A1C and Survival in Maintenance Hemodialysis Patients

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OBJECTIVE — The optimal target for glycemic control has not been established in diabetic dialysis patients.

RESEARCH DESIGN AND METHODS — To address this question, the national database of a large dialysis organization (DaVita) was analyzed via time-dependent survival models with repeated measures.

RESULTS — Of 82,933 patients undergoing maintenance hemodialysis (MHD) in DaVita outpatient clinics over 3 years (July 2001 through June 2004), 23,618 diabetic MHD patients had A1C measurements at least once. Unadjusted survival analyses indicated paradoxically lower death hazard ratios (HRs) with higher A1C values. However, after adjusting for potential confounders (demographics, dialysis vintage, dose, comorbidity, anemia, and surrogates of malnutrition and inflammation), higher A1C values were incrementally associated with higher death risks. Compared with A1C in the 5–6% range, the adjusted all-cause and cardiovascular death HRs for A1C ≥10% were 1.41 (95% CI 1.25–1.60) and 1.73 (1.44–2.08), respectively ($P < 0.001$). The incremental increase in death risk for rising A1C values was monotonic and robust in nonanemic patients (hemoglobin >11.0 g/dl). In subgroup analyses, the association between A1C >6% and increased death risk was more prominent among younger patients, those who had undergone dialysis for >2 years, and those with higher protein intake (>1 $g \cdot kg^{-1} \cdot day^{-1}$), blood hemoglobin (>11 g/dl), or serum ferritin values (>500 ng/ml).

CONCLUSIONS — In diabetic MHD patients, the apparently counterintuitive association between poor glycemic control and greater survival is explained by such confounders as malnutrition and anemia. All things equal, higher A1C is associated with increased death risk. Lower A1C levels not related to malnutrition or anemia appear to be associated with improved survival in MHD patients.

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Patients with chronic kidney disease (CKD) stage 5 undergoing maintenance dialysis treatment have a high mortality, currently over 20% per year in the U.S. and mainly attributed to cardiovascular disease (1). However, in observational studies of dialysis populations, most traditional cardiovascular risk factors, including metabolic syndrome components such as hyperlipidemia and obesity, do not exhibit conventional association with mortality (2). Indeed, obesity and hyperlipidemia appear to be paradoxically associated with better survival (3–5). The strong association between indicators of good nutrition and improved survival is thought to be an important etiology for the counterintuitive cardiovascular constellations observed in the CKD population (2,6).

Diabetes is a consequence of the metabolic syndrome and a strong cardiovascular risk factor (7). Even though the annual incidence of diabetes at the start of dialysis has shown less growth in recent years (8), diabetes comprises almost one-half of all causes of end-stage CKD in the U.S. dialysis population (1,9). Several studies indicate higher comorbidity and poorer outcome in diabetic dialysis patients compared with nondiabetic subjects (1,10–12). Tight glycemic control as measured by A1C levels (e.g., <6 or 7%) decreases the risk of developing retinopathy, nephropathy, and neuropathy in the general population (13,14). A1C is a powerful predictor of cardiovascular complications, including myocardial infarctions and hospitalizations for coronary artery disease (7,15). Despite the foregoing supportive data, there have been very few studies to examine the association between A1C and clinical outcome in the dialysis population (16–20). All of these studies but one (20) had small sample sizes (≤150 subjects). Three of these studies (16,17,19) were performed exclusively in Asian dialysis populations. In a recent study by Williams et al. (20) in 24,875 U.S. diabetic dialysis patients, no correlation between A1C and survival at 12 months was found. This finding has led to confusion and serious questions about the role of glycemic control and utility of A1C in diabetic dialysis patients, who comprise almost one-half of all dialysis patients in the U.S. (21). It was suggested that the guidelines of glycemic control for individuals without advanced CKD may not apply to the dialysis population (20,21).

Given the known associations between glycemic control and survival in the non-CKD diabetic population and the confounding role of nutrition and anemia in dialysis survival, we hypothesized that the underlying association between A1C and survival in dialysis patients is similar

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Abbreviations: AGE, advanced glycation end product; CKD, chronic kidney disease; MHD, maintenance hemodialysis; MICS, malnutrition-inflammation complex syndrome; USRDS, U.S. Renal Data System.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

to that of the general population if appropriately controlled for confounders. We sought to explore the underlying nature of these associations in a large and contemporary national database of dialysis patients using time-dependent repeated-measures models.

