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

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Objective: The impact of glycemic control in diabetic patients with chronic kidney disease (CKD) who may or may not transition to dialysis remains uncertain, given recent interest in the conservative management of advanced CKD without dialysis therapy, which may benefit from alternative glycemic control strategies.

Design and Methods: Among a national cohort of US Veterans, we examined the association of glycemic status, defined by averaged random blood glucose and hemoglobin A1c (HbA1c), with mortality after transitioning to dialysis over 2007-2011 (Transition Cohort) compared with patients in a one-to-one matched cohort of CKD patients with diabetes who did not transition to dialysis (Nontransition Cohort).

Results: Among 17,121 patients in the Transition Cohort, averaged random glucose ≥200 mg/dL was associated with higher mortality in expanded case-mix analyses (reference: 100-<120 mg/dL): adjusted hazard ratio (95% confidence interval) 1.26 (1.13-1.40). In the transition cohort, HbA1c 8-<10% and ≥10% were associated with higher mortality (reference: 6-<8%): adjusted hazard ratios (95% confidence interval) 1.21 (1.11-1.33) and 1.43 (1.21-1.69), respectively. Among 8,711 patients in the Nontransition Cohort, averaged random glucose <100 mg/dl and ≥160 mg/dl were associated with higher death risk, whereas HbA1c was not associated with mortality.

Conclusion: In diabetic CKD patients transitioning to dialysis, higher averaged random glucose and HbA1c were associated with early dialysis mortality, whereas in matched CKD patients who did not transition, both lower and higher glucose levels were associated with higher mortality. These data suggest the need for different glycemic strategies based on whether there are plans to transition to dialysis versus pursue conservative management among diabetic patients with CKD.

This article has an online CPE activity available at www.kidney.org/professionals/CRN/ceuMain.cfm

Introduction

THE IDEAL GLYCEMIC target in chronic kidney disease (CKD) patients with diabetes remains uncertain, as most trials of glycemic control excluded advanced kidney disease patients.[1,2] Early randomized controlled trials and their long-term corollary studies have demonstrated the

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microvascular and macrovascular benefits of intensive glycemic control among patients with type 1 and 2 diabetes with minimal-to-no kidney damage.[3-8] However, contemporary trials showing lack of benefit and heightened mortality in populations with longstanding type 2 diabetes and cardiovascular risk[9-11] (whose characteristics are more akin to advanced CKD patients) have challenged the safety of lower glycemic targets, particularly among those with greater comorbidity burden.[2]

Current clinical practice guidelines lack precise recommendations for the optimal glycemic target in patients with advanced CKD and diabetes. While Kidney Disease Outcomes Quality Initiative and Kidney Disease Improving Global Outcomes guidelines propose a target hemoglobin A1c (HbA1c) of 7% to prevent or reduce progression of microvascular complications, they advise higher HbA1c levels >7% among patients with comorbidities, limited life expectancy, and heightened risk of hypoglycemia (e.g., stages 4-5 CKD; receipt of insulin or sulfonylureas) with an undefined upper threshold.[12,13] Furthermore, as HbA1c levels may be influenced by nonglycemic factors in patients with advanced CKD, a recent consensus conference held by the *American Diabetes Association, American Society of Nephrology,* and *National Kidney Foundation* has indicated that, "…while HbA1c levels between 7% to 8% appear to be associated with the highest survival rates in retrospective analyses of diabetic kidney disease (DKD) patients, the imprecision of HbA1c measurements makes specific targets for people with DKD difficult to define."[14,15] The absence of clear-cut guidelines is in part due to the sparse study of glycemic status and outcomes in CKD patients with diabetes, which have shown mixed findings and provide limited evidence due to exclusion of patients with advanced kidney disease and sole reliance on HbA1c to define glycemic status.[16,17]

To address this knowledge gap, we recently showed that, among US Veterans with diabetes and advanced CKD progressing to end-stage renal disease (ESRD), higher averaged random glucose and HbA1c levels measured in the pre-ESRD period were associated with higher post-ESRD mortality risk.[1] However, nongranular examination of random glucose levels may have concealed an association between lower glycemic levels and mortality risk. Furthermore, these findings may not be generalizable to CKD patients with diabetes who do not transition to dialysis. Thus, to better inform the field, we reexamined the association of pre-ESRD glycemic status, defined by averaged random glucose and HbA1c levels, with post-ESRD mortality among a national cohort of Veterans with CKD and diabetes transitioning to dialysis. We then compared the inter-relationships between glycemic status and survival among a matched cohort of patients with CKD who did not transition to dialysis.

