Glycated Hemoglobin and Risk of Death in Diabetic Patients Treated With Hemodialysis: A Meta-analysis

Christopher J. Hill, MB,1,2 Alexander P. Maxwell, PhD,1,2 Christopher R. Cardwell, PhD,1 Barry I. Freedman, MD,3 Marcello Tonelli, MD,4 Masanori Emoto, MD,5 Masaaki Inaba, MD,5 Yasuaki Hayashino, MD,6 Shunichi Fukuhara, MD,7,8 Tomonari Okada, MD,9 Christiane Drechsler, MD,9 Christoph Wanner, MD,10 Anna Casula, MS,11 Amanda I. Adler, PhD,12 Claudia Lamina, PhD,13 Florian Kronenberg, MD,13 Elani Streja, PhD,14 Kamyar Kalantar-Zadeh, PhD,14 and Damian G. Fogarty, MD1,2,10

Background: Studies investigating the association between glycated hemoglobin (HbA1c) level and mortality risk in diabetic patients receiving hemodialysis have shown conflicting results.

Study Design: We conducted a systematic review and meta-analysis using MEDLINE, EMBASE, Web of Science, and the Cochrane Library.

Setting & Population: Diabetic patients on maintenance hemodialysis therapy.

Selection Criteria for Studies: Observational studies or randomized controlled trials investigating the association between HbA1c values and mortality risk. Study authors were asked to provide anonymized individual patient data or reanalyze results according to a standard template.

Predictor: Single measurement or mean HbA1c values. Mean HbA1c values were calculated using all individual-patient HbA1c values during the follow-up period of contributing studies.

Outcome: HR for mortality risk.

Results: 10 studies (83,684 participants) were included: 9 observational studies and one secondary analysis of a randomized trial. After adjustment for confounders, patients with baseline HbA1c levels ≥8.5% (≥69 mmol/mol) had increased mortality (7 studies; HR, 1.14; 95% CI, 1.09-1.19) compared with patients with HbA1c levels of 6.5%-7.4% (48-57 mmol/mol). Likewise, patients with a mean HbA1c value ≥8.5% also had a higher adjusted risk of mortality (6 studies; HR, 1.29; 95% CI, 1.23-1.35). There was a small but nonsignificant increase in mortality associated with mean HbA1c levels ≥5.4% (≥36 mmol/mol; 6 studies; HR, 1.09; 95% CI, 0.89-1.34). Sensitivity analyses in incident (>90 days of hemodialysis) and prevalent patients (>90 days of hemodialysis) showed a similar pattern. In incident patients, mean HbA1c levels ≥5.4% also were associated with increased mortality risk (4 studies; HR, 1.29; 95% CI, 1.23-1.39).

Limitations: Observational study data and inability to adjust for diabetes type in all studies.

Conclusions: Despite concerns about the utility of HbA1c measurement in hemodialysis patients, high levels (≥8.5%) are associated with increased mortality risk. Very low HbA1c levels (≤5.4%) also may be associated with increased mortality risk.

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INDEX WORDS: HbA1c; diabetes mellitus; hemodialysis; survival.

Diabetes mellitus is the most common cause of chronic kidney failure necessitating renal replacement therapy in many countries.1,2 Diabetic patients with end-stage renal disease (ESRD) have higher mortality while receiving dialysis, are less likely to undergo kidney transplantation, and have poorer transplantation outcomes compared with patients with other kidney diseases.3,5

From the 1Centre for Public Health, Queen’s University Belfast; 2Regional Nephrology Unit, Belfast City Hospital, Belfast, Northern Ireland; 3Wake Forest School of Medicine, Winston-Salem, NC; 4University of Alberta, Edmonton, Alberta, Canada; 5Department of Metabolism, Endocrinology and Molecular Medicine, Osaka City University Graduate School of Medicine, Osaka; 6Department of Endocrinology, Tenri Hospital, Nara; 7Department of Healthcare Epidemiology, Kyoko University Graduate School of Medicine and Public Health, Kyoto; 8Fukushima Medical University Center for Innovation in Clinical Research, Fukushima; 9Department of Nephrology, Tokyo Medical University, Tokyo, Japan; 10Department of Medicine, Division of Nephrology, University Hospital, Würzburg, Germany; 11United Kingdom Renal Registry, Southmead Hospital, Bristol; 12Addenbrooke’s Hospital, Cambridge, United Kingdom; 13Division of Genetic Epidemiology, Department of Medical Genetics, Molecular and Clinical Pharmacology, Innsbruck Medical University, Innsbruck, Austria; and 14Division of Nephrology and Hypertension, University of California, Irvine, CA.

