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AJKD
Original Investigation

Predialysis Cardiovascular Disease Medication Adherence and Mortality After Transition to Dialysis

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Background: Medication nonadherence is a known risk factor for adverse outcomes in the general population. However, little is known about the association of predialysis medication adherence among patients with advanced chronic kidney disease and mortality following their transition to dialysis.

Study Design: Observational study.

Setting & Participants: 32,348 US veterans who transitioned to dialysis during 2007 to 2011.

Predictors: Adherence to treatment with cardiovascular drugs, ascertained from pharmacy database records using proportion of days covered (PDC) and persistence during the predialysis year.

Outcomes: Post–dialysis therapy initiation all-cause and cardiovascular mortality, using Cox models with adjustment for confounders.

Results: Mean age of the cohort was 72 ± 11 (SD) years; 96% were men, 74% were white, 23% were African American, and 69% had diabetes. During a median follow-up of 23 (IQR, 9-36) months, 18,608 patients died. Among patients with PDC > 80%, there were 14,006 deaths (mortality rate, 283 [95% CI, 278-288]/1,000 patient-years]); among patients with PDC > 60% to 80%, there were 3,882 deaths (mortality rate, 294 [95% CI, 285-304]/1,000 patient-years); among patients with PDC ≤ 60%, there were 720 deaths (mortality rate, 291 [95% CI, 271-313]/1,000 patient-years). Compared with patients with PDC > 80%, the adjusted HR for post–dialysis therapy initiation all-cause mortality for patients with PDC > 60% to 80% was 1.12 (95% CI, 1.08-1.16), and for patients with PDC ≤ 60% was 1.21 (95% CI, 1.11-1.30). In addition, compared with patients showing medication persistence, adjusted HR risk for post–dialysis therapy initiation all-cause mortality for patients with nonpersistence was 1.11 (95% CI, 1.05-1.16). A similar trend was detected for cardiovascular mortality and in subgroup analyses.

Limitations: Large number of missing values; results may not be generalizable to women or the general US population.

Conclusions: Predialysis cardiovascular medication nonadherence is an independent risk factor for post-dialysis mortality in patients with advanced chronic kidney disease transitioning to dialysis therapy. Further studies are needed to assess whether interventions targeting adherence improve survival after dialysis therapy initiation. *Am J Kidney Dis.* 68(4):609-618. *Published by Elsevier Inc. on behalf of the National Kidney Foundation, Inc. This is a US Government Work. There are no restrictions on its use.*

INDEX WORDS: Transition to dialysis; medication adherence; treatment compliance; proportion of days covered (PDC); medication possession ratio (MPR); drug therapy; cardiovascular mortality; mortality; advanced chronic kidney disease; anti-hypertensive medications; statins; aspirin; cardiovascular pharmacotherapy; pharmacy database analysis.

Mortality rates in patients with end-stage renal disease (ESRD) continue to be high.[1] Therefore, identification and correction of modifiable risk factors influencing all-cause mortality in patients with ESRD is of paramount importance.

Only a limited number of interventions, such as timely arteriovenous fistula creation and adequate access to specialist care during the predialysis period, have been shown to be associated with better outcomes in patients with ESRD.[2-6] Cardiovascular

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disease is the leading cause of mortality in predialysis patients,[7] and antihypertensive medications, statins, and aspirin are widely used in the cardiovascular risk management of these patients.[8] Adherence to pharmacotherapy in general hypertensive populations has been linked to reduced risk for various outcomes.[9-13] However, little is known about the association of medication adherence during the predialysis period with all-cause and cardiovascular mortality after dialysis therapy initiation.

We investigated the association of adherence to medications targeting cardiovascular risk in the last year prior to initiating dialysis therapy with all-cause and cardiovascular mortality after dialysis therapy initiation in a cohort of US veterans with advanced chronic kidney disease (CKD) transitioning to dialysis therapy. We applied 3 methods of adherence determination using pharmacy databases: (1) proportion of days covered (PDC) and (2) medication possession ratio (MPR) to evaluate adherence (the extent to which patients follow prescribed dosing regimens) and (3) persistence with drug therapy (time from initial drug dispensation to "unauthorized" discontinuation). We hypothesized that lower medication adherence results in higher all-cause and cardiovascular mortality.

METHODS

Study Population

We analyzed data from the Transition of Care in CKD (TC-CKD) Study, a retrospective cohort study examining US veterans with CKD transitioning to dialysis therapy from October 1, 2007, through September 30, 2011. A total of 52,172 patients were identified from the US Renal Data System (USRDS). We excluded patients whose medication adherence could not be calculated due to missing pharmacy data (n = 19,697) and those who had lack of follow-up data (n = 127). The final cohort consisted of 32,348 patients (Fig 1).

