Title
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Journal
American Journal of Kidney Diseases, 63(1)

ISSN
0272-6386

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Publication Date
2014

DOI
10.1053/j.ajkd.2013.06.020

AJKD
Original Investigation

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

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Background: Studies investigating the association between glycated hemoglobin (HbA_{1c}) 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 HbA_{1c} 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 HbA_{1c} values. Mean HbA_{1c} values were calculated using all individual-patient HbA_{1c} 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 HbA_{1c} levels ≥8.5% (≥69 mmol/mol) had increased mortality (7 studies; HR, 1.14; 95% CI, 1.09-1.19) compared with patients with HbA_{1c} levels of 6.5%-7.4% (48-57 mmol/mol). Likewise, patients with a mean HbA_{1c} 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 HbA_{1c} 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 HbA_{1c} levels ≤5.4% also were associated with increased mortality risk (4 studies; HR, 1.29; 95% CI, 1.23-1.35).

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

Conclusions: Despite concerns about the utility of HbA_{1c} measurement in hemodialysis patients, high levels (≥8.5%) are associated with increased mortality risk. Very low HbA_{1c} levels (≤5.4%) also may be associated with increased mortality risk.

Am J Kidney Dis. 63(1):84-94.

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

Editorial, p. 10

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]

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Received April 10, 2013. Accepted in revised form June 27, 2013. Originally published online August 19, 2013.

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0272-6386/$36.00
http://dx.doi.org/10.1053/j.ajkd.2013.06.020

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.[6,7] 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 (HbA_{1c}) is used as a measure of blood glucose control during the preceding 8 weeks.[8-10] HbA_{1c} levels correlate well with the risk of developing diabetes-related complications such as diabetic nephropathy, as well as with increased mortality risk.[11-16]

However, significant changes occur in HbA_{1c} metabolism as kidney function declines. Because HbA_{1c} 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 HbA_{1c} 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 HbA_{1c} may not be a reliable marker of blood glucose control or useful in predicting outcomes in patients with ESRD.[17-22]

Current clinical practice guidelines for hemodialysis patients suggest a variety of target HbA_{1c} levels due to a lack of high-quality evidence.[6,7] 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 HbA_{1c} 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 HbA_{1c} 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). HbA_{1c} 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. HbA_{1c} values were expressed in National Glycohemoglobin Standardization Program (NGSP) format.[23] HbA_{1c} values reported in Japanese Diabetes Society format were converted to NGSP format. HbA_{1c} results were categorized as $\leq$5.4% ($\leq$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 $\geq$8.5% ($\geq$69 mmol/mol).

For generation of HRs, the 6.5%-7.4% HbA_{1c} 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.[24]

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[25] and χ^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.[26]

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 HbA_{1c} 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.[27]

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			
						Baseline HbA_{1c}	Mean HbA_{1c}	Incident Patients	Prevalent Patients
Adler et al[28] (2012; UK)[a]	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 al[29] (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 al[30] (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 al[31] (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 al[32] (2007; Japan)	Prospective observational	78 maintenance HD pts with T2DM	63 ± 10	Age, sex, dialysis vintage, hemoglobin	Median: 3.4		✓		✓
Oomichi et al[33] (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 al[34] (2012; USA)	Retrospective observational	54,757 maintenance HD patients; diabetes type not recorded	63 ± 13	Age, sex, dialysis vintage, hemoglobin[b]	Median: 2.4	✓	✓	✓	✓
Shurraw et al[35] (2010; Canada)	Retrospective observational	1,484 maintenance HD pts; diabetes type not reported	66 [54-75]	Age, sex, dialysis vintage, hemoglobin	Median: 1.5	✓		✓	
Sturm et al[36] (2011; Austria)	Prospective observational	78 maintenance dialysis pts (94% HD) with T2DM	65.5 ± 9.2	Age, sex, hemoglobin	Median: 2.7	✓	✓	✓	
Williams et al[37] (2010; USA)	Retrospective observational	24,875 maintenance HD pts; 94.5% T2DM	63.7 ± 12.1	No adjustments available[c]	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_{1c}, hemoglobin A_{1c} (glycated hemoglobin); HD, hemodialysis; pts, patients; T2DM, type 2 diabetes mellitus; UK, United Kingdom; USA, United States.

[a]Unpublished.

[b]Results supplied from the study by Ricks et al were adjusted additionally for entry quarter into study.