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Address correspondence to Christopher J. Hill, MB, Centre for Public Health, Queen’s University Belfast, Institute of Clinical Sciences Block B, Royal Victoria Hospital, Grosvenor Road, Belfast, Northern Ireland, United Kingdom BT12 6BA. E-mail: chill05@qub.ac.uk

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Given the increasing prevalence of diabetic kidney disease in many countries, there is surprisingly little evidence to guide blood glucose control in patients with ESRD. In many cases, best practice is extrapolated from studies of diabetic patients with normal kidney function. In diabetic patients with normal kidney function, glycated hemoglobin (HbA1c) is used as a measure of blood glucose control during the preceding 8 weeks. HbA1c levels correlate well with the risk of developing diabetes-related complications such as diabetic nephropathy, as well as with increased mortality risk.

However, significant changes occur in HbA1c metabolism as kidney function declines. Because HbA1c is formed through a nonenzymatic reaction between hemoglobin and glucose, hemoglobin concentration and duration of red blood cell survival are critical factors in determining final HbA1c concentrations. In advanced kidney disease, a combination of altered iron metabolism, reduced erythropoietin, reduced red blood cell production, and increased red blood cell turnover occurs. This results in limited time for the nonenzymatic reaction between hemoglobin and glucose to occur. Additionally, the use of erythropoiesis-stimulating agents results in the production of large numbers of immature red blood cells with variable hemoglobin concentrations. These metabolic changes have led to concerns that HbA1c may not be a reliable marker of blood glucose control or useful in predicting outcomes in patients with ESRD.

Current clinical practice guidelines for hemodialysis patients suggest a variety of target HbA1c levels due to a lack of high-quality evidence. There is a clear need to establish an evidence base for best practice to help hemodialysis patients and guide not just supervising nephrologists, but also diabetologists and general practitioners managing persons with diabetes-related ESRD.

We investigated the association between HbA1c values and mortality risk in diabetic patients receiving hemodialysis.

**METHODS**

**Search Strategy**

We undertook a systematic review in accordance with recognized methods. We searched MEDLINE, MEDLINE In-Process, Embase, Cochrane Library, and Web of Science for studies published between each database’s inception and April 30, 2012. This was updated later to include up to December 1, 2012, and no new records eligible for inclusion were identified. Search terms are detailed in Table S1 (provided as online supplementary material). We also searched reference lists of included studies.

**Inclusion/Exclusion Criteria**

Reports were reviewed by one author and cross-checked by a second. We included observational studies or randomized controlled trials that assessed the association of HbA1c level and mortality. We included studies in which laboratory measurements were taken at or after the initiation of hemodialysis. We excluded studies with only peritoneal dialysis patients. To avoid duplication of results, we excluded studies for which a subsequent study with longer follow-up of the same patient cohort had been reported.

**Statistical Analysis**

Due to differing reporting methods in published studies, we developed a minimum data set and a standardized results template (Table S2). We contacted corresponding authors and requested either anonymized individual patient-level data or that authors reanalyze their data using our template. Mortality risk was assessed using hazard ratios (HRs). HbA1c values were separated into baseline (single measurement taken at study enrollment) and mean (mean of values during each contributing study period) results as determined from the original articles or data provided. HbA1c values were expressed in National Glycohemoglobin Standardization Program (NGSP) format. HbA1c values reported in Japanese Diabetes Society format were converted to NGSP format. HbA1c results were categorized as $<5.5\% (\leq 36 \text{ mmol/mol})$, $5.5\%-6.4\% (37-46 \text{ mmol/mol})$, $6.5\%-7.4\% (48-57 \text{ mmol/mol})$, $7.5\%-8.4\% (58-68 \text{ mmol/mol})$, and $\geq 8.5\% (\geq 69 \text{ mmol/mol})$.

