Adherence and Persistence to Prescribed Medication Therapy Among Medicare Part D Beneficiaries on Dialysis: Comparisons of Benefit Type and Benefit Phase

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ABSTRACT

BACKGROUND: The implementation of Medicare Part D provided insurance coverage for outpatient medications, but when persons reach the "gap," they have very limited or no medication insurance coverage until they reach a second threshold for catastrophic coverage. In addition, some patients have a low-income subsidy (LIS), and their out-of-pocket costs do not reach the threshold for the gap. Little is known about how these Part D types (LIS versus non-LIS) and benefit phases (before the gap, during the gap, after the gap) affect medication adherence and persistence of dialysis patients.

OBJECTIVE: To examine medication use, adherence, and persistence for Medicare-eligible dialysis patients by Part D benefit type and benefit phase.

METHODS: A retrospective cohort study using data from the U.S. Renal Data System (USRDS) was conducted for Medicare-eligible dialysis patients. Outcomes included medication use, adherence, and persistence. Patients were categorized into 4 cohorts based on their Part D benefit phase that the beneficiaries reached at the end of the year and LIS receipt in 2007: Cohort 1 = non-LIS and did not reach the coverage gap; Cohort 2 = non-LIS and reached the coverage gap; Cohort 3 = non-LIS and reached catastrophic coverage after the gap; and Cohort 4 = received an LIS and none of the LIS patients reached the coverage gap. Outcomes were measured separately for 5 therapeutic classes of outpatient prescription drugs: antihyperglycemics, antihypertensives, antilipidemics, phosphate binders, and calcimimetics.

RESULTS: A total of 11,732 patients met the study inclusion criteria. Patients were distributed among the cohorts as follows: 3,678 (31.3%) patients in Cohort 1 who did not reach the coverage gap; 4,349 (37.1%) patients in Cohort 2 who reached the coverage gap but not catastrophic coverage; 1,310 (11.2%) patients in Cohort 3 who reached catastrophic coverage; and 2,395 (20.4%) patients in Cohort 4 who had an LIS (none of whom reached the gap). Overall, the percentage of patients who were adherent to their medications (≥ 80% medication possession ratio) was low: 39% for antihyperglycemics, 59% for antihypertensives, 54% for antilipidemics, 22% for phosphate binders, and 35% for cinacalcet. There were wide ranges in adherence rates depending on the cohort. For patients on antihyperglycemics, antihypertensives, antilipidemics, phosphate binders, and cinacalcet, the odds ratios for adherence to therapy were 0.76 (95% CI = 0.63-0.92), 1.06 (0.94-1.19), 0.80 (0.67-0.95), 0.65 (0.55-0.76), and 0.39 (0.30-0.49), respectively; the hazard ratios for discontinuation of therapy were 1.18 (95% CI 1.06-1.31), 1.01 (0.93-1.10), 1.25 (1.12-1.40), 1.13 (1.05-1.21), and 1.61 (1.75-1.82), respectively, for Cohort 2 patients who reached the coverage gap compared with those in Cohort 4 who received an LIS. In addition, when comparing adherence before and after the benefit gap, patients in Cohort 2 were significantly more likely to be nonadherent to medications for diabetes (relative risk (RR) = 1.71, 95% CI = 1.48-1.99), hypertension (RR = 1.69, 95% CI = 1.54-1.85), hyperlipidemia (RR = 2.01, 95% CI = 1.76-2.29), hyperphosphatemia (RR = 1.74, 95% CI = 1.55-1.95), and hyperparathyroidism (RR = 2.08, 95% CI = 1.66-2.60) after reaching the coverage gap.

CONCLUSIONS: More than half of Medicare beneficiaries on dialysis reached the Part D coverage gap in 2007. Our findings suggest that the Part D coverage gap was significantly associated with decreases in adherence and persistence for medications frequently used in patients undergoing dialysis. Patients who reached the coverage gap (Cohort 2) often decreased use of or discontinued critical medications after reaching the coverage gap. Compared with patients who had an LIS (Cohort 4), patients in Cohort 2 had significantly lower medication adherence and persistence levels. The negative impact of the Part D coverage gap (high out-of-pocket cost sharing) on medication adherence and persistence for Medicare-eligible dialysis patients has implications for currently proposed Medicare end-stage renal disease bundled reimbursement payment and requires more research.

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What is already known about this subject

- Poor adherence with prescribed medications is a widely recognized problem in dialysis patients due to the complexity of the regimen and lifelong duration of therapy. A recent systematic literature review found that more than half of the included studies reported nonadherence rates of ≥ 50% in the end-stage renal disease (ESRD) population.
- The Part D coverage gap has been associated with reduced medication adherence in the general Medicare population; in other words, beneficiaries are significantly more likely to adopt cost-lowering strategies when entering the coverage gap.
- ESRD patients have a higher risk of reaching the coverage gap compared with other Medicare beneficiaries with Part D benefits (48% vs. 23%).

What this study adds

- Throughout 2007, non–low-income subsidy (LIS) Part D Medicare patients on dialysis who reached the coverage gap, but not the catastrophic phase, had mean out-of-pocket expenses of $1,854 (41.9% of medication costs), while patients who received an LIS had mean out-of-pocket expenses of only $192 (3.6% of medication costs).

What this study adds *(continued)*

- About 60% of the Part D non-LIS enrollees reached the coverage gap in 2007. Patients who reached the coverage gap were significantly more likely to be nonadherent to medications for diabetes, hypertension, dyslipidemia, hyperphosphatemia, and hyperparathyroidism after reaching the coverage gap.
- After controlling for covariates, patients who reached the coverage gap, but not catastrophic coverage, were significantly less likely to be adherent and persistent to antihyperglycemics, antilipidemics, phosphate binders, and calcimimetics compared with patients who had an LIS.

As a result of incomplete replacement of kidney function, chronic dialysis patients with end-stage renal disease (ESRD) face many health problems, including chronic inflammatory states, malnutrition, increased risk for cardiovascular morbidity and mortality, phosphate retention, secondary hyperparathyroidism, diabetes, and dyslipidemia.[1] Most dialysis patients, therefore, require many medications and have a high pill burden.[2,3] It has been reported that dialysis patients are prescribed, on average, 12-19 different medications.[2,3] Unfortunately, poor adherence with prescribed medications is a widely recognized problem in dialysis patients due to the complexity of the regimen and lifelong duration of therapy.[2,4,5] A recent systematic literature review found that more than half of the included studies reported nonadherence rates of ≥ 50% in the ESRD population.[5]

High out-of-pocket costs borne by patients can be a deterrent to therapeutic adherence and, therefore, to the effectiveness of prescribed medications.[6] Even small increases in these costs can lead to potentially significant reductions in medication adherence, which, in turn, can have serious consequences for patients' health.[7] A national survey found that prescription coverage and out-of-pocket costs were determinants of underuse across medication types, although rates of underuse varied substantially across treatments.[8] To date, researchers have observed reduced drug utilization among Medicare Part D beneficiaries who reach the coverage gap and have no other financial assistance to pay for drugs.[9-11] Several other studies have demonstrated decreases in medication adherence and associated health outcomes for Part D beneficiaries who reached the coverage gap phase.[12-16] More specifically, Fung et al. (2010) reported that out-of-pocket expenditures were 189% higher, and adherence to 3 chronic medications—including oral medications used to treat diabetes, hypertension, and dyslipidemia—was significantly lower among beneficiaries with a coverage gap versus no gap.[14]

The recent U.S. Renal Data System (USRDS) report estimated that 72% of hemodialysis patients received Medicare Part D coverage.[17] In 2008, 47% of dialysis patients reached the coverage gap, and 13% reached the catastrophic coverage phase, compared with 23% and 3%, respectively, in the general Medicare program.[18] Given their need for chronic medication therapy and multiple medications to treat comorbid conditions, patients with ESRD are at a particularly high risk of facing high out-of-pocket medication costs.[17] The high levels of clinical need for drug therapy combined with substantial out-of-pocket costs for patients with ESRD may make them more vulnerable to cost-related medication nonadherence.

Although inadequate adherence with prescribed medication is a widely recognized problem, very few studies have been conducted to understand cost-related medication nonadherence in the ESRD population.[19] The majority of the ESRD population is enrolled in Medicare, but little is known about how Part D benefit types and benefit phases affect medication adherence in this population.

The Affordable Care Act of 2010 is gradually closing the coverage gap by reducing the coinsurance in the donut hole until it reaches 25% in 2020. At the same time, the Centers for Medicare and Medicaid (CMS) implemented the new Medicare bundled ESRD prospective payment system (PPS) in 2011. Under this system, a single payment covers dialysis, supplies, laboratory tests, intravenous, and oral drugs.[20] The inclusion of dialysis-specific oral medications into the bundle is expected to be effective beginning in 2016, which is 2 years later than originally planned.[21] With these important Part D benefit changes in the near future, understanding how the coverage gap and low-income subsidy (LIS) affect medication use and adherence is critical to to designing adequate drug benefits for Medicare beneficiaries.

