

Association Between Glycemic Control and Adverse Outcomes in People With Diabetes Mellitus and Chronic Kidney Disease

A Population-Based Cohort Study

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Background: Better glycemic control as reflected by lower hemoglobin A_{1c} (HbA_{1c}) level may prevent or slow progression of nephropathy in people with diabetes mellitus (DM). Whether a lower HbA_{1c} level improves outcomes in people with DM and chronic kidney disease (CKD) is unknown.

Methods: From all people with serum creatinine measured as part of routine care in a single Canadian province from 2005 through 2006, we identified those with CKD based on laboratory data (estimated glomerular filtration rate [eGFR], <60.0 mL/min/1.73 m²) and DM using a validated algorithm applied to hospitalization and claims data. Patients were classified based on their first HbA_{1c} measurement; Cox regression models were used to assess independent associations between HbA_{1c} level and 5 study outcomes (death, progression of kidney disease based on a doubling of serum creatinine level, or new end-stage renal disease [ESRD], cardiovascular events, all-cause hospitalization).

Results: We identified 23 296 people with DM and an eGFR lower than 60.0 mL/min/1.73 m². The median HbA_{1c} level was 6.9% (range, 2.8%-20.0%), and 11% had an HbA_{1c} value higher than 9%. Over the median follow-up period of 46 months, 3665 people died, and 401 developed ESRD. Regardless of baseline eGFR, a higher HbA_{1c} level was strongly and independently associated with excess risk of all 5 outcomes studied ($P < .001$ for all com-

parisons). However, the association with mortality was U-shaped, with increases in the risk of mortality apparent at HbA_{1c} levels lower than 6.5% and higher than 8.0%. The increased risk of ESRD associated with a higher HbA_{1c} level was attenuated at a lower baseline eGFR (P value for interaction, <.001). Specifically, among those with an eGFR of 30.0 to 59.9 mL/min/1.73 m², the risk of ESRD was increased by 22% and 152% in patients with HbA_{1c} levels of 7% to 9% and higher than 9%, respectively, compared with patients with an HbA_{1c} level lower than 7% ($P < .001$), whereas corresponding increases were 3% and 13%, respectively, in those with an eGFR of 15.0 to 29.9 mL/min/1.73 m².

Conclusions: A hemoglobin A_{1c} level higher than 9% is common in people with non-hemodialysis-dependent CKD and is associated with markedly worse clinical outcomes; lower levels of HbA_{1c} (<6.5%) also seemed to be associated with excess mortality. The excess risk of kidney failure associated with a higher HbA_{1c} level was most pronounced among people with better kidney function. These findings suggest that appropriate and timely control of HbA_{1c} level in people with DM and CKD may be more important than previously realized, but suggest also that intensive glycemic control (HbA_{1c} level <6.5%) may be associated with increased mortality.

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DIABETES MELLITUS (DM) and chronic kidney disease (CKD) are potent independent risk factors for cardiovascular (CV) events and progression to end-stage renal disease (ESRD).^{1,2} Patients with both conditions are therefore at exceedingly high risk of adverse events, and diabetic nephropathy is the most common cause of ESRD in North America, accounting for approximately 40% of patients undergoing incident dialysis.^{3,4} Given projected increases in the prevalence of DM in developing coun-

tries, the global burden of diabetic kidney disease is expected to increase dramatically in the coming decades.⁵

See Invited Commentary at end of article

Targeting hemoglobin A_{1c} (HbA_{1c}) values lower than 7% slows progression of diabetic kidney disease, including both the onset of microalbuminuria and progression to overt nephropathy.^{6,7} (To convert HbA_{1c} to a proportion of total hemoglo-

bin, multiply by 0.01.) However, the link between intensive glycemic control and CV events or all-cause mortality is more complex and still debated.⁸ For example, one recent trial demonstrated that targeting HbA_{1c} levels lower than 6% increased mortality in higher-risk patients with type 2 DM.⁹

Despite the importance of diabetic kidney disease, the impact of glycemic control on outcomes in patients with DM and CKD is unknown because most trials of glycemic control have excluded those with reduced glomerular filtration rate (GFR). Indeed, while current National Kidney Foundation's Kidney Disease Outcomes Quality Initiative guidelines^{10(p562)} suggest a target HbA_{1c} level of 7% "for all diabetic patients with or without chronic kidney disease," very little evidence supports this recommendation.

We designed this study to determine whether HbA_{1c} level is independently associated with important clinical outcomes, such as all-cause mortality, CV events, hospitalizations, and kidney failure, in people with DM and stage 3 to 4 CKD. We hypothesized that an increased HbA_{1c} level would be associated with an increased risk of all adverse outcomes.

