Glycemic Control and Extended Hemodialysis Survival in Patients with Diabetes Mellitus: Comparative Results of Traditional and Time-Dependent Cox Model Analyses

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Background and objectives: The benefits and risks of aggressive glycemic control in diabetes mellitus complicated by end-stage kidney failure remain uncertain but have importance because of the large patient population with inferior overall prognosis. Recent large observational studies with differing methodologies reached somewhat contrasting conclusions regarding the association of hemoglobin A1c with survival in diabetic chronic hemodialysis patients.

Design, setting, participants, & measurements: This study supplements the authors’ previous analysis (which found no correlation) by extending the follow-up period to 3 years and using time-dependent survival models with repeated measures. Among 24,875 nationally distributed study patients, 94.5% had type 2 diabetes, allowing additional analysis in the subset with type 1 diabetes. Data were collected at baseline and every quarter to a maximum of 3 years’ follow-up.

Results: Adjusted standard and time-dependent Cox models indicated that only extremes of glycemia were associated with inferior survival. There was no effect modification by serum albumin levels, a marker of protein nutrition status, and no trend associated with random glucose measurements in a post hoc analysis. In type 1 diabetic patients, upper extreme hemoglobin A1c values indicated lower survival risk.

Conclusions: Sustained extremes of glycemia were only variably and weakly associated with decreased survival in this population. In the absence of randomized, controlled trials, these results suggest that aggressive glycemic control cannot be routinely recommended for all diabetic hemodialysis patients on the basis of reducing mortality risk. Physicians are encouraged to individualize glycemic targets based on potential risks and benefits in diabetic ESRD patients.


Suboptimal glycemic control is a major determinant of mortality worldwide (1). Specifically, elevated hemoglobin A1c (HgbA1c) is an independent risk factor for coronary heart disease in persons with diabetes (2,3). Recently, three large randomized trials have indicated that intensive glucose lowering in patients with type 2 diabetes mellitus (who comprise 95% of diabetic ESRD patients in the United States) did not reduce the risks of cardiovascular disease, the most common source of ESRD mortality (4–7). Although diabetic ESRD patients continue to comprise approximately half of all prevalent patients in the United States and substantial portions elsewhere (8), very few diabetic chronic kidney disease (CKD) patients have been evaluated in trials for which the results provided evidence for the benefit of aggressive glucose control (9,10). Furthermore, the objectives of glycemic management in this population remain uncertain (11). Although the Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines for diabetes and CKD support standard HgbA1c targets in patients with advanced kidney disease (12), the glyemic control targets were devised for patients without advanced CKD. Support for universal targets for glycemic control in those with renal insufficiency was lacking (because of insufficient evidence), even in recent guidelines, such as those developed by the American College of Physicians (13) and the Department of Veterans Affairs (14).

We previously reported findings from a large national ESRD database that survival curves in diabetic patients grouped by HgbA1c levels did not differ statistically, and that there was no correlation between HgbA1c levels and 12-month mortality risk singly or when adjusted for case-mix and laboratory variables (15). However, those results were not independently confirmed by a similar-sized retrospective database analysis that indicated that higher HgbA1c was associated with increased death risk in diabetic ESRD patients (16). In addition to contrasting results, the two studies had significant methodological differences, with the latter study using a longer follow-up period, time-dependent survival models (i.e., with repeated measures), and adjustments for certain surrogates of malnutrition and inflammation.

In light of these unresolved differences, this report attempts to build on our previous analysis by providing standardized
time-independent (Cox) and time-dependent models. It extends patient follow-up to a maximum of 3 years and, for the first time, provides a separate analysis of the subgroup of patients with type 1 diabetes mellitus. Finally, it includes an analysis stratified by serum albumin levels, the most common marker of protein nutrition status.

