

Association of Pretransplant Glycemic Control With Posttransplant Outcomes in Diabetic Kidney Transplant Recipients

MIKLOS Z. MOLNAR, MD, PHD^{1,2}
EDMUND HUANG, MD³
JUNICHI HOSHINO, MD^{1,4}
MAHESH KRISHNAN, MD, MPH, MBA⁵

ALLEN R. NISSENSON, MD^{3,5}
CSABA P. KOVESDY, MD^{6,7}
KAMYAR KALANTAR-ZADEH, MD, MPH, PHD^{1,3,4}

OBJECTIVE—Observational studies have yielded inconsistent findings regarding the association of hemoglobin A_{1c} (HbA_{1c}) with survival in diabetic patients on dialysis. The association between pretransplant glycemic control and short- and long-term posttransplant outcomes in kidney transplant recipients is not clear.

RESEARCH DESIGN AND METHODS—Linking the 5-year patient data of a large dialysis organization (DaVita) to the Scientific Registry of Transplant Recipients, we identified 2,872 diabetic dialysis patients who underwent first kidney transplantation. Mortality or graft failure and delayed graft function (DGF) risks were estimated by Cox regression (hazard ratio [HR]) and logistic regression (odds ratio), respectively.

RESULTS—Patients were 53 ± 11 years old and included 36% women and 24% African Americans. In our fully adjusted model, allograft failure–censored, all-cause death HR and 95% CI for time-averaged pretransplant HbA_{1c} categories of 7 to <8%, 8 to <9%, 9 to 10%, and ≥10%, compared with 6 to <7% (reference), were 0.89 (0.59–1.36), 2.06 (1.31–3.24), 1.41 (0.73–2.74), and 3.43 (1.56–7.56), respectively; and graft failure–censored cardiovascular death HR was 0.38 (0.13–1.05), 1.78 (0.69–4.55), 1.59 (0.44–5.76), and 4.28 (0.85–21.64), respectively. We did not find any difference in risk of death–censored graft failure or DGF with different pretransplant HbA_{1c} levels.

CONCLUSIONS—Poor pretransplant glycemic control appears associated with decreased posttransplant survival in kidney transplant recipients, whereas allograft outcomes may not be affected.

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Diabetes is a potent cardiovascular risk factor in the general population as well as in those undergoing maintenance dialysis and kidney transplant recipients (1,2). Clinical trials have shown that tight glycemic control decreases the risk of developing retinopathy, nephropathy, and neuropathy in the general population (3,4). Furthermore, glycemic control, as measured by glycosylated hemoglobin (HbA_{1c}), is a predictor of cardiovascular

complications, including myocardial infarctions and hospitalizations for coronary artery disease (2). Expert groups have recommended that diabetic dialysis patients should follow the American Diabetes Association (ADA) guidelines; however, there is no consistent evidence to support these recommendations for patients with end-stage renal disease (5–7). In concordance with the ADA guidelines, the Kidney Disease Outcomes Quality

Initiative (K-DOQI) recommendations, last updated in 2007, state that “Target HbA_{1c} for people with diabetes should be <7%, irrespective of presence or absence of CKD” (8).

Large observational studies with differing methodologies reached somewhat contrasting conclusions regarding the association of glycemic control with survival in diabetic maintenance hemodialysis and peritoneal dialysis patients. Recently, a large randomized trial has indicated that intensive glucose lowering in patients with type 2 diabetes did not reduce the risks of cardiovascular disease, the most common source of end-stage renal disease mortality (9). Additionally, Williams et al. (10) reported a higher risk for death only in type 2 diabetic hemodialysis patients with HbA_{1c} levels >11% (11). Shurraw et al. (12) found higher casual glucose and HbA_{1c} levels were not associated with mortality in maintenance hemodialysis patients with or without diabetes. In contrast, we reported that after adjusting for potential confounders, higher HbA_{1c} values were incrementally associated with higher death risks in patients on maintenance dialysis (13). Furthermore, in peritoneal dialysis patients, only poor glycemic control (HbA_{1c} ≥8% and/or glucose ≥300 mg/dL) was incrementally associated with lower survival (14). Alas, mortality is only one measure of the deleterious impact of poor glycemic control. Other potential benefits of glycemic control include slowing the rate of progression of micro- and macrovascular disease, decreasing the presence of nonfatal strokes and myocardial infarctions, and slowing the rate progression of neuropathy. These factors have a strong impact on survival in kidney transplant recipients.