METHODS

SETTING AND PARTICIPANTS

Data from the Alberta Kidney Disease Network¹¹ (Canada) and the provincial health ministry (Alberta Health and Wellness) were used for this study. From all outpatients older than 18 years who had their serum creatinine level measured in Alberta at least once between January 1, 2005, and December 31, 2006, we selected those with an eGFR of 15.0 to 59.9 mL/min/1.73 m² and DM. We estimated GFR using the Modification of Diet in Renal Disease (MDRD) study equation because it is the most widely used formula and is recommended by current guidelines.¹⁰ We identified DM using validated algorithms (2 physician billing claims in a 2-year period or 1 hospital discharge ever with a diagnosis of DM, excluding gestational DM).¹² Of 32 555 people with DM and an eGFR of 15.0 to 59.9 mL/min/1.73 m², we excluded 436 people (1%) with ESRD receiving hemodialysis or transplantation before their first creatinine measurement in 2005 or 2006 (their index date), those without HbA_{1c} measurements during the 6-month period after the first eGFR index date (8041 [25%]), and those of First Nations origin (782 [2%]); because we did not have complete data for this population. Patients were classified into 3 groups based on their first HbA_{1c} measurement during the study period: HbA_{1c} level lower than 7%; HbA_{1c} level of 7% to 9%; and HbA_{1c} level greater than 9%. Comorbidity was assessed by using physician claims and hospitalization data together with validated algorithms¹³ for the variables listed in **Table 1**. The median household income for each postal code was obtained using data from the 2006 Canadian census.¹⁴

OUTCOMES

The primary outcome for this study was all-cause mortality. All-cause mortality, dates of hospitalization, first hospitalization for CV events (myocardial infarction, stroke, coronary revascularization, heart failure requiring hospitalization), and the date of first renal replacement therapy for people who developed ESRD were determined by linkage to the provincial

health ministry and the provincial renal databases. Coronary revascularization (percutaneous coronary intervention or coronary artery bypass graft surgery) was identified by procedure codes from records of hospitalizations; myocardial infarction, stroke, and heart failure were based on most responsible diagnosis for hospitalizations using validated algorithms.¹⁵⁻¹⁷ Progression of kidney disease was based on a sustained doubling in serum creatinine value¹⁸ and defined only for participants with at least 2 serum creatinine values; participants whose serum creatinine value doubled from baseline but then declined to less than twice the original value on a subsequent measurement were not considered to have experienced disease progression.

STATISTICAL ANALYSIS

Baseline characteristics stratified by HbA_{1c} level were given as means or proportions. Poisson regression models (including the number of days at risk as offset) were used for hospitalization rate analyses. Cox proportional hazards models were used for time-to-event analyses, stratified by health service regions. The proportional hazards assumption was tested using log-negative-log survival plots. All models to assess association between HbA_{1c} levels and outcomes were adjusted for the following potential confounders: age, sex, index eGFR, individual health insurance premium level (a marker of individual-level income), median neighborhood income, comorbidity, and residence location. Because services available to Albertans with CKD may differ by residence location, we did Poisson regression using robust estimates of variance, defining the cluster (grouping) variable by the health region. Because remote residence location was associated with adverse outcomes in patients with CKD, and to further account for any effect of residence location on outcomes, we adjusted both Cox and Poisson models for distance between each patient's residence and the closest nephrologist as previously described.^{19,20} We used a restricted cubic spline function with 3 knots to allow for a nonlinear association between the clinical outcomes and HbA_{1c} level. Statistical significance was set at $P = .05$, and all statistical tests were 2 sided. Censoring occurred with death, first event of interest in analyses of nonfatal events, disenrollment from the health plan, or end-of-study date (March 31, 2009).

We also performed several sensitivity analyses. First, we explored the potential effect of misclassification of HbA_{1c} level by using the mean value of all measurements made during the 6-month exposure period to reclassify HbA_{1c} categories. Second, we considered HbA_{1c} level as a continuous rather than a categorical variable. Third, we considered baseline eGFR as a continuous variable in a similar manner. Fourth, we considered HbA_{1c} level as a time-dependent covariate using all available HbA_{1c} values prior to the date of each adverse outcome.

The institutional review boards for the Universities of Alberta and Calgary approved the study. Analyses were performed using SAS (version 9.2; SAS Institute Inc, Cary, North Carolina) and Stata SE (version 10.1; StataCorp LP, College Station, Texas) software.

RESULTS

Characteristics of the 23 296 participants by HbA_{1c} level are shown in Table 1; a comparison between included and excluded participants is shown in eTable 1 (<http://archinternmed.com>). Overall, 21 155 participants had stage 3 CKD (eGFR, 30.0-59.9 mL/min/1.73 m²), and 2141 had stage 4 CKD (eGFR, 15.0-29.9 mL/min/1.73 m²). As shown in Table 1, people with a higher HbA_{1c} level were

Table 1. Demographic and Clinical Characteristics, by Baseline Hemoglobin A_{1c} Level^a