Materials and Methods

Source Population: Transition Cohort

We conducted a cohort study with longitudinal data from the Transition of Care in CKD study, a retrospective study specifically examining transition to dialysis in a cohort of US Veterans with incident ESRD.[1,18-21] Our source population consisted of 52,172 patients from the national Veterans Affairs (VA) database who transitioned to dialysis over the period of October 1, 2007 to September 30, 2011 (designated as the "Transition Cohort"). From these patients, we identified our primary "Averaged Random Glucose Cohort" among whom the association of averaged random glucose levels with mortality was estimated. The Averaged Random Glucose Cohort was comprised of patients who did not have missing censor data, were aged 18 years or older at the time of dialysis initiation, underwent one or more random blood glucose measurement(s) within 1 year before transitioning to ESRD (i.e., 1-year "prelude" period[18]), and had either an International Classification of Diseases, Ninth Revision (ICD-9) code for diabetes and/or cause of ESRD due to diabetes (Fig. 1). In secondary analyses, we designated a "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 aged 18 years or older at dialysis initiation, and underwent one or more HbA1c measurement(s) during the 1-year prelude period.

Source Population: Nontransition Cohort

We conducted parallel analyses among a matched sample of adult patients with CKD from the "Racial and Cardiovascular Risk Anomalies in CKD" (RCAV) cohort of US Veterans who underwent care within the VA Healthcare system over the period of 2004-2013.[22-24] In these analyses, we first identified all *RCAV* patients with an ICD-9 diagnostic code for diabetes who underwent at least one or more random glucose measurement(s) with a subsequent 365-day period during which all subsequent random glucose measurements were averaged (designated as the "1-year averaged random glucose exposure period" in which the patients did not experience death nor transition to dialysis) (Fig. 1). To create a cohort with a similar distribution of characteristics as the Transition Cohort's averaged random glucose population, we created an index variable of age (at the time of the baseline glucose measurement), sex, race, ethnicity, and stage of CKD (on the date of or up to 1-year before the baseline glucose measurement) based on the Transition Cohort's characteristics, as well as counts for each index combination of these 4 variables. We then created index variables for each observation and patient within the *RCAV* cohort. Using PROC SURVEYSELECT, we created a matched cohort of patients with a similar distribution of counts to the Transition Cohort per index category. In this matched cohort, <1% of

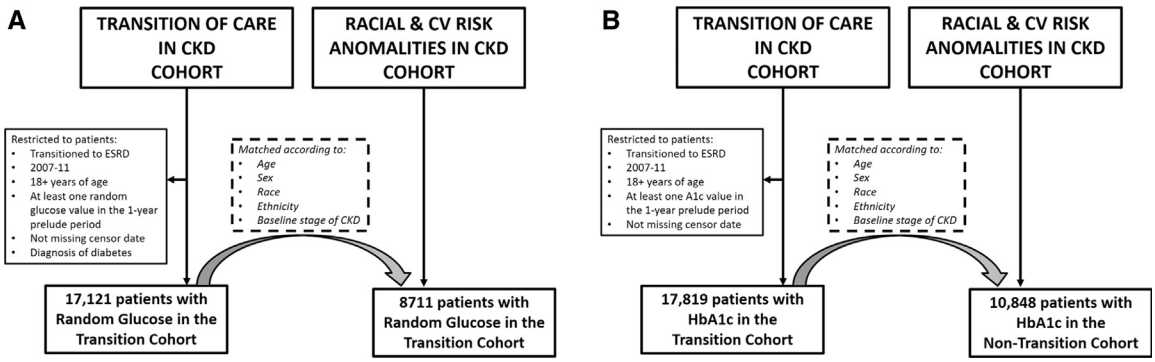

Figure 1. Study cohort creation for averaged random glucose analyses (A) and HbA1c analyses (B). CKD, chronic kidney disease; CV, cardiovascular; ESRD, end-stage renal disease; HbA1c, hemoglobin A1c.

patients (N = 101) transitioned to dialysis within 1 year following the "1-year averaged random glucose exposure period" who were excluded from the analysis, resulting in the Nontransition Averaged Random Glucose Cohort.