Covariates

Data from the USRDS Patient and Medical Evidence files were used to determine patients' baseline demographic information and type of vascular access at the time of dialysis therapy initiation. We used the national US Department of Veterans Affairs (VA) Corporate Data Warehouse LabChem data files to extract data about predialysis serum creatinine levels.[14] Other laboratory variables were collected from the Decision Support System National Data Extracts Laboratory Results file,[15] and baseline values were defined as the last quarterly average before dialysis therapy initiation or the second-from-last quarterly average if the last data point was missing. Data for medication exposure were obtained from both Centers for Medicare & Medicaid Services (CMS; Medicare Part D) and VA pharmacy dispensation records.[16] Patients who received at least 1 dispensation of outpatient medication within 1 year of dialysis therapy initiation were recorded as having been treated with these medications. Information about comorbid conditions at the time of dialysis therapy initiation was extracted from the VA Inpatient and Outpatient Medical SAS Datasets[17] and from CMS data sets using diagnostic and procedure codes. Cardiovascular/cerebrovascular disease was defined as the presence of diagnostic codes for coronary artery disease, angina, myocardial infarction, or cerebrovascular disease. We calculated Charlson Comorbidity Index score using the Deyo modification for administrative data sets, without including kidney disease.[18]

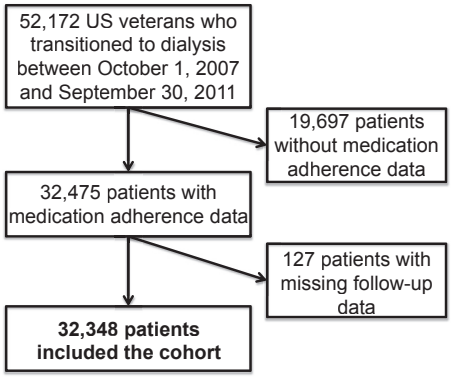

Figure 1. Flow chart of patient selection.

Exposure Variables

Figure S1 (provided as online supplementary material) depicts schematics of different methods of adherence calculation. PDC was defined as proportion of days with drug available in the measurement period, capped at 100%. MPR was calculated as percentage of total days covered by the dispensed drug supply during the measurement period. Numerically, MPR can take values between 0% and >100%.[19,20] For medication persistence, the following algorithm was used: persistence was coded as 1 (present) if a patient refilled each subsequent prescription with gaps not exceeding 60 days; otherwise, it was coded as 0 (absent, or nonpersistent).[20]

Detailed information about each prescription was collected during the last year before dialysis therapy for the following cardiovascular drugs: angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, calcium channel blockers, β-blockers, α-blockers, direct vasodilators, diuretics (loop and thiazide), aspirin, and statins. The index date was the date of the first available prescription (in the last year before dialysis therapy initiation) regardless of any prescriptions before this date. The last prescription had to be dispensed before dialysis therapy initiation, and the full prescription period was included in the denominator regardless of whether the supply lasted until after the dialysis therapy initiation date. Only outpatient prescriptions were taken into account. Any inpatient time was added to the denominator. Averaged values of the PDCs and MPRs of all medication groups were used as exposure variables in analyses. Medication adherence was categorized as follows: (1) for PDC: >80%, >60% to ≤80%, and ≤60%; (2) for MPR: ≥100%, >80% to <100%, >60% to ≤80%, and ≤60%. We dichotomized medication persistence as average persistence < 50% or ≥50%, derived from individual drug prescription refills. PDCs and MPRs were also treated as continuous variables to examine nonlinear associations using restricted cubic spline analyses.

Outcome Assessment

The coprimary outcomes of this study were all-cause and cardiovascular mortality after dialysis therapy initiation. Death dates were obtained from the USRDS and VA Vital Status Files (up to December 27, 2012). Cause of death was obtained from the USRDS (up to October 6, 2011).

Statistical Analysis

Data are presented as number and percentage for categorical variables and as mean ± standard deviation or median and interquartile range (IQR) as appropriate. Categorical variables were compared with χ^2 tests. Continuous variables were compared using *t* tests, Mann-Whitney *U* tests, or analysis of variance, as appropriate. We used Cox proportional hazard regressions to

Table 1. Baseline Characteristics of Study Population Overall and by PDC Categories