Characteristic	Patients With Baseline HbA _{1c} Level, No. (%)			P Value
	<7% (n=11 781)	7%-9% (n=8853)	>9% (n=2662)	
Age, y	73.0 [10.6]	71.9 [11.1]	65.9 [13.3]	<.001
Female	6684 (57)	4812 (54)	1384 (52)	<.001
Socioeconomic status ^b				
Assistance	345 (3)	277 (3)	153 (6)	<.001
Normal	3233 (27)	2623 (30)	1062 (40)	
Subsidy	8203 (70)	5953 (67)	1447 (54)	
Index eGFR, mL/min/1.73 m ²	47.0 (10.5)	46.8 (10.4)	46.3 (10.9)	.006
15.0-29.9	1072 (9)	793 (9)	276 (10)	.08
30.0-59.9	10709 (91)	8060 (91)	2386 (90)	
Comorbidity				
Cancer	1343 (11)	900 (10)	206 (8)	<.001
Cardiovascular disease	1330 (11)	974 (11)	220 (8)	<.001
Heart failure	2207 (19)	1796 (20)	513 (19)	.02
COPD	2792 (24)	2077 (23)	624 (23)	.91
Dementia	883 (8)	544 (6)	117 (4)	<.001
HIV	3 (0.03)	1 (0.01)	0 (0)	.65 ^c
Metastatic cancer	164 (1)	125 (1)	23 (1)	.08
Myocardial infarction	1389 (12)	1151 (13)	347 (13)	.02
Mild liver disease	235 (2)	134 (2)	49 (2)	.04
Moderate-severe liver disease	71 (1)	23 (0.3)	10 (0.4)	.001
Paraplegia	190 (2)	128 (1)	37 (1)	.52
Peptic ulcer disease	507 (4)	346 (4)	101 (4)	.30
Peripheral vascular disease	1024 (9)	810 (9)	235 (9)	.52
Rheumatological disease	332 (3)	229 (3)	57 (2)	.13
Income ^d				
Below poverty line	1080 (9)	846 (9)	249 (9)	.43
Between poverty line and Alberta (Canada) median income	6326 (54)	4371 (54)	1472 (56)	
Higher than median	4293 (37)	3201 (36)	925 (35)	

Abbreviations: COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; HIV, human immunodeficiency virus.

SI conversion factor: To convert HbA_{1c} to a proportion of total hemoglobin, multiply by 0.01.

^aValues are given as number (percentage) or mean [SD] as appropriate.

^bSocioeconomic status: "Assistance" refers to participants with health insurance premium paid under a program sponsored by Alberta Employment, Immigration, and Industry. "Subsidy" refers to participants who pay less than the full premium or no premium to Alberta Health and Wellness, or in the premium is subsidized through a government-sponsored program. "Normal" refers to all other participants.

^cFisher exact test.

^dMedian income was unavailable for 173 participants. The Alberta median individual employment income (in Canadian dollars, which are approximately equal to US dollars) was \$29 500 per year in 2005. The poverty line is \$14 914 per year for rural, \$18 659 per year for urban (except Calgary and Edmonton), and \$21 666 per year for Calgary and Edmonton.

younger, more likely to be male, and had lower socioeconomic status.

The distribution of HbA_{1c} levels in study participants with stage 3 and stage 4 CKD is shown in **Figure 1** and as a function of eGFR in the eFigure. During the median follow-up period (3.8 years [range, 1-51 months]), 16% of patients died, 49% were hospitalized, 16% had any CV event (3% stroke, 5% myocardial infarction, 8% acute heart failure), 6% had sustained doubling of serum creatinine value, and 2% developed ESRD.

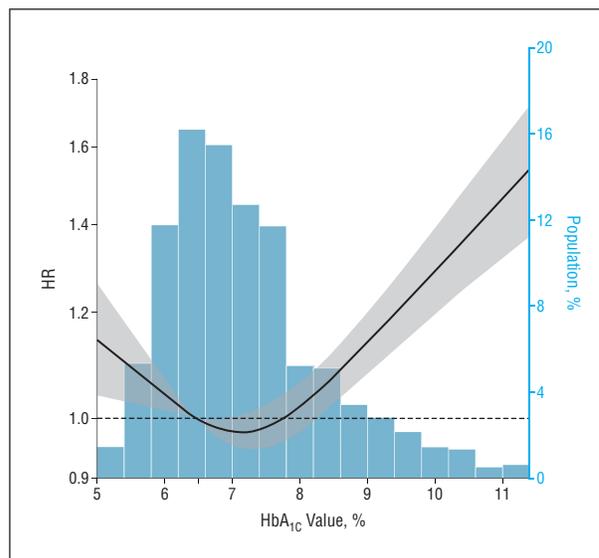


Figure 1. Histogram of observed hemoglobin A_{1c} (HbA_{1c}) values in people with stage 3 to 4 chronic kidney disease. The superimposed spline plot shows the adjusted risk of all-cause mortality as a function of HbA_{1c} level. The solid black line represents the adjusted hazard ratio (HR) of all-cause mortality associated with a given HbA_{1c} level higher than 9% compared with a level lower than 6.5%. The shaded area represents the 95% CIs. Models were adjusted for age, sex, index estimated glomerular filtration rate, individual health insurance premium level, median neighborhood income, comorbidity, and residence location. To convert HbA_{1c} to a proportion of total hemoglobin, multiply by 0.01.

RELATION BETWEEN HbA_{1c} LEVEL AND ALL-CAUSE MORTALITY

For both stage 3 and stage 4 CKD, there was an increased risk of death associated with higher levels of HbA_{1c} (*P* value for trend <.001 for both comparisons). Compared with an HbA_{1c} level lower than 7%, an HbA_{1c} level higher than 9% was associated with significantly higher mortality among people with stage 3 and 4 CKD (adjusted hazard ratio [HR], 1.35; 95% CI, 1.21-1.50); the magnitude of the increased risk was similar for stage 3 and stage 4 CKD when considered separately (**Table 2** and **Table 3**). A test for interaction between stage of CKD and HbA_{1c} level and the risk of mortality was nonsignificant (*P* = .72).

