PVI = peripheral endovascular intervention.
Unadjusted model: Cox model accounting for patient clustering within hospitals.
IPW model: Cox model accounting for patient clustering within hospitals and weighted. IPW estimates were calculated using logistic regression with any DCB (yes vs no) as the outcome adjusting for age, sex, race, Medicaid dual eligibility, region, baseline comorbidities, physician specialty, PVI severity, and inpatient setting.

Discussion

There were three key findings of this study. First, in 2015–2016, DCB were used in 29% of all femoropopliteal interventions, and significant patient and clinician variation in the utilization of DCB within this Medicare population was observed. Second, the rate of repeat revascularization following index PVI was high (27.3%) in all patients, and was not lower in patients initially treated with DCB although a significant number of these repeat revascularization procedures are early and therefore possibly due to planned, staged revascularization. Finally, patients treated with DCB during index PVI had lower risks of all-cause mortality, all-cause hospitalization, and major amputation. When adjustment was performed using inverse probability treatment weighting and after accounting for Part D medication prescriptions, these differences were attenuated but the risks of hospitalization and amputation were lower in patients treated with DCB. These findings represent the contemporary use of DCB in clinical practice, include patients with comorbid conditions (eg, end-stage renal disease, malignancy) that were excluded from previous DCB studies, and suggest that based on intermediate term (1-year) outcomes, usage

Table 4. Cardiovascular and limb outcomes and all-cause hospitalizations for patients treated with DCB vs conventional PTA during index PVI among Part D subgroup (N = 44,613)

Outcome	Unadjusted HR (95% CI)	*P*	IPW: HR (95% CI)	IPW: *P*	IPW + prior medications: HR (95% CI)	IPW + prior medications: *P*
All-cause mortality	0.72 (0.67, 0.76)	<.001	0.94 (0.88, 1.00)	.06	0.95 (0.89, 1.02)	.15
All-cause hospitalization	0.78 (0.76, 0.81)	<.001	0.91 (0.88, 0.94)	<.001	0.92 (0.89, 0.95)	<.001
Repeat femoropopliteal revascularization	1.06 (1.02, 1.11)	.007	1.01 (0.97, 1.06)	.60	1.01 (0.96, 1.06)	.69
Major lower extremity amputation	0.65 (0.60, 0.69)	<.001	0.90 (0.84, 0.97)	.007	0.92 (0.86, 0.99)	.02

Unadjusted model: Cox model accounting for patient clustering within hospitals.
IPW: Cox model accounting for patient clustering within hospitals and weighted.
IPW + prior medications: Cox model accounting for patient clustering within hospitals and weighted + adjusted for prior medications (oral anticoagulant, P2Y12, statin, other). IPW estimates were calculated among the part D subgroup using logistic regression with any DCB (yes vs no) as the outcome adjusting for age, sex, race, Medicaid dual eligibility, region, baseline comorbidities, physician specialty, PVI severity, and inpatient setting.

of drug coated balloons is at least as safe as conventional balloon angioplasty in femoropopliteal intervention.

The current results reflect how new peripheral vascular technology and devices are introduced and used in clinical practice in the United States. The creation of specific, transitional pass-through codes by CMS offered the ability to specifically identify and study patients treated with DCB, an opportunity that will go away with CMS claims data when the codes are eliminated at the end of 2018. Several key characteristics were associated with the uptake and use of these devices in 2015–2016, including patient demographic and clinical characteristics and clinical care location. DCBs were used less frequently for femoropopliteal PVI in black patients when compared to white patients. Furthermore, dual Medicare-Medicaid eligible patients, often used as a surrogate for lower social economic status, were less commonly treated with DCB during femoropopliteal PVI. DCBs were also less likely to be used in inpatient hospital settings when compared with outpatient settings, despite the fact that multiple studies have shown that inpatient PVI often involves sicker patients with more complex disease and worse clinical outcomes.[26] While the explanation for these differences remains unclear, some possibilities include differences in access to care, patient disparities, and hospital guidelines regarding reimbursement for devices like DCB.

The differences in delivery and utilization of DCB not only revolved around patient characteristics and clinical care location, but they also varied due to the specialty of the physician billing for the index PVI procedure. During 2015–2016, cardiologists more frequently utilized DCB when compared with surgeons and radiologists. The reasons for these differences are likely multifactorial, and may reflect differences in marketing efforts/strategies towards different clinician groups, a more keen interest and/or acceptance of this technology on the part of cardiologists, and the difference in scope of practice between specialty groups.

