# Association Between Glycemia and Mortality in Diabetic Individuals on Renal Replacement Therapy in the U.K.

*Amanda Adler,[1] Anna Casula,[2] Retha Steenkamp,[2] Damian Fogarty,[3] Martin Wilkie,[4] Laurie Tomlinson,[5] Dorothea Nitsch,[5] Paul Roderick,[6] and Charles R.V. Tomson[7]*

**OBJECTIVE**

**In the U.K., one-third of patients receiving treatment with dialysis have diabetes. Guidelines from organizations representing patients with renal disease or diabetes advocate tight glycemic control in patients with end-stage renal disease, despite glucose-lowering trials having excluded these patients.**

**RESEARCH DESIGN AND METHODS**

**Using national UK Renal Registry data, we tested whether glycemia as measured by hemoglobin (Hb) $A_{1c}$ ($HbA_{1c}$) level is associated with death in adults with diabetes starting hemodialysis or peritoneal dialysis between 1997 and 2006, and observed for at least 6 months. Of 7,814 patients, we excluded those who had died within 6 months; had received transplants; were lost/recovered; or lacked measures of $HbA_{1c}$, ethnicity, or Hb. Categorizing $HbA_{1c}$ measured in the first 6 months of starting dialysis as <6.5% (<48 mmol/mol), 6.5–7.4% (48–57 mmol/mol) (reference value), 7.5–8.4% (58–68 mmol/mol), and ≥8.5% (≥69 mmol/mol), we adjusted in proportional hazards models for age, sex, ethnicity, deprivation, year, dialysis type, and Hb, and tested for interactions.**

**RESULTS**

**Of 3,157 patients observed for a median time of 2.7 years, 1,688 died. For patients ≥60 years of age, we found no association between $HbA_{1c}$ and death; among younger patients, relative to those with $HbA_{1c}$ values 6.5–7.4%, the hazard ratio for $HbA_{1c}$ level 7.5–8.4% was 1.2 (95% CI 0.9–1.5), and for $HbA_{1c}$ level >8.5% was 1.5 (1.2–1.9). The projected difference in median survival time between younger patients with a reference $HbA_{1c}$ value versus >8.5% was 1 year.**

**CONCLUSIONS**

**In the absence of trials, and confounding notwithstanding, these observational data support improved glycemic control in younger patients prior to and during dialysis.**

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*[1]Wolfson Diabetes and Endocrine Clinic, Institute of Metabolic Science, Addenbrooke's Hospital, Cambridge, U.K.*
*[2]UK Renal Registry, Southmead Hospital, Bristol, U.K.*
*[3]Public Health, Health Services, and Primary Care, Queen's University, Belfast, U.K.*
*[4]Sheffield Kidney Institute, Sheffield, U.K.*
*[5]Department of Non-Communicable Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, U.K.*
*[6]Primary Care and Population Sciences, University of Southampton, Southampton, U.K.*
*[7]Academic Renal Unit, School of Clinical Sciences, University of Bristol, Bristol, U.K.*

*Corresponding author: Amanda Adler, amanda.adler@addenbrookes.nhs.uk.*

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Diabetes mellitus increases the risk of chronic kidney disease (CKD), and, among dialysis patients, increases the risk of death independent of age, ethnicity, and comorbidities (1). For diabetic patients with renal failure, The Renal Association in the U.K. suggests that all CKD, dialysis, and transplant patients with diabetes achieve a level of hemoglobin (Hb) $A_{1c}$ ($HbA_{1c}$) between 6.5 and 7.5% (48–58 mmol/mol) (2). The National Kidney Foundation advocates a target $HbA_{1c}$ level of 7.0% (53 mmol/mol), but that the target be "extended above 7.0% for patients with comorbidities" (3). While individual trials have shown that intensive glycemic control lowers the risks of aspects of nephropathy, a meta-analysis (4) from the Cochrane protocol did not show a decrease in the occurrence of nephropathy. The authors of another meta-analysis (5), who separated manifestations of nephropathy, reported that intensive glycemic control lowers the risk of albuminuria, but not of worsening serum creatinine levels or the development of end-stage renal disease (ESRD) together. Of more direct relevance to patients who already have ESRD, the major glucose-lowering trials in diabetes on which renal guidelines base recommendations uniformly excluded patients with significant renal insufficiency. Generalizing $HbA_{1c}$ target levels of 6.5–7.5% (48–58 mmol/mol) for patients with ESRD may be inappropriate, particularly given the increased risk of hypoglycemia associated with more intensive blood glucose lowering, and because of the increased prevalence of hypo-unawareness and cardiovascular disease in people with long-standing diabetes. Commentary has cast doubt on the safety of attempting to obtain "tight" glycemic control among patients with CKD (6).