RELATION BETWEEN HbA_{1c} LEVEL AND NONFATAL EVENTS

Similar findings were observed for each of myocardial infarction, stroke, and heart failure, as well as CV events in aggregate and all-cause hospitalization: a graded independent increase in risk was observed at higher levels of HbA_{1c} in all analyses and remained significant for stage 3 and stage 4 CKD separately in 4 stratified analyses (Table 2 and Table 3). Tests for interaction between stage of CKD and the risk of these events were all nonsignificant (*P* = .49, .89, .07, .30, and .34, respectively).

RELATION BETWEEN HbA_{1c} LEVEL AND PROGRESSIVE KIDNEY FUNCTION LOSS

We also observed independent and statistically significant relationships between higher HbA_{1c} level and the risk

Table 2. Adjusted Risk of Adverse Outcomes Among People With Stage 3 CKD, by Baseline HbA_{1c} Level

Characteristic ^a	HbA _{1c} Level, No. (%)		
	<7% (n=10 709)	7%-9% (n=8060)	>9% (n=2386)
All-cause mortality			
Events, No.	1487	1128	329
Adjusted HR (95% CI)	1 [Reference]	1.04 (0.96-1.13)	1.35 (1.20-1.53)
All-cause hospitalization			
Events, No., at least once	4910	3870	1224
Adjusted RR (95% CI)	1 [Reference]	1.09 (1.04-1.15)	1.44 (1.36-1.52)
Myocardial infarction			
Events, No.	415	420	145
Adjusted HR (95% CI)	1 [Reference]	1.33 (1.16-1.53)	1.85 (1.53-2.25)
Stroke			
Events, No.	307	280	103
Adjusted HR (95% CI)	1 [Reference]	1.24 (1.05-1.46)	1.96 (1.56-2.47)
Heart failure			
Events, No.	597	616	214
Adjusted HR (95% CI)	1 [Reference]	1.32 (1.18-1.48)	1.89 (1.61-2.21)
ESRD			
Events, No.	42	47	40
Adjusted HR (95% CI)	1 [Reference]	1.22 (0.80-1.86)	2.52 (1.58-4.02)
Sustained doubling of serum creatinine level ^a			
People, No.	10 537	7957	2331
Events, No.	456	386	169
Adjusted HR (95% CI)	1 [Reference]	1.10 (0.95-1.26)	1.77 (1.48-2.13)

Abbreviations: CKD, chronic kidney disease; ESRD, end-stage renal disease; HR, hazard ratio.

SI conversion factor: To convert HbA_{1c} to a proportion of total hemoglobin, multiply by 0.01.

^aP value for trend <.001 for all comparisons.

^bDoubling of serum creatinine values could not be assessed for 330 patients because their creatinine level was measured only at the index date. Models were adjusted for age, sex, index estimated glomerular filtration rate, individual health insurance premium level, median neighborhood income, comorbidity, and residence location.

Table 3. Adjusted Risk of Adverse Outcomes Among People With Stage 4 CKD, by Baseline HbA_{1c} Level

Characteristic ^a	HbA _{1c} Level, No. (%)		
	<7% (n=1072)	7%-9% (n=793)	>9% (n=276)
All-cause mortality			
Events, No.	374	255	92
Adjusted HR (95% CI)	1 [Reference]	1.03 (0.87-1.21)	1.39 (1.10-1.76)
All-cause hospitalization			
Events, No., at least once	688	531	180
Adjusted RR (95% CI)	1 [Reference]	1.13 (1.02-1.25)	1.25 (1.01-1.54)
Myocardial infarction			
Events, No.	58	57	28
Adjusted HR (95% CI)	1 [Reference]	1.35 (0.85-2.15)	2.35 (1.32-4.18)
Stroke			
Events, No.	43	43	14
Adjusted HR (95% CI)	1 [Reference]	1.64 (1.00-2.71)	1.20 (0.51-2.80)
Heart failure			
Events, No.	153	140	41
Adjusted HR (95% CI)	1 [Reference]	1.16 (0.89-1.52)	1.32 (0.88-1.98)
ESRD			
Events, No.	116	102	54
Adjusted HR (95% CI)	1 [Reference]	1.03 (0.78-1.35)	1.13 (0.80-1.59)
Sustained doubling of serum creatinine value ^b			
Events, No.	142	114	54
Adjusted HR (95% CI)	1 [Reference]	1.05 (0.78-1.41)	1.40 (1.17-1.67)

Abbreviations: CKD, ESRD, end-stage renal disease; HR, hazard ratio.

SI conversion factor: To convert HbA_{1c} to a proportion of total hemoglobin, multiply by 0.01.

^aP for trend <.001 for all comparisons.

^bDoubling of serum creatinine value could not be assessed for 19 patients because their creatinine level was measured only at the index date. Models were adjusted for age, sex, index estimated glomerular filtration rate, individual health insurance premium level, median neighborhood income, comorbidity, and residence location.

