Predialysis Cardiovascular Disease Medication Adherence and Mortality After Transition to Dialysis

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Abstract

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

Study Design—Observational study.

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

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

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

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Results—The mean age of the cohort was 72±11 (SD) years, among whom 96% were male, 74% were white, 23% were African American, and 69% were diabetic. During 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]/1000 patient-years [PY]); among patients with PDC >60%–80%, there were 3,882 deaths (mortality rate, 294 [95% CI, 285–304]/1000 PY); among patients with PDC 60%, there were 720 deaths (mortality rate, 291 [95% CI, 271–313]/1000 PY). Compared to patients with PDC >80%, adjusted HR for post-dialysis initiation all-cause mortality for patients with PDC >60%–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 to patients showing medication persistence, adjusted HR risk for post-dialysis initiation all-cause mortality for patients with non-persistence 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; the results may not be generalizable to women or the general US population.

Conclusions—Pre-dialysis cardiovascular medication non-adherence is an independent risk factor for post-dialysis mortality among advanced chronic kidney disease patients transitioning to dialysis. Further studies are needed to assess whether interventions targeting adherence improve survival after dialysis initiation.

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 ESRD patients is of paramount importance.

Only a limited number of interventions, such as timely arteriovenous fistula creation and adequate access to specialist care during the pre-dialysis period, have been shown to be associated with better outcomes in ESRD patients.(2–6) Cardiovascular disease is the leading cause of mortality in pre-dialysis patients,(7) and anti-hypertensive 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 of various outcomes.(9–13) However, little is known about the association of medication adherence during the pre-dialysis period with all-cause and cardiovascular mortality after dialysis initiation.

We investigated the association of adherence to medications targeting cardiovascular risk in the last year prior to initiating dialysis with all-cause and cardiovascular mortality after dialysis initiation in a cohort of US veterans with advanced chronic kidney disease (CKD) transitioning to dialysis. We applied three methods of adherence determination using pharmacy databases: (1) proportion of days covered (PDC) and (2) medication possession ratio (MPR) to evaluate compliance (the extent to which patients follow prescribed dosing

regimens), and (3) persistence with drug therapy (duration of 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 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 (Figure 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 initiation. We used the national VA Corporate Data Warehouse LabChem data files to extract data about pre-dialysis serum creatinine.[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 initiation or the second-from-last quarterly average if the last data point was missing. Data on medication exposure was obtained from both Centers for Medicare & Medicaid Services (CMS, Medicare Part D) and US Department of Veterans Affairs (VA) pharmacy dispensation records.[16] Patients who received at least one dispensation of outpatient medication within one year of dialysis initiation were recorded as having been treated with these medications. Information about comorbidities at the time of dialysis initiation was extracted from the VA Inpatient and Outpatient Medical SAS Datasets,[17] and from CMS datasets 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 the Charlson Comorbidity Index score using the Deyo modification for administrative data sets, without including kidney disease.[18]

Exposure Variables

Figure S1 (provided as online supplementary material) depicts schematics of different methods of adherence calculation. The PDC was defined as the proportion of days with drug available in the measurement period, capped at 100%. The MPR was calculated as the 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 being 1 (present) if a patient refilled each subsequent prescription with gaps not exceeding 60 days; otherwise, it was coded as 0 (absent, or non-persistent).[20]

Detailed information about each prescription was collected during the last year before dialysis for the following cardiovascular drugs: angiotensin-converting enzyme inhibitors/

angiotensin receptor blockers, calcium channel blockers, ß-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 initiation), regardless of any prescriptions before this date. The last prescription had to be dispensed before dialysis initiation, and the full prescription period was included in the denominator, regardless of whether the supply lasted until after the dialysis initiation date. Only outpatient prescriptions were taken into account. Any inpatient time period was added to the denominator. The 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%– 80%, and 60%; (2) for MPR: 100%, >80%–<100%, >60%– 80%, and 60%. We dichotomized medication persistence as average persistence of <50% or >50%, derived from individual drug prescription refills. The PDCs and MPRs were also treated as continuous variables to examine non-linear associations using restricted cubic spline analyses.