Therefore, the objectives of this study were the following: (a) to examine medication use among Medicare beneficiaries on dialysis stratified by the Part D benefit phase that the non-LIS beneficiaries reached at the end of the year (i.e., initial coverage, coverage gap, catastrophic coverage), as well as those with an LIS; (b) to compare medication adherence and persistence of dialysis patients by Part D benefit phase and LIS receipt; and (c) to determine whether medication adherence differs before and after the coverage gap was reached among patients reaching the coverage gap but not catastrophic coverage.

Methods

Data Source

A retrospective analysis using data from the USRDS was conducted for Medicare-eligible dialysis patients. The USRDS is a national registry of patients with ESRD based on Medicare claims submitted to the CMS by providers. This database has near universal inclusion of ESRD patients in the United States.[18] The USRDS used the billing information from the CMS

ESRD database to create a longitudinal history of ESRD treatment for each patient in the database. Patient demographics, ESRD onset, and dialysis treatment history were derived from the CMS Medicare Enrollment Database and the ESRD Medical Evidence Report. The payer information and medical and pharmacy claims were obtained from the CMS Medicare Enrollment Database and the CMS claims billing files. Institutional review board approval was obtained from The University of Texas at Austin.

Study Sample

Patients were included in the study if they met the following criteria: (a) were designated by the CMS as having ESRD, identified using the Medical Evidence Report (CMS-2728); (b) underwent hemodialysis from January 2006 to December 2007; (c) were at least aged 18 years on January 1, 2006, and alive on December 31, 2007; (e) were enrolled in both Medicare Parts A and B coverage from January 2006 to December 2007; and (d) were continuously enrolled in a Medicare Part D plan in 2007 (to capture 12 complete months of pharmacy data). Patients were excluded if they (a) received a kidney transplant between January 2006 and December 2007; (b) were Medicare/Medicaid dual-eligible beneficiaries; or (c) were in employer-sponsored health benefit plans.

Under the Medicare Part D standard plan cost-sharing structure in place in 2007, beneficiaries paid a deductible and 25% coinsurance up to $2,250 in total drug spending (which corresponds to $799 in out-of-pocket [OOP] expenses.) Once the $2,250 threshold was reached ($799 OOP), a coverage gap occurred and beneficiaries paid 100% of their medication costs OOP until a second (catastrophic coverage) threshold ($3,850 in OOP costs or $5,100 in total drug spending) was reached. After reaching the catastrophic level, patients paid the greater of 5% of medication costs or $2 copayment for generic drugs and $5 for branded drugs for the remainder of the year.

First, patients were categorized based on type of coverage—LIS versus non-LIS. LIS patients did not reach the coverage gap. The non-LIS group was then subcategorized into 3 cohorts based on their benefit phases at the end of the year. The resulting 4 cohorts included the following: Cohort 1 = non-LIS patients who did not reach the coverage gap (paid OOP costs < $799) by the end of the year; Cohort 2 = non-LIS patients who reached the coverage gap but not the catastrophic coverage phase (paid $799 ≤ OOP costs < $3,850) by the end of the year; Cohort 3 = non-LIS patients who reached catastrophic coverage (paid ≥ $3,850 OOP costs); and Cohort 4 = LIS patients, none reached the coverage gap.

Medication Use and Costs

Medication use was defined as 1 or more prescription fills in any of the therapeutic classes for the period of January 1, 2007, through December 31, 2007. Pharmacy claims were identified using generic names from Part D prescription claims data (see Appendix A). Medication use was measured for 5 therapeutic classes of outpatient prescription drugs: antihyperglycemics, antihypertensives, antilipidemics, phosphate binders, and calcimimetics. Medication costs were defined as total drug costs and OOP costs for each therapeutic class and all medications. OOP costs for each prescription are equal to the amount paid directly by the patient. Total drug costs for each prescription are defined payments including the amount Medicare paid plus patient OOP costs.

Adherence

Before calculating medication adherence, medication treatment patterns were assessed (i.e., mono, dual, triple, or quadruple therapy). Monotherapy was defined as treatment with only 1 medication class within each therapeutic class (e.g., sulfonylureas, biguanides, or thiazolidinediones in antihyperglycemics). Dual (triple or quadruple) therapy refers to a co-administration of 2 (3 or 4) separate medication classes with at least 2 overlapping periods of 30 days or 1 overlapping period of 60 days (e.g., sulfonylureas and biguanides or sulfonylureas and thiazolidinediones, etc.).

Medication adherence was defined using the medication possession ratio (MPR), which is the sum of total days' supply for all fills divided by the number of days between first and last fills plus days supply of the last fill or the number of days between first fill and December 31, whichever ends later.[22] Patients who received at least 2 prescriptions for the same therapeutic class were included to estimate MPR. MPR for dual, triple, and quadruple therapies were determined by calculating the average of the MPRs of the individual medications that constituted the dual, triple, and quadruple therapies. Medication adherence was dichotomized, with adherence defined as MPR ≥ 80% and nonadherence defined as MPR < 80%. In addition, we conducted a separate analysis to determine whether medication adherence differed before and after the coverage gap was exceeded among patients in Cohort 2. For this analysis, patients were included if they received at least 2 prescriptions total and at least 1 prescription before the coverage gap date in each therapeutic class.

Persistence

Medication persistence was defined as the duration of therapy from the first fill date until discontinuation. Persistence was calculated by summing the number of days from the filling of the first medication to the end date of the last medication claim (fill date plus days supply before a 30-day gap and a 60-day gap).[22,23]

Data Analyses

Descriptive statistics included means [standard deviations (SD)] and relative frequencies for continuous and categorical data, respectively. Individual variables were compared among

TABLE 1 Demographic and Clinical Characteristics Among Study Cohorts

Baseline Characteristics	All (N = 11,732)	Cohort 1 Initial Coverage (n = 3,678)	Cohort 2 Coverage Gap (n = 4,349)	Cohort 3 Catastrophic Coverage (n = 1,310)	Cohort 4 Low-Income Subsidy (n = 2,395)	*P* Value[a]
Age, mean (SD)	69.4 (12.7)	69.8 (12.7)	72.5 (10.8)	71.7 (10.9)	61.8 (13.0)	<0.001
Gender, n (%), male	6,589 (56.2)	2,272 (61.8)	2,404 (55.3)	655 (50.0)	1,258 (52.5)	<0.001
Race, n (%)						
Black	3,552 (30.3)	1,233 (33.5)	912 (21.0)	220 (16.8)	1,187 (49.6)	<0.001
White	7,767 (66.2)	2,302 (62.6)	3,304 (76.0)	1,055 (80.5)	1,106 (46.2)	
Other	413 (3.5)	143 (3.9)	133 (3.1)	35 (2.7)	102 (4.3)	
Region of residence, n (%)						
Midwest	2,595 (22.1)	806 (21.9)	1,169 (26.9)	320 (24.4)	300 (12.5)	<0.001
Northeast	3,044 (26.0)	975 (26.5)	1,162 (26.7)	386 (29.5)	521 (21.8)	
South	4,752 (40.5)	1,422 (38.7)	1,484 (34.1)	421 (32.1)	1,425 (59.5)	
West	1,341 (11.4)	475 (12.9)	534 (12.3)	183 (14.0)	149 (6.2)	
Primary disease-causing ESRD, n (%)						
Diabetes	5,051 (43.1)	1,463 (39.8)	1,958 (45.0)	567 (43.3)	1,063 (44.4)	<0.001
Hypertension	3,611 (30.8)	1,202 (32.7)	1,292 (29.7)	373 (28.5)	744 (31.1)	
Glomerulonephritis	1,219 (10.4)	415 (11.3)	433 (10.0)	118 (9.0)	253 (10.6)	
Cystic kidney	337 (2.9)	108 (2.9)	128 (2.9)	47 (4.0)	54 (2.3)	
Other	1,514 (12.9)	490 (13.3)	538 (12.4)	205 (15.6)	281 (11.7)	
ESRD duration, y mean (SD)	5.3 (4.1)	5.4 (4.3)	4.8 (3.6)	5.2 (4.1)	5.9 (4.5)	<0.001
Comorbidity, mean (SD)						
CCI	2.11 (0.79)	1.97 (1.75)	2.26 (1.83)	2.36 (1.83)	1.93 (1.72)	<0.001
Presence of chronic disease, n (%)						
Cardiovascular disease	6,478 (55.2)	1,917 (52.1)	2,562 (58.9)	797 (60.8)	1,202 (50.2)	<0.001
Diabetes mellitus	6,173 (52.6)	1,819 (49.5)	2,372 (54.5)	709 (54.1)	1,273 (53.2)	<0.001
Hypertension	4,472 (38.1)	1,282 (34.9)	1,722 (39.6)	538 (41.1)	930 (38.8)	<0.001
Dyslipidemia	1,511 (12.9)	431 (11.7)	628 (14.4)	201 (15.3)	251 (10.5)	<0.001
Cancer	847 (7.2)	259 (7.0)	353 (8.1)	123 (9.4)	112 (4.7)	<0.001
Chronic lung disease	2,412 (20.6)	684 (18.6)	974 (22.4)	321 (24.5)	433 (18.1)	<0.001

