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Diabetes Control and the Risks of ESRD and Mortality in Patients With CKD

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Abstract

Background—Diabetes is the leading cause of end-stage renal disease (ESRD) and a significant contributor to mortality in the general population. We examined the associations of hemoglobin A_{1c} (HbA_{1c}) levels with ESRD and death in a population with diabetes and chronic kidney disease (CKD).

Study Design—Cohort study.

Setting & Participants—6,165 patients with diabetes (treated with oral hypoglycemic agents and/or insulin) and CKD stages 1 to 5 at a large health care system.

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Financial Disclosure

Dr Navaneethan has served as consultant for Bayer and Boeringher-Ingelheim. The other authors declare that they have no relevant financial interests.

Contributions

Research idea and study design: SDN, JDS, SEJ, SA, JVN; data acquisition: SA; data analysis/interpretation: SDN, JDS, SEJ, SA, WCW, JVN; statistical analysis: SA, JDS. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. SDN takes responsibility that this study has been reported honestly, accurately, and transparently; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Peer Review

Evaluated by 2 external peer reviewers, a statistician, and an Acting Editor-in-Chief.

SUPPLEMENTARY MATERIAL

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Because an author of this article was an editor for AJKD at the time of manuscript submission, the peer-review and decision-making processes were handled entirely by a member of the Editorial Board (Luxia Zhang, MD) who served as Acting Editor-in-Chief. Details of the journal's procedures for potential editor conflicts are given in the Information for Authors & Journal Policies.

Predictor—HbA_{1c} level (examined as a categorical and continuous measure).

Outcomes—All-cause and cause-specific mortality ascertained from the Ohio Department of Health mortality files and ESRD ascertained from the US Renal Data System.

Results—During a median 2.3 years of follow-up, 957 patients died (887 pre-ESRD deaths) and 205 patients reached ESRD. In a Cox proportional hazards model, after multivariable adjustment including for kidney function, HbA_{1c} level < 6% was associated with higher risk for death when compared with HbA_{1c} levels of 6% to 6.9% (HR, 1.23; 95% CI, 1.01–1.50). Similarly, HbA_{1c} level ≥ 9% was associated with higher risk for all-cause death (HR, 1.34; 95% CI, 1.06–1.69). In competing-risk models, baseline HbA_{1c} level was not associated with ESRD. For cause-specific mortality, diabetes accounted for >12% of deaths overall and >19% of deaths among those with HbA_{1c} levels > 9%.

Limitations—Small proportion of participants with advanced kidney disease; single-center population.

Conclusions—In this cohort of patients with CKD with diabetes, HbA_{1c} levels < 6% and ≥9% were associated with higher risk for death. HbA_{1c} levels were not associated with ESRD in this specific CKD population. Diabetes-related deaths increased with higher HbA_{1c} levels.

INDEX WORDS

Glycated hemoglobin; HbA_{1c}; end stage renal disease (ESRD); diabetes mellitus; diabetes control; incident ESRD; chronic kidney disease (CKD); death and kidney disease; diabetic nephropathy; mortality

Diabetes is considered as a coronary artery disease equivalent, and the presence of diabetes and chronic kidney disease (CKD) poses the highest risk for death compared to diabetes or CKD alone.[1,2] The prevalence of diabetic kidney disease is also increasing, and diabetic nephropathy is the leading cause of end-stage renal disease (ESRD).[1,3,4] What constitutes an ideal glycated hemoglobin (hemoglobin A_{1c} [HbA_{1c}]) level has been a matter of debate, and some clinical trials in the general population have reported that intensive glycemic control in diabetic patients is associated with adverse outcomes.[5–8] Based on available evidence, the American Diabetes Association has recommended targeting an HbA_{1c} level < 7% for most nonpregnant adults and <8% for those at risk for hypoglycemia, extensive comorbid conditions, and long-standing diabetes.[9]

Few studies have evaluated associations between HbA_{1c} levels and clinical outcomes in those with CKD. Shurraw et al[10] reported that HbA_{1c} levels > 9% were associated with worse clinical outcomes, such as faster kidney disease progression, more cardiovascular events, and increased mortality, among patients with non–dialysis-dependent CKD. In addition, lower HbA_{1c} levels (<6.5%) were associated with higher hazards of death. Findings from a cohort of Taiwanese adults with type 2 diabetes showed that HbA_{1c} levels > 7.0% were associated with increased risk for ESRD compared with HbA_{1c} levels of 6% to 7%, but HbA_{1c} levels < 6.0% were also associated with increased risk for ESRD.[11] However, a secondary analysis of the ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial reported that tighter glycemic control in patients with CKD was associated with a significant increase in cardiovascular and all-cause mortality.[12] Although secondary

analysis of the ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron-MR Controlled Evaluation) trial reported a reduced risk for ESRD with intense glucose control, no significant effects of intensive glycemic control on ESRD were noted in other studies.[13,14] Patients with CKD are generally at higher risk for hypoglycemia, making a case for avoiding intense glycemic control in this population.[15] Hence, given these inconsistent findings in the literature, we examined associations between HbA_{1c} levels and ESRD and death in a cohort of patients with diabetes and non–dialysis-dependent CKD receiving care in a large US health care system.