Materials and Methods
The study population consisted of 24,751 patients with analyzable information out of the 24,875 (99.5%) chronic hemodialysis patients with a documented diagnosis of diabetes mellitus (DM) (by review of source information that were likely utilized to complete the ESRD form 2728 and of dialysis unit admission records) that were actively treated in Fresenius Medical Care–North America (FMCNA) facilities as of January 1, 2003, with at least one HgbA1c result from the last quarter of 2002. We previously reported 1-year survival in the same cohort (15) and now extend follow-up until December 31, 2005 for a maximum duration of up to 3 years. The mean (SD) duration of follow-up was 671 ± 397 days. The main outcome was mortality, a combined end point of all deaths and withdrawals from dialysis. Surviving patients contributed exposure time until they were lost to follow-up (e.g., because of kidney transplant or transfer out of FMCNA) or the end of the study.

Demographic variables were collated as of January 1, 2003 to include age, gender, race, dialysis vintage, body surface area (BSA, calculated from height and postdialysis weight), and vascular access type (fistula, graft, catheter, and unknown). All baseline laboratory results were presented as the 3-month average of all available values from November 1 to December 31, 2002. The means of available HgbA1c, equilibrated Kt/V (eKt/V), albumin, hemoglobin, phosphorous, creatinine, white blood cell count, and calcium results were also recorded every quarter thereafter until the patient reached an end point, was lost to follow-up, or at the study conclusion. Individual physicians determined the frequency of monitoring HgbA1c levels, whereas the other laboratory results were routinely measured at least once per month. When subsequent quarterly HgbA1c values were missing, the previous value was carried forward in time-dependent analysis. A single laboratory (Spectra Laboratory, Rockleigh, NJ) performed all blood tests. The Roche Cobas Integra 800 whole blood immunoturbidimetric assay standardized according to the National Hemoglobin Standardization Program was utilized to determine HgbA1c, with a normal range from 4.5% to 5.7%. Albumin was measured using the bromcresol green method, consistent with previously referenced studies (15,16). Dialysis dose was derived from two-sample variable volume urea kinetic modeling and reported as eKt/V.

The primary statistical analyses were performed on all study patients, whereas secondary analyses were conducted on subgroups of type I DM patients and type II DM patients. Differences between type I and type II DM patients were tested using the t test or χ² test when appropriate. Kaplan–Meier curves were drawn to compare the survival distribution among varying levels of HgbA1c categorized into five levels, ≤5.5% to >8.5% at 1.0% increments, to be consistent with our prior work (15). Standard and time-dependent Cox models were constructed as (1) unadjusted, (2) case-mixed adjusted (including age, gender, race, dialysis vintage, BSA), and (3) case-mixed + labs adjusted (including eKt/V, albumin, hemoglobin, phosphorous, creatinine, and calcium as well as vascular access) models. Risk profiles were constructed based on HgbA1c categories from ≤5.0% to >11.0% at 0.5% increments, also consistent with our prior work (15). A different grouping strategy was used for the subset of type I DM with wider HgbA1c categories from <5.0% to >10.0% at 1.0% increments because of significantly fewer patients. For the time-dependent models, laboratory values were updated every quarter and <10% of patients had missing values each quarter, with the last quarter’s value imputed for the missing data. Three sensitivity analyses were conducted. First, overall mean values were substituted for missing data with no substantial change in the findings. Second, the primary standard Cox models for mortality were repeated with adjustment for case-mix + albumin alone, case-mix + labs (except for albumin), and the latter series were also modeled with stratification by albumin (<3.5, 3.5 to 3.9, and ≥4.0 g/dl) to evaluate for potential effect modification. Third, post hoc we included additional covariates to the case-mixed + labs adjusted models such as baseline primary insurance status, number of comorbidity diagnoses, and body mass index, as well as quarterly means for erythropoietin dose per treatment, normalized protein catabolic rate, ferritin, and bicarbonate—designed to approximate as closely as possible the time-dependent models performed by Kalantar-Zadeh et al. (16). All analyses were performed using SAS version 9.2 (Cary, NC).