Outcome Assessment

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

Statistical Analysis

Data are presented as number (percentage) for categorical variables and as mean ± standard deviation or median (interquartile range [IQR]), as appropriate. Categorical variables were compared with $\chi 2$ tests. Continuous variables were compared using *t* tests or Mann–Whitney U tests, or ANOVA, as appropriate. We used Cox proportional hazard regressions to determine the association of medication adherence with all-cause and cardiovascular mortality, considering the time from the date of dialysis 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), and 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) and type of vascular access (model 3); and model 3 plus blood/serum hemoglobin, bicarbonate, albumin, urea nitrogen, and last estimated glomerular filtration rate (eGFR) before ESRD (model 4). Model 4 had high proportions of missing data (40%–50%, see below); therefore, we used *model 3* as the main multivariable adjusted model.

Restricted cubic spline models were used to investigate non-linearity 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, 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 eGFR [23% missing]) with the use of multiple imputation procedures (creating 5 datasets) 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, more likely to be male, white (74% versus 70%), had higher arteriovenous fistula rate (23% versus 14%) and had higher prevalence of diabetes (69% versus 55%), cardiovascular/cerebrovascular disease (50% versus 29%), hypertension (91% versus 69%) and congestive heart failure (60% versus 50%) (Table S1).

P values are two-sided and reported as significant at <0.05 for all analyses. All analyses were conducted using STATA MP Version 14 (STATA Corp LP, College Station, TX). 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

The mean age of the cohort at baseline was 72±11 (standard deviation) years; 96% were male, 74% were white, 23% were African American, and 69% were diabetic. The median of the last pre-ESRD outpatient eGFR was 16 (IQR, 10–26) ml/min/1.73m^2. Baseline characteristics of patients categorized by PDC categories are shown in Table 1. Patients with a higher PDC (>80%) were older; more likely to be white and married; more likely to initiate dialysis with an arteriovenous fistula; more likely to be on a statin and on angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; had a higher prevalence of hypertension; had higher serum albumin and calcium; lower serum phosphate, PTH, total and low-density lipoprotein cholesterol levels, and urine albumin-creatinine ratio; and more favorable metabolic and anemia markers (Table 1). Table S2 shows the adherence parameters in different medication groups. In individual medication groups, PDC, MPR and non-persistence were very similar (Table S2).

Predialysis PDC and All-Cause and Cardiovascular Mortality

The median follow-up time was 23 (IQR, 9–36) months. There were 18,608 deaths (58%; mortality rate, 286 [95% CI, 281–290]/1000 patient-years [PY]) in the entire cohort, with 14,006 deaths (57%; mortality rate, 283 [95% CI, 278–288]/1000 PY) in patients with PDC >80%, 3,882 deaths (59%; mortality rate, 294 [95% CI, 285–304]/1000 PY) in patients with PDC >60%–80%, and 720 deaths (57%; mortality rate, 291 [95% CI, 271–313]/1000 PY) in patients with PDC   60%. Compared to patients with PDC >80%, patients with PDC >60%–80% were at higher risk for all-cause mortality (hazard ratio [HR]: 1.04; 95% CI: 1.00–

1.08), while 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 socio-demographic parameters and comorbidities, patients with PDC >60%–80% (HR, 1.12; 95% CI, 1.08–1.16), as well as patients with PDC 60% (HR, 1.21; 95% CI, 1.11–1.30) had significantly higher risk of mortality compared to 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%–80% (HR, 1.11; 95% CI, 1.07–1.15), as well as patients with PDC 60% (HR, 1.20; 95% CI, 1.12–1.30) reported significantly higher risk for all-cause mortality compared to patients with PDC >80%. Figure 2 shows an inverse linear association between PDC and all-cause (panel A) and cardiovascular (panel B) mortality in analyses using restricted cubic splines. A higher risk of death was also observed in the various studied subgroups (Figure 3). Table S3 shows the associations between the different PDCs of each medication category and all-cause mortality. The PDCs of loop and thiazide diuretics and of ß-blockers showed significant inverse association with all-cause mortality (Table S3). Similar results were found for cardiovascular mortality (Table 3).

