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Relationship of Hemoglobin A1C and Mortality in Heart Failure Patients With Diabetes

David Aguilar, MD,*† Biykem Bozkurt, MD,*† Kumudha Ramasubbu, MD,*† Anita Deswal, MD, MPH*†‡

Houston, Texas

Objectives This study was designed to examine the relationship between glycosylated hemoglobin (HbA1C) and adverse outcomes in diabetic patients with established heart failure (HF).

Background Despite the common coexistence of diabetes and HF, previous studies examining the association between HbA1C and outcomes in this population have been limited and have reported discrepant results.

Methods We assessed the association between increasing quintiles (Q1 to Q5) of HbA1C and risk of death or risk of HF hospitalization by conducting a retrospective study in a national cohort of 5,815 veterans with HF and diabetes treated in ambulatory clinics at Veterans Affairs medical centers.

Results At 2 years of follow-up, death occurred in 25% of patients in Q1 (HbA1C ≤6.4%), 23% in Q2 (6.4% < HbA1c ≤7.1%), 17.7% in Q3 (7.1% < HbA1c ≤7.8%), 22.5% in Q4 (7.8% < HbA1c ≤9.0%), and 23.2% in Q5 (HbA1c >9.0%). After adjustment for potential confounders, the middle quintile (Q3) had reduced mortality when compared with the lowest quintile (risk-adjusted hazard ratio: 0.73, 95% confidence interval: 0.61 to 0.88, p = 0.001). Hospitalization rates for HF at 2 years increased with increasing quintiles of HbA1C (Q1: 13.3%, Q2: 13.1%, Q3: 15.5%, Q4: 16.4%, and Q5: 18.2%), but this association was not statistically significant when adjusted for potential confounders.

Conclusions The association between mortality and HbA1C in diabetic patients with HF appears U-shaped, with the lowest risk of death in those patients with modest glucose control (7.1% < HbA1C ≤7.8%). Future prospective studies are necessary to define optimal treatment goals in these patients. (J Am Coll Cardiol 2009;54:422–8) © 2009 by the American College of Cardiology Foundation

Diabetes mellitus and heart failure (HF) are major health problems. There are nearly 5 million individuals who have HF and over 500,000 new cases are diagnosed each year in the U.S. (1). It has been well-established that diabetes, a disease that is increasing in prevalence (2), is a significant risk factor for the development of cardiovascular disease (3) and amplifies the risk for the development of HF (4–6). In addition, HF itself is considered an insulin-resistant state and is associated with significant risk for the future development of diabetes (7). Given these relationships, it is not surprising that diabetes and HF commonly coexist. The prevalence of diabetes in major HF trials is approximately 20% to 30% (8), although recent data from an acute HF registry suggest that the prevalence may be as high as 45% (9). Importantly, in cohorts of patients with established HF, diabetes has been associated with increased mortality and morbidity (10–12). Given the scope and growing burden of diabetes and HF, efforts to understand risk factors contributing to this increased hazard are increasingly important.

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One potential risk factor associated with adverse outcomes is poor glycemic control. Glycosylated hemoglobin (HbA1C) reflects the ambient blood glucose over the preceding 2 to 3 months, is used as an index of mean glycemia (13), and serves as a treatment target in patients

From the *Winters Center for Heart Failure Research and Section of Cardiology, Department of Medicine, Baylor College of Medicine, Houston, Texas; and the †Section of Cardiology and ‡Houston Center for Quality of Care and Utilization Studies, Michael E. DeBakey V.A. Medical Center, Houston, Texas. This study was supported in part by VA Health Services Research and Development Service grant # IIR 02-082-1 (to Dr. Deswal). Dr. Aguilar is a recipient of a National Institutes of Health Mentored Career Development Award (5K01-HL092585-02). The views expressed in this article are those of the authors and do not necessarily represent those of the Department of Veteran Affairs.

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with diabetes (14). In individuals free of HF, elevated HbA1C has been associated with an increased risk of adverse cardiovascular outcomes (15), including increased risk of incident HF (16). Despite these data, studies examining the association between HbA1C and outcomes in diabetic patients with established HF have been limited and have reported discrepant results (17,18). Therefore, we sought to determine the association between HbA1C and total mortality or HF hospitalization in a large, national cohort of ambulatory diabetic patients with established HF.

