AJKD
Original Investigation

Predialysis Cardiovascular Disease Medication Adherence and Mortality After Transition to Dialysis

Miklos Z. Molnar, MD, PhD,[1] Elvira O. Gosmanova, MD,[2,3] Keiichi Sumida, MD,[1] Praveen K. Potukuchi, MS,[1] Jun Ling Lu, MD,[1] Jennie Jing, MS,[4] Vanessa A. Ravel, MPH,[4] Melissa Soohoo, MPH,[4] Connie M. Rhee, MD, MSc,[4] Elani Streja, MPH, PhD,[4] Kamyar Kalantar-Zadeh, MD, MPH, PhD,[4] and Csaba P. Kovesdy, MD[1,5]

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

From the [1]Division of Nephrology, University of Tennessee Health Science Center, Memphis, TN; [2]Nephrology Section, Stratton VA Medical Center; [3]Nephrology Division, Department of Medicine, Albany Medical College, Albany, NY; [4]Harold Simmons Center for Chronic Disease Research and Epidemiology, Division of Nephrology and Hypertension, University of California-Irvine, Orange, CA; and [5]Nephrology Section, Memphis VA Medical Center, Memphis, TN.

Received October 21, 2015. Accepted in revised form February 21, 2016. Originally published online April 12, 2016.

Address correspondence to Csaba P. Kovesdy, MD, Nephrology Section, Memphis VA Medical Center, 1030 Jefferson Ave, Memphis, TN 38104. E-mail: ckovesdy@uthsc.edu

0272-6386
http://dx.doi.org/10.1053/j.ajkd.2016.02.051

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]

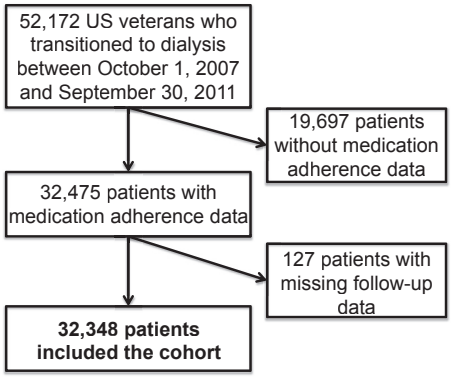

Figure 1. Flow chart of patient selection.

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