[a]*By X^2 test to compare distributions of categorical variables and ANOVA to compare continuous variables among 4 cohorts.*
CCI = Charlson Comorbidity Index; ESRD = end-stage renal disease; SD = standard deviation.

the 4 cohorts. One-way analyses of variance (ANOVAs) and Kruskal-Wallis tests (a nonparametric alternative to ANOVA) were used to determine statistical significance for continuous variables, and Pearson chi-square tests were used for categorical variables. Paired t-tests and McNemar tests were used for repeated measures. For regression analyses, we adjusted for age, gender, race, region, primary disease causing ESRD, ESRD duration, Charlson Comorbidity Index (CCI) scores,[24] and presence of chronic diseases (i.e., cardiovascular disease, diabetes mellitus, hypertension, dyslipidemia, cancer, chronic lung disease) during 2006. Logistic regression was used to measure the proportion of patients who were adherent (MPR ≥ 80%). A Generalized Estimating Equation (GEE) model was used to compare before and after the coverage gap was reached among patients in Cohort 2.[25] Kaplan-Meier survival curves were used to depict the percentage of patients who remained persistent among the cohorts. Cox proportional hazards regression was used to measure the difference in persistence among the cohorts controlling for covariates.

All statistical analyses were two-tailed, with the significance level set a priori at $\alpha = 0.05$. All analyses were conducted using SAS software (version 9.2; SAS Institute Inc., Cary, NC) and Stata (version 11.1; Stata Corp., College Station, TX).

Results

Patient Characteristics

There were 11,732 patients who met the inclusion criteria: Cohort 1 = 3,678 non-LIS patients (31.4%) who had OOP medication costs < $799; Cohort 2 = 4,349 non-LIS patients (37.1%) who had OOP medication costs between $799 and $3,850; Cohort 3 = 310 non-LIS patients (11.2%) who had OOP medication costs ≥ $3,850; and Cohort 4 = the remaining 2,395 LIS patients (20.4%) who had OOP medication costs < $799 (Appendix B). For the entire study group, the mean age was 69.4 years [SD = 12.7 years]; 56% were male; and 66% were white (Table 1). The primary diseases causing ESRD were diabetes (43.1%) and hypertension (30.8%). The mean ESRD duration was 5.3 [4.1] years. The mean CCI score was 2.11

TABLE 2 Number of Pharmacy Claims, Total Pharmacy Costs, and Out-of-Pocket Costs Among Study Cohorts

	Cohort 1 Initial Coverage (n = 3,678)	Cohort 2 Coverage Gap (n = 4,349)	Cohort 3 Catastrophic Coverage (n = 1,310)	Cohort 4 Low-Income Subsidy (n = 2,395)
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Total				
Number of pharmacy claims	32.4 (20.0)	61.0 (26.6)	88.1 (36.8)	53.5 (32.3)
Total pharmacy costs ($)	1,820 (1,618)	4,431 (2,614)	10,659 (7,112)	5,312 (4,869)
Out-of-pocket costs ($)	423 (217)	1,854 (827)	4,153 (780)	192 (157)
Ratio of out-of-pocket/total costs (%)	23.25	41.85	38.96	3.62
Initial phase				
Number of pharmacy claims	32.4 (20.0)	36.7 (16.0)	25.1 (11.9)	53.5 (32.3)
Total pharmacy costs ($)	1,820 (1618)	2,617 (1,599)	2,375 (542)	5,312 (4,869)
Out-of-pocket costs ($)	423 (217)	736 (94)	677 (149)	192 (157)
Ratio of out-of-pocket/total costs (%)	23.25	28.12	28.50	3.62
Coverage gap phase				
Number of pharmacy claims		24.3 (19.6)	32.9 (18.1)	
Total pharmacy costs ($)		1,814 (1,811)	3,375 (1,075)	
Out-of-pocket costs ($)		1,118 (843)	2,974 (288)	
Ratio of out-of-pocket/total costs (%)		61.64	88.14	
Catastrophic coverage phase				
Number of pharmacy claims			30.4 (25.9)	
Total pharmacy costs ($)			4,935 (7,218)	
Out-of-pocket costs ($)			520 (952)	
Ratio of out-of-pocket/total costs (%)			10.53	

SD = standard deviation.

[1.79], and 55.2% had a cardiovascular diagnosis during 2006. For patients in Cohort 2 (coverage gap), the mean age was 73 years; 55% were male; 76% were white; and ESRD duration was 5 years. Patients in Cohort 4 were more likely to be younger (62 years) and African American (50%) than the other cohorts.

Medication Use and Cost

Table 2 shows the changes of OOP and total medication costs for patients at the different levels of coverage. For example, patients in Cohort 3 (catastrophic coverage) paid, on average, 29% of their medication expenses OOP before reaching the coverage gap. Their portion increased to 88% during the gap phase and decreased to 11% during the catastrophic coverage phase. Throughout 2007, patients who reached the coverage gap (Cohort 2) and those who reached the catastrophic coverage gap (Cohort 3) had mean OOP expenses of $1,854 (41.9% of medication costs) and $4,153 (39.0% of medication costs), respectively, while patients who received an LIS had mean OOP expenses of only $192 (3.6% of medication costs). Medication use and costs also were estimated by therapeutic class of outpatient prescription medications (Table 3). OOP costs for phosphate binders ($592) and calcimimetics ($377) were higher compared with OOP costs for medications to treat for diabetes ($207), hypertension ($247), or dyslipidemia ($183).

Adherence

Medication treatment patterns and adherence are summarized in Table 4. For the entire study cohort, most patients who received antihyperglycemics (93.9%), antilipidemics (95.3%), and phosphate binders (97.1%) had monotherapy. About 60% of the patients who received antihypertensives had polytherapy. The mean MPR was 66.1% for antihyperglycemics, 79.8% for antihypertensives, 75.1% for antilipidemics, 57.3% for phosphate binders, and 63.4% for cinacalcet. The mean MPR and number of patients who achieved adherence rates ≥ 80% were significantly associated with patients' Part D type and benefit phase. After controlling for covariates, patients who reached the coverage gap but not catastrophic coverage (Cohort 2) were 24%, 20%, 35%, and 61% less likely to be adherent to antihyperglycemics (odds ratio [OR] = 0.76, 95% confidence interval [CI] = 0.63-0.92), antilipidemics (OR = 0.80, 95% CI = 0.67-0.95), phosphate binders (OR = 0.65, 95% CI = 0.55-0.76), and calcimimetics (OR = 0.39, 95% CI = 0.30-0.49) compared with patients in Cohort 4, who had an LIS.

Persistence

Table 5 shows medication persistence until a 30-day gap. For the entire study cohort, the mean persistence to therapy before discontinuation was 166 days for antihyperglycemics, 253 days for antihypertensives, 218 days for antilipidemics, 141 days for

TABLE 3 Medication Use and Costs by 5 Therapeutic Classes of Outpatient Prescription Medications Among Study Cohorts