Methods

Study design and sample. We performed a retrospective study of a national cohort of veterans with HF treated in ambulatory clinics at Veterans Affairs (VA) medical centers using the VA External Peer Review Program (EPRP) data between October 2000 and September 30, 2002. As described in detail previously (19,20), the sampling pool of outpatients for EPRP included ambulatory patients with common chronic diseases such as HF, diabetes, ischemic heart disease, and chronic obstructive pulmonary disease identified by specific ICD-9 (International Classification of Diseases-Ninth Revision) codes. Abstractors reviewed electronic medical records for validation of sample selection criteria, including documentation of a HF diagnosis in outpatient records (20). The overall outpatient cohort for the EPRP for this period included 21,794 outpatients with HF. Patient-level data from the EPRP HF cohort was linked with 5 existing national VA databases to obtain further demographic, laboratory, pharmacy, and outcome data.

Individuals from the EPRP HF cohort who had diabetes, as identified in the EPRP data (n = 8,842), were prescribed hypoglycemic medications in the pharmacy database (n = 7,148) and had a recorded HbA1C level (in the laboratory database) within 1 year before or up to 2 weeks after the index outpatient visit were included for this analysis (n = 5,815). Diabetic therapy was ascertained using pharmacy data and was based on prescriptions filled 90 days before or 30 days following the index outpatient visit. Baseline demographics and concomitant cardiac medications were assessed at the index visit. A covariate that reflected diabetes severity included a variable documenting a diabetic complication including neuropathy, nephropathy, retinopathy, or peripheral vascular disease. For laboratory data, the most recent laboratory data within 1 year before and up to 2 weeks after the index clinic visit were used. Glomerular filtration rate (GFR) was calculated using the 4-variable Modification of Diet in Renal Disease equation (21).

Individuals were classified into categories based on quintiles of HbA1C. The levels of HbA1C in each quintile were as follows: quintile (Q)1: HbA1C $\leq$6.4%; Q2: 6.4% $<$ HbA1C $\leq$7.1%; Q3: 7.1% $<$ HbA1C $\leq$7.8%; Q4: 7.8% $<$ HbA1C $\leq$9.0%, and Q5: HbA1C $>$9.0%.

The primary outcome was time to death or time to hospitalization for HF over 2 years after the index outpatient visit. Complete follow-up over the 2-year period was available for all participants.

Abbreviations and Acronyms

EPRP = External Peer Review Program
GFR = glomerular filtration rate
HbA1C = glycosylated hemoglobin
HF = heart failure
LVEF = left ventricular ejection fraction
Q = quintile
VA = Veterans Affairs

Statistical analysis. Differences in baseline variables were ascertained using chi-square tests for categorical variables and analysis of variances for continuous variables. Two-sided p values <0.05 were considered statistically significant. Univariate and multivariable Cox proportional hazards models were used to assess the relationship between outcomes and quintiles of HbA1c (using Q1 as the reference group). In the Cox proportional hazards model for HF hospitalization, the patients were censored when they died. From 29 candidate variables collected at baseline (including diabetic therapy), separate multivariable Cox proportional hazards models for death and for hospitalization for HF were constructed using forward stepwise selection with variables with $p \leq 0.1$ being entered into the model. Variables common to both models included: left ventricular ejection fraction (LVEF), GFR, hemoglobin, hyponatremia, COPD, atrial fibrillation, race, cancer, and previous HF hospitalization within the last 2 years. The multivariable model for death also included main effects of age, gender, angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker use, beta-blocker use, statin use, peripheral vascular disease, dementia, sulfonylurea use, and biguanide use. The multivariable model for HF hospitalization included diabetes with complications, insulin use, psychiatric disorders, and rheumatologic disease. Missing laboratory values (other than HbA1C) were imputed using the median value of the study cohort for that parameter (missing: 245 [4.2%] for serum sodium, 387 [6.7%] for serum creatinine, 752 [12.9%] for total cholesterol, and 1,035 [17.8%] for hemoglobin) and a dummy variable was used to indicate replacement of missing data. Models including only patients without missing laboratory data yielded no significant change in overall results. Statistical analysis was performed using Intercooled Stata 9.2 for Windows (StataCorp LP, College Station, Texas).