	All (N = 32,348)	PDC > 80% (n = 24,455)	PDC > 60%-80% (n = 6,633)	PDC ≤ 60% (n = 1,260)	*P*
Sociodemographic					
Age, y	72 ± 11	73 ± 11	71 ± 12	67 ± 13	<0.001
Male sex	31,045 (96)	23,627 (97)	6,264 (94)	1,154 (92)	<0.001
Race					<0.001
White	24,064 (74)	18,943 (78)	4,410 (67)	711 (56)	
African American	7,531 (23)	4,966 (20)	2,049 (31)	516 (41)	
Marital status					<0.001
Married	18,654 (58)	14,576 (60)	3,529 (54)	549 (44)	
Nonmarried	13,242 (42)	9,561 (40)	2,996 (46)	685 (56)	
Comorbid conditions					
Charlson Comorbidity Index score	5 [3-7]	5 [3-7]	5 [3-7]	5 [3-7]	0.003
Diabetes	22,144 (69)	16,605 (69)	4,694 (71)	845 (68)	<0.001
Cardiovascular/cerebrovascular diseases	16,117 (50)	12,278 (50)	3,263 (49)	576 (46)	0.004
Myocardial infarction	9,674 (30)	7,361 (31)	1,979 (30)	334 (27)	0.02
Congestive heart failure	19,270 (60)	14,348 (59)	4,147 (63)	775 (62)	<0.001
Peripheral vascular disease	13,608 (43)	10,435 (43)	2,699 (41)	474 (38)	<0.001
Hypertension	28,764 (91)	21,923 (91)	5,796 (89)	1,045 (85)	<0.001
Cerebrovascular diseases	10,743 (34)	8,203 (34)	2,170 (33)	370 (30)	0.005
Dementia	989 (3)	718 (3)	219 (3)	52 (4)	0.03
Chronic pulmonary diseases	14,924 (47)	11,207 (46)	3,147 (48)	570 (46)	0.09
Connective tissue diseases	1,486 (5)	1,157 (5)	286 (4)	43 (3)	0.04
Peptic ulcer diseases	2,757 (9)	2,036 (8)	602 (9)	119 (10)	0.08
Mild liver diseases	3,695 (12)	2,601 (11)	890 (14)	204 (16)	<0.001
Moderate to severe liver diseases	785 (2)	532 (2)	205 (3)	48 (4)	<0.001
Paraplegia and hemiplegia	1,182 (4)	881 (4)	246 (4)	55 (4)	0.4
Malignancy	8,110 (25)	6,297 (26)	1,554 (24)	259 (21)	<0.001
Metastatic carcinoma	1,033 (3)	792 (3)	202 (3)	39 (3)	0.7
Depression	9,957 (31)	7,221 (30)	2,265 (34)	471 (38)	<0.001
Anxiety	2,102 (6)	1,586 (6)	442 (7)	74 (6)	0.6
AIDS/HIV	281 (1)	167 (1)	81 (1)	33 (3)	<0.001
Vascular access					<0.001
Arteriovenous fistula	7,494 (23)	5,802 (24)	1,474 (22)	218 (17)	
Arteriovenous graft	716 (2)	556 (2)	142 (2)	18 (1)	
Catheter	3,140 (10)	2,328 (10)	687 (10)	125 (10)	
Unknown	20,998 (65)	15,769 (64)	4,330 (65)	899 (71)	
Laboratory results					
Serum sodium, mEq/L	139 ± 3	139 ± 3	139 ± 3	139 ± 3	<0.001
Blood hemoglobin, g/dL	10.6 ± 1.6	10.7 ± 1.6	10.5 ± 1.6	10.2 ± 1.7	<0.001
Serum albumin, g/dL	3.39 ± 0.6	3.42 ± 0.6	3.32 ± 0.6	3.18 ± 0.7	<0.001
Serum potassium, mEq/L	4.51 ± 0.6	4.51 ± 0.6	4.50 ± 0.6	4.51 ± 0.6	0.2
Serum urea nitrogen, mg/dL	64 [48-80]	64 [49-80]	63 [48-81]	61 [48-78]	0.4
Serum glucose, mg/dL	130 ± 50	130 ± 50	131 ± 52	134 ± 54	0.2
Blood hemoglobin A_{1c}, %	6.8 ± 1.4	6.8 ± 1.4	6.9 ± 1.6	7.0 ± 1.7	0.02
Serum cholesterol					
Total, mg/dL	145 [119-176]	143 [118-173]	150 [123-185]	159 [130-199]	<0.001
LDL, mg/dL	78 [59-102]	76 [58-100]	82 [61-111]	91 [66-124]	<0.001
HDL, mg/dL	36 [29-45]	36 [29-44]	37 [30-46]	38 [30-48]	<0.001
Serum triglycerides, mg/dL	120 [83-176]	121 [83-176]	118 [84-175]	117 [81-168]	0.3
Serum calcium, mg/dL	8.71 ± 0.8	8.75 ± 0.8	8.58 ± 0.8	8.38 ± 0.9	<0.001
Serum phosphate, mg/dL	5.22 ± 1.4	5.20 ± 1.4	5.28 ± 1.4	5.45 ± 1.4	<0.001
Serum alkaline phosphatase, U/L	84 [65-111]	82 [65-109]	87 [67-115]	90 [72-123]	<0.001
Serum intact PTH, pg/mL	221 [126-368]	212 [120-349]	249 [149-416]	301 [167-496]	<0.001
Serum bicarbonate, mEq/L	22.9 ± 4.2	23.0 ± 4.2	22.6 ± 4.3	22.1 ± 4.3	<0.001
White blood cells, 1,000/μL	7.4 [6.0-9.1]	7.4 [6.1-9.1]	7.3 [5.9-9.0]	7.3 [5.9-9.1]	0.008
Urine ACR, mg/g	349 [34-1,810]	299 [32-1,565]	477 [51-2,181]	2,412 [341-4,606]	<0.001
Body mass index, kg/m^2	30.0 ± 6.6	30.1 ± 6.7	29.7 ± 6.5	28.8 ± 6.3	<0.001
Last outpatient eGFR, mL/min/1.73 m^2	16 [10-26]	16 [10-26]	15 [10-25]	17 [10-30]	0.9

(Continued)

Table 1 (Cont'd). Baseline Characteristics of Study Population Overall and by PDC Categories

	All (N = 32,348)	PDC > 80% (n = 24,455)	PDC > 60%-80% (n = 6,633)	PDC ≤ 60% (n = 1,260)	*P*
Medication use					
Vitamin D analogue	10,549 (33)	8,030 (33)	2,182 (33)	337 (27)	<0.001
β-Blocker	24,778 (77)	18,560 (76)	5,286 (80)	932 (74)	<0.001
α-Blocker	12,055 (37)	9,399 (38)	2,343 (35)	313 (25)	<0.001
Bicarbonate	4,629 (14)	3,494 (14)	974 (15)	161 (13)	0.2
Calcium channel blocker	22,080 (68)	18,848 (69)	4,449 (67)	783 (62)	<0.001
Diuretic	26,199 (81)	19,591 (80)	5,614 (85)	994 (79)	<0.001
EPO	7,655 (24)	5,730 (23)	1,659 (25)	266 (21)	0.003
NSAID	34 (0)	28 (0)	4 (0)	2 (0)	0.4
Phosphate binder	8,740 (27)	6,458 (26)	1,920 (29)	362 (29)	<0.001
ACEi/ARB	19,117 (59)	14,593 (60)	3,876 (58)	648 (51)	<0.001
Direct vasodilator	1,483 (5)	1,093 (4)	347 (5)	43 (3)	0.004
Aspirin	7,865 (24)	5,782 (24)	1,796 (27)	287 (23)	<0.001
Statin	22,684 (70)	17,432 (71)	4,545 (69)	707 (56)	<0.001