RESEARCH DESIGN AND METHODS

We extracted, refined, and examined data from all individuals with CKD stage 5 who underwent maintenance hemodialysis (MHD) treatment from July 2001 through June 2004 in 1 of the 580 outpatient dialysis facilities of DaVita, a large dialysis organization in the U.S. The study was approved by relevant institutional review committees; because of the large sample size, the anonymity of the patients studied, and the nonintrusive nature of the research, the requirement for a written consent form was exempted.

Clinical and demographic measures

The creation of the cohort has been described previously (5,22). 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 estimates used in all models. Averaged values were obtained for up to 12 calendar quarters (q1 through q12) for each laboratory and clinical measure for each patient over the 3-year cohort period. Dialysis vintage was defined as the duration of time between the 1st day of dialysis treatment and the 1st day the patient entered the cohort. The first (baseline) studied quarter for each patient was the calendar quarter in which patient's vintage was >90 days during at least half of the time of that given quarter.

Thirteen-week averaged postdialysis weight and baseline height were used to calculate BMI (weight in kilograms divided by the square of height in meters). The dose of administered recombinant human erythropoietin (rHuEPO, EPOGEN; Amgen, Thousand Oaks, CA) was also calculated for each calendar quarter (23). The computerized causes of death were obtained, and cardiovascular death was defined as death due to myocardial infarction, cardiac arrest, heart failure, cerebrovascular accident, and other cardiac causes.

In addition to the presence or absence of diabetes, histories of tobacco smoking and preexisting comorbid conditions were obtained by linking the DaVita database to the Medical Evidence Form 2728 of the U.S. Renal Data System (USRDS) (24) and categorized into 10 comorbid conditions: ischemic heart disease, congestive heart failure, status post–cardiac arrest, status post–myocardial infarction, pericarditis, cardiac dysrhythmia, cerebrovascular events, peripheral vascular disease, chronic obstructive pulmonary disease, and cancer.

Blood samples were drawn using uniform techniques in all dialysis clinics and were transported to the DaVita Laboratory in Deland, Florida, within 24 h. All laboratory values, including A1C, were measured by automated and standardized methods. Most laboratory values were measured monthly. Hemoglobin was measured at least monthly in all patients and weekly to biweekly in most patients. A1C was usually measured semiannually or quarterly. Kt/V was used to estimate dialysis dose, and normalized protein equivalent of total nitrogen appearance, also known as normalized protein catabolic rate, was measured monthly as a measure of daily protein intake. Most blood samples were collected predialysis with the exception of the postdialysis serum urea nitrogen to calculate urea kinetics.

Epidemiologic and statistical methods

Survival analyses including Kaplan-Meier, log-rank tests, and time-dependent Cox proportional hazard regressions with repeated quarterly measures examined whether the 3-year survival rates were associated with A1C. For each analysis, three models were examined based on the level of multivariate adjustment, as follows: *1*) unadjusted model that included mortality data, A1C categories, and entry calendar quarter (q1 through q12); *2*) case-mix adjusted models that included all of the above plus age, sex, race and ethnicity (African Americans and other self-categorized blacks, non-Hispanic Caucasians, Asians, Hispanics, and others), diabetes, 10 preexisting comorbid states, history of tobacco smoking, categories of dialysis vintage (<6 months, 6 months to 2 years, 2–5 years, and ≥5 years), primary insurance (Medicare, Medicaid, private, and other), 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 dialysis catheter, and residual renal function during the entry quarter, i.e., urinary urea clearance; and *3*) malnutrition-inflammation complex syndrome (MICS)-adjusted models that included all of the covariates in the case-mix model as well as 13 surrogates of nutritional status and inflammation, including BMI, rHuEPO dose, and 11 laboratory surrogates of MICS with known association with clinical outcomes in MHD patients (5) including total nitrogen appearance, serum levels of albumin, total iron-binding capacity, ferritin, creatinine, phosphorus, calcium, and bicarbonate and blood white blood cell count, lymphocyte percentage, and hemoglobin.

Missing covariate data (under 2% for most laboratory and demographic variables and under 18% for any of the 10 comorbid conditions) were imputed by the mean or median of the existing values, whichever was most appropriate. All descriptive and multivariate statistics were carried out with SAS version 9.1 (SAS Institute, Cary, NC) and Stata version 9.0 (Stata, College Station, TX).

