Hemoglobin A_{1c} Levels and Mortality in the Diabetic Hemodialysis Population

Findings from the Dialysis Outcomes and Practice Patterns Study (DOPPS)

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OBJECTIVE—Lowering hemoglobin A_{1c} to <7% reduces the risk of microvascular complications of diabetes, but the importance of maintaining this target in diabetes patients with kidney failure is unclear. We evaluated the relationship between A_{1c} levels and mortality in an international prospective cohort study of hemodialysis patients.

RESEARCH DESIGN AND METHODS—Included were 9,201 hemodialysis patients from 12 countries (Dialysis Outcomes and Practice Patterns Study 3 and 4, 2006–2010) with type 1 or type 2 diabetes and at least one A_{1c} measurement during the first 8 months after study entry. Associations between A_{1c} and mortality were assessed with Cox regression, adjusting for potential confounders.

RESULTS—The association between A_{1c} and mortality was U-shaped. Compared with an A_{1c} of 7–7.9%, the hazard ratios (95% CI) for A_{1c} levels were 1.35 (1.09–1.67) for <5%, 1.18 (1.01–1.37) for 5–5.9%, 1.21 (1.05–1.41) for 6–6.9%, 1.16 (0.94–1.43) for 8–8.9%, and 1.38 (1.11–1.71) for ≥9.0%, after adjustment for age, sex, race, BMI, serum albumin, years of dialysis, serum creatinine, 12 comorbid conditions, insulin use, hemoglobin, LDL cholesterol, country, and study phase. Diabetes medications were prescribed for 35% of patients with A_{1c} <6% and not prescribed for 29% of those with A_{1c} ≥9%.

CONCLUSIONS—A_{1c} levels strongly predicted mortality in hemodialysis patients with type 1 or type 2 diabetes. Mortality increased as A_{1c} moved further from 7–7.9%; thus, target A_{1c} in hemodialysis patients may encompass values higher than those recommended by current guidelines. Modifying glucose-lowering medicines for dialysis patients to target A_{1c} levels within this range may be a modifiable practice to improve outcomes.

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Diabetes is present in more than 66% of U.S. hemodialysis patients and is a major contributor to the increased morbidity and mortality in this population (1). Optimal management of glycemia in diabetic hemodialysis patients, however, is uncertain. Although hemoglobin A_{1c} is the standard measure of glycemic control in diabetes, its interpretation in dialysis patients may be compromised by reduced red cell life span and the use of exogenous erythropoietin (2,3). Moreover, published findings on the association between A_{1c} and clinical outcomes in diabetic hemodialysis patients are conflicting (4–6), and current guidelines for the management of these patients are based primarily on data from nondialysis patients (7,8). We reported previously that an A_{1c} level >7.3% was associated with increased mortality in the Japan Dialysis Outcomes and Practice Pattern Study (9). Whether findings in the Japanese diabetic hemodialysis patients are relevant in other ethnic groups is uncertain, however, and suggests the need for larger multinational studies to evaluate appropriate A_{1c} levels in the hemodialysis population.

In this study, we estimate the effect of glycemic control, based on A_{1c} level, on all-cause mortality in the Dialysis Outcomes and Practice Patterns Study (DOPPS). DOPPS is a prospective cohort study of randomly selected in-center hemodialysis patients from a representative sample of facilities within each of 12 countries (Australia, Belgium, Canada, France, Germany, Italy, Japan, New Zealand, Spain, Sweden, the U.K., and the U.S.).

RESEARCH DESIGN AND METHODS

Study population

Across the DOPPS phases, the study design and methodology were structured with the following key elements: *1*) random selection of dialysis units stratified by type of facility and geographic region in each country; *2*) collection of demographic data, diabetes as cause of end-stage renal disease (ESRD), and mortality data for all hemodialysis patients in each study unit; *3*) collection of detailed patient data from a random selection of 20 to 40 patients within each dialysis unit at study entry and at 4-month intervals; *4*) collection of kidney disease quality of life information; and *5*) collection of facility practice information, determined from questionnaires completed annually by the dialysis unit's medical director (medical directors survey) and by the unit's nurse manager.