Note: Values for categorical variables are given as number (percentage); values for continuous variables, as mean ± standard deviation or median [interquartile range]. Conversion factors for units: bilirubin in mg/dL to μmol/L, ×17.1; calcium in mg/dL to mmol/L, ×0.2495; cholesterol in mg/dL to mmol/L, ×0.02586; glucose in mg/dL to mmol/L, ×0.05551; triglycerides in mg/dL to mmol/L, ×0.01129; serum urea nitrogen in mg/dL to mmol/L, ×0.357.

Abbreviations: ACR, albumin-creatinine ratio; ACEi/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; EPO, erythropoietin; HDL, high-density lipoprotein; HIV, human immunodeficiency virus; LDL, low-density lipoprotein; NSAID, nonsteroidal anti-inflammatory drug; PDC, proportion of days covered; PTH, parathyroid hormone.

determine the association of medication adherence with all-cause and cardiovascular mortality, considering the time from the date of dialysis therapy initiation until the event of interest. Patients were followed up until death or other censoring events, including kidney transplantation, loss to follow-up, or until December 27, 2012, whichever happened first. For cardiovascular mortality, patients were followed up until death or other censoring events or until October 6, 2011. The influence of potential confounders was analyzed by incremental adjustments based on a priori considerations: unadjusted (model 1); age, sex, race/ethnicity (whites, African Americans, Hispanics, and others), marital status (married, divorced, single, and widowed), and zip code (model 2); model 2 plus comorbid conditions (diabetes mellitus, congestive heart failure, cardiovascular/cerebrovascular disease, depression, anxiety, and Charlson Comorbidity Index score), and type of vascular access (model 3); and model 3 plus blood/serum hemoglobin, bicarbonate, albumin, and urea nitrogen levels and last estimated glomerular filtration rate before ESRD (model 4). Model 4 had high proportions of missing data (40%-50%, discussed next); therefore, we used model 3 as the main multivariable-adjusted model.

Restricted cubic spline models were used to investigate nonlinearity in model 3. The associations of PDC with all-cause mortality were examined in subgroups of patients categorized by age, race, Charlson Comorbidity Index level, and the presence of diabetes mellitus, congestive heart failure, and cerebro- and cardiovascular disease. Interactions were formally tested for by the inclusion of interaction terms.

For model 4, we had only 13,693 (42%) patients with complete data available. Missing values were not imputed in primary analyses, but were substituted after adding the laboratory data (blood hemoglobin [49% missing], serum bicarbonate [47% missing], serum albumin [49% missing], serum urea nitrogen [45% missing], and last outpatient estimated glomerular filtration rate [23% missing]) with the use of multiple imputation procedures (creating 5 data sets) using STATA's "mi" set of commands in sensitivity analyses. We also assessed the association of separate PDCs of each medication category with all-cause mortality as sensitivity analysis.

Compared with patients excluded due to missing medication data, included patients were older, were more likely to be men and white (74% vs 70%), had a higher arteriovenous fistula rate (23% vs 14%), and had higher prevalences of diabetes (69% vs 55%), cardiovascular/cerebrovascular disease (50% vs 29%), hypertension (91% vs 69%), and congestive heart failure (60% vs 50%; Table S1).

P values are 2 sided and reported as significant at <0.05 for all analyses. All analyses were conducted using STATA MP, version 14 (STATA Corp LP). The study was approved by the institutional review boards of the Memphis and Long Beach VA Medical Centers, with exemption from informed consent.

RESULTS

Baseline Characteristics

Mean age of the cohort at baseline was 72 ± 11 (standard deviation) years; 96% were men, 74% were white, 23% were African American, and 69% had diabetes. The median of the last pre-ESRD outpatient estimated glomerular filtration rate was 16 (IQR, 10-26) mL/min/1.73 m^2. Baseline characteristics of patients categorized by PDC categories are shown in Table 1. Patients with a higher PDC (>80%) were older; were more likely to be white and married; were more likely to initiate dialysis therapy with an arteriovenous fistula; were more likely to be receiving a statin and angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; had a higher prevalence of hypertension; had higher serum albumin and calcium levels; had lower serum phosphate, parathyroid hormone, total and low-density lipoprotein cholesterol levels, and urine albumin-creatinine ratios; and had more favorable metabolic and anemia markers (Table 1). Table S2 shows adherence parameters in

Table 2. Association of PDC With All-Cause Mortality After Dialysis Therapy Initiation

	Model 1 (32,348 patients, 18,608 events)		Model 2 (30,943 patients, 17,789 events)		Model 3 (30,592 patients, 17,610 events)		Model 4 (13,693 patients, 6,904 events)	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
PDC > 80%	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
PDC > 60%-80%	1.04 (1.00-1.08)	0.04	1.17 (1.12-1.21)	<0.001	1.12 (1.08-1.16)	<0.001	1.06 (1.00-1.13)	0.05
PDC ≤ 60%	1.02 (0.95-1.10)	0.5	1.31 (1.21-1.41)	<0.001	1.21 (1.11-1.30)	<0.001	1.18 (1.03-1.36)	0.02

Note: Model 1: unadjusted; model 2: adjusted for age, sex, race/ethnicity, marital status, and zip code; model 3: adjusted for model 2 plus Charlson Comorbidity Index score and presence of diabetes, congestive heart failure, cardiovascular/cerebrovascular disease, depression, anxiety, and type of vascular access; and model 4: adjusted for model 3 plus blood/serum hemoglobin, bicarbonate, albumin, and urea nitrogen levels and last estimated glomerular filtration rate before end-stage renal disease.