For generation of HRs, the $6.5\%-7.4\%$ HbA1c category was used as the reference. Adjustments were made for as many of the following variables as were available: age, sex, diabetes type, dialysis vintage, and hemoglobin concentration. We highlighted studies in which all the covariates were not available (Table 1). When hemoglobin concentration was not available, we accepted hematocrit and converted this to a hemoglobin concentration using previously described methodology.

Anonymized patient data were analyzed using Cox proportional hazards methodology to calculate HRs. Patients were censored if they changed to peritoneal dialysis therapy, underwent successful kidney transplantation, or moved out of the study area. Schoenfeld residuals or visual inspection of log($-$log) plots were used to check compliance with proportional hazards assumptions. Logarithms of HRs (and corresponding standard errors) were used to pool estimates. Pooled estimates were generated using RevMan, version 5.2 (The Nordic Cochrane Centre, The Cochrane Collaboration). We assessed statistical heterogeneity using the $I^2$ statistic and the $\chi^2$ test. We anticipated study heterogeneity due to inclusion of observational data and therefore adopted a conservative approach using random-effects models to generate pooled estimates.

We conducted an a priori sensitivity analysis by dividing patients into incident and prevalent groups defined by their hemodialysis vintage. This was undertaken primarily to investigate whether HbA1c level remained a significant modifier of mortality risk in both new hemodialysis patients and those who had been established on treatment. Incident patients were defined as those who had been receiving maintenance hemodialysis for 90 or fewer days at the date of study enrollment. Prevalent patients were those who had been receiving maintenance hemodialysis for more than 90 days at study enrollment. HRs and pooled estimates were generated using the same methodology as described previously for the overall analysis.

All results were reported in accordance with the MOOSE (Meta-analysis of Observational Studies in Epidemiology) criteria.

**RESULTS**

**Identification of Studies**

We identified 947 records from database searches and one of us (A.I.A.) provided one additional unpublished study. After exclusion of duplicate records and those that were not observational studies or
Table 1. Characteristics of Included Studies

| Study & Location | Study Type | Participants | Age (y) | Adjustments Available for Meta-analysis | Follow-up (y) | Data Available |
|------------------|------------|--------------|---------|----------------------------------------|---------------|----------------|
| Adler et al28 (2012; UK) | Retrospective observational | 3,157 maintenance dialysis pts (72.4% HD); diabetes type not recorded | 60 [50-71] | Age, sex, dialysis vintage, hemoglobin | Median: 2.7 | ✔ ✔ |
| Drechsler et al29 (2009; Germany) | Secondary analysis of randomized controlled trial data | 1,255 HD pts with T2DM enrolled in 4D Study | 65.7 ± 8.3 | Age, sex, dialysis vintage, hemoglobin | Median: 4 | ✔ ✔ ✔ ✔ |
| Freedman et al30 (2011; USA) | Prospective observational | 444 maintenance dialysis pts (90.3% HD); 91.4% T2DM | 62.3 ± 12.4 | Age, sex, diabetes type, dialysis vintage, hemoglobin | Median: 2.25 | ✔ ✔ ✔ ✔ |
| Hayashino et al31 (2006; Japan) | Prospective observational | 4,911 maintenance HD pts; 1,569 had diabetes | 59 | Age, sex, diabetes type, dialysis vintage, hemoglobin | Median: 1.9 | ✔ ✔ ✔ ✔ |
| Okada et al32 (2007; Japan) | Prospective observational | 78 maintenance HD pts with T2DM | 63 ± 10 | Age, sex, dialysis vintage, hemoglobin | Median: 3.4 | ✔ ✔ |
| Oomichi et al33 (2006; Japan) | Prospective observational | 114 maintenance HD pts; 91.2% T2DM | 60.8 ± 10.2 | Age, sex, diabetes type, dialysis vintage, hemoglobin | Mean: 3.8 | ✔ ✔ |
| Ricks et al34 (2012; USA) | Retrospective observational | 54,757 maintenance HD patients; diabetes type not recorded | 63 ± 13 | Age, sex, dialysis vintage, hemoglobin<sup>b</sup> | Median: 2.4 | ✔ ✔ ✔ ✔ |
| Shurraw et al35 (2010; Canada) | Retrospective observational | 1,484 maintenance HD pts; diabetes type not reported | 66 [54-75] | Age, sex, dialysis vintage, hemoglobin<sup>b</sup> | Median: 1.5 | ✔ ✔ |
| Sturm et al36 (2011; Austria) | Prospective observational | 78 maintenance dialysis pts (94% HD) with T2DM | 65.5 ± 9.2 | Age, sex, hemoglobin | Median: 2.7 | ✔ ✔ ✔ |
| Williams et al37 (2010; USA) | Retrospective observational | 24,875 maintenance HD pts; 94.5% T2DM | 63.7 ± 12.1 | No adjustments available<sup>c</sup> | Mean: 1.8 | ✔ ✔ |

