Chapter 2: Transition of Care in Chronic Kidney Disease

Highlights

- The USRDS Transition of Care in Chronic Kidney Disease (TC-CKD) study team under the United States Renal Data System (USRDS) Special Study Center contract has provided datasets with select laboratory data of 102,477 US veterans and 12,242 Kaiser Permanente Southern California (KP-SC) members with non-dialysis dependent (NDD) chronic kidney disease (CKD), who transitioned to end-stage renal disease (ESRD) including dialysis therapy between 10/1/2007-3/31/2015 and 1/1/2007-12/31/2016, respectively, to the USRDS for further analysis by requesting investigators.

- A new risk prediction tool for mortality during the first year after transition to dialysis has been developed (available at www.DialysisScore.com) based on data in the US veteran cohort and validated with good performance in the racially, ethnically, and gender diverse KP-SC cohort.

- Initiation of dialysis at Veterans Health Administration (VHA) dialysis units compared to outsourced units under non-VHA dialysis providers, or as outpatient compared to inpatient dialysis initiation, is associated with better post-transition survival including after multivariate adjustments.

- Pre-dialysis care as indicated by more frequent laboratory testing of serum hemoglobin, potassium, and creatinine or use of a mature arteriovenous fistula (AVF) access type as an initial modality is associated with better survival after transition to dialysis.

- Faster estimated glomerular filtration rate (eGFR) decline, in particular with a higher eGFR at dialysis transition, or abrupt declines in eGFR prior to transition are associated with higher risk of post-ESRD transition outcomes.

- Lower levels of systolic blood pressure and serum albumin, and higher levels of serum calcium and alkaline phosphatase levels are associated with higher risk of post-ESRD transition mortality. Serum hemoglobin pre-ESRD has a U-shaped association with post-ESRD mortality, whereas higher serum hemoglobin variability is also associated with post-transition mortality risk.

- Higher pre-ESRD blood hemoglobin A1c and glucose levels as well as higher frequency of pre-ESRD hospitalization for hypoglycemia were associated with higher post-ESRD

mortality risk, while in late-stage CKD patients who did not transition, there was a U-shaped association between serum glucose level and mortality risk.

- Hypothyroidism defined as a serum pre-ESRD thyrotropin (TSH) level >5.0 mIU/L is associated with a higher post-ESRD mortality risk in US veterans with NDD-CKD who transitioned to dialysis therapy. Hypothyroidism (a pre-ESRD TSH level >5.0mIU/L) is associated with a higher post-ESRD mortality risk.
- Statin use prior to dialysis transition and its continued use post-transition are associated with lower mortality risk in US veterans who transitioned to dialysis.
- Poor cardiovascular medication adherence prior to ESRD is associated with worse post-ESRD outcomes.
- Mental health conditions including depression and dementia diagnosed prior to ESRD transition are associated with a higher risk of post-transition mortality; however, kidney transplant outcomes did not differ in patients who had a diagnosis of psychosis/mania or post-traumatic stress disorder prior to kidney transplantation.

Introduction

During the contract years 2013 and 2019, the USRDS Transition of Care in Chronic Kidney Disease, also known as the TC-CKD Special Study Center examined patterns in the transition of care to renal replacement therapy (i.e., dialysis or transplantation) including patients with very-late-stage (advanced) NDD-CKD. Each year the TCCKD team contributed a USRDS Annual Data Report (ADR) chapter focusing on characteristics of patients transitioning to ESRD. These reports provided data on seasonal trends in mortality and transition rates, patterns of access type at transition across the US, changes in medication prescription frequency throughout the transition period, and changes in laboratory parameters upon ESRD-transition. Cohort sizes increased across each study chapter year as more patients transitioned to dialysis and as more data became available for both respective cohorts of 102,477 US Veterans and 12,242 Kaiser Permanente Southern California (KP-SC) members. As stated in the original goals of this Special Study Center, we tested hypotheses that a pre-ESRD (prelude) data-driven personalized approach to the transition of care into ESRD in very-late-stage NDD-CKD is associated with more favorable outcomes, particularly if the decision is based on pre-ESRD factors

such as clinical and laboratory variables, including the CKD progression rate, comorbid conditions during the prelude period, and patient demographics. Some of these concepts and data have been published in the form of abstracts and peer-reviewed manuscripts over the option years 2014-2019[1-26]. In this year's chapter, we will highlight our TC-CKD key findings, including the development and validation of a predictive scoring system derived from these pre-ESRD data to better ascertain the extent to which timing, preparation, and modality of ESRD may be associated with better patient outcomes[13].

The primary sources used in these analyses were created from the linkage between the national USRDS data and two large longitudinal data sources of NDD-CKD patients— the national Veterans Affairs (VA) database and the electronic medical records capturing the care delivered to members of the Kaiser Permanente Southern California (KP-SC) health plan. These and other linkages have allowed us to identify nearly all VA and KP-SC patients who have transitioned to ESRD from the index point (Year 2007) in time onwards. Each of these linked databases includes thousands of NDD-CKD patients who have transitioned to ESRD each year, in whom historical data as far back as -5 (minus five) years prior to ESRD ("prelude" period) and up to +2 (plus two) years after ESRD transition (early "vintage" period) were examined.

Veterans Health Administration

Annually, approximately six to seven million veterans receive healthcare from the Veterans Health Administration (VHA), representing one third of all veterans in the US. Although the cohort is approximately 90% male, it is estimated that in the next decade the proportion of females will rise to 18-20%.[27, 28] Minority veterans currently comprise about 22% of the overall veteran population, among whom the majority are of Black or African American race (12% of all veterans) and Hispanic or Latino ethnicity (7% of all veterans).[29, 30] Each year approximately 13,000 veterans transition to renal replacement therapy, mostly in the form of maintenance dialysis treatment[3], representing a crude ESRD incidence rate between 620-670 per million US veterans between 2008-2014. This ESRD rate is 29-38% higher than that observed for the overall US population. As highlighted in our 2018 ADR chapter, VHA enrolled veterans comprised 12% (n=102,477) of the total 879,969 USRDS patients who transitioned to ESRD throughout the nation. Compared to the total ESRD population transitioning during that time period, veterans

were older with an average age of 70.2 ±12.0 years, and more likely to be non-Hispanic and white. Veterans were also more likely than non-VHA patients transitioning to ESRD to have reported a cardiovascular or pulmonary comorbidity on the CMS 2728 form at the time of transition. They were also less likely to have peritoneal dialysis as the first dialysis modality, but more likely to have pre-transition nephrology care or have an arteriovenous fistula (AVF) as their primary access type.

Kaiser Permanente of Southern California

Kaiser Permanente of Southern California (KP-SC), the largest Kaiser Permanente region in the nation, is an integrated health care system that provides comprehensive health services for over 4.4 million members. California is the most populous (39.8 million) and racially/ethnically diverse US state. Southern California (SC) is the most populous mega-region of California with almost 23 million people (58% of California's population), and bears two of the top 10 most populated cities in the nation (Los Angeles and San Diego). It encompasses the Los Angeles Metropolitan region, including more than 17 million people in Los Angeles, San Diego and Orange Counties combined, and is the 15th largest economy in the world. In addition to substantial socioeconomic diversity, SC has remarkable racial/ethnic diversity that is reflective among the KP-SC member population. According to the 2010 US Census estimates, the KP-SC member population, like the California-specific total population, has greater racial/ethnic diversity as compared to the nation. KP-SC is comprised of 37.6% Hispanic patients, 28% patients between ages 25-64 years, and 12% patients 65 years of age and over. The age and gender distribution in KP-SC are similar to those in California and in the US overall.

Over the 10 years between 01/01/2007 and 12/31/2016, 12,242 KP-SC members transitioned to ESRD, i.e. dialysis and transplant. KP-SC ESRD transition incidence rates were lower than the US general population, likely due to several factors related to obtaining better and earlier pre-transition care for NDD-CKD patients, representing a larger proportion of people who were healthier and employed and receiving healthcare coverage via their employers.

Using data from these TC-CKD cohorts provided an opportunity to further examine patterns of care and predictors of outcomes in patients transitioning to ESRD. We were also able to leverage this data to make important discoveries regarding the relationships

of timing of dialysis transition, pre-dialysis care, and characteristics at the time of transition with early post-ESRD transition mortality. Many of these findings were incorporated in the development and validation of a clinical tool that can be used to assist in decision making regarding dialysis transition. As a part of the USRDS TC-CKD Study Center, we have also created deidentified datasets representing 102,477 VA and 12,242 KP-SC TC-CKD patients who transitioned to ESRD between 10/1/2007-3/31/2015 or 1/1/2007-12/31/2016, respectively. These datasets include demographic data as well as summary pre-ESRD or prelude lab data that go as far back as five years (or 20 patient quarters). These data have become available as Standard Analytic Files (SAF), which can be used for further analysis by other investigators to improve outcomes in all patients transitioning to ESRD. The remainder of this year's chapter feature the recent publications by the TCCKD team using the above-described VA and KPSC datasets, in that we present new diagrams and analyses not previously published in these papers or elsewhere.

Development of a Clinical Scoring Tool for Prediction of Outcome Risk in Persons Transitioning to Dialysis

Development and Validation of Prediction Scores for Early Mortality at Transition to Dialysis

Using data from a cohort of 35,878 US veterans with incident ESRD who transitioned to dialysis between 10/1/2007-3/31/2014, Obi et al. developed a risk prediction tool to ascertain mortality risk during the first year of dialysis. The risk calculator was also externally validated among 4,284 patients in the KP-SC health care system who transitioned to dialysis treatment between January 1, 2007 and September 30, 2015. The innovation of this risk calculator was its use of pre-ESRD characteristics to determine post-transition mortality at the first 3, 6, 9, and 12 months following dialysis initiation. From the results of this study, an online tool was developed (www.dialysisscore.com) which could assist with identifying high-risk populations, and guide management strategies. The tool estimates a risk prediction score according to whether the patient had an estimated glomerular filtration rate (eGFR) of less than or greater than/equal to 15mL/min/1.73m². The findings showed that the tool-predicted survival was consistent with observed survival across risk groups and time points, except for patients in the high

eGFR group at month 6, the highest risk category in which survival was overestimated, which could have been due to the early mortality phenomena amongst the elderly. In Figure 1 below, we show Kaplan-Meier survival curves of patients stratified according to their calculated risk score category and demonstrated that survival decreases at faster rates in patients with higher risk scores. As an example, the calculator would estimate that a 71-year old Hispanic male with hyperlipidemia, history of myocardial infarction, congestive heart failure and peripheral vascular disease, diabetes as the primary cause of ESRD, body mass index (BMI) of 28 kg/m², eGFR of 12 mL/min/1.73m², white blood cell count of 9 per 10³, serum albumin of 3.4 g/dL, serum urea nitrogen of 63 mg/dL, serum sodium of 132 per mEq/L and serum alkaline phosphatase (ALP) of 178 per IU/L would have a post-transition mortality risk of 6.8%, 13.3%, 18.1%, and 22.9%, at month 3, 6, 9, and 12, respectively. Scores obtained per patient from this calculator can help clinicians and patients make more informed decisions and help develop individualized treatment plans for care.

vol 1 Figure 1. Observed Kaplan-Meier survival curves during the first year of dialysis and predicted survival at months 3, 6, 9, and 12 across five risk score categories in 35,878 US veterans with last eGFR before initiation of dialysis of <15 mL/min/1.73m² or ≥15 mL/min/1.73 m² in the development VA cohort

eGFR ≥ 15mL/min/1.73 m^2
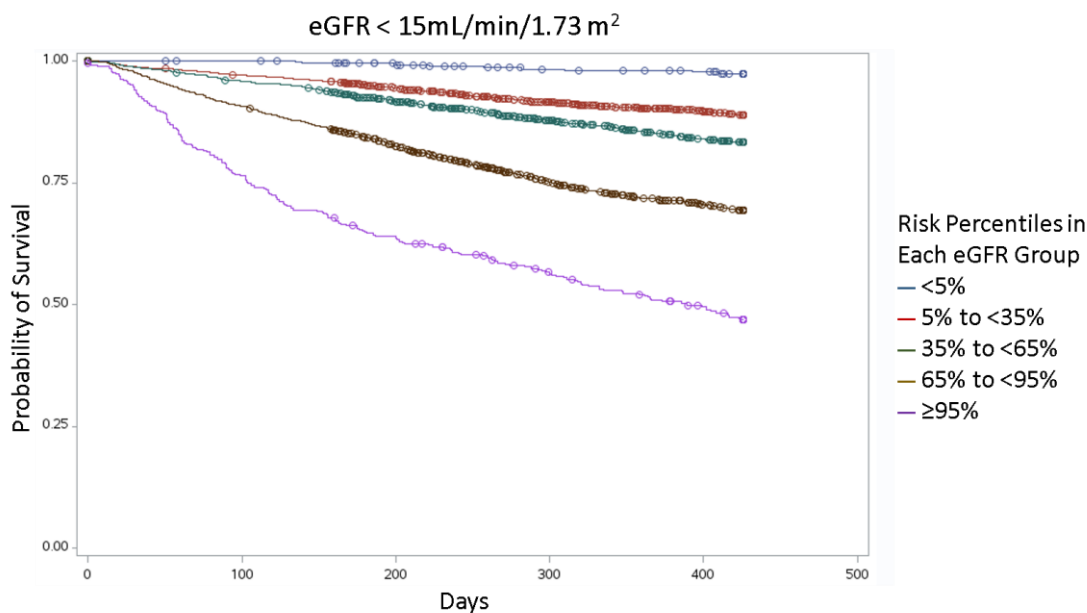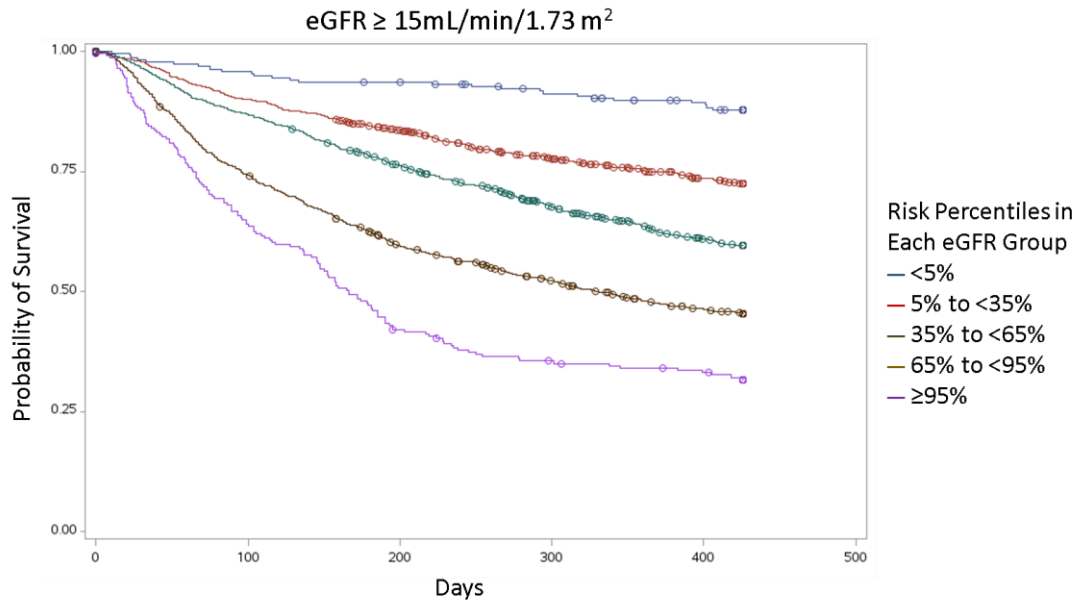
Survival *curves (solid lines) were based on Kaplan-Meier estimates. Points and bars represent means and 95% CIs of predicted survival for the risk score categories. Cutoff points were selected at 5th, 35th, 65th, and 95th percentiles in respective strata of eGFR. Abbreviations: eGFR, estimated glomerular filtration rate; m, meter; min, minute; mL, milliliter; VA, Veterans Affairs.*

Facility of Dialysis Transition

In this next section, we will discuss our results pertaining to the facility where patients transitioned to dialysis and how this setting itself may serve as a proxy for factors related to post-transition survival.

In the VHA system, there are approximately 70 VHA dialysis centers operating nationwide, while there are more than 6,000 dialysis units overall across the country[3]. Given that approximately 13,000 veterans transition to dialysis each year and the low number of VA dialysis centers and their limited capacity, only 10% of all incident dialysis veterans initiate treatment in a VA center[3]. Other veterans are sent to large dialysis organizations or other dialysis providers. Although there are no certain criteria for which veterans are assigned to initiate dialysis within the VHA and which patients are outsourced to other centers, we identified that compared to veteran patients who initiated dialysis outside the VA, those who transitioned at a VA dialysis facility were more likely to be African American or Hispanic unmarried males with a history of homelessness, alcohol or drug dependence, depression, or post-traumatic stress disorder,

and who were more likely to have interacted with the VHA for outpatient visits or pharmacy prescriptions in the year prior to transition. Although these VHA patients were more likely to have diabetes or liver disease compared to veterans who transitioned to dialysis outside of the VHA, they were less likely to have other comorbidities but were more likely to initiate dialysis during an inpatient hospitalization. In a cohort of 68,727 US veterans who transitioned to dialysis between 10/1/2007 to 3/31/2014, we found that initiation of dialysis within a VHA facility was associated with a 13% lower mortality risk but a 10% higher hospitalization risk in the year post-dialysis transition in models adjusted for a number of demographics and comorbidities (Figure 2). Compared to unadjusted models, associations were modestly attenuated for mortality and strengthened for hospitalization outcomes after adjustment for demographics and were similar to estimates after further adjustment for comorbidities and other patient characteristics. We explained in the discussion that although many patients switch to another provider outside of the VHA soon after dialysis transition, we postulate that observed differences in mortality and hospitalization rates may be related to distinctions in care practices and ease of admitting patients for hospitalization in the integrated healthcare system. However, we stipulate that further analysis is needed to support these findings and hypotheses.

vol 1 Figure 2. Associations of dialysis provider (VHA vs. non-VHA) at dialysis initiation with 1-year post-ESRD all-cause mortality and hospitalization in 68,727 veterans who transitioned to ESRD during 10/1/2007-3/31/2014
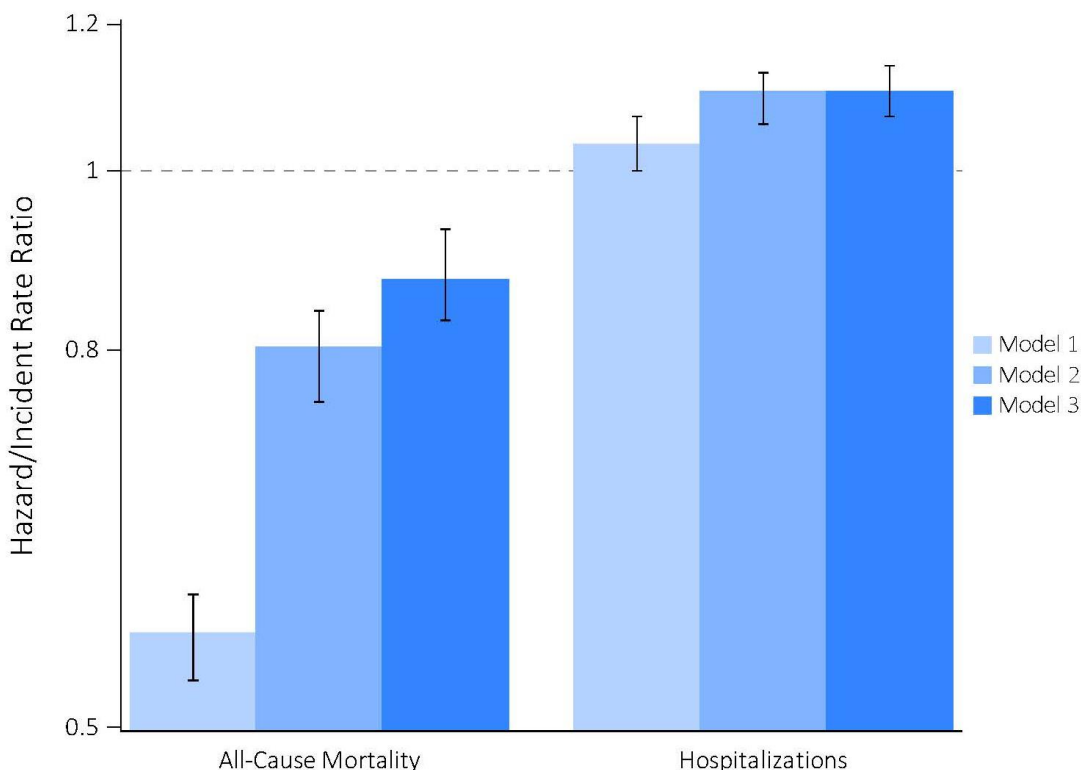
Hazard ratios and incidence rate ratios with 95% confidence intervals are presented for all-cause mortality and hospitalization, respectively. Model 1: unadjusted; Model 2: age, sex, race, ethnicity, marital status, geographic region, year of dialysis initiation, and service-connected status; Model 3: Model 2 plus comorbidities (heart disease, liver disease, chronic obstructive pulmonary disease, diabetes, cancer, depression, post-traumatic stress disorder, and homelessness), Charlson Comorbidity Index, socioeconomic status income category, tobacco use, drug and alcohol dependence, BMI (kg/m²) and eGFR at dialysis initiation, distance from patient to dialysis provider zip code, and dialysis access type.

Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; ESRD, end stage renal disease; kg, kilogram; m, meter; VHA, Veterans Health Administration.

Early Mortality Associated with Inpatient vs. Outpatient Hemodialysis Initiation in a Large Cohort of US Veterans with Incident

In another analysis of 48,261 veteran patients transitioning to hemodialysis between 10/1/2007-9/30/2011, we also examined differences in early post-transition mortality according to whether the patient initiated dialysis as an inpatient or outpatient. Among the veteran patients, 46% initiated dialysis during an inpatient hospitalization. Patients who initiated hemodialysis in the hospital were more likely to be older, non-Hispanic white, have a higher prevalence of comorbid conditions and were less likely to have

reported having pre-dialysis nephrology care or having had an AVF (versus a central venous catheter) as their initial dialysis access type. Survival analysis demonstrated that patients who initiated dialysis as an inpatient had higher mortality rates across different time points post transition in unadjusted analyses (Figure 3). After accounting for differences in patient characteristics in the multivariable adjusted models, hazard ratios attenuated and showed little difference in survival over longer follow up (>6 months or >12 months), but showed a 7% and 5% higher mortality risk in the early (<6 month or <12 months) post hemodialysis transition period. The discussion of the article pointed to the importance of improving pre-dialysis care and preparation for dialysis transition with timely access placement in order to improve patient outcomes.

vol 1 Figure 3. Associations of inpatient vs. outpatient hemodialysis transition with post-ESRD all-cause mortality in 48,261 veterans who transitioned to ESRD during 10/1/2007-09/30/2011
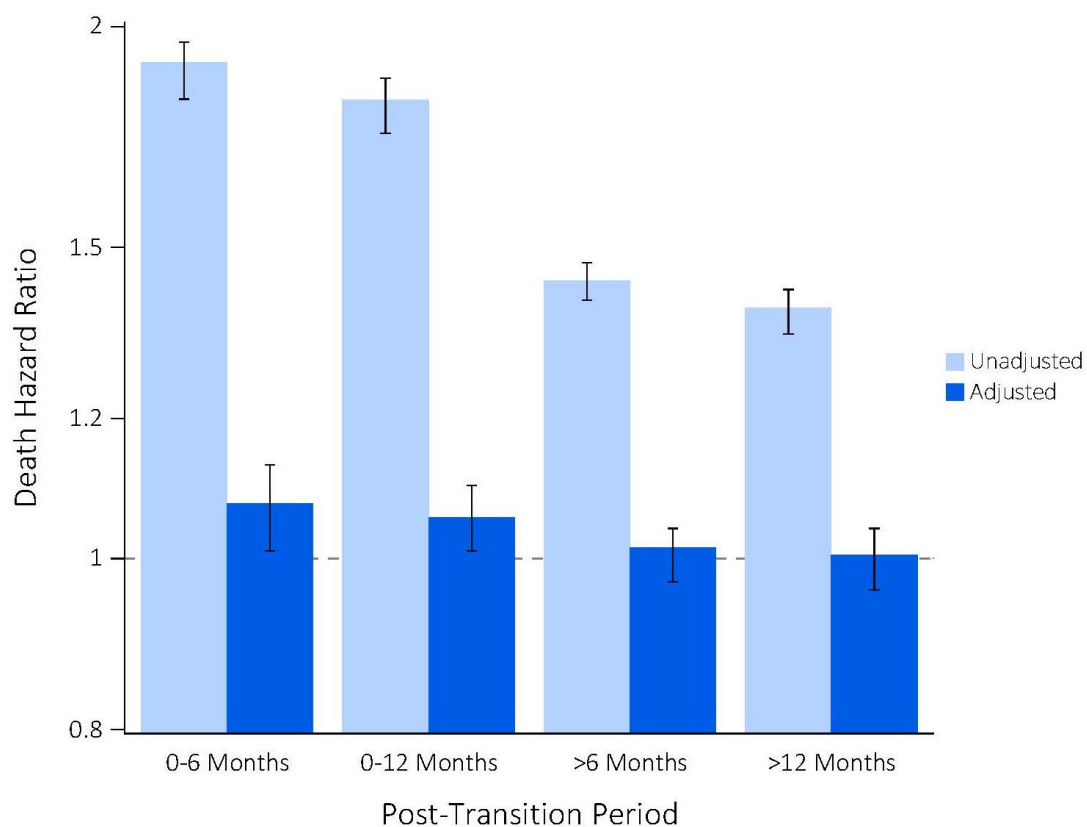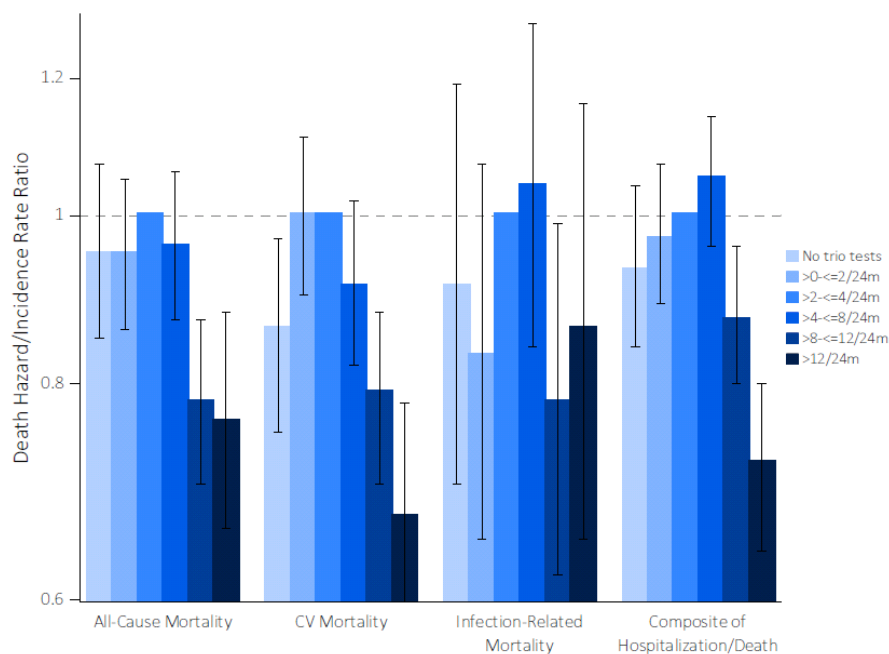

Hazard ratios with 95% confidence intervals are presented for all-cause mortality. Multivariable model: age, gender, race, individual comorbid conditions (history of diabetes mellitus, myocardial infraction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic lung disease, liver disease and malignancies), Charlson Comorbidity Index, medications (angiotensin converting enzyme inhibitors of angiotensin receptor blockers, statins, erythropoietin, and active and nutritional vitamin D), last eGFR, hemoglobin level prior to hemodialysis start, and the number and average length of hospitalizations during prelude period.

Abbreviations: eGFR, estimated glomerular filtration rate; ESRD, end stage renal disease.

Association of the Frequency of Pre-End-Stage Renal Disease Medical Care with Post-End-Stage Renal Disease Mortality and Hospitalization

We sought to further characterize pre-dialysis care in veterans transitioning to ESRD and its impact on post-transition outcomes by examining frequency of pre-dialysis laboratory testing as a metric of care. In a cohort of 23,089 veterans transitioning to dialysis between 10/1/2007-9/30/2011 with available outpatient laboratory tests performed within 2 years prior to transition, the number of months (0-24) a patient had one of each test trio (serum hemoglobin, potassium or creatinine) measured over 24 months was estimated, and associations with post-transition all-cause, cardiovascular and infection related mortality as well as a composite hospitalization-mortality outcome were examined. Frequency of pre-dialysis testing varied from 14% of patients who had a test trio less than twice in 24 months to 8.9% of patients who had lab measures more often than that every month. Patients with more frequent tests were younger, had a lower prevalence of cardiovascular comorbidity, better medication adherence, but higher prevalence of diabetes, while patients with no measurements had a lower median income, were less likely to be married, had higher prevalence of lung disease, heart failure and malignancies. Over a median follow-up period of 2.5 years, compared to patients who had the test trio 2-4 times/24 months, patients who had the test trio more than 50% of the time (>12/24 months) had a 23% lower all-cause, and 33% lower cardiovascular mortality risk post-transition and a 28% lower odds of the composite hospitalization and mortality outcome (Figure 4). When associations were examined according to strata of self-reported pre-dialysis nephrology care at the time of transition, associations remained robust among patients who indicated they had pre-dialysis nephrology care, but were null for patients who did not. This finding may point to both the importance of monitoring patients' kidney disease progression and disease status with lab testing and appropriate referral to nephrologists who can provide further examinations. The study does not identify the physician specialty for lab testing requests, and discusses how kidney progression may be monitored by other specialties, including in the primary care setting.

vol 1 Figure 4. Associations of the frequency of combined laboratory tests with post-ESRD all-cause mortality in 23,089 veterans who transitioned to ESRD during 10/1/2007-9/30/2011

Hazard ratios with 95% confidence intervals are presented for all-cause, CV and infection related mortality, and incidence rate ratios with 95% confidence intervals are presented for the composite hospitalization and death outcome. Multivariable model: baseline age, race, gender, baseline blood pressure, blood pressure variability assessed during the 2-year prelude period, per capita income, marital status, VA service connection percentage, comorbid conditions assessed from ICD-9 codes recorded at inpatient and outpatient encounters during the entire available pre-ESRD period [CV disease, cerebrovascular disease, hypertension, congestive heart failure, dementia, rheumatologic disease, malignancy, depression, liver disease, chronic lung disease, diabetes, HIV and CCI] and, medication adherence measured during the 2-year prelude period (PDC, medication possession ratio and persistence), baseline eGFR (first outpatient eGFR at the beginning of the prelude period) and prelude eGFR slope.

Abbreviations: CCI, Charlson Comorbidity Index; eGFR, estimated glomerular filtration rate; ESRD, end stage renal disease; HIV, human immunodeficiency virus; ICD-9, International Classification of Diseases, Ninth Revision; PDC, proportion of days covered; VA, Veterans Affairs.

Access Type

Effect of Age on the Association of Vascular Access Type with Mortality in a Cohort of Incident End-Stage Renal Disease Patients

Initiating dialysis with a matured or placed and maturing AVF or arteriovenous graft (AVG) may also be an indicator of pre-transition nephrology care and preparation for dialysis transition. In a cohort of 46,786 US veterans transitioning to hemodialysis between 10/1/2007-9/30/2011, we examined the association of initial access type with 12-month post-transition all-cause, cardiovascular and infection related mortality across

strata of age groups (<60, 60-<70, 70-<80, and ≥80 years old). Data from the CMS 2728 medical evidence form was used to ascertain if patients initiated dialysis with an AVF(18%), AVG(2%), or tunneled catheter (11%) with or without (61%) a maturing AVF or AVG. Compared to veteran patients initiating dialysis with an AVF, those who initiated with a tunneled catheter and no maturing AVF or AVG were less likely to have reported receiving pre-dialysis nephrology care at the time of transition and additionally were more likely to have cardiovascular and lung disease comorbidities. Patients who initiated with a tunneled catheter with a maturing AVF or AVG had less comorbidities but higher prevalence of diabetes and reported pre-dialysis nephrology care than those who initiated with a tunneled catheter without a maturing AVF or AVG. Compared to patients initiating hemodialysis with an AVF, patients initiating with other access types had a nearly three-fold or higher all-cause, cardiovascular and infection related mortality (Figure 5). Patients initiating dialysis with a tunneled catheter without a maturing AV access had the highest mortality rates across all age groups even after multivariable adjustment. Associations were similar across strata of age. The results of the analysis point to the importance of pre-dialysis care and preparation for patients transitioning to ESRD and support prior findings advocating for AVF access type in hemodialysis patients.

Vol 1 Figure 5. Associations of vascular access type (AVF, AVG, and TDC with and without a maturing AVF/AVG) at dialysis initiation with 1-year post-ESRD (a) all-cause, (b) cardiovascular, and (c) infection related mortality in pre-specified age subgroups of 46,786 veterans who transitioned to ESRD during 10/1/2007-9/30/2011
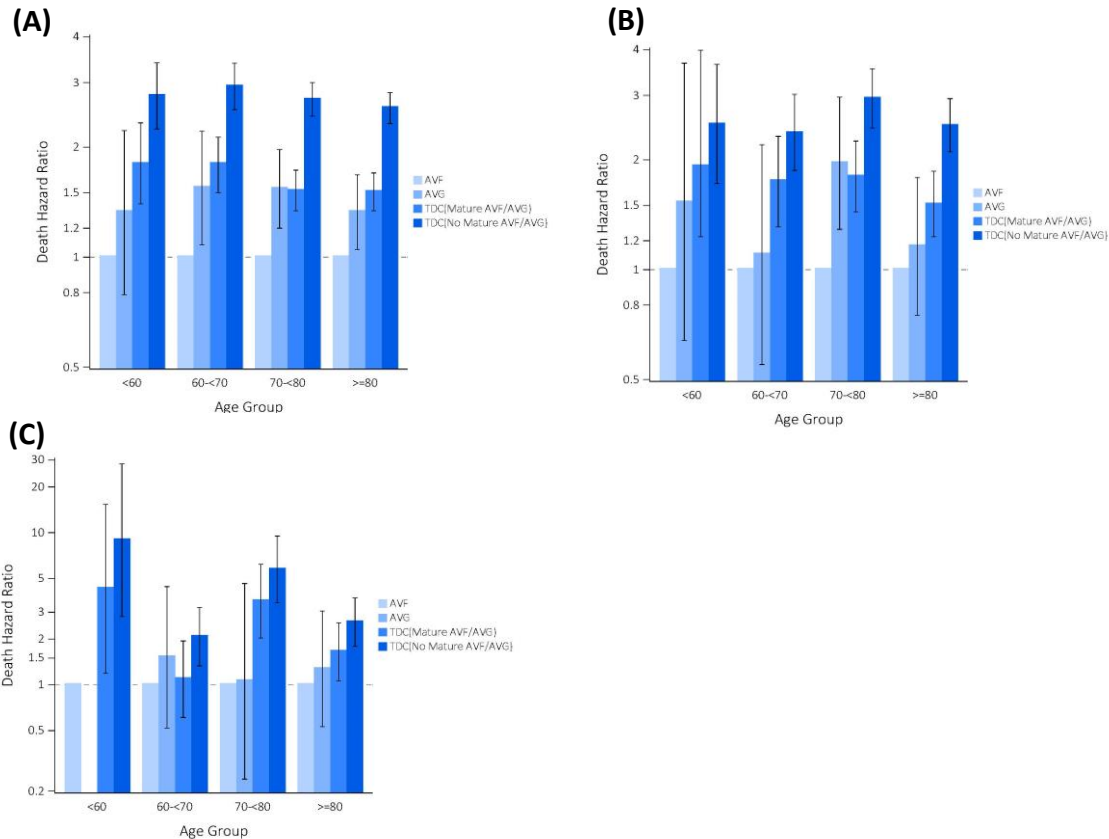
Sub-hazard ratios with 95% confidence intervals are presented for all-cause, cardiovascular and infection related mortality. Sub-hazard ratios are not shown for infection related deaths in the <60 years old age group due to the very low number of events. Multivariable model: age, gender, race, comorbid conditions (history of diabetes mellitus, myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic lung disease, liver disease and malignancies), and for the Charlson comorbidity index as an omnibus measure of illness.
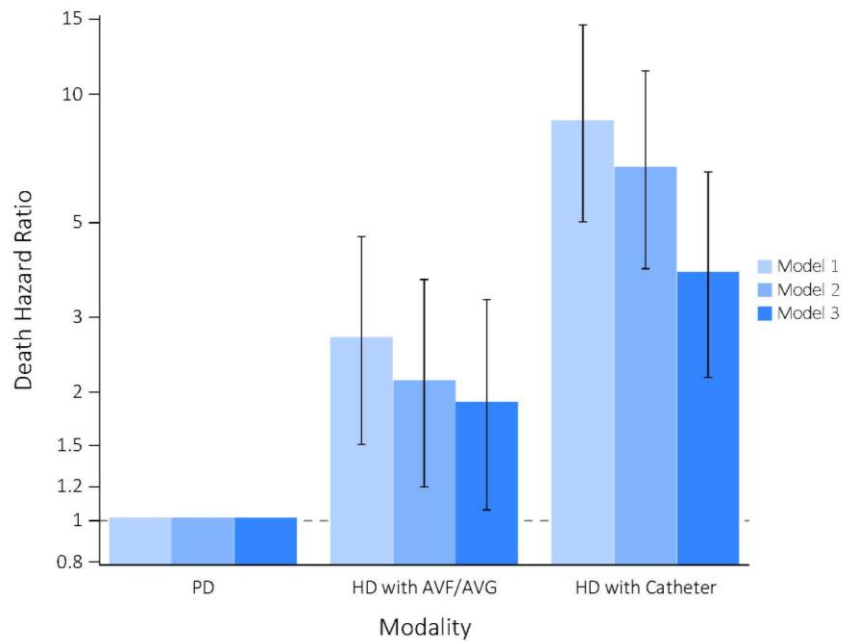
Abbreviations: AVF, arteriovenous fistula; AVG, arteriovenous graft; ESRD, end stage renal disease; TDC, tunneled catheter; VA, Veterans Affairs.

Disparities in early mortality among chronic kidney disease patients who transition to peritoneal dialysis and hemodialysis with and without catheters

Associations between access type at dialysis initiation and post-transition early (6-month) mortality were also examined in a cohort of 5,373 KP-SC patients who transitioned to dialysis between 1/1/2002-12/31/2013. The study compared hemodialysis patients with either an AVF or AVG or those with a catheter to patients initiating dialysis with peritoneal dialysis (PD) modality. In their cohort, 13% of patients with PD, and 52%

and 35% initiated hemodialysis with an AVF or AVG or a central venous catheter, respectively. Patients initiating dialysis with PD were more likely to be younger (<50 years old), Hispanic and less likely to have diabetes or heart failure comorbidity. Hemodialysis patients initiating treatment with a catheter were more likely to be older, African American, have heart failure comorbidity, transition as inpatient, had acute kidney injury (AKI) within 90 days prior to transition, and had a higher eGFR at transition. Compared to PD patients, those initiating dialysis with hemodialysis and a catheter access type had an almost three-fold high mortality risk in fully adjusted models, while hemodialysis patients with an AVF or AVG had an 87% higher mortality risk (Figure 6). In a follow up study including 1,082 propensity score matched KP-SC patients who transitioned to dialysis between 1/1/2002-12/31/2015, patients who initiated dialysis with PD were compared to those who initiated HD patients with an AVF or AVG. In logistic regression analysis, they found no difference in the odds of mortality at 6 months, 12 months, and 2 years (Figure 7). Since both PD and HD with AVF or AVG at dialysis start may indicate optimal pre-dialysis care, the results of these analyses support the call for more aggressive and timely management strategies and preparation for dialysis transition in pre-dialysis nephrology care with little difference in outcomes whether the preparation is in the direction towards PD or in-center hemodialysis with an AVF or AVG.

vol 1 Figure 6. Associations of access type at dialysis initiation with 6-month post-ESRD all-cause mortality among three treatment groups (PD, HD with AVF/AVG, and HD with catheter) in 5,373 KP-SC incident dialysis patients who transitioned to ESRD during 01/01/2002-03/31/2015


Hazard ratios with 95% confidence intervals are presented for all-cause mortality. Model 1: unadjusted; Model 2: age, sex, and race/ethnicity; and Model 3: Model 2 plus eGFR prior to transition, diabetes, heart failure, acute kidney injury, inpatient transition, bicarbonate level, and albumin.

Abbreviations: AVF, arteriovenous fistula; AVG, arteriovenous graft; eGFR, estimated glomerular filtration rate; ESRD, end stage renal disease; HD, hemodialysis; KP-SC, Kaiser Permanente Southern California; PD, peritoneal dialysis.