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

Compared to patients with MPR >80%–<100%, patients with MPR >60%– 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 of 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 socio-demographic parameters and comorbidities (Table S4). Similar trends were detected after further adjustment for laboratory variables (Table S4). In the multiple imputation model, patients with MPR >60%– 80% (HR, 1.10; 95% CI, 1.05–1.15), as well as patients with MPR 60% (HR, 1.18; 95% CI, 1.08–1.29) had significantly higher risk for all-cause mortality, while patients with MPR 100% (HR, 0.96; 95% CI, 0.93–0.99) had significantly lower risk for all-cause mortality compared to patients with MPR >80%-<100%. Figure S2 shows the association between MPR and all-cause (panel A) and cardiovascular (panel B) mortality using restricted cubic splines. Results were similar in all examined subgroups (Figure S3). Similar trends were found with cardiovascular mortality (Table S5).

Compared to patients who were persistent with their medication refills, non-persistent 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 (Figure 4) and for cardiovascular mortality (Table 5).

DISCUSSION

In a large cohort of patients with advanced CKD, we examined the association between one-year pre-dialysis adherence to cardiovascular medications and all-cause and cardiovascular mortality following dialysis initiation. We utilized a pharmacy database analysis to assess two parts of medication adherence: adherence and persistence.(21) Inadequate adherence to

cardiovascular pharmacotherapy was associated with reduced survival, independent of demographic, co-morbidity and laboratory characteristics.

Several pre-dialysis demographic and co-morbidity factors such as age, gender, race, socioeconomic status, and co-morbidities were linked to post-dialysis 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 co-morbidity characteristics to help with shared decision-making about dialysis initiation in elderly ESRD patients.(25) On the other hand, it is equally important to understand potentially modifiable pre-dialysis risk factors and behaviors influencing survival after initiating dialysis. Timely arteriovenous fistula placement and pre-dialysis care involving a nephrology specialist were shown to be associated with reduced all-cause mortality in the post-dialysis initiation period.(2–6, 26) The quality of pre-dialysis 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 pre-dialysis visits in the six-month period before dialysis initiation had 28% higher survival compared to patients who had <3 visits during the same time period.(27) In addition to the number of visits, nephrology care of <6 months' duration before ESRD onset was linked to 23%–27% higher one-year all-cause mortality in two recent studies.(28, 29)

To our knowledge, no other studies have attempted to evaluate the influence of pre-dialysis adherence to cardiovascular medications on all-cause and cardiovascular mortality after initiation of dialysis. 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 anti-hypertensive drugs was associated with 45% lower risk of all-cause mortality and good adherence to statins was associated with 29% reduced risk of death.(11) Our study involved a population of patients with advanced CKD transitioning to dialysis, and its results further strengthen the overall importance of adherence to cardiovascular drugs. Because 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 have better survival as they may retain better cardiovascular health and live longer once 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, the condition, the therapy, the socio-economic background, and the 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 two 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 pre-dialysis 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% as 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 a 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, the results may not be generalizable to women or the general US population. Even though 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 three 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 the discontinuation by indication versus self-discontinuation (i.e. non-adherence) by the patients. The dispensation of medicine does not guarantee its consumption, nor does it give any 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 of the two evaluated pharmacy systems (VA and Medicare Part D). Another limitation of our study is that we only included patients who survived until dialysis initiation; therefore we were not able to examine chronic kidney failure patients receiving conservative management (i.e., 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 as well as the multiple imputation models led to similar conclusions.

Adherence to cardiovascular medications is emerging as a novel risk factor for mortality after initiating dialysis. Poor pre-dialysis medication compliance 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 pre-dialysis patients due to the potentially modifiable nature of medication-taking behavior. It would be very practical if pharmacies and/or insurance companies could start the routine provision of pharmacy dispensation records with calculations of compliance 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 to develop measures enhancing adherence to cardiovascular drugs in patients with advanced CKD.