Results

The study cohort consisted of 5,815 diabetic patients with HF. The cohort, consistent with VA medical centers population, was 94% men with a mean age of 69.2 $\pm$ 9.2 years. The mean body mass index was 31.7 $\pm$ 6.7 kg/m^2. Thirty-five percent of patients had a previous myocardial infarction. A total of 4,840 (83%) patients had a documented assessment of LVEF; of these pa-

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Table 1 Clinical Characteristics

	Quintile 1 HbA1C ≤6.4% (n = 1,264)	Quintile 2 6.4% < HbA1C ≤7.1% (n = 1,152)	Quintile 3 7.1% < HbA1C ≤7.8% (n = 1,092)	Quintile 4 7.8% < HbA1C ≤9.0% (n = 1,198)	Quintile 5 HbA1C >9.0% (n = 1,109)	p Value
Age, yrs	70.5 ± 9.3	70.5 ± 9.0	69.6 ± 8.9	68.8 ± 9.1	66.2 ± 9.9	<0.001
Men	93.4	94.1	92.8	94.6	92.6	0.25
Race						<0.001
White	76.0	75.4	77.7	75.9	71.8	
Black	12.0	9.4	10.7	11.3	16.6	
Other/unknown	12.0	15.3	11.6	12.9	11.6	
BMI, kg/m^2	31.3 ± 6.9	31.7 ± 6.6	31.8 ± 6.4	31.7 ± 6.6	32.1 ± 7.0	0.05
SBP, mm Hg	131 ± 21.4	131 ± 20.5	132 ± 21.8	131 ± 21.5	132 ± 22.2	0.18
LVEF						<0.001
Normal or mildly reduced	48.0	48.7	45.5	44.5	39.5	
Moderate or severely reduced	33.3	33.4	37.9	40.1	45.5	
Unknown	18.7	17.9	16.6	15.4	15.1	
Diabetes with complications	51.7	55.0	57.8	62.2	64.1	<0.001
Peripheral vascular disease	22.2	23.7	21.6	25.3	27.0	0.02
Atrial fibrillation	29.3	28.3	29.0	27.9	28.9	0.94
Past myocardial infarction	34.7	33.5	37.1	36.1	33.0	0.21
Prior HF hospitalization within 2 yrs	17.7	14.7	16.8	18.7	22.3	<0.001
COPD	29.5	28.0	24.6	26.0	25.5	0.05
Cancer	18.4	16.9	16.9	15.8	14.3	0.08
HbA1C	5.9 ± 0.5	6.8 ± 0.2	7.5 ± 0.2	8.4 ± 0.3	10.5 ± 1.7	<0.001
GFR, ml/min/m^2	54.8 ± 22.7	55.2 ± 21.5	55.3 ± 21.6	55.5 ± 21.5	58.3 ± 23.3	<0.001
Hemoglobin, mg/dl	13.1 ± 1.9	13.3 ± 1.7	13.4 ± 1.7	13.4 ± 1.6	13.6 ± 1.7	<0.001
Cholesterol, mg/dl	166 ± 39.0	168 ± 36.4	169 ± 37.4	172 ± 40.1	180 ± 42.6	<0.001
Medications						
Insulin	33.6	41.2	48.2	57.9	64.4	<0.001
Sulfonylurea	63.9	60.7	58.7	55.9	51.1	<0.001
Biguanide	20.4	25.1	26.2	28.1	29.4	<0.001
TZD	7.9	10.7	11.8	13.3	16.4	<0.001
Other diabetic therapy	1.0	1.6	1.5	1.3	2.6	0.03
Mean no. of diabetic drugs receiving	1.3	1.4	1.5	1.6	1.6	<0.001
ACE/ARB	80.5	83.3	84.0	84.1	86.4	0.004
Beta-blocker	60.4	59.5	59.9	61.1	62.3	0.67
Statin	52.6	55.6	56.8	60.5	59.2	0.001

Data expressed as mean ± SD or %.