To the best of our knowledge, no study has examined the association between pretransplant glycemic control and either short-term outcome, such as delayed graft function (DGF), or long-term outcomes, such as mortality and graft failure after kidney transplantation. We hypothesized that higher pretransplant HbA_{1c} during the dialysis period prior to kidney transplantation is associated with

From the ¹Harold Simmons Center for Chronic Disease Research and Epidemiology, Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, Torrance, California; the ²Institute of Pathophysiology, Semmelweis University, Budapest, Hungary; the ³David Geffen School of Medicine at UCLA, Los Angeles, California; the ⁴Department of Epidemiology, UCLA School of Public Health, Los Angeles, California; ⁵DaVita, Inc., Denver, Colorado; the ⁶Division of Nephrology, Salem VA Medical Center, Salem, Virginia; and the ⁷Division of Nephrology, University of Virginia, Charlottesville, Virginia.

Corresponding author: Kamyar Kalantar-Zadeh, kamkal@ucla.edu.

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worse posttransplant patient and graft survival and with DGF in a large prospective cohort of incident kidney transplant recipients across the U.S.

RESEARCH DESIGN AND METHODS

Patients

We linked data on all kidney transplant recipients listed in the Scientific Registry of Transplant Recipients (SRTR) up to June 2007 to a list of individuals with chronic kidney disease (CKD) who underwent maintenance hemodialysis or peritoneal dialysis treatment from July 2001 to June 2006 in one of the outpatient dialysis facilities of a U.S.-based large dialysis organization (DaVita, Inc., prior to its acquisition of former Gambro dialysis facilities) using patients' social security numbers. The study was approved by the Institutional Review Boards of both Los Angeles Biomedical Research Institute at Harbor-UCLA and DaVita Clinical Research. Inclusion criteria were patients who had been undergoing dialysis for at least 90 days, had a history of diabetes, and had at least one HbA_{1c} measurement in the first quarter of entry into the cohort.

Clinical and demographic measures

The creation of the national DaVita dialysis patient cohort has been described previously (14,15). To minimize measurement variability, all repeated measures for each patient during any given calendar quarter, i.e., over a 13-week interval, were averaged, and the summary estimate was used in all models. Average values were obtained from up to 20 calendar quarters (q1–q20) for each laboratory and clinical measure for each patient for up to 6 years of follow-up. The first (baseline) studied quarter for each patient was the calendar quarter in which the patient's dialysis vintage was >90 days. Demographic data and details of medical history were collected, with information on age, sex, race, type of insurance, marital status, height, posthemodialysis dry weight (to calculate averaged BMI), and dialysis vintage. Dialysis vintage was defined as the duration of time between the first day of dialysis treatment and the day of kidney transplantation.

Laboratory measures

All HbA_{1c} values were measured using the Roche Cobar Integra 800 whole-blood immune-turbidimetric assay (standardized according to the Diabetes Complications

Control Trial/National Glycohemoglobin Standardization Program) performed by a single laboratory (DaVita Laboratory, Deland, FL). Most laboratory values were measured monthly, including serum urea, creatinine, albumin, calcium, phosphorus, bicarbonate, and total iron binding capacity. Serum ferritin and intact parathyroid hormone were measured at least quarterly. Hemoglobin was measured at least monthly in essentially all patients and weekly to biweekly in most patients. Most blood samples were collected predialysis, with the exception of postdialysis serum urea nitrogen to calculate urea kinetics. HbA_{1c} was usually measured quarterly or semiannually. We divided patients into seven a priori–defined categories based on HbA_{1c} values: <5%, ≥10%, and 1% increments in between, to examine the dose-response association between HbA_{1c} categories and outcome risk.