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Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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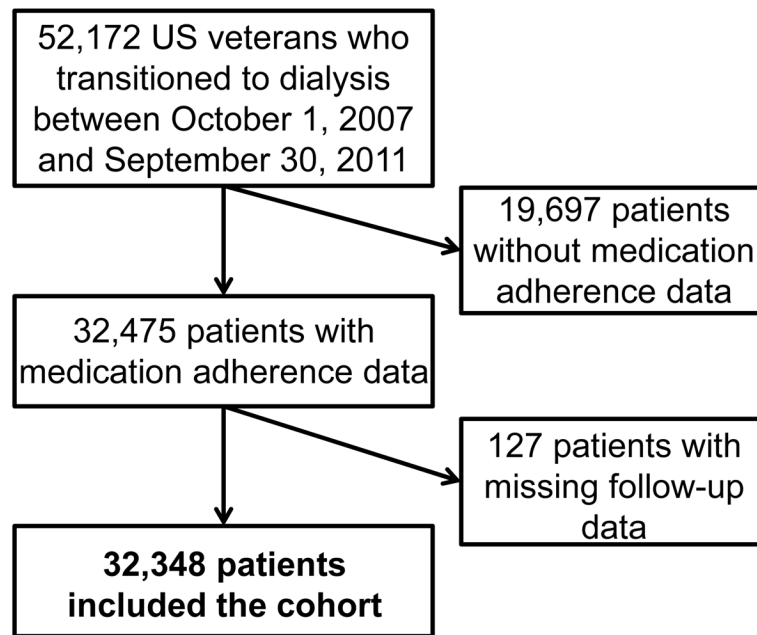
Figure 1.
Flow chart of patients' selection
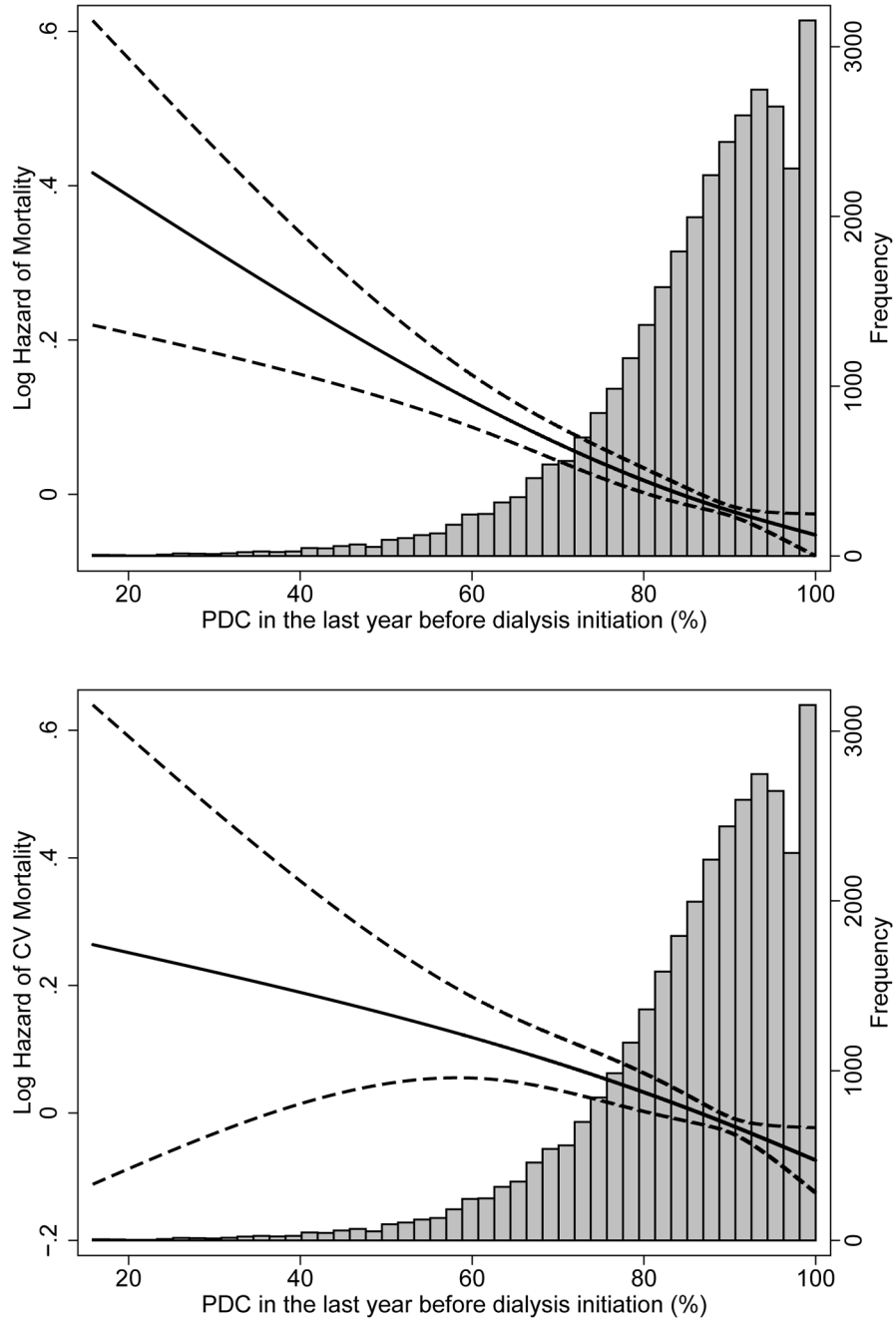
Figure 2.
Association between percentage of days a subject had medication available (proportion of days covered, PDC) in the last year before ESRD and post-dialysis initiation all-cause mortality (panel A) and cardiovascular mortality (panel B) using fractional polynomials and restricted cubic splines (model adjusted for age, sex, race, marital status, ZIP code, CCI, presence of