Abbreviations: CI, confidence interval; HR, hazard ratio; PDC, proportion of days covered.

different medication groups. In individual medication groups, PDC, MPR, and nonpersistence were very similar (Table S2).

Predialysis PDC and All-Cause and Cardiovascular Mortality

Median follow-up was 23 (IQR, 9-36) months. There were 18,608 deaths (58%; mortality rate, 286 [95% confidence interval (CI), 281-290]/1,000 patient-years) in the entire cohort, with 14,006 deaths (57%; mortality rate, 283 [95% CI, 278-288]/1,000 patient-years) in patients with PDC > 80%, 3,882 deaths (59%; mortality rate, 294 [95% CI, 285-304]/1,000 patient-years) in patients with PDC > 60% to 80%, and 720 deaths (57%; mortality rate, 291 [95% CI, 271-313]/1,000 patient-years) in patients with PDC ≤ 60%. Compared with patients with PDC > 80%, patients with PDC > 60% to 80% were at higher risk for all-cause mortality (hazard ratio [HR], 1.04; 95% CI, 1.00-1.08), whereas patients with PDC ≤ 60% had similar risk (HR, 1.02; 95% CI, 0.95-1.10) in the unadjusted model (Table 2). After adjustment for sociodemographic parameters and comorbid conditions, patients with PDC > 60% to 80% (HR, 1.12; 95% CI, 1.08-1.16) and patients with PDC ≤ 60% (HR, 1.21; 95% CI, 1.11-1.30) had significantly higher risk for mortality compared with patients with PDC > 80% (Table 2). Similar trends were detected after further adjustment for laboratory variables, although the number of observations decreased substantially due to missing values (Table 2). In the multiple imputation model, patients with PDC > 60% to 80% (HR, 1.11; 95% CI, 1.07-1.15) and patients with PDC ≤ 60% (HR, 1.20; 95% CI, 1.12-1.30) had significantly higher risk for all-cause mortality compared with patients with PDC > 80%. Figure 2 shows an inverse linear association between PDC and all-cause (Fig 2A) and cardiovascular (Fig 2B) mortality in analyses using restricted cubic splines. Higher risk for death was also observed in the various studied subgroups (Fig 3). Table S3 shows associations between the different PDCs of each medication category and all-cause mortality. The PDCs of loop and thiazide diuretics and β-blockers showed significant inverse associations with all-cause mortality (Table S3). Similar results were found for cardiovascular mortality (Table 3).

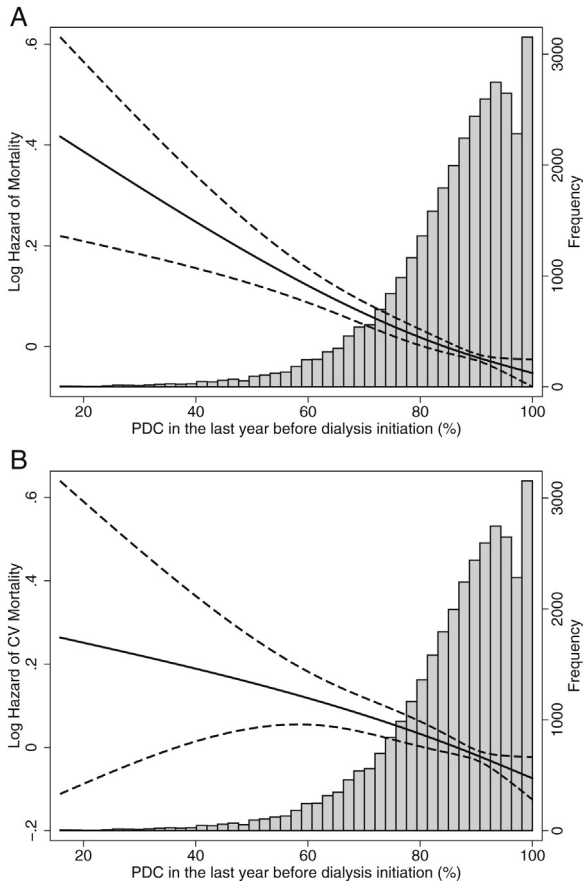

Figure 2. Association between percentage of days a participant had medication available (proportion of days covered [PDC]) in the last year before end-stage renal disease and (A) post–dialysis therapy initiation all-cause mortality and (B) cardiovascular (CV) mortality using fractional polynomials and restricted cubic splines (model adjusted for age; sex; race; marital status; zip code; Charlson Comorbidity Index score; presence of diabetes, congestive heart failure, cardiovascular/cerebrovascular disease, depression, and anxiety; and type of vascular access).