Results
Characteristics of the study cohort (n = 24,751) along with a breakdown between type 1 (5.5%) and type 2 (94.5%) DM are shown in Table 1. The differences between patients with types 1 and 2 DM were as described previously (15). Patients with type 1 DM tended to be younger, with proportionately more male and white patients, and potentially better intake and muscle mass (i.e., higher HgbA1c, creatinine, phosphorus, and BSA). They also had proportionately more fistulas and slightly longer vintage.

The Kaplan–Meier 3-year survival curves categorized by baseline HgbA1c are shown in Figure 1. Patients in the lowest HgbA1c category exhibited the worst survival, whereas those in the highest category had the best survival (P < 0.0001). With longer follow-up, the survival curves layered from the highest to the lowest HgbA1c categories—findings that were not apparent in our initial report of 1-year follow-up (15). Survival models indicated no discernable pattern of risk between HgbA1c and mortality hazard ratios (HRs), shown in Figure 2. Standard Cox models (Figure 2A) showed a significant unadjusted HR of 1.20 (P < 0.001) for HgbA1c ≤5.0% and lost significance when adjusted for case-mix + lab (including vascular access type). In the other extreme, for HgbA1c >11%, HRs from unadjusted models were NS, but the HR for case-mix adjusted models was 1.28 (P < 0.001) and for case-mix + lab-adjusted models was 1.21 (P < 0.05). Utilizing time-dependent Cox models (Figure 2B) exaggerated the HRs for several HgbA1c categories ≤6.5% and >11% but was similarly absent of any particular trend. A sensitivity analysis utilizing standard Cox models with and without adjustment for albumin as well as stratified by albumin (<3.5, 3.5 to 3.9, and ≥4.0 g/dl) indicated no significant effect modification (data not shown).

The subset of patients with type 2 DM comprised 94.5% of all study patients, hence reflecting essentially the same HR profile as the entire cohort. However, the HR profile for the smaller subset of patients with type 1 DM revealed increased death risk beyond HgbA1c levels of ≥9% in the adjusted standard Cox models (Figure 3A). For HgbA1c of 9.0% to 9.9%, the case-mix adjusted HR was 1.41 and case-mix + lab-adjusted HR was 1.52 (both P < 0.05), whereas for HgbA1c ≥10%, HRs were 1.73 (P <
0.05) and 2.06 (P < 0.001), respectively. There was a similar trend, albeit attenuated, from the time-dependent models (Figure 3B), with only HgbA1c ≥10% indicating increased death risk at case-mix adjusted HR of 1.52 and case-mix lab-adjusted HR of 1.49 (both P < 0.05).

Additionally, we modified our analysis further to more closely approximate the previous methodology in the Kalantar-Zadeh report (Figure 4). In this time-dependent analysis adopting the same HgbA1c reference range (5.0% to 5.9%) and similarly constructed HgbA1c categories, our results

Table 1. Demographic characteristics of the study cohort and important subgroups

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>DM Patients with HgbA1c</th>
</tr>
</thead>
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<tr>
<td></td>
<td>All Patients</td>
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<tr>
<td>Number of patients</td>
<td>24,751</td>
</tr>
<tr>
<td>Age (years)</td>
<td>63.7 (12.1)</td>
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<tr>
<td>Percent femalec</td>
<td>51.5%</td>
</tr>
<tr>
<td>Racec</td>
<td></td>
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<tr>
<td>white</td>
<td>53.1%</td>
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<tr>
<td>black</td>
<td>36.4%</td>
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<tr>
<td>other</td>
<td>10.6%</td>
</tr>
<tr>
<td>Vintage (days)</td>
<td>1048 (948)</td>
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<tr>
<td>BSA (m²)</td>
<td>1.86 (0.25)</td>
</tr>
<tr>
<td>Access typec</td>
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</tr>
<tr>
<td>fistula</td>
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<td>graft</td>
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<td>catheter</td>
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<tr>
<td>unknown</td>
<td>0.8%</td>
</tr>
<tr>
<td>Hemodialysis dose (eKt/V)</td>
<td>1.41 (0.29)</td>
</tr>
<tr>
<td>Albumin (g/dl)</td>
<td>3.82 (0.38)</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>11.71 (1.10)</td>
</tr>
<tr>
<td>Calcium (mg/dl)</td>
<td>9.29 (0.70)</td>
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<tr>
<td>Phosphorus (mg/dl)</td>
<td>5.60 (1.45)</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>8.22 (2.87)</td>
</tr>
<tr>
<td>White blood cells (×10³/µl)</td>
<td>7.77 (2.87)</td>
</tr>
<tr>
<td>HgbA1c (%)</td>
<td>6.77 (1.71)</td>
</tr>
</tbody>
</table>