diabetes, congestive heart failure, cardiovascular/cerebrovascular disease, presence of depression, presence of anxiety and type of vascular access)
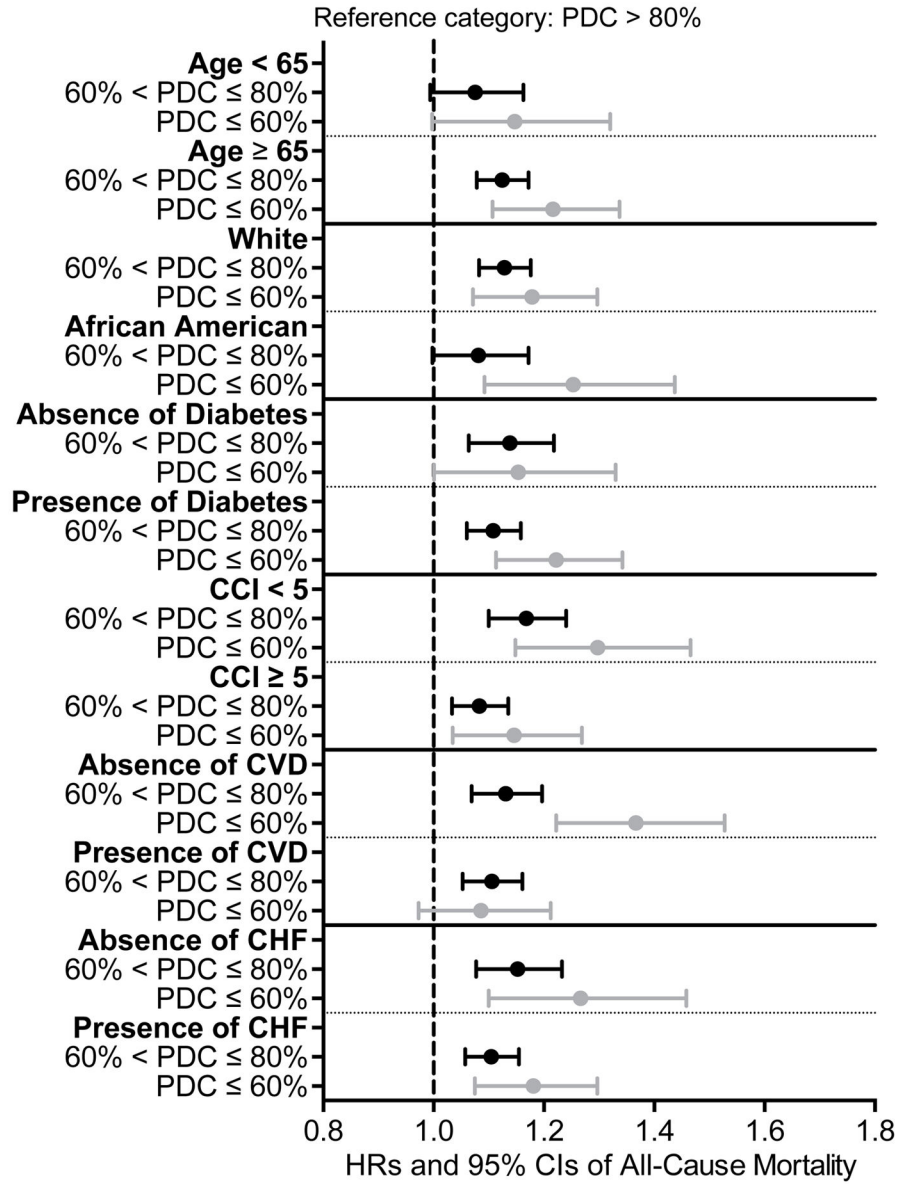
Figure 3.
Association between percentages of days a subject had medication available (proportion of days covered, PDC) in the last year before ESRD and post-dialysis initiation mortality in different subgroups of patients using adjusted Cox regression analyses (model adjusted for age, sex, race, marital status, ZIP code, CCI, presence of diabetes, congestive heart failure, cardiovascular/cerebrovascular disease, presence of depression, presence of anxiety and type of vascular access)