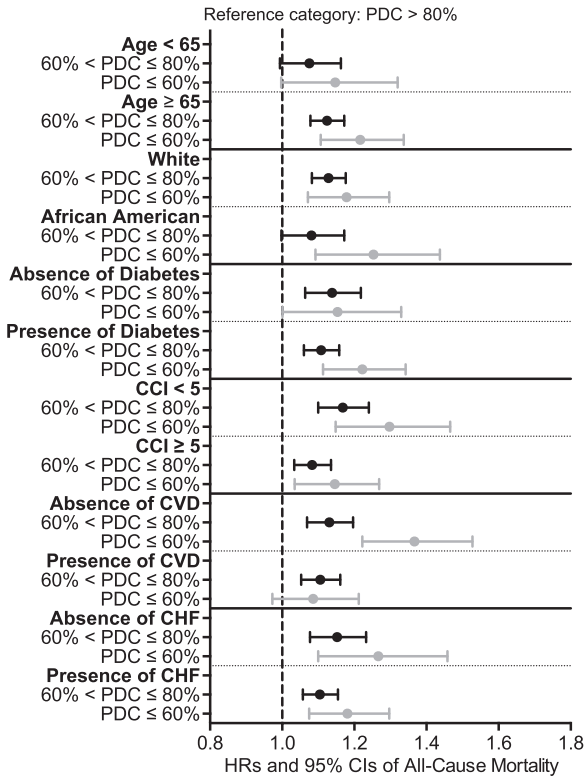

Figure 3. Association between percentages of days a participant had medication available (proportion of days covered [PDC]) in the last year before end-stage renal disease and post–dialysis therapy initiation mortality in different subgroups of patients using adjusted Cox regression analyses (model adjusted for age, sex, race, marital status, zip code, Charlson Comorbidity Index [CCI] score, presence of diabetes, congestive heart failure [CHF], cardiovascular [CVD]/cerebrovascular disease, presence of depression, presence of anxiety, and type of vascular access). Abbreviations: CI, confidence interval; HR, hazard ratio.

Predialysis MPR, Medication Persistence, and All-Cause and Cardiovascular Mortality

Compared with patients with MPR > 80% to <100%, patients with MPR > 60% to ≤80% (HR, 1.11; 95% CI, 1.06-1.17) and patients with MPR ≤ 60% (HR, 1.19; 95% CI, 1.08-1.30) had significantly higher risk for all-cause mortality. Meanwhile, patients with MPR ≥ 100% (HR, 0.96; 95% CI, 0.93-0.99) had significantly lower risk for all-cause mortality after adjustment for sociodemographic parameters and comorbid conditions (Table S4). Similar trends were detected after further adjustment for laboratory variables (Table S4). In the multiple imputation model, patients with MPR > 60% to ≤80% (HR, 1.10; 95% CI, 1.05-1.15) and patients with MPR ≤ 60% (HR, 1.18; 95% CI, 1.08-1.29) had significantly higher risk for all-cause mortality, whereas patients with MPR ≥ 100% (HR, 0.96; 95% CI, 0.93-0.99) had significantly lower risk for all-cause mortality compared with patients with MPR > 80% to <100%. Figure S2 shows the association between MPR and all-cause (Fig S2A) and cardiovascular (Fig S2B) mortality using restricted cubic splines. Results were similar in all examined subgroups (Figure S3). Similar trends were found with cardiovascular mortality (Table S5).

Compared with patients who were persistent with their medication refills, nonpersistent patients (HR, 1.11; 95% CI, 1.05-1.16) had significantly higher risk for all-cause mortality (Table 4). Similar results were detected (HR, 1.10; 95% CI, 1.05-1.16) after further adjustment for laboratory variables in our multiple imputation model, in subgroup analyses (Fig 4), and for cardiovascular mortality (Table 5).

DISCUSSION

In a large cohort of patients with advanced CKD, we examined the association between 1-year predialysis adherence to cardiovascular medications and all-cause and cardiovascular mortality following dialysis therapy initiation. We used a pharmacy database analysis to assess 2 parts of medication adherence: adherence and persistence.[21] Inadequate adherence to cardiovascular pharmacotherapy was associated with reduced survival independent of demographic, comorbid condition, and laboratory characteristics.

Table 3. Association of PDC With Cardiovascular Mortality After Dialysis Therapy Initiation

	Model 1 (32,065 patients, 5,375 events)		Model 2 (30,692 patients, 5,132 events)		Model 3 (30,366 patients, 5,066 events)		Model 4 (13,606 patients, 1,951 events)	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
PDC > 80%	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
PDC > 60%-80%	1.03 (0.97-1.10)	0.3	1.16 (1.08-1.24)	<0.001	1.11 (1.03-1.18)	0.004	1.05 (0.94-1.17)	0.4
PDC ≤ 60%	1.00 (0.87-1.15)	0.9	1.24 (1.07-1.43)	0.005	1.15 (0.99-1.33)	0.06	1.09 (0.83-1.43)	0.5

Note: Model 1: unadjusted; model 2: adjusted for age, sex, race/ethnicity, marital status, and ZIP code; model 3: adjusted for model 2 plus Charlson Comorbidity Index score and presence of diabetes, congestive heart failure, cardiovascular/cerebrovascular disease, depression, anxiety, and type of vascular access; and model 4: adjusted for model 3 plus blood/serum hemoglobin, bicarbonate, albumin, and urea nitrogen levels and last estimated glomerular filtration rate before end-stage renal disease.

Abbreviations: CI, confidence interval; HR, hazard ratio; PDC, proportion of days covered.