In the absence of evidence from clinical trials in patients with ESRD in the near future, observational evidence must guide the treatment of diabetes. Observational data relating the degree of glycemia to outcomes in patients receiving renal replacement therapy (RRT) remains relatively sparse and may vary not only as to whether an association exists, but in its reported direction. Using national data from the UK Renal Registry, we investigated longitudinally whether an association exists in individuals with diabetes between glycemia measured at the start of dialysis and subsequent mortality.

## RESEARCH DESIGN AND METHODS

### Definition of Glycemia

The main exposure was glycemia measured by $HbA_{1c}$ levels within 6 months after the start of dialysis. If more than one value existed, we chose the value obtained within the same 3-month period of starting dialysis. All $HbA_{1c}$ measurements were performed in National Health Service (NHS)-accredited laboratories. We categorized $HbA_{1c}$ defining the reference category by the $HbA_{1c}$ level recommended by the Renal Association, that is, an $HbA_{1c}$ level of 6.5–7.4% (48–57 mmol/mol), and to which we compared categories defined by levels of $<$6.5% ($<$48 mmol/mol), 7.5–8.4% (58–68 mmol/mol), and $\geq$8.5% ($\geq$69 mmol/mol). We also modeled $HbA_{1c}$ level as a continuous variable, assuming both a linear relationship and a nonlinear relationship with log-transformed $HbA_{1c}$ level as the exposure.

### Definition of Outcome

Death was documented by clinicians and confirmed with national death records.

### Population

The UK Renal Registry records demographic and clinical data updated quarterly on all patients receiving RRT in the U.K., extracted electronically from databases used for clinical care in centers offering hemodialysis (HD) or peritoneal dialysis (7). Launched in 1997 with nine centers, it now receives data from all 71 centers providing RRT in the U.K., including data from centers in Northern Ireland and Scotland, which are shared with the UK Renal Registry by the Scottish Renal Registry.

The population in these analyses included diabetic patients $\geq$18 years of age with biochemical data, including an $HbA_{1c}$ value, who started dialysis (either HD or peritoneal dialysis) during a 10-year period from 1 January 1997 to 31 December 2006. The patients were observed for at least 6 months until they died, were lost to follow-up, or 31 December 2009. The population included patients for whom diabetes was defined by physician diagnosis, but for whom diabetes was not necessarily coded as the primary cause of ESRD. The data set shared by the Scottish Renal Registry did not include biochemical variables, so the nine Scottish centers were excluded.

From an initial population of 7,814, we excluded patients who, within the first 6 months of follow-up, died ($n$ = 797), were lost to follow-up ($n$ = 21), recovered or stopped treatment ($n$ = 36), underwent renal transplant without having started dialysis ($n$ = 150), or underwent renal transplant having started dialysis ($n$ = 78), leaving 6,732 individuals. We excluded other individuals who had no data on $HbA_{1c}$ level ($n$ = 3,386) or Hb level ($n$ = 19) measured within the first 6 months of starting dialysis or who had no data on ethnicity ($n$ = 170). This left 3,157 individuals with information on $HbA_{1c}$ and Hb levels measured within 6 months of starting dialysis, age, sex, ethnicity, Hb level, mode of dialysis, year of starting dialysis, and a measure of social deprivation.

### Statistical Analyses

We performed descriptive analyses of the population by level of $HbA_{1c}$, as well as by level of $HbA_{1c}$ stratified by age. We tested differences across levels using Kruskal-Wallis one-way ANOVA or $\chi^2$ test. We compared the characteristics of patients included in the analyses to those excluded. We estimated the age-adjusted mortality rates using Poisson regression and number of person-years at risk by category of $HbA_{1c}$ level. We performed survival analysis using proportional hazards modeling, checking for proportionality using Schoenfeld residuals. We used $HbA_{1c}$ level as the main exposure, and time from 6 months from the start of dialysis to death or censoring as the outcome. We defined censoring as loss to follow-up, renal transplantation, or alive without transplantation. We tested for interaction defining the product between $HbA_{1c}$ level by group and a binary variable for age in years ($<$60 or $\geq$60 years), reflecting a value approximating the median age in this

population. To address the possibility of nonrandom (namely, "informative") censoring at transplant, we performed sensitivity analyses assuming instead that individuals were censored only at loss-to-follow-up or were alive at the end of the follow-up period. Last, we estimated median survival from Kaplan-Meier curves.