Reference category: persistence w/ more than half of the medication
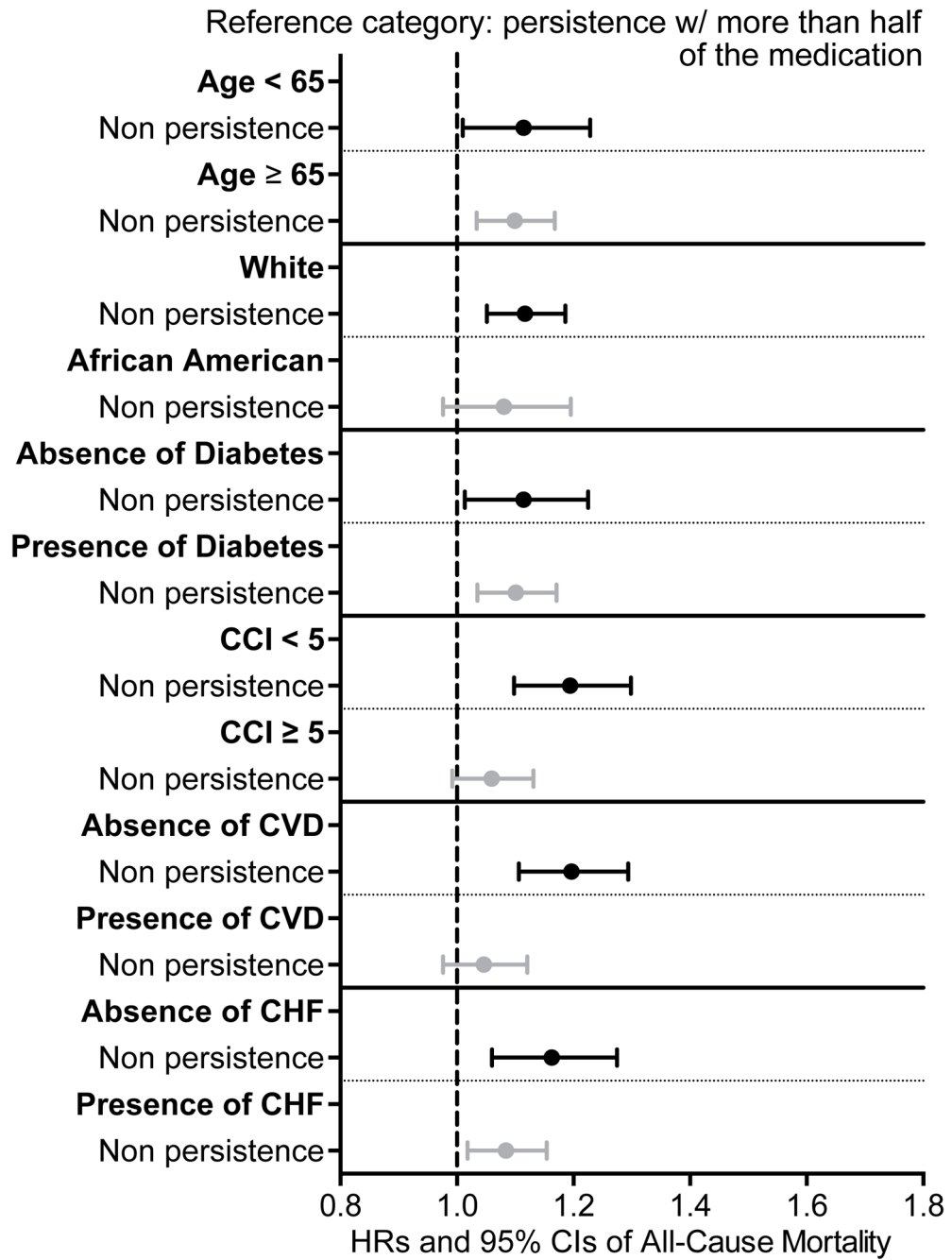
Figure 4.
Association between medication persistence (60 days gap for more than 50% of medications) in the last year before ESRD and post-dialysis initiation mortality in different subgroups of patients using adjusted Cox regression analyses (model adjusted for age, sex, race, marital status, ZIP code, CCI, presence of diabetes, congestive heart failure, cardiovascular/cerebrovascular disease, presence of depression, presence of anxiety and type of vascular access)