METHODS

Overview

We conducted an analysis using a pre-existing electronic medical record (EMR)-based CKD registry. The development and validation of this registry at Cleveland Clinic has been described in detail previously.[16] This study and the CKD registry were approved by the Cleveland Clinic Institutional Review Board (IRB #09-015). Informed consent was not obtained because these data were developed using electronic medical records and Cleveland Clinic has an opt-in policy for collecting data for research purposes using electronic medical records.

Study Population

Patients who were residents of Ohio and had (1) at least 1 outpatient encounter with a Cleveland Clinic health care provider and either 2 estimated glomerular filtration rate (eGFR) values < 60 mL/min/1.73 m^2 more than 90 days apart or *International Classification of Diseases, Ninth Revision* codes for various kidney diseases, (2) diabetes and were using oral hypoglycemic agents and/or insulin, and (3) HbA_{1c} measured in the year prior to the second eGFR < 60 mL/min/1.73 m^2 or a CKD diagnosis were included (Fig S1, available as online supplementary material). Patients younger than 18 years and those who already had ESRD diagnosed (ie, dialysis dependent or having received a kidney transplant) were excluded. Patients who met the inclusion/exclusion criteria from January 1, 2005, to September 15, 2009, were included in this analysis.

Definitions and Outcome Measures

Demographics, Comorbid Conditions, and Laboratory Parameters—

Demographic details were extracted from the EMR. Diabetes mellitus, hypertension, coronary artery disease, and other comorbid conditions were defined using prespecified criteria and validated. Relevant outpatient laboratory values were obtained from the EMR. Medication details were obtained from the EMR and were validated in the past. The automated chemistry laboratory at Cleveland Clinic runs HbA_{1c} testing on a Roche Integra 800 platform using a method called TinaQuant Gen2, an immune-based turbidimetric assay. It measures both hemoglobin concentration and HbA_{1c} concentration, then calculates the glycated hemoglobin percentage. The laboratory follows the National Glycohemoglobin Standardization Program guidelines for standardizing these measures. Baseline HbA_{1c} measurements in the year prior to the second eGFR < 60 mL/min/1.73 m^2 or diagnosis of CKD were used in this study, and when multiple measurements were available for a patient,

the result closest to the date of diagnosis of CKD was selected for analytical purposes. For the time-dependent repeated-measures analysis, we included the baseline HbA_{1c} value and the first HbA_{1c} value measured each month during study follow-up. We used carry-forward values to fill in data for months when HbA_{1c} data were not available.

Kidney Function Measures—All creatinine measurements were performed by the modified kinetic Jaffé reaction using an Hitachi D 2400 Modular Chemistry Analyzer thereafter (Roche Diagnostics) at the Cleveland Clinic laboratory. In patients who had at least 2 serum creatinine levels measured 90 days apart during January 2005 to September 15, 2009, at the Cleveland Clinic health system,[17] the CKD-EPI (CKD Epidemiology Collaboration) creatinine equation was used to calculate eGFR. Urinary protein studies were not available for the entire study population. Therefore, to be comprehensive and reflect clinical practice, patients who had urine dipstick measurements, urine albumin-creatinine ratio, urine protein-creatinine ratio, and 24-hour urine studies were included to assess whether they had proteinuria. The following cutoffs were considered in determining whether someone had proteinuria: presence of proteinuria ≥ 1+ in dipstick studies, >30 mg/g in those who had urine albumin-creatinine ratio and urine protein-creatinine ratio studies, and proteinuria with protein excretion > 30 mg in 24-hour studies. Urinalysis chemstrip is performed on the iRICELL 3000 using iChem VELOCITY test strips (both Beckman Coulter) or on the AX-4280 using AUTION 9EB test strips (both ARKRAY).

Urine albumin was measured by immunoturbidimetric assay with antigen excess check, and urine creatinine was measured using a multistep enzymatic procedure that produces a quinone imine chromogen on the Roche Modular platform at the Cleveland Clinic laboratory.

Outcome Measures—The primary outcomes of interest were all-cause mortality and ESRD. ESRD was defined as the need for renal replacement therapy: dialysis or transplantation. Mortality details were ascertained from the Ohio Department of Health mortality files, which also provided cause-specific mortality data[18]; deaths from the Cleveland Clinic EMR were also captured. Incident treated ESRD was ascertained from linkage of our registry with the US Renal Data System (USRDS). Patients were followed up from their date of inclusion in the registry until September 15, 2009.