Table 4. Association of Medication Persistence With All-Cause Mortality After Dialysis Therapy Initiation

	Model 1 (32,348 patients, 18,608 events)		Model 2 (30,943 patients, 17,789 events)		Model 3 (30,592 patients, 17,610 events)		Model 4 (13,693 patients, 6,904 events)	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Persistence with >50% of medication	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
Nonpersistence	0.99 (0.94-1.04)	0.8	1.16 (1.10-1.22)	<0.001	1.11 (1.05-1.16)	<0.001	1.08 (0.99-1.17)	0.06

Note: Medication persistence defined as patient refilling prescription without a gap exceeding 60 days. Model 1: unadjusted; model 2: adjusted for age, sex, race/ethnicity, marital status, and ZIP code; model 3: adjusted for model 2 plus Charlson Comorbidity Index score and presence of diabetes, congestive heart failure, cardiovascular/cerebrovascular disease, depression, anxiety, and type of vascular access; and model 4: adjusted for model 3 plus blood/serum hemoglobin, bicarbonate, albumin, and urea nitrogen levels and last estimated glomerular filtration rate before end-stage renal disease.

Abbreviations: CI, confidence interval; HR, hazard ratio.

Several predialysis demographic factors such as age, sex, race, socioeconomic status, and comorbid conditions were linked to post–dialysis therapy initiation survival.[22-25] These factors are difficult or impossible to modify but bear importance in the risk stratification and estimation of prognosis after initiating renal replacement therapy. For example, a new prediction risk score was recently developed based on demographic and comorbid condition characteristics to help with shared decision making about dialysis therapy initiation in elderly patients with ESRD.[25] However, it is equally important to understand potentially modifiable predialysis risk factors and behaviors influencing survival after initiating dialysis therapy. Timely arteriovenous fistula placement and predialysis care involving a nephrology specialist were shown to be associated with reduced all-cause mortality in the post–dialysis therapy initiation period.[2-6,26] The quality of predialysis care as defined by the number of provider visits before ESRD onset was also shown to influence survival. One study found that patients having 3 or more predialysis visits in the 6-month period before dialysis therapy initiation had 28% higher survival compared with patients who had fewer than 3 visits during the same period.[27] In addition to number of visits, nephrology care of 6 months' duration or less before ESRD onset was linked to 23% to 27% higher 1-year all-cause mortality in 2 recent studies.[28,29]

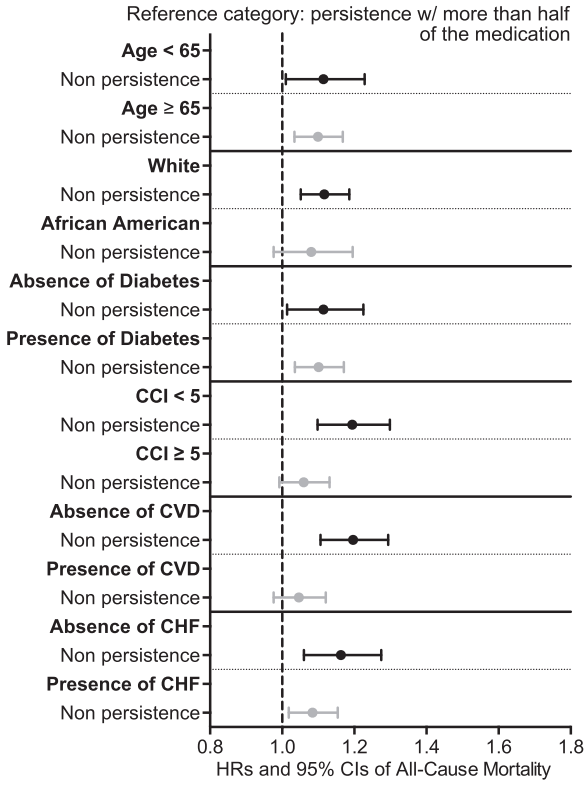

Figure 4. Association between medication persistence (less than 60-day prescription refill gap for >50% of medications) in the last year before end-stage renal disease and post–dialysis therapy initiation mortality in different subgroups of patients using adjusted Cox regression analyses (model adjusted for age, sex, race, marital status, zip code, Charlson Comorbidity Index [CCI] score, presence of diabetes, congestive heart failure [CHF], cardiovascular [CVD]/cerebrovascular disease, presence of depression, presence of anxiety, and type of vascular access).

To our knowledge, no other studies have attempted to evaluate the influence of predialysis adherence to cardiovascular medications on all-cause and cardiovascular mortality after initiation of dialysis therapy. However, adequate adherence to cardiovascular medications has been shown to be associated with better outcomes in the general population.[9,13,30] A large meta-analysis including 1,978,919 individuals concluded that good medication adherence to antihypertensive drugs was associated with 45% lower risk for all-cause mortality and good adherence to statins was associated with 29% reduced risk for death.[11] Our study involved a population of patients with advanced CKD transitioning to dialysis therapy, and its results further strengthen the overall importance of adherence to cardiovascular drugs. Because

Table 5. Association of Medication Persistence With Cardiovascular Mortality After Dialysis Therapy Initiation

	Model 1 (32,065 patients, 5,375 events)		Model 2 (30,692 patients, 5,132 events)		Model 3 (30,366 patients, 5,066 events)		Model 4 (13,606 patients, 1,951 events)	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Persistence with >50% of medication	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
Nonpersistence	0.99 (0.91-1.09)	0.9	1.15 (1.04-1.26)	0.004	1.11 (1.06-1.22)	0.04	1.06 (0.91-1.23)	0.5

Note: Persistence defined as patient refilling prescription without a gap exceeding 60 days. Model 1: unadjusted; model 2: adjusted for age, sex, race/ethnicity, marital status, and ZIP code; model 3: adjusted for model 2 plus Charlson Comorbidity Index score and presence of diabetes, congestive heart failure, cardiovascular/cerebrovascular disease, depression, anxiety, and type of vascular access; and model 4: adjusted for model 3 plus blood/serum hemoglobin, bicarbonate, albumin, and urea nitrogen levels and last estimated glomerular filtration rate before end-stage renal disease.