### Potential Confounders

We adjusted for risk factors for death that were also plausibly related to glycemia. Potential confounders included age, sex, ethnicity, mode of dialysis, year of starting dialysis, cause of ESRD, and a measure of social deprivation. In addition, because anemia can affect the interpretation of $HbA_{1c}$ level, we adjusted for the concentration of Hb in the blood. Ethnicity was defined as white, Afro-Caribbean, South Asian, and other. Social deprivation was estimated using the Townsend Deprivation Score (a measure of material deprivation derived from postcode, and based on car and home ownership, overcrowding and unemployment) (8), with higher scores representing more deprivation. Hb (in grams per deciliter) was measured from 0 to 6 months after starting dialysis.

Returns to the UK Renal Registry from many centers are incomplete for data pertaining to BMI, blood pressure, concurrent cardiovascular disease, and timing of presentation with ESRD prior to start of dialysis, and so we excluded these variables from the analysis. Because they were not available in the registry data set, we could not control for type of diabetes, duration of diabetes, or medications used to treat diabetes.

## RESULTS

The mode of dialysis in this diabetic population was predominantly HD (70%). Diabetes was recorded as the cause of renal failure for the majority of patients (85%). The median age of the population was 62 years; half of the patients were aged 50–71 years. The median year of starting dialysis was 2004. Women comprised 38.6% of the population. The median $HbA_{1c}$ level was 7.0%. Table 1 provides a summary of patient characteristics by $HbA_{1c}$ grouping, and Supplementary Table 1 summarizes patient characteristics by age at the start of dialysis. Patients excluded from the study were similar to included patients with respect to age, sex, ethnicity, and cause of renal failure (Supplementary Table 2).

Of the 3,157 individuals in the defined cohort, 1,688 died (53.4%) during a median follow-up time of 2.7 years. Follow-up time ranged from 0 to 11.7 years. For patients <60 years of age, the median $HbA_{1c}$ value of the 583 patients who died was higher at 7.7% (61 mmol/mol) than those who did not die ($n$ = 828; $HbA_{1c}$ 7.4% [57 mmol/mol]). For patients ≥60 years of age, the median $HbA_{1c}$ level among the 1,105 people who died was also higher at 6.8% (51 mmol/mol) than for the 641 patients who did not die ($HbA_{1c}$ 6.6% [49 mmol/mol]). By category of $HbA_{1c}$, the age-adjusted death rate was as follows: $HbA_{1c}$ <6.5% (46 mmol/mol), 163.3/1,000 person-years; $HbA_{1c}$ 6.5–7.4% (48–57 mmol/mol), 183.5/1,000 person-years; $HbA_{1c}$ 7.5–8.4% (58–68 mmol/mol), 187.4/1,000 person-years; and $HbA_{1c}$ ≥8.5% (≥69 mmol/mol), 219.1/1,000 person-years. Figure 1 shows mortality rate by age and $HbA_{1c}$ category, showing higher rates of death

**Table 1—Characteristics of population ($N$ = 3,157) by $HbA_{1c}$ (%)**

| Characteristics | <6.5% (<48 mmol/mol), $n$ = 1,100 | 6.5–7.4% (48–57 mmol/mol), $n$ = 815 | 7.5–8.4% (58–68 mmol/mol), $n$ = 557 | ≥8.5% (≥69 mmol/mol), $n$ = 685 | $P$ value |
|---|---|---|---|---|---|
| Follow-up (years) | — | — | — | — | — |
| Median | 2.8 | 2.7 | 2.7 | 2.3 | <0.0001 |
| IQR | 1.5–4.0 | 1.4–3.9 | 1.4–4.0 | 0.9–3.6 | — |
| $HbA_{1c}$ (percentage points) | — | — | — | — | — |
| Median | 5.8 | 7.0 | 7.9 | 9.5 | <0.0001 |
| IQR | 5.4–6.1 | 6.7–7.2 | 7.7–8.2 | 8.9–10.4 | — |
| Age (years) | — | — | — | — | — |
| Median | 66 | 65 | 58 | 54 | <0.0001 |
| IQR | 56–73 | 54–72 | 47–68 | 42–64 | — |
| Hb, mean (SD), g/dL | 10.2 (1.5) | 10.4 (1.5) | 10.5 (1.6) | 10.6 (1.6) | <0.0001 |
| Female sex (%) | 36.6 | 39.4 | 39.1 | 40.3 | NS |
| Ethnicity (% white) | 71.3 | 74.7 | 78.3 | 84.4 | <0.0001 |
| Deprivation (Townsend score) | — | — | — | — | — |
| Median | 0.37 | 0.21 | 0.12 | 0.05 | NS |
| IQR | −1.84 to 3.0 | −2.1 to 2.8 | −2.04 to 2.8 | −2.17 to 2.7 | — |
| Dialysis mode (% HD) | 78.4 | 71.8 | 63.4 | 57.4 | <0.0001 |
| Cause of renal failure (% diabetes) | 78.6 | 84.7 | 89.6 | 93 | <0.0001 |
| Year of starting dialysis | — | — | — | — | — |
| Median | 2004 | 2004 | 2004 | 2004 | <0.0001 |
| IQR | 2003–2006 | 2002–2005 | 2002–2005 | 2002–2005 | — |