Note: Values for age are given as mean, mean ± standard deviation, or median [interquartile range].
Abbreviations: 4D Study, Die Deutsche Diabetes Dialyse Studie; HbA<sub>1c</sub>, hemoglobin A<sub>1c</sub> (glycated hemoglobin); HD, hemodialysis; pts, patients; T2DM, type 2 diabetes mellitus; UK, United Kingdom; USA, United States.
<sup>a</sup>Unpublished.
<sup>b</sup>Results supplied from the study by Ricks et al were adjusted additionally for entry quarter into study.
<sup>c</sup>Results from Williams et al could not be included in adjusted analyses or in any sensitivity analyses.
randomized controlled trials, 18 full-text articles and one unpublished study were reviewed.\textsuperscript{19,28-45} Thirteen studies met the inclusion criteria (Fig 1). Due to differing study methodology and reporting, it proved impossible to combine estimates using data from published articles (Table S3). The corresponding author of each study was contacted and asked to either provide anonymized individual patient data or reanalyze results. Three authors did not respond and the necessary data could not be extracted from the published articles, so these studies were excluded (Table S4).\textsuperscript{19,38,41} Four studies provided anonymized data\textsuperscript{29,30,32,33} and 5 provided reanalyzed results according to our template (Table S2).\textsuperscript{28,31,34-36} Some results from the publication by Williams et al\textsuperscript{37} were extracted using previously described methodology,\textsuperscript{46} although they could be incorporated in only an unadjusted baseline HbA\textsubscript{1c} analysis.

**Study Characteristics**

Descriptions of studies included in the analysis are listed in Table 1. In brief, there were 5 prospective observational studies, 4 retrospective observational studies, and one reanalysis of a randomized controlled trial (that originally investigated the effect of statin use in diabetic patients on hemodialysis therapy). The number of diabetic patients analyzed from these studies was 83,684. In the included studies, there were 32,669 deaths (excluding the study by Williams et al,\textsuperscript{37} for which this information was not available). Individual study numbers varied significantly from 78 to 54,757 patients. Some studies also included peritoneal dialysis patients or patients who did not have diabetes who were removed prior to analysis. Three studies could not adjust for diabetes type, 3 studies included only type 2 diabetic patients, and in the rest, most patients had type 2 diabetes. Eight studies measured baseline (single) HbA\textsubscript{1c} levels\textsuperscript{29,31,33-37} and 6 studies contributed data to the mean HbA\textsubscript{1c} analysis\textsuperscript{28,30,32,34,36}.

**Baseline HbA\textsubscript{1c} Analysis**

Eight studies\textsuperscript{29,31,33-37} were used to produce pooled unadjusted estimates; however, only 7 could be used in the adjusted analysis. The pooled analysis of
baseline HbA1c values is shown in Table 2. Unadjusted analysis showed no significant associations between HbA1c values and mortality risk (Fig 2). After adjustment, compared with HbA1c levels of 6.5%-7.4%, patients with HbA1c levels ≥8.5% had an increased risk of death (HR, 1.14; 95% confidence interval [CI], 1.09-1.19; P < 0.001), which was consistent across studies (I² = 0%; P = 0.6). There was no evidence of a difference in risk of death in patients with HbA1c levels ≤5.4% (HR, 1.08; 95% CI, 0.79-1.49; P = 0.6). However, this was not consistent across studies (I² = 73%; P = 0.001).