Statistical Analysis

Baseline characteristics among strata of HbA_{1c} levels (<6, 6%–6.9%, 7%–7.9%, 8%–8.9%, and ≥9%) were compared using χ^2 and analysis of variance tests for categorical and continuous variables, respectively. These categories were chosen because they are used in clinical practice and other studies. To evaluate whether unadjusted survival and ESRD among persons with CKD was associated with baseline HbA_{1c} levels, we fitted cumulative incidence functions that adjusted for competing risks using the Fine and Gray method with date of second eGFR < 60 mL/min/1.73 m^2 or date of CKD diagnosis as the time of origin. We tabulated causes of death for all deaths (both before and after ESRD).

We evaluated the independent relationship between various baseline HbA_{1c} categories and pre-ESRD mortality using a Cox proportional hazards regression model with HbA_{1c} levels

of 6% to 6.9% as the reference group. We also used Fine and Gray's extension of the Cox regression that models the cumulative incidence to fit competing-risk regression models and evaluate the association between baseline HbA_{1c} levels and ESRD.[19] We adjusted for the following covariates in the models: age; race; sex; malignancy; coronary artery disease; congestive heart failure; cerebrovascular disease; peripheral vascular disease; use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, statins, and β-blockers; albumin level; hemoglobin level; body mass index group (underweight, normal, overweight, and obese); smoking; eGFR; and albuminuria. Linearity assumptions for continuous covariates were relaxed as needed by using splines at the 10th, 50th, and 90th percentiles. We tested 2-way interactions between baseline HbA_{1c} level and the following prespecified covariates in the adjusted ESRD and mortality models: age, sex, race, coronary artery disease, and eGFR. We also evaluated the association between baseline continuous HbA_{1c} levels and pre-ESRD mortality and ESRD using splines at the 10th, 50th, and 90th percentiles of HbA_{1c} and plotted continuous HbA_{1c} versus the log hazard of mortality. To incorporate HbA_{1c} results obtained after inception, we fitted a Cox proportional hazards model of mortality with time-dependent repeated measures of HbA_{1c} using the categories defined. Percentages of missing information for individual variables were as follows: body mass index, 3%; serum albumin, 15%; hemoglobin, 21%; and proteinuria, 27%. Because complete case analyses are prone to yielding biased results, we used multiple imputation (SAS proc MI; version 9.4, SAS Institute Inc) with the Markov chain Monte Carlo method and a single chain to impute 5 data sets with complete data. Cox models were performed on each of the 5 imputed data sets, and parameter estimates were combined using SAS MIanalyze. We conducted several sensitivity analyses on the pre-ESRD mortality and ESRD models by excluding: (1) those with malignancy, (2) those with type 1 diabetes, and (3) events in the first 6 months of follow-up.

All data analyses were conducted using Linux SAS version 9.4 and R statistical software, version 3.0.1 (The R Foundation for Statistical Computing) with the rms package. The cmprsk package was used for competing-risk analysis in R.

RESULTS

Baseline Patient Characteristics

We included 6,165 patients with non–dialysis-dependent CKD in this analysis (Fig S1). Mean age of the study population was 70.1 ± 11.8 (standard deviation) years, with 46.7% men and 20.7% blacks. Mean body mass index of the study cohort was 32.3 ± 7.2 kg/m^2. Prevalences of hypertension, malignancy, and coronary artery disease were 96.3%, 17.0%, and 30.2%, respectively. Mean eGFR was 50.5 ± 16.6 mL/min/1.73 m^2, with 58.8% in stage 3a, 24.5% in stage 3b, and 7.4% in stage 4 CKD. Table 1 outlines further details of the study population overall and by HbA_{1c} categories.

HbA_{1c}, ESRD, and Mortality

Categorical Analysis—During a median follow-up of 2.3 years, 957 patients died (887 pre-ESRD deaths) and 205 patients reached ESRD. Unadjusted competing-risk analyses (Fig 1) showed differences in the incidence of ESRD across different HbA_{1c} levels ($P < 0.001$)

and also differences in all-cause mortality ($P < 0.05$; Fig 1). In multivariable Cox proportional hazards regression, HbA_{1c} level was independently associated with pre-ESRD mortality. HbA_{1c} level < 6% was associated with higher risk for death when compared with HbA_{1c} levels of 6% to 6.9%, as was an HbA_{1c} level ≥ 9% (Table 2). All 2-way interaction terms between HbA_{1c} level and age, sex, race, coronary artery disease, and eGFR were nonsignificant. In the adjusted competing-risk model of ESRD, baseline HbA_{1c} levels < 6% and ≥9% were not significantly different from HbA_{1c} levels of 6% to 6.9% (Table 3). The interaction between HbA_{1c} level and eGFR was statistically significant ($P < 0.01$), suggesting that HbA_{1c} level < 6% was associated with lower risk among those with lower eGFRs, and HbA_{1c} level ≥ 9% was associated with higher risk only among those with higher eGFRs (Table S1). Interactions between HbA_{1c} level and age, sex, race, and coronary artery disease were not statistically significant. In the multivariable mortality model with time-dependent repeated measures of HbA_{1c}, results were similar to those in the primary analysis (Table S2).