IQR, interquartile range; NS, not significant. $P$ value across levels of $HbA_{1c}$ by characteristics: all were associated with differences of $P < 0.001$, with the exception of sex and level of deprivation ($P > 0.05$)

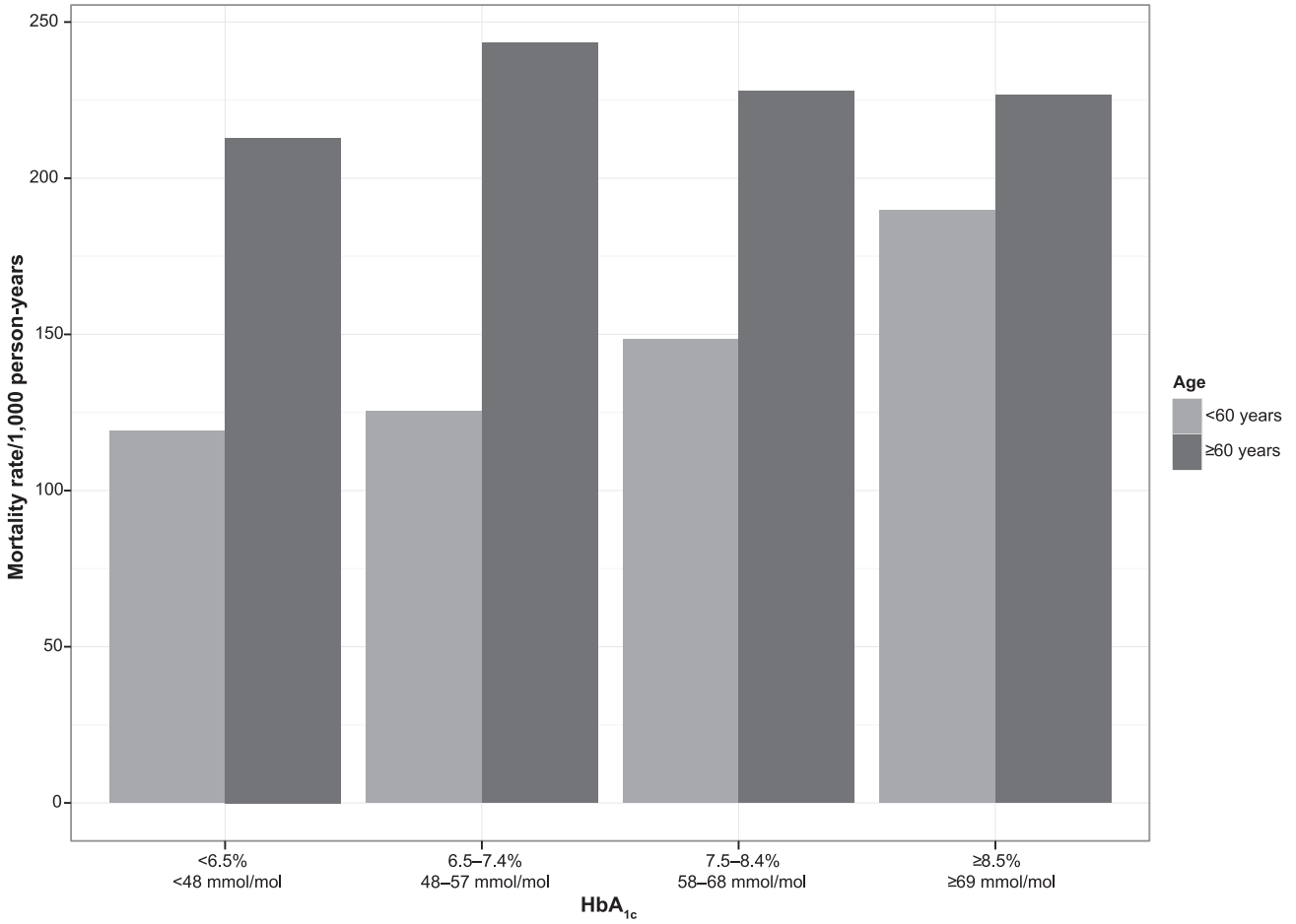


**Figure 1—**Mortality rate by age and $HbA_{1c}$.

among older patients and by category of $HbA_{1c}$ among younger patients. In sensitivity analyses, the rates observed showed the same pattern when we did not censor patients at transplant.