Medication Use and Costs	All (N = 11,732)		Cohort 1 Initial Coverage (n = 3,678)		Cohort 2 Coverage Gap (n = 4,349)		Cohort 3 Catastrophic Coverage (n = 1,310)		Cohort 4 Low-Income Subsidy (n = 2,395)		*P* Value[b]
	Mean (SD)[a]		Mean (SD)[a]		Mean (SD)[a]		Mean (SD)[a]		Mean (SD)[a]		
Antihyperglycemics, n (%)	**4,288**	**(36.6)**	**1,027**	**(27.9)**	**1,799**	**(41.4)**	**556**	**(42.4)**	**906**	**(37.8)**	**< 0.001**
Number of prescriptions	7.0	(5.4)	5.2	(3.9)	7.2	(5.4)	9.7	(6.6)	7.2	(5.4)	< 0.001
Total cost ($)	572	(668)	327	(412)	585	(607)	927	(897)	608	(741)	< 0.001
Out-of-pocket cost ($)	207	(285)	102	(97)	287	(307)	428	(402)	32	(35)	< 0.001
Antihypertensives, n (%)	**10,273**	**(87.6)**	**2,975**	**(80.9)**	**3,976**	**(91.4)**	**1,189**	**(90.8)**	**2,133**	**(89.1)**	**< 0.001**
Number of prescriptions	17.42	(13.25)	12.37	(10.30)	18.86	(12.98)	23.08	(15.78)	18.63	(13.64)	< 0.001
Total cost ($)	696	(701)	405	(420)	758	(640)	1,056	(972)	785	(790)	< 0.001
Out-of-pocket cost ($)	247	(323)	120	(118)	365	(339)	518	(496)	51	(52)	< 0.001
Antilipidemics, n (%)	**5,191**	**(44.3)**	**1,160**	**(31.5)**	**2,312**	**(53.2)**	**793**	**(60.5)**	**926**	**(38.7)**	**< 0.001**
Number of prescriptions	6.84	(4.48)	5.09	(3.71)	7.07	(4.41)	8.70	(4.74)	6.89	(4.54)	< 0.001
Total cost ($)	504	(456)	304	(314)	517	(453)	733	(520)	525	(452)	< 0.001
Out-of-pocket cost ($)	183	(227)	82	(90)	240	(242)	346	(274)	29	(33)	< 0.001
Phosphate binders, n (%)	**8,862**	**(75.5)**	**2,194**	**(59.7)**	**3,544**	**(81.5)**	**1,200**	**(91.6)**	**1,924**	**(80.3)**	**< 0.001**
Number of prescriptions	5.63	(3.99)	4.03	(2.99)	5.74	(3.88)	8.20	(4.65)	5.65	(3.85)	< 0.001
Total cost ($)	1,520	(1,739)	810	(898)	1,291	(1,288)	2,922	(2,301)	1,877	(2,151)	< 0.001
Out-of-pocket cost ($)	377	(545)	133	(109)	454	(455)	1,130	(824)	42	(59)	< 0.001
Calcimimetics, n (%)	**3,018**	**(25.7)**	**439**	**(11.9)**	**1,077**	**(24.8)**	**647**	**(49.4)**	**855**	**(35.7)**	**< 0.001**
Number of prescriptions	5.11	(3.65)	2.77	(2.42)	4.42	(3.15)	7.40	(3.74)	5.45	(3.67)	< 0.001
Total cost ($)	2,653	(2,739)	1,385	(1,906)	2,044	(2,076)	3,925	(3,129)	3,109	(3,012)	< 0.001
Out-of-pocket cost ($)	592	(847)	152	(134)	674	(626)	1,481	(1,159)	44	(83)	< 0.001

[a]*Unless otherwise indicated.*

[b]*By X^2 test to compare distributions of categorical variables and Kruskal-Wallis test to compare continuous variables among 4 cohorts.*

SD = standard deviation.

phosphate binders, and 154 days for cinacalcet. The Cox proportional hazards regression model showed a significant difference in discontinuation of therapy among cohorts (Table 6). For patients on antihyperglycemics or antilipidemics, the hazard ratios for discontinuation therapy as defined by a 30-day gap were 1.18 (95% CI = 1.06-1.31) and 1.25 (95% CI = 1.12-1.40) in Cohort 2 (coverage gap) compared with those in Cohort 4 (LIS). Those on phosphate binders or cinacalcet also had an increased risk for discontinuation in Cohort 2 (HR = 1.13; 95% CI = 1.05-1.21; HR = 1.61; 95% CI = 1.75-1.82, respectively) versus patients in Cohort 4. Appendix C shows the Kaplan-Meier survival curves describing percentage of patients who remained persistent on medication. Results using a 60-day gap to determine discontinuation rates trended in the same direction as the 30-day gap (see Appendix D).

Medication Costs and Adherence Before and After Coverage Gap

Medication costs and adherence before and after the coverage gap among patients in Cohort 2 are shown in Table 6. Patients' OOP costs increased significantly after the patient reached the gap in Cohort 2 ($P < 0.05$), although total medication costs decreased significantly ($P < 0.05$). The GEE model showed that patients who reached the coverage gap (Cohort 2) were significantly more likely to be nonadherent to medications for diabetes (relative risk (RR) = 1.71, 95% CI = 1.48-1.99), hypertension (RR = 1.69, 95% CI = 1.54-1.85), dyslipidemia (RR = 2.01, 95% CI = 1.76-2.29), hyperphosphatemia (RR = 1.74, 95% CI = 1.55-1.95), and hyperparathyroidism (RR = 2.08, 95% CI = 1.66-2.60) after reaching the coverage gap.

Discussion

This retrospective analysis examined the effects of the level of Part D OOP expenses on medication use adherence and persistence in Medicare beneficiaries on dialysis using a nationally representative database. This study adds to a limited literature on medication-taking behaviors related to Part D type and benefit phase among dialysis patients. Overall, the percentage of patients who are adherent to their medications (≥ 80% MPR) was low: 39% for antihyperglycemics; 59% for antihypertensives; 54% for antilipidemics; 22% for phosphate binders; and 35% for cinacalcet. High medication discontinuation (using a 30-day treatment gap) was also observed, ranging from 48% to 83%. These results were similar to previous adherence studies

TABLE 4 Medication Treatment Patterns and Adherence by 5 Therapeutic Classes of Outpatient Prescription Medications Among Study Cohorts

Medication Treatment Patterns and Adherence	All (N = 11,732)	Cohort 1 Initial Coverage (n = 3,678)	Cohort 2 Coverage Gap (n = 4,349)	Cohort 3 Catastrophic Coverage (n = 1,310)	Cohort 4 Low-Income Subsidy (n = 2,395)	*P* Value[a]
Antihyperglycemics, n (%)	**3,819**	**851**	**1,630**	**523**	**815**	
Mono	3,585 (93.9)	835 (98.1)	1,532 (94.0)	458 (87.6)	760 (93.3)	
Dual	228 (6.0)	15 (1.8)	96 (5.9)	63 (12.1)	54 (6.6)	
Triple	6 (0.1)	1 (0.1)	2 (0.4)	2 (0.4)	1 (0.1)	
MPR						
Mean (SD)	66.1 (27.2)	59.5 (27.5)	65.7 (27.0)	75.5 (24.8)	67.8 (26.8)	<0.001
Number of patients ≥80%, n (%)	1,481 (38.8)	250 (29.4)	622 (38.2)	275 (52.6)	334 (41.0)	<0.001
Adjusted OR (95% CI)[b]	N/A	0.52 (0.42-0.65)	0.76 (0.63-0.92)	1.40 (1.11-1.77)	1.00	
Antihypertensives, n (%)	**9,863**	**2,975**	**3,976**	**1,189**	**2,133**	
Mono	3,988 (40.4)	1,522 (54.9)	1,359 (35.2)	361 (30.9)	746 (36.2)	
Dual	3,172 (32.2)	819 (29.6)	1,289 (33.4)	369 (31.6)	695 (33.7)	
Triple	2,666 (27.0)	431 (15.6)	1,190 (30.8)	433 (37.1)	612 (26.7)	
Quad	37 (0.4)	0 (0)	25 (0.7)	4 (0.4)	8 (0.4)	
MPR						
Mean (SD)	79.8 (21.9)	73.7 (24.2)	82.4 (19.9)	86.8 (17.8)	79.1 (22.3)	<0.001
Number of patients ≥ 80%, n (%)	5,765 (58.5)	1,311 (47.3)	2,431 (62.9)	849 (72.8)	1,174 (57.0)	<0.001
Adjusted OR (95% CI)[b]	N/A	0.59 (0.52-0.67)	1.06 (0.94-1.19)	1.68 (1.43-1.98)	1.00	
Antilipidemics, n (%)	**4,607**	**922**	**2,119**	**746**	**820**	
Mono	4,392 (95.3)	911 (98.8)	2,011 (94.9)	680 (91.2)	790 (96.3)	
Dual	208 (4.5)	11 (1.2)	106 (5.0)	62 (8.3)	29 (3.5)	
Triple	7 (0.2)	0 (0)	2 (0.1)	4 (0.5)	1 (0.1)	
MPR						
Mean (SD)	75.1 (23.7)	67.8 (26.2)	75.3 (23.3)	84.2 (18.1)	74.5 (23.4)	<0.001
Number of patients ≥80%, n (%)	2,489 (54.0)	394 (42.7)	1,144 (54.0)	529 (70.9)	422 (51.5)	<0.001
Adjusted OR (95% CI)[b]	N/A	0.51 (0.42-0.63)	0.80 (0.67-0.95)	1.71 (1.37-2.13)	1.00	
Phosphate binders, n (%)	**7,753**	**1,729**	**3,185**	**1,151**	**1,688**	
Mono	7,528 (97.1)	1,709 (98.8)	3,103 (97.4)	1,087 (94.4)	1,629 (96.5)	
Dual	221 (2.9)	20 (1.2)	80 (2.5)	62 (5.4)	59 (3.5)	
Triple	4 (0.1)	0 (0)	2 (0.1)	2 (0.2)	0 (0)	
MPR						
Mean (SD)	57.3 (24.5)	48.7 (23.4)	57.0 (23.7)	70.8 (22.6)	57.2 (24.2)	<0.001
Number of patients ≥ 80%, n (%)	1,685 (21.7)	218 (12.6)	655 (20.6)	457 (39.7)	355 (21.0)	<0.001
Adjusted OR (95% CI)[b]	N/A	0.39 (0.32-0.47)	0.65 (0.55-0.76)	1.68 (1.40-2.01)	1.00	
Calcimimetics, n (%)	**2,436**	**261**	**854**	**606**	**718**	
MPR						
Mean (SD)	63.4 (26.7)	48.7 (4.0)	56.8 (25.8)	77.2 (22.1)	65.1 (25.7)	<0.001
Number of patients ≥80%, n (%)	849 (34.8)	45 (17.2)	204 (23.9)	334 (55.1)	266 (37.1)	<0.001
Adjusted OR (95% CI)[b]	N/A	0.27 (0.19-0.39)	0.39 (0.30-0.49)	1.45 (1.13-1.85)	1.00	