Statistical methods

Data were summarized using proportions, means (±SD) or medians, and interquartile ranges as appropriate. We examined *P* values for trends across HbA_{1c} categories. For all-cause and cardiovascular mortality and graft failure, defined as reinitiation of dialysis treatment or retransplantation, time to event was used in all survival analyses. For DGF, defined as the need for any dialysis therapy in the first week after transplantation, time to event was not accounted for. Survival analyses to calculate hazard ratio (HR) and 95% CI of death or graft failure used Cox proportional hazards regression. In the mortality analyses, the patients were followed until event (death) or censoring (graft failure or end of follow-up period), whichever happened first. Our uncensored, all-cause mortality analysis patients were followed until event (death) or censoring for end of follow-up period, whichever happened first. In the graft failure analyses, the patients were followed until event (graft failure) or censoring (death or end of follow-up period), whichever happened first. In the combined outcome analyses, patients were followed until event (death or graft failure) or censoring (end of follow-up period), whichever happened first. Logistic regression models were used to estimate the odds ratio and 95% CI of posttransplant DGF.

For each regression analysis, four levels of multivariate adjustment were examined: *I*) an unadjusted model that included HbA_{1c} categories (reference, HbA_{1c} 6 to <7%) as the predictor; *II*)

case mix–adjusted models that included the above plus age, sex, recipient race/ethnicity (African Americans and other self-categorized blacks, non-Hispanic whites, Asians, Hispanics, and others), dialysis vintage (<6 months, 6 months to 2 years, 2 to <5 years, and ≥5 years), primary insurance (Medicare, Medicaid, private, and others), marital status (married, single, divorced, widowed, and other or unknown), standardized mortality ratio of the dialysis clinic during entry quarter, dialysis dose as indicated by Kt/V (single pool), presence or absence of a hemodialysis catheter, residual renal function during the entry quarter and eight comorbidities (atherosclerotic heart disease, congestive heart failure, cancer, chronic obstructive pulmonary disease, cerebrovascular disease, hypertension, peripheral vascular disease, and tobacco use); *III*) malnutrition inflammation complex syndrome (MICS)–adjusted models, which included all of the above covariates plus 11 surrogates of nutritional status and inflammation measured during the last calendar quarter before transplantation, including BMI and 10 laboratory variables, i.e., normalized protein catabolic rate as an indicator of daily protein intake, also known as the normalized protein nitrogen appearance (nPNA), and serum or blood concentrations of total iron binding capacity, ferritin, phosphorus, calcium, bicarbonate, peripheral white blood cell count (WBC), lymphocyte percentage, albumin and hemoglobin; and *IV*) case mix–, MICS–, and transplant data–adjusted models included all of the above plus seven transplant-related variables: (1) donor type (deceased or living), (2) donor age, (3) donor sex, (4) panel-reactive antibody titer (last value prior to transplant), (5) number of HLA mismatches, (6) cold ischemia time, and (7) DGF (except when DGF was a dependent variable in our logistic regression models). Nonlinear association between pretransplant, time-averaged HbA_{1c} and posttransplant outcomes was assessed using fractional polynomials and restricted cubic splines. Based on goodness of fit of these models, we used a model with two degrees of freedom (knot in all models was 6.59). All analyses were carried out with SAS version 9.1 (SAS Institute, Inc., Cary, NC) and STATA version 11.1 (STATA Corporation, College Station, TX).

RESULTS—The original 5-year (July 2001–June 2006) national database of all DaVita patients included 164,789

adult subjects. Out of 65,386 DaVita patients who were identified in the SRTR database, 17,629 had undergone one or more kidney transplantations during their lifetime, of which 14,508 dialysis patients had undergone kidney transplantation for the first time. From these 14,508 dialyzed patients, we excluded patients without diabetes ($n = 9,482$) and patients who did not have HbA_{1c} measured ($n = 2,154$). We examined the remaining 2,872 patients who underwent first kidney transplantation during the observation period and who were followed until death, graft failure, loss of follow-up, or survival until 30 June 2007 (Supplementary Fig. 1). There were 331 deaths (11.5%) and 191 graft failures (6.7%) irrespective of subsequent deaths. The median follow-up time was 736 days (interquartile range, 353–1,216 days).

Table 1 shows the clinical, demographic and laboratory data of the 2,872 transplanted patients across seven categories of HbA_{1c}. Patients with higher HbA_{1c} were more likely to be women and to be younger, and to have lower dialysis duration, lower serum creatinine level, and higher WBC level. The crude rates of mortality, graft failure, and DGF were not different between the groups (Table 2).