Continuous Analysis (using baseline HbA_{1c} data)—When considered as a continuous variable, HbA_{1c} level was significantly associated with pre-ESRD mortality (Fig 2). The relationship was nonlinear, with very low and high HbA_{1c} levels having the higher risk for mortality and risk being lowest at HbA_{1c} levels of about 7% to 8%. In the analysis of continuous HbA_{1c} versus ESRD, neither the main effect nor any of the splines were significantly associated with the outcome.

Causes of Death

Cause-of-death details were available from the Ohio Department of Health mortality data for 942 patients. Table 4 shows causes of death overall and by HbA_{1c} categories.

Sensitivity Analyses

Sensitivity analysis excluding those with malignancy (n = 1,048) yielded similar results to the primary analysis and is shown in Table S3. Sensitivity analysis excluding those with type 1 diabetes (n = 575) yielded qualitatively similar findings as in the primary analyses, with HbA_{1c} levels < 6% and ≥9% having mortality hazard ratios (HRs) of 1.28 (95% confidence interval [CI], 1.002–1.64) and 1.43 (95% CI, 1.08–1.88), respectively, when compared with HbA_{1c} levels of 6% to 6.9%. In the ESRD model excluding type 1 diabetes, other HbA_{1c} levels were not significantly different from HbA_{1c} levels of 6% to 6.9%. Sensitivity analysis excluding events during the first 6 months of follow-up yielded similar results to those in the primary analysis (Table S3).

DISCUSSION

In this observational analysis of a large cohort of patients with CKD receiving treatment for diabetes with either oral hypoglycemic medications and/or insulin, we noted a U-shaped association in that HbA_{1c} levels < 6% and ≥9% were independently associated with increased mortality compared with patients with HbA_{1c} levels of 6% to 6.9%. By contrast, HbA_{1c} levels were not independently associated with the incidence of ESRD in this CKD population. However, associations between HbA_{1c} level and ESRD were modified by

baseline eGFR, and higher HbA_{1c} levels appeared to be associated with higher risk for ESRD in those with relatively preserved kidney function. For cause-specific mortality, diabetes accounted for at least 12% of deaths overall, and among those with HbA_{1c} levels ≥ 9%, nearly 20% of deaths were attributed to diabetes.

Previous studies have examined associations between HbA_{1c} levels and death in CKD populations. In a large database analysis from the Canadian province of Alberta, HbA_{1c} levels < 6.5% and >9% were associated with higher risks for death.[10] Another report from Taiwan indicated that HbA_{1c} level > 9% was associated with ESRD, cardiovascular events, and death in those with CKD stages 3 to 4, but not those with CKD stage 5.[11] A secondary analysis of the ACCORD trial that compared the effects of HbA_{1c} targets < 6.0% versus 7% to 7.9% reported higher risks for cardiovascular and all-cause mortality in their diabetic population with lower HbA_{1c} levels.[13] Our findings add to the existing literature and highlight the potential risk of targeting lower HbA_{1c} levels (<6%) in patients with CKD while at the same time highlighting the potential harmful effects of higher HbA_{1c} levels. Cumulatively, the available data are in agreement with the KDIGO (Kidney Disease: Improving Global Outcomes) guideline statements on glycemic targets of HbA_{1c} of 7.0% (graded 1A) and not treating to an HbA_{1c} target < 7.0% in patients who are at risk for hypoglycemia.[20] It is also worth noting that ~25% of our study population had HbA_{1c} levels > 8%, suggesting an opportunity for better glycemic control in this population.

The observed harmful associations with higher HbA_{1c} levels could be attributed to the macrovascular complications associated with diabetes. As for the inferior outcomes among patients with very low HbA_{1c} concentrations, previous analysis reported that patients with CKD were at higher risk for sustaining hypoglycemia and the risk for death was higher within 1 day after hospitalization for hypoglycemic episodes.[15] Although hypoglycemia could explain the higher risk that we observed in those with HbA_{1c} levels < 6%, we cannot corroborate this hypothesis in our data because hypoglycemia-related deaths are not separately reported in the Ohio Department of Health mortality files. In the general population, diabetes remains the 7th leading cause of death in the United States.[21] In this study population of patients with CKD and diabetes, diabetes accounted for at least 12% of deaths. Of note, the proportion of diabetes-related deaths increased as HbA_{1c} levels worsened, thus highlighting the detrimental impact of uncontrolled diabetes mellitus in those with CKD.