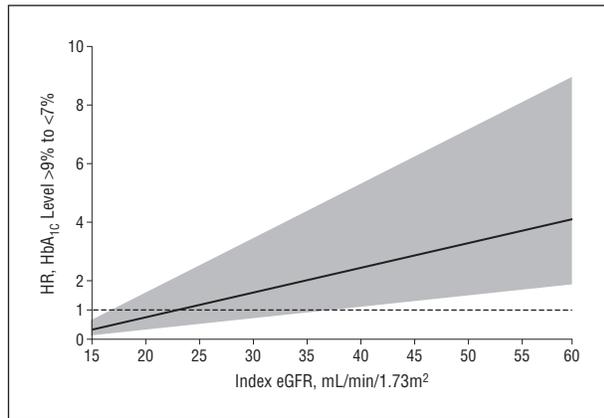


Figure 2. Association between hemoglobin A_{1c} (HbA_{1c}) and risk of end-stage renal disease (ESRD) modeled as a spline function of baseline glomerular filtration rate. The solid black line represents the adjusted hazard ratio (HR) of ESRD associated with an HbA_{1c} level higher than 9% compared with a level lower than 7%, modeled as a function of estimated glomerular filtration rate (eGFR). The shaded area represents the 95% CIs. Models were adjusted for age, sex, index eGFR, individual health insurance premium level, median neighborhood income, comorbidity, and residence location. To convert HbA_{1c} to a proportion of total hemoglobin, multiply by 0.01.

of a sustained doubling of serum creatinine or the development of ESRD (P value for trend $<.001$ for both comparisons). For doubling of creatinine, there was no significant interaction according to stage of CKD ($P=.65$). The magnitude of the increased risk for ESRD associated with higher HbA_{1c} levels seemed lower for those with stage 4 CKD at baseline, compared with those with stage 3 CKD (P value for interaction $<.001$): among those with stage 4 CKD, the risk of ESRD was increased by 3% and 13% in patients with HbA_{1c} levels of 7% to 9% and higher than 9%, respectively, compared with patients with HbA_{1c} levels lower than 7% ($P<.001$; Table 3); corresponding findings for those in stage 3 were 22% and 152%, respectively (Table 2).

SENSITIVITY ANALYSES

Because of suggestions that both high and low values of HbA_{1c} might be harmful,^{9,21} we performed additional analyses that used nonlinear splines to examine the association between adverse outcomes and HbA_{1c} level modeled as a continuous variable. We observed a U-shaped relation between HbA_{1c} level and mortality, and visual inspection of these plotted data suggested 2 inflection points: there was a significant increase in risk when HbA_{1c} values were higher than 8% and when they were lower than 6.5% (Figure 1). There was no evidence of increased risk for myocardial infarction, stroke, heart failure, or ESRD at lower levels of HbA_{1c} (data not shown).

EFFECT MODIFICATION OF BASELINE eGFR ON ASSOCIATION BETWEEN HbA_{1c} LEVEL AND OUTCOMES

We tested for interactions between baseline HbA_{1c} level and baseline eGFR (as a continuous variable) on the risk of the clinical outcomes. None were statistically significant except for analyses related to ESRD ($P=.02$). Therefore, we modeled the association between HbA_{1c} level and

the risk of ESRD as a continuous variable and found a direct relation between the excess risk associated with higher HbA_{1c} level and baseline eGFR (**Figure 2**).

ALTERNATIVE METHODS OF CLASSIFYING HbA_{1c} LEVEL STATUS

In primary analyses, only the first HbA_{1c} value during the study period was included to represent overall glycemic control. To reduce the risk that our results were influenced by misclassification, we repeated all analyses using the mean of all measurements made during the exposure period to classify participants with respect to HbA_{1c} level. Results of these analyses were very similar to those of the primary analyses; the magnitude of the association between higher HbA_{1c} levels and the risk of adverse outcomes seemed similar or stronger, and all tests for trend remained significant ($P<.001$ for all comparisons). Finally, we repeated analyses using HbA_{1c} level as a time-varying covariate, and all results were very similar to those in the primary analysis (eTable 2 and eTable 3).

COMMENT

We studied data from almost 24 000 adults with DM and stage 3 to 4 CKD (eGFR, 15.0-59.9 mL/min/1.73 m²) treated in a universal health care system within a single Canadian province. In contrast to findings from patients with kidney failure,²²⁻²⁴ we found strong and independent associations between higher levels of HbA_{1c} and multiple clinically relevant outcomes, including mortality, CV events, hospitalization, and progression to kidney failure. These relations remained significant after controlling for multiple potential confounders, were observed in both stage 3 and stage 4 CKD, and were robust to a variety of sensitivity analyses. Consistent with findings from trials in the general population with DM,^{9,25} we also found that levels of HbA_{1c} greater than 8.0% as well as levels lower than 6.5% were associated with increased mortality. Furthermore, our results suggest that many previous analyses that have considered HbA_{1c} values of less than 6% to 7% as a homogenous reference group may have systematically underestimated the strength of association between elevated HbA_{1c} levels and adverse events.^{26,27} Thus, our results have both clinical and scientific implications with respect to studies of glycemic control and adverse events.