Using a similar approach to identify the Nontransition HbA1c Cohort, we also identified all patients from the *RCAV* cohort who underwent at least one or more HbA1c measurement(s) with a subsequent 365-day period during which all subsequent HbA1c measurements were averaged (designated as the "1-year averaged HbA1c exposure period" in which the patients did not experience death nor transition to dialysis). We similarly identified a Nontransition HbA1c Cohort with a similar distribution of baseline age sex, race, ethnicity, and baseline stage of CKD to that of the Transition Cohort. In this matched cohort, <1% of patients (N = 78) transitioned to dialysis within 1 year following the "1-year averaged HbA1c exposure period" who were excluded from the analysis, resulting in the Nontransition HbA1c Cohort. The study was approved by the institutional review boards of the University of California Irvine, VA Long Beach Healthcare System, and Memphis VA Medical Center.

Exposure Ascertainment

In the Transition Cohort, our primary exposure of interest was random glucose averaged over the 1-year prelude period, categorized as <80, 80-<100, 100-<120, 120-<140, 140-<160, 160-<180, 180-<200, and ≥200 mg/dl. Our secondary exposure was HbA1c level(s) averaged over the 1-year prelude period, categorized as <6, 6-<8, 8-<10, and ≥10%. The median (interquartile [IQR]) and minimum-maximum number of random glucose measurements per patient averaged over the 1-year prelude period were 6 (2, 16) and 1-637, respectively. The median (IQR) and minimum-maximum number of HbA1c measurements per patient averaged over the 1-year prelude period were 2 (1, 3) and 1-15, respectively.

Among the Nontransition Cohort patients who were matched to the Transition Cohort, we examined random glucose and HbA1c levels averaged over 1-year following study entry (i.e., study entry date designated as the date of the baseline glucose and HbA1c measurements) with the same categorizations used in the Transition Cohort. To examine averaged random glucose and HbA1c levels as continuous predictors of mortality, we conducted restricted cubic spline analyses with knots at the 25th, 50th, and 75th percentiles of observed values.

Outcome Ascertainment

In the Transition Cohort, our primary outcome of interest was 1-year post-ESRD all-cause mortality. Follow-up began the day after dialysis initiation and ended 1 year afterward. Patients were censored for kidney transplantation, loss to follow-up, end of the study period (i.e., 1-year after at-risk time commenced), or last date of available follow-up data (December 27, 2012), whichever occurred first.[1,19–21] Mortality data, censoring events, and associated dates were obtained from the VA Vital Status File (observed to have a sensitivity and specificity of 98.3% and 99.8%, respectively, in comparison with the National Death Index), Center for Medicare and Medicaid Services (CMS), and United States Renal Data System (USRDS) data sources.[22–24]

In parallel analyses of the Nontransition Cohort, we examined associations of 1-year averaged random glucose and HbA1c with 1-year all-cause mortality, with at-risk time beginning the day after the 1-year averaged random glucose and HbA1c exposure periods. Patients were censored for kidney transplantation, loss to follow-up, end of the study period (i.e., 1-year after at-risk time commenced), or last date of available follow-up data (July 26, 2013), whichever occurred first. Mortality data, censoring events, and associated dates were obtained from the VA Vital Status File.[22–24]

Socio-demographic, Comorbidity, Medication, and Laboratory Covariates

In the Transition Cohort, data from the USRDS Patient and Medical Evidence files were used to determine patients' baseline socio-demographic information (age, sex, race, ethnicity) at the time of dialysis initiation. The cause

of ESRD was obtained from CMS data, and information on initial dialysis modality was obtained from USRDS sources. In the Nontransition Cohort, patients' baseline sociodemographic information was obtained from the VA Corporate Data Warehouse and from Medicare through the VA-Medicare data merge project.[25]