Early Mortality among Peritoneal Dialysis

vol 1 Figure 7. Among the propensity-matched cohorts, crude and adjusted odds ratio of mortality in peritoneal dialysis (PD) versus hemodialysis (HD) at 6 months, 1 year, or 2 years among 2,094 patients transitioning to ESRD between 01/01/2002 – 03/31/2015.
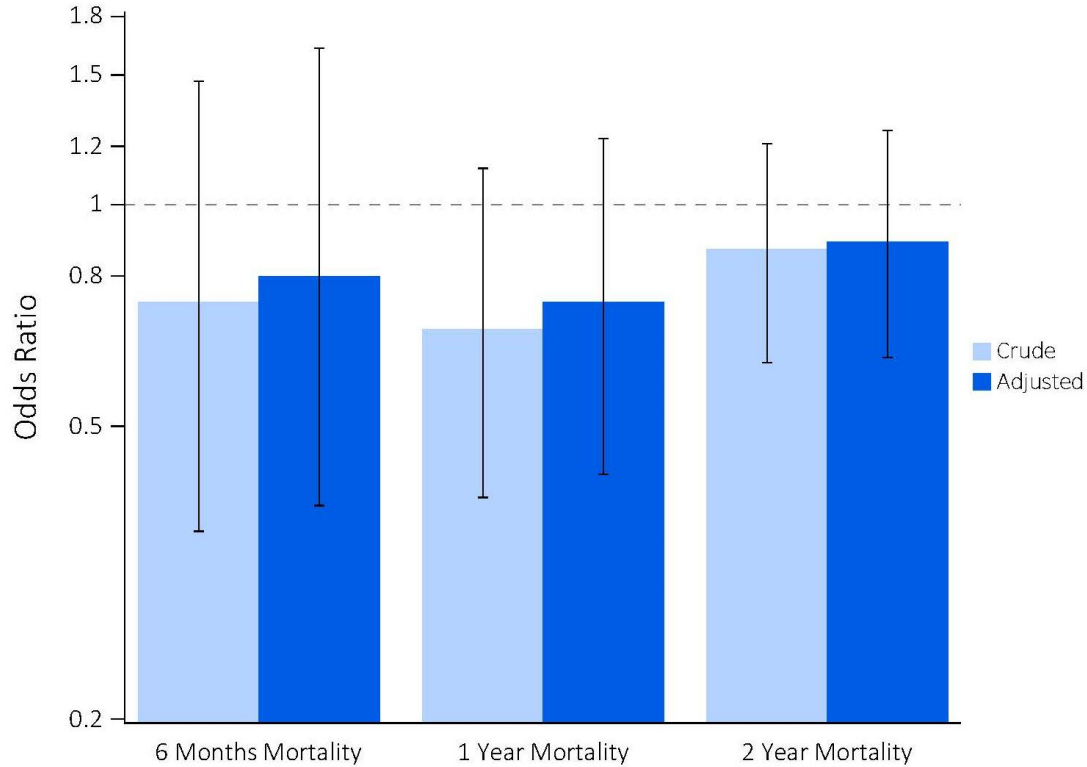

Adjusted odds ratios accounted for age, sex, and race/ethnicity.

Association between vascular access creation and deceleration of estimated glomerular filtration rate decline in late-stage chronic kidney disease patients transitioning to end-stage renal disease

Another potential benefit of earlier placement of an AVF or AVG may be that graft placement is associated with deceleration in eGFR slopes of CKD progression as shown in our findings. In Sumida et al.'s study, they examined the association of AVF or AVG creation (placement procedure) with change in eGFR slopes in 3,026 patients who transitioned to dialysis from 10/1/2007- 09/30/2011 and initiated dialysis with an AVF or AVG. As a comparison, they also estimated eGFR slopes within 6 months prior to transition and before 6 months in patients with a catheter placement procedure only, but no procedure for AVG or AVG and who initiated dialysis with a catheter. The eGFR slopes

were estimated using mixed effects models before and after the procedure date or 6-month pre-ESRD index date, respectively, in patients who had at least three eGFR measurements in the pre- and post- periods. In catheter patients, the average slope of eGFR accelerated from -6.0 to -16.3 mL/min per 1.73m² per year in a median 1.7 years in the before and after 6-month pre-ESRD index date, respectively (Figure 8A). However, for patients with an AVF or AVG, the eGFR slope in the median 1.4 years prior to the procedure date was -5.6 mL/min per 1.73m² per year and decelerated to -4.1 mL/min per 1.73m² per year. Results were similar in estimated slopes with covariate adjustment (Figure 8B). The authors attributed these findings to potential vasodilation and improved renal tissue perfusion from the creation of the graft or fistula, or additionally cardiovascular effects such as reduction in arterial stiffness, blood pressure and stroke volume and ischemic preconditioning. Nonetheless, the study results suggest that receiving a procedure for AVF or AVG may also contribute to delaying the onset of dialysis initiation by slowing eGFR slope or CKD progression, and also further support the ideology that improvement in pre-dialysis care may improve post dialysis transition outcomes.

vol 1 Figure 8. (A) Unadjusted and (B) adjusted eGFR slopes before and after arteriovenous fistula (AVF)/ arteriovenous graft (AVG) creation in patients with AVF/AVG, in contrast to non-AVF/AVG patients, in 3,026 patients from 10/01/2007 – 9/30/2011.
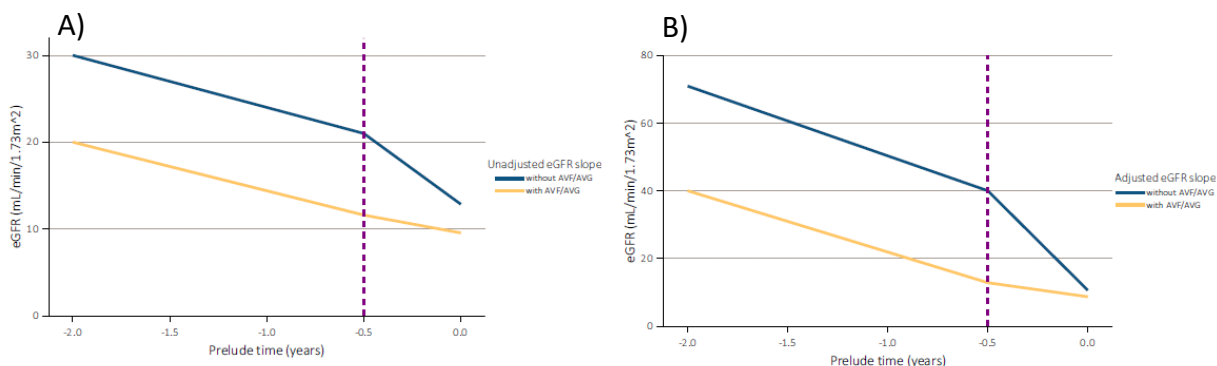

Model adjustment: eGFR slopes were estimated from (A) unadjusted and (B) multivariable-adjusted mixed-effects models. Models were adjusted for fixed (age, sex, race, diabetes mellitus and Charlson comorbidity index) and time-dependent confounders (systolic BP and angiotensin-converting enzyme inhibitors/angiotensin receptor blockers use).

eGFR

Association of Slopes of Estimated Glomerular Filtration Rate (eGFR) With Post-End-Stage Renal Disease Mortality in Patients With Advanced Chronic Kidney Disease Transitioning to Dialysis

Management of kidney disease progression is not only important for delaying transition to dialysis but estimates of eGFR slope may also be useful in predicting post-transition mortality. In a study 18,874 veterans who transitioned to dialysis between 10/1/2007-9/30/2011, Sumida et al. estimated per patient eGFR slopes up to 7 years before dialysis transition using ordinary least squares regression models. Associations of eGFR slope category defined as fast (eGFR slope <-10mL/min/1.73m²/year), moderate (-10-<-5mL/min/1.73m²/year), slow eGFR decline (-5-<0mL/min/1.73m²/year), and increasing eGFR (≥0mL/min/1.73m²/year), with post-transition all-cause, cardiovascular and infection related mortality were examined. Compared to the 42% of patients with a slow eGFR decline, the 24% with a fast decline and 30% with a moderate decline had an 11% and 6% higher post-transition adjusted mortality risk, respectively (Figure 9). Similar associations were observed for cardiovascular mortality. For infection related mortality, only an increasing eGFR before transition was associated with higher infection related mortality. The latter associations may be explained by a decreasing creatinine leading to an increasing eGFR in patients with muscle wasting which may impair antimicrobial defenses, while the former associations may be explained by underlying development of cardiovascular disease, development of frailty with decreased appetite and physical function, and alteration in blood pressure, bone and mineral metabolism and inflammation regulation. Nonetheless, the findings highlight the importance of monitoring the change in eGFR for ascertaining the risk of mortality post-transition to ESRD.

vol 1 Figure 9. Associations of pre-ESRD eGFR slopes (≥0, -5-<0 [ref.], -10-<-5, and <-10 mL/min/1.73 m²/year) with post-ESRD all-cause, cardiovascular, and infection related mortality in 18,874 veterans who transitioned to ESRD during 10/01/2007-9/30/2011
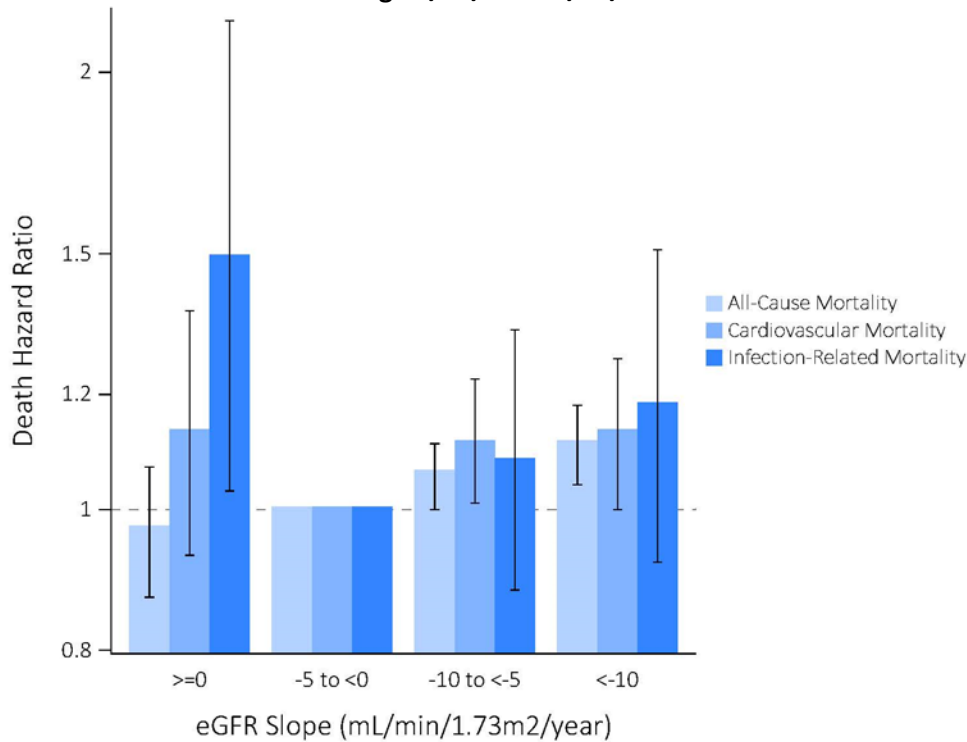
Death hazard ratios with 95% confidence intervals are presented for all-cause, cardiovascular and infection related mortality. Model 1: age, sex, race/ethnicity and marital status; Model 2: Model1 plus body mass index, diabetes mellitus, hypertension, Charlson Comorbidity Index score, and last eGFR before dialysis initiation; and Model 3: Model 2 plus medications (angiotensin-converting enzyme inhibitors or angiotensin receptor blockers; b-blockers; calcium channel blockers; vasodilators; loop, thiazide, and potassium-sparing diuretics; statins; active vitamin D analogues; phosphate binders [calcium acetate, sevelamer, or lanthanum]; nonsteroidal anti-inflammatory drugs; sodium bicarbonate; and erythropoiesis-stimulating agents).

Abbreviations: eGFR, estimated glomerular filtration rate; ESRD, end stage renal disease; m, meter; min, minute; mL, milliliter; ref, reference.

Predialysis Kidney Function and Its Rate of Decline Predict Mortality and Hospitalizations after Starting Dialysis

Examining a combination of the rate of eGFR decline and last eGFR prior to dialysis transition may provide further insight into patient outcomes in the first year on dialysis. In a subsequent study, Soohoo et al. examined the 12-month post-ESRD outcomes according to four categories (2x2 factorial design) of combined pre-transition kidney function and slope in a cohort of 19,985 US veterans who transitioned to dialysis between 1/1/2007-12/30/2014. Slow vs. fast eGFR slope estimated over one year prior to transition

was defined according to a threshold of -10 mL/min/1.73 m²/year, while low vs. high eGFR at transition (within 31 days prior) was dichotomized at 10 mL/min/1.73 m². Compared to patients who transitioned with a slow slope and low eGFR, patients with other combinations had higher all-cause and cardiovascular risk as well as higher hospitalization rates in the 12 months post-dialysis transition (Figure 10). The highest risk group were those who had a combined fast pre-transition eGFR slope and a high eGFR at transition. The lower risk of post-transition outcomes observed in patients who transitioned with a lower eGFR and slower eGFR decline may be explained by a better health status at the time of transition, which may be related to closer monitoring of the NDD-CKD patient or managing the disease progression. Although further studies are needed, this study points to the importance of pre-dialysis care in improving outcomes post-transition as well as the benefits of slowing disease progression and monitoring patients so that they may transition to dialysis at a lower eGFR.

vol 1 Figure 10. Association of combined 31-day prelude eGFR and 12-month eGFR slope with 12-month (A) all-cause mortality, (B) cardiovascular mortality, (C) and 12-month hospitalization incidence rate ratio.
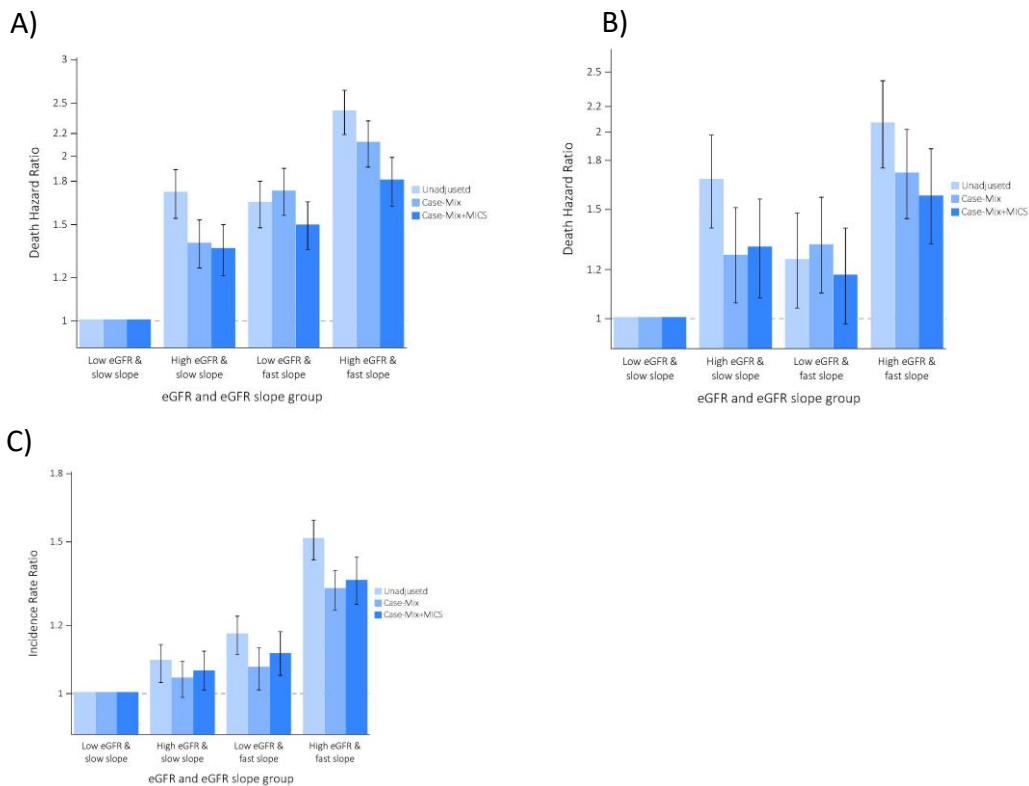
Model 1, unadjusted; Model 2 (Casemix): time interval between the last eGFR measurement and transition date, age, sex, race, ethnicity, incidence year, marital status, Charlson comorbidity index, diabetes, ischemic heart disease (ISHD), myocardial infarction, congestive heart failure (CHF), cerebrovascular disease, and chronic obstructive pulmonary disease (COPD); Model 3 (Casemix+MICS): Model 2 plus baseline measurements of bicarbonate, blood urea nitrogen, hemoglobin, albumin, phosphorus, calcium, potassium, BMI, and systolic and diastolic blood pressure.

Abbreviations: eGFR, estimated glomerular filtration rate; prelude, pre-ESRD; MICS, malnutrition-inflammation cachexia syndrome.

Abrupt Decline in Kidney Function Precipitating Initiation of Chronic Renal Replacement Therapy

Although CKD progression or eGFR decline can often occur at a somewhat steady rate, adverse events or acute kidney injury (AKI) can alter eGFR trajectories and cause abrupt declines in kidney function calling for patients to transition to dialysis sooner than expected. In an analysis of 23,349 US veterans who transitioned to dialysis between 1/1/2007-3/31/2014, 21% of patients had a >50% lower eGFR than predicted according to trajectories of eGFR calculated in the year prior to transition to dialysis. Although abrupt eGFR decline was strongly associated with renal recovery within the first six months after transition, only 12.2% of these patients were able to discontinue dialysis. Patients with abrupt deterioration experienced higher mortality compared to those without abrupt deterioration. Similar findings were observed across multivariable adjusted models using a threshold of a 25% or 50% increase in serum creatinine than predicted (Figure 11). Abrupt deterioration may indicate severe comorbidities after transition to chronic renal replacement therapy. Focusing on the prevention of an abrupt decline in eGFR and renal recovery could lead to better ESRD patient outcomes.

vol 1 Figure 11. A) Mortality hazard ratios associated with AKI defined as 50% and 25% increase in serum creatinine compared to expected serum creatinine B) Renal recovery subhazard ratios associated with AKI defined as 50% and 25% increase in serum creatinine compared to expected serum creatinine
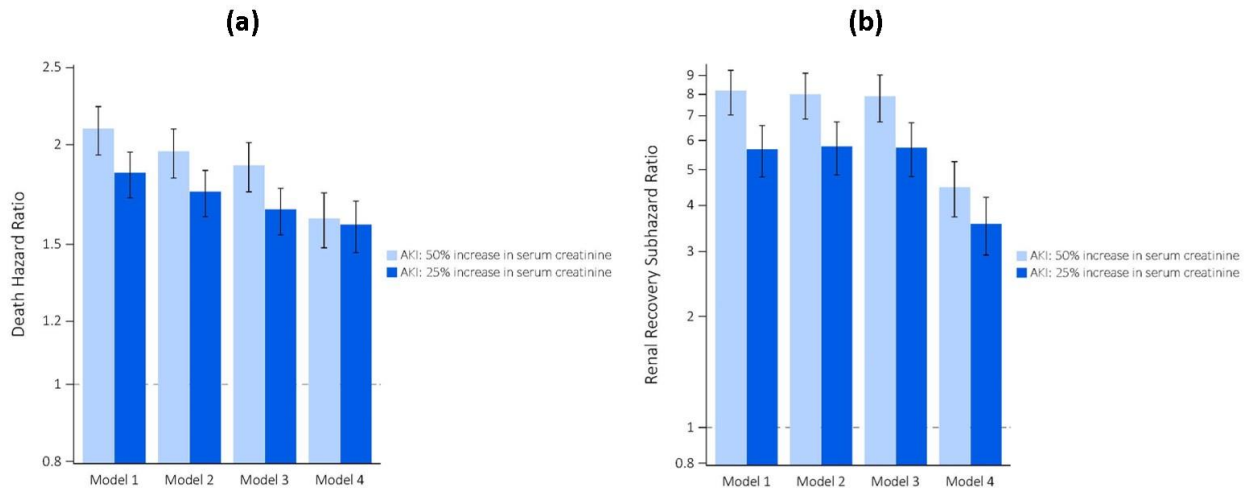
model 1: adjusted for demographics (age, sex, race/ethnicity, marital status and income); model 2: additionally adjusted for comorbidities (diabetes, malignancy, liver diseases, hypertension, ischemic heart disease, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disease, peptic ulcer disease, anemia, atrial fibrillation, depression, hyperlipidemia) and BMI; model 3: additionally adjusted for medications (anticoagulants, aspirin, digitalis, beta-blockers, alpha-blockers, CCBs, antianginals, statins, vasodilators, thiazide diuretics, loop diuretics, potassium-sparing diuretics, ACEIs/ARBs and antidiabetic agents), procedure type (single versus multivessel); model 4: additionally adjusted for baseline blood hemoglobin, serum albumin, eGFR and systolic and diastolic blood pressure.