Better glycemic control does help to prevent nephropathy and other microvascular complications of DM in people without CKD. For example, in patients with type 1 DM, the Diabetes Control and Complications Trial (DCCT) showed that a target HbA_{1c} level of 7% (vs 9%) over 9 years reduced the risk of microalbuminuria and macroalbuminuria by 34% and 56%, respectively.⁶ The DCCT-EDIC (Epidemiology of Diabetes Interventions and Complications) study followed patients for another 8 years after DCCT closeout and showed evidence of so-called legacy effects with respect to glycemic control: ongoing benefits in terms of developing microalbuminuria or macroalbuminuria as well as a significant 75% reduction in the risk of incident "renal failure" (creatinine level >177 $\mu\text{mol/L}$; to convert

to conventional units, divide by 88.4).²⁸ Similarly, the UK Prospective Diabetes Study (UKPDS) showed that more intensive glycemic control (HbA_{1c} level of 7.0% vs 7.9%) in patients newly diagnosed as having type 2 DM was associated with significant and sustained reductions in the risk of microalbuminuria, macroalbuminuria, and doubling of serum creatinine level over a 10-year period.⁷ Based on trials such as these, most guidelines have extrapolated broadly and recommend an HbA_{1c} target level of 7.0% for patients with CKD, even though this population has been specifically excluded from the seminal trials of glycemic control for type 1 or type 2 DM.^{10,29}

Since the risk of adverse events such as hypoglycemia may be greater at lower levels of kidney function,³⁰ some have suggested that more liberal target levels for glycemic control may be appropriate for people with CKD,³¹ especially since microvascular damage has already occurred. Although better glycemic control was associated with lower risk of all-cause mortality irrespective of baseline kidney function, we found that the association between better glycemic control and decreased risk of ESRD was attenuated at lower levels of baseline eGFR. We speculate that this finding may represent a “point of no return” for kidney function—beyond which better glycemic control may simply not be enough to prevent progressive kidney function loss.

In contrast to data on microvascular outcomes, the link between better glycemic control and macrovascular outcomes in the general population of patients with DM is less clear. Long-term follow-up from DCCT and UKPDS suggest that more intensive glycemic control may reduce the risk of CV events and death.^{25,28} However, 2 recent trials found that HbA_{1c} target levels below 6.5% led to increased CV mortality⁹ or no reduction in CV events³² in people with type 2 DM. Our findings of higher risk associated with both lower and higher levels of HbA_{1c} are broadly consistent with these results and suggest that there is little evidence of benefit with respect to macrovascular events when HbA_{1c} levels are much below 7.0%. That said, to our knowledge, there are no prior studies addressing the potential benefits or harms of better glycemic control on macrovascular outcomes in people with stage 3 or 4 CKD. As with participants in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, it is plausible that patients with DM and CKD who are treated to an HbA_{1c} level lower than 6.5% might experience iatrogenic harm owing to serious hypoglycemic events or too precipitous a fall in average glucose.⁹

Our current findings contrast with those of previous studies in patients undergoing hemodialysis, several of which show little or no association between HbA_{1c} level and mortality.²¹⁻²³ While these studies were not designed to explain the mechanism mediating the association between glycemic control and outcomes, one might speculate that competing causes of mortality in patients undergoing hemodialysis may attenuate any such association. In addition, the largest such study found that higher levels of HbA_{1c} were associated with increased mortality in patients undergoing hemodialysis³³ after adjustment for markers of malnutrition or chronic inflammation. Although it is possible that residual confounding by these characteristics have influenced our findings, the

malnutrition-inflammation syndrome is substantially less common in patients with milder forms of CKD, such as those in the current study.^{34,35} Perhaps for these reasons, our findings seem more similar to the association between HbA_{1c} level and outcomes in the general population than in people with hemodialysis-dependent kidney failure.

Strengths of our study include the inclusion of a population-based cohort treated in a universal health care system. We used validated techniques to select patients with diagnosed DM and CKD, and we studied clinically relevant outcomes. Our findings were robust to multiple sensitivity analyses, and the excess risk was both statistically and clinically significant. Despite its novelty and strengths, our study also has several important limitations that deserve mention. First, this was a retrospective observation study that cannot confirm the benefit (or harm) of more intensive glycemic control or the manner in which this control is achieved. Second, while we controlled for many important clinical and demographic factors, we could not control for certain potential confounders, such as use of insulin, epoetin, or other medications; overall intensity of DM care; blood pressure control; and laboratory markers, such as hemoglobin or markers of inflammation or malnutrition. Third, we included only patients with HbA_{1c} measured as part of their routine clinical care and not part of a study protocol. Although all patients had access to medical services in Alberta's publicly funded health care system, we may not have captured data for individuals who chose not to be tested or who were unaware of their DM status. Fourth, we used HbA_{1c} level as our index of glycemic control. Although HbA_{1c} level may not correlate well with measured glycemic control in the setting of kidney failure (especially when epoetin is used), this does not seem to apply to earlier stages of CKD,³¹ suggesting that HbA_{1c} level is an appropriate index of glycemic control for our study population. Fifth, our definition of CKD was based on a single measurement of serum creatinine, which may have led to misclassification in some individuals. At the least, our sensitivity analyses suggest this misclassification is likely either nondifferential or at worst would tend to bias our findings to the null because of regression to the mean. Finally, we could not distinguish type 1 from type 2 DM, nor did we have any measures of the clinical severity of DM itself.

In summary, we found that both higher and lower levels of HbA_{1c} were associated with adverse events in a large population of patients with DM and stage 3 to 4 CKD. Our findings are consistent with the hypothesis that (as in the general population of patients with DM) better glycemic control in patients with stage 3 to 4 CKD tends to improve clinical outcomes, but that overly intensive therapy (ie, HbA_{1c} target level lower than 7%) may be harmful. This speculation requires confirmation in an adequately powered randomized trial.