[a]*By X^2 test to compare distributions of categorical variables and Kruskal-Wallis test to compare continuous variables.*

[b]*Logistic regression was used to adjust for age, gender, race, and region of residence, primary disease causing ESRD, ESRD duration, CCI scores, and presence of chronic diseases (cardiovascular disease, diabetes mellitus, hypertension, dyslipidemia, cancer, and chronic lung disease).*

CCI = Charlson Comorbidity Index; CI = confidence interval; ESRD = end-stage renal disease; MPR = medication possession ratio; N/A = not applicable; OR = odds ratio; SD = standard deviation.

in dialysis patients, which found antihypertensive adherence to be 58%,[26] and cinacalcet adherence to be 29% (with a refill rate of 37%).[27] The adherence to phosphate binders was lower in the current study (22%) than in a previous study (38%), which was conducted in 3 different dialysis centers,[2] but the difference could be explained by differences in study populations.

Unlike previous studies, we also calculated adherence and persistence measures for 4 cohorts of Medicare Part D beneficiaries categorized by type of coverage (LIS vs. non-LIS) and benefit phase at the end of the year. In the present study, we found that a significantly higher proportion of the Part D non-LIS enrollees (Cohorts 1, 2, and 3) reached the coverage gap than

TABLE 5 Medication Persistence Until 30-Day Gap by 5 Therapeutic Classes of Outpatient Prescription Medications Among Study Cohorts

Medication Persistence	All (N = 11,732)	Cohort 1 Initial Coverage (n = 3,678)	Cohort 2 Coverage Gap (n = 4,349)	Cohort 3 Catastrophic Coverage (n = 1,310)	Cohort 4 Low-Income Subsidy (n = 2,395)	*P* Value[a]
Antihyperglycemics, n	**3,819**	**851**	**1,630**	**523**	**815**	
Persistence (mean, SD)	166.4 (132.8)	139.4 (125.9)	166.2 (131.2)	209.1 (135.4)	167.6 (134.5)	< 0.001
Discontinuation (n, %)	2,852 (74.7)	674 (79.2)	1,259 (77.2)	328 (62.7)	591 (72.5)	< 0.001
Adjusted HR (95% CI)[b]	N/A	1.38 (1.23-1.55)	1.18 (1.06-1.31)	0.78 (0.68-0.90)	1.00	
Antihypertensives, n	**9,863**	**2,975**	**3,976**	**1,189**	**2,133**	
Persistence (mean, SD)	252.5 (129.8)	210.8 (135.7)	271.3 (120.9)	291.3 (112.5)	251.6 (132.1)	< 0.001
Discontinuation (n, %)	4,714 (47.8)	1,673 (60.4)	1,680 (43.5)	397 (34.0)	964 (46.8)	< 0.001
Adjusted HR (95% CI)[b]	N/A	1.69 (1.56-1.84)	1.01 (0.93-1.10)	0.73 (0.65-0.83)	1.00	
Antilipidemics, n	**4,607**	**922**	**2,119**	**746**	**820**	
Persistence (mean, SD)	218.1 (129.0)	178.6 (127.9)	222.0 (126.2)	262.3 (119.4)	212.4 (132.2)	< 0.001
Discontinuation (n, %)	2,759 (59.9)	637 (69.1)	1,307 (61.7)	344 (46.1)	471 (57.4)	< 0.001
Adjusted HR (95% CI)[b]	N/A	1.71 (1.51-1.94)	1.25 (1.12-1.40)	0.78 (0.68-0.90)	1.00	
Phosphate binders, n	**7,753**	**1,729**	**3,185**	**1,151**	**1,688**	
Persistence (mean, SD)	141.2 (120.8)	103.4 (101.8)	146.0 (117.5)	194.8 (131.9)	134.3 (122.7)	< 0.001
Discontinuation (n, %)	6,425 (82.9)	1,549 (89.6)	2,690 (84.5)	784 (68.1)	1,402 (83.1)	< 0.001
Adjusted HR (95% CI)[b]	N/A	1.55 (1.43-1.67)	1.13 (1.05-1.21)	0.71 (0.65-0.78)	1.00	
Calcimimetics, n	**2,436**	**261**	**854**	**606**	**718**	
Persistence (mean, SD)	154.0 (119.2)	100.2 (89.2)	132.1 (103.4)	200.0 (128.0)	160.9 (124.4)	< 0.001
Discontinuation (n, %)	1,766 (72.4)	220 (84.3)	706 (82.7)	338 (55.8)	502 (69.9)	< 0.001
Adjusted HR (95% CI)[b]	N/A	2.07 (1.75-2.44)	1.61 (1.42-1.82)	0.77 (0.67-0.90)	1.00	

[a]By X^2 test to compare distributions of categorical variables and ANOVA to compare continuous variables among 4 cohorts.

[b]Cox proportional hazards regression model was used to adjust for age, gender, race, and region of residence, primary disease causing ESRD, ESRD duration, CCI scores, and presence of chronic diseases (cardiovascular disease, diabetes mellitus, hypertension, dyslipidemia, cancer, and chronic lung disease).

CCI = Charlson Comorbidity Index; CI = confidence interval; ESRD = end-stage renal disease; HR = hazard ratio; N/A = not applicable; SD = standard deviation.

proportions reported in the 2012 USRDS annual report (61% vs. 47%).[18] Our findings suggest that patients who reached the coverage gap but not catastrophic coverage (Cohort 2) had significantly lower adherence and persistence levels to therapy for diabetes, lipid-lowering medications, phosphate binders, and cinacalcet compared with those who received an LIS (Cohort 4). Interestingly, after adjustment for the covariates measured in our study, patients in Cohort 1 (non-LIS who did not reach the coverage gap) had the lowest adherence and persistence, while those in Cohort 3 (reached catastrophic coverage) had the highest adherence and persistence among the 4 cohorts. This result was somewhat surprising because patients who did not reach the coverage gap would be expected to be relatively healthier and to not require many medications. However, only 17%-47% of patients were adherent to their medications among those who did not reach the coverage gap. Dialysis patients may be especially sensitive to the coverage gap issue even prior to the coverage gap, given the large number of medications needed to treat their comorbid conditions. A recent study found that Part D enrollees' adherence decreased prior to the gap because patients anticipated that continued spending would make them more likely to reach the gap.[28] Patients use different strategies to face the coverage gap and mitigate the effects of the coverage gap. Patients may fall into the initial coverage phase (Cohort 1), evidenced by OOP spending < $799, due to lack of medication adherence and persistence. These patients might have avoided or delayed reaching the coverage gap by reducing and/or discontinuing their medications. In addition, patients may fall into the catastrophic coverage phase (Cohort 3), evidenced by OOP spending ≥ $3,850, because they were adherent and persistent with filling prescriptions. Some sicker patients, who entered the coverage gap early in the year, might increase their spending, trying to come out of the coverage gap as soon as possible to reach the catastrophic coverage phase.[10] Other patients may adopt cost-lowering strategies (i.e., using less of medications, discontinuing medications, or not filling prescriptions) during the coverage gap,[29,30] making them more likely to reach the coverage gap but not the catastrophic coverage phase (Cohort 2).