[c]Results from Williams et al could not be included in adjusted analyses or in any sensitivity analyses.

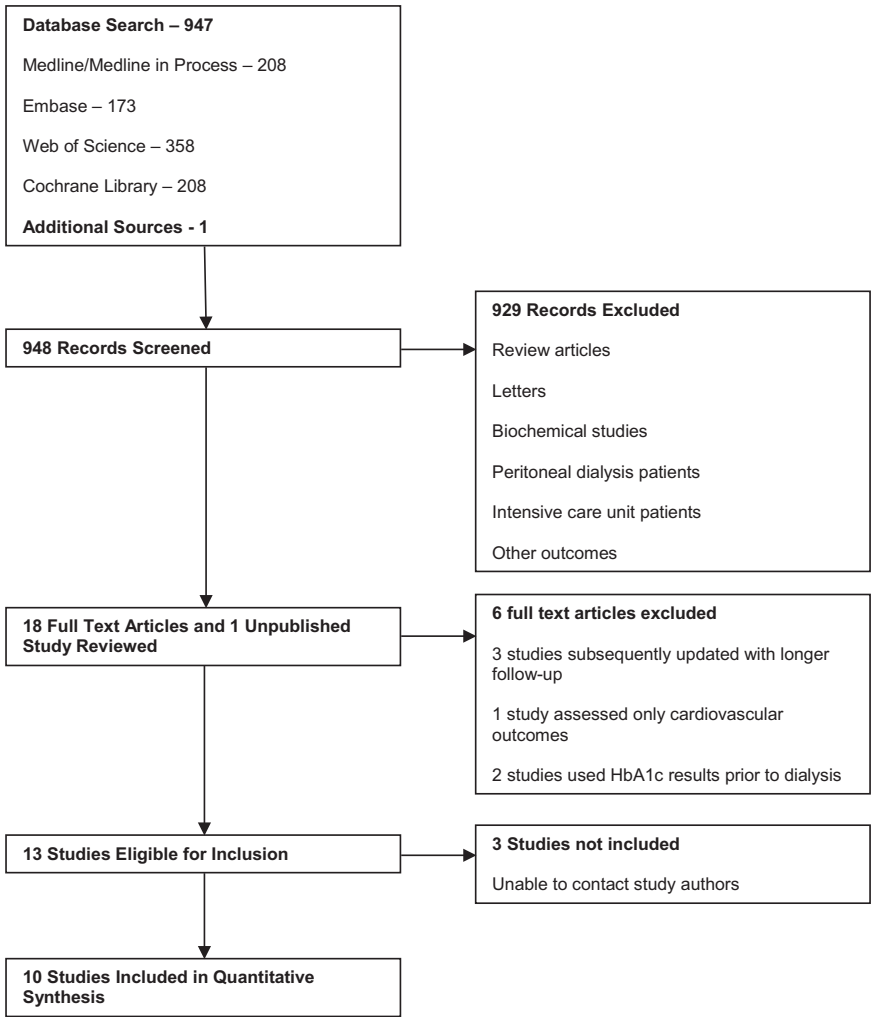

Figure 1. Study flow diagram. Abbreviation: HbA_{1c}, hemoglobin A_{1c}.

randomized controlled trials, 18 full-text articles and one unpublished study were reviewed.[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).[19,38,41] Four studies provided anonymized data[29,30,32,33] and 5 provided reanalyzed results according to our template (Table S2).[28,31,34-36] Some results from the publication by Williams et al[37] were extracted using previously described methodology,[46] although they could be incorporated in only an unadjusted baseline HbA_{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,[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_{1c} levels[29-31,33-37] and 6 studies contributed data to the mean HbA_{1c} analysis.[28-30,32,34,36]