Acute kidney injury following coronary revascularization procedures in patients with advanced CKD

In further analysis of 730 patients from the same cohort, the authors sought to examine whether odds of AKI may be related to type of coronary intervention. Patients with a coronary artery bypass graft (CABG) or percutaneous coronary intervention (PCI) within the five years prior to dialysis transition were compared for odds of subsequent development of AKI. The results showed that CABG patients had a higher incidence of AKI compared to PCI, 61% versus 31%, respectively, and in fully adjusted analysis, CABG was associated with a 3.5 to 4.3 higher odds of AKI. In additional analyses using competing-risks regression, compared to patients with no AKI, an AKI defined as the subhazard ratios for renal recovery and mortality showed higher risk for CABG compared to PCI. In their conclusion, the authors thereby suggest that the risks of AKI and its

sequelae should be taken into consideration when deciding on a revascularization strategy for patients in late stage NDD-CKD.

Blood Pressure

Pre-ESRD visit-to-visit systolic blood pressure variability and post-ESRD mortality and incident dialysis patients

Other indices of poor health or insufficient care ascertained through measured vital signs or laboratory measurements prior to dialysis transition may also predict outcomes in the post-transition period. In an analysis of 17,729 US veterans transitioning to dialysis between 10/1/2007-09/30/2011, Sumida et al. examined relationships of averaged systolic blood pressure (SBP) and diastolic blood pressure (DBP) with post-transition all-cause mortality within <3 (main analysis), 3-<6, 6-<12, or ≥12 months after transition to dialysis. SBP was divided into five categories of <120 to ≥160 mmHg in 10 mmHg increments. Results of multivariable adjusted survival analysis showed an inverse linear relationship, where compared to SBP of 140–<150 mmHg, patients with SBP<140 mmHg had a higher risk of 3-month mortality risk, with the highest death risk in the lowest strata of SBP <120 mmHg (Figure 12). Associations of mortality risk with six categories of DBP (<60 to ≥90 mmHg in 10 mmHg increments) were also examined; however, no significant associations were found in multivariable adjusted models. The authors caution about the limited ability to assess causality given the observational nature of the analysis. However, they mention that these findings may imply that aggressive blood pressure lowering strategies to very low levels in NDD-CKD patients may have adverse consequences for patients transitioning to dialysis. In an additional study in the same cohort, the authors examined SBP variability over the year prior to dialysis initiation and found that the highest quartile of variability was associated with higher all-cause mortality (Figure 13). High SBP variability was also associated with diabetes and cardiovascular comorbidity as well as a higher average SBP, use of antihypertensive medications, and poor cardiovascular medication adherence. Higher SBP variability can lead to blood vessel stress, endothelial dysfunction, and inflammation, which in turn can lead to organ damage and consequently higher mortality risk. Monitoring SBP levels and additionally SBP stability

prior to dialysis transition is indicated and may be used as a predictive marker of post-transition mortality risk.

vol 1 Figure 12. Adjusted hazard ratios for all-cause mortality in the first 3 months after dialysis initiation by categories of (A) pre-dialysis SBP and (B) pre-dialysis DBP among 17,729 veterans transitioning to dialysis between 10/ 1/2007 and 09/30/2011
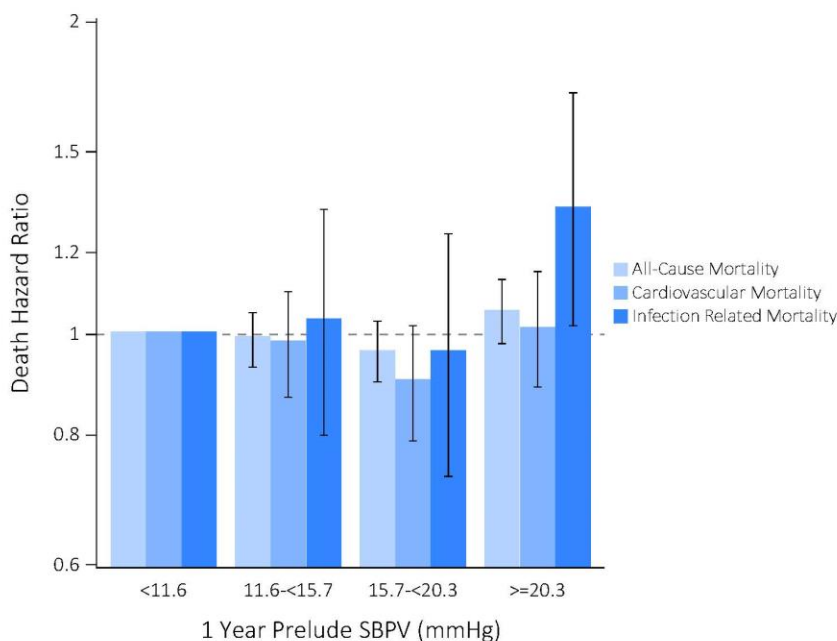
A)
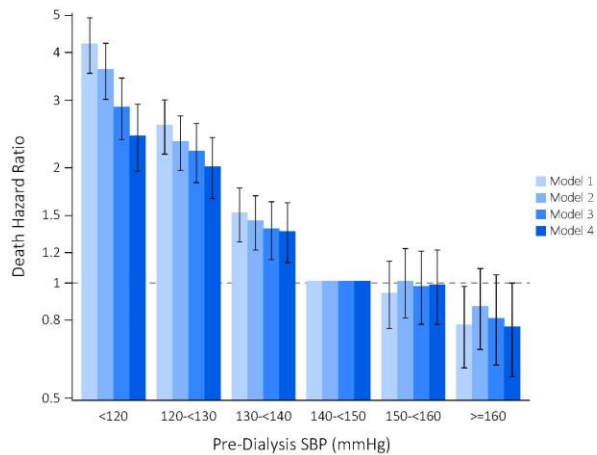
B)
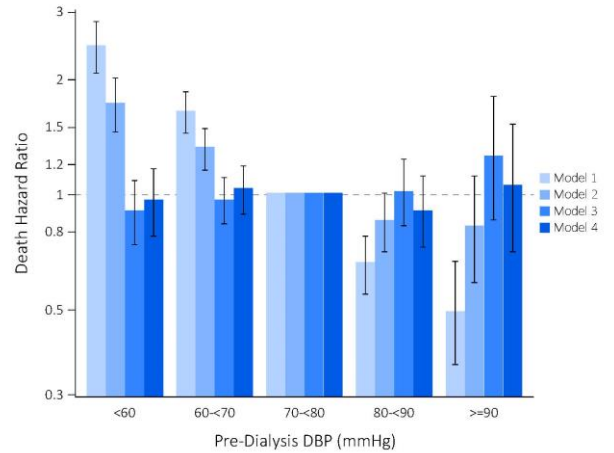
model 1, unadjusted; model 2, adjusted for age, sex, race/ethnicity, and marital status; model 3 additionally accounted for comorbidities (cardiovascular disease, congestive heart failure [CHF], peripheral vascular disease, lung disease, diabetes mellitus, liver disease, and Charlson comorbidity index), and body mass index (BMI) (and SBP for the associations with pre-dialysis DBP) averaged over the one-year pre-dialysis period, eGFR slope, and last eGFR before dialysis initiation; model 4 additionally included medications (angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, β-blockers, calcium channel blockers, vasodilators, diuretics, statins, and erythropoiesis-stimulating agents), cardiovascular medication adherence, and type of vascular access (arteriovenous fistula, arteriovenous graft, or catheter).

vol 1 Figure 13. Associations of 1-year pre-ESRD SBP visit-to-visit variability with (A) all-cause, (B) cardiovascular and (C) infection-related mortality after dialysis initiation in 17,729 patients from 10/01/2007 - 9/30/2011

The lowest quartile of SBPV was the reference group. Models were as follows: model 1 was adjusted for age, sex, race/ethnicity and marital status; model 2 additionally accounted for comorbidities (hypertension, cardiovascular disease, congestive heart failure, peripheral vascular disease, lung disease, diabetes mellitus, liver disease, and Charlson comorbidity index) and SBP, BMI, and estimated glomerular filtration rate averaged over the 1-year prelude period; and model 3 additionally included medications (angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, β-blockers, calcium-channel blockers, vasodilators, diuretics, statins, and erythropoietin-stimulating agents), cardiovascular medication adherence, and type of vascular access (arteriovenous fistula, arteriovenous graft, or catheter).

Lab

Pre-End-Stage Renal Disease Hemoglobin with Early Dialysis Outcomes

Management of anemia, mineral bone metabolism, glycemic status, and nutritional status in NDD-CKD patients is essential to improve survival, and aberrant levels of these clinical indicators may also provide insight into CKD risk after patients' transition to dialysis.

Kleine et al. examined associations of 6-month average pre-ESRD hemoglobin with 12-month post-ESRD outcomes, including all-cause and cardiovascular mortality as well

as hospitalization rates among 31,472 US veterans transitioning to dialysis between 10/1/2007-03/31/2014. Outcome risk within 12 months post-ESRD transition was assessed according to five categories of hemoglobin. Compared to hemoglobin 10-11 g/dL, patients with lower hemoglobin levels had a higher risk of all outcomes post-transition to ESRD; however, higher hemoglobin was associated with higher risk of all-cause and cardiovascular mortality (Figure 14), but not hospitalization rates post-transition. Trajectories of hemoglobin across transition were also examined, as well as the association of pre-ESRD hemoglobin slopes with post-transition outcomes. Most patients had a decline in hemoglobin in the year prior to transition that was corrected after dialysis initiation. A decline in hemoglobin was associated with higher risk of all post-transition outcomes; however, the associations were attenuated to the null in multivariable models accounting for eGFR decline. Conversely, an increase in hemoglobin in the year prior to transition was associated with higher rates of hospitalization, which the authors speculated may be attributed to increased blood viscosity from anemia correction therapies leading to higher rates of thromboembolism. Findings of the study indicate the importance of anemia management prior to transition to dialysis and suggest that hemoglobin levels and slopes may be used as a predictor for post-transition outcomes.

vol 1 Figure 14. Associations of 6-month pre-ESRD hemoglobin with 1-year post-ESRD (a) all-cause and (b) cardiovascular mortality in 31,472 veterans who transitioned to ESRD during 10/1/2007-3/31/2014
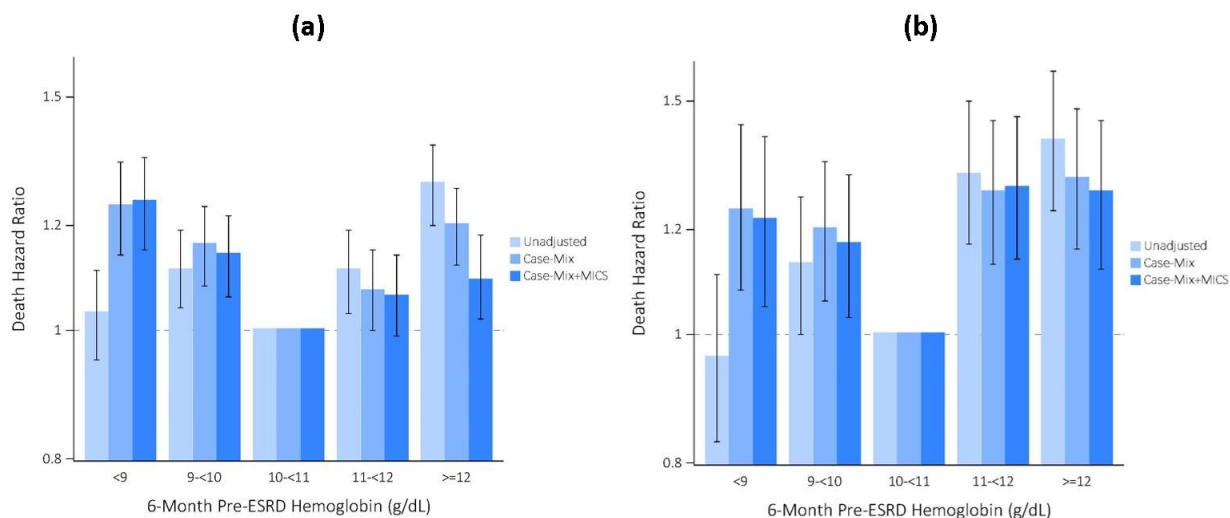
Model 1: unadjusted; Model 2 (Case-Mix): age, gender, race, ethnicity, marital status, Charlson Comorbidity Index, atrial fibrillation, hyperlipidemia, ischemic heart disease, myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, chronic obstructive pulmonary disease, peptic ulcer disease, liver disease, diabetes mellitus, cancer, and

primary cause of ESRD; Model 3 (Casemix+MICS): Model 2 plus last eGFR prior to transition and baseline laboratory measures of bicarbonate, albumin, calcium, phosphorus, white blood cell count, alkaline phosphatase, BMI, and ever use of oral or intravenous (IV) iron and ESA in the 6-month pre-ESRD period.

Abbreviations: BMI, body mass index; dL, deciliter; eGFR, estimated glomerular filtration rate; ESA, erythropoietin stimulating agent; ESRD, end stage renal disease; g, gram; MICS, malnutrition inflammation complex syndrome.

Pre-ESRD Hemoglobin Variability Predicts Post-ESRD Mortality in Patients Transitioning to Dialysis

However, not only is patient hemoglobin level an important predictor for patients transitioning to ESRD, but its stability of staying within range during the pre-transition NDD-CKD period may also give insight into patient health and potential risk in the post-transition period. Sumida et al. examined the association of 6-month pre-ESRD hemoglobin variability with post-ESRD all-cause, cardiovascular, and infection-related mortality among 11,872 US veterans transitioning to dialysis between 10/1/2007-09/30/2011. Hemoglobin-variability was determined by estimates of residual standard deviation from within-subject linear regression estimates over the 6 months prior to ESRD transition. Averaged hemoglobin was mostly similar across quartiles, but slightly lower in higher quartiles of variability. Mortality risks across quartiles of hemoglobin variability were examined across hierarchical multivariable adjusted models (<0.46, 0.46–<0.69, 0.69–<0.96, and ≥0.96 g/dL). Compared to the lowest quartile, patients in the highest quartile of hemoglobin variability had a 10% higher risk of all-cause mortality in fully adjusted models (Figure 15). Subgroup analyses revealed that these associations were stronger in African American patients. In fully adjusted models, the highest variability quartile was also associated with a 28% higher risk of infection-related mortality; however, no differences in mortality risk were observed for cardiovascular mortality. Associations of hemoglobin variability with infection related mortality were particularly stronger in patients with eGFR <15 mL/min/1.73m² and those treated with erythropoietin stimulating agents. The authors suggested that the variability hemoglobin may be related to the pharmacokinetics of drugs administered for anemia management, comorbidities with concomitant anemia requiring these drugs, or systemic inflammation leading to problems responding to anemia management medications. The large fluctuations in hemoglobin may lead to ischemic tissue events and cardiovascular complications. Patients with larger hemoglobin variability may have died of cardiovascular

complications prior to reaching dialysis transition, and thereby may explain the lack of associations with cardiovascular mortality in the post-transition period. Nonetheless, the findings suggest the importance of closely monitoring hemoglobin level, trajectory and variability in the pre-transition to ESRD period.

vol 1 Figure 15. Associations of 6-month pre-ESRD hemoglobin variability with post-ESRD (a) all-cause, (b) cardiovascular, and (c) infection-related mortality in 11,872 veterans who transitioned to ESRD during 10/1/2007-9/30/2011
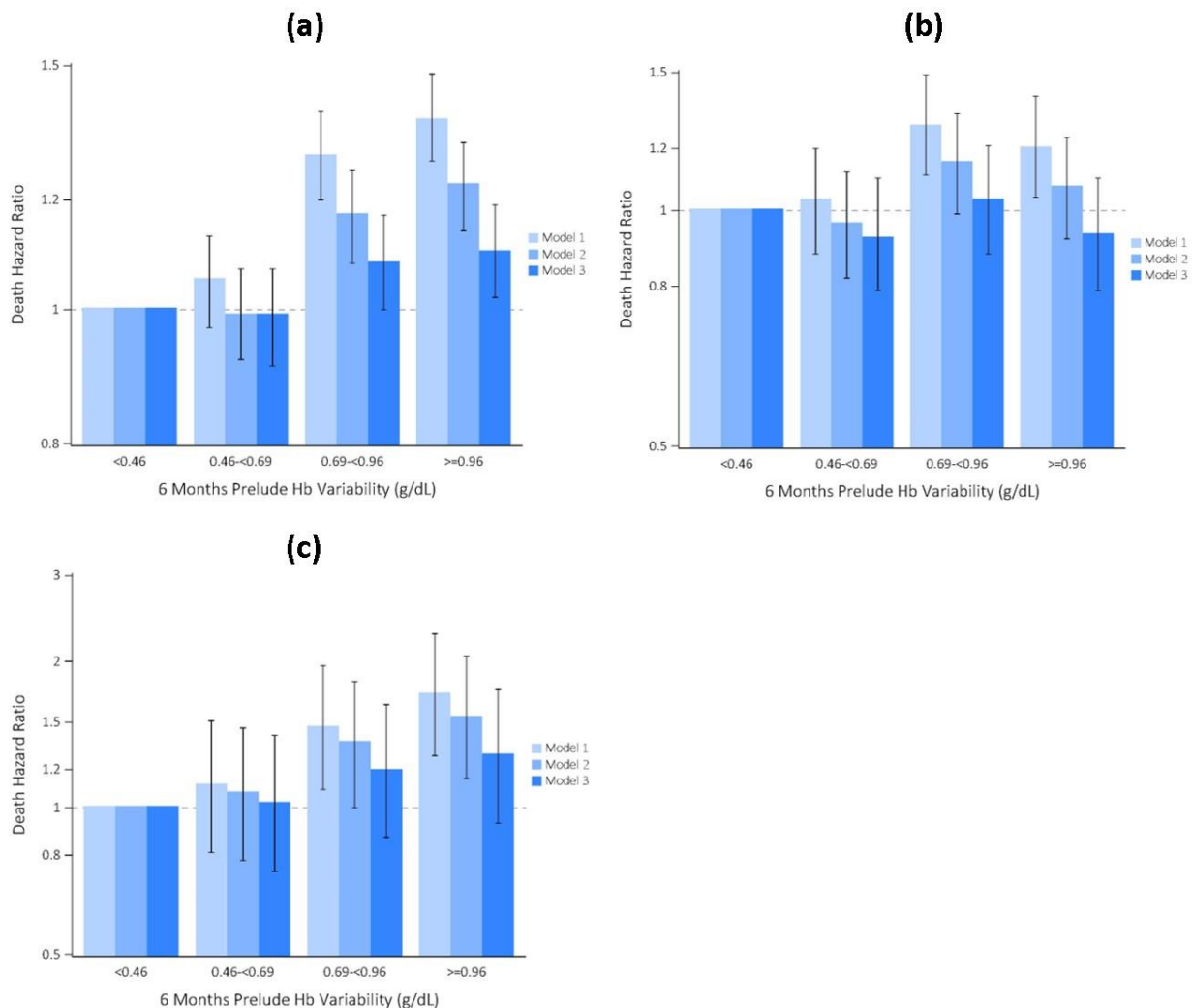

Death hazard ratios with 95% confidence intervals are presented for all-cause, cardiovascular and infection-related mortality. Model 1: age, sex, race/ethnicity, and marital status; Model 2: Model 1 plus comorbidities (diabetes mellitus, cardiovascular disease, CHF, peripheral vascular disease, lung disease, peptic ulcer disease, liver disease, malignancy, and HIV/AIDS), Charlson Comorbidity Index, and cumulative length of hospitalization during the six-month prelude period as an indicator of sickness; and Model 3: Model 2 plus medications (ESAs, intravenous or oral iron, vitamin D analogs, ACEIs/ARBs, antiplatelet agents, and warfarin), eGFR, type of vascular access (arteriovenous fistula, arteriovenous graft, or catheter), baseline Hb, change in Hb, and number of Hb measurements over the six-month prelude period.