Further analysis of medication adherence before and after reaching the coverage gap (Cohort 2) provides information regarding the association between the coverage gap and adherence. After adjustment for the covariates, patients were up to 2 times more likely to be nonadherent to prescription medications after reaching the coverage gap. These findings

TABLE 6 Medication Cost and Adherence Before and After Reaching Coverage Gap by 5 Therapeutic Classes of Outpatient Prescription Medications Among Cohort 2

Medication Cost and Adherence	Before Reaching Coverage Gap		After Reaching Coverage Gap		*P* Value[a]
Antihyperglycemics (n = 1,578)					
Study period, days, mean (SD)	176	(77)	158	(73)	
Total medication cost ($), mean (SD)	390	(374)	260	(350)	<0.001
Out-of-pocket cost ($), mean (SD)	132	(109)	185	(253)	<0.001
MPR, days, mean (SD)	72.4	(26.6)	57.9	(34.3)	<0.001
MPR >80%, n (%)	760	(48.2)	547	(34.7)	<0.001
Adjusted RR of nonadherence[b]	1.00		1.71	(1.48-1.99)	
Antihypertensives (n = 3,815)					
Study period, days, mean (SD)	200	(74)	159	(75)	
Total medication cost ($), mean (SD)	498	(410)	288	(344)	<0.001
Out-of-pocket cost ($), mean (SD)	185	(145)	194	(248)	0.019
MPR, days, mean (SD)	84.9	(19.6)	75.4	(28.5)	<0.001
MPR >80%, n (%)	2,613	(68.5)	2,135	(56.0)	<0.001
Adjusted RR of nonadherence[b]	1.00		1.69	(1.54-1.85)	
Antilipidemics (n = 2,051)					
Study period, days, mean (SD)	179	(76)	159	(75)	
Total medication cost ($), mean (SD)	350	(287)	218	(252)	<0.001
Out-of-pocket cost ($), mean (SD)	116	(99)	147	(189)	<0.001
MPR, days, mean (SD)	81.1	(24.4)	67.3	(33.1)	<0.001
MPR >80%, n (%)	1,348	(65.7)	992	(48.4)	<0.001
Adjusted RR of nonadherence[b]	1.00		2.01	(1.76-2.29)	
Phosphate binders (n = 3,101)					
Study period, days, mean (SD)	179	(76)	148	(72)	
Total medication cost ($), mean (SD)	846	(775)	563	(814)	<0.001
Out-of-pocket cost ($), mean (SD)	170	(131)	329	(416)	<0.001
MPR, days, mean (SD)	65.7	(24.7)	48.9	(33.0)	<0.001
MPR >80%, n (%)	1,041	(33.6)	694	(22.4)	<0.001
Adjusted RR of nonadherence[b]	1.00		1.74	(1.55-1.95)	
Calcimimetics (n = 779)					
Study period, days, mean (SD)	142	(78)	166	(74)	
Total medication cost ($), mean (SD)	1,333	(1,326)	1,208	(1,493)	0.049
Out-of-pocket cost ($), mean (SD)	248	(164)	551	(596)	<0.001
MPR, days, mean (SD)	69.0	(25.9)	47.8	(34.4)	<0.001
MPR >80%, n (%)	329	(42.2)	188	(24.1)	<0.001
Adjusted RR of nonadherence[b]	1.00		2.08	(1.66-2.60)	

[a]*By McNemar test to compare distributions of categorical variables and paired t-test to compare continuous variables before and after reaching coverage gap.*
[b]*Generalized estimating equation regression was used to adjust for age, gender, race, and region of residence, primary disease causing ESRD, ESRD duration, CCI scores, and presence of chronic diseases (cardiovascular disease, diabetes mellitus, hypertension, dyslipidemia, cancer, and chronic lung disease).*
CCI = Charlson Comorbidity Index; ESRD = end-stage renal disease; MPR = medication possession ratio; RR = relative risk; SD = standard deviation.

were consistent with previous studies in general Medicare populations. Several studies assessing the effects of the Part D coverage gap used the number of prescriptions filled as the outcome variable,[10,11,18] while few studies compared the adherence or discontinuation before and after reaching the coverage gap.[13,31] Gu et al. (2010) found that compared with Part D beneficiaries with full coverage, beneficiaries with no coverage were 62% less likely to be adherent to diabetic medication after reaching the coverage gap.[31] Polinski et al. (2011) also found that gap-exposed patients were twice as likely to discontinue their medications for cardiovascular conditions, diabetes, depression, dementia, or rheumatoid arthritis.[13]

In addition, this study found that for patients who reached the coverage gap (Cohort 2), adherence and persistence to dialysis-specific medications (i.e., phosphate binders and cinacalcet) were lower than to nondialysis-specific medications (i.e., antihyperglycemics, antihypertensives, and antilipidemics). A possible explanation for these differences could be differences in medication costs by therapeutic classes. Based on the findings from pharmacy costs, total and OOP costs were significantly higher for dialysis medications (e.g., phosphate binders and cinacalcet) compared with medications for diabetes mellitus, hypertension, and dyslipidemia.

Beginning in 2016, payment for dialysis-specific medications, currently covered under Medicare Part D, will be integrated into the Medicare Part B ESRD bundled PPS, whereas payment for other oral medications (e.g., antihyperglycemics, antihypertensives, and antihyperlipidemics) will continue to be covered by Part D. This study adds a rationale for filling the coverage gap in the Part D phase design because the coverage gap was significantly associated with cost-related nonadherence in dialysis patients. Furthermore, the implementation of the bundled PPS is expected to lead to pronounced adjustments in the treatment of dialysis patients. In the present study, dialysis-specific medications accounted for 70% of total medication costs. However, integrating Part D drugs into Part B payments is believed to lack any policy precedent, and there is concern regarding the potential for inadequate funding.[21] Our study provides a timely, needed assessment of medication use, costs, and adherence under Part D and can help in setting an adequate bundle rate for dialysis-specific medications. Under Part B, patients are responsible for 20% of drug costs and may have supplemental insurance (Medigap) that covers their coinsurance responsibility for Part B drugs, whereas many of those with an LIS under Part D will have no subsidy under Part B.[21] It is uncertain whether the new ESRD bundled PPS will increase or decrease patients' OOP spending and how the bundled rate will affect patients' access to their medications. Our findings provide important policy implications for the beneficiaries who have high drug use and high OOP spending under Part B. Policy decision makers are encouraged to include adequate reimbursement for medications when bundle rates are being set to ensure that patients have reasonable access to critical medications.

Limitations

Studies using administrative claims have a number of limitations. While the standard benefit under Medicare Part D was used to classify subjects, the exact plan in which an individual was enrolled is unknown. Many prescription drug plans have no deductible or use drug copayments instead of coinsurance, and some include coverage during the coverage gap. In 2010, 60% of hemodialysis subjects had no deductible, and 15% had gap coverage (typically for generic medications).[18] The structure of the standard Part D plans used for this study may differ from some subjects' nonstandard plans. However, we used actual OOP drug spending to categorize subjects, which ascertained that they had actuarially equivalent OOP spending before reaching the coverage gap regardless of plan type. In this study, most of the OOP drug spending was observed for phosphate binders and cinacalcet—for which generics are not available. Thus, generic gap coverage would have a limited impact on OOP spending, and relatively few individuals have insurance for branded medications during the coverage gap.

Because this was an observational study, we could not conclude that a causal effect was present between high OOP expenses and poor adherence/persistence. It is a critical question whether our findings indicate direct consequences from Part D OOP expense levels or inherent differences between cohorts. However, we found consistent associations for patients who reached the coverage gap (Cohort 2)—they had significantly poorer adherence and persistence to most outpatient prescription medications compared with patients who received an LIS (Cohort 4), after adjusting for demographic and clinical factors. Furthermore, for Cohort 2 (those reaching the coverage gap), adherence decreased significantly for all 5 therapeutic classes of prescription medications after the patient reached the gap (again after adjusting for covariates). Nevertheless, unmeasured confounding variables might influence the results. In addition, as a general limitation with the use of a claims database, MPR was used as a proxy measure of adherence because it was not possible to determine if the patients actually used the medications as prescribed, but merely that they had received their medications. There is the possibility that MPR calculations might have under- or overestimated adherence. Patients were classified as using polytherapy (i.e., dual, triple, or quadruple therapy) only during the period when the medications overlapped and using monotherapy for the remaining part of the study period. This might have underestimated adherence measures. Patients classified as using monotherapy may have received 2 different medications in the same class of medication (e.g., 2 beta blockers), which might have overestimated adherence measures. In addition, patients may have filled prescriptions outside the Part D benefit. The extent to which dialysis patients fill prescriptions outside of their Part D plans is unknown.[32] However, the inclusion/exclusion criteria in this study probably were conservative, since patients were excluded if they were dual-eligible, received a retiree drug subsidy, or were on an employer-sponsored health benefit plan.