The methodologies of sample selection and data collection were substantially similar in phases 3 and 4, with possible differences in operational aspects, such as the proportion of data collected electronically.

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Many of the selected facilities in phase 3 continued participation in phase 4, and there was overlap in the patient populations but not in the follow-up periods.

The DOPPS 3 (2005–2008) and DOPPS 4 (2008–2011) populations included 12,954 patients with type 1 or type 2 diabetes. Patients were coded as having diabetes if they had a diagnosis of type 1 or type 2 diabetes, if they had received medications for diabetes (insulin or oral) before enrollment, if they had diabetic gastroparesis, or if they were marked as "diabetic" on the patient census, which is a complete listing of patients dialyzed in the participating facility. There were 28,458 patients in the DOPPS phases 3 and 4 sample, of whom 12,954 had diabetes. An additional 296 patients were excluded because of missing dates for age, study entry, or study exit. The population for this study consisted of 9,201 patients with type 1 or type 2 diabetes after exclusion of patients with no A_{1c} measurements during the first 8 months of DOPPS follow-up.

Covariates

The primary analyses were performed with the first available A_{1c} value in those with at least one measurement during the first 8 months of data collection. In our data collection design, laboratory values and medication use were reported at study entry and by interval summary forms collected every 4 months afterward. Covariate data were collected at study entry on patient age, sex, race (Black vs. other races), BMI, albumin, years of dialysis, creatinine, 12 comorbid conditions, insulin use, oral diabetes medication use, LDL cholesterol, hemoglobin, country, and study phase.

Missing data for covariates (potential confounders), described in the footnote of Table 1, were accounted for by using multiple imputation on the population of patients with at least one valid A_{1c} measurement, as implemented by the IVEware program (10), and analyzed with the MIAnalyze procedure in SAS STAT 9.2 (11). Missing A_{1c} levels were not imputed, because patients whose physicians did not order measurement of A_{1c} levels are likely to differ in important ways from patients whose physicians did order the test, invalidating the assumptions behind missing data imputation. Analytical results derived from the multiply imputed data were compared with results obtained with other methods for dealing with missing data (including complete case analyses and with missing data indicators with single-value imputation). The differences were trivial (most of the hazard ratio [HR] estimates were within 0.03; the largest difference was 0.08) and did not affect our conclusions. Further sensitivity testing of the effects of missing data for variables missing in more than 10% of the patients (BMI, weight loss, and cholesterol) consisted of imputation without these variables and without controlling for these variables and of complete case analyses excluding these variables. In general, the relationships between A_{1c} and mortality were similar among all three methods.

Certain models evaluated patients with and without indicators of poor nutrition, or with and without recent diabetes treatment. For these models, patients were identified as having poor nutritional status if they had any one or more of the following factors (n = 2,037): BMI <19 kg/m^2, weight loss during the first 8 months of DOPPS follow-up at a rate equivalent to 10% of body weight per year; albumin <3.0 mg/dL, or cachexia. Patients were identified as recently treated for diabetes if at the start of follow-up they were receiving oral diabetes medicines (n = 768), insulin (n = 2,685), or both (n = 293). No diabetes medications were recorded for 3,477 patients, and 1,978 patients had insufficient drug information for coding before imputation.

Analyses

Standard descriptive statistics were used to characterize the DOPPS patients with type 1 or type 2 diabetes. Follow-up started at A_{1c} measurement and ended at the time of death (outcome event), 7 days after transfer from the facility, or as of the date of most recent data availability (December 2011 or earlier), whichever came first.