Supplementary Table 1 shows the calculated HRs of all-cause and cardiovascular death and/or graft failure for different HbA_{1c} categories. Case mix-, MICS-, and transplant data-adjusted graft failure censored all-cause death HRs and 95% CIs for time-averaged pretransplant HbA_{1c} categories of 7 to <8%, 8 to <9%, 9 to 10%, and $\geq 10\%$, compared with 6 to <7% (reference), were 0.89 (0.59–1.36), 2.06 (1.31–3.24), 1.41 (0.73–2.74), and 3.43 (1.56–7.56), respectively. Fig. 1A shows cubic spline models for the association of the entire range of pretransplant HbA_{1c} with posttransplant mortality consistent with the findings in Supplementary Table 1. Similar trends were found for cardiovascular death. Fully adjusted cardiovascular death HRs and 95% CIs for time-averaged pretransplant HbA_{1c} categories of 7 to <8%, 8 to <9%, 9 to 10%, and $\geq 10\%$, compared with 6 to <7% (reference), were 0.38 (0.13–1.05), 1.78 (0.69–4.55), 1.59 (0.44–5.76), and 4.28 (0.85–21.64), respectively. Similar results were found when we adjusted for variables in fully adjusted model plus erythropoiesis-stimulating agent dose as sensitivity analysis (data not shown).

Fig. 1B shows cubic spline models for the association of the entire range of pretransplant HbA_{1c} with posttransplant uncensored, all-cause mortality that were consistent with the findings in Supplementary Table 1. Fig. 1C shows cubic spline models for the association of the entire range of pretransplant HbA_{1c} with posttransplant cardiovascular mortality that were consistent with the findings in Supplementary Table 1. Fig. 1D shows cubic spline models for the association of the entire range of pretransplant HbA_{1c} with posttransplant graft failure, again consistent with the findings in Supplementary Table 1. We did not find any difference in the risk of all-cause death-censored graft failure with different pretransplant HbA_{1c} levels.

To examine the association of pretransplant HbA_{1c} levels with posttransplant DGF, multivariate logistic regression analyses were performed using the same covariates as in the Cox models. Compared with HbA_{1c} levels between 6 and <7%, patients with HbA_{1c} levels <5%, 5 to <6%, 7 to <8%, 8 to <9%, 9 to 10%, and $\geq 10\%$ had similar risks of DGF (Supplementary Table 1).

CONCLUSIONS—In 2,872 kidney transplant recipients with comprehensive pretransplant data during hemodialysis treatment who were followed for up to 6 years posttransplantation, poor glycemic control appears to be associated with higher all-cause and cardiovascular mortality. Pretransplant HbA_{1c} level was not a predictor of either posttransplant graft failure or DGF. These findings may have important clinical implications, especially since they imply mild hyperglycemia during the dialysis period may not be a risk factor for negative posttransplant short-term and long-term outcomes.

It is currently not known what the ideal level of glycemic control is in dialysis patients (16,17). The literature on the relationship between glycemic control and survival in CKD populations is somewhat limited. In a cohort of 840 nondiabetic patients with moderate CKD who participated in the Modification of Diet in Renal Disease trial, HbA_{1c} was a predictor of all-cause mortality (18). However, a recent study was unable to demonstrate any association between HbA_{1c} and 1-year survival (7). This contrasts with several other observational studies. Wu et al. (19) studied 137 hemodialysis patients with type 2 diabetes and reported that the cumulative survival was lower in the

group with poor glycemic control (13). In kidney transplant recipients, pretransplant diabetes, maximal glucose levels, and insulin treatment were independently associated with higher rates of mortality (1). However, until now, it has been unclear if poor glycemic control during the dialysis period affected posttransplant outcomes.

Based on our analyses, pretransplant, time-averaged HbA_{1c} levels $\geq 8\%$ were associated with increased all-cause and cardiovascular mortality. There are several possible mechanisms that might explain the relationship between poor glycemic control during the dialysis period and worse posttransplant survival of kidney transplant recipients. Diabetes after transplantation is a predictor of mortality in some (20), but not all, studies (1). It is also associated with different risk factors of mortality, such as higher infection rates or other diabetes complications (21). Poor glycemic control might induce macrovascular complications, possibly secondary to the generation of advanced glycation end products, and hence shorten the survival of these patients. Moreover, in renal transplant recipients, high HbA_{1c} is associated with chronic inflammation (22), and the latter is a predictor of mortality and graft failure (23).