Higher HbA_{1c} levels have been associated with higher risk for kidney disease progression in some previous analyses, but not in others. In a meta-analysis, Coca et al[14] reported that for those with type 2 diabetes, lower HbA_{1c} levels were associated with reduced risk for micro- and macroalbuminuria, but its effects on ESRD were uncertain. More recently, a secondary analysis of the ADVANCE trial reported that intensive glucose control led to a long-term reduction in ESRD while not increasing the risk for cardiovascular events or death.[13] We did not note a general association between HbA_{1c} level and ESRD in those with pre-existing CKD, but this relationship appeared to be modified by eGFR; that is, patients with higher HbA_{1c} levels had higher risks for ESRD if they had relatively preserved kidney function. It is important to note that 89% of our study population were using renin–angiotensin–aldosterone system (RAAS) blockers; hence, it is unclear whether the relationship between

intense HbA_{1c} control and kidney disease progression varied based on the use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. Prior reports either refrained from reporting the use of RAAS inhibitors or did not adjust for their use in multivariable models; clearly, RAAS inhibitors have been shown to reduce the risk for ESRD in those with diabetic CKD.[22]

Certain limitations of our study deserve mention. Being an observational study, patients achieved their HbA_{1c} levels as a result of their care and treatment and other health-related behavior rather than by randomization into specific glycemic control target groups. Hence, a causal relationship cannot be established. Our study population is derived from the EHRs of a large integrated health system and may not be generalizable to other settings. Providers may have differed in their treatment recommendations and patients may have differed in their treatment adherence. Whether these findings can be extrapolated to community-based CKD populations is unknown. The pragmatic clinical data from within a single health system carry the limitation that we cannot account for care obtained outside of Cleveland Clinic health system. We also lacked information for duration of diabetes and other diabetes-related complications such as diabetic neuropathy, diabetic retinopathy, and macrovascular diabetic complications. In addition, we lacked information relating to newer noninsulin injectable antidiabetic drugs. Furthermore, we included a limited number of patients with CKD stage 5, for whom the reliability of HbA_{1c} measurements is unclear. Additionally, we did not have detailed and longitudinal medication data to examine any differences across medication subgroups or from medication changes over time.

However, the strengths of this study include a large diverse clinical population of patients with CKD stages 3 and 4 and availability of information for all-cause mortality, cause-specific death details (which to our knowledge have not been reported before), and ESRD incidence from merging our data with outside state and federal data sources, which provided validated end points for our analysis.

In summary, we report increased risk for all-cause mortality among patients with diabetes and CKD who had HbA_{1c} levels < 6% and among those who had HbA_{1c} levels ≥ 9%. By contrast, HbA_{1c} level was not associated with ESRD in this study population. The proportion of deaths due to diabetes increased as HbA_{1c} levels increased. Clinical trials comparing different diabetes control targets and specific medication strategies in patients with established CKD are warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Results of this study were presented as an abstract at the 2016 Kidney Week of the American Society of Nephrology in Chicago, IL, November 18, 2016.

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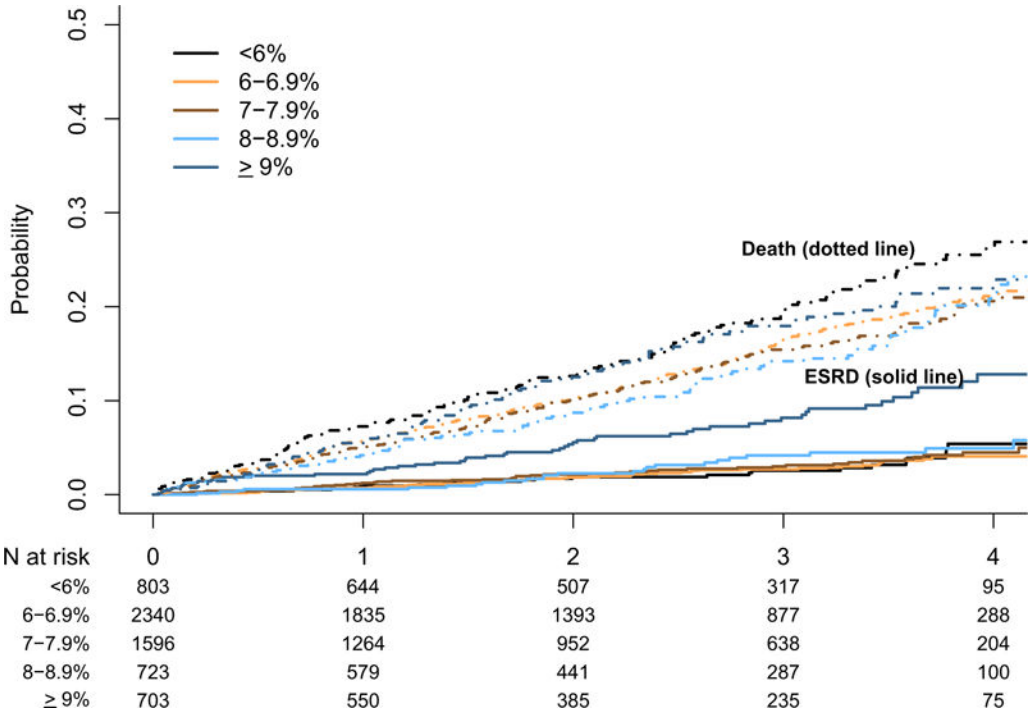