The effect of A_{1c} on all-cause mortality was examined by Cox proportional hazards analyses. All models were adjusted for patient age, sex, race (Black vs. other races), BMI, hemoglobin, albumin, years of dialysis, creatinine (because this is a marker of dietary protein intake and muscle mass and is a predictor of clinical outcome in ESRD patients), 12 comorbid conditions, insulin use, LDL cholesterol, country, and study phase.

Tests of the interaction between A_{1c} and either nutritional status or diabetes treatment involved likelihood ratio tests of each covariate multiplied by the six indicator variables of A_{1c} categories, although effect estimates and confidence limits were produced with separate models for each population (i.e., with and without diabetes treatment, or with and without indicators of poor nutritional status). The assumption of proportional hazards for the A_{1c} categories was evaluated by visual inspection of the log(−log [survival]) versus log(time) plot and by testing the interaction between these categories and log(time), yielding P = 0.03. Although the relationship was slightly stronger during earlier periods of follow-up for mortality, there was reasonable adherence to proportional hazards.

Sensitivity analyses

Sensitivity analyses were performed by comparing the results obtained through the approach described here with models, with mean A_{1c} during the first 8 months of DOPPS follow-up as the main predictor and restricting to 6,669 patients with at least two A_{1c} measurements during that baseline period. These analyses were also adjusted for weight loss during the 8-month period. Because follow-up for this latter analysis started after the baseline period, the duration of follow-up was on average about 4 months shorter than in the main analysis. Serum glucose concentration was also examined, but it had a much weaker relation with mortality, presumably because serum glucose levels are more easily influenced by short-term factors.

Another sensitivity analysis tested the impact of dialysis information on the adjusted relationship between A_{1c} and mortality. The dialysis information included Kt/V (dialyzer clearance of urea × dialysis time/volume of distribution of urea), vascular access type, number of sessions per week, and dialysis duration.

RESULTS

Clinical and demographic characteristics

The first available A_{1c} ranged from 3.1 to 19.2%, whereas the mean A_{1c} across 8 months ranged from 3.4 to 15.0%. Table 1 shows clinical and demographic characteristics of the patients with type 1 or type 2 diabetes according to the number of A_{1c} measurements made during the initial 8-month baseline period, as well as the first available A_{1c} level among those with at least one A_{1c} measurement during that period. Patients with more A_{1c} measurements during the first 8 months were treated more frequently with insulin or oral medicine than those with fewer A_{1c} measurements and differed with respect

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Table 1—*Clinical and demographic characteristics by number and A_{1c} category*

	No. of measurements		First A_{1c} level (among 1+)		
Factor	0	1+	<6	6–8	8+
No. of patients	3,451	9,201	3,271	4,542	1,388
Age (years)	65.3	64.9	66.6	65.5	59.0
Male (%)	60	58	61	58	56
Black (%)	16	12	11	12	16
BMI (kg/m^2)*	27.7	27.9	26.6	28.4	29.4
Dialysis at study start (patient-years)	3.0	2.8	3.2	2.7	2.4
Preenrollment albumin (g/dL)*	3.6	3.7	3.6	3.7	3.7
Preenrollment creatinine (mg/dL)*	7.7	7.6	7.8	7.5	7.2
Coronary heart disease (%)*	50	51	50	52	48
Cancer, other than skin (%)	12	10	13	10	6
Other cardiovascular (%)	29	31	35	31	25
Cerebrovascular disease (%)	19	18	19	18	17
Congestive heart failure (%)	41	40	41	39	41
Gastrointestinal bleeding (%)	6	5	6	4	3
Hypertension (%)	87	85	84	86	85
Lung disease (%)	15	13	14	13	12
Neurologic disease (%)	12	11	12	10	10
Psychiatric disorder (%)	16	15	16	15	18
Peripheral vascular disease (%)	34	37	34	38	42
Recurring cellulitis, gangrene (%)	13	16	14	16	20
Insulin therapy (%)	30	41	25	47	62
Oral diabetes medicine only (%)	11	15	12	17	12
Cachectic	8	7	8	6	5
Weight change during first 8 months (%/4 months)*,†	−0.1	−0.2	−0.4	−0.2	0.0
Preenrollment LDL cholesterol (mg/dL)*	77.8	77.1	75.5	77.2	80.9
Preenrollment hemoglobin (g/L)*	11.2	11.3	11.1	11.4	11.5
A_{1c} (%)	NA	6.6	5.4	6.8	9