In our contemporary study, the pretransplant HbA_{1c} level was not a predictor of posttransplant graft failure or DGF. Similar results were found in studies conducted in kidney transplant recipients that examined new-onset diabetes after transplantation, which was not a predictor of graft loss in some studies (24). A potential explanation for the lack of association between poor pretransplant and posttransplant glycemic control and increased risk of allograft loss is the relatively short follow-up time. Poor glycemic control is associated with micro- and macrovascular complication, but the development of these complications in the allografts may take >6 years. It is possible that studies with longer follow-up time may find significant associations between poor glycemic control and graft loss.

Our study should be qualified for several potential limitations. Like all observational studies, ours too cannot prove causality. Repeated posttransplant measures of HbA_{1c} or other laboratory variables and immunosuppressive and other medical regimens were not available in the SRTR database, but in the full model, we did adjust for a number of transplant-related variables. A potential limitation of our study is

Table 1—Baseline characteristics of 2,872 dialysis patients who underwent renal transplantation between July 2001 and June 2006

	HbA _{1c}										P for trend
	<5	5 to <6	6 to <7	7 to <8	8 to <9	9 to <10	≥10				
N (%)	171 (6)	708 (25)	873 (30)	591 (20)	315 (11)	154 (5)	60 (2)	NA			
Age (years) (mean ± SD)	52 ± 13	55 ± 10	55 ± 10	54 ± 10	50 ± 11	48 ± 12	46 ± 11	<0.001			
Sex (% women)	41	33	35	34	40	45	45	0.01			
Race (% African American)	24	26	23	23	18	27	35	0.07			
BMI (kg/m ²) (mean ± SD)	27.3 ± 5.3	28.3 ± 5.0	28.5 ± 5.6	28.2 ± 5.5	27.0 ± 5.6	27.6 ± 5.4	26.8 ± 5.7	0.004			
Presence of ischemic heart disease (%)	7	16	17	16	14	14	15	0.06			
Presence of congestive heart failure (%)	12	15	17	21	18	18	15	0.09			
Presence of hypertension (%)	78	84	80	81	81	82	77	0.49			
Presence of cerebrovascular events (%)	1	4	4	4	3	4	10	0.10			
Presence of peripheral vascular disease (%)	5	7	9	8	7	8	10	0.78			
Presence of chronic obstructive pulmonary disease (%)	2	2	1	2	1	1	0	0.76			
Presence of cancer (%)	4	2	1	1	2	1	0	0.35			
Tobacco use (%)	4	4	3	4	3	5	8	0.24			
Dialysis vintage (%)								0.002			
0–6 months	11	8	9	8	9	13	18	—			
6–24 months	24	30	30	32	32	31	40	—			
2–5 years	37	42	45	43	43	36	25	—			
>5 years	27	20	16	17	16	20	17	—			
nPCR (g/kg/day) (mean ± SD)	1.01 ± 0.27	1.07 ± 0.27	1.06 ± 0.25	1.06 ± 0.26	1.04 ± 0.25	1.00 ± 0.22	0.99 ± 0.24	0.06			
Serum creatinine (mg/dL) (mean ± SD)	9.8 ± 2.9	9.8 ± 3.0	9.2 ± 2.9	9.1 ± 2.8	8.8 ± 2.6	8.9 ± 2.8	8.3 ± 2.4	<0.001			
Blood hemoglobin (g/dL) (mean ± SD)	12.1 ± 1.4	12.3 ± 1.2	12.3 ± 1.2	12.3 ± 1.2	12.3 ± 1.1	12.3 ± 1.2	12.5 ± 1.1	0.13			
WBC (×10 ³ /L) (mean ± SD)	6.4 ± 1.9	6.9 ± 2.1	7.1 ± 2.1	7.3 ± 2.1	7.4 ± 2.2	7.3 ± 1.9	7.3 ± 1.8	<0.001			
Number of HLA mismatch (median [IQR])	4 (3–5)	4 (2–5)	4 (3–5)	4 (2–5)	4 (2–5)	4 (2–5)	4 (3–5)	0.26			
PRA >80% (%)	7	3	4	5	4	5	4	0.39			
PRA (%) (median [IQR])	0 (0–6)	0 (0–0)	0 (0–1)	0 (0–0)	0 (0–1)	0 (0–2)	0 (0–4)	0.63			
Donor age (years) (mean ± SD)	39 ± 14	41 ± 16	41 ± 16	41 ± 15	39 ± 15	38 ± 15	37 ± 17	0.005			
Donor sex (% women)	44	50	49	49	45	48	41	0.49			
Donor type (% living)	34	28	31	30	32	34	45	0.15			
Cold ischemia time (hours) (median [IQR])	14 (7–19)	14 (9–20)	14 (7–20)	14 (9–20)	14 (7–19)	14 (8–20)	14 (3–15)	0.40			