In an unadjusted proportional hazards model, we found a weak association ($P$ = 0.2) between $HbA_{1c}$ and death. In analyses adjusting for age, sex, ethnicity, Hb level, mode of dialysis, year of starting dialysis, and social deprivation, relative to the reference $HbA_{1c}$ range of 6.5–7.4%, (48–57 mmol/mol), patients with $HbA_{1c}$ values $<$6.5% ($<$48 mmol/mol) had a hazard ratio (HR) of 0.9 (95% CI 0.8–1.0), patients with values between 7.5 and 8.4% (58 and 68 mmol/mol) had an HR of 1.0 (95% CI 0.8–1.1), and patients with values $\geq$8.5% ($\geq$69 mmol/mol) had an HR of 1.2 (95% CI 1.0–1.3). When modeled as a continuous variable, we observed an $\sim$10% increase in the risk of death associated with each 1 percentage point increase in $HbA_{1c}$ (11 mmol/mol) ($P < 0.0001$). Specifically, for patients $\geq$60 years of age at the start of dialysis, the association between each 1 percentage point increase in $HbA_{1c}$ (equivalent to an 11 mmol/mol increase) and mortality adjusted for other covariates was associated with an HR of 1.03 (95% CI 0.98–1.07; $P$ = 0.2), while for patients $<$60 years of age at the start of dialysis the HR for the association between each 1 percentage point increase in $HbA_{1c}$ level and mortality was 1.10 (95% CI 1.05–1.15; $P < 0.0001$), which was also adjusted for covariates. Assuming other than a linear association, and using a log-transformed $HbA_{1c}$ level, in adjusted analyses for patients $\geq$60 years of age at dialysis the HR was 1.19 (95% CI 0.88–1.63; $P$ = 0.2), while for younger patients the HR was 2.11 (95% CI 1.45–3.07; $P < 0.0001$).

As suggested by the preceding results, we found a significant interaction ($P$ = 0.001) between age and $HbA_{1c}$ level; we observed an association between the group with the highest $HbA_{1c}$ values and death only among patients who had started dialysis before age 60 years. Figure 2 presents crude survival data by $HbA_{1c}$ and age at the start of dialysis, showing lower survival among patients with higher $HbA_{1c}$ values, which is more noticeable among younger patients with a log-rank $P$ value of $<$0.0001 for patients $<$60 years of age and a log-rank $P$ value of 0.3 for those $\geq$60 years of age. Table 2 provides HRs and estimated median times to death among patients who started dialysis before or after age 60 years, and suggests that younger patient with $HbA_{1c}$ values in the reference range may live some 1.2 years longer than do patients with $HbA_{1c}$ values $\geq$8.5% (69 mmol/mol). The association did not change when censoring patients at transplant or when adjusting for the cause of renal failure