### Mean HbA1c Analysis

Six studies contributed to the pooled unadjusted and adjusted estimates. Six studies contributed to the sensitivity analysis of baseline HbA1c values in incident patients. The unadjusted HRs in this subanalysis did not differ significantly from the reference category (HbA1c, 6.5%-7.4%), except for those with baseline HbA1c levels ≥8.5% (HR, 0.91; 95% CI, 0.86-0.97; P = 0.001), but this effect was lost after adjustment (HR, 1.11; 95% CI, 0.96-1.28; P = 0.2). This result was consistent across all studies (I² = 0%; P = 0.8). After adjustment, no statistically significant differences in HRs were found irrespective of baseline HbA1c values. Full results are listed in Table 3.

Five studies contributed to the sensitivity analysis of baseline HbA1c values in prevalent patients. No statistically significant differences in risk of death were present in the unadjusted analysis. After adjustment, baseline HbA1c values of 7.5%-8.4% and ≥8.5% were associated with increased risk of death (HRs of 1.29 [95% CI, 1.01-1.15; P = 0.03] and 1.20 [95% CI, 1.01-1.42; P = 0.04], respectively). These effects were consistent across studies (Table 4).

Four studies contributed to the sensitivity analysis of mean HbA1c values in incident patients. Unadjusted analysis revealed a higher risk of death if mean HbA1c values were lower than the reference category (HRs of 1.45 [95% CI, 1.38-1.52; P < 0.001] for HbA1c ≤5.4% and 1.13 [95% CI, 0.91-1.07; P = 0.3]) and 1.20 [95% CI, 0.98-1.08; P = 0.05]) with no heterogeneity (I² = 0%; P = 0.9).

### Sensitivity Analysis in Incident and Prevalent Hemodialysis Patients

As shown in Table 1, not all studies could contribute to each of the sensitivity analyses. Six studies contributed to the sensitivity analysis of baseline HbA1c values in incident patients. The unadjusted HRs in this subanalysis did not differ significantly from the reference category (HbA1c, 6.5%-7.4%), except for those with baseline HbA1c levels ≥8.5% (HR, 0.91; 95% CI, 0.86-0.97; P = 0.001), but this effect was lost after adjustment (HR, 1.11; 95% CI, 0.96-1.28; P = 0.2). This result was consistent across all studies (I² = 0%; P = 0.8). After adjustment, no statistically significant differences in HRs were found irrespective of baseline HbA1c values. Full results are listed in Table 3.

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Four studies contributed to the sensitivity analysis of mean HbA1c values in incident patients. Unadjusted analysis revealed a higher risk of death if mean HbA1c values were lower than the reference category (HRs of 1.45 [95% CI, 1.38-1.52; P < 0.001] for HbA1c ≤5.4% and 1.13 [95% CI, 0.91-1.07; P = 0.3]).
Abbreviation: CI, confidence interval.

**Table 3. Unadjusted and Adjusted HRs for Incident Patients**

| HbA1c (%) | Pooled HR (95% CI) | P | I²; P for Heterogeneity | Pooled HR (95% CI) | P | I²; P for Heterogeneity |
|----------|-------------------|---|-------------------------|-------------------|---|-------------------------|
| **Baseline** |                   |               |                         |                   |               |                         |
| ≤5.4     | 1.01 (0.77-1.34)  | 0.9 | 34% ; 0.2               | 0.94 (0.68-1.31)  | 0.7 | 49% ; 0.1               |
| 5.5-6.4  | 0.99 (0.81-1.21)  | 0.9 | 24% ; 0.2               | 0.95 (0.75-1.22)  | 0.7 | 41% ; 0.1               |
| 6.5-7.4  | 1.00 (reference)  |    |                         | 1.00 (reference)  |    |                         |
| 7.5-8.4  | 1.29 (0.82-2.01)  | 0.3 | 54% ; 0.07              | 1.10 (0.78-1.54)  | 0.6 | 50% ; 0.09              |
| ≥8.5     | 0.91 (0.86-0.97)  | 0.001 | 0% ; 0.8             | 1.11 (0.96-1.28)  | 0.2 | 56% ; 0.06              |
| **Mean** |                   |               |                         |                   |               |                         |
| ≤5.4     | 1.45 (1.38-1.52)  | <0.001 | 0% ; 0.8             | 1.29 (1.23-1.35)  | <0.001 | 0% ; 0.8             |
| 5.5-6.4  | 1.13 (1.08-1.18)  | 0.0 | 0% ; 0.9                | 1.05 (1.00-1.10)  | 0.04 | 0% ; 0.8               |
| 6.5-7.4  | 1.00 (reference)  |    |                         | 1.00 (reference)  |    |                         |
| 7.5-8.4  | 1.09 (0.68-1.74)  | 0.7 | 59% ; 0.06              | 1.27 (0.78-2.05)  | 0.4 | 57% ; 0.07              |
| ≥8.5     | 1.06 (0.71-1.58)  | 0.8 | 39% ; 0.2               | 1.24 (1.17-1.32)  | <0.001 | 0% ; 0.7             |