In both the Transition and Nontransition Cohorts, information about comorbidities at the time of dialysis initiation was extracted from the VA Inpatient and Outpatient Medical SAS data sets using ICD-9 diagnostic and procedure codes and Current Procedural Terminology codes[26]; the Transition Cohort additionally used CMS data. Charlson Comorbidity Index (CCI) scores were estimated using the Deyo modification for administrative data sets without including kidney disease.[27] Body mass index data were obtained from the VA Vital Status file. Medication data were obtained from both CMS Part D and VA pharmacy dispensation records.[28] Random glucose, HbA1c, and other laboratory data except serum creatinine were obtained from the Decision Support System-National Data Extracts Laboratory Results files.[29] VA Corporate Data Warehouse LabChem data files were used to extract data about predialysis serum creatinine.[30] Using serum creatinine and demographic data, estimated glomerular filtration rate (eGFR) was calculated using the CKD Epidemiology Collaboration equation.[31]

Statistical Analyses

In the Transition Cohort, associations between 1-year pre-ESRD averaged random glucose and HbA1c with 1-year post-ESRD mortality were determined using Cox proportional hazard models with 4 adjustment levels with the following covariates, in which we *a priori* defined the expanded case-mix adjusted model as our preferred model: (1) minimally adjusted model: adjusted for patient's calendar quarter of dialysis initiation to account for secular changes in care over time, (2) case-mix model: adjusted for covariates in the minimally adjusted model, as well as age, sex, race, ethnicity, cause of ESRD, CCI score, diabetes, congestive heart failure (CHF), and cerebrovascular disease (CVD); (3) expanded case-mix model: adjusted for covariates in the case-mix model, as well as residential region, initial dialysis modality, and body mass index; and (4) expanded case-mix + laboratory adjusted model: adjusted for covariates in the expanded case-mix model, as well as serum albumin, hemoglobin, serum bicarbonate, eGFR averaged over the 1-year prelude period (i.e., proxy of residual kidney function), and last eGFR level measured before dialysis initiation (i.e., proxy of dialysis practice patterns). To compare the association of glycemic status with mortality among patients with CKD who did not transition to dialysis within 1-year of follow-up, we examined averaged random glucose and HbA1c with death risk among matched samples of patients from the Nontransition Cohort using similar adjustment levels: (1) minimally adjusted model: adjusted for patient's study entry quarter; (2) case-mix model: adjusted for covariates in the minimally adjusted model, as well as age, sex, race, ethnicity, CCI score, diabetes, CHF, and CVD; (3) expanded case-mix model: adjusted for covariates in the case-mix model, as well as residential region and body mass index; and (4) expanded case-mix + laboratory model: adjusted for covariates in the expanded case-mix model, as well as 1-year averaged serum albumin, hemoglobin, serum bicarbonate, and eGFR levels.

Missing data were handled using methods that included multiple imputation. Proportional hazards assumptions were confirmed by graphical analysis. Analyses and figures were generated using SAS, version 9.4 (SAS Institute Inc., Cary, NC), Stata, version 13.1 (Stata Corporation, College Station, TX), and SigmaPlot, version 12.5 (Systat Software, San Jose, CA).

Results

Baseline Characteristics of the Transition and Nontransition Cohorts

In primary analyses of averaged random glucose, there were 17,121 patients in the Transition Cohort who met eligibility criteria, among whom the mean ± SD age was 69 ± 11 years and who were comprised of 28% Blacks and 8% Hispanic patients (Table S1). Most patients had moderate-to-advanced CKD: 0.9%, 4%, 19%, and 77% were categorized as stages 1, 2, 3, and 4 + 5 CKD, respectively. These patients were matched to 8,711 patients in the Nontransition Cohort who had a similar balance of baseline characteristics (Table S1). Granular examination of patients' baseline characteristics in the Transition Cohort showed that, compared with patients in the lowest averaged random glucose category (<80 mg/dL), those in the highest category (≥200 mg/dL) tended to be younger, were more likely to have diabetes and less likely to have hypertension as their underlying cause of ESRD, were more likely to be residing in the northeast and less likely to be living in the west, had higher CCI scores, and had higher 1-year averaged eGFR and lower serum albumin levels (Table S2).

In secondary analyses of HbA1c, there were 17,819 patients in the Transition Cohort who met eligibility criteria, among whom the mean ± SD age was 68 ± 11 years and who were comprised of 28% Blacks and 7% Hispanic patients (Table S1). Most patients had moderate-to-advanced CKD: 1%, 4%, 19%, and 76% were categorized as stages 1, 2, 3, and 4 + 5 CKD, respectively. These patients were matched to 10,848 patients in the Nontransition Cohort who had a similar balance of baseline characteristics (Table S1).