NA, not applicable. *Data were missing for these variables at the following rates: BMI, 8%; years of dialysis, 1%; albumin, 6%; creatinine, 3%; comorbid factors, 3%; weight gain, 32%; cholesterol, 55%; and hemoglobin, 1%. †Weight change was not used in the models that used initial A_{1c} because the data collection period used to determine weight loss would have overlapped the follow-up period. Weight change was used in the sensitivity analyses, which used the mean A_{1c} during the first 8 months.

to a number of other demographic and comorbid conditions. In addition, patients in whom A_{1c} levels were not measured had a slightly lower prevalence of peripheral vascular disease and were more often Black. Among patients with at least one measurement of A_{1c}, those with higher initial A_{1c} values were also treated more frequently with insulin than were those with lower values; on average they were younger, more likely to be Black, higher in BMI, and were likely to have initiated dialysis more recently.

A_{1c} and mortality

Among patients with at least one measurement of A_{1c}, average follow-up was 1.4 years (1st–99th percentile, 8 days–3.3 years). The death rate was 0.16/year (1,983 deaths /12,513 patient-years). Among these patients (the main analysis), the adjusted mortality rate was lowest at A_{1c} levels of 7–7.9% (Fig. 1*A*). A log likelihood test for nonlinearity showed an overall *P* value of 0.01 for the combined contribution of the squared and cubic A_{1c} terms to the linear model between A_{1c} and mortality. The relation was similar in shape in an unadjusted analysis, though slightly steeper at lower A_{1c} levels and less steep at higher levels.

Sensitivity analyses

Our sensitivity analysis used the mean A_{1c} during the first 8 months of DOPPS follow-up, and this showed a death rate of 0.20 deaths/year (1,337 deaths/6,679 patient-years). When examined in a Cox model, the mortality rates were similar among patients with zero, one, or two measures of A_{1c} during the initial 8 months of follow-up when restricted to patients who survived through all 8 months (HR for 0 vs. 2, 1.01; 95% CI 0.89–1.15; , 1 vs. 2, 1.09; , 0.95–1.25), with adjustment for phase and country. The conclusions reached with mean A_{1c} were not different from those based on the initial A_{1c}. Most of the HR estimates based on the mean A_{1c} were within 0.12 of the estimates made from the first available A_{1c} in the adjusted model. The results of the adjusted models that used first available A_{1c} level were substantially similar to the results from models that used mean A_{1c} levels (Fig. 1*B*). Another sensitivity analysis, excluding BMI, weight loss, and cholesterol and performing a complete case analysis on the remaining variables, yielded similar effect estimates, with the largest difference in the HR being at A_{1c} <5%; namely 1.41 (1.13–1.77) in the complete case model instead of 1.30 (1.05–1.61) in the imputed data. A final sensitivity analysis, adding dialysis information (Kt/V, vascular access type, duration, and sessions per week) resulted in a model very similar to the one shown in Fig. 1*A*. The largest change in an A_{1c} category's HR was only 0.019, and there were no appreciable differences in statistical significance of any of the categories.

Impact of nutritional status

In the examination of whether nutritional status modified the relationship between A_{1c} and mortality, markers of poor nutritional status were more common in A_{1c} categories below 6% (Table 2). Figure 2 shows the estimated effects of A_{1c} on mortality by nutritional status (good vs. poor). The shapes of the estimated dose-response associations differed noticeably ($P = 0.12$ for the likelihood ratio test of the interaction) between patients with and without indicators of poor nutritional status (Fig. 2). For patients without those indicators, there was little association with mortality for patients with A_{1c} <9%, but the rate increased for patients with A_{1c} ≥9%. In contrast, the association for patients with indicators of poor nutrition demonstrated higher mortality rates for patients with A_{1c} <7% and ≥8%.