ACE = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; BMI = body mass index; COPD = chronic obstructive pulmonary disease; GFR = glomerular filtration rate; HbA1C = glycosylated hemoglobin; HF = heart failure; LVEF = left ventricular ejection fraction; SBP = systolic blood pressure; TZD = thiazolidinedione.

tients, 54.5% had preserved or mildly reduced LVEF (LVEF ≥40%) and 45.5% had moderate or severely reduced ejection fraction.

The mean HbA1C level of the cohort was 7.75 ± 1.7%. Patient characteristics for each quintile are shown in Table 1. Individuals in the lower quintiles tended to be older; to have a lower GFR, hemoglobin, and total cholesterol; and were more likely to have preserved LVEF. As the HbA1C quintiles increased, there was an increased prevalence of diabetic complications, and individuals were more likely to require a greater number of medications for glycemic therapy and were more likely to be receiving insulin therapy. Individuals in the higher quintiles were more likely to receive angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers and statins.

Mortality. Over 2 years of follow-up, 316 (25.0%) Q1 patients, 265 (23.0%) Q2 patients, 193 (17.7%) Q3 patients, 269 (22.5%) Q4 patients, and 257 (23.2%) Q5 patients died (Fig. 1, Table 2). The unadjusted and adjusted hazard ratios for death are shown in Table 2. Using Q1 as the reference group, the middle quintile (Q3) had significantly reduced mortality (risk-adjusted hazard ratio [HR]: 0.73, 95% confidence interval [CI]: 0.61 to 0.88, p = 0.001).

Given the crude U-shaped relationship between mortality and quintiles of HbA1C levels, additional analyses were performed with multivariable Cox proportional hazard models using the middle quintile (Q3) as the reference group. Compared with Q3, the other 4 quintiles had a significantly increased risk of death over 2 years (Q1 risk-adjusted HR: 1.37 [95% CI: 1.14 to 1.64, p = 0.001]; Q2 risk-adjusted HR: 1.31 [95% CI: 1.09 to 1.58, p = 0.004]; Q4 risk-adjusted HR: 1.31 [95% CI: 1.09 to 1.58, p = 0.004]; Q5 risk-adjusted HR: 1.45 [95% CI: 1.20 to 1.76, p < 0.001]).

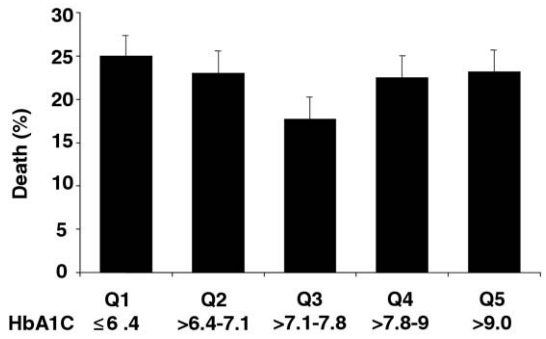

Figure 1 **Proportion of Patients Who Died at 2-Year Follow-Up by Quintiles of HbA1C**

The graph represents the proportion of patients who died at 2-year follow-up by quintiles (Q) of glycosylated hemoglobin (HbA1C). Global chi-square p = 0.001. **Error bars** indicate the 95% confidence intervals.

Additional analyses (data not shown) demonstrated similar relationships between HbA1C quintiles and mortality when patients were stratified according to LVEF (preserved or mildly reduced vs. moderate to severely reduced), renal insufficiency (GFR ≥60 ml/min/m^2 vs. <60 ml/min/m^2), advanced age (age ≥65 years vs. <65 years), and insulin use.

HF and all-cause hospitalization. The incidence of HF hospitalization over 2 years increased with increasing levels of HbA1C (Fig. 2, Table 2). In adjusted analyses (using Q1 as the reference group), the hazard of HF hospitalization increased with increasing quintiles, but this hazard was no longer statistically significant after adjustment for potential confounders (Table 2).