Abbreviations: Hb, hemoglobin; CHF, congestive heart failure; eGFR, estimated glomerular filtration rate; ESA, erythropoietin stimulating agent; ESRD, end stage renal disease

Prognostic significance of pre-end-stage renal disease serum alkaline phosphatase for post-end-stage renal disease mortality in late-stage chronic kidney disease patients transitioning to dialysis

As a consequence of anemia in CKD, patients often develop disruptions of bone and mineral metabolism, which can lead to adverse outcomes in these patients. In prior ADR chapters, we demonstrated that therapies aimed at management of these markers increase in their prescription throughout the transition period and for some medications remain higher in ESRD. However, in two studies of bone and mineral metabolism markers, namely calcium and alkaline-phosphatase (ALP), we sought to examine whether aberrant levels in these markers measured prior to transition to dialysis were associated with post-transition outcomes. Sumida et al. examined risks of all-cause, cardiovascular and infection-related mortality following dialysis initiation in 17,732 patients who transitioned to dialysis from 10/2007-9/2011 , according to quartiles of ALP, and using Cox regression models adjusted for demographics, comorbidities, medications, eGFR and serum albumin levels over the 6-month prelude period, and vascular access type at dialysis initiation. They found that compared to the lowest ALP quartile, the highest ALP quartile were associated with a 42%, 43%, and 39% higher risk of all-cause, cardiovascular and infection-related mortality following dialysis initiation, independent of comorbid conditions and other known risk factors (Figure 16).

vol 1 Figure 16. Associations of 6-month pre-ESRD alkaline phosphatase with post-ESRD (a) all-cause, (b) cardiovascular, and (c) infection-related mortality in 17,732 veterans who transitioned to ESRD during 10/1/2007-9/30/2011
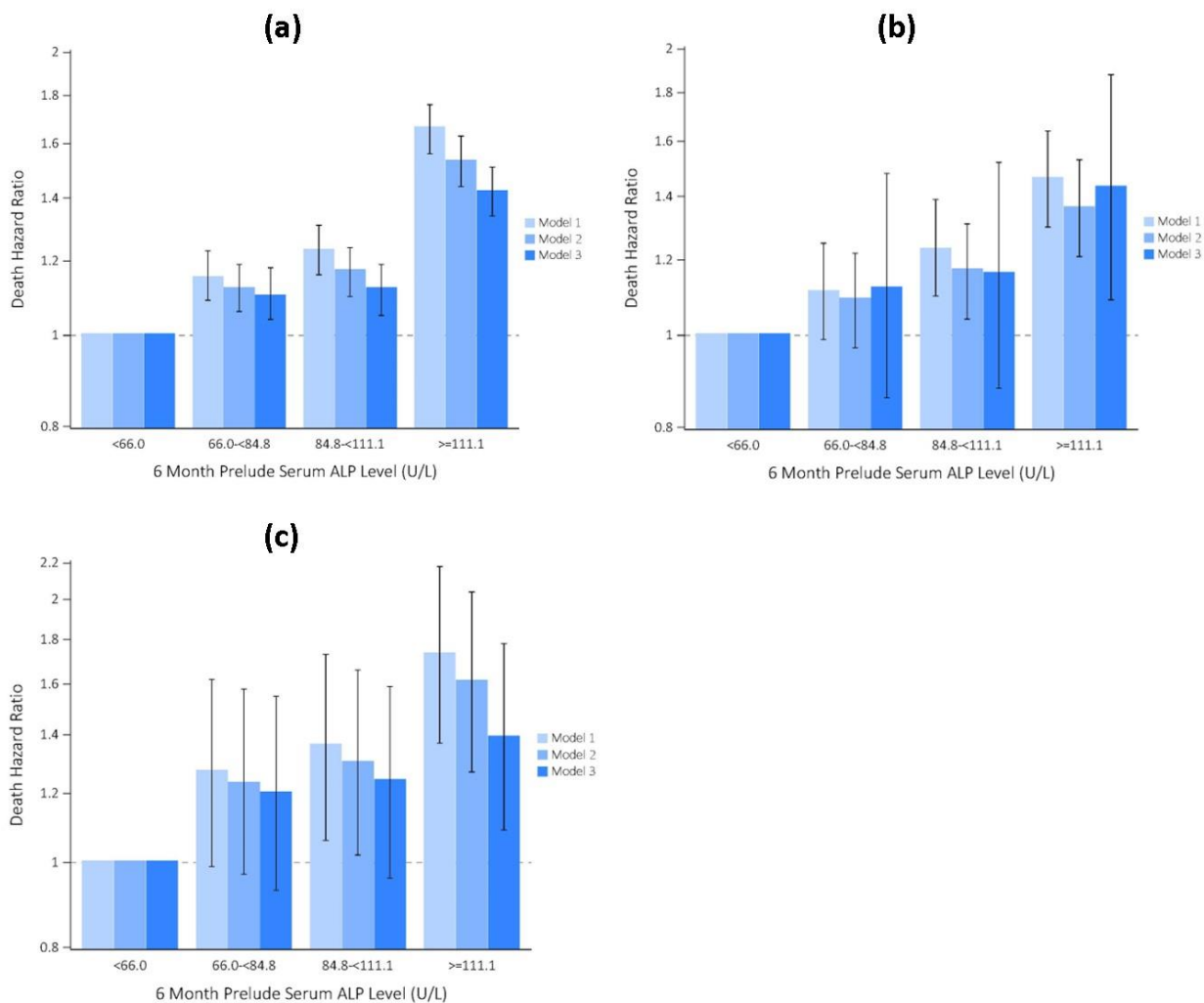

The lowest quartile of serum ALP was the reference group. Models were as follows: model 1 was adjusted for age, sex, race/ethnicity and marital status; model 2 additionally accounted for comorbidities (cardiovascular disease, congestive heart failure, peripheral vascular disease, dementia, lung disease, diabetes mellitus, liver disease, malignancy and Charlson Comorbidity Index); and model 3 additionally included medications (vitamin D analogs, phosphate binders, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, statins, bicarbonate and erythropoietin stimulating agents), eGFR and serum albumin averaged over the 6-month prelude period, and type of vascular access (arteriovenous fistula, arteriovenous graft or catheter).

Association of Pre-ESRD Serum Calcium with Post-ESRD Mortality among Incident ESRD Patients: A Cohort Study

Obi et al. then examined associations of post-ESRD risks of all-cause, cardiovascular and non-cardiovascular mortality with 6-month averaged pre-ESRD albumin-corrected serum calcium (cSCa) and its one-year pre-ESRD slope in a cohort of 21,826 US veterans who transitioned between 10/1/2009- 3/31/2014. Additional analysis examined potential effect modification on these associations by use of calcium supplement or Active Vitamin D in the pre-ESRD period. Pre-ESRD mean concentrations and median rate of decline of cSCa were 9.3 +/- 0.7 mg/dL and -0.15 (interquartile range -0.39 to 0.07) mg/dL/year, respectively. Outcome risks were examined according to six categories of cSCa (<8.0 to ≥10.0 mg/dL in 0.5 mg/dL increments) with a reference group of 8.5-<9.0 mg/dL. The relationship of pre-ESRD cSCa with post-ESRD all-cause and non-cardiovascular mortality was linear across models of multivariable adjustment, whereas patients with the highest cSCa level had a 28% and 14% higher risk of these respective outcomes in the primary adjustment model (Figure 17A, C). For cardiovascular mortality, associations of lower cSCa (<8.0 mg/dL) with lower mortality risk attenuated with multivariable adjustment; however, associations for higher cSCa with higher cardiovascular mortality risk were robust and were 14% higher in the primary adjustment model (Figure 17B). In stratified analysis according to medications, associations of higher cSCa (≥9.0 mg/dL) with higher mortality risk were attenuated among active vitamin D users (P interaction < 0.001). Conversely, associations did not differ according to use of calcium supplements. Additionally, patients with faster decline in pre-ESRD cSCa showed lower mortality (particularly for non-cardiovascular mortality) irrespective of baseline cSCa concentrations.

Both studies indicate the utility in monitoring markers of bone and mineral metabolism disorders in the NDD-CKD pre-ESRD period and indicate their potential in determining outcomes in the post-transition period. Further studies are also needed in best management strategies for correcting these disorders and how prescriptions should be altered across transition to ESRD.

vol 1 Figure 17. Associations of 6-month pre-ESRD serum calcium with post-ESRD (a) all-cause, (b) cardiovascular, and (c) infection-related mortality in 21,826 veterans who transitioned to ESRD during 10/1/2007-3/31/2014

(A)

(B)

(C)
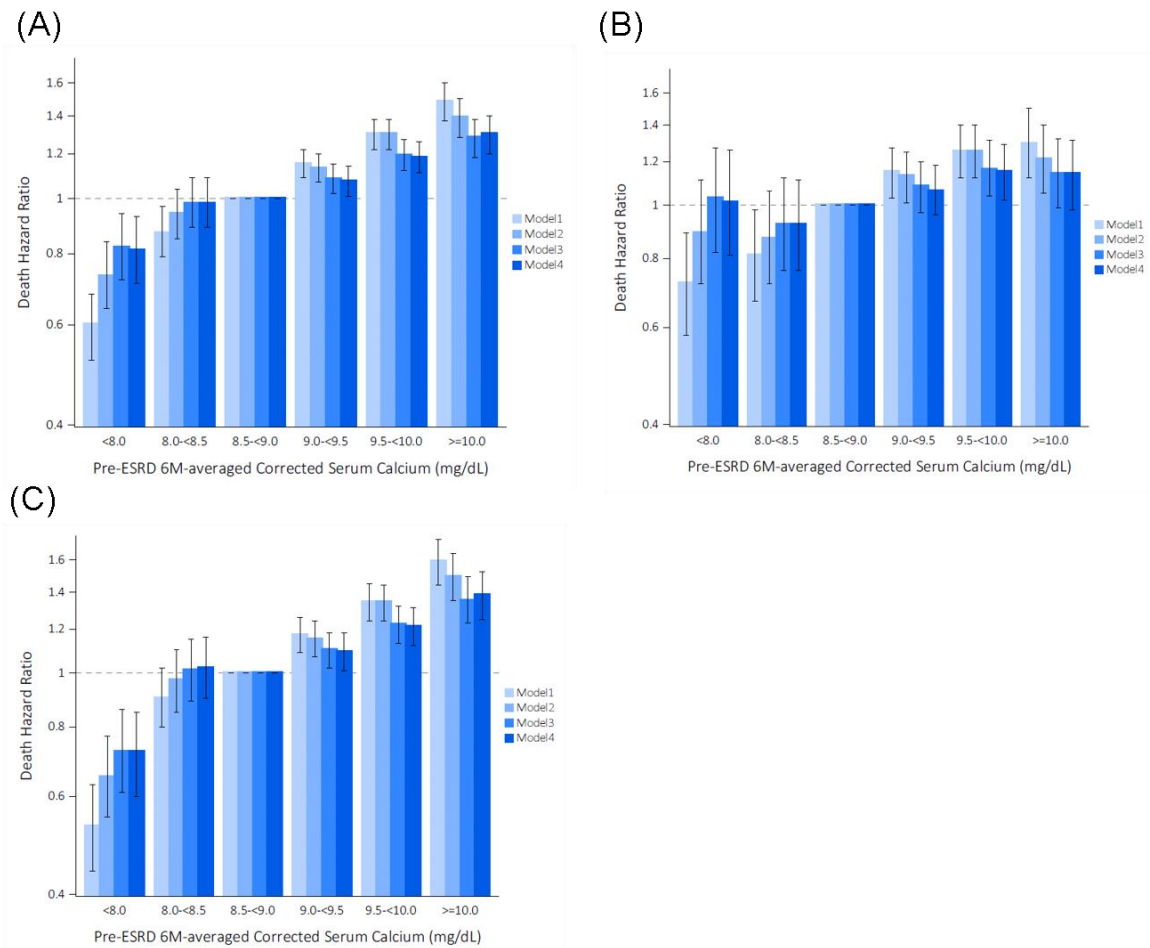
model 1: unadjusted; model 2: included age, sex, race, ethnicity, and marital status; model 3: included all covariates in model 2 plus Charlson comorbidity index, diabetes, prior history of ischemic heart disease, congestive heart failure, atrial fibrillation, cerebrovascular disease, chronic pulmonary disease, depression, and cancer, serum albumin, body mass index, and estimated GFR; model 4: included all covariates in model 3 plus baseline medications, which were composed of calcium supplements, active vitamin D, nutritional vitamin D (either ergocalciferol or cholecalciferol), calcium-containing phosphate binders, erythropoiesis-stimulating agents, RAAS inhibitors, sodium bicarbonate, and loop and/or thiazide diuretics.

Association of Pre-End-Stage Renal Disease Serum Albumin with Post-End-Stage Renal Disease Outcomes among Patients Transitioning to Dialysis

Patients with progressing CKD often have complications related to malnutrition and inflammation. In the literature, albumin has been noted as one of the most potent

biomarkers in determining nutrition and inflammatory status in CKD patients. Although a patient's status improves after transitioning to dialysis with better appetite and less inflammation, examining a patient's albumin status prior to transition may indicate his or her outcome risk in the post-transition period. In a study of 29,124 veterans who transitioned to dialysis between 10/1/2007–3/31/2015, Hsiung et al. examined the association of 3-month averaged pre-ESRD serum albumin with 12-month post-ESRD outcomes. Serum albumin was separated into seven strata (reference group: albumin ≥4.0 g/dL). Associations with 12-month mortality and 12-month post-ESRD hospitalization rates were examined. Across all models of multivariable adjustment, there was an inverse linear relationship between pre-ESRD serum albumin and post-ESRD outcome risk (Figure 18). Patients with albumin <2.8 g/dL had a greater than two-fold higher risk of all mortality outcomes and a 50% higher rate of hospitalization in fully adjusted models. Additionally, associations of all-cause mortality risk according to slopes of albumin estimated over the year prior to dialysis initiation had similar linear associations, whereas there was a nearly two-fold higher risk for patients whose albumin had a steeper decline (≤-0.5 g/dl/year). Although albumin levels generally appeared to improve in the post-ESRD period, trajectories examining albumin levels across transition showed very little change within the first quarter of dialysis. Thereby, the study findings suggest that poor and declining nutritional and inflammatory status prior to ESRD transition may demonstrate a patient's high risk of early mortality after transitioning to ESRD.

vol 1 Figure 18. Associations of 3-month pre-ESRD serum albumin with post-ESRD (a) all-cause, (b) cardiovascular, (c) infection related mortality, and (d) hospitalization in 29,124 veterans who transitioned to ESRD during 10/1/2007-3/31/2015
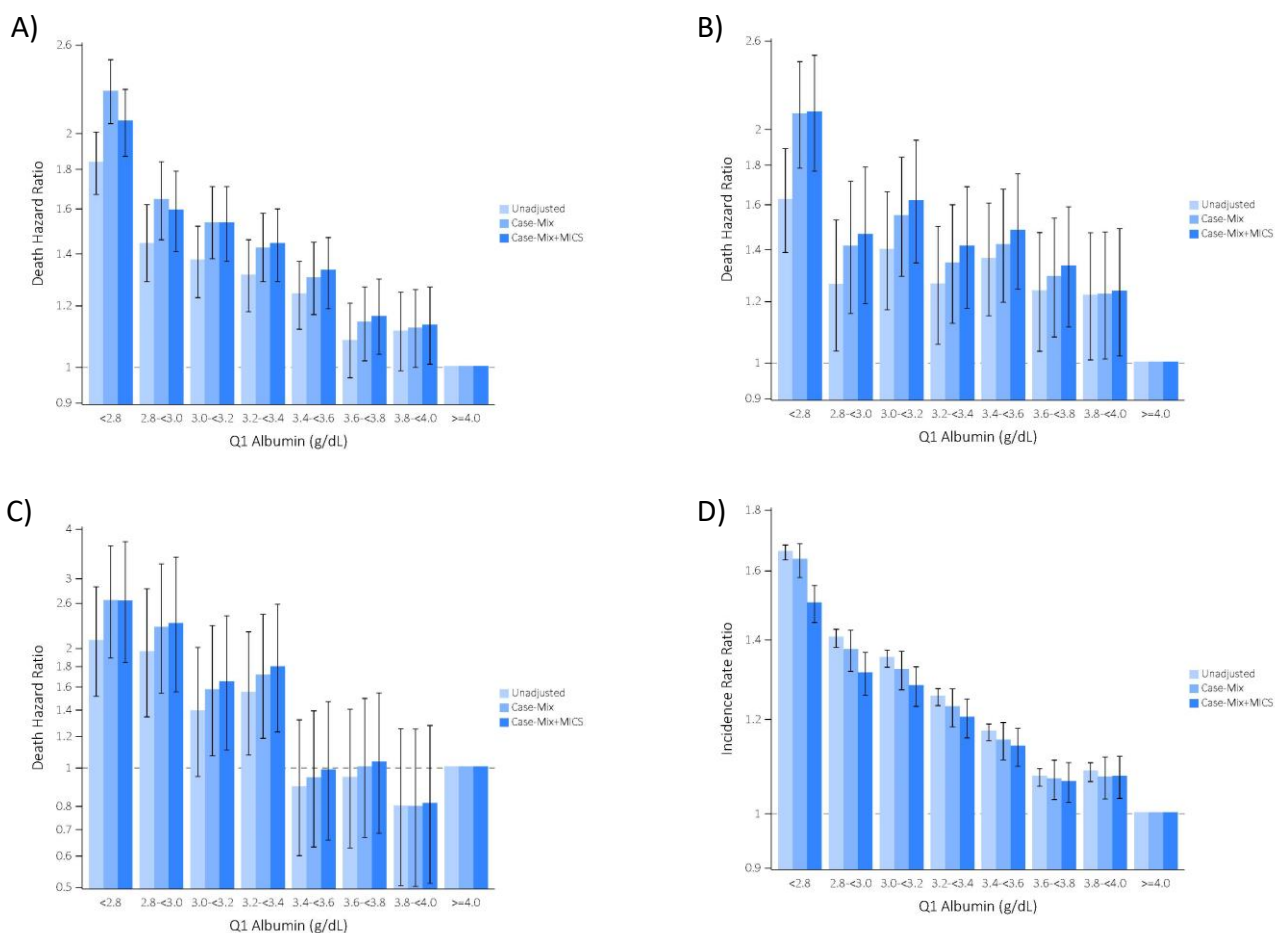
Model 1, unadjusted; Model 2 (Casemix): age, sex, race, ethnicity, marital status, Charlson Comorbidity Index (CCI), anemia, atrial fibrillation depression, hyperlipidemia, ischemic heart disease, myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disease (rheumatic disease), peptic ulcer disease, paraplegia and hemiplegia, AIDS and HIV, liver disease, diabetes mellitus, cancer and primary cause of ESRD; Model 3 (Casemix+MICS): Model 2 plus baseline laboratory measures of hemoglobin, bicarbonate, phosphorus, white blood cell count, alkaline phosphatase, body mass index, potassium, cholesterol, eGFR, and corrected calcium.

Association of Glycemic Status during Progression of Chronic Kidney Disease with Early Dialysis Mortality in Patients with Diabetes

While early trials have reported that intensive glycemic targets reduce diabetic complications, contemporary trials have shown no cardiovascular (CV) benefit and potentially higher mortality risk and also did not consider advanced CKD patients transitioning to dialysis. To better inform the ideal glycemic target in these patients, Rhee

et al. sought to examine the relationship between pre-ESRD glycemic status, defined by hemoglobin A1c (HbA1c) levels and random glucose levels, with 1-year post-ESRD mortality among patients transitioning to dialysis from 10/2007-9/2011.

The primary cohort was designated as the "Overall HbA1c Cohort" (N=17,819), which was intended to include all patients with diabetes, using a history of HbA1c measurement as a sensitive indicator, and who were comprised of patients who did not have missing censoring event dates, were ≥18 years of age, and underwent one or more HbA1c measurements up to 1 year preceding dialysis initiation. Given the ongoing debate regarding the optimal glycemic metric in CKD patients, we also created a complementary "Mean Random Glucose Cohort" (N=17,121), that was composed of patients who did not have missing censor data, were ≥18 years of age or older, underwent one or more random blood glucose measurements during the 1-year prelude period, and had either an ICD-9 code or cause of ESRD due to diabetes. Cox proportional hazards models were used to estimate the association between 1-year pre-ESRD mean HbA1c and mean random glucose levels with post-ESRD mortality outcomes. Fine and Gray competing risks regression models were used to estimate cardiovascular death.