Figure 1.

Cumulative incidence curves for end-stage renal disease (ESRD) and death among patients with chronic kidney disease across hemoglobin A_{1c} categories using competing risks.

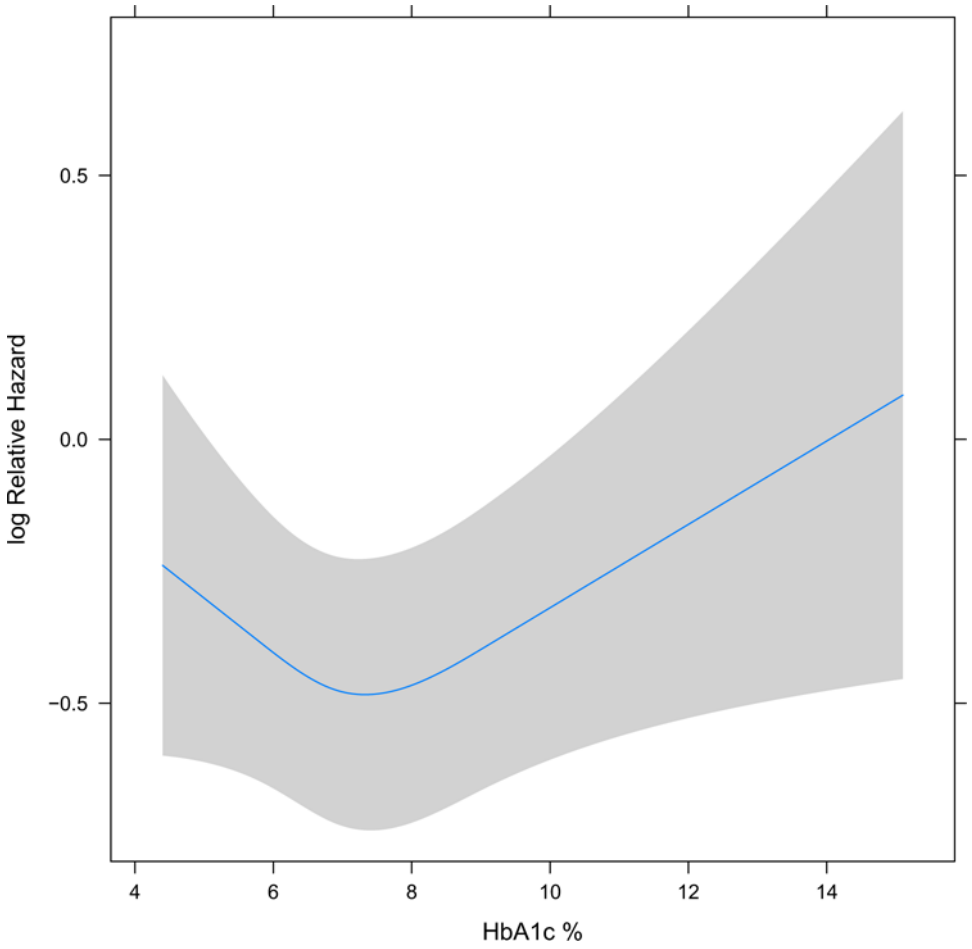

Figure 2.

Associations of hemoglobin A_{1c} (HbA_{1c}) with all-cause mortality (baseline HbA_{1c} considered as continuous measure with splines at the 10th, 50th, and 90th percentile: 5.8, 6.9, and 9.1 respectively; main effect $P = 0.07$, nonlinear $P = 0.04$).