Data are presented as mean ± SD or median and interquartile range (IQR) as appropriate. nPCR, normalized protein catabolic rate; PRA, panel-reactive antibody.

Table 2—Outcomes of 2,872 dialysis patients who underwent renal transplantation between July 2001 and June 2006

	HbA _{1c}							P for trend
	<5	5 to <6	6 to <7	7 to <8	8 to <9	9 to <10	≥10	
Deaths (n) [crude death rate %]	23 [13]	87 [12]	91 [10]	63 [11]	41 [13]	16 [10]	10 [17]	0.55
CV deaths (n) [crude CV death rate %]	6 [4]	16 [2]	23 [3]	10 [2]	10 [3]	3 [2]	3 [5]	0.56
Graft failure (n) [crude graft failure rate %]	15 [9]	42 [6]	54 [6]	39 [7]	23 [7]	14 [9]	4 [7]	0.70
DGF (n) [crude DGF %]	32 [20]	177 [26]	208 [24]	136 [24]	82 [27]	29 [19]	12 [20]	0.39

Values in brackets indicate the crude death and cardiovascular death rate, crude graft failure rate, and crude DGF rate in the indicated group during the 6 years of observation. CV, cardiovascular.

that HbA_{1c} is not a good reflection of blood glucose levels in individuals with advanced chronic kidney disease. It may be difficult to accurately assess glycemic control in this population because of changes in erythrocyte survival in renal failure and the effects of erythropoiesis-stimulating agents on HbA_{1c} levels (25). We did not have access to data pertaining to death after graft loss, which is another important outcome. Patients who did not have measured

HbA_{1c} were excluded from the analyses. The excluded patients may have been different from those included in our study, which may have biased our results. We have tested this hypothesis and the only clinically significant difference was in the number of graft failures (Supplementary Table 2). The proportion of graft failures was more than twice higher in excluded patients than the group included. It is possible that the lower HbA_{1c} levels in the included

patients were the reason why we did not detect any association between high HbA_{1c} level and graft failure. To our knowledge this is the first study examining the association between pretransplant HbA_{1c} levels and posttransplant short- and long-term outcomes. Strengths of this study include the high number of patients, the relatively long follow-up time, and multilevel adjustment, which includes several important pretransplant measures.