Similarly, the incidence of all-cause hospitalization increased across the HbA1C quintiles. In total, 550 (43.5%) Q1 patients, 491 (42.6%) Q2 patients, 492 (45.1%) Q3 patients, 564 (47.1%) Q4 patients, and 572 (51.6 %) Q5 patients were hospitalized for any cause during the 2 years of follow-up. After adjustments for potential confounders, there was a trend toward increased all-cause hospitalization in the highest quintile (Q5) when compared with the lowest quintile (Q1) (risk-adjusted HR: 1.12, 95% CI: 0.99 to 1.26, p = 0.08). The hazard ratios for the other quintiles were not significantly different than the first quintile (data not shown).

Discussion

In a cohort of ambulatory patients with established HF who were receiving medical treatment for diabetes, the relationship between mortality and HbA1C was U-shaped. Individuals in the middle quintile with modest glycemic control (7.1% < HbA1C ≤7.8%) had the lowest mortality when compared with individuals in the other quintiles of HbA1C. Although the rates of HF hospitalization increased with increasing levels of HbA1C, this crude relationship was no longer statistically significant after adjustment for potential confounders, suggesting that the associated baseline demographic and treatment differences seen in patients with elevated HbA1c levels may be accounting for the increased rates of HF hospitalization.

Although elevated HbA1C has been associated with increased risk of adverse cardiovascular events in the general population (15), the relationship between HbA1C levels and prognosis in diabetic patients with established HF has been less well studied. A recent analysis of 2,412 HF participants (of which only 907 participants had prior diabetes) enrolled in the CHARM (Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity) study (18) demonstrated that the adjusted risks of total mortality, HF hospitalization, and a composite outcome of cardiovascular death or HF hospitalization increased progressively with increasing levels of HbA1C. Of note, this relationship between HbA1C levels and death in the CHARM study was more pronounced in the nondiabetic patients enrolled in CHARM and did not reach statistical significance for the outcomes of cardiovascular death (p for heterogeneity = 0.04) and total mortality (p for heterogeneity = 0.008) in the 907 patients with prior diabetes after adjustment for differences in baseline characteristics. Additionally, in a smaller study of 123 diabetic patients with advanced systolic HF referred to a HF management program, a paradoxical relationship between HbA1C levels and mortality was identified (17). In this study of 123 patients with advanced systolic HF, an HbA1C level ≤7% was associated with an increased risk of death when compared with a level of >7%, even after adjustments for potential confounders.

Table 2 **Outcomes**

Outcome	Quintile 1 HbA1C ≤6.4% (n = 1,264)	Quintile 2 6.4% < HbA1C ≤7.1% (n = 1,152)	Quintile 3 7.1% < HbA1C ≤7.8% (n = 1,092)	Quintile 4 7.8% < HbA1C ≤9.0% (n = 1,198)	Quintile 5 HbA1C >9.0% (n = 1,109)
Death, n (%)	316 (25.0)	265 (23.0)	193 (17.7)	269 (22.5)	257 (23.2)
Unadjusted HR (95% CI)*	1.00	0.89 (0.76–1.05, p = 0.17)	0.67 (0.56–0.80, p < 0.001)	0.87 (0.74–1.03, p = 0.11)	0.91 (0.77–1.07, p = 0.26)
Adjusted HR (95% CI)*†	1.00	0.96 (0.81–1.13, p = 0.63)	0.73 (0.61–0.88, p = 0.001)	0.96 (0.81–1.13, p = 0.61)	1.06 (0.90–1.26, p = 0.48)
HF hospitalization, n (%)	168 (13.3)	151 (13.1)	169 (15.5)	196 (16.4)	202 (18.2)
Unadjusted HR (95% CI)*	1.00	0.96 (0.77–1.20, p = 0.72)	1.14 (0.92–1.41, p = 0.24)	1.22 (0.99–1.49, p = 0.06)	1.39 (1.13–1.70, p = 0.002)
Adjusted HR (95% CI)*†	1.00	1.01 (0.81–1.26, p = 0.96)	1.14 (0.92–1.41, p = 0.25)	1.11 (0.90–1.37, p = 0.34)	1.17 (0.94–1.44, p = 0.16)

*Quintile 1 is the reference group. †Text describes multivariable model.
CI = confidence interval; HR = hazard ratio; other abbreviations as in Table 1.