Values are shown as percentages or means (SD).

aP < 0.0001; bP = 0.002; cP < 0.0001 by χ² test: all comparing type 1 versus type 2 patients.

Figure 1. Kaplan-Meier survival curve. Shown are survival rates for baseline HgbA1c groups.
were not changed. Because potential explanations for the attenuated relationships between HgbA1c and survival in our analyses included somewhat different laboratory adjustments and case-mix characteristics (comorbid status, dialysis vintage categories) of the study cohorts, we performed a post hoc analysis to include additional adjustors adapted from the Kalantar-Zadeh report such as baseline primary insurance status, number of comorbidity diagnoses, and body mass index, as well as quarterly means for erythropoietin dose per treatment, normalized protein catabolic rate, ferritin, and bicarbonate for the time-dependent models, (data on total iron binding capacity, lymphocyte percentage, and smoking were inadequate for inclusion). The results did not affect the findings of the study presented here. Finally, we also examined in a post hoc analysis Cox models for 17,182 patients who survived for a full year using the mean of all available predialysis random blood glucose measurements (three of four patients drawn at least every month) throughout the year as the predictor variable of interest, with no associated trends appreciated, as with HgbA1c (data not shown).

Discussion
The study presented here, which consists of the survival data on the same cohort as our 2006 publication (15), supplements that analysis in several ways and provides a more direct comparison with the report by Kalantar-Zadeh et al. (16). With extending the follow-up to 3 years, the study presented here allows comparison of standard and time-dependent Cox models and provides separate analysis of the type 1 diabetic hemodialysis population. We highlight two key findings. First, unadjusted data using Kaplan–Meier survival curves, with longer follow-up, indicated that patients in the lowest overall HgbA1c category suffered inferior survival. Adjusted standard Cox analyses (worse survival at high and low HgbA1c extremes) and time-
dependent Cox analyses (survival particularly impaired at the low HgbA1c extreme) further established that extremes of glycemia portend worse survival in diabetic hemodialysis patients. Second, the smaller subgroup population of type 1 DM patients indicated a lower survival risk at the upper extreme range of HgbA1c values.

Hyperglycemia is proven to play a fundamental role in diabetic complications in nondialysis patients (9,10). In the general diabetic population, glycemic control represented by HgbA1c levels <7% reduces complications of diabetes and reduces the need for hospitalization (17). The burden of mortality attributed to higher blood glucose levels is approximately 3 times higher than that attributed to diabetes alone (1). However, excess mortality was recently associated with intensive glycemic control in the ACCORD trial, in which the intensive arm was stopped early because of a 22% increase in all-cause mortality compared with the standard treatment arm (4). Such results have provoked a reassessment of the benefit of aggressive glycemic control, particularly in patients whose complications are already advanced, and have highlighted the potential risks. Although glycemic control targets in CKD currently recommended by K/DOQI guidelines do not meet the definition of “tight” in the ACCORD study, this elderly population with multiple comorbidities is at particularly high risk of hypoglycemic complications even with the “standard” target of <7% (18–22).

The role of glycemic control in diabetic ESRD is of growing importance because of the magnitude of the population worldwide and associated worse overall prognosis compared with the general dialysis population. Evidence of mortality risk reduction has been sought to help set glycemic guidelines on the optimal target for glucose control.