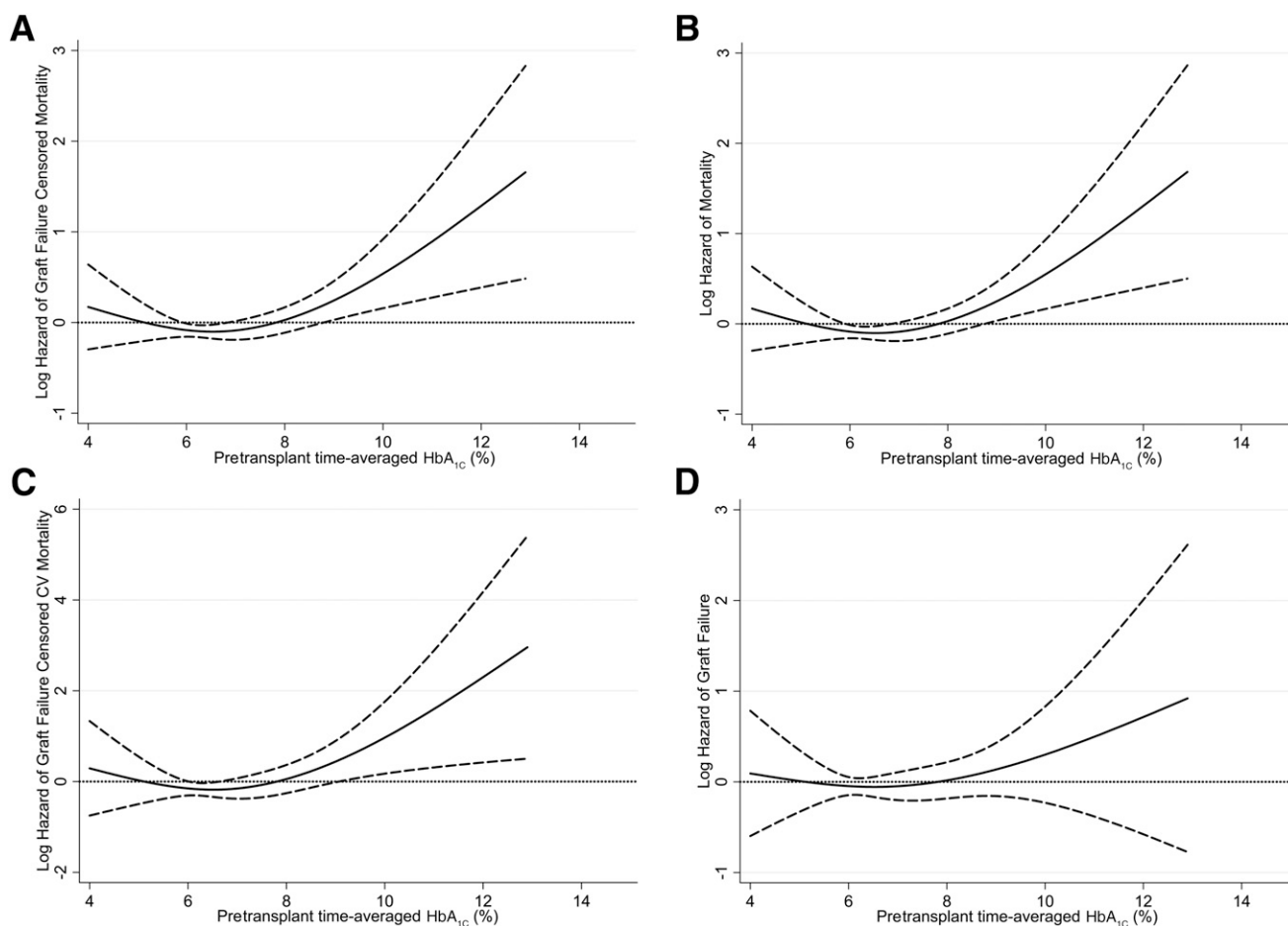


Figure 1—HR (95% CI) of posttransplant, graft failure–censored all-cause death (A), posttransplant, all-cause death (B), posttransplant, graft failure–censored cardiovascular death (C), and death–censored graft failure (D) across the entire range of the pretransplant, time-averaged HbA_{1c} using fully adjusted Cox regression analyses in 2,872 long-term hemodialysis transplant patients who underwent renal transplantation and who were observed over a 6-year observation period (July 2001–June 2007).

In our large and contemporary national database of 2,872 kidney transplant recipients, a pretransplant, time-averaged HbA_{1c} \geq 8% appears to be associated with higher all-cause and cardiovascular mortality. Pretransplant HbA_{1c} levels were not predictive of posttransplant graft failure or DGF. Clinical trials are needed to better define optimal target HbA_{1c} levels in dialysis patients.

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M.Z.M. contributed to analyzing and interpreting data and writing the manuscript. E.H., J.H., M.K., and A.R.N. contributed to analyzing and interpretation of data. C.P.K. contributed to analyzing and interpretation of data and writing the manuscript. K.K.-Z. designed, organized, and coordinated the study; managed data entry; contributed to data analysis and interpretation of data; and wrote the manuscript.

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