

Hemoglobin A1c and Survival in Maintenance Hemodialysis Patients

Received for publication 16 October 2006 and accepted in revised form 13 February 2007.

Running Head: HbA1c and Dialysis Survival

Kamyar Kalantar-Zadeh, MD PhD MPH^{1,2}; Joel D Kopple, MD^{2,3}; Deborah L Regidor, MPH^{1,3};
Jennie Jing, MS¹; Christian S Shinaberger, MPH^{1,3}; Jason Aronovitz, DO⁴;
Charles J McAllister, MD⁴; David Whellan, MD MPH⁵; Kumar Sharma, MD⁶

- (1) Harold Simmons Center for Kidney Disease Research and Epidemiology, and
- (2) Division of Nephrology and Hypertension, Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, and David Geffen School of Medicine at UCLA, Torrance, CA 90502;
- (3) UCLA School of Public Health, Department of Epidemiology, Los Angeles, CA;
- (4) DaVita, Inc, El Segundo, CA 90245;
- (5) Division of Cardiology, and
- (6) Center for Novel Therapies for Kidney Disease, Dorrance Hamilton Research Laboratories , Thomas Jefferson University, Philadelphia, PA 19107

Correspondence:

Kamyar Kalantar-Zadeh, MD PhD MPH
Division of Nephrology and Hypertension, Harbor-UCLA Medical Center
1124 West Carson Street, C1-Annex, Torrance, CA 90509-2910
E-mail: kamkal@ucla.edu

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 yrs (7/01-6/04), 23,618 diabetic MHD patients had hemoglobin A1c (HbA1c) measurements at least once. Unadjusted survival analyses indicated paradoxically lower death hazard ratios (HR) with higher HbA1c values. However, after adjusting for potential confounders (demographics, dialysis vintage and dose, comorbidity, anemia and surrogates of malnutrition and inflammation), higher HbA1c values were incrementally associated with higher death risks. Compared to HbA1c in 5-6% range, the adjusted all-cause and cardiovascular death HR for HbA1c \geq 10% was 1.41 (95% confidence interval [CI]: 1.25-1.60) and 1.73 (95%CI: 1.44-2.08), respectively (p<0.001). The incremental increase in death risk for rising HbA1c values was monotonic and robust in non-anemic patients (Hb>11.0 g/dL). In subgroup analyses, the association between HbA1c>6% and increased death risk was more prominent among younger patients, those who had undergone dialysis >2 yrs, and those with higher protein intake (>1 gm/kg/day), 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 HbA1c is associated with increased death risk. Lower HbA1c levels not related to malnutrition or anemia appears associated with improved survival in MHD patients.

Introduction

Patients with chronic kidney disease (CKD) stage 5 undergoing maintenance dialysis treatment have a high mortality, currently over 20% per year in the USA and mainly attributed to cardiovascular disease.(1) However, in observational studies of dialysis populations most traditional cardiovascular risk factors, including such metabolic syndrome components as hyperlipidemia and obesity, do not exhibit conventional association with mortality.(2) Indeed, obesity and hyperlipidemia appear 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 mellitus (DM) is a consequence of the metabolic syndrome and a strong cardiovascular risk factor.(7) Even though the annual incidence of DM at the start of dialysis has shown less growth in recent years,(8) DM comprises almost half of all causes of end-stage CKD in the US dialysis population.(1; 9) Several studies indicate higher comorbidity and poorer outcome in diabetic dialysis patients as compared to non-diabetic subjects.(1; 10-12) Tight glycemic control as measured by hemoglobin A1c (HbA1c) levels (e.g. <6% or <7%) decreases the risk of developing retinopathy, nephropathy and neuropathy in the general population.(13; 14) HbA1c is a powerful predictor of cardiovascular complications, including myocardial infarctions and hospitalizations for coronary artery disease.(7; 15) Despite the foregoing data supporting, there have been very few studies to examine the association between HbA1c and clinical outcome in the dialysis population.(16-20). All of this studies but one (20) have small sample sizes (≤ 150 subjects). Three of these studies (16; 17; 19) are performed exclusively in Asian dialysis populations. In the recent study by Williams et al (20) in 24,875 US diabetic dialysis patients no correlation between HbA1c

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 HbA1c in diabetic dialysis patients, who comprise almost half of all dialysis patients in the US.(21) It was suggested that the guidelines of glycemic controls for individuals without advanced CKD may not apply to dialysis population.(20; 21)

Given the known associations between glycemic control and survival in non-CKD diabetic population and the confounding role of nutrition and anemia in dialysis survival, we hypothesized that the underlying association between HbA1c and survival in dialysis patients is similar to the general population if it is 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. .