Averaged Random Glucose and Mortality in the Transition Cohort Versus Nontransition Cohort

In the Transition Cohort, patients contributed a total of 13,207 patient-years of follow-up during which time

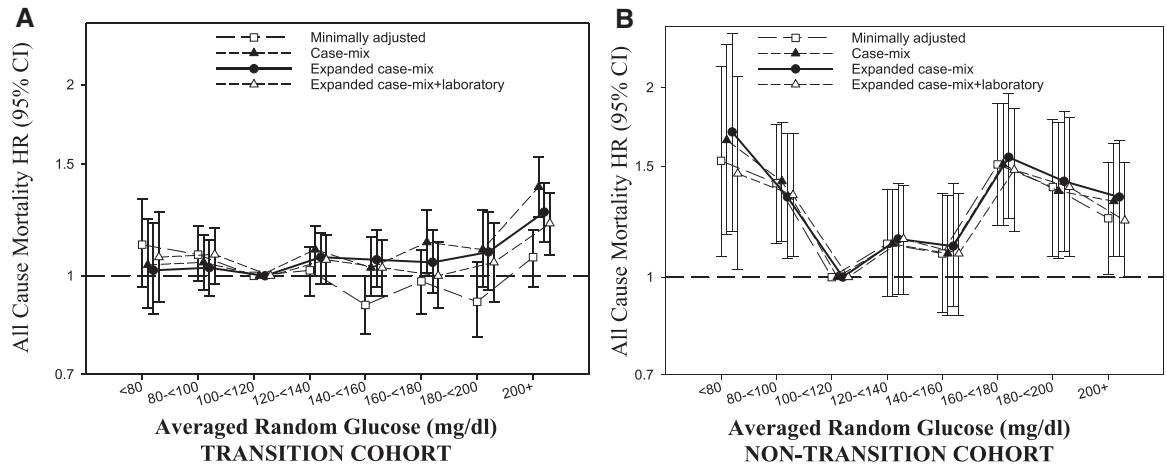

Figure 2. Association of averaged random glucose and mortality in the Transition Cohort (A) versus Nontransition Cohort (B). HR, hazard ratio; CI, confidence interval.

3,850 deaths occurred. In expanded case-mix analyses, we observed a J-shaped association between averaged random glucose and mortality such that the highest category ≥200 mg/dL was associated with higher death risk (reference: 100-<120 mg/dL): adjusted HR (aHR) (95% CI) 1.26 (1.13-1.40) (Fig. 2 and Table S3). Following incremental adjustment for laboratory covariates, the association between averaged random glucose ≥200 mg/dL and higher mortality persisted: aHR (95% CI) 1.21 (1.08-1.35). On examining averaged random glucose as a continuous variable using expanded case-mix adjusted restricted cubic splines, glucose levels exceeding ~170 mg/dL were monotonically associated with higher death risk (Fig. 3)

Among the matched sample of patients from the Nontransition Cohort who underwent one or more random glucose measurements, we observed 1,092 deaths over 6,699 patient-years of follow-up. In expanded case-mix analyses, we observed a U-shaped association between averaged random glucose and mortality such that lower levels <100 mg/dL and higher levels ≥160 mg/dL were associated with higher death risk: aHRs (95% CI) 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), 1.42 (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 ≥200 mg/dL, respectively (Fig. 2 and Table S3). In expanded case-mix adjusted splines, a similar pattern was