*Note: For HbA1c values, 5.4% = 36 mmol/mol, 5.5%-6.4% = 37-46 mmol/mol, 6.5%-7.4% = 48-57 mmol/mol, 7.5%-8.4% = 58-68 mmol/mol, and 8.5% = 69 mmol/mol.*

Abbreviations: CI, confidence interval; HbA1c, hemoglobin A1c (glycated hemoglobin); HR, hazard ratio.

*aAdjusted for age, sex, diabetes type, dialysis vintage, and hemoglobin concentration when available.*
mean HbA1c values ≥8.5% were associated with increased mortality risk; HR, 1.11 (95% CI, 1.06-1.17; P < 0.001). After adjustment, the risk of death in this category was more significant (HR, 1.31; 95% CI, 1.12-1.52; P < 0.001). This effect was consistent across studies (I² = 43%; P = 0.1). In comparison, HbA1c levels ≤5.4% were not associated with increased mortality risk (HR, 1.06; 95% CI, 0.87-1.28; P = 0.4; Table 4).

**DISCUSSION**

This study has shown that HbA1c level remains a useful clinical tool in predicting mortality risk in diabetic patients on maintenance hemodialysis therapy. We have shown that HbA1c levels ≥8.5% (≥69 mmol/mol) are associated with up to a 29% increase in the adjusted risk of death compared to the reference category of 6.5%-7.4% (48-57 mmol/mol).

In patients with normal kidney function, higher HbA1c levels are associated with increased risk of developing complications. The association between glycemic control (measured by HbA1c) and mortality risk, particularly in type 2 diabetes, is less consistent, with some observational studies suggesting associations that have not been confirmed in subsequent clinical trials. There are also concerns about using HbA1c measurements in hemodialysis patients, with some authors arguing that alternative glycemic measures such as fructosamine or glycated albumin should be used. However, both fructosamine and glycated albumin measurements are associated with methodological difficulties. Fructosamine is a collective term used to describe all serum glycated proteins (including albumin) that have formed stable ketoamines, whereas glycated albumin is a single molecule. Serum levels of both therefore can be affected by conditions that alter total serum protein concentrations (such as malnutrition). Adoption of these alternative approaches would necessitate significant re-education of clinicians in how to interpret and act on a new measurement system used in only a subset of diabetic patients.

By pooling data from multiple sources, we have shown that HbA1c levels ≥8.5% (≥69 mmol/mol) are predictive of increased mortality risk. In addition, although in overall analyses there appeared to be no association between very low mean HbA1c values (≤5.4% [≤36 mmol/mol]) and mortality, this result was influenced by one outlier. If the study by Adler et al was excluded from this comparison, a mean HbA1c value ≤5.4% (≤36 mmol/mol) would have been associated with increased mortality risk (HR, 1.23; 95% CI, 1.19-1.27; P < 0.001). Adler et al included patients who had already survived on hemodialysis for more than 180 days. It is possible that this may have introduced a survivor effect whereby only fitter patients survived beyond the early period of high mortality risk after hemodialysis therapy initiation. Heterogeneity between studies also was consistently highest in the category with HbA1c levels ≥8.5% (≥69 mmol/mol), possibly indicating that this subgroup of patients has differing characteristics. Conceivably, this category could contain patients with low HbA1c values because of excellent diabetes control who might be expected to have better survival. However, this group also could contain patients who have low HbA1c values due to overly stringent control (leading to recurrent hypoglycemic episodes) or who are so nutritionally depleted that their HbA1c values are very low and therefore might be