Methods

Patients

We extracted, refined, and examined data from all individuals with chronic kidney disease (CKD) stage 5, who underwent maintenance hemodialysis (MHD) treatment from July 2001 to June 2004 in one of the 580 outpatient dialysis facilities of DaVita, a large dialysis organization in the US. The study was approved by relevant Institutional Review Committees; because of the large sample size, the anonymity of the patients studied, and the non-intrusive nature of the research, the requirement for 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 estimate was 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 first day of dialysis treatment and the first day that 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 post-dialysis weight and baseline height were used to calculate the body mass index ($BMI = \text{weight}[\text{kg}] / \text{height squared}[\text{m}^2]$). The dose of administered recombinant human erythropoietin (rHuEPO, EPOGEN™, Amgen, Inc, 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 DM, histories of tobacco smoking and preexisting comorbid conditions were obtained by linking the DaVita database to the Medical Evidence Form 2728 of the United States Renal Data System (USRDS) (24) and categorized into 10 comorbid conditions: ischemic heart disease, congestive heart failure, status post cardiac arrest, s/p myocardial infarction, pericarditis, cardiac dysrhythmia, cerebrovascular events, peripheral vascular disease, chronic obstructive pulmonary disease, and cancer.

Laboratory Measures

Blood samples were drawn using uniform techniques in all dialysis clinics and were transported to the DaVita Laboratory in Deland, Florida, within 24 hrs. All laboratory values, including HbA1c, 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 bi-weekly in most patients. HbA1c was usually measured semi-annually or quarterly. Kt/V was used to estimate

dialysis dose and normalized protein equivalent of total nitrogen appearance (nPNA), also known as normalized protein catabolic rate (nPCR), were measured monthly as a measure of daily protein intake. Most blood samples were collected pre-dialysis with the exception of the post-dialysis 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 HbA1c. For each analysis, three models were examined based on the level of multivariate adjustment:

(I) Unadjusted model that included mortality data, HbA1c categories and entry calendar quarter (q1 through q12);

(II) Case-mix adjusted models that included all of the above plus age, gender, race and ethnicity (African Americans and other self-categorized Blacks, Non-Hispanic Caucasians, Asians, Hispanics and others), diabetes mellitus and 10 pre-existing comorbid states, history of tobacco smoking, categories of dialysis vintage (<6 mos, 6 mos to 2 yrs, 2-5 yrs and ≥ 5 yrs), primary insurance (Medicare, Medicaid, private and others), marital status (married, single, divorced, widowed and other or unknown), the 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

(III) Malnutrition-inflammation-complex syndrome (MICS) adjusted models which 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 nPNA, serum levels of albumin, TIBC, 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 the SAS, version 9.1, SAS Institute, Inc., Cary, North Carolina, and Stata version 9.0, Stata Corporation, College Station, Texas.

Results

The original 3-year (7/2001-6/2004) 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 DM and at least one HbA1C measurement. Of the 56,771 patients who did not have any HbA1c testing, 24% also carried an original diagnosis of DM. The BMI was higher and serum albumin and creatinine levels were lower in those whose HbA1c was measured, indicating that diabetic MHD patients tended to be more obese but with worse nutritional status. Among bivariate associations examined, HbA1c 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 HbA1C values.

We divided HbA1c values into 7 *a priori* selected categories, i.e., <5%, >=10%, and 1% increments inbetween. Figure 1 shows 3-year death hazard ratios according to the HbA1c

values at 3 multivariate adjustment levels. 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 HbA1c values above 6% (p trend <0.001). Fully adjusted all-cause death hazard ratio (HR) and 95% confidence interval (95% CI) for HbA1c increments of 7-7.9%, 8-8.9%, 9-9.9% and $\geq 10\%$, compared to 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). The adjusted cardiovascular death HR for HbA1c $\geq 10\%$ was 1.73 (1.44-2.08).