RESULTS

— The original 3-year (July 2001 through June 2004) national database of all DaVita MHD patients included 102,255 cumulative subjects. After deleting those patients who did not maintain beyond 45 days of hemodialysis treatment, 82,933 MHD patients remained for analyses, of whom 37,049 patients (45%) originated from the first calendar quarter dataset (q1) and the rest from the subsequent calendar quarters (q2 through q12).

Table 1 shows baseline demographic, clinical, and laboratory characteristics of the studied MHD patients during the baseline calendar quarter; 23,618 patients had diabetes and at least one A1C measurement. Of the 56,771 patients who did not have any A1C testing, 24% also carried an original diagnosis of diabetes. The BMI was higher and serum albumin and creatinine levels were lower in those whose A1C was measured, indicating that diabetic MHD patients tended to be more obese but with worse nutritional status. Among bivariate associations examined, A1C had negative correlations with age ($r = -0.25$), serum creatinine ($r = -0.10$), and prescribed rHuEPO dose ($r = -0.10$), suggesting that younger patients and those with reduced muscle mass tended to have higher A1C values.

We divided A1C values into seven a priori selected categories, i.e., <5%, ≥10%, and 1% increments in between. Figure 1 shows 3-year death hazard ratios (HRs) according to the A1C values at three multivariate adjustment levels.

Table 1—*Demographic, clinical, and laboratory characteristics in 82,958 MHD patients during the 3-year cohort (July 2001 to June 2004, i.e., 12 calendar quarters) including 23,618 diabetic MHD patients who underwent A1C measurement*

Variable	Patients with diabetes and A1C values	Patients without A1C values
n	23,618	56,771
Age (years)	63 ± 13	60 ± 17
Sex (% women)	50	44
Diabetes as the cause of ESRD (%)	100	24
Race/ethnicity (%)		
Caucasian	37	41
Black	30	32
Hispanic	19	13
Vintage (time on dialysis, %)		
3–6 months	32	27
6–24 months	18	15
2–5 years	21	19
>5 years	30	40
Primary insurance		
Medicare (%)	67	64
Known causes of death		
Cardiovascular (% of all-cause)*	52	50
Infectious (% of all-cause)†	13	13
Standardized mortality ratio‡	0.81 ± 0.27	0.80 ± 0.29
BMI (kg/m^2)	27.7 ± 6.4	26.0 ± 5.9
Kt/V (single pool)	1.5 ± 0.3	1.5 ± 0.3
nPCR or nPNA (g · kg^{-1} · day^{-1})	1.0 ± 0.3	1.0 ± 0.3
Serum albumin (g/dl)	3.67 ± 0.40	3.76 ± 0.45
Creatinine (mg/dl)	7.8 ± 2.8	9.2 ± 3.5
Ferritin (ng/ml)	445 (281)	466 (300)
TIBC (mg/dl)	205 ± 43	203 ± 45
Bicarbonate (mg/dl)	21.9 ±2.8	21.8 ± 3.0
Phosphorus (mg/dl)	5.6 ± 1.4	5.7 ± 1.6
Calcium (mg/dl)	9.2 ± 0.7	9.3 ± 0.8
Blood hemoglobin (g/dl)	12.1 ± 1.2	12.0 ± 1.4
WBC count (×10^3/μl)	7.5 ± 2.3	7.3 ± 2.5
Lymphocyte (% of total WBC count)	20 ± 7	21 ± 8

Data are means ± SD for continuous values if normally distributed and median (interquartile range) if skewed and represent 13-week average measurements during the baseline (first calendar) quarter. $P < 0.001$ for the difference between the two groups, unless otherwise specified; *$P = 0.01$; †$P > 0.05$; ‡$P = 0.03$. ESRD, end-stage renal disease; nPCR, normalized protein catabolic rate; nPNA, normalized protein nitrogen appearance; TIBC, total iron-binding capacity; WBC, white blood cell.