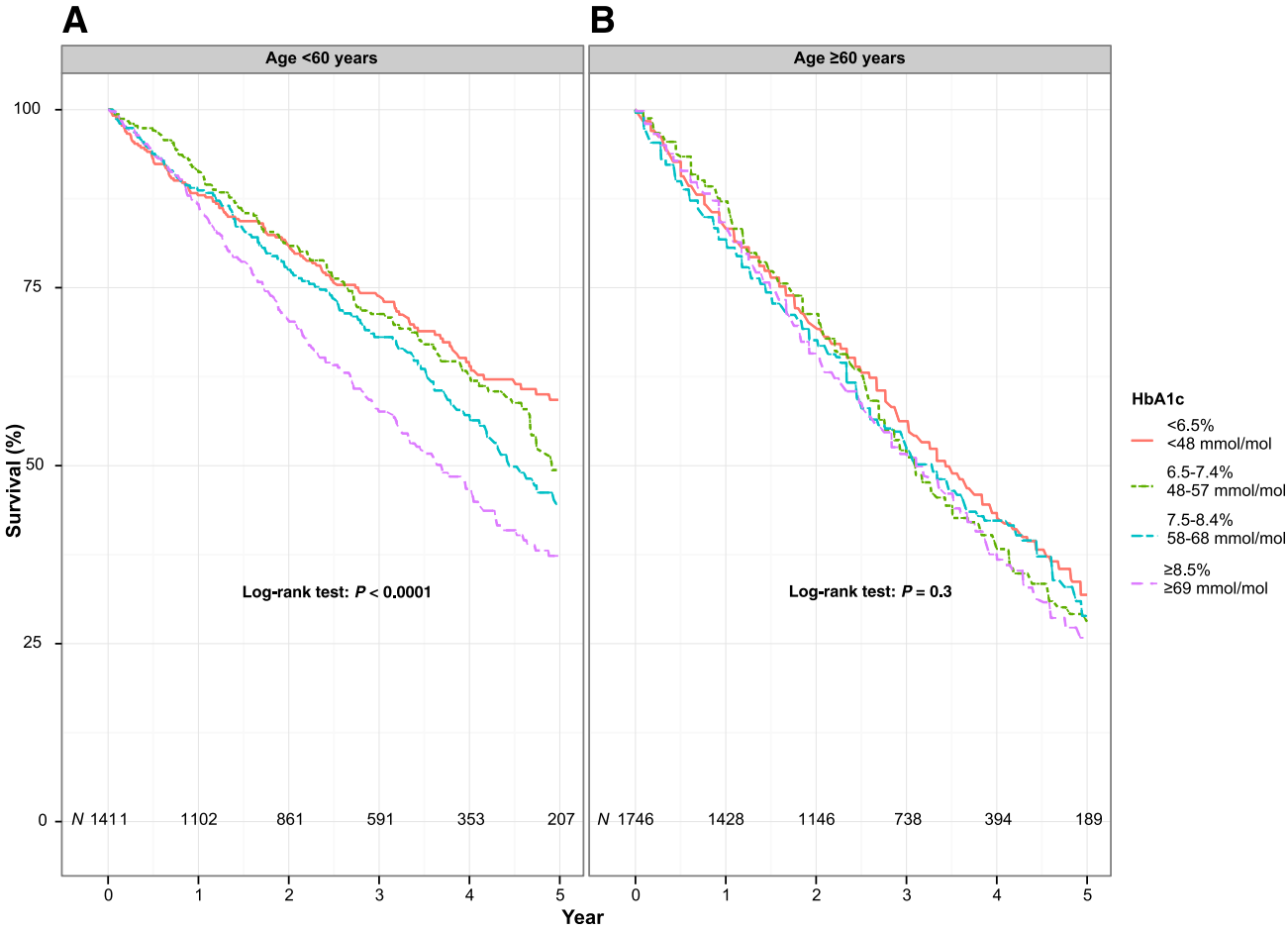


**Figure 2**—Kaplan-Meier survival function by $HbA_{1c}$ level (%) group in patients who start dialysis <60 years of age (*A*) and ≥60 years of age (*B*).

(diabetes or otherwise) in the multivariate model.

## CONCLUSIONS

These observational data from the U.K. show that among patients with diabetes who start dialysis before age 60 years, higher values of $HbA_{1c}$ are associated with poorer survival. We observed this only for patients whose $HbA_{1c}$ values exceeded 8.5% (69 mmol/mol), our definition of the highest category. This increase in risk was independent of sex, Hb, mode of dialysis, and social deprivation. This study suggests that patients with an $HbA_{1c}$ level within the reference range currently advocated by professional organizations may live over a year longer while receiving treatment with dialysis than patients with $HbA_{1c}$ values starting at >8.5% (69 mmol/mol).

The association we observed was modified by age at onset of dialysis. Since younger patients were more likely than older patients to have diabetes as a listed cause of renal failure, it is possible that younger patients also had a higher burden of other diabetes complications to which glycemia also contributed. Age at the start of dialysis may reflect more aggressive renal disease, and may therefore be a marker for severity of concurrent diabetes complications.

This study relied on $HbA_{1c}$ values measured in local rather than in a central laboratory. Although variation is likely, it is minimized since all NHS laboratories that report glycated Hb participate in national external quality assessment schemes such as the U.K. National External Quality Assessment Service. While a laboratory may have chosen to change methods during the years covered by this study, this study adjusted for calendar year. In addition, most methods used to measure glycated Hb in the U.K. detect and correct for hemoglobinopathies, although this correction may not be complete; in addition, we adjusted for ethnicity, and limiting analysis to white patients did not alter the associations we observed.

We attempted to adjust for other biases, including the possibility that anemia might lead to $HbA_{1c}$ values that underestimate or overestimate glycemia. The possibility that anemia might confound the association between glycemia and death is supported by a U.S. study that reported that adjusting for Hb level in analyses abolished the apparent high risk of death in dialysis patients with low $HbA_{1c}$ values (9). However, the National Glycohemoglobin Standardization Program concludes that the role of renal anemia, erythropoietin intake, and other factors in chronic renal failure makes evaluating $HbA_{1c}$ levels difficult (10). This suggests that adjusting for Hb alone would not adequately adjust for