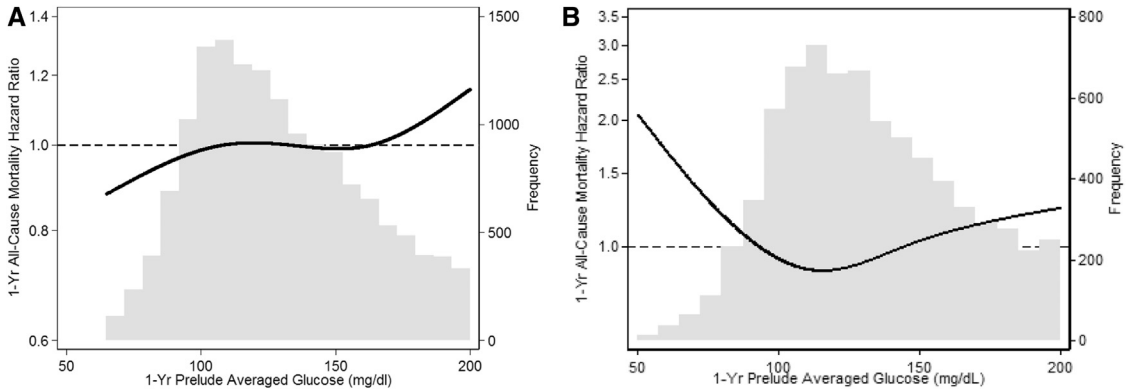

Figure 3. Spline analyses of averaged random glucose and mortality in the Transition Cohort (A) versus Nontransition Cohort (B). Transition Cohort analyses adjusted for expanded case-mix + laboratory covariates, which included patient's calendar quarter of dialysis initiation, age, sex, race, ethnicity, cause of ESRD, CCI score, diabetes, CHF, CVD, residential region, initial dialysis modality, body mass index, serum albumin, hemoglobin, serum bicarbonate, eGFR averaged over the 1-year prelude period, and last eGFR level measured prior to dialysis initiation. Nontransition Cohort analyses adjusted for expanded case-mix + laboratory covariates, which included patient's study entry quarter, age, sex, race, ethnicity, CCI score, diabetes, CHF, CVD, residential region, body mass index, serum albumin, hemoglobin, serum bicarbonate, and eGFR levels. CCI, Charlson Comorbidity Index; CHF, congestive heart failure; CVD, cerebrovascular disease; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease.

observed in which glucose levels below ~90 mg/dL and greater than ~160 mg/dL were associated with higher death risk (Fig. 3).

HbA1c and Mortality in the Transition Cohort Versus Nontransition Cohort

In the Transition Cohort, patients contributed a total of 15,119 patient-years of follow-up during which 4,374 deaths occurred. In expanded case-mix analyses, we observed a J-shaped association between HbA1c and mortality such that the higher categories of 8-<10% and ≥10% were each associated with higher death risk (reference: 6-<8%): aHRs (95% CI) 1.21 (1.11-1.33) and 1.43 (1.21-1.69), respectively (Fig. S1 and Table S4). Following incremental adjustment for laboratory covariates, this pattern of association persisted: aHRs (95% CI) 1.15 (1.05-1.26) and 1.30 (1.10-1.54) for HbA1c categories 8-<10% and ≥10%, respectively. On examining HbA1c as a continuous variable using expanded case-mix adjusted splines, HbA1c levels exceeding ~7.5% were monotonically associated with higher death risk (Fig. 4). While there appeared to be a trend between HbA1c levels below 5% and greater survival, the low prevalence of patients with these lower HbA1c levels rendered estimates unstable.

Among the matched sample of patients from the Nontransition Cohort who underwent one or more HbA1c measurements, we observed 1,130 deaths over 5,402 patient-years of follow-up. In expanded case-mix and expanded case-mix + laboratory adjusted analyses, a significant association between HbA1c levels and mortality was not observed (Fig. S1 and Table S4). In expanded case-mix adjusted splines, there was a trend toward HbA1c levels below 5% and higher mortality, as well as HbA1c levels above ~8.5% and greater survival; however, the prevalence of patients in these outlier HbA1c ranges was low (Fig. 4).

Discussion

To our knowledge, this is the first large population-based study that has separately examined glycemic status and mortality across 2 diabetic CKD populations according to whether they transitioned versus did not transition to ESRD. In the Transition Cohort, granular examination of averaged random glucose levels showed that higher pre-ESRD averaged random glucose levels ≥200 mg/dL were independently associated with higher post-ESRD mortality risk, whereas lower levels were not associated with higher death risk. We similarly observed that higher pre-ESRD HbA1c levels ≥8% were associated with higher post-ESRD death risk. Furthermore, analyses of averaged random glucose and HbA1c as continuous splines suggested a trend toward lower glycemic levels and better survival. In contrast, among a matched sample of CKD patients with comparable case-mix characteristics in the Nontransition Cohort, both lower averaged random glucose levels <100 mg/dL and higher levels ≥160 mg/dL were associated with higher death risk. While examination of HbA1c as a categorical variable did not show associations with mortality in the Nontransition Cohort, spline analyses suggested an inverse pattern to that of the Transition Cohort, such that lower HbA1c levels trended toward lower mortality while higher levels were associated with higher death risk.