### Table 4. Unadjusted and Adjusted HRs for Prevalent Patients

| HbA1c (%) | Unadjusted HR (95% CI) | P | I²; P for Heterogeneity | Adjusted HR (95% CI) | P | I²; P for Heterogeneity |
|----------|------------------------|---|-------------------------|---------------------|---|-------------------------|
| Baseline |                        |   |                         |                     |   |                         |
| ≤5.4     | 1.32 (0.87-2.01)       | 0.2| 79%; 0.007              | 1.16 (0.79-1.70)    | 0.5| 75%; 0.003              |
| 5.5-6.4  | 1.07 (0.79-1.46)       | 0.7| 78%; 0.001              | 1.04 (0.78-1.37)    | 0.8| 72%; 0.006              |
| 6.5-7.4  | 1.00 (reference)       |   |                         | 1.00 (reference)    |   |                         |
| 7.5-8.4  | 0.99 (0.94-1.06)       | 0.9| 0%; 0.5                 | 1.08 (1.01-1.15)    | 0.03| 0%; 0.7                |
| ≥8.5     | 1.01 (0.87-1.16)       | 0.9| 16%; 0.3                | 1.20 (1.01-1.42)    | 0.04| 24%; 0.3                |
| Mean     |                        |   |                         |                     |   |                         |
| ≤5.4     | 1.19 (0.94-1.52)       | 0.2| 75%; 0.003              | 1.06 (0.87-1.28)    | 0.4| 60%; 0.04               |
| 5.5-6.4  | 1.00 (0.91-1.10)       | 0.9| 31%; 0.2                | 0.92 (0.83-1.03)    | 0.2| 25%; 0.3                |
| 6.5-7.4  | 1.00 (reference)       |   |                         | 1.00 (reference)    |   |                         |
| 7.5-8.4  | 0.95 (0.85-1.05)       | 0.3| 25%; 0.3                | 1.03 (0.91-1.16)    | 0.4| 33%; 0.2                |
| ≥8.5     | 1.11 (1.06-1.17)       | <0.001| 0%; 0.6 | 1.31 (1.12-1.52) | <0.001| 43%; 0.1 |

**Note:** For HbA1c values, 5.4% = 36 mmol/mol, 5.5%-6.4% = 37-46 mmol/mol, 6.5%-7.4% = 48-57 mmol/mol, 7.5%-8.4% = 58-68 mmol/mol, and 8.5% = 69 mmol/mol.

Abbreviations: CI, confidence interval; HbA1c, hemoglobin A1c (glycated hemoglobin); HR, hazard ratio.

*Adjusted for age, sex, diabetes type, dialysis vintage, and hemoglobin concentration when available.
expected to have reduced survival. Conversely, comparisons of patients with the highest HbA1c values (≥8.5% [≥69 mmol/mol]) tended to have very low levels of heterogeneity, suggesting that such patients represent a much more homogenous group, possibly because there are fewer causes of high HbA1c levels (other than poor glycemic control).

We undertook an a priori sensitivity analysis by separating patients into those who had been on hemodialysis therapy for 90 or fewer days or more than 90 days. There is a significant mortality rate in the period after hemodialysis therapy initiation and we aimed to investigate whether HbA1c level remained a significant modifier of mortality risk in this setting. A similar association between HbA1c level (especially mean values) and mortality risk was evident in both incident and prevalent patients, suggesting that glycemic control may still be important, even in the early stages of hemodialysis therapy. As noted previously, there was significant heterogeneity present in comparisons involving patients with HbA1c values <5.4% (<36 mmol/mol), and although there was a higher risk of death among incident patients whose mean HbA1c value was ≤5.4% (<36 mmol/mol), this was not present in prevalent patients.

The lack of evidence to guide best practice in managing diabetes in chronic kidney disease is reflected in the variety of target HbA1c values suggested by current national and international guidance documents. UK Renal Association guidance on the management of cardiovascular disease risk indicates a target value of 6.5%-7.5% (48-57 mmol/mol). In contrast, the NKF-KDOQI (National Kidney Foundation–Kidney Disease Outcomes Quality Initiative) guideline suggests that all patients, irrespective of chronic kidney disease stage, should target an HbA1c level <7% (<53 mmol/mol). However, the KDOQI guideline suggests that patients at increased risk of hypoglycemia or of limited life expectancy might not benefit from strict control based on evidence from studies such as the ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial. Patients with moderately or severely decreased kidney function were excluded from the majority of such studies. Therefore, it is arguable whether evidence from them can be extrapolated to hemodialysis patients. We believe that this meta-analysis, although primarily of observational studies, provides the strongest evidence currently available for the adoption of a minimum HbA1c target of <8.5% (<69 mmol/mol) in diabetic hemodialysis patients due to the associated increased mortality risk above this level. Given the higher mortality risk in some patients with lower HbA1c values (≤5.4% [≤36 mmol/mol]), these very low values should be avoided, particularly in incident hemodialysis patients. Further prospective clinical trials are needed to confirm these findings, investigate the impact of glycemic control on other diabetes-related complications, and investigate other glycemic assays in hemodialysis patients.