We also performed subgroup analyses to examine the existence of interaction between anemia and HbA1c. 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 Figure 1 for non-anemic (upper panel) and anemic (lower panel) MHD patients. Among non-anemic patients, HbA1c>6% was incrementally and monotonically associated with increased death risk whereas in anemic patients the association did not show the said pattern.

After dichotomizing HbA1c values at 6% threshold level in the unadjusted model, the 3-year death HR (and 95% CI) for all-cause mortality for having a HbA1c>6% in all MHD patients was 0.87 (0.82-0.89, $p<0.001$). However, after multivariate adjustment, the death hazard ratio was 1.05 (1.01-1.10, $p=0.04$), showing that the counterintuitive association between higher values of HbA1c 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 hazard ratios of death for the HbA1c>=6% among relevant demographic, clinical, and laboratory categories of MHD patients (Figure 3). A similar reversal of the direction of the associations was observed in most categories. The association between high HbA1c and increased cardiovascular death risk was more prominent among MHD patients who

were younger than 65 years, who had undergone dialysis >2 yrs, and who had higher protein intakes (>1 gm/kg/day), higher hemoglobin levels (>11 g/dl), or higher serum ferritin values (>500 ng/ml).

Discussion

We found that in 23,618 MHD patients from a large national dialysis organization, lower HbA1c values appeared associated with higher mortality rates. However, after adjusting for potential confounders, higher HbA1c values were incrementally associated with increased death risks. The association between higher HbA1c 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 HbA1c is not a result of malnutrition, anemia or other confounders.

DM 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 DM and its complications, and requires serial monitoring of blood glucose or HbA1c. Improved glycemic control has been reported to slow the progression of nephropathy (14; 26). DM 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 to 23% per year in the United States, 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 HbA1c and increased death risk (Figure 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 HbA1c (Figure 2).

Glycosylated hemoglobin, also known as HbA_{1c}, 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 HbA_{1c} to be a predictor of future CVD events in the general population (7; 30), whereas others have found no such association(31). Other potential measure 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 non-diabetic patients with moderate CKD, who participated in the *Modification of Diet in Renal Disease* trial HbA1c was a predictor of all-cause mortality (33). Wu et al (16) studied 137 MHD patients with type II DM and reported that cumulative survival rates were lower in the poor glycemic control group than in the good glycemic group (16). In another observational study in 114 diabetic MHD patients in Japan, the 7.5 year death risk of patients with HbA1c ≥8% was higher than those with HbA1c <6.5% (19). However, a recent study using a large national database did not indicate any association between HgbA1c and one-year survival in 24,875 MHD patients from Fresenius dialysis clinics in the United States(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 HbA1c 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 cachexia 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 HbA1c and increased all-cause and cardiovascular death risk among younger patients, those who had undergone dialysis >2 yrs, and those with higher protein intake (>1 gm/kg/day), 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 indices of glycemic control. Hence, an unusually low HbA1c <5% in dialysis patients may herald the existence of other risk factors such as malnutrition with associated increased death risk (Figures 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, nor did we study patient compliance with DM 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 and TIBC, blood WBC, lymphocyte percentage, hemoglobin, and administered rHuEPO dose, which have significant associations with inflammation in MHD patients (5). Our study is based on 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 sugars were not examined in our study. In dialysis patients, pre-dialysis treatment blood sugar may not optimally represent the average level of serum glucose, whereas HbA1c 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 non-diabetic patient on dialysis. Since insulin resistance is common 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 DM management and outcome in MHD patients.

Funding Source:

The study was supported by research grants from American Heart Association grant (#0655776Y), Philanthropist Mr. Harold Simmons (KKZ), and clinical research grants from DaVita (KKZ and KS)

Acknowledgement:

The abstract of this paper was presented orally during the American Society of Nephrology (ASN) annual conference, November 12-16, 2006, in San Diego, CA. Parts of these data were supplied by the USRDS and the findings do not represent the opinion of the U.S. government or the USRDS.