The optimal glycemic level among patients with advanced CKD has remained elusive due to a paucity of data that have shown mixed findings in this population. In

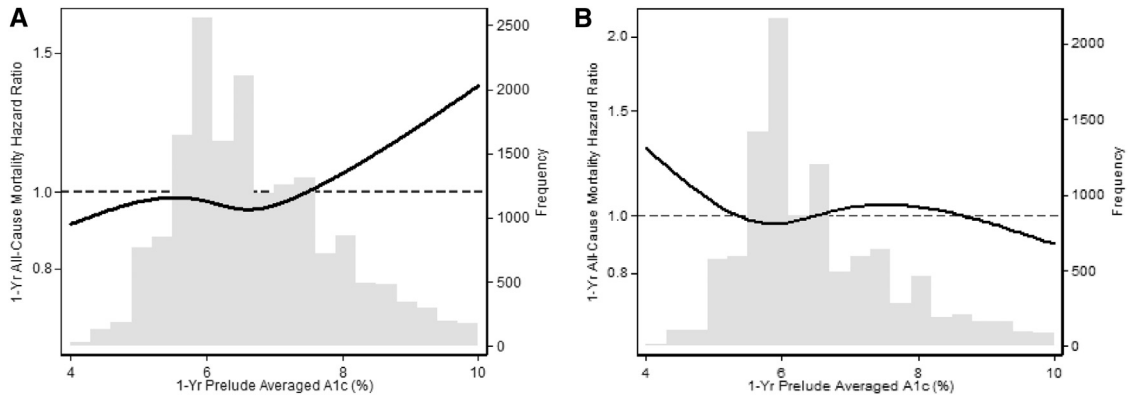

Figure 4. Spline analyses of HbA1c and mortality in the Transition Cohort (A) versus Nontransition Cohort (B). Transition Cohort analyses adjusted for expanded case-mix + laboratory covariates, which included patient's calendar quarter of dialysis initiation, age, sex, race, ethnicity, cause of ESRD, CCI score, diabetes, CHF, CVD, residential region, initial dialysis modality, body mass index, serum albumin, hemoglobin, serum bicarbonate, eGFR averaged over the 1-year prelude period, and last eGFR level measured before dialysis initiation. Nontransition Cohort analyses adjusted for expanded case-mix + laboratory covariates, which included patient's study entry quarter, age, sex, race, ethnicity, CCI score, diabetes, CHF, CVD, residential region, body mass index, serum albumin, hemoglobin, serum bicarbonate, and eGFR levels. CCI, Charlson Comorbidity Index; CHF, congestive heart failure; CVD, cerebrovascular disease; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; HbA1c, hemoglobin A1c.

a reanalysis of the Action to Control Cardiovascular Risk in Diabetes trial that stratified patients according to presence versus absence of mild-to-moderate CKD (i.e., stages 1-3 CKD) by Papademetriou et al., intensive glycemic control was associated with a 31% and 41% higher all-cause and cardiovascular death risk, respectively, among those with CKD, but not in those without CKD.[16] However, in a study of 23,296 diabetic patients with more advanced levels of CKD (i.e., stages 3-4 CKD) by Shurraw et al., examination of HbA1c as a categorical predictor showed that levels >9% were associated with faster decline in kidney function and higher risk of cardiovascular events, hospitalization, and mortality, while analyses of HbA1c as a continuous variable showed that both lower and higher levels (<6.5% and >8%) were associated with worse survival.[17] Most recently, in a study of 17,819 US Veterans with diabetes and CKD transitioning to dialysis by Rhee et al., we observed a robust association of higher HbA1c levels ≥8% and averaged random glucose levels ≥200 mg/dL with higher death risk across multiple secondary and sensitivity analyses, whereas lower glycemic levels were not associated with diminished survival.[1] However, as this study exclusively examined diabetic patients who transitioned to ESRD, these findings may provide limited inference to those who do not ultimately receive dialysis (i.e., patients who maintain stable kidney function, experience death or kidney transplantation prior to developing ESRD, or decline dialysis). In addition, while growing evidence has highlighted the hazards of hypoglycemia in the advanced CKD population,[32-34] this study did not specifically examine very low glucose levels (i.e., <80 mg/dL).