The strengths of our analysis are the large number of patients included and its multinational nature. This increases the applicability of our findings across many countries with varying incidence rates of diabetes, as well as different health care systems and diabetes management strategies. A further strength is that individual patient data (or results from prespecified analyses) were used in the analyses, which allowed consistent categorization of HbA1c values across studies and consistent adjustment for confounders. To our knowledge, there are no clinical trials investigating the role of improved blood glucose control in reducing diabetes-related complications or mortality in hemodialysis patients and previous studies have actively excluded patients with advanced diabetic kidney disease. Therefore, this systematic review and meta-analysis currently represents the most significant investigation into the benefits of glycemic control conducted on hemodialysis patients.

However, there are some potential limitations to this study. First, our analysis is driven primarily by large numbers of patients with type 2 diabetes. Unfortunately, although we attempted to adjust for diabetes type, some studies such as that by Ricks et al64 (the largest study in our meta-analysis) could not adjust for this variable. Because most of these patients were likely to have type 2 diabetes, it is probable that this influenced our results. It therefore is not possible to comment on whether the risk of death in a sample of exclusively patients with type 1 diabetes would differ significantly from those we report. However, because most diabetic patients have type 2 diabetes, this study is still applicable to a large number of patients. Second, we could adjust for only a relatively small set of covariates across all the studies. Due to significant study heterogeneity, we developed a “minimum” data set to produce pooled estimates. Although we adjusted for a number of factors associated with survival on hemodialysis therapy, there are other potential confounders, such as urea clearance on dialysis (Kt/V), nutritional status, and comorbid conditions. Ideally, we would have liked to use a time-dependent covariate analysis to account more accurately for changes in HbA1c levels over time rather than using mean values; however, this was not possible with the available data. Reverse causality also may affect the mean HbA1c analysis because HbA1c values near the time of death could reflect declining health status rather than cause it. Within the sensitivity analyses, we would have preferred to examine within-study interactions between HbA1c level and incident/prevalent status. However, this was
not possible with the data available and this could have introduced bias into the sensitivity analyses. This study also investigated the association only between HbA$1c$ values and mortality in diabetic patients on hemodialysis therapy and therefore we cannot comment on potential benefits of improved blood glucose control on other diabetes-related complications. As with all systematic reviews, we cannot exclude the possibility that publication bias may have influenced our results, but the extensive literature searches and contact with experts in this field who published the included studies will have reduced this possibility. Finally, all studies included in this meta-analysis were essentially observational in nature, and although it is biologically plausible that blood glucose control, as measured by HbA$1c$ level, would have a significant impact on mortality, it is possible that other unmeasured potential confounders might be influencing the results.

In conclusion, our findings suggest that HbA$1c$ values $\geq 8.5\%$ (\(\geq 69\) mmol/mol) are associated with increased mortality risk in diabetic patients on maintenance hemodialysis therapy. This association is present in both new (incident) hemodialysis patients and patients established on treatment (prevalent). Given the increasing prevalence of diabetic patients on hemodialysis therapy in many countries, it is recognized that other health care professionals outside nephrology will come into contact with increasing numbers of these patients. Therefore, the findings of this study should be incorporated into general diabetes management guidance.

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**SUPPLEMENTARY MATERIAL**

Table S1: Search strategy.
Table S2: Results template.
Table S3: Characteristics of studies analyzed.
Table S4: Characteristics of studies not analyzed.

Figure S1: Hazard ratios of mortality associated with mean HbA$1c$ values.

Note: The supplementary material accompanying this article (http://dx.doi.org/10.1053/j.ajkd.2013.06.020) is available at www.ajkd.org

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