Conclusions

More than half of Medicare beneficiaries on dialysis reached the Part D coverage gap in 2007. Our results indicate that patients often decreased the use of or discontinued critical medications after reaching the coverage gap. In addition, compared with patients who had an LIS, patients who reached the coverage gap had significantly lower medication adherence and persistence levels. This finding may reflect the large economic burden of medication costs faced by Medicare dialysis patients without any subsidy and raises concerns that the lack of drug coverage could lead to adverse health consequences for financially vulnerable patients. To improve medication adherence for necessary drug use for dialysis patients, a Medicare drug plan may consider offering more generously subsidized coverage than would be provided in the current proposal for the new bundled payment.

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DISCLOSURES

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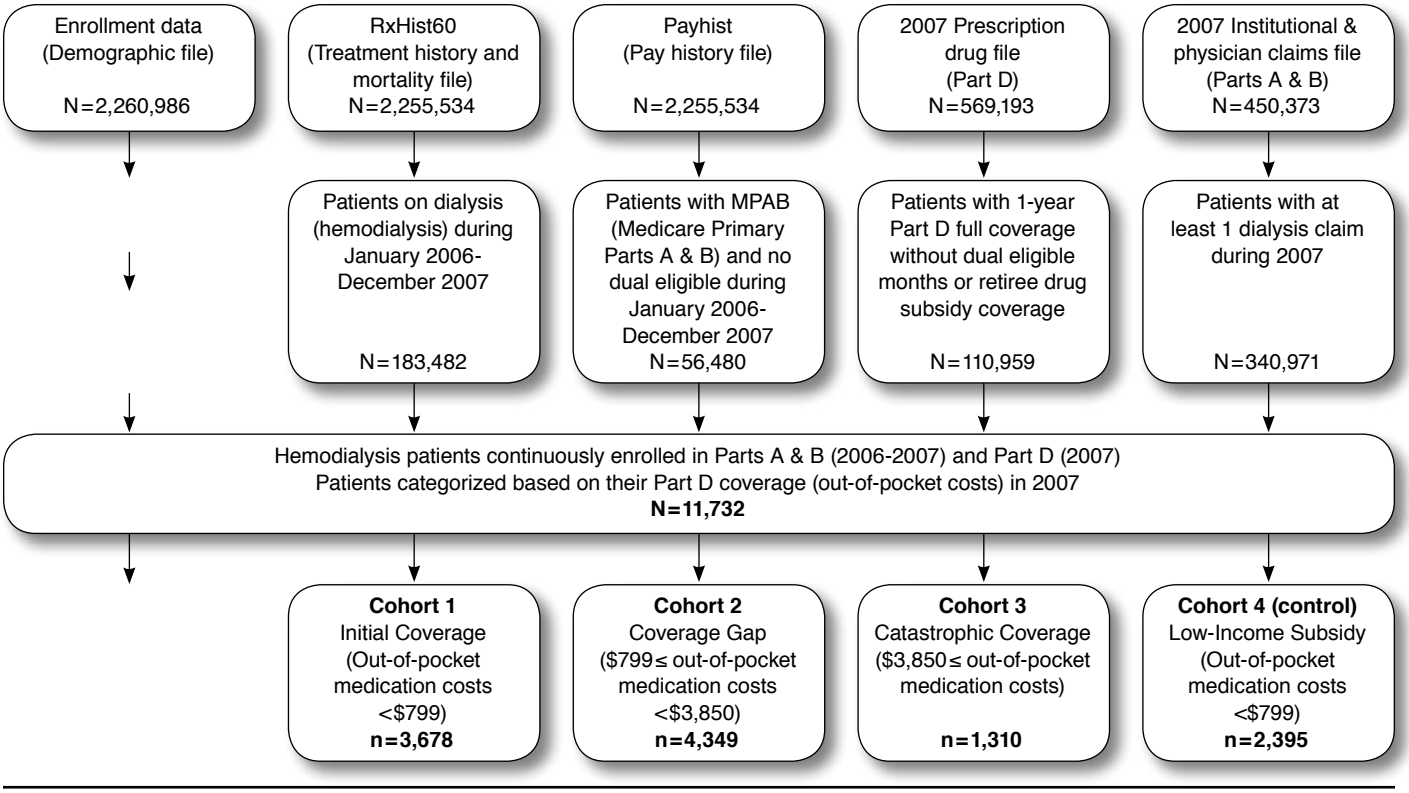
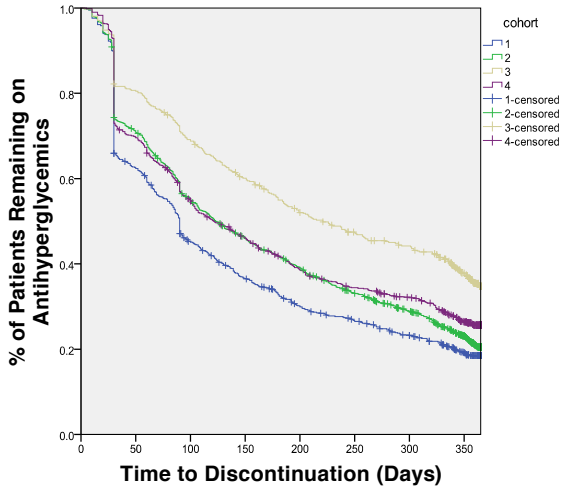
APPENDIX A Drug Generic Names Used to Define Medications

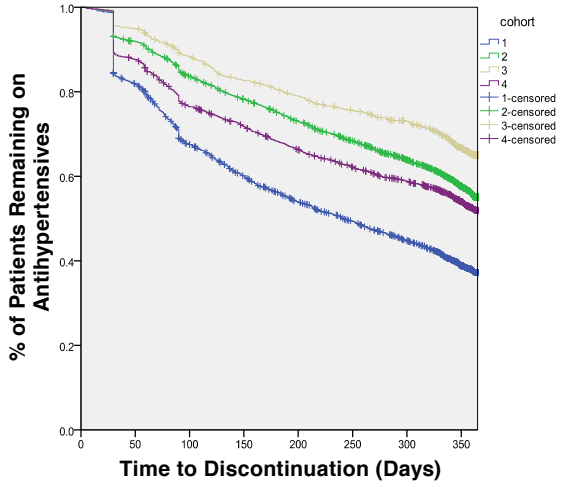
Drug Class	Generic Name
1. Antihyperglycemics	
Sulfonylureas	Glipizide, Acetohexamide, Chlorpropamide, Tolazamide, Tolbutamide, Glyburide, Glimepiride, Glipizide/Metformin, Glyburide/Metformin
Alpha-glucosidase inhibitors	Acarbose, Miglib
Biguanides	Metformin
Meglitinides	Repaglinide, Nateglinide
Thiazolidinediones	Pioglitazone, Pioglitazone/glimepiride, Pioglitazone/Metformin, Rosiglitazone, Rosiglitazone/Glimepiride, Rosiglitazone/Metformin
DPP-4 inhibitors	Sitagliptin, Sitagliptin/Metformin, Saxagliptin
GLP agonist	Exenatide, Pramlintide
Insulin	Any insulin
2. Antihypertensives	
Angiotensin-converting enzyme (ACE) inhibitors	Benazepril, Benazepril/Hydrochlorothiazide, Captopril, Captopril/Hydrochlorothiazide, Enalapril, Enalapril/Felodipine, Enalapril/Hydrochlorothiazide, Enalaprilat, Fosinopril, Fosinopril/Hydrochlorothiazide, Lisinopril, Lisinopril/Hydrochlorothiazide, Moexipril, Moexipril/Hydrochlorothiazide, Perindopril, Quinapril, Quinapril/Hydrochlorothiazide, Ramipril, Trandolapril, Trandolapril/Verapamil
Angiotensin II receptor blockers (ARBs)	Candesartan, Candesartan/Hydrochlorothiazide, Eprosartan, Eprosartan/Hydrochlorothiazide, Irbesartan, Irbesartan/Hydrochlorothiazide, Losartan, Losartan/Hydrochlorothiazide, Olmesartan, Olmesartan/Hydrochlorothiazide, Telmisartan, Telmisartan/Hydrochlorothiazide, Valsartan, Valsartan/Hydrochlorothiazide
Calcium-channel blockers	Amlodipine/Olmesartan, Amlodipine, Amlodipine/Benazepril, Amlodipine/Atorvast, Amlodipine/Valsartan, Diltiazem, Felodipine, Isradipine, Nicardipine, Nifedipine, Nimodipine, Nisoldipine, Verapamil
Beta blockers	Acebutolol, Atenolol, Atenolol/Chlorthalidone, Betaxolol, Bisoprolol, Bisoprolol/Hydrochlorothiazide, Carteolol, Carvedilol, Carvedilol, Labetalol, Metoprolol, Metoprolol/Hydrochlorothiazide, Nadolol, Pindolol, Propranolol, Propranolol/Hydrochlorothiazide, Timolol
Alpha-agonists	Clonidine, Clonidine/Chlorthalidone, Guanabenz, Guanfacine, Methyldopa, Methyldopa/Hydrochlorothiazide
Alpha-blockers	Doxazosin, Prazosin, Terazosin
Aldosteron blocker	Eplerenone, Spironolact/Hydrochlorothiazid, Spironolactone
Direct renin inhibitor	Aliskiren
Diuretic	Indapamide, Hydrochlorothiazide, Torsemide, Chlorothiazide, Bumetanide, Furosemide, Chlorthalidone, Bumetanide, Amiloride, Triamterene, Triamterene/Hydrochlorothiazide
Vasodilator	Aspirin/Dipyridamole, Dipyridamole, Hydralazine, Hydralazine/Hydrochlorothiazide, Isosorb Dinit/Hydralazine, Isosorbide, Isosorbide, Minoxidil, Nitroglycerin
Other	Reserpine
3. Antilipidemics	
Statins	Atorvastatin, Fluvastatin, Lovastatin, Pravastatin, Simvastatin
Fibrate	Bezafibrate, Clofibrate, Ciprofibrate, Fenofibrate, Gemfibrozil
Niacin	Niacin
Bile acid sequestrants	Cholestyramine/Aspartame, Cholestyramine/Sucrose
Ezetimibe	Ezetimibe
4. Phosphate binders	
Lanthanum	Lanthanum
Sevelamer	Sevelamer
Calcium	Calcium, Calcium/Mag Carb/Fa, Calcium/Vitamin D2, Calcium/Vitamin D3
5. Calcimimetics	
Cinacalcet	Cinacalcet