Coauthors' contribution:

KKZ contributed to the design and funding of the study, collation and analysis of data, and writing of the manuscript and its revisions. CSS, DLR and RDK contributed to the analysis of the data and reviewed and approved the final manuscript. CJM contributed to the design of the study, provision of data, and final review and approval of the manuscript. JDK, SG, DW and KS contributed to the study design and manuscript preparation.

References:

1. United States Renal Data System: Excerpts from the USRDS 2005 Annual Data Report: Atlas of End-Stage Renal Disease in the United States, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, . *Am J Kid Dis* 47, Supplement 1:1-286, 2006
2. Kalantar-Zadeh K, Block G, Humphreys MH, Kopple JD: Reverse epidemiology of cardiovascular risk factors in maintenance dialysis patients. *Kidney Int* 63:793-808, 2003
3. Kalantar-Zadeh K, Abbott KC, Salahudeen AK, Kilpatrick RD, Horwich TB: Survival advantages of obesity in dialysis patients. *Am J Clin Nutr* 81:543-554, 2005
4. Kalantar-Zadeh K, Kopple JD, Kilpatrick RD, McAllister CJ, Shinaberger CS, Gjertson DW, Greenland S: Association of morbid obesity and weight change over time with cardiovascular survival in hemodialysis population. *Am J Kidney Dis* 46:489-500, 2005
5. Kilpatrick RD, McAllister CJ, Kovesdy CP, Derose SF, Kopple JD, Kalantar-Zadeh K: Association between Serum Lipids and Survival in Hemodialysis Patients and Impact of Race. *J Am Soc Nephrol* 18:293-303, 2007
6. Kalantar-Zadeh K, Ikizler TA, Block G, Avram MM, Kopple JD: Malnutrition-inflammation complex syndrome in dialysis patients: Causes and consequences. *Am J Kidney Dis* 42:864-881, 2003
7. Gaede P, Vedel P, Larsen N, Jensen GV, Parving HH, Pedersen O: Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. *N Engl J Med* 348:383-393, 2003
8. Friedman EA, Friedman AL, Eggers P: End-stage renal disease in diabetic persons: Is the pandemic subsiding? *Kidney Int Suppl*:S51-54, 2006
9. Broumand B: Diabetes: changing the fate of diabetics in the dialysis unit. *Blood Purif* 25:39-47, 2007
10. Friedman EA: Renal syndromes in diabetes. *Endocrinol Metab Clin North Am* 25:293-324, 1996
11. Abbott KC, Bakris GL: Treatment of the diabetic patient: focus on cardiovascular and renal risk reduction. *Prog Brain Res* 139:289-298, 2002
12. Kimmel PL, Varela MP, Peterson RA, Weihs KL, Simmens SJ, Alleyne S, Amarashinge A, Mishkin GJ, Cruz I, Veis JH: Interdialytic weight gain and survival in hemodialysis patients: effects of duration of ESRD and diabetes mellitus. *Kidney Int* 57:1141-1151, 2000
13. Warram JH, Manson JE, Krolewski AS: Glycosylated hemoglobin and the risk of retinopathy in insulin-dependent diabetes mellitus. *N Engl J Med* 332:1305-1306, 1995
14. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. *N Engl J Med* 329:977-986, 1993
15. Chaturvedi N, Fuller JH: Glycosylated hemoglobin and the risk of microalbuminuria in insulin-dependent diabetes mellitus. EURODIAB IDDM Complications Study Group. *N Engl J Med* 333:940-941, 1995
16. Wu MS, Yu CC, Yang CW, Wu CH, Haung JY, Hong JJ, Fan Chiang CY, Huang CC, Leu ML: Poor pre-dialysis glycaemic control is a predictor of mortality in type II diabetic patients on maintenance haemodialysis. *Nephrol Dial Transplant* 12:2105-2110, 1997
17. Morioka T, Emoto M, Tabata T, Shoji T, Tahara H, Kishimoto H, Ishimura E, Nishizawa Y: Glycemic control is a predictor of survival for diabetic patients on hemodialysis. *Diabetes Care* 24:909-913, 2001
18. McMurray SD, Johnson G, Davis S, McDougall K: Diabetes education and care management significantly improve patient outcomes in the dialysis unit. *Am J Kidney Dis* 40:566-575, 2002
19. Oomichi T, Emoto M, Tabata T, Morioka T, Tsujimoto Y, Tahara H, Shoji T, Nishizawa Y: Impact of glycemic control on survival of diabetic patients on chronic regular hemodialysis: a 7-year observational study. *Diabetes Care* 29:1496-1500, 2006
20. Williams ME, Lacson E, Jr., Teng M, Ofsthun N, Lazarus JM: Hemodialyzed type I and type II diabetic patients in the US: Characteristics, glycemic control, and survival. *Kidney Int* 70:1503-1509, 2006