In adjusted Cox models examining all-cause mortality, higher pre-ESRD HbA1c levels ≥8% were associated with higher post-ESRD all-cause mortality in the first year after dialysis initiation (reference: HbA1c 6% to <7%): adjusted HRs (aHRs) (95% CI) 1.19 (1.07–1.32) and 1.48 (1.31–1.67) for HbA1c 8% to <9% and ≥9%, respectively (Figure 19A). Random glucose levels ≥200 mg/dL were associated with higher all-cause mortality (reference: 100 to <125 mg/dL): aHR (95% CI) 1.34 (1.20–1.49). In adjusted Fine and Gray competing risks regression models examining cardiovascular mortality, HbA1c levels ≥9% were associated with higher cardiovascular death risk (Figure 19B). Similarly, higher mean random glucose levels ≥200 mg/dL were associated with higher cardiovascular death risk (Figure 20).

vol 1 Figure 19. Adjusted hazard ratios for (A) all-cause and (B) cardiovascular mortality after transition to dialysis across categories of pre-end stage renal disease (ESRD) mean hemoglobin A1c (HbA1c) levels averaged over the 1-year prelude period (the time prior to transition to ESRD) (reference: HbA1c 6-<7%) in 17,819 patients from 10/01/2007 – 9/30/2011.
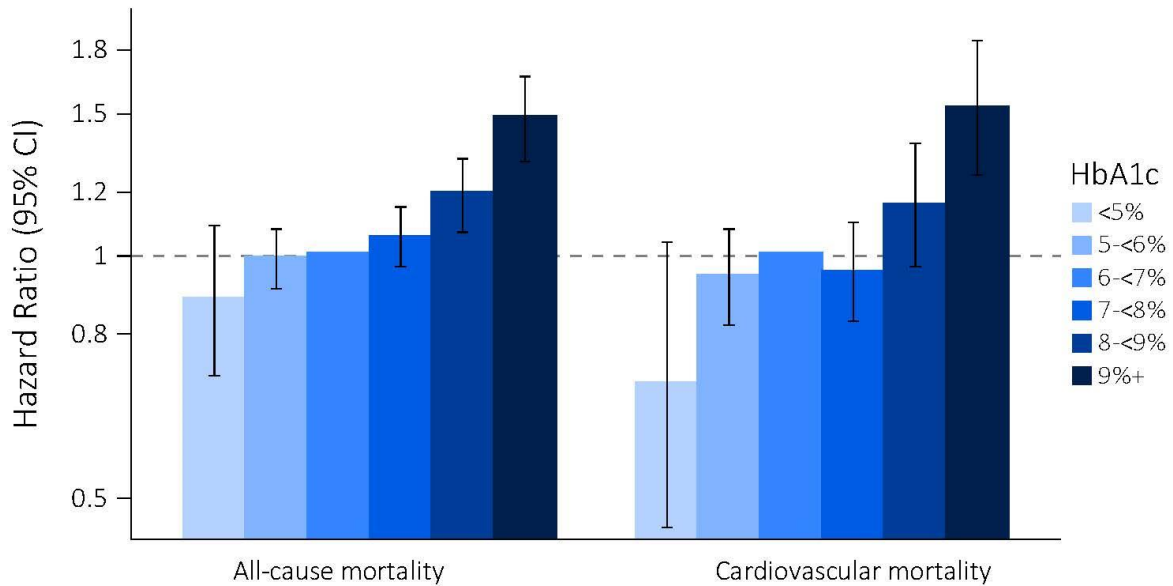
Associations of pre-end stage renal disease (ESRD) mean hemoglobin A1c (HbA1c) levels averaged over the 1-year prelude period (categorized as <5%, 5% to <6%, 6% to <7%, 7% to <8%, 8% to <9%, and ≥9%) with (A) all-cause and (B) cardiovascular mortality after transition to dialysis are shown in 17,819 patients from 10/2007 to 9/2011. HbA1c levels of 6-<7% were the reference group. Models were adjusted for case-mix covariates, which included patient's calendar quarter of dialysis initiation to account for secular changes in care over time, age, sex, race, ethnicity, cause of ESRD, Charlson Comorbidity Index (CCI), diabetes, congestive heart failure (CHF), and cerebrovascular disease (CVD).

vol 1 Figure 20. Adjusted hazard ratios for (A) all-cause and (B) cardiovascular mortality after transition to dialysis across categories of pre-end stage renal disease (ESRD) mean random glucose levels averaged over the 1-year prelude period (the time prior to transition to ESRD) (reference: random glucose 100-<125mg/dl) in 17,121 patients with diabetes from 10/01/2007-9/30/2011.
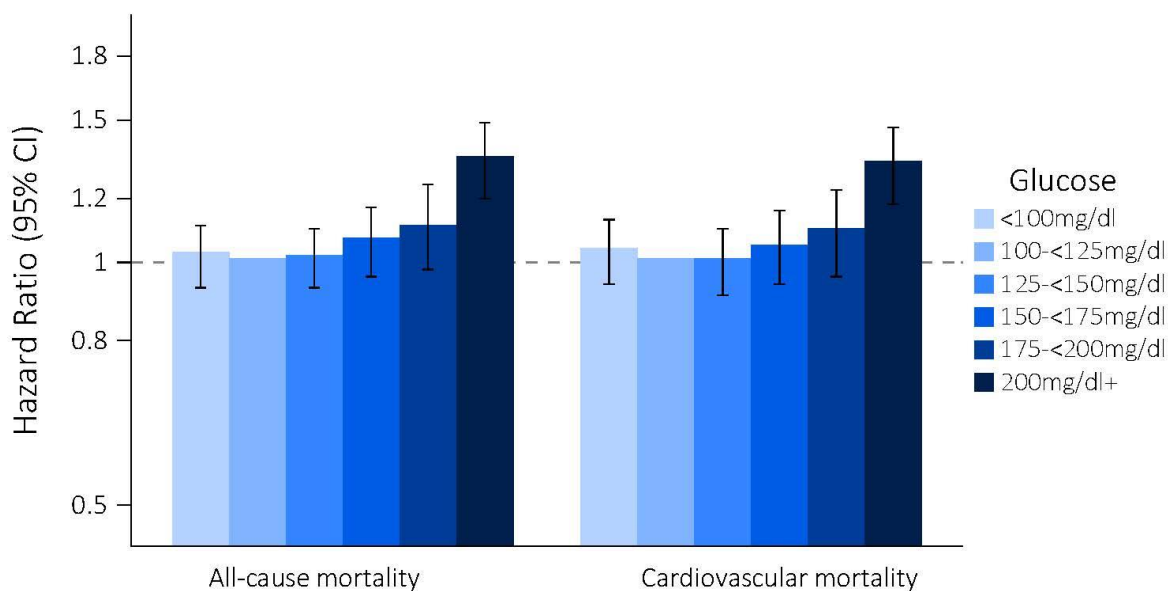
Associations of pre-end stage renal disease (ESRD) mean random glucose levels averaged over the 1-year prelude period (categorized as <100, 100 to <125, 125 to <150, 150 to <175, 175 to <200, and ≥200 mg/dL) with (A) all-cause and (B) cardiovascular mortality after transition to dialysis are shown in 17,121 patients with diabetes from 10/2007 to 9/2011. Random glucose levels 100-<125mg/dl were the reference group. Models were adjusted for case-mix covariates, which included patient's calendar quarter of dialysis initiation to account for secular changes in care over time, age, sex, race, ethnicity, cause of ESRD, Charlson Comorbidity Index (CCI), diabetes, congestive heart failure (CHF), and cerebrovascular disease (CVD).

Hypoglycemia-Related Hospitalizations and Mortality among Patients with Diabetes Transitioning to Dialysis

Diabetic patients with declining kidney function are at higher risk for hypoglycemia due to decreased renal gluconeogenesis, reduced anti-diabetic medication metabolism and excretion, and co-existing comorbidities (i.e., diabetic gastroparesis, protein energy-wasting). In the general population, hypoglycemia has been found to be a risk factor for mortality, hospitalization, and higher health care costs. However, there has been limited examination of the consequences of hypoglycemia in diabetic patients with kidney

disease, particularly among those progressing to ESRD. Rhee et al. thus sought to determine whether hypoglycemia-related hospitalizations prior to dialysis initiation are associated with post-ESRD mortality among advanced diabetic CKD patients transitioning to ESRD.

Rhee et al. examined associations between frequency of pre-ESRD hypoglycemia-related hospitalization events (categorized 1, 2, 3, and ≥3 hypoglycemia-related hospitalizations) with post-ESRD all-cause mortality in patients transitioning to dialysis from 10/2007 to 9/2011 using Cox proportional hazards models. In primary analyses, they examined hypoglycemia-related hospitalization events over the >1-2 year prelude interval (comprised of 30,156 patients), and in sensitivity analyses they examined events over the >6-12 month and >2-5 year prelude intervals (comprised of 30,992 and 28,729 patients, respectively).

In adjusted Cox models, increasing frequency of hypoglycemia-related hospitalizations during the >1-2 year prelude interval was associated with incrementally higher mortality risk: adjusted HRs (aHRs) (95% CI) of 1.21 (1.12-1.30), 1.47 (1.19-1.82), and 2.07 (1.46-2.95) for 1, 2, and 3 or more hypoglycemia-related hospitalizations, respectively (reference group: no hypoglycemia hospitalization) (Figure 21). A similar pattern was observed for hypoglycemia-related hospitalizations during the >6-12 month and >2-5 year prelude intervals. Further studies of diabetic management strategies that avoid hypoglycemia events in advanced CKD patients transitioning to ESRD are needed.

vol 1 Figure 21. Associations between frequency of pre-ESRD hypoglycemia-related hospitalization events over varying prelude intervals (the time prior to transition to ESRD) with post-ESRD all-cause mortality risk (reference: no hypoglycemia-related hospitalizations) in patients transitioning to dialysis from 10/2007 to 9/2011.
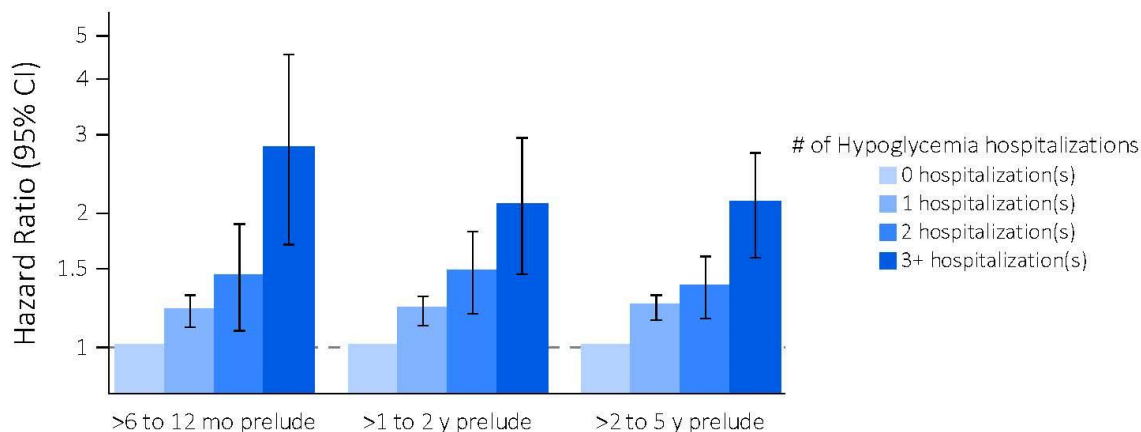
Associations between frequency of pre-ESRD hypoglycemia-related hospitalization events (categorized 1, 2, 3, and ≥3 hypoglycemia-related hospitalizations) over >6-12 month, >1-2 year and >2-5 year prelude intervals with post-ESRD all-cause mortality in patients transitioning to dialysis from 10/2007 to 9/2011. The >6-12 month, >1-2 year, and >2-5 year prelude cohorts were comprised of 30,992, 30,156, and 28,729 patients. Patients who did not experience any hypoglycemia-related hospitalizations served as the reference group. Models were adjusted for patient's calendar quarter of dialysis therapy initiation to account for secular changes in care over time, age at dialysis therapy initiation, sex, race, and ethnicity.

Glycemic Status and Mortality in Chronic Kidney Disease According to Transition versus Nontransition to Dialysis

Our previous research under the NIH U01 TC-CKD USRDS Special Study has shown that, among US veterans with diabetes and advanced CKD progressing to ESRD, higher averaged random glucose and hemoglobin A1c (HbA1c) levels measured in the pre-ESRD period were associated with higher post-ESRD mortality risk. However, these findings may not be generalizable to CKD patients with diabetes who do not transition to dialysis. Thus, Rhee et al. sought to examine the association of pre-ESRD glycemic status, defined by averaged random glucose and HbA1c levels, with post-ESRD mortality among patients with CKD and diabetes transitioning to dialysis. Rhee et al. then compared the inter-relationships between glycemic status and survival among a matched cohort of CKD patients who did not transition to dialysis.

Rhee et al. first designated a "Transition Cohort" who were comprised of patients who transitioned to dialysis over October 2007 to September 2011. From these patients, they

identified their primary "Transition Averaged Random Glucose Cohort" comprised of patients who did not have missing censor data, were age ≥18 years at the time of dialysis initiation, underwent ≥ random blood glucose measurement(s) within 1-year prior to transitioning to ESRD, and had either an ICD-9 code for diabetes and/or cause of ESRD due to diabetes. In secondary analyses, they designated a "Transition HbA1c Cohort," intended to capture all patients with a HbA1c measurement as a sensitive proxy for underlying diabetes, which included patients who did not have missing censoring event dates, were age ≥ 18 years at dialysis initiation, and underwent ≥1 HbA1c measurement(s) during the 1-year prelude period.

Rhee et al. concurrently designated matched sample of adult patients with CKD who did not transition to ESRD from the national VA database, defined as the "Non-Transition Averaged Random Glucose Cohort," who were comprised of patient with an ICD-9 code for diabetes with ≥1 random glucose measurement(s) with a subsequent 1-year period during which all subsequent random glucose measurements were averaged, and who had a similar distribution of characteristics as the Transition Cohort with respect to age (at the time of the baseline glucose measurement), sex, race, ethnicity, and stage of CKD (on the date of or up to one-year before the baseline glucose measurement) based upon the Transition Cohort's characteristics. A similar approach was used to define the "Non-Transition Averaged HbA1c Cohort."

In the Transition Averaged Random Glucose Cohort, glucose levels ≥200mg/dl were associated with higher mortality in adjusted models: aHR (95%CI) 1.26 (1.13-1.40) (Figure 22). In the Transition HbA1c Cohort, HbA1c 8-<10% and ≥10% were associated with higher mortality (reference: 6-<8%): aHRs (95%CIs) 1.21 (1.11-1.33) and 1.43 (1.21-1.69), respectively (Figure 23). Among patients in the Non-Transition Averaged Random Glucose Cohort, glucose levels <100mg/dl and ≥160mg/dl were associated with higher death risk: aHRs (95%CIs) 1.70 (1.18-2.44), 1.34 (1.07-1.69), 1.15 (0.94-1.41), 1.12 (0.90-1.41), 1.55 (1.10-1.83), and 1.34 (1.08-1.65) for glucose categories <80, 80-<100, 120-<140, 140-<160, 160-<180, 180-<200, and ≥200mg/dl, respectively. Yet in the Non-Transition HbA1c Cohort, HbA1c was not associated with mortality. The findings suggest the need for different glycemic strategies based on whether there are plans to transition to dialysis vs. pursue conservative management among diabetic patients with CKD.

vol 1 Figure 22. Associations of glycemic status, defined by mean random blood glucose (reference: 100-<120 mg/dl) averaged over a 1-year period with all-cause mortality (A) after transitioning to dialysis over 2007-2011 (Transition Cohort) compared with (B) patients in a one-to-one matched cohort of CKD patients with diabetes who did not transition to dialysis (Non-Transition Cohort).
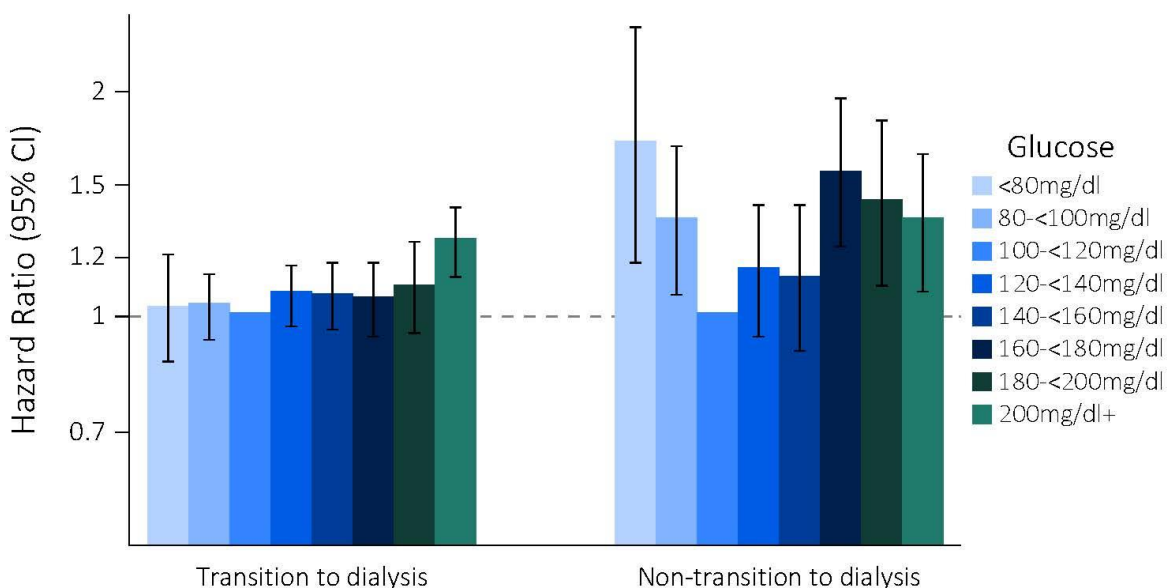
Associations of glycemic status, defined by mean random blood glucose (reference: 100-<120 mg/dl) averaged over a 1-year period (categorized as <80, 80-<100, 100-<120, 120-<140, 140-<160, 160-<180, 180-<200, and ≥200 mg/dl) with all-cause mortality (A) after transitioning to dialysis over 2007-2011 (Transition Cohort, N=17,121) compared with (B) patients in a one-to-one matched cohort of CKD patients with diabetes who did not transition to dialysis (Non-Transition Cohort, N=8711). Mean glucose levels of 100-<120 mg/dl were the reference group. In the Transition Cohort, models were adjusted for patient's calendar quarter of dialysis initiation to account for secular changes in care over time, age, sex, race, ethnicity, cause of ESRD, Charlson Comorbidity Index (CCI) score, diabetes, congestive heart failure (CHF), cerebrovascular disease (CVD), residential region, initial dialysis modality, and body mass index. In the Non-Transition Cohort, models were adjusted for patient's study entry quarter, age, sex, race, ethnicity, CCI score, diabetes, CHF, CVD, residential region and body mass index

vol 1 Figure 23. Associations of glycemic status, defined by mean hemoglobin A1c (HbA1c) (reference: 6-<8%) averaged over a 1-year period with all-cause mortality (A) after transitioning to dialysis over 2007-2011 (Transition Cohort) compared with (B) patients in a one-to-one matched cohort of CKD patients with diabetes who did not transition to dialysis (Non-Transition Cohort).
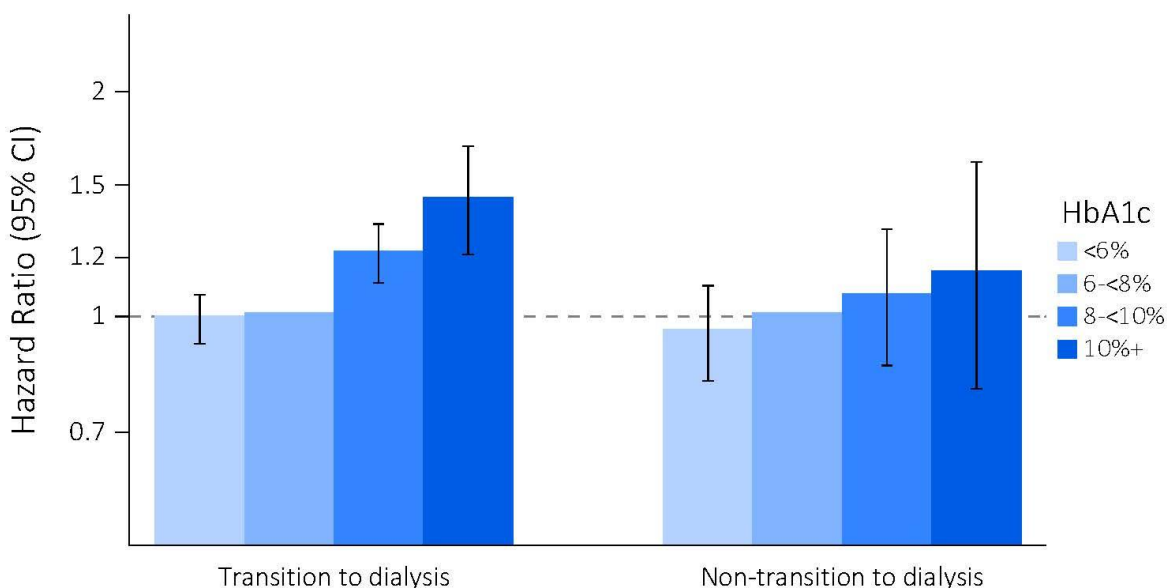
Associations of glycemic status, defined by hemoglobin A1c (HbA1c) (reference: 6-<8%) over a 1-year period (categorized as <6, 6-<8, 8-<10, and ≥10%) with all-cause mortality (A) after transitioning to dialysis over 2007-2011 (Transition Cohort, N=17,189) compared with (B) patients in a one-to-one matched cohort of CKD patients with diabetes who did not transition to dialysis (Non-Transition Cohort, N=10,848). Mean HbA1c levels of 6-<8% were the reference group. In the Transition Cohort, models were adjusted for patient's calendar quarter of dialysis initiation to account for secular changes in care over time, age, sex, race, ethnicity, cause of ESRD, Charlson Comorbidity Index (CCI) score, diabetes, congestive heart failure (CHF), cerebrovascular disease (CVD), residential region, initial dialysis modality, and body mass index. In the Non-Transition Cohort, models were adjusted for patient's study entry quarter, age, sex, race, ethnicity, CCI score, diabetes, CHF, CVD, residential region and body mass index.