Case-mix adjustment led to a striking alteration in the direction of the associations, in that a significant upward trend in death risk was observed for A1C values >6% (P for trend <0.001). Fully adjusted all-cause death HRs (95% CIs) for A1C increments of 7–7.9, 8–8.9, 9–9.9, and ≥10%, compared with 5.0–5.9%, were 1.08 (1.01–1.15), 1.13 (1.04–1.24), 1.18 (1.05–1.33), and 1.41 (1.25–1.60), respectively. The adjusted cardiovascular death HR (95% CI) for A1C ≥10% was 1.73 (1.44–2.08).

We also performed subgroup analyses to examine the existence of interaction between anemia and A1C. In 19,306 or 82% of diabetic MHD patients, blood hemoglobin was >11.0 g/dl, consistent with the target anemia treatment (25). Figure 2 shows the same analyses as in Fig. 1 for nonanemic (*A*) and anemic (*B*) MHD patients. Among nonanemic patients, A1C >6% was incrementally and monotonically associated with increased death risk, whereas in anemic patients the association did not show said pattern.

After dichotomizing A1C values at 6% threshold level in the unadjusted model, the 3-year death HR (95% CI) for all-cause mortality for having an A1C >6% in all MHD patients was 0.87 (0.82–0.89, $P < 0.001$). However, after multivariate adjustment, the death HR was 1.05 (1.01–1.10, $P = 0.04$), showing that the counterintuitive association between higher values of A1C and increased death risk in unadjusted models was due to the confounding effect of demographic and clinical factors. Subsequent subgroup analyses were performed to examine the statistical interaction by estimating the 3-year HRs of death for A1C ≥6% among relevant demographic, clinical, and laboratory categories of MHD patients (Fig. 3). A similar reversal of the direction of the associations was observed in most categories. The association between high A1C and increased cardiovascular death risk was more prominent among MHD patients who were younger than 65 years, who had undergone dialysis for >2 years, and who had higher protein intakes (>1 g · kg^{-1} · day^{-1}), higher hemoglobin levels (>11 g/dl), or higher serum ferritin values (>500 ng/ml).

CONCLUSIONS — We found that in 23,618 MHD patients from a large national dialysis organization, lower A1C values appeared associated with higher mortality rates. However, after adjusting for potential confounders, higher A1C values were incrementally associated with increased death risks. The association between higher A1C values and mortality was more prominent and monotonous among younger patients, those who had undergone dialysis longer, and those with higher protein intake, blood hemoglobin, or serum ferritin levels. Hence, in diabetic MHD patients, the apparently counterintuitive association or lack of any obvious association between the poor glycemic control and greater survival appears to be mostly due to confounding by demographics, anemia, and nutritional factors. These findings may have important clinical implications, especially since they imply that glycemic control is beneficial for this population as long as a decreased A1C is not a result of malnutrition, anemia, or other confounders.

Diabetes constitutes a major health problem among CKD patients and is currently the leading cause of end-stage (stage 5) CKD (1). In the non-CKD population, glycemic control is fundamental to the management of diabetes and its complications and requires serial monitoring of blood glucose or A1C. Improved glycemic control has been reported to