21. Feldt-Rasmussen B: Is there a need to optimize glycemic control in hemodialyzed diabetic patients? *Kidney Int* 70:1392-1394, 2006
22. Kalantar-Zadeh K, Kilpatrick RD, McAllister CJ, Greenland S, Kopple JD: Reverse epidemiology of hypertension and cardiovascular death in the hemodialysis population: the 58th annual fall conference and scientific sessions. *Hypertension* 45:811-817, 2005
23. Kalantar-Zadeh K, McAllister CJ, Lehn RS, Lee GH, Nissenson AR, Kopple JD: Effect of malnutrition-inflammation complex syndrome on EPO hyporesponsiveness in maintenance hemodialysis patients. *Am J Kidney Dis* 42:761-773, 2003
24. Longenecker JC, Coresh J, Klag MJ, Levey AS, Martin AA, Fink NE, Powe NR: Validation of comorbid conditions on the end-stage renal disease medical evidence report: the CHOICE study. Choices for Healthy Outcomes in Caring for ESRD. *J Am Soc Nephrol* 11:520-529., 2000
25. National Kidney Foundation I, Kidney-Dialysis Outcome Quality Initiative: K/DOQI Clinical Practice Guidelines: Anemia. *Am J Kidney Dis* 37 (suppl 1), 2001
26. Tanaka Y, Atsumi Y, Matsuoka K, Onuma T, Tohjima T, Kawamori R: Role of glycemic control and blood pressure in the development and progression of nephropathy in elderly Japanese NIDDM patients. *Diabetes Care* 21:116-120, 1998
27. Kalantar-Zadeh K, Abbott KC, Kronenberg F, Anker SD, Horwich TB, Fonarow GC: Epidemiology of dialysis patients and heart failure patients. *Semin Nephrol* 26:118-133, 2006
28. Testa MA, Simonson DC, Turner RR: Valuing quality of life and improvements in glycemic control in people with type 2 diabetes. *Diabetes Care* 21, 1998
29. Friedman EA: Advanced glycation end-products in diabetic nephropathy. *Nephrol Dial Transplant* 14 Suppl 3:1-9, 1999
30. Khaw KT, Wareham N, Luben R, Bingham S, Oakes S, Welch A, Day N: Glycated haemoglobin, diabetes, and mortality in men in Norfolk cohort of european prospective investigation of cancer and nutrition (EPIC-Norfolk). *Bmj* 322:15-18, 2001
31. Blake GJ, Pradhan AD, Manson JE, Williams GR, Buring J, Ridker PM, Glynn RJ: Hemoglobin A1c level and future cardiovascular events among women. *Arch Intern Med* 164:757-761, 2004
32. Lamb E, Venton TR, Cattell WR, Dawney A: Serum glycated albumin and fructosamine in renal dialysis patients. *Nephron* 64:82-88, 1993
33. Menon V, Greene T, Pereira AA, Wang X, Beck GJ, Kusek JW, Collins AJ, Levey AS, Sarnak MJ: Glycosylated hemoglobin and mortality in patients with nondiabetic chronic kidney disease. *J Am Soc Nephrol* 16:3411-3417, 2005
34. Schwedler SB, Metzger T, Schinzel R, Wanner C: Advanced glycation end products and mortality in hemodialysis patients. *Kidney Int* 62:301-310, 2002
35. Eshaghian S, Horwich TB, Fonarow GC: An unexpected inverse relationship between HbA1c levels and mortality in patients with diabetes and advanced systolic heart failure. *Am Heart J* 151:91, 2006
36. Kalantar-Zadeh K, Block G, Horwich T, Fonarow GC: Reverse epidemiology of conventional cardiovascular risk factors in patients with chronic heart failure. *J Am Coll Cardiol* 43:1439-1444, 2004