**Table 2—Association between glycemia and death using proportional hazards analyses stratified by age and adjusted for sex, ethnicity, cause of ESRD, deprivation, year, dialysis mode, Hb level, and median time to death from starting dialysis**

| $HbA_{1c}$ level (%) | *n* | Deaths, *n* | Crude mortality rate per 1,000 person-years | Adjusted HR | 95% CI | *P* value | Median estimated time to death (years)* | Difference in median time to death from reference category |
|---|---|---|---|---|---|---|---|---|
| <60 years of age | — | — | — | — | — | <0.001 | — | — |
| <6.5 | 359 | 134 | 119 | 1.00 | 0.8–1.3 | 0.96 | 5.6 | — |
| 6.5–7.4 | 313 | 120 | 125 | Reference 1.0 | — | — | 4.9 | Reference |
| 7.5–8.4 | 313 | 135 | 148 | 1.2 | 0.9–1.5 | 0.2 | 4.4 | 0.5 years |
| ≥8.5+ | 426 | 194 | 190 | 1.5 | 1.2–1.9 | 0.0004 | 3.6 | 1.3 years |
| ≥60 years of age | — | — | — | — | — | 0.36 | — | — |
| <6.5 | 741 | 448 | 213 | 0.9 | 0.8–1.0 | 0.08 | 3.4 | — |
| 6.5–7.4 | 502 | 334 | 243 | Reference 1.0 | — | — | 3.1 | Reference |
| 7.5–8.4 | 244 | 157 | 228 | 0.9 | 0.8–1.1 | 0.33 | 3.0 | — |
| ≥8.5+ | 259 | 166 | 226 | 0.95 | 0.8–1.1 | 0.57 | 3.2 | — |

$HbA_{1c}$ levels: <6.5% = <48 mmol/mol; 6.5–7.4% = 48–57 mmol/mol (reference value); 7.5–8.4% = 58–68 mmol/mol; and ≥8.5% = ≥69 mmol/mol.
*Median time to death from Kaplan-Meier analyses.

factors that confound the relationship between Hb and $HbA_{1c}$.

It has been suggested that $HbA_{1c}$ level does not reflect glycemia as well in people with ESRD as it does in people without ESRD. For example, a higher correlation coefficient of 0.82 between glycemia and $HbA_{1c}$ level was observed in people with type 1 diabetes without ESRD in the Diabetes Control and Complications Trial (DCCT) (11) than in dialysis patients in Alberta, Canada (correlation coefficient 0.51) (12) or in the U.S. (correlation coefficient 0.47) (13). Nonetheless, as with patients not receiving dialysis, the relationship between blood glucose and $HbA_{1c}$ levels among patients receiving dialysis is linear (13). Regardless, the purpose of this study was not to measure the association between $HbA_{1c}$ level and glycemia, but between $HbA_{1c}$ level and death. While better measures of glycemia in dialysis patients may exist (14), the findings we observe are likely to hold true given the effect across the categories of glycemic control.

Among the limitations to these analyses, we were not able to take into account hypoglycemia, type of diabetes, neither of which are routinely collected in registry data, or BMI. We were not able to test among people with similar values of $HbA_{1c}$ whether mortality differed among people with and without hypoglycemia. In the absence of BMI, we could not test whether BMI confounded the relationship between $HbA_{1c}$ and mortality. However, as higher values of BMI are associated with longer survival time in dialysis patients (15), if BMI is also associated with poorer glycemic control in dialysis patients, then, had we adjusted for BMI, our results may have shown a greater association between high $HbA_{1c}$ level and mortality. Also with respect to the possibility of residual confounding, and with respect to glycemia per se, it remains possible that patients with higher $HbA_{1c}$ values had a fundamentally higher risk of death independent of glycemia than did patients with more modest values of $HbA_{1c}$. We were not able to perform robust analyses of changing glycemia over time. If $HbA_{1c}$ improved to a greater degree in those with the highest values of $HbA_{1c}$, and if lowering $HbA_{1c}$ levels benefits patients, then again our findings may have underestimated the true association. Of note, Shurraw et al. (12) found similar results when adjusting for $HbA_{1c}$ level, either as a baseline or as a time-dependent variable.

Another limitation of this study is the degree of missing data in the main exposure, glycemia. The data for the UK Renal Registry comes from computerized data management systems aligned with renal units. Depending on local service arrangements and data sharing, blood samples for $HbA_{1c}$ measurement obtained by other practitioners (e.g., including general practitioners and diabetologists) may not be transferred to the renal physicians who do not have primary responsibility for diabetes care. All patients in the NHS have a general practitioner whose services are free at the point of care, and, insofar as the patients included in this study are dialysis patients, they are, by definition, interacting with the NHS. We have previously observed that patients with missing data often have additional comorbidities (16); however, there was no difference in mortality between patients included and excluded from this study (Supplementary Table 1). In addition, included and excluded patients were similar with respect to Hb concentration, sex, ethnicity, mode of dialysis, and cause of renal failure, suggesting that it is possible that patients included and excluded from the study also had similar values of $HbA_{1c}$.