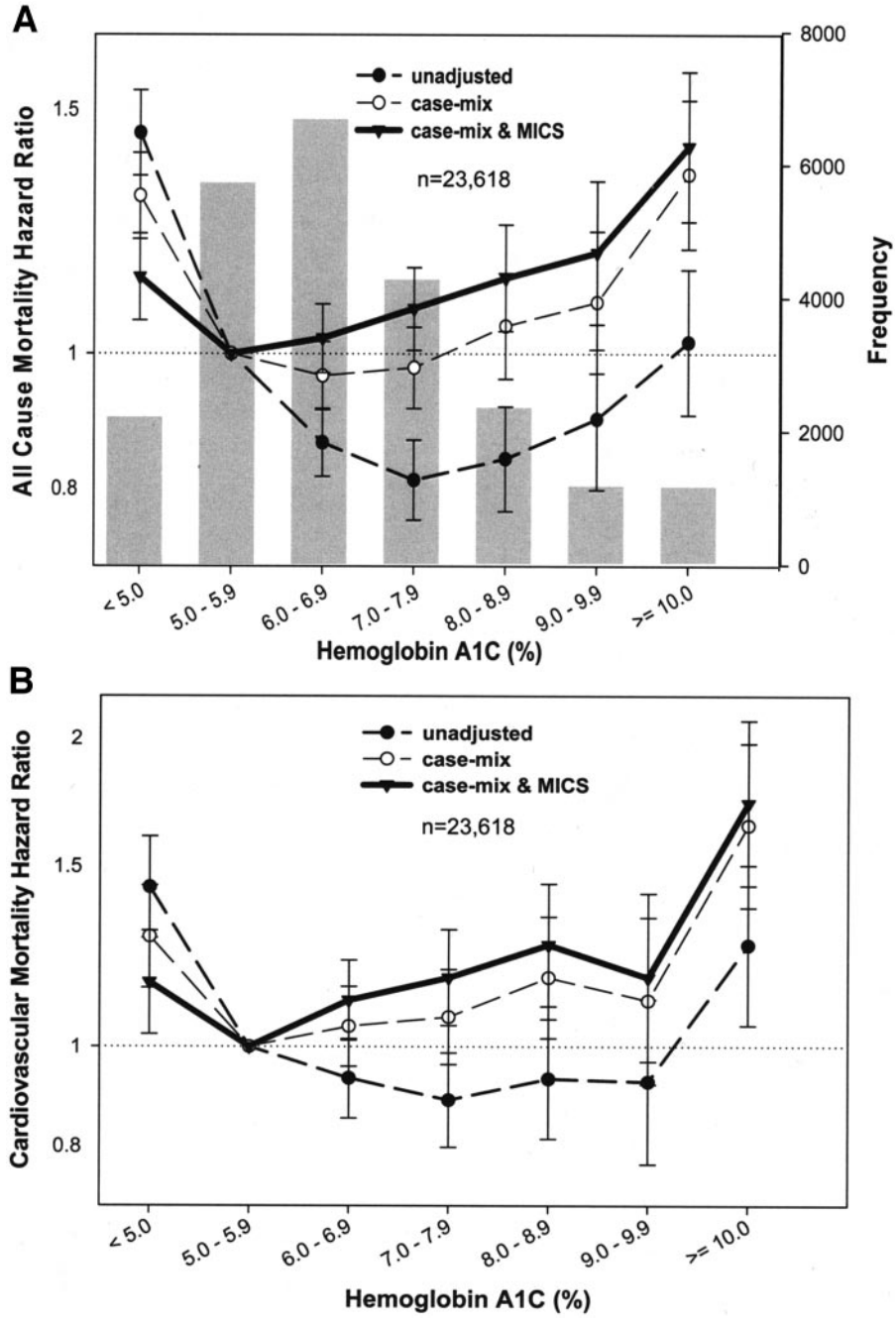

Figure 1—*HRs of all-cause* (A) *and cardiovascular* (B) *mortality for the entire range of A1C in 23,618 diabetic MHD patients over 3 years (July 2001 through June 2004). Case-mix model is adjusted for age, sex, race/ethnicity, preexisting comorbid states, tobacco smoking, dialysis vintage, primary insurance, marital status, standardized mortality ratio, dialysis dose, dialysis catheter, and residual renal function. MICS-adjusted model includes all of the case-mix covariates as well as BMI, average dose of rHuEPO, and 11 laboratory variables of nutrition and inflammation.*

slow the progression of nephropathy (14,26). Diabetes is also an established risk factor for cardiovascular disease, which is the main cause of death in CKD patients (7). Crude mortality of maintenance dialysis patients is currently 21–23% per year in the U.S., a mortality rate that is worse than most cancers at the dawn of the 21st century (27).

According to our current study, the degree of glycemic control appears associated with mortality in a direct, incremental fashion. The adjusted associations between higher A1C and increased death risk (Fig. 1) indicate a dose-response phenomenon, especially after adjustment for demographics and markers of nutrition and inflammation. Of major clinical interest is the interaction between anemia and mortality predictability of A1C (Fig. 2).

Glycosylated hemoglobin, also known as A1C, is an Amadori-modified protein or a type of advanced glycation end product (AGE), a measure of chronic hyperglycemia, and a sensitive and reliable marker of impaired glucose metabolism (26,28,29). Some studies have shown A1C to be a predictor of future CVD events in the general population (7,30), whereas others have found no such association (31). Other potential measures of long-term glycemic control such as fructosamine depend on normal serum albumin levels, which are frequently abnormal in dialysis patients (32).