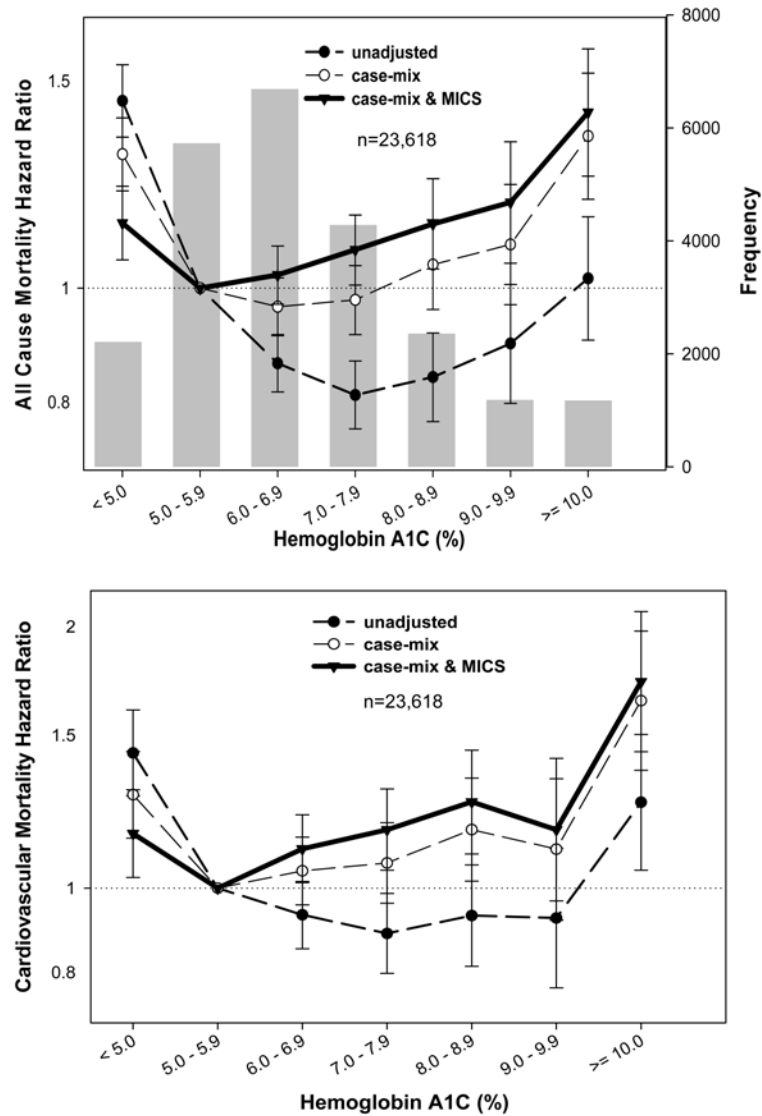
Table 1: Demographic, clinical and laboratory characteristics in 82,958 MHD patients during the 3-year cohort (July 2001 to June 2004, i.e., 12 calendar quarters) including 23,618 diabetic MHD patients who underwent HbA1c measurement. Data represent 13-week average measurements during the baseline (first calendar) quarter.

Variable	Patients with DM and HbA1c values n=23,618	Patients without HbA1C N=56,771
Age (years)	63±13	60±17
Gender (% women)	50	44
DM as the cause of ESRD (%)	100	24
Race/ethnicity (%):		
Caucasians	37	41
Blacks	30	32
Hispanics	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) ^b	52	50
Infectious (% of all-cause) ^c	13	13
Standardized mortality ratio ^d	0.81±0.27	0.80±0.29
Body mass index (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/day)	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 (x10 ³ / μ l)	7.5±2.3	7.3±2.5
Lymphocyte (% of total WBC count)	20±7	21±8