Diabetes treatment

We also examined whether diabetes treatment modified the estimated effect of A_{1c} on mortality. The pattern of dose-response associations between patients who were treated with oral diabetes medicines or insulin and those patients who were not treated with these medicines were similar; however, the mortality rate among patients with low A_{1c} levels was somewhat

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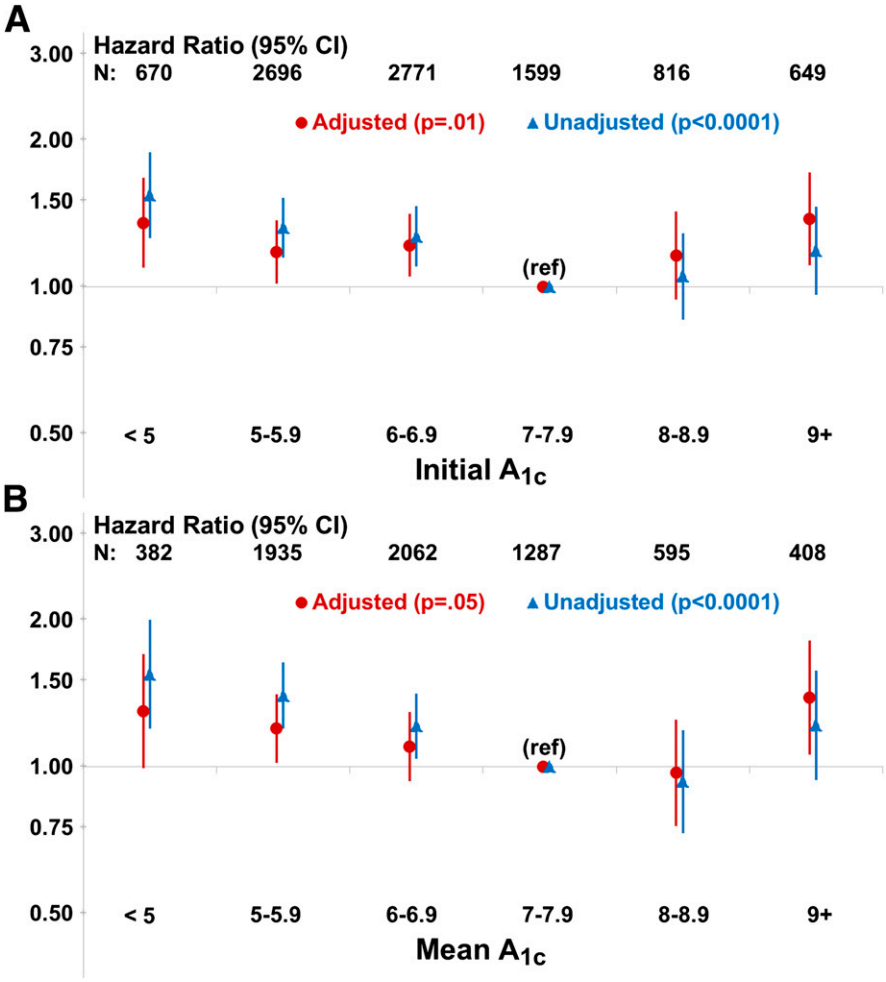

Figure 1—A: *Risk of mortality by initial A_{1c}, adjusted for age, sex, race, BMI, years of dialysis, albumin, creatinine, 10 comorbid conditions, insulin use, hemoglobin, HDL cholesterol, country, and study phase.* B: *Risk of mortality by mean A_{1c}, adjusted for age, sex, race, BMI, years of dialysis, albumin, creatinine, 10 comorbid conditions, insulin use, hemoglobin, HDL cholesterol, country, and study phase. (A high-quality color representation of this figure is available in the online issue.)*

higher among patients receiving oral medicine or insulin. The *P* value for the overall log-likelihood test of interaction between diabetes treatment and A_{1c} category was 0.97.