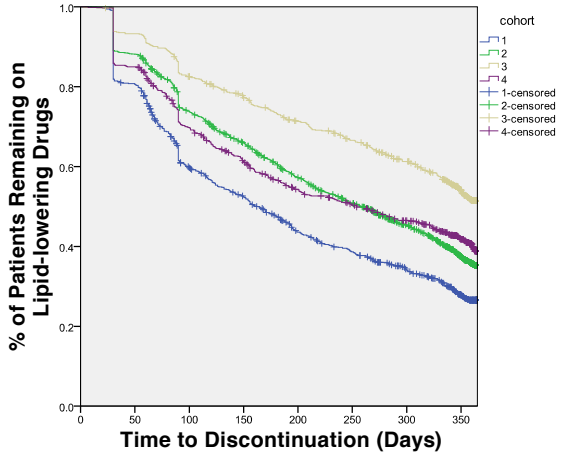
APPENDIX B Patient Selection

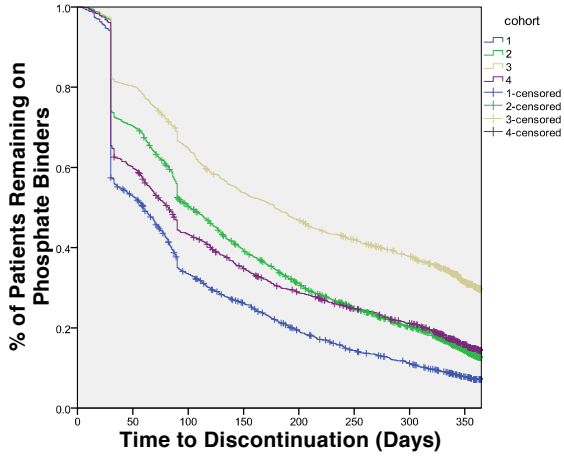


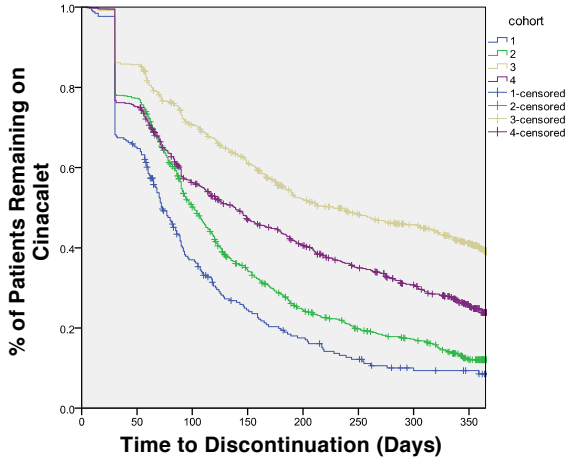
APPENDIX C Kaplan-Meier Survival Curves Describing Percentage of Patients Who Remain Persistent on Medication Among Study Cohorts











APPENDIX D Medication Persistence Until 60-Day Gap by 5 Therapeutic Classes of Outpatient Prescription Medications Among Study Cohorts

Medication Persistence	All (N = 11,732)	Cohort 1 Initial Coverage (n=3,678)	Cohort 2 Coverage Gap (n = 4,349)	Cohort 3 Catastrophic Coverage (n = 1,310)	Cohort 4 Low-Income Subsidy (n = 2,395)	*P* Value[a]
Antihyperglycemics, n	**3,819**	**851**	**1,630**	**523**	**815**	
Persistence (mean, SD)	219.7 (130.5)	191.4 (130.7)	220.2 (128.5)	259.1 (121.3)	223.2 (133.0)	<0.001
Discontinuation (n, %)	2,412 (63.2)	583 (68.5)	1,089 (66.8)	259 (49.5)	481 (59.0)	<0.001
Hazard ratio (95% CI)[b]	N/A	1.46 (1.29-1.66)	1.26 (1.13-1.42)	0.78 (0.66-0.91)	1.00	
Antihypertensives, n	**9,863**	**2,975**	**3,976**	**1,189**	**2,133**	
Persistence (mean, SD)	289.3 (110.7)	254.1 (124.6)	304.5 (99.2)	320.3 (87.2)	290.6 (111.3)	<0.001
Discontinuation (n, %)	3,610 (36.6)	1,346 (48.6)	1,264 (32.7)	272 (23.3)	728 (35.3)	<0.001
Hazard ratio (95% CI)[b]	N/A	1.82 (1.66-2.00)	1.05 (0.95-1.15)	0.70 (0.60-0.80)	1.00	
Antilipidemics, n	**4,607**	**922**	**2,119**	**746**	**820**	
Persistence (mean, SD)	257.0 (117.2)	222.7 (123.7)	258.7 (114.7)	297.5 (98.4)	254.3 (120.1)	<0.001
Discontinuation (n, %)	2,208 (47.9)	524 (56.8)	1,066 (50.3)	246 (33.0)	372 (45.4)	<0.001
Hazard ratio (95% CI)[b]	N/A	1.84 (1.60-2.11)	1.38 (1.22-1.57)	0.74 (0.63-0.88)	1.00	
Phosphate binders, n	**7,753**	**1,729**	**3,185**	**1,151**	**1,688**	
Persistence (mean, SD)	202.0 (126.1)	158.7 (119.4)	204.7 (121.0)	258.0 (118.5)	203.1 (131.3)	<0.001
Discontinuation n, %)	5,505 (71.0)	1,401 (81.0)	2,365 (74.3)	590 (51.3)	1,149 (68.1)	<0.001
Hazard ratio (95% CI)[b]	N/A	1.83 (1.69-1.99)	1.34 (1.24-1.45)	0.70 (0.63-0.78)	1.00	
Calcimimetics, n	**2,436**	**261**	**854**	**606**	**718**	
Persistence (mean, SD)	195.2 (122.1)	136.6 (106.0)	171.5 (111.1)	244.7 (119.4)	202.9 (125.9)	<0.001
Discontinuation (n, %)	1,511 (62.0)	198 (75.9)	643 (75.3)	257 (42.4)	413 (57.5)	<0.001
Hazard ratio (95% CI)[b]	N/A	2.31 (1.93-2.75)	1.83 (1.60-2.09)	0.73 (0.62-0.86)	1.00	

[a] *By X^2 test to compare distributions of categorical variables and ANOVA to compare continuous variables among 4 cohorts.*

[b] *Cox proportional hazards regression model was used to adjust for age, gender, race, and region of residence, primary disease causing ESRD, ESRD duration, CCI scores, and presence of chronic diseases (cardiovascular disease, diabetes mellitus, hypertension, dyslipidemia, cancer, and chronic lung disease).*

CCI = Charlson Comorbidity Index; CI = confidence interval; ESRD = end-stage renal disease; N/A = not applicable; SD = standard deviation.