Table 1

Patient Characteristics Across Categories of Baseline HbA_{1C} Levels

Factor	N	All Patients	HbA_{1c} <6% (n = 803)	6%–6.9% (n = 2,340)	7%–7.9% (n = 1,596)	8%–8.9% (n = 723)	≥9% (n = 703)	*P*
Age, y	6,165	70.1 ± 11.8	70.2 ± 12.0	72.5 ± 10.1	70.6 ± 11.4	68.6 ± 12.2	62.7 ± 13.8	<0.001[a]
Male sex	6,165	46.7	46.0	46.3	48.0	46.6	46.4	0.8[b]
African American	6,165	20.7	17.2	17.9	21.1	22.7	31.6	<0.001[b]
Smoking	5,735	8.6	7.7	7.3	8.3	9.8	13.4	<0.001[b]
BMI, kg/m^2	5,979	32.3 ± 7.2	32.1 ± 7.9	31.8 ± 6.7	32.4 ± 7.2	32.8 ± 7.3	33.4 ± 8.0	<0.001[a]
BMI category	6,165							<0.001[b]
< 18.5 kg/m^2		0.37	0.12	0.43	0.25	0.55	0.57	
18.5–24.9 kg/m^2		12.6	14.7	13.7	11.0	10.8	12.5	
25–29.9 kg/m^2		28.9	30.3	30.1	30.2	26.6	22.5	
30–34.9 kg/m^2		25.4	22.5	25.6	26.1	25.3	26.3	
35–39.9 kg/m^2		16.2	14.4	15.7	15.7	19.2	17.9	
≥40 kg/m^2		13.5	14.3	11.8	13.4	14.5	17.9	
Missing		3.0	3.6	2.8	3.4	3.0	2.3	
eGFR, mL/min/1.73 m^2	6,165	50.5 ± 16.6	47.7 ± 14.3	50.0 ± 13.8	50.7 ± 16.6	51.2 ± 18.4	54.0 ± 23.6	<0.001[a]
eGFR category	6,165							<0.001[b]
≥90 mL/min/1.73 m^2		4.0	1.6	2.3	4.2	5.0	10.7	
60–89 mL/min/1.73 m^2		4.6	2.7	4.0	4.6	6.5	7.1	
45–59 mL/min/1.73 m^2		58.8	58.7	62.6	58.8	55.9	48.9	
30–44 mL/min/1.73 m^2		24.5	28.1	24.0	24.7	23.0	23.2	
15–29 mL/min/1.73 m^2		7.4	7.3	7.0	7.0	9.0	8.3	
<15 mL/min/1.73 m^2		0.71	1.5	0.17	0.63	0.69	1.8	
Hypertension	6,165	96.3	96.0	96.8	96.6	95.7	94.7	0.09[b]
CAD	6,165	30.2	28.0	29.2	33.3	32.4	26.6	0.003[b]
CHF	6,165	10.9	12.1	9.7	10.5	12.0	13.8	0.02[b]

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Factor	N	All Patients	HbA_{1c} <6% (n = 803)	6%–6.9% (n = 2,340)	7%–7.9% (n = 1,596)	8%–8.9% (n = 723)	≥9% (n = 703)	*P*
CBVD	6,165	11.2	10.7	11.6	12.2	10.7	8.8	0.2[b]
PVD	6,165	4.9	3.5	4.3	5.3	6.8	5.7	0.02[b]
Hyperlipidemia	6,165	91.7	87.0	91.9	92.7	93.6	92.2	<0.001[b]
Malignancy	6,165	17.0	21.5	19.4	15.9	11.6	12.1	<0.001[b]
Statin use	6,165	79.1	70.1	79.7	81.5	83.1	78.1	<0.001[b]
ACEi/ARB use	6,165	89.0	86.3	88.2	89.5	90.9	91.7	0.003[b]
β-Blocker use	6,165	62.6	64.9	61.4	63.2	64.7	60.2	0.2[b]
Oral hypoglycemic use	6,165	87.8	89.4	92.0	87.3	83.5	77.4	<0.001[b]
Insulin use	6,165	41.0	27.3	25.9	44.7	63.2	75.5	<0.001[b]
Albumin, g/dl	5,214	4.1 ± 0.42	4.1 ± 0.47	4.1 ± 0.40	4.1 ± 0.40	4.1 ± 0.43	4.0 ± 0.43	<0.001[a]
Hemoglobin, mg/dl	4,856	12.6 ± 1.7	12.3 ± 1.9	12.6 ± 1.6	12.6 ± 1.7	12.7 ± 1.7	12.7 ± 1.7	<0.001[a]
Proteinuria	4,498	39.4	31.2	32.8	39.1	48.2	60.9	<0.001[b]

Note: Values for categorical variables are given as column percentage; for continuous variables, as mean ± standard deviation.

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CAD, coronary artery disease; CBVD, cerebrovascular disease; CHF, congestive heart failure; eGFR, estimated glomerular filtration rate; HbA_{1C}, hemoglobin A_{1C}; PVD, peripheral vascular disease.