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REFERENCES

- Matsushita K, van der Velde M, Astor BC, et al; Chronic Kidney Disease Prognosis Consortium. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. *Lancet*. 2010;375(9731):2073-2081.
- Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med*. 2004;351(13):1296-1305.
- Canadian Institute for Health Information. *Canadian Organ Replacement Register Annual Report: Treatment of End-Stage Organ Failure in Canada, 2000 to 2009*. Ottawa, ON: Canadian Institute for Health Information; 2009.
- U.S. Renal Data System. *USRDS 2010 Annual Data Report: Atlas of End-Stage Renal Disease in the United States*. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2010.
- Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. *Diabetes Care*. 2004;27(5):1047-1053.
- Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med*. 1993;329(14):977-986.
- UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet*. 1998;352(9131):837-853.
- Ray KK, Seshasai SR, Wijesuriya S, et al. Effect of intensive control of glucose on cardiovascular outcomes and death in patients with diabetes mellitus: a meta-analysis of randomised controlled trials. *Lancet*. 2009;373(9677):1765-1772.
- Gerstein HC, Miller ME, Byington RP, et al; Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med*. 2008;358(24):2545-2559.
- KDOQI. KDOQI Clinical Practice Guidelines and Clinical Practice Recommendations for Diabetes and Chronic Kidney Disease. *Am J Kidney Dis*. 2007;49(2)(suppl 2):S12-S154.
- Hemmelgarn BR, Clement F, Manns BJ, et al. Overview of the Alberta Kidney Disease Network. *BMC Nephrol*. 2009;10:30.
- Hux JE, Ivis F, Flintoft V, Bica A. Diabetes in Ontario: determination of prevalence and incidence using a validated administrative data algorithm. *Diabetes Care*. 2002;25(3):512-516.
- Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med Care*. 2005;43(11):1130-1139.
- Wilkins R. *PCCF+ Version 4J User's Guide: Automated Geographic Coding Based on the Statistics Canada Postal Code Conversion Files, Including Postal Codes Through September 2006: Catalogue 82F0086-XDB*. Ottawa, ON: Health Analysis and Measurement Group, Statistics Canada; 2007.
- Austin PC, Daly PA, Tu JV. A multicenter study of the coding accuracy of hospital discharge administrative data for patients admitted to cardiac care units in Ontario. *Am Heart J*. 2002;144(2):290-296.
- Lee DS, Donovan L, Austin PC, et al. Comparison of coding of heart failure and comorbidities in administrative and clinical data for use in outcomes research. *Med Care*. 2005;43(2):182-188.
- Kokotailo RA, Hill MD. Coding of stroke and stroke risk factors using *International Classification of Diseases, Revisions 9 and 10*. *Stroke*. 2005;36(8):1776-1781.
- Levey AS. Assessing the effectiveness of therapy to prevent the progression of renal disease. *Am J Kidney Dis*. 1993;22(1):207-214.
- Rucker D, Hemmelgarn BR, Lin M, et al. Quality of care and mortality are worse in chronic kidney disease patients living in remote areas. *Kidney Int*. 2011;79(2):210-217.
- Tonelli M, Manns B, Culleton B, et al; Alberta Kidney Disease Network. Association between proximity to the attending nephrologist and mortality among patients receiving hemodialysis. *CMAJ*. 2007;177(9):1039-1044.
- Johnston SS, Conner C, Aagren M, Smith DM, Bouchard J, Brett J. Evidence linking hypoglycemic events to an increased risk of acute cardiovascular events in patients with type 2 diabetes. *Diabetes Care*. 2011;34(5):1164-1170.
- Shurraw S, Majumdar SR, Thadhani R, Wiebe N, Tonelli M; Alberta Kidney Disease Network. Glycemic control and the risk of death in 1,484 patients receiving maintenance hemodialysis. *Am J Kidney Dis*. 2010;55(5):875-884.
- Williams ME, Lacson E Jr, Wang W, Lazarus JM, Hakim R. Glycemic control and extended hemodialysis survival in patients with diabetes mellitus: comparative results of traditional and time-dependent Cox model analyses. *Clin J Am Soc Nephrol*. 2010;5(9):1595-1601.
- Okada T, Nakao T, Matsumoto H, et al. Association between markers of glycaemic control, cardiovascular complications and survival in type 2 diabetic patients with end-stage renal disease. *Intern Med*. 2007;46(12):807-814.
- Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med*. 2008;359(15):1577-1589.
- Chen H, Cohen P, Chen S. Biased odds ratios from dichotomization of age. *Stat Med*. 2007;26(18):3487-3497.
- Gamble JM, Eurich DT, Marrie TJ, Majumdar SR. Admission hypoglycemia and increased mortality in patients hospitalized with pneumonia. *Am J Med*. 2010;123(6):e56-e11-e16.
- Nathan DM, Cleary PA, Backlund JY, et al; Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. *N Engl J Med*. 2005;353(25):2643-2653.
- American Diabetes Association. Standards of medical care in diabetes: 2011. *Diabetes Care*. 2011;34(suppl 1):S11-S61.
- Moen MF, Zhan M, Hsu VD, et al. Frequency of hypoglycemia and its significance in chronic kidney disease. *Clin J Am Soc Nephrol*. 2009;4(6):1121-1127.
- Scherthner G, Ritz E, Scherthner GH. Strict glycaemic control in diabetic patients with CKD or ESRD: beneficial or deadly? *Nephrol Dial Transplant*. 2010;25(7):2044-2047.
- Patel A, MacMahon S, Chalmers J, et al; ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2008;358(24):2560-2572.
- Kalantar-Zadeh K, Kopple JD, Regidor DL, et al. A1C and survival in maintenance hemodialysis patients. *Diabetes Care*. 2007;30(5):1049-1055.