^aCount data are in percentage, and continuous values are in mean±SD if normally distributed or median(IQR) if skewed. P value <0.001 for the difference between the two groups, unless otherwise specified. ^bP = 0.01 ^cP>0.05 ^dP=0.03

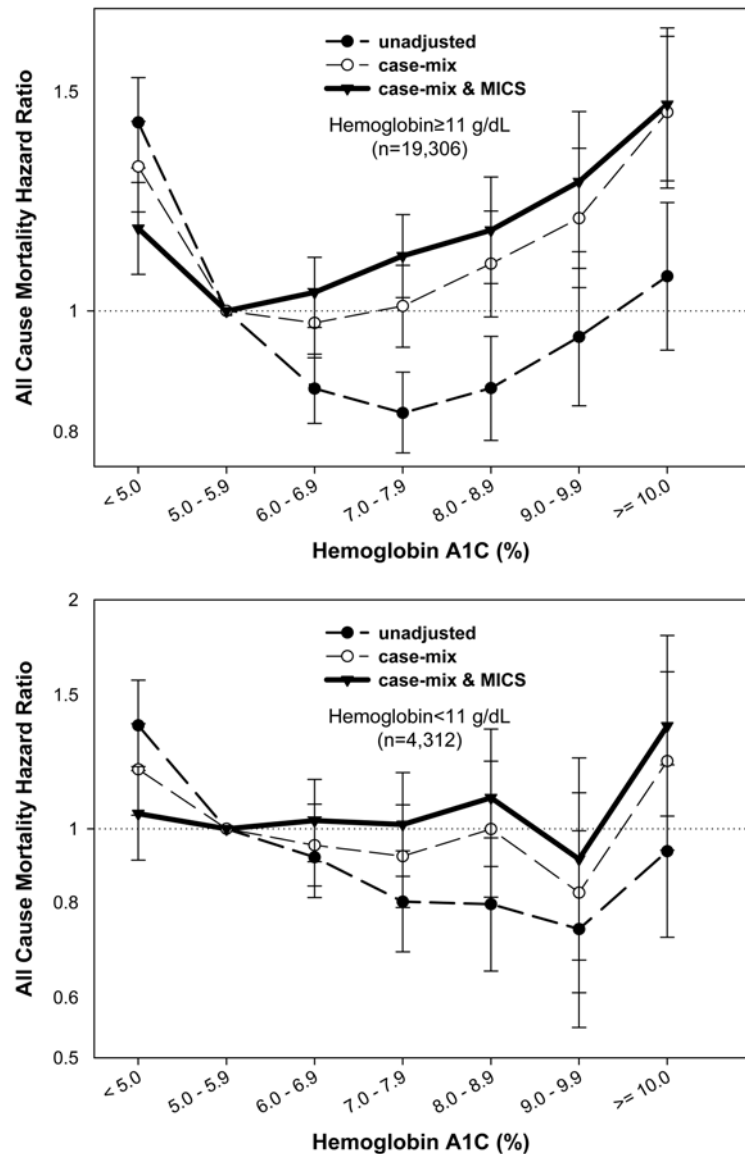
Figure legends:

Figure 1: Hazard ratio of all-cause (upper panel) and cardiovascular (lower panel) mortality for the entire range of HbA1c in 23,618 diabetic MHD patients over 3 years (July 2001- June 2004)