The literature concerning the relation between glycemic control and survival in the CKD population is somewhat limited. In a cohort of 840 nondiabetic patients with moderate CKD, who participated in the Modification of Diet in Renal Disease trial, A1C was a predictor of all-cause mortality (33). Wu et al. (16) studied 137 MHD patients with type 2 diabetes and reported that cumulative survival rates were lower in the poor glycemic control group than in the good glycemic control group (16). In another observational study in 114 diabetic MHD patients in Japan, the 7.5-year death risk of patients with A1C ≥8% was higher than in those with A1C <6.5% (19). However, a recent study using a large national database did not indicate any association between A1C and 1-year survival in 24,875 MHD patients from Fresenius dialysis clinics in the U.S. (20). Even though the lack of a survival association or trend in the foregoing study could be due to the short-term follow-up and other methodological differences including use of traditional and non–time-dependent survival models and lack of stratified analyses to detect interactions, this study has led to some confusion among both physicians and patients about the role of glycemic control in dialysis patients (21).

It is important to note that in a recent observational study, higher AGE levels in 312 MHD patients were found to be paradoxically associated with better survival over 32 months of follow-up (34). Another cohort study found a paradoxically inverse association between A1C and survival in chronic heart failure patients (35). The authors explained their counterintuitive finding as yet another manifestation of "reverse epidemiology," in which the dominating role of malnutrition and ca-