There have been no randomized clinical trials to evaluate the effects of glycemic control in patients with advanced complications such as ESRD (23), and it remains unclear to what extent tight control might justify the risks involved. However, a recent cohort study of type 2 diabetes indicated diminished cardiovascular benefit from intensive blood glucose control in patients with high levels of comorbidity (24). Until the past few years, there had been few studies that examined the association between HgbA1c and clinical outcomes in the diabetic dialysis population (25–27), most of them small observational studies performed outside of the United States. Limited data from older studies appeared to suggest that poor glycemic control in patients with diabetes on dialysis was associated with increased morbidity (28,29). The question whether glycemic control affects survival outcomes in dialysis patients has benefited from two recent large observational reports of comparable size, contrasting methodologies, and somewhat different conclusions.

We were previously unable to demonstrate the expected parallel association between increasing HgbA1c and greater mortality risk over 1 year in the first large national U.S. database analysis (15). HgbA1c was associated with only a weak correlation of 1-year death risk at low and high extreme values of HgbA1c. In 24,875 hemodialysis patients who had diabetes in a large national dialysis organization database, there was no overall relationship between glycemic control as measured by baseline HgbA1c levels, and 12-month survival, for case-mix or case-mix + laboratory-adjusted data. After our study, Kalantar-Zadeh et al. reported an analysis from a second large national ESRD database of 23,618 patients with diabetes using time-dependent survival models with repeated measures (16). In contrast to our earlier findings, they concluded that higher HgbA1c (>10%) was associated with a 41% greater death risk for all-cause and cardiovascular death. The authors proposed that the general population’s conventional association between HgbA1c and survival would hold in dialysis patients if the confounding effects of malnutrition, anemia, and other factors were controlled for in the analysis and concluded that certain subgroups (nonanemic, younger) would still benefit from improved glycemic control. In our current analyses, adjusted time-dependent Cox models indicated that extremes of glycemia could be associated with inferior survival.

Although HgbA1c remains the most widely used index of glycemic control in the diabetic population, it is not without its limitations (30). Recent studies have raised concerns about its validity in ESRD. HgbA1c may not optimally represent the general glycemic state in ESRD patients because of unique physiologic and pathologic changes in this population (31,32). In our own national database analysis, HgbA1c showed only a weak correlation with mean random glucose values ($R^2 = 0.37$). Glycated hemoglobin indicates the percentage of circulating hemoglobin that has chemically reacted with glucose (32). The shortened half-life of erythrocytes in uremia and the use of erythropoietin, by increasing the proportion of younger erythrocytes, appear to reduce HbA1c relative to plasma glucose levels. As a result, HgbA1c tends to be lower in diabetic patients with kidney impairment or on renal replacement therapy (33). Nonetheless, glycated hemoglobin remains the best available tool for monitoring glycemic control (34).

In summary, sustained extremes of glycaemia are associated with increased mortality risk in diabetic ESRD patients. We have previously reported similar associations with risk of hospitalization (31). However, the overall relationships between glycemic control and survival are relatively weak and may depend in part on statistical methodology. Although randomized controlled trials will be required to determine whether meeting conventional HgbA1c targets can improve survival outcomes in this population, our results suggest that improved survival should not be used to justify aggressive glycemic control strategies. Finally, emphasis should be placed on the risks associated with hypoglycemia (35,36). Our preliminary findings indicate that risk of hypoglycemia is especially significant in diabetic ESRD patients with glycemic variability (37). Therefore, pending the performance of randomized clinical trials, it may be prudent to consider the risks associated with aggressive glycemic control relative to expected benefits, to individualize glycemic targets, and to tailor specific therapy on the basis of clinical status in diabetic patients with ESRD.

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Disclosures
E.L., W.W., J.M.L., and R.H. are employed by FMCNA.

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Access to UpToDate on-line is available for additional clinical information at http://www.cjasn.org/