[a] *P* by analysis of variance.

[b] *P* by Pearson χ^2 test.

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Table 2

Associations Between HbA_{1c} and Pre-ESRD Mortality in CKD

	HbA_{1c} < 6%	**HbA_{1c} 7%–7.9%**	**HbA_{1c} 8%–8.9%**	**HbA_{1c} > 9%**
Unadjusted	1.27 (1.04–1.54)	0.96 (0.81–1.14)	0.92 (0.73–1.15)	1.15 (0.92–1.43)
Adjusted for				
1) Age, race, sex	1.35 (1.11–1.64)	1.00 (0.85–1.19)	1.01 (0.80–1.27)	1.60 (1.27–2.00)
2) 1 + comorbid conditions, BMI group, albumin, hemoglobin, smoking	1.28 (1.05–1.56)	0.95 (0.80–1.13)	0.99 (0.78–1.25)	1.41 (1.12–1.78)
3) 2 + ACEi/ARB, statin, β-blocker, eGFR, proteinuria	1.23 (1.01–1.50)	0.94 (0.79–1.12)	0.96 (0.76–1.22)	1.34 (1.06–1.69)

Note: Values are given as hazard ratio (95% confidence interval). Estimates combined using MIanalyze on the 5 imputed data sets. Reference category is 6% to 6.9%.

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; HbA_{1C}, hemoglobin A_{1C}.

Table 3

Associations of HbA_{1c} With ESRD: Competing-Risk Model With Death as Competing Risk

	HbA_{1c} < 6%	**HbA_{1c} 7%–7.9%**	**HbA_{1c} 8%–8.9%**	**HbA_{1c} ≥ 9%**
Unadjusted	1.10 (0.68–1.78)	1.18 (0.80–1.73)	1.31 (0.82–2.11)	3.15 (2.17–4.57)
Adjusted for				
1) Age, race, sex	0.98 (0.61–1.59)	1.05 (0.73–1.55)	1.07 (0.66–1.73)	1.95 (1.32–2.87)
2) 1 + comorbid conditions, BMI group, albumin, hemoglobin, smoking	0.87 (0.53–1.41)	0.99 (0.67–1.47)	1.02 (0.62–1.68)	1.76 (1.15–2.67)
3) 2 + ACEi/ARB, statin, β-blocker, eGFR, proteinuria	0.58 (0.32–1.02)	0.92 (0.62–1.37)	0.65 (0.38–1.12)	1.35 (0.88–2.09)

Note: Values given as subdistribution hazard ratio (95% confidence interval). Estimates combined using MIanalyze on the 5 imputed data sets. Reference category is 6% to 6.9%.

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; HbA_{1c}, hemoglobin A_{1c}.

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Table 4

Cause of Death Overall and by HbA_{1c} Level for Patients in Whom Cause-of-Death Details Available

Factor	Overall (N = 942)	HbA_{1c} <6% (n = 153)	6%–6.9% (n = 346)	7%–7.9% (n = 225)	8%–8.9% (n = 99)	≥9% (n = 119)
Cardiovascular diseases	38.6	38.6	38.7	34.7	47.5	38.7
Ischemic heart disease	22.5	18.3	23.4	18.2	31.3	26.1
Heart failure	1.9	2.6	2.0	1.8	0.0	2.5
Cerebrovascular disease	3.3	3.9	2.6	4.9	2.0	2.5
All other cardiovascular disease	10.9	13.7	10.7	9.8	14.1	7.6
Malignant neoplasms	19.5	25.5	19.1	16.0	23.2	16.8
All other diseases	40.4	34.0	39.9	48.9	29.3	43.7
Diabetes mellitus	12.2	5.9	9.8	17.3	10.1	19.3
Chronic lower respiratory diseases	3.7	3.3	3.8	4.9	4.0	1.7
Nephritis, nephrotic syndrome, and nephrosis	2.2	2.0	2.3	3.1	0.0	2.5
Septicemia	2.2	1.3	2.9	2.2	2.0	1.7
Influenza and pneumonia	2.2	2.6	1.4	2.7	3.0	2.5
Chronic liver disease and cirrhosis	1.3	3.3	0.87	0.44	0.0	1.3
Alzheimer disease	1.3	0.65	1.7	1.8	1.0	0.0
Pneumonitis due to solids and liquids	0.96	0.0	1.2	1.8	0.0	0.84
Parkinson disease	0.42	0.0	0.58	0.89	0.0	0.0
All other diseases	13.9	15.0	15.3	13.8	9.1	12.6
Non–disease-related deaths	1.4	2.0	2.3	0.44	0.0	0.84

Note: Values are given as column percentages.

Abbreviation: HbA_{1c}, hemoglobin A_{1c}.