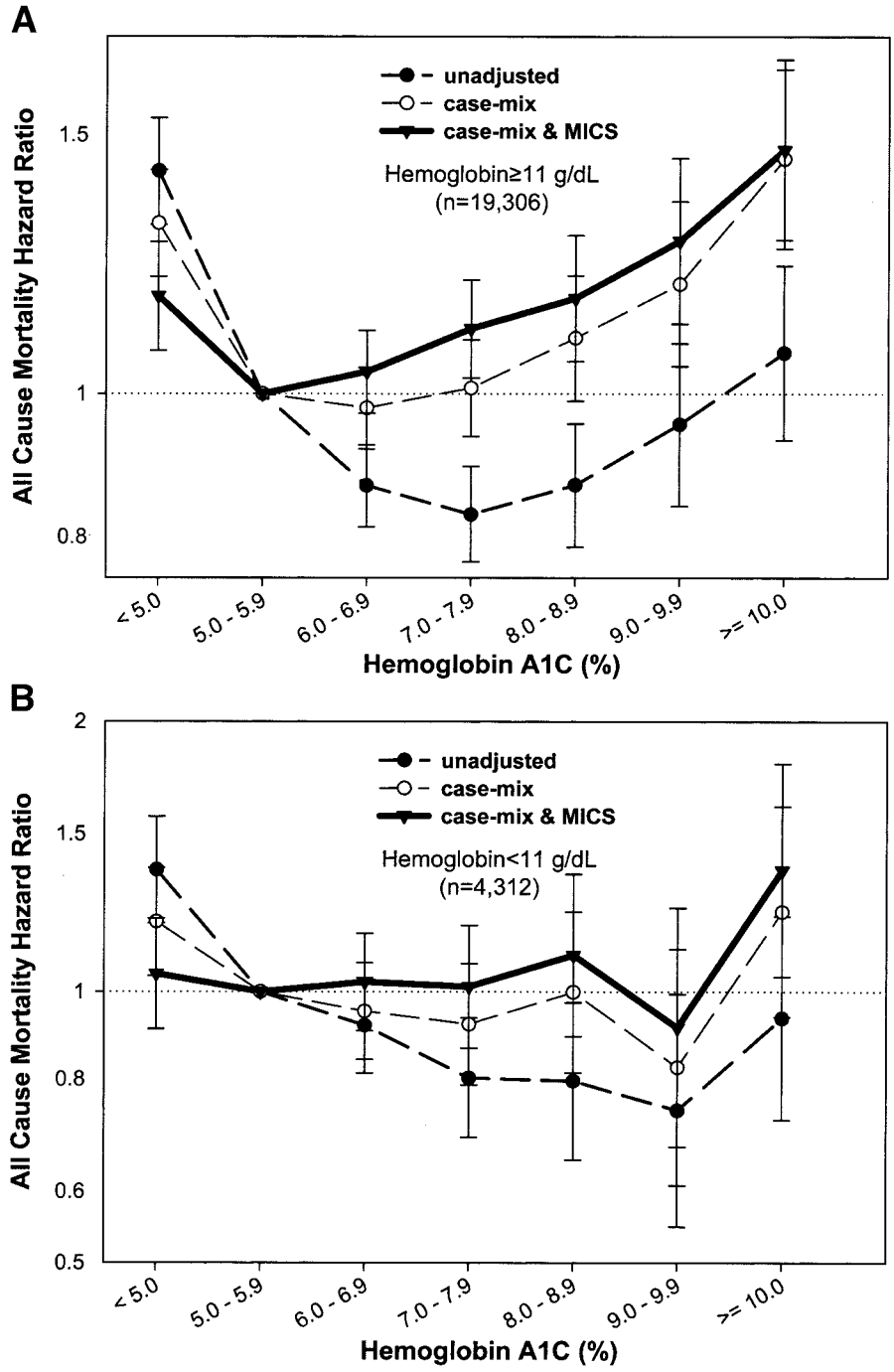

Figure 2—*HRs of all-cause mortality for the entire range of A1C in 19,306 diabetic MHD patients with blood hemoglobin ≥11.0 g/dl* (A) *and 4,312 diabetic MHD patients with hemoglobin <11 g/dl* (B) *over 3 years (July 2001 through June 2004). Case-mix model is adjusted for age, sex, race/ethnicity, preexisting comorbid states, tobacco smoking, dialysis vintage, primary insurance, marital status, standardized mortality ratio, dialysis dose, dialysis catheter, and residual renal function. MICS-adjusted model includes all of the case-mix covariates as well as BMI, average dose of rHuEPO, and 11 laboratory variables of nutrition and inflammation.*

chexia in leading to short-term mortality may overwhelm the impact of conventional risk factors (36). Whether the benefit of high serum AGEs in these types of observational studies is an epiphenomenon or reflects a better nutritional support needs further study. In this regard, an interesting finding in our analyses was the stronger association between high A1C and increased all-cause and cardiovascular death risk among younger patients, those who had undergone dialysis for >2 years, and those with higher protein intake ($>1\ g \cdot kg^{-1} \cdot day^{-1}$), higher hemoglobin (>11 g/dl), or higher serum ferritin values (>500 ng/ml). These findings may indicate the possible interaction of factors related to nutrition, inflammation, and anemia with indexes of glycemic control. Hence, an unusually low A1C <5% in dialysis patients may herald the existence of other risk factors such as malnutrition with associated increased death risk (Figs. 1 and 2).

Our study was limited to comorbidity data from the dialysis initiation form (form 2728), in which comorbid conditions are significantly underreported (24). Moreover, we did not have the data on insulin or oral hypoglycemic agents and their doses, and we did not study patient compliance with diabetes treatment. However, the required dose of these medications can be confounded by the residual renal function and its deterioration over time (18). Another potential limitation is lack of explicit laboratory markers of inflammation such as C-reactive protein. However, we used data on serum albumin, ferritin, total iron-binding capacity, white blood cells, lymphocyte percentage, hemoglobin, and administered rHuEPO dose, which have significant associations with inflammation in MHD patients (5). Our study is based on a 3-year period of the cohort, rather than a longitudinal follow-up of many years, and cannot be generalized to peritoneal dialysis patients. Nonetheless, over half of dialysis patients are dead within 3 years. Hence, any insight into the short-term survival of dialysis patients is of major clinical relevance. Additional tests of glycemic monitoring such as serial blood glucose levels were not examined in our study. In dialysis patients, predialysis treatment blood glucose may not optimally represent the average level of serum glucose, whereas A1C is a better tool to that end. The strengths of our study include contemporary nature, uniform laboratory measurements from one single laboratory, large sample size, 3-month averaged laboratory data, and use of time-dependent survival models.