INVITED COMMENTARY

Glycemic Control and Cardiorenal Outcomes in Patients With Advanced Chronic Kidney Disease

Relative or Absolute Risks?

Diabetes mellitus (DM) confers very high risk for cardiovascular disease (CVD).¹ Chronic kidney disease (CKD) is a common complication of DM that further increases risk of CVD, the development of end-stage renal disease (ESRD), and other complications.² Multiple interventions have been tested in patients with DM with the hope that these interventions might reduce the risk of CVD and microvascular complications.³ Unfortunately, persons with CKD have been excluded or, at least, underrepresented in these trials. For example, on the one hand, in order to use metformin in a manner consistent with its product label in the ACCORD trial (Action to Control Cardiovascular Risk in Diabetes), we excluded patients with elevated levels of creatinine, and, therefore, most individuals with CKD.⁴ On the other hand, the ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicon Modified-Release Controlled Evaluation) trial included individuals with CKD.⁵ The ADVANCE investigators have reported the efficacy of the blood pressure (BP) lowering intervention on cardiovascular and renal outcomes in participants with CKD⁶; however, they have not yet published the results of their glucose-lowering intervention in this subgroup. Nevertheless, the results of the ADVANCE BP-lowering trial in CKD may be informative.

Only 51 ADVANCE participants had stage 4 CKD; hence, the ADVANCE investigators examined stages 3 and 4 combined in comparison with the no-CKD group and the combined stage 1 and 2 CKD group. They examined the outcomes of combined macrovascular events, cardiovascular mortality, all-cause mortality, major coronary events, major cerebrovascular events, and new or worsening nephropathy. They found no evidence of heterogeneity in the relative treatment effect across the 3 subgroups (no CKD, CKD stage 1-2, and CKD stage 3-4); hence, the absolute risk reductions related to treatment were greater in the higher-risk CKD stage 3-4 subgroup than in the lower-risk subgroups.⁶

These results underscore the importance of considering relative and absolute risks (or benefits) when examining potential subgroup differences in risk (or treatment) effects. Shurraw et al⁷ report results of analyses of observational data from a large, high-quality clinical registry in this issue of the *Archives*. They examined whether the degree of control of DM, represented by achieved hemoglobin A_{1c} (HbA_{1c}) level, was associated similarly with

cardiovascular and renal outcomes in patients with stage 3 and stage 4 CKD. Their results, presented in relative risk terms, suggest that the relative risk associated with higher (vs lower) HbA_{1c} was similar in the 2 CKD subgroups for 6 of the 7 outcomes they examined, including all-cause mortality, all-cause hospitalizations, myocardial infarction, stroke, heart failure, and sustained doubling of the serum creatinine level. Only for development of end-stage renal disease (ESRD) did the relative risks differ. The relative risk of developing ESRD related to having a higher HbA_{1c} level (>9%) vs a lower HbA_{1c} level (<7%) was 2.52 in stage 3 CKD. The analogous estimate was 1.13 in stage 4 CKD (interaction $P < .001$).⁷ Shurraw et al^{7(pxxx)} speculate “that this finding may represent a ‘point of no return’ for kidney function—beyond which better glycemic control may simply not be enough to prevent progressive kidney function loss.” Several caveats should be considered.

First, there was no (statistical) difference between CKD groups in the association of HbA_{1c} level and sustained doubling of serum creatinine level.⁷ Higher HbA_{1c} level was associated with the risk of doubling of serum creatinine level regardless of CKD stage. The lack of internal consistency for these 2 renal outcomes raises some uncertainties regarding the clinical importance of the differential association of HbA_{1c} level with ESRD between stage 3 and stage 4 CKD. Second, because 7 potential interactions were tested,⁷ the probability of detecting at least 1 interaction with $P < .05$ was 30.2%. Although the reported P value was $< .001$, the probability that this result represents a chance finding is not trivial. Third, the absolute risk differences should also be considered when drawing clinical inferences. The authors did not report adjusted estimates of incidence; however, one can apply the adjusted hazard ratios (HRs) associated with high HbA_{1c} level to the estimates of cumulative incidence among participants with low HbA_{1c} level to provide estimates of adjusted absolute risk differences. In participants with stage 3 CKD and low HbA_{1c} level, the cumulative incidence of ESRD was 42 in 10 709 or 0.39%. Applying the adjusted HR of 2.52 for high HbA_{1c} level results in an estimated adjusted cumulative incidence of 0.99% and an estimated adjusted absolute risk difference of 0.60% in persons with stage 3 CKD and high HbA_{1c} level. In participants with stage 4 CKD and low HbA_{1c} level, the cumulative incidence of ESRD was 116 in 1072 or 10.82%. Applying the adjusted HR of 1.13 for high