Baseline HbA_{1c} Analysis

Eight studies[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

Table 2. Unadjusted and Adjusted HRs for Baseline and Mean HbA_{1c} Values

	Unadjusted			Adjusted[a]		
HbA_{1c} (%)	Pooled HR (95% CI)	*P*	I^2; *P* for Heterogeneity	Pooled HR (95% CI)	*P*	I^2; *P* for Heterogeneity
Baseline						
≤5.4	1.12 (0.99-1.28)	0.08	75%; <0.001	1.08 (0.79-1.49)	0.6	73%; 0.001
5.5-6.4	1.00 (0.89-1.12)	0.9	72%; <0.001	1.01 (0.79-1.28)	0.9	73%; 0.001
6.5-7.4	1.00 (reference)	—	—	1.00 (reference)	—	—
7.5-8.4	0.84 (0.68-1.03)	0.1	89%; <0.001	1.05 (0.90-1.22)	0.6	30%; 0.2
≥8.5	0.89 (0.76-1.03)	0.1	71%; <0.001	1.14 (1.09-1.19)	<0.001	0%; 0.6
Mean						
≤5.4	1.23 (0.97-1.55)	0.09	73%; 0.002	1.09 (0.89-1.34)	0.2	63%; 0.02
5.5-6.4	1.02 (0.93-1.13)	0.7	33%; 0.2	0.98 (0.91-1.06)	0.3	18%; 0.3
6.5-7.4	1.00 (reference)	—	—	1.00 (reference)	—	—
7.5-8.4	0.93 (0.89-0.97)	<0.001	0%; 0.8	1.04 (1.00-1.08)	0.05	0%; 0.9
≥8.5	1.01 (0.97-1.05)	0.6	0%; 0.9	1.29 (1.23-1.35)	<0.001	0%; 0.5

Note: For HbA_{1c} 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; HbA_{1c}, hemoglobin A_{1c} (glycated hemoglobin); HR, hazard ratio.

[a]Adjusted for age, sex, diabetes type, dialysis vintage, and hemoglobin concentration when available.

baseline HbA_{1c} values is shown in Table 2. Unadjusted analysis showed no significant associations between HbA_{1c} values and mortality risk (Fig 2). After adjustment, compared with HbA_{1c} levels of 6.5%-7.4%, patients with HbA_{1c} 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 ($I^2 = 0\%$; $P = 0.6$). There was no evidence of a difference in risk of death in patients with HbA_{1c} levels ≤5.4% (HR, 1.08; 95% CI, 0.79-1.49; $P = 0.6$). However, this was not consistent across studies ($I^2 = 73\%$; $P = 0.001$).

Mean HbA_{1c} Analysis

Six studies contributed to the pooled unadjusted and adjusted estimates.[28-30,32,34,36] The pooled analysis of mean HbA_{1c} values is also shown in Table 2. In the unadjusted analysis, mean HbA_{1c} values of 7.5%-8.4% were associated with lower mortality risk compared with mean HbA_{1c} values of 6.5%-7.4% (HR, 0.93; 95% CI, 0.89-0.97; $P < 0.001$; Fig S1). Compared with HbA_{1c} levels of 6.5%-7.4%, no other significant differences in risk of death were apparent. After adjustment, this effect was no longer present; however, mean HbA_{1c} values ≥8.5% were associated with increased mortality risk (HR, 1.29; 95% CI, 1.23-1.35; $P < 0.001$; Fig S1). This effect was consistent across studies ($I^2 = 0\%$; $P = 0.5$). Very low HbA_{1c} values (≤5.4%) were not associated with increased mortality risk. Heterogeneity in the category of mean HbA_{1c} level ≤5.4% was relatively high ($I^2 = 64\%$; $P = 0.02$) and was due largely to one study by Adler et al[28] that used slightly different inclusion criteria. If the study by Adler et al[28] was excluded, the risk of death would have been increased (HR, 1.23; 95% CI, 1.19-1.27; $P < 0.001$) with no heterogeneity ($I^2 = 0\%$; $P = 0.9$).

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[29-31,34-36] contributed to the sensitivity analysis of baseline HbA_{1c} values in incident patients. The unadjusted HRs in this subanalysis did not differ significantly from the reference category (HbA_{1c}, 6.5%-7.4%), except for those with baseline HbA_{1c} 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 ($I^2 = 0\%$; $P = 0.8$). After adjustment, no statistically significant differences in HRs were found irrespective of baseline HbA_{1c} values. Full results are listed in Table 3.