As expected, the proportion of patients being prescribed oral diabetes medicines or insulin during the baseline period was positively associated with A_{1c} level. The percentage of patients on any diabetes medicine was 22% for patients with A_{1c} levels below 5% and 35% for patients with A_{1c} levels below 6%. This percentage rose to 71% for patients with A_{1c} levels at 9% or above, leaving 29% of these patients untreated.

CONCLUSIONS—A_{1c} levels strongly predict all-cause mortality in hemodialysis patients with type 1 or type 2 diabetes. In the current study, mortality was lowest at A_{1c} levels of 7–7.9% and increased progressively for either lower or higher A_{1c} levels. The relationship between low A_{1c} and mortality appeared to be even stronger in patients with indicators of poor nutritional status, including low serum albumin, low BMI, or presence of cachexia. These findings suggest that optimal A_{1c} levels among hemodialysis patients with diabetes may need to be less stringent than levels recommended for patients with diabetes who do not have advanced chronic kidney disease (CKD). Careful attention to the use of diabetes medicines, which our data indicate are frequently prescribed to hemodialysis patients with A_{1c} <6% and frequently not prescribed to those with A_{1c} levels ≥9%, is a readily modifiable practice that may improve clinical outcomes.

Our findings differ from previous studies that did not show a relationship between A_{1c} levels and mortality. A recent study did not show a relationship between A_{1c} level and patient survival, whereas glycated albumin levels were more predictive of patient outcomes (12). That study was limited by a relatively small sample size (444 subjects), however, and thus by a low power for detecting A_{1c} effects on clinical outcomes. Elevated A_{1c} levels were also found not to be associated with mortality in a retrospective cohort study of maintenance hemodialysis patients in Canada (13). Differences in findings between these studies and ours may relate to variations in patient case mix, other confounding factors, or differences in duration of follow-up. Indeed, although a study based on data from a large dialysis organization did not identify an association between A_{1c} level and survival during a 12-month follow-up period (6), updated analyses of the same study population were consistent with our findings, with increased mortality rates observed at extremes of A_{1c} levels (5). Our findings are also consistent with those previously published on data from another large dialysis organization in the U.S., in which a similar increased mortality rate was seen at both low and high A_{1c} levels (4,14). Our findings differ somewhat from both those studies in that we found the lowest mortality rate for patients with A_{1c} levels between 7 and 7.9%, whereas Kalantar-Zadeh et al. (4) found the lowest rate, after adjustment for malnutrition-inflammation complex syndrome, for patients with A_{1c} levels between 5 and 5.9%. The Molnar et al. (14) abstract showed approximately constant rates throughout the 5–7.9% range after adjusting for malnutrition-inflammation complex syndrome when using a baseline measure and the lowest rate to be in the 7–7.9% range when using the time-averaged measure. Analyses in Japanese populations also revealed increased mortality with high A_{1c} levels (9,15). Thus our findings and those presented by others suggest that intensive glycemic control (A_{1c} <6.0% or perhaps <5%) may not be optimal in the ESRD) population.