The current results provide reassurance that DCB use in contemporary, real-world practice is associated with lower rates of all-cause mortality, all-cause hospitalization, and major amputation at 1 year, despite no improvement in repeat revascularization. A recent analysis of inpatient Medicare beneficiary claims found similar 1 year survival trends between drug-coated and nondrug-coated interventions within the femoropopliteal segment.[27] This study differed from our analysis in that the authors used inpatient claims only (approximately 40% of all PVI procedures) and primarily examined all-cause mortality (rather than secondary endpoints included in the present analysis). The three main randomized controlled trials (RCTs) have been primarily designed to evaluate patency and target lesion revascularization, showing the superiority of DCB over conventional PTA at several time intervals.[13-15,18,28,29] Due to insufficient power, no studies of DCB versus conventional PTA have demonstrated a difference in mortality or amputation rate; however, a recent meta-analysis has reported a significantly higher mortality rate in patients treated with paclitaxel-coated balloons and paclitaxel-eluting stents after 1 year.[13-15,17-19,28,29] This study was limited in that cause-specific mortality was not reported and the mortality rates were estimated without accounting for patients withdrawal or being lost to follow-up. Unlike the pivotal studies, patients in our Medicare cohort had equal distribution of intermittent claudication and critical limb ischemia (as opposed to a very small fraction of critical limb ischemia patients in the pivotal studies), and all patients were included regardless of prevalent cancer, renal dysfunction,

congestive heart failure, and diabetes mellitus. While there is no question that baseline differences existed in the DCB and conventional PTA cohorts in this Medicare analysis, there was a lower all-cause mortality rate in patients treated with DCB, suggesting that it is at least as safe to use this technology when compared with conventional PTA in a broad group of patients undergoing femoropopliteal PVI. While not currently available, we expect to be able to publish longer term (>1 year) outcomes in this Medicare cohort once additional CMS data are available in the 2nd quarter of 2019.

A key opportunity for this study was to evaluate the rates of repeat revascularization, a surrogate for target lesion revascularization and/or patency, in patients treated with DCB versus conventional PTA. The disparate findings from the previous RCTs (eg, an unadjusted, higher rate of repeat revascularization and adjusted, similar rate of repeat revascularization) were unexpected. While it is entirely plausible that patients who underwent PVI with DCB had more severe anatomic burden and lesion severity, we were unable to determine this with CMS data. Using the data available, we first attempted to discern laterality of interventions based on the procedure codes that were available; however, the use of specific *ICD-10* procedure codes limited analyses to the inpatient setting. Furthermore, since the transitional pass-through code was introduced in April 2015 and *ICD-10* codes were introduced in October 2015, laterality was not defined well for half the study period (using *ICD-9* codes). Finally, of the small group of patients that were characterized by the laterality of index PVI, in order to classify target limb or vessel revascularization, these patients had to have inpatient revascularization to be able to accurately distinguish whether or not the repeat revascularization procedure was ipsilateral or contralateral. Overall, this resulted in a small number of patients available for laterality analysis (shown in Supplementary Table 5), and this led to insufficient power to reach definitive conclusions. It is possible that the differences in rates of death and amputation could partially explain the finding of no difference in repeat revascularization between DCB and conventional PTA, but due to similar laterality issues, amputation of the index limb was not able to be determined with the current Medicare dataset.

As stated, there were significantly lower rates of all-cause mortality, all-cause hospitalization, and major amputation in patients treated with DCB when compared with conventional PTA. Given that these findings remained statistically significant after inverse probability treatment weighting despite no significant difference in repeat revascularization, the underlying reasons for this remain unclear. A very real possibility is that selection bias was present and clinicians appropriately selected patients who would do well with DCB following femoropopliteal PVI. Conversely, it is possible that patients who had to be hospitalized following index PVI (all-cause hospitalization) and who died (all-cause mortality) had other, unmeasured (and potentially non-cardiovascular) reasons for hospitalization and death, thus leading to a higher rate of both outcomes in the conventional PTA group. We did attempt to control for known factors, evaluate the top reasons for all-cause hospitalization, and include negative-control studies (using metabolic/nutritional disorders and hip fractures as surrogates for frailty and subsequent mortality, see Supplemental methods and Supplemental Table 6) but we were unable to determine any specific findings that explained the association of DCB with lower rates of all-cause mortality, all-cause hospitalization, and major amputation.

There are several limitations to our study that are largely inherent in the design of any retrospective cohort analysis of Medicare claims data. First, our analysis was limited to patients over the age of 40 at the time of their index peripheral vascular intervention and enrolled in FFS Medicare for at least 12 months prior to the index intervention. Given these inclusion criteria, the results may not be applicable to other patient populations. We were unable to capture lesion anatomy to assess severity or burden of atherosclerosis. The inability to consistently determine laterality with regard to repeat intervention was a major factor in not being able to comment more confidently on the rates of target lesion revascularization. Lastly, it is important to note that Medicare claims represent the care that was received during that encounter and not necessarily the care indicated or appropriate for the condition.

Conclusion

This large, contemporary study of femoropopliteal vascular intervention shows that drug coated balloons were associated with lower all-cause mortality, all-cause hospitalization and major lower extremity amputation when compared with conventional balloon angioplasty. Once adjustment for treatment assignment and medication use was performed, the risk of all-cause death was similar in patients treated with DCB and conventional angioplasty. While treatment assignment was decided by individual operators (ie, not randomized) and few lesion-specific and procedural characteristics were available, this study encompassed a broad clinical practice and included all fee-for-service Medicare patients with peripheral artery disease undergoing femoropopliteal intervention. Future work will be required to understand the impact of other treatment decisions (eg, atherectomy use, medications) and anatomic disease severity on the long-term outcomes of patients treated with drug coated balloons.

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Appendix. Supplementary data

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