Five studies[29-31,33,34] contributed to the sensitivity analysis of baseline HbA_{1c} values in prevalent patients. No statistically significant differences in risk of death were present in the unadjusted analysis. After adjustment, baseline HbA_{1c} values of 7.5%-8.4% and ≥8.5% were associated with increased risk of death (HRs of 1.08 [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[29,30,34,36] contributed to the sensitivity analysis of mean HbA_{1c} values in incident patients. Unadjusted analysis revealed a higher risk of death if mean HbA_{1c} values were lower than the reference category (HRs of 1.45 [95% CI, 1.38-1.52; $P < 0.001$] for HbA_{1c} ≤5.4% and 1.13 [95% CI,

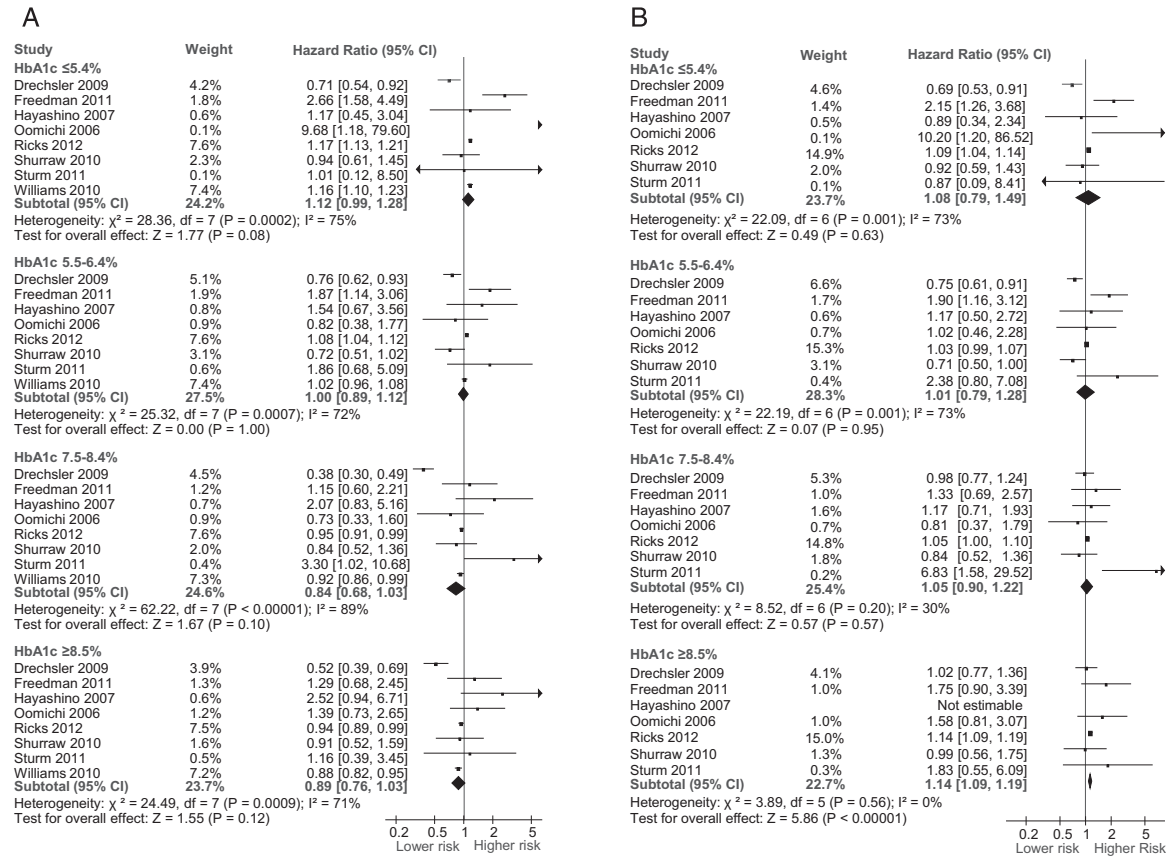

Figure 2. (A) Unadjusted and (B) adjusted hazard ratios for mortality risk associated with baseline hemoglobin A_{1c} (HbA_{1c}) values. Abbreviation: CI, confidence interval.

1.08-1.18; $P < 0.001$] for HbA_{1c} of 5.5%-6.4%, respectively). After adjustment, only mean HbA_{1c} values ≤5.4% and ≥8.5% were associated with increased risk of death (HRs of 1.29 [95% CI, 1.23-1.35; $P < 0.001$] and 1.24 [95% CI, 1.17-1.32; $P < 0.001$], respectively; Table 3). These effects were consistent across studies ($I^2 = 0\%$ in both; $P = 0.8$ and $P = 0.7$, respectively).

Five studies[28-30,32,34] included mean HbA_{1c} values for prevalent patients. In the unadjusted analysis only,

Table 3. Unadjusted and Adjusted HRs for Incident Patients

	Unadjusted			Adjusted[a]		
HbA_{1c} (%)	Pooled HR (95% CI)	*P*	I^2; *P* for Heterogeneity	Pooled HR (95% CI)	*P*	I^2; *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)	<0.001	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 HbA_{1c} 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; HbA_{1c}, hemoglobin A_{1c} (glycated hemoglobin); HR, hazard ratio.