The National Kidney Foundation (NKF) released the Kidney Disease Outcomes Quality Initiative (KDOQI) clinical practice guidelines for the management of diabetes in CKD in 2007 (8). These guidelines recommend that the target A_{1c} for persons with diabetes and CKD be set at

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Table 2—*Counts of patients with indicators of poor nutrition by mean A_{1c} status*

	A_{1c}						
	<5	5–5.9	6–6.9	7–7.9	8–8.9	9+	Total
Poor nutrition*	160 (27%)	494 (18%)	412 (14%)	222 (13%)	113 (14%)	77 (13%)	1,478 (16%)
No poor nutritional indicators	425 (73%)	2,192 (82%)	2,432 (86%)	1,476 (87%)	694 (86%)	504 (87%)	7,723 (84%)
Total	585	2,686	2,844	1,698	807	581	9,201

*Poor nutrition was indicated by one or more of the following: BMI <19 kg/m^2, albumin <3, or cachexia.

<7%, the same as for diabetes patients without CKD. Given the limited published literature on this topic among patients with advanced CKD, the NKF workgroup based their recommendation primarily on data obtained from diabetes patients with CKD stages 1 and 2. New evidence from both clinical trials and observational studies published since release of these guidelines point to the need for a higher A_{1c} target in some patient groups (4,6). For instance, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, conducted in the non-ESRD population, showed that intensive therapy to normalize A_{1c} levels was associated with increased mortality, a result similar to the findings of this study, and did not result in significant reduction in cardiovascular events (16). In response to the new evidence, the NKF is updating the KDOQI guidelines. The American Diabetes Association also updated its 2012 Clinical Practice Recommendations by strengthening the evidence for its recommendation that higher A_{1c} goals may be appropriate in some patients with diabetes (7).

It should be noted that caveats exist in evaluating A_{1c} measures in the ESRD population. First, a reduced life span of erythrocytes, as is common in dialysis patients, may result in lower A_{1c} levels than for non-ESRD diabetes patients with the same degree of glycemic control (2). Furthermore, treatment with exogenous erythropoietin results in an increased proportion of reticulocytes in the circulation, which may be associated with less time for hemoglobin glycosylation to occur (3). Indeed, recent work suggests the potential for glycated albumin, which, unlike A_{1c}, is not influenced by changes in erythrocyte survival or erythropoiesis-stimulating agent dose, as a measure of glucose control in the ESRD population (12,17). In addition, there are concerns that HbA_{1c} may not reflect glycemic control in the short term because of its prolonged half-life, whereas glycated albumin may potentially reflect short-term changes in plasma glucose (17). Further study is required to evaluate the use of glycated albumin (18,19), however, especially in light of a recent study that suggests alteration in albumin quantitation among hemodialysis patients because of increased oxidative stress (20). Despite differences in the use of A_{1c} for measuring glycemic control in diabetes patients with and without ESRD, the current KDOQI guidelines proposed similar standards for diabetes management as set by the American Diabetes Association (21), with an A_{1c} target below 7%.

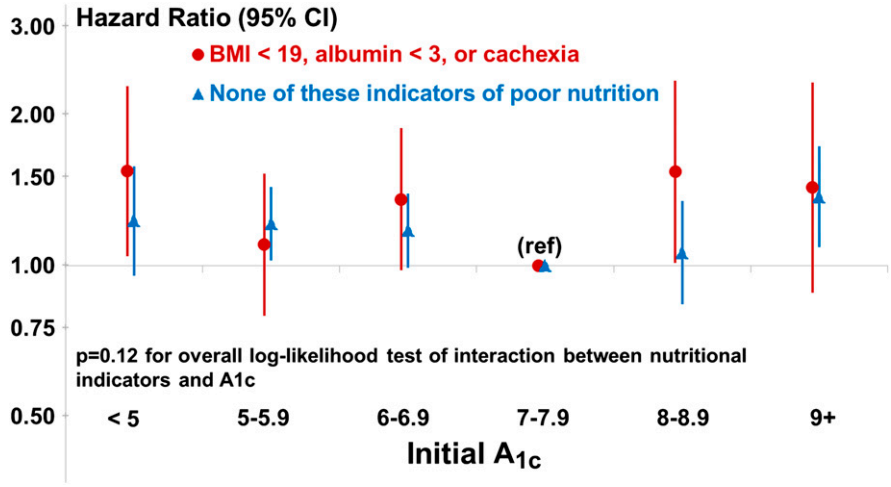

Figure 2—*Risk of mortality by initial A_{1c} among patients with and without indicators of poor nutrition, adjusted for age, sex, race, BMI, years of dialysis, albumin, creatinine, 10 comorbid conditions, insulin use, hemoglobin, HDL cholesterol, country, and study phase. (A high-quality color representation of this figure is available in the online issue.)*