Other investigators have analyzed cohorts and described the association between $HbA_{1c}$ level and death. In North Carolina, investigators observed a crude, but not an independent, association between $HbA_{1c}$ level and mortality among 444 patients, of whom 156 died (14). Investigators in Alberta, Canada, observed no association among 540 patients with measured $HbA_{1c}$ values, 83% of whom were known to have diabetes, when the exposure was modeled either as a continuous or categorical variable, or as a baseline or a time-varying variable (12). The investigators also evaluated blood glucose levels (as distinct from $HbA_{1c}$ levels), finding no association between

one and seven values per patient and mortality. Using a larger database from Fresenius Medical Care North America, investigators found that "sustained extremes of glycemia were only variably and weakly associated with decreased survival," but reported a 21% increase in risk in adjusted models associated with $HbA_{1c}$ values of >11.0% (97 mmol/mol) (9). In 137 dialysis patients in Taiwan, patients in whom $HbA_{1c}$ values exceeded 10% (86 mmol/mol) had considerably poorer survival ($P < 0.0001$) (17). A meta-analysis incorporating some of the data presented in this article has found an association between higher values of $HbA_{1c}$ and higher mortality, but observed heterogeneity between effect measures and did not test for interaction by age (18).

Strengths of the current study in relation to existing studies include being a national and population-based study. The patients derive from the general population and have access to health care free of charge at the point of service, including dialysis and all preceding treatments for nephropathy and diabetes. The study had adequate numbers of deaths among patients with measured $HbA_{1c}$ values to detect an association between glycemia and mortality. To emphasize, a potential weakness of this study, as with most cohort studies, is that we did not have complete data on all individuals, nor could we rule out residual confounding including, but not limited to, duration of diabetes, type of diabetes, comorbid conditions, and adverse effects of treatment.

With respect to generalizability, the included and excluded populations are similar with respect to age, sex, ethnicity, and the proportion for which diabetes is the cause of renal failure. With respect to generalizability to dialysis populations outside of the U.K., although patients in this cohort had a median $HbA_{1c}$ value of 7.0% (53 mmol/mol) comparable to the mean of 6.8% (51 mmol/mol) among 24,751 patients in North America, the populations may differ in other ways (9).

The clinical implications of this study relate to whether patients with poor glycemic control should strive for improved glycemic control prior to starting dialysis as well as during early dialysis. Insofar as observational data may be confounded, these data provide less solid evidence to support glucose lowering than would an interventional study designed to minimize bias. In addition, glucose lowering in patients with diabetes but without ESRD has not been shown to prolong life (19). Helping patients with CKD achieve glycemic control has been discussed among diabetologists and is considered "problematic" (6), as fewer options for treatment exist. Marketing authorizations frequently proscribe the use of newer drugs for diabetes in patients with CKD, which likely reflects manufacturers having excluded these patients from trials. Nonetheless, insulin remains a treatment option to offer patients.

This observational study cannot rule out the possibility that higher $HbA_{1c}$ values do not cause patients to die sooner, but are instead a marker of comorbidities or other factors. With these caveats, in the absence of direct trial data, this study provides support to perform such a trial, or, until this occurs, for glycemic control in patients with advanced renal disease prior to and early in the course of dialysis. Aggressive glycemic control striving for values of $HbA_{1c}$ sought in the ACCORD study (i.e., targeting a glycated Hb level of <6.0% [42 mmol/mol]) is not advocated (20), and increasingly, physicians appreciate the importance of minimizing the risk of hypoglycemia in elderly patients and those with other medical problems. It is not clear whether good glycemic control can reverse long-standing damage from hyperglycemia, nor is it clear what $HbA_{1c}$ target is the most appropriate. A true threshold is unlikely to exist, and our study shows that patients with values of $HbA_{1c}$ at or exceeding 8.5% (69 mmol/mol), assuming they start dialysis at a younger age, are those at the highest relative risk of death. In the absence of trials to minimize confounding, these observational data support the need for improved glycemic control in younger patients prior to and during dialysis.

**Duality of Interest.** No potential conflicts of interest relevant to this article were reported.

**Author Contributions.** A.A. helped guide the analyses and wrote the paper. A.C. performed analyses and wrote the paper. R.S. performed analyses. D.F. and M.W. wrote the paper. L.T. reviewed and edited the paper. D.N. helped guide analyses and edited the paper. P.R. advised on the analyses. C.R.V.T. oversaw the project, helped guide analyses, and wrote the paper. A.A. and C.R.V.T. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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