[a]Adjusted for age, sex, diabetes type, dialysis vintage, and hemoglobin concentration when available.

Table 4. Unadjusted and Adjusted HRs for Prevalent Patients

	Unadjusted			Adjusted[a]		
HbA_{1c} (%)	Pooled HR (95% CI)	*P*	I^2; *P* for Heterogeneity	Pooled HR (95% CI)	*P*	I^2; *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 HbA_{1c} 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; HbA_{1c}, hemoglobin A_{1c} (glycated hemoglobin); HR, hazard ratio.

[a]Adjusted for age, sex, diabetes type, dialysis vintage, and hemoglobin concentration when available.

mean HbA_{1c} 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 ($I^2 = 43\%$; $P = 0.1$). In comparison, HbA_{1c} 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 HbA_{1c} level remains a useful clinical tool in predicting mortality risk in diabetic patients on maintenance hemodialysis therapy. We have shown that HbA_{1c} 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 HbA_{1c} levels are associated with increased risk of developing complications.[12,13,16,47,48] The association between glycemic control (measured by HbA_{1c}) 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.[11,16,48-52] There also are concerns about using HbA_{1c} measurements in hemodialysis patients, with some authors arguing that alternative glycemic measures such as fructosamine or glycated albumin should be used.[18-20,22,53] 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.[54] Serum levels of both therefore can be affected by conditions that alter total serum protein concentrations (such as malnutrition).[54] 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 HbA_{1c} 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 HbA_{1c} values (≤5.4% [≤36 mmol/mol]) and mortality, this result was influenced by one outlier. If the study by Adler et al[28] was excluded from this comparison, a mean HbA_{1c} 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[28] 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.[55-57] Heterogeneity between studies also was consistently highest in the category with HbA_{1c} levels ≤5.4% (≤36 mmol/mol), possibly indicating that this subgroup of patients has differing characteristics. Conceivably, this category could contain patients with low HbA_{1c} values because of excellent diabetes control who might be expected to have better survival. However, this group also could contain patients who have low HbA_{1c} values due to overly stringent control (leading to recurrent hypoglycemic episodes) or who are so nutritionally deplete that their HbA_{1c} values are very low and therefore might be

expected to have reduced survival. Conversely, comparisons of patients with the highest HbA_{1c} 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 HbA_{1c} 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 HbA_{1c} level remained a significant modifier of mortality risk in this setting.[55-57] A similar association between HbA_{1c} 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 HbA_{1c} values ≤5.4% (≤36 mmol/mol), and although there was a higher risk of death among incident patients whose mean HbA_{1c} 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 HbA_{1c} 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).[7] 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 HbA_{1c} level <7% (<53 mmol/mol).[6] 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.[48] 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 HbA_{1c} 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 HbA_{1c} 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 HbA_{1c} values across studies and consistent adjustment for confounders. To our knowledge, there currently 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 al[34] (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),[58] nutritional status,[59,60] and comorbid conditions.[57] Ideally, we would have liked to use a time-dependent covariate analysis to account more accurately for changes in HbA_{1c} levels over time rather than using mean values; however, this was not possible with the available data. Reverse causality also may affect the mean HbA_{1c} analysis because HbA_{1c} 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 HbA_{1c} 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.

ACKNOWLEDGEMENTS

We thank all corresponding authors from the analyzed studies who contributed data to this analysis. We also thank the various institutions involved for granting us access to their data; in particular, we acknowledge the assistance of the Steering Committee of the Japanese arm of DOPPS (Dialysis Outcomes & Practice Patterns Study; Drs Tadao Akizawa, Takashi Akiba, Akira Saito, and Kiyoshi Kurokawa) and Dr Mahesh Krishnan at DaVita Clinical Research. We also thank Gregory Russell (Senior Biostatistician, Wake Forest School of Medicine) and Natasha Wiebe (Senior Statistician, Alberta Kidney Disease Network) for assistance in providing data from their respective institutions.

Support: The Northern Ireland Kidney Research Fund (NIKRF) supports Dr Hill's clinical research fellowship. The NIKRF had no role in study design, data collection, analysis, or interpretation.

Financial Disclosure: The authors declare that they have no other relevant financial interests.

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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