Our findings clearly suggest the continued importance of periodic A_{1c} measurement, because A_{1c} level is strongly associated with mortality. The potential target A_{1c} level appears to differ from that in the general population, however, in that a higher range should be considered for ESRD dialysis patients. Our findings of a higher target range or a less intensive target may potentially be explained by greater fluctuation in glucose levels in the hemodialysis diabetes population (22). It is possible that the net catabolic balance (23) combined with the frequent occurrence of poor nutritional status of patients on hemodialysis (24) may require some degree of liberalization of target glucose levels. Various competing factors in the chronic dialysis setting may also alter the net balance of glucose control, such as changes in tissue sensitivity to insulin, existence of metabolic acidosis, variations in dextrose concentration in dialysate solution, all of which may all have varying effects on glycemic control (22). Patients with ESRD also have reduced clearance of insulin and certain oral hypoglycemic drugs used to treat diabetes. Prolonged circulation of these agents may therefore precipitate hypoglycemic episodes.

Certain limitations should be considered in the interpretation of our findings. For example, unmeasured confounders may have biased our estimates of the A_{1c} association with mortality. We also observed a significant percentage of patients with diabetes who had no recorded measurement of A_{1c} levels, and generalization of our findings to these patients may not be appropriate. In addition, there may be a potential for selection bias if the presence or absence of an A_{1c} measurement during

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the 8-month period is associated with both the level of A_{1c} and mortality. It is encouraging to note, however, that our effect estimates were similar when we restricted the study population to patients who had at least two A_{1c} measurements during the first 8 months of DOPPS follow-up.

Our analyses also suggest that 78% of patients with $A_{1c}<5\%$ were not receiving glucose-lowering agents. A potential explanation for the low A_{1c} levels among these untreated patients may relate to poor nutritional status, which is highly prevalent among ESRD patients (23). Another possible explanation for the low A_{1c} despite lack of treatment is the concept of "burnout" of diabetes with onset of ESRD, in which some observations have suggested spontaneous decreases of hemoglobin A_{1c} levels among ESRD patients (25). Whereas there is a possibility that patients with $A_{1c}<5\%$ and who were not receiving glucose-lowering agents may actually have been mislabeled as having diabetes, it is unlikely that any such misclassification is selective or biased toward those with low A_{1c}, and any such random misclassification would only have biased our findings toward the null hypothesis.

In summary, our findings of a strong association of both high and low A_{1c} levels with elevated mortality suggest the importance of A_{1c} measurement in the management of patients with diabetes undergoing chronic hemodialysis. This analysis supports accumulating evidence that a target range hemoglobin A_{1c} may be indicated in dialysis patients, rather than upper limit cut-point of <7%, as noted in previous practice guidelines. Clinical trials comparing target goals are warranted. The DOPPS is an international population, and the consistency of our findings with those limited to U.S. -specific analyses is reassuring. Finally, opportunities for improved use of hypoglycemic agents are suggested by these international data.

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S.P.B.R. wrote the manuscript. K.P.M. researched data, wrote the manuscript, contributed to discussion, and reviewed and edited the manuscript. J.R.T. researched data. R.G.N., H.M., B.W.G., M.I., S.H.J., R.L.P., and F.K.P. contributed to discussion and reviewed and edited the manuscript. B.M.R. reviewed and edited the manuscript. R.V. researched data, contributed to discussion, and reviewed and edited the manuscript. S.P.B.R. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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