Abbreviations: CI, confidence interval; HR, hazard ratio.

cardiovascular death is the main cause of morbidity and mortality in patients with CKD,[7] it is biologically plausible that patients adherent to cardiovascular drugs may retain better cardiovascular health and live longer after they progress to ESRD. Therefore, adherence to cardiovascular medications should be monitored and reinforced.

Adherence to medications is a complex behavior that is influenced by a broad array of factors, including those related to the patient, condition, therapy, socioeconomic background, and health care system. Therefore, providers should be familiar with available methods for adherence screening[21] and routinely apply them while treating patients with CKD. The PDC, MPR, and persistence methods that were used in the current study are indirect screening methods for the evaluation of medication-taking behavior based on pharmacy database evaluation.[31,32] In the absence of a gold standard of adherence assessment, pharmacy database analysis is becoming the most practical way to assess real-world adherence, especially using large databases. This method is easily quantifiable and objective. In addition, it allows evaluation of 2 aspects of medication-taking behavior: (1) adherence, the extent to which patients follow prescribed dosing regimens (assessed by PDC and MPR), and (2) persistence, the duration from initiation to unauthorized discontinuation of therapy. In the current study, we modified the approach to persistence assessment and used a prescription date closest to the 1-year predialysis mark as the initial date and evaluated subsequent 12-month persistence. The PDC and MPR are both related to the number of available medication doses given out in relationship to the number of days during the period of interest. The key difference is that PDC is capped at 100% because the number of days covered by a drug cannot exceed 100%. Numerically, MPR can exceed 100% and therefore it can account for medication overfills; alas, it has been contended that MPR might overestimate medication adherence.

Our study has large sample size and event numbers and is representative of male veterans who received care in the VA system in the entire United States. This study must be interpreted in light of several limitations. Our study was observational and hence the results do not allow us to infer causality, but merely associations. Most of our patients consisted of male US veterans; therefore, results may not be generalizable to women or the general US population. Although we adjusted our analyses for a variety of important covariates as potential confounders, we cannot eliminate the possibility of unmeasured confounders, such as proteinuria and quality of nephrology care. Several limitations of pharmacy database analysis need to be acknowledged. Although we applied 3 accepted methods of adherence determination using pharmacy databases, we did not have data about discontinuation orders for these drugs, so we were not able to differentiate between discontinuation by indication versus self-discontinuation (ie, nonadherence) by patients. The dispensation of medicine does not guarantee its consumption and does not give information about when medications are taken by patients. Additionally, patients should be enrolled in a closed pharmacy system; in our cohort, it is possible that some veterans received medications outside the 2 evaluated pharmacy systems (VA and Medicare Part D). Another limitation of our study is that we only included patients who survived until dialysis therapy initiation; therefore, we were not able to examine patients with chronic kidney failure receiving conservative management (ie, no dialysis). Finally, we had large amounts of missing data for some laboratory values; therefore, we were not able to include these variables in our main multivariable model. However, models that included these variables and the multiple imputation models led to similar conclusions.

Adherence to cardiovascular medications is emerging as a novel risk factor for mortality after initiating dialysis therapy. Poor predialysis medication adherence and persistence in the year preceding ESRD onset are associated with increased all-cause and cardiovascular mortality. Our findings may have important implications for the management of predialysis patients due to the potentially modifiable nature of medication-taking behavior. It would be very useful if pharmacies and/or insurance companies could start the routine provision of pharmacy dispensation records with calculations of adherence and persistence, which would allow providers to have an opportunity to discuss barriers and encourage medication adherence. Future prospective studies are needed to understand adherence barriers and develop measures enhancing adherence to cardiovascular drugs in patients with advanced CKD.

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Contributions: Study concept and design: all authors; acquisition of data: CPK, MZM, ES, JLL, JJ, CMR, VAR, MS, PKP; data analysis/interpretation: MZM, CPK, KS, and KK-Z. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. CPK and MZM take responsibility that this study has been reported honestly, accurately, and transparently; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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SUPPLEMENTARY MATERIAL

Table S1: Baseline characteristics of included versus excluded patients.

Table S2: Adherence parameters in different medication groups.

Table S3: Association of each PDC drug category with all-cause mortality after dialysis initiation.

Table S4: Association of MPR with all-cause mortality after dialysis initiation.

Table S5: Association of MPR with CV mortality after dialysis initiation.

Figure S1: Different methods of adherence calculation.

Figure S2: Association between MPR in last year pre-ESRD and postdialysis initiation all-cause and CV mortality.

Figure S3: Association between MPR in last year pre-ESRD and postdialysis initiation mortality in different subgroups.

Note: The supplementary material accompanying this article (http://dx.doi.org/10.1053/j.ajkd.2016.02.051) is available at www.ajkd.org

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