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)	
Non-married	13,242 (42)	9,561 (40)	2,996 (46)	685 (56)	
Comorbidities					
Charlson Comorbidity Index	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

	All (N=32,348)	PDC>80% (n=24,455)	PDC >60%-80% (n=6,633)	PDC 60% (n=1,260)	P
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 A1c (%)	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 Phosphate (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 (1000/mm^3)	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 (34–1810)	299 (32–1565)	477 (51–2181)	2412 (341–4606)	<0.001

	All (N=32,348)	PDC>80% (n=24,455)	PDC >60%–80% (n=6,633)	PDC 60% (n=1,260)	P
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/1.73m^2)	16 (10–26)	16 (10–26)	15 (10–25)	17 (10–30)	0.9
Medication use					
Vitamin D analog	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: AIDS/HIV: Acquired Immune Deficiency Syndrome/Human Immunodeficiency Virus; PDC: Proportion of Days Covered; PTH: Parathyroid Hormone; ACR, albumin-creatinine ratio; ACEi/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; LDL, low-density lipoprotein; HDL, high-density lipoprotein; EPO, erythropoietin; NSAID, nonsteroidal anti-inflammatory drug

Table 2

Association of PDC with all-cause mortality after dialysis 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

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

Note: Model1: unadjusted; Model 2: adjusted for age, sex, race/ethnicity, marital status and ZIP code; Model 3: adjusted for model 2 plus Charlson Comorbidity Index and presence of diabetes, congestive heart failure, cardiovascular/cerebrovascular disease, presence of depression, presence of anxiety and type of vascular access; and Model 4: adjusted for model 3 plus blood/serum hemoglobin, bicarbonate, albumin, urea nitrogen, last estimated glomerular filtration rate before end-stage renal disease.

Table 3

Association of PDC with cardiovascular mortality after dialysis 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

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

Note: Model1: unadjusted; Model 2: adjusted for age, sex, race/ethnicity, marital status and ZIP code; Model 3: adjusted for model 2 plus Charlson Comorbidity Index and presence of diabetes, congestive heart failure, cardiovascular/cerebrovascular disease, presence of depression, presence of anxiety and type of vascular access; and Model 4: adjusted for model 3 plus blood/serum hemoglobin, bicarbonate, albumin, urea nitrogen, last estimated glomerular filtration rate before end-stage renal disease

Table 4

Association of medication persistence with all-cause mortality after dialysis 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)	
Non persistence	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

Abbreviations: CI: confidence interval; HR: hazard ratio

Note: Medication persistence with 60-d gap for >50% of medications. Model1: unadjusted; Model 2: adjusted for age, sex, race/ethnicity, marital status and ZIP code; Model 3: adjusted for model 2 plus Charlson Comorbidity Index plus presence of diabetes, congestive heart failure, cardiovascular/cerebrovascular disease, presence of anxiety and type of vascular access; and Model 4: adjusted for model 3 plus blood/serum hemoglobin, bicarbonate, albumin, urea nitrogen, last estimated glomerular filtration rate before end-stage renal disease

Table 5

Association of medication persistence (60 days gap for more than 50% of medications) with cardiovascular mortality after dialysis 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)	
Non persistence	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

Abbreviations: CI: confidence interval; HR: hazard ratio

Note: Persistence with 60-d gap for >50% of medications. Model1: unadjusted; Model 2: adjusted for age, sex, race/ethnicity, marital status and ZIP code; Model 3: adjusted for model 2 plus Charlson Comorbidity Index and presence of diabetes, congestive heart failure, cardiovascular/cerebrovascular disease, presence of depression, presence of anxiety and type of vascular access; and Model 4: adjusted for model 3 plus blood/serum hemoglobin, bicarbonate, albumin, urea nitrogen, last estimated glomerular filtration rate before end-stage renal disease