Association of thyroid status prior to transition to end-stage renal disease with early dialysis mortality

There is a high prevalence of thyroid dysfunction among advanced CKD patients, including those receiving dialysis. In the general population, hypothyroidism is known to engender endothelial dysfunction, accelerated atherosclerosis, and alterations in cardiac function. An increasing body of evidence has also shown that hypothyroidism is associated with higher mortality risk in dialysis patients, presumably due to cardiovascular pathways. However, no studies have examined whether thyroid status

among advanced CKD patients transitioning to dialysis is associated with adverse outcomes. Rhee et al. thus sought to examine the relationship between pre-ESRD thyroid status, defined serum thyrotropin (TSH) levels, with post-ESRD mortality among patients transitioning to dialysis from 10/2007 to 9/2011.

Rhee et al. first examined associations between pre-ESRD serum thyrotropin (TSH) levels, categorized as hyperthyroid (<0.5 mIU/L), euthyroid (0.5 to 5.0 mIU/L), and hypothyroid range (>5.0 mIU/L) (ref: euthyroidism), with post-ESRD all-cause mortality in patients transitioning to dialysis from 10/2007 to 9/2011 using Cox proportional hazards models. In secondary analyses, they examined finer gradations of serum TSH, categorized as overt hyperthyroid range (<0.1 mIU/L), subclinical hyperthyroid range (0.1 to <0.5 mIU/L), low-normal (0.5 to 3.0mIU/L), high-normal (>3.0 to 5.0 mIU/L), subclinical hypothyroid range (>5.0 to 10.0 mIU/L) and overt hypothyroid range TSH levels (>10.0 mIU/L) (reference: serum TSH 0.5 to 3.0 mIU/L).

In primary analyses, higher pre-ESRD serum TSH levels >5.0 mIU/L (i.e., hypothyroid range) over the 2-year prelude period were associated with higher post-ESRD mortality risk: adjusted HR (aHR) (95% CI) 1.11 (1.02-1.21) (Figure 24). In secondary analyses, point estimates of incrementally higher serum TSH levels >3.0 mIU/L trended towards increasingly higher death risk: aHRs (95% CIs) 1.04 (0.97-1.11), 1.06 (0.96-1.17), and 1.37 (1.16-1.63) for serum TSH levels >3.0 to 5.0, >5.0 to 10.0, and >10.0 mIU/L, respectively. Further studies are needed to determine the impact of serum TSH reduction with thyroid hormone supplementation in advanced CKD patients transitioning to dialysis.

vol 1 Figure 24. Adjusted hazard ratios for all-cause after transition to dialysis across categories of pre-end stage renal disease (ESRD) thyroid status defined by serum thyrotropin (TSH) levels over the 2-year prelude period (the time prior to transition to ESRD) in 19,860 patients transitioning to dialysis from 10/01/2007 - 9/30/2011.
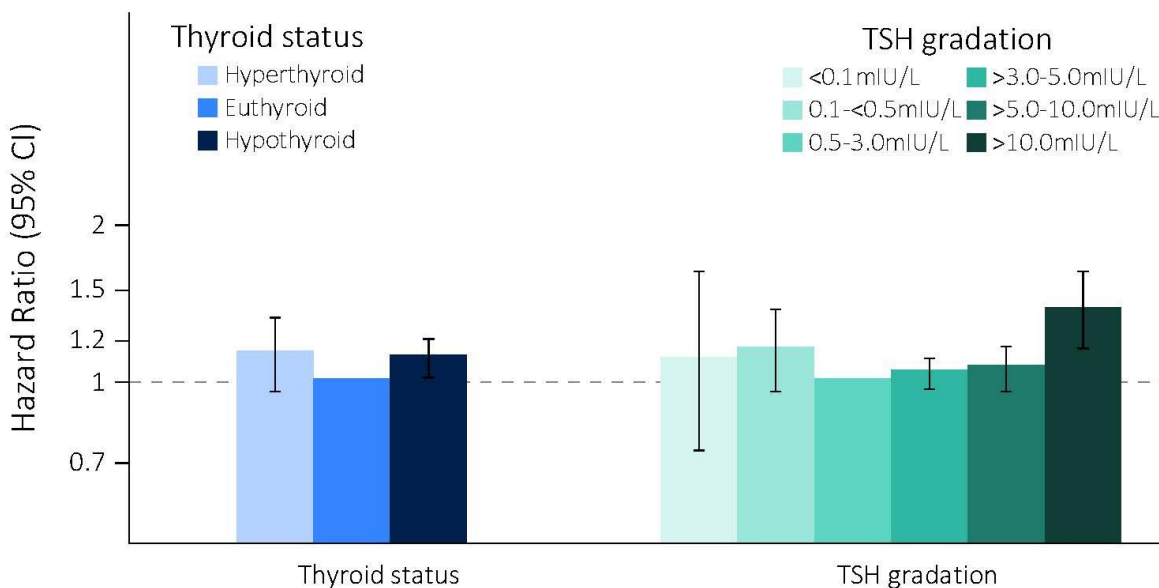
Associations of pre-end stage renal disease (ESRD) thyroid status defined by serum thyrotropin (TSH) levels averaged over the 2-year prelude period in 19,860 patients transitioning to dialysis from 10/2007 to 9/2011. Panel (A) shows thyroid status defined as hyper-, eu-, and hypothyroidism (ref: euthyroidism). Panel (B) shows finer gradations of serum TSH, categorized as overt hyperthyroid range (<0.1 mIU/L), subclinical hyperthyroid range (0.1 to <0.5 mIU/L), low-normal (0.5 to 3.0mIU/L), high-normal (>3.0 to 5.0 mIU/L), subclinical hypothyroid range (>5.0 to 10.0 mIU/L) and overt hypothyroid range TSH levels (>10.0 mIU/L) (reference: serum TSH 0.5 to 3.0 mIU/L). Models were adjusted for case-mix covariates, which included patient's calendar quarter of dialysis initiation to account for secular changes in care over time, age, sex, race, ethnicity, cause of ESRD, Charlson Comorbidity Index (CCI) score, congestive heart failure (CHF), cerebrovascular disease (CVD), coronary artery disease (CAD), hypertension and hyperlipidemia.

Medication

NDD-CKD patients are often prescribed a number of medications to slow CKD progression, manage symptoms and risk factors, or treat comorbidities prevalent in these patients. Poor medication adherence may be a patient symptom of depression or other psychological issues, may be related to development of adverse symptoms from certain medications alone or in polypharmacy combination, and it may also be related to other factors such as socioeconomic status or quality of care. Poor adherence to medication can

lead to abnormal blood levels and subsequent adverse events, as noted for the potential relationship between poor anemia medication adherence and hemoglobin variability.

Predialysis Cardiovascular Disease Medication Adherence and Mortality after Transition to Dialysis

Recognizing that assessing the patient's medication adherence may give insight to his or her health status, Molnar et al. examined the relationship between adherence to cardiovascular medications, including angiotensin-converting enzyme inhibitors/ angiotensin receptor blockers, calcium channel blockers, ß-blockers, α-blockers, direct vasodilators, diuretics (loop and thiazide), aspirin and statins, and mortality outcomes in the post-dialysis transition. The cohort study included 32,348 US veterans who transitioned to dialysis between 10/1/2007-9/30/2011, and adherence was measured using the proportion of days covered (PDC) by the medications as ascertained from pharmacy records. Over a median follow-up period of 23 months and compared to patients with a PDC >80%, those who had a PDC >60-80% had a 12% higher all-cause mortality risk, and those who had a PDC≤60% had a 12% higher mortality risk in the primary adjustment models (Figure 25). Associations between PDC and cardiovascular mortality outcomes trended in a similar direction. The study findings point to the importance for monitoring and improving these potentially modifiable risk factors, and moreover suggest the importance in their evaluation for determining the patient's mortality risk after dialysis transition.

vol 1 Figure 25. Associations of cardiovascular medication adherence (ascertained by proportion of days covered, medication possession ratio, and persistence with drug therapy from pharmacy records) over a 1-year period before transition to dialysis with all-cause and cardiovascular mortality in 32,348 veterans who transitioned to dialysis during 10/1/2007-9/30/2011.
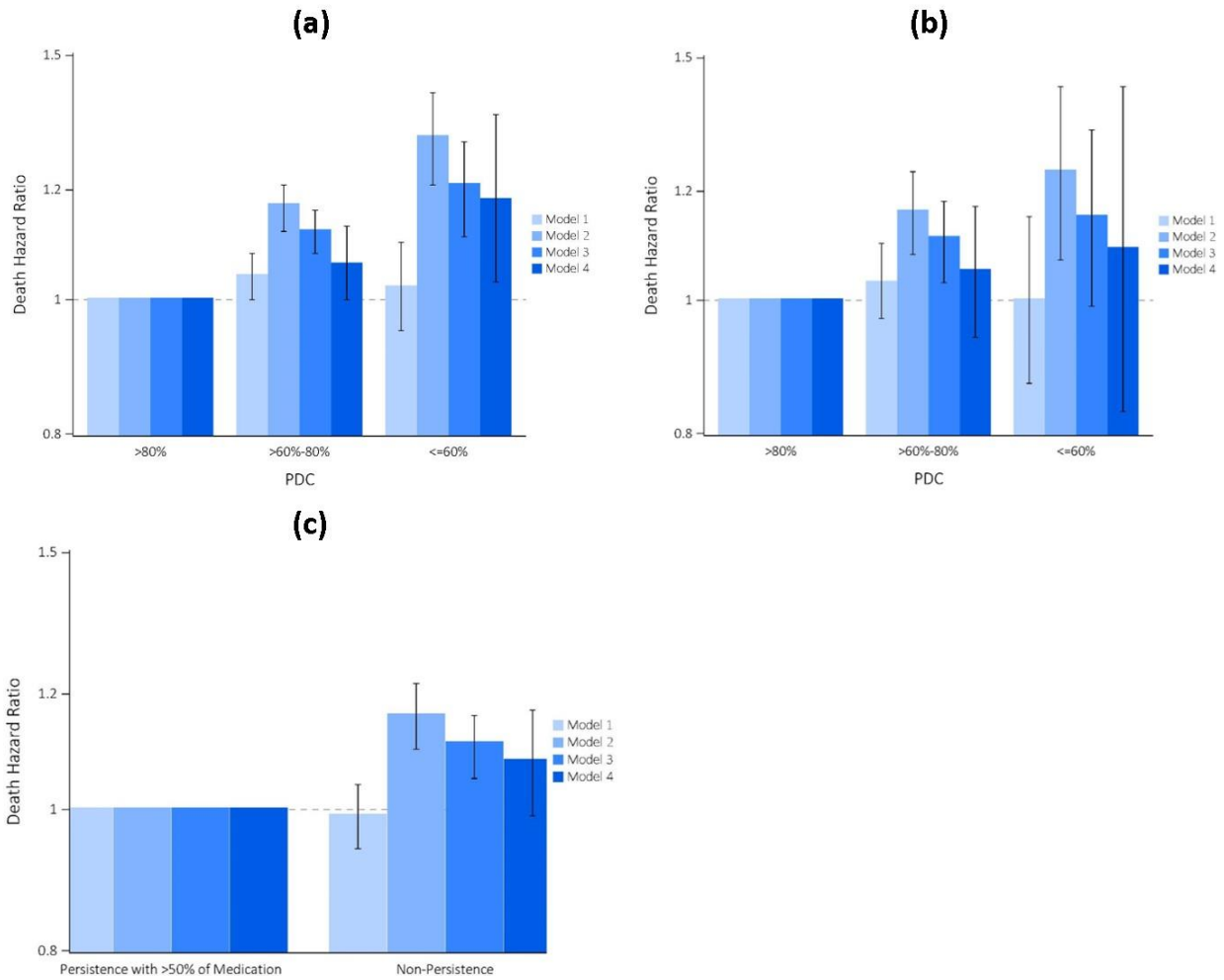
Death hazard ratios with 95% confidence intervals are presented for all-cause and cardiovascular mortality. Model1: unadjusted; Model 2: age, sex, race/ethnicity, marital status, and ZIP code; Model 3: Model 2 plus comorbid conditions (diabetes mellitus, congestive heart failure, cardiovascular/cerebrovascular disease, depression, anxiety, and Charlson Comorbidity Index), and vascular access type; and Model 4: Model 3 plus blood/serum hemoglobin, bicarbonate, albumin, urea nitrogen, and last eGFR.

Abbreviations: eGFR, estimated glomerular filtration rate; ESRD, end stage renal disease; PDC, proportion of days covered.

Statin Therapy before Transition to End-Stage Renal Disease with Posttransition Outcomes

According to current kidney and cardiology guidelines, statins should be initiated in all NDD-CKD patients. Nonetheless, in a cohort of 57,755 US veterans who initiated

dialysis between 10/1/2007-3/31/2014 and had medication information in the one year prior to dialysis initiation, we identified 22,151(38%) who did not take any statins in the year prior to dialysis initiation. In the primary analysis of 47,720 US veterans in whom we were able to ascertain consistent use or non-use of statin prior to transition, we compared patients who did not take any statins to those who took statins for over half of the time (>183 days) in the one year prior to dialysis initiation. Pre-transition statin use compared to no statin use was evaluated for all-cause and cardiovascular mortality risk and hospitalization rates in the year post-transition. Statin use was associated with 21% lower all-cause and 17% lower cardiovascular mortality risk as well as an 11% lower rate of hospitalizations post-transition in fully adjusted models (Figure 26). Statin users were more likely to initiate dialysis with an AVF or AVG and were more likely to have nephrology outpatient visits in the year prior to transition indicating statin use as a proxy of better pre-dialysis care. However, sensitivity analysis further adjusting for these indicators showed robust results to the main analysis. In spline analysis, there was an inverse linear relationship between number of days of statin use prior to transition and post-transition all-cause and cardiovascular mortality. The findings suggest that statin therapy should be initiated in patients in the NDD-CKD period and prior to dialysis transition.

vol 1 Figure 26. Associations of statin therapy (vs. no statin therapy) use over a 1-year period before transition to dialysis with 1-year post-ESRD all-cause and cardiovascular mortality and hospitalization in 47,720 veterans who transitioned to ESRD during 10/1/2007-3/31/2014
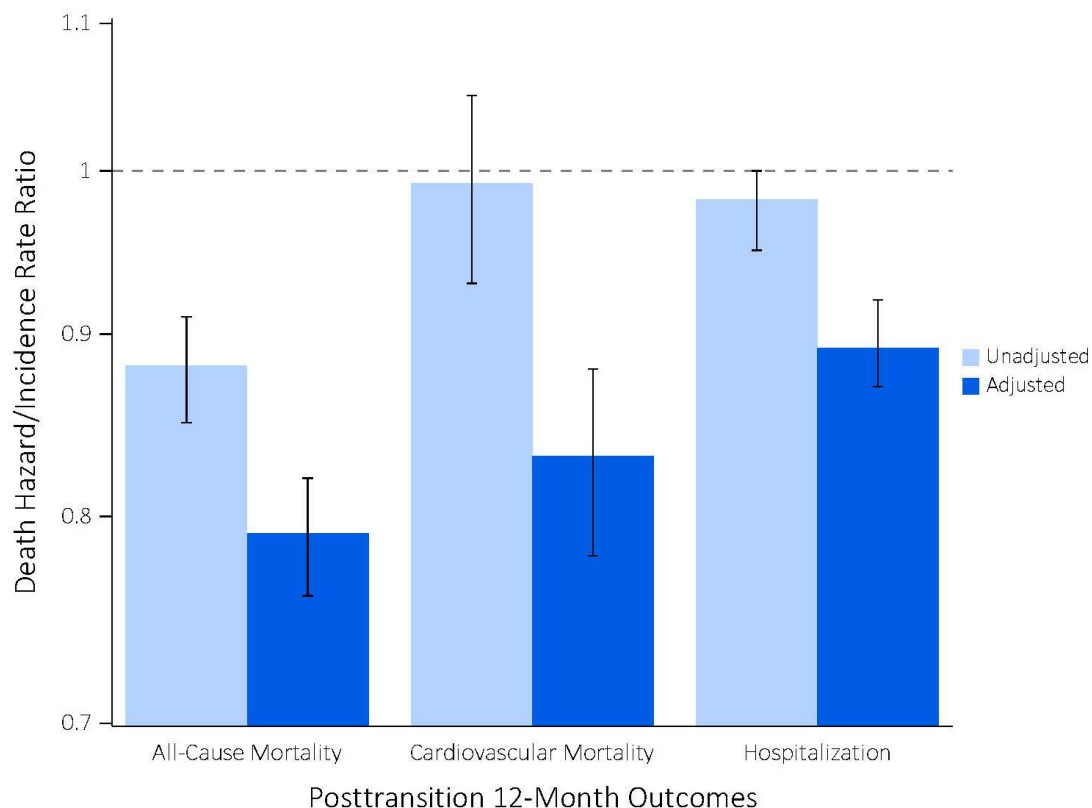
Death hazard ratios and incidence rate ratios with 95% confidence intervals are presented for all-cause and cardiovascular mortality, and hospitalization, respectively. Multivariable model: age, sex, race, and ethnicity, as well as the following comorbidities: Charlson Comorbidity Index, diabetes mellitus, atherosclerotic cardiovascular disease (defined as the presence of myocardial infarction, peripheral vascular disease, or ischemic heart disease), atrial fibrillation, congestive heart failure, and cerebrovascular disease.

Abbreviations: ESRD, end stage renal disease.