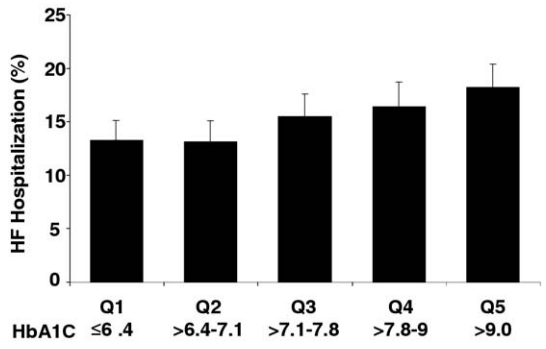

Figure 2 **Proportion of Patients With HF Hospitalization at 2-Year Follow-Up by Quintiles**

The graph represents the proportion of patients with heart failure (HF) hospitalization at 2-year follow-up by quintiles. Global chi-square p = 0.002. **Error bars** indicate the 95% confidence intervals. Abbreviations as in Figure 1.

Our data add to this existing body of published reports and support a more complex relationship between HbA1C and mortality in diabetic patients with established HF. By studying a large sample of ambulatory HF patients with established diabetes, we demonstrate that patients in the lower and higher HbA1C quintiles have a higher mortality than patients with modest glycemic control (7.1% < HbA1C ≤7.8%). The increased mortality associated with the higher HbA1C levels is likely multifactorial and may include both direct and indirect effects of hyperglycemia. Potential adverse effects of hyperglycemia include increased endothelial dysfunction (22), increased oxidative stress (23), increased protein kinase C activation (24), and potentially accelerated atherosclerosis. In addition, increased advanced glycation end products, as a result of chronic hyperglycemia, may lead to a variety of detrimental processes such as increased myocardial stiffness (25) and activation of the receptor for advanced glycation end products that in turn leads to up-regulation of cellular signals that lead to cellular dysfunction (26,27). Also, elevated levels of HbA1C may be a marker for a greater degree of insulin resistance with the associated derangements of cardiac metabolism and myocardial energy utilization in the insulin-resistant myocardium (28) and increased activation of the sympathetic nervous system (29). Finally, elevated HbA1C levels may also be reflective of poor compliance with medications that in turn may be associated with poor outcomes.

In addition to the increased risk of death in the higher HbA1C quintiles, we also demonstrate that lower quintiles of HbA1C are associated with an increased mortality when compared with modest glycemic control (7.1% < HbA1C ≤7.8%). There are several possible explanations for these findings. First, intensive glucose therapy to achieve normal or near-normal HbA1C levels may be hazardous in diabetic patients with established HF. In the recently completed ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial (30), a strategy of intensive glucose control targeting normal levels of HbA1C (below 6%) to reduce cardiovascular events was compared with standard therapy (targeting a level from 7.0% to 7.9%) in patients with type 2 diabetes and either established cardiovascular disease or additional cardiovascular risk factors. In the ACCORD trial, there was an unexpected increase in mortality in patients assigned to the intensive treatment arm with no significant reduction in major cardiovascular events when compared with mortality of patients receiving standard care. Our data differ from the ACCORD trial in that patients who achieved the lowest HbA1C levels in ACCORD were also receiving more antihyperglycemic medications than those in the standard therapy group. Nonetheless, our data, in a higher-risk population, are consistent with the unexpected hazard associated with a strategy of intensive glucose control that was seen in the ACCORD study. A second possible explanation for our findings includes "reverse epidemiology" (31,32). This concept refers to the observation of several, paradoxical relationships between conventional cardiovascular risk factors and clinical outcomes in patients with established HF. Such risk factors have included obesity and hypercholesterolemia, in which higher levels of body weight or cholesterol are paradoxically associated with increased survival in patients with established HF (31). Although there are several potential causes for this risk factor pattern, more commonly