In conclusion, we showed that tight glycemic control in CKD patients who undergo MHD may be associated with better survival, especially among certain subgroups of these patients. Our results may have implications not only for the management of diabetic MHD patients but also for the nondiabetic patient on dialysis. Since insulin resistance is com-

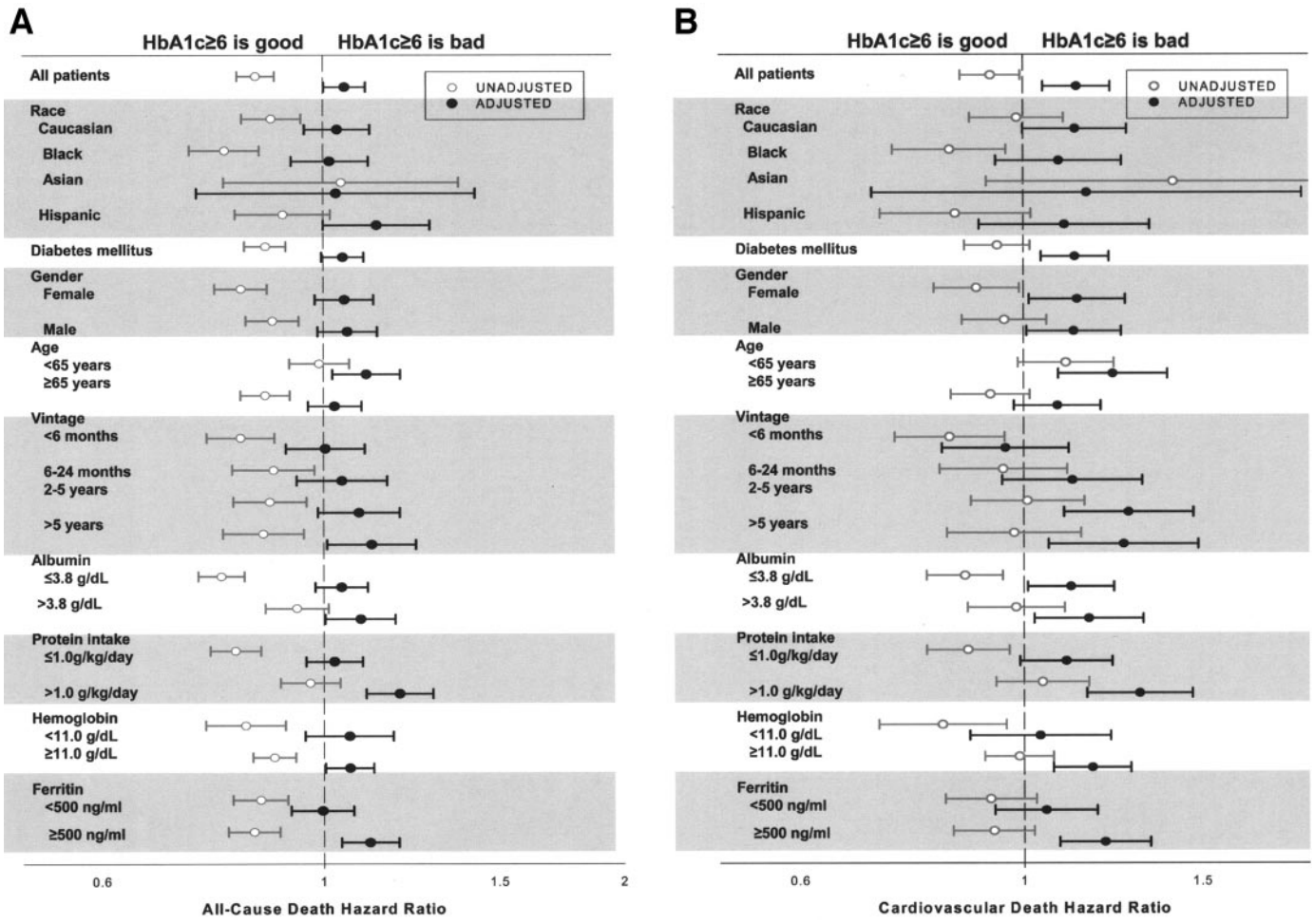

Figure 3—*HRs of all-cause* (A) *and cardiovascular* (B) *mortality for the dichotomized A1C ≥6% in different subgroups of 23,618 MHD patients over 3 years. Adjusted model is controlled for age, sex, race/ethnicity, preexisting comorbid states, tobacco smoking, dialysis vintage, primary insurance, marital status, standardized mortality ratio, dialysis dose, dialysis catheter, residual renal function, BMI, average dose of rHuEPO, and 11 laboratory variables of nutrition and inflammation.*

mon in the CKD population, there may be an effect of glycemic control on survival in this population as well. Diligent glycemic control may be an effective measure to improve survival in CKD. More prospective, controlled studies are needed to verify the true relationships between different methods of diabetes management and outcome in MHD patients.

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