In our study, the divergent patterns observed in the Transition versus Nontransition Cohorts may potentially be explained by a differential effect of glycemic status upon long-term versus short-term survival in patients with advanced CKD (i.e., time-dependent effect of glycemic status).[35] For example, the Transition Cohort showed a J-shaped relationship between averaged random glucose and HbA1c levels with mortality risk, suggesting that, among those who survive and progress to ESRD, liberal glycemic control may have long-term detrimental outcomes vis-à-vis generation of oxidative stress, activation of protein kinase C, accumulation of advanced glycosylation end products, and progressive microvascular and macrovascular damage over time.[36,37] However, the U-shaped association between glycemic status and mortality in the Nontransition Cohort also suggest that glucose levels in the hypoglycemic (<80 mg/dL) and low-normal (80-<100 mg/dL) ranges are associated with short-term death risk, possibly due to (1) central nervous system toxicity leading to encephalopathy, seizures, coma, disequilibrium, and subsequent falls;[38,39] and/or (2) adrenergic stimulation, resulting in coronary ischemia, ventricular arrhythmias, and sudden cardiac death.[40] These latter observations corroborate findings from Papademetriou et al. and Shurraw et al. indicating that intensive glycemic control may be harmful in patients with advanced CKD.[16,17] Our findings suggest that the glycemic management of diabetic CKD patients should be individualized according to patients' longevity and underlying health status, as opposed to applying a "one size fits all" approach. While further studies are needed to more precisely define the optimal glycemic target in DKD subgroups, our data suggest that moderate glycemic levels may be a prudent target in the overall advanced diabetic CKD population.

The unique strengths of our study include its examination of 2 large contemporary cohorts of nationally representative CKD patients with comprehensive capture of detailed patient-level information, including longitudinal laboratory data; granular examination of 2 complementary glycemic metrics; and reduced confounding by differential health-care access and nonuniform medical care due to receipt of care in the VA Healthcare system. However, several limitations bear mention. First, as our primary analyses defined glycemic status according to random glucose levels measured in the clinical setting, they may not have captured hypoglycemic events occurring in the field (i.e., home capillary blood glucose measurements). Second, our secondary analyses used HbA1c as the exposure of interest, which may be influenced by factors independent of glycemic status in patients with advanced CKD (e.g., hemoglobin, serum bicarbonate levels[2]) with subsequent confounding of the HbA1c—mortality association and misclassification of glycemic status. However, we accounted for multiple confounders in expanded case-mix + laboratory adjusted analyses which yielded robust associations. Third, owing to data limitations, we were unable to account for confounding of the high glycemic status—lower survival relationship on the basis of patient noncompliance or poor doctor effect. Finally, as with all observational studies, our study's findings cannot prove a causal association between glycemic status and death risk.

In summary, our study is the first to show a differential relationship between glycemic status and survival among diabetic CKD patients who did versus did not transition to ESRD after 1 year of follow-up. Our observations of a J-shaped association between glycemic status and post-ESRD mortality suggest liberal glycemic status is associated with long-term mortality risk, whereas the U-shaped glucose—mortality relationship among patients who did not transition indicate intensive glycemic status is associated with short-term risk. Further studies are needed to define individualized optimal glycemic targets among diabetic CKD patients according to their underlying longevity and health status.

Practical Application

In this study, a differential relationship between glycemic status and outcomes was observed among CKD patients who did versus did not transition to dialysis over 1-year of follow-up. Among diabetic CKD patients transitioning

to dialysis, higher averaged random glucose and HbA1c were associated with early dialysis mortality, whereas in matched CKD patients who did not transition, both lower and higher glucose levels were associated with higher mortality. These findings suggest that different glycemic strategies should be applied based on whether there are plans to transition to dialysis versus pursue conservative management among diabetic patients with CKD.

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Supplementary Data

Supplementary data related to this article can be found at https://doi.org/10.1053/j.jrn.2018.07.003.

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