Association of Continuation of Statin Therapy Initiated before Transition to Chronic Dialysis Therapy with Mortality after Dialysis Initiation

Results from randomized clinical trials have not shown a statistically significant benefit of initiating statin therapy in patients on dialysis. Current guidelines advocate for continuing statin therapy when patients transition to dialysis if they were on statins during the NDD-CKD period and at the time of transition. Although this guideline is directed, according to data shown in our 2016 and 2017 ADR chapters, the percentage of

statin prescriptions in the post-transition period immediately declines. Furthermore, although this suggestion is based on results not showing statistically significant benefit in the dialysis period, no study examined impact of continuation of statin therapy across transition with subsequent outcomes risk in dialysis patients. Streja et al. thereby examined the relationship of continuation versus discontinuation of statin therapy with mortality outcomes in a cohort of 14,298 US veterans who were statin users in the year pre-transition (>183 days) and survived the first year on dialysis. Statin continuation in primary analysis was defined as use of statins for >183 days in the year post-transition. In multivariable adjusted analysis, statin continuation compared to discontinuation (no prescriptions in the post-transition period) was associated with a 28% and 18% lower risk of all-cause and cardiovascular mortality (Figure 27). The study findings supported guideline recommendations and demonstrated the benefits of continuing statin therapy in patients transitioning to dialysis.

vol 1 Figure 27. Associations of continuation (vs. discontinuation) of statin therapy over a 1-year period before transition to dialysis with 1-year post-ESRD all-cause and cardiovascular mortality in 14,298 veterans who transitioned to ESRD during 10/1/2007-3/31/2014
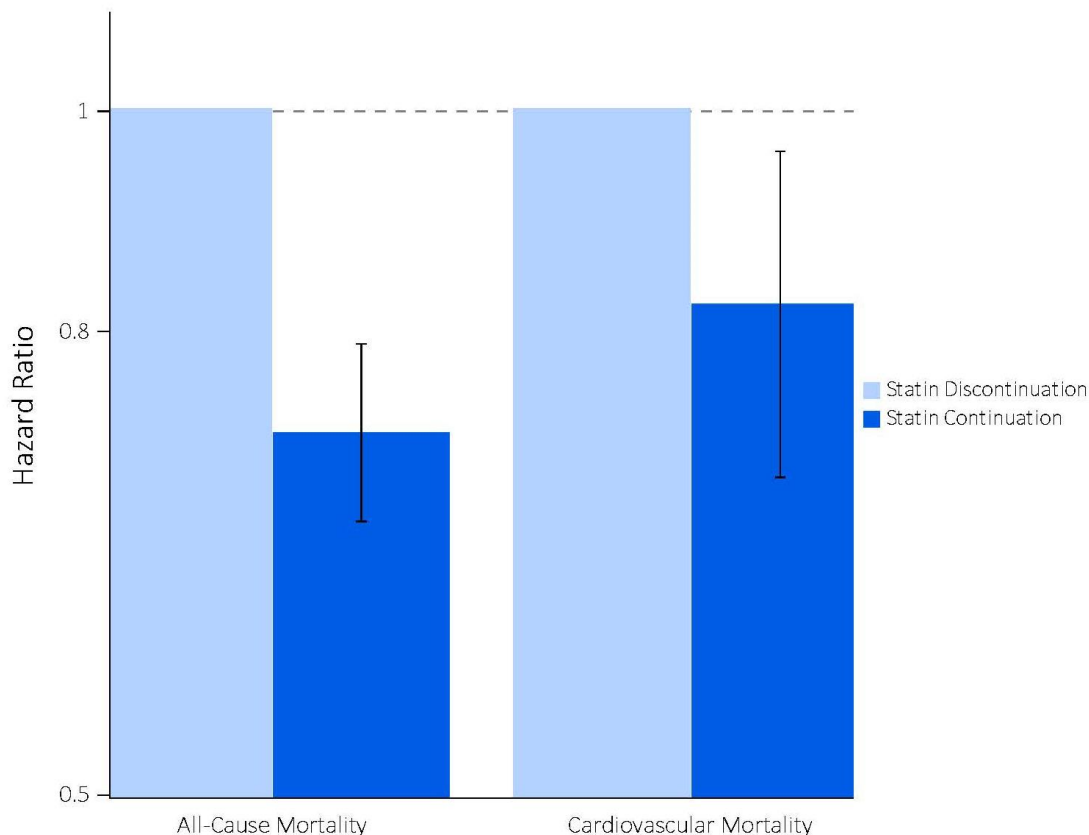
Hazard ratios with 95% confidence intervals are presented for all-cause and cardiovascular mortality. Multivariable model: age, sex, race, ethnicity, Deyo Charlson Comorbidity Index, presence of diabetes, atherosclerotic cardiovascular disease (defined as presence of myocardial infarction, peripheral vascular disease, or ischemic heart disease), atrial fibrillation, congestive heart failure, and cerebrovascular disease.

*Abbreviations: ESRD, end stage renal disease.*

Psych

Mental health is an issue of paramount importance in the US population, particularly among veterans. There have been challenges in screening for depression and dementia, but presence of these conditions may represent underlying health issues and may be related to adverse outcomes, particularly among the CKD population. As discussed above comorbidities of mental health conditions may lead to challenges in medication compliance, may worsen patients' health status, and may severely impact patients' quality of life. In several studies, we examined the relationship between depression, dementia and psychosis with outcomes in ESRD patients.

Pre-ESRD Depression and Post-ESRD Mortality in Patients with Advanced CKD Transitioning to Dialysis

Molnar et al. examined a cohort of 45,076 US veterans who transitioned to ESRD between 10/1/2007-09/30/2011, and found 23% had a depression diagnosis prior to transition. Depression was more often diagnosed in NDD-CKD patients that were younger, female, African-American, or had a cardiovascular comorbidity. In the primary model of adjustment, compared to patients without a depression diagnosis, those with a depression diagnosis had a 6% higher risk of all-cause mortality after ESRD transition. In further analysis, patients were additionally stratified by use of depression pharmacotherapy. Compared to patients with neither a depression diagnosis, nor pharmacotherapy, patients with pharmacotherapy treated depression had a 14% higher adjusted mortality risk, and patients with diagnosed depression but no record of pharmacotherapy had a 4% higher adjusted mortality risk in the primary adjusted model.

vol 1. Figure 28. Associations of pre-ESRD depression (ascertained by combinations of diagnosis or antidepressant medication prescription) with all-cause mortality in 45,076 veterans who transitioned to ESRD during 10/1/2007-9/30/2011
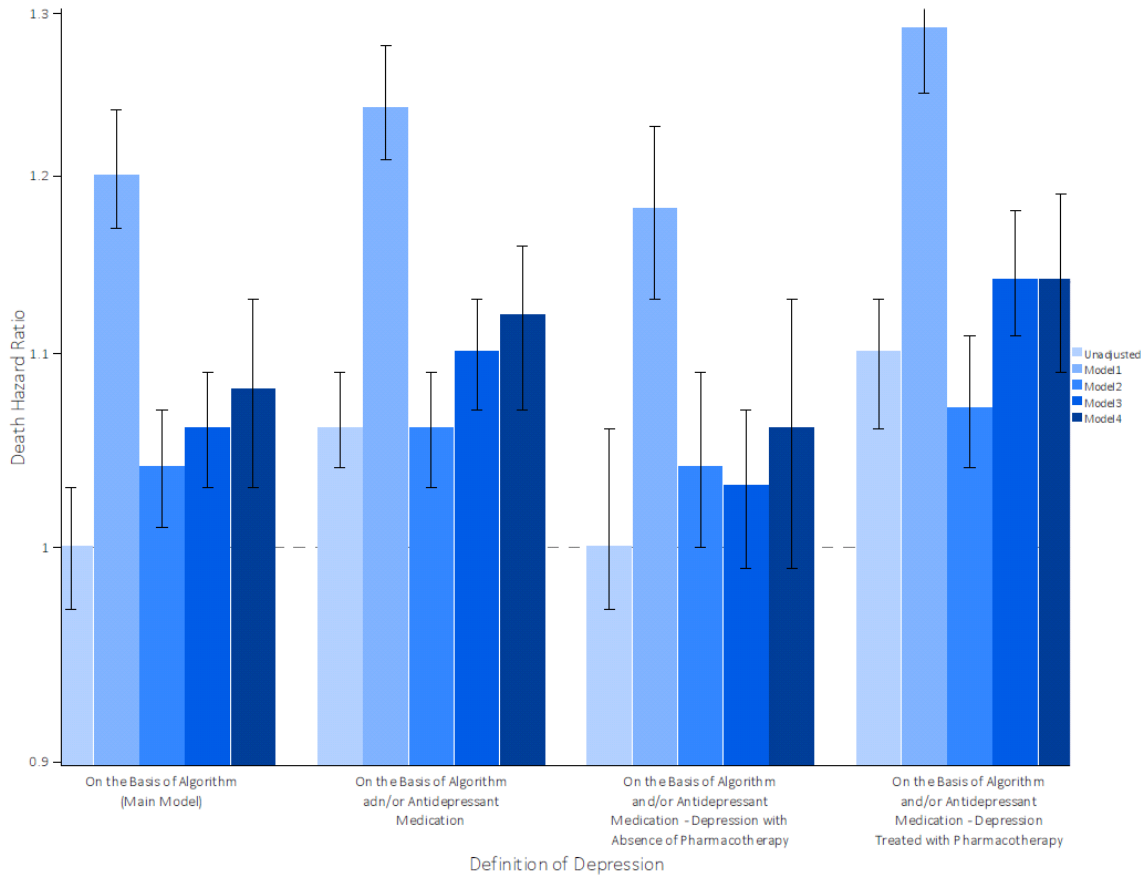
model 1: age, sex, race/ethnicity, and marital status; model 2: comorbidities (dementia, myocardial infarction, congestive heart failure, peripheral vascular disease, connective tissue disease, lung disease, peptic ulcer disease, HIV, diabetes mellitus, stroke/paraplegia, liver disease, malignancy, and hypertension), type of vascular access (arteriovenous fistula, arteriovenous graft, or catheter), eGFR slope before ESRD initiation, post-traumatic stress disorder, substance abuse, and numbers of mental health care and emergency department visits in the last year; model 3 (main model): medications (phosphorous binder, active vitamin D, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, bicarbonate, β-blockers, calcium channel blockers, vasodilators, diuretics, statins, and erythropoietin stimulating agents); model 4: blood hemoglobin, serum albumin, income, and cardiovascular medication adherence.

Pre-ESRD Dementia and Post-ESRD Mortality in a Large Cohort of Incident Dialysis Patients

In the same cohort of 45,076 US veterans transitioning to ESRD between 10/1/2007-09/30/2011, Molnar et al. examined associations of dementia diagnosis prior to transition with all-cause mortality within the first six months after transition. There were 1,336 (3%) patients that had dementia prior to transition. Dementia patients were slightly older and had more comorbidities including para or hemiplegia, cerebrovascular disease,

diabetes, and chronic obstructive pulmonary disease. 30% of dementia patients died within the first six months and nearly 50% died over the first year after dialysis transition. In a propensity score matched subset of patients consisting of 1,328 matched pairs, pre-ESRD dementia was associated with a 19% higher all-cause mortality risk in the first 6 months, as well as a 26% and 30% higher all-cause mortality risk in first 12 months and over the full follow up period until December 2012, respectively. The findings of the study may support guidelines cautioning the initiation of dialysis in patients with dementia. However, further studies are needed to examine how quality of life is affected for hemodialysis patients with dementia.

vol 1 Figure 29. Associations of pre-ESRD dementia with all-cause mortality in 45,076 veterans who transitioned to ESRD during 10/1/2007-9/30/2011
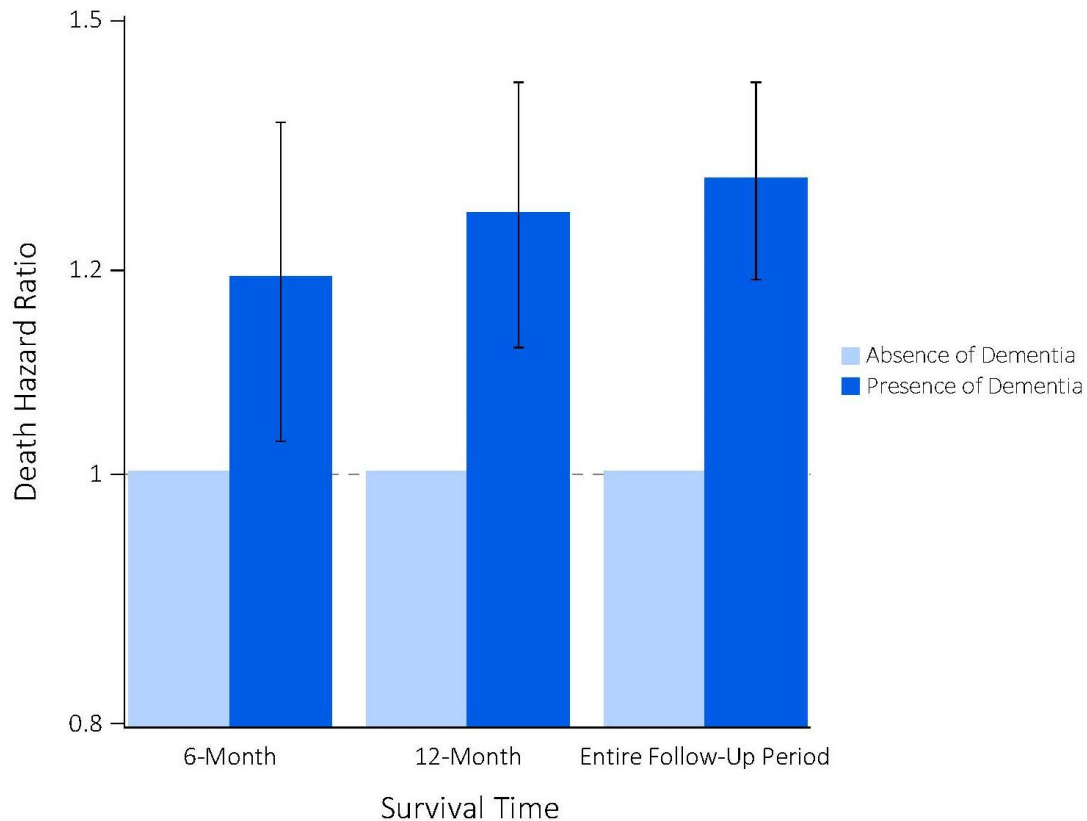

logistic regression model: age, gender, race/ethnicity, marital status, comorbidities at baseline (myocardial infarction, congestive heart failure (CHF), peripheral vascular disease, cerebrovascular disease, paraplegia/hemiplegia, lung disease, rheumatic disease, peptic ulcer disease, HIV/AIDS, malignancy, liver disease, diabetes, hypertension), and medications at baseline (statins, vasodilatators, renin-angiotensin-aldosterone system

(RAAS) blockers, phosphate binders, erythropoietin stimulating agents (ESAs), diuretics, calcium channel blockers, bicarbonates, beta-blockers, active Vitamin D)

History of psychosis and mania, and outcomes after kidney transplantation

Mental health conditions such as bipolar disorder and schizophrenia may be rare in the general population, but may be more prevalent among US veterans. According to guidelines supported by transplant societies, the presence of these conditions are contraindications for kidney transplants, in consideration of concerns regarding compliance, support, comorbidities, and drug interactions. Few data are shown to support this recommendation, and thereby Molnar et al. examined the relationship between a history of psychosis or mania with post-transplant outcomes in a cohort of US veterans who received a kidney transplant between 10/1/2007-3/31/2014. Among a cohort of 3,680 US veteran kidney transplant recipients, 126 (3.4%) had a history of psychosis or mania. In a propensity score matched cohort of 120 patients with a history of psychosis or mania matched to 322 patients without these diagnoses, no significant differences in death risk, graft loss, rejection, or immunosuppressive medication compliance was observed. The study acknowledges that the results may reflect a successful selection of kidney transplant recipients among US veterans with mental health conditions that will perform well on renal replacement therapy; suggesting that transplantation can be safe even in patients with a history of these conditions. Further studies are needed to define guidelines on how ESRD patients with psychosis or mania should be selected for kidney transplantation.

vol 1 Figure 30. Associations of pre-kidney transplant psychosis or mania with post-transplant outcomes among 442 US veterans who received a kidney transplant between 10/1/2007-9/30/2014.
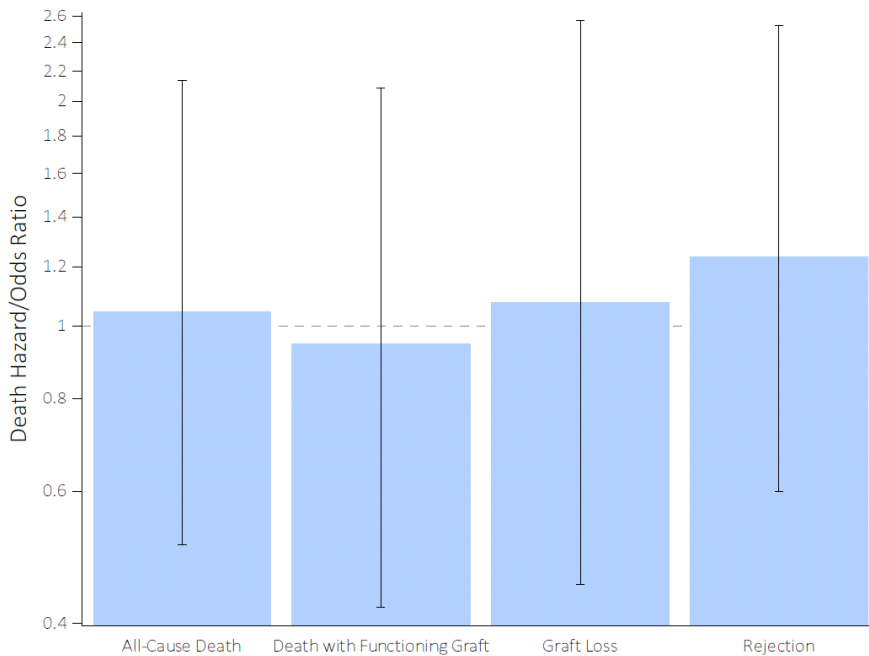

Models were created using cox proportional regression, competing risks regression and logistic regression in the propensity-matched cohort. Hazard ratios with 95% confidence intervals are presented for all-cause death, subhazard ratio with 95% confidence intervals are presented for death with functioning graft and graft loss, and odds ratios with 95% confidence intervals are presented for rejection.

History of Posttraumatic Stress Disorder and Outcomes after Kidney Transplantation

Posttraumatic Stress Disorder (PTSD) has a high prevalence among US veterans, but may also be included in the mental health assessment for determining whether a patient should be a candidate to receive a kidney transplant. Among a cohort of 4,479 US veterans who received a kidney transplant between 10/1/2007- 03/31/2015, there were 282 (6%) with a PTSD diagnosis prior to transplantation. In a propensity score analysis among 280 matched pairs of PTSD and no-PTSD kidney transplant recipients, no differences in all-cause mortality, graft loss, death with a functioning graft, or medication non-adherence were observed. Similar to the study of psychosis or mania prior to transplantation, the findings of this study suggest successful selection of kidney transplant candidates with a history of PTSD. More studies are needed to identify optimal strategies in improving health outcomes in patients with mental health conditions.

vol 1 Figure 31. Associations of pre-kidney transplant post-traumatic stress disorder (PTSD) with post-transplant outcomes among 442 veterans who received a kidney transplant between 10/1/2007-9/30/2015
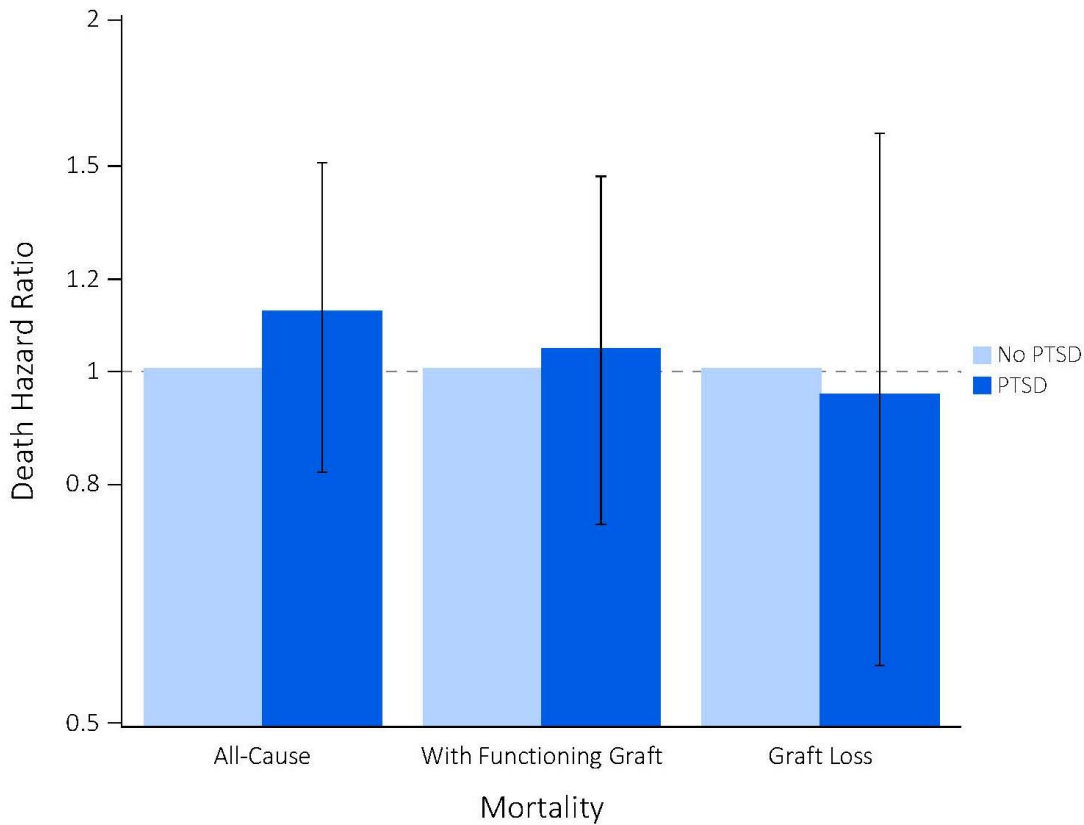
Multivariate models adjusted for the following variables: age at transplant, gender, race/ethnicity, service connection, marital status, income, smoking status, type of transplant donor (deceased vs living), type of dialysis modality, Charlson Comorbidity Index (CCI), presence of comorbidities (peripheral vascular disease, cerebrovascular disease, dementia, peptic ulcer disease, malignancy, liver disease, diabetes, depression), and medication use (phosphorus binders, active vitamin D (native or active), renin-angiotensin-aldosterone system inhibitors, alpha-blockers, β-blockers, calcium channel blockers, vasodilators, insulin, diuretics, statins, antianginals, anticoagulants, thrombolytic, aspirin, digitalis, and erythropoietin-stimulating agents).

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