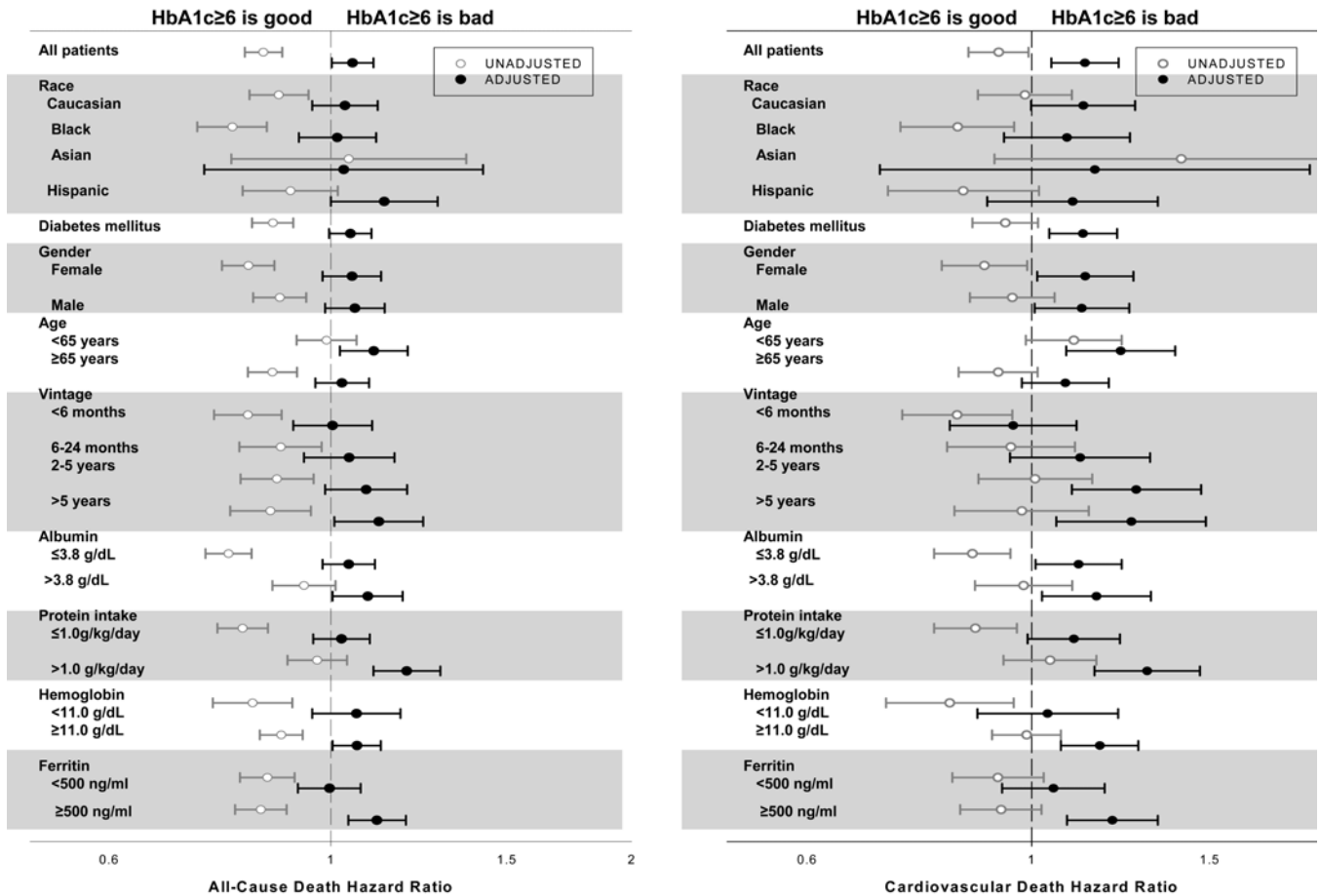
Footnote: Case-mix model is adjusted for age, gender, race/ethnicity, pre-existing comorbid states, tobacco smoking, dialysis vintage, primary insurance, marital status, standardized mortality ratio, dialysis dose, dialysis catheter, and residual renal function. Malnutrition-inflammation-complex syndrome (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.

Figure 2: Hazard ratio of all-cause mortality for the entire range of HbA1c in 19,306 diabetic MHD patients with blood hemoglobin (Hb) ≥ 11.0 g/dL (upper panel) and 4,312 diabetic MHD patients with Hb < 11 g/dL (lower panel) over 3 years (July 2001- June 2004)



Footnote: Case-mix model is adjusted for age, gender, race/ethnicity, pre-existing comorbid states, tobacco smoking, dialysis vintage, primary insurance, marital status, standardized mortality ratio, dialysis dose, dialysis catheter, and residual renal function. Malnutrition-inflammation-complex syndrome (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.

Figure 3: Hazard ratio of all-cause (left panel) and cardiovascular (right panel) mortality for the dichotomized HbA1c \geq 6% in different subgroups of 23,618 MHD patients over 3 years.



Footnote: Adjusted model is controlled for age, gender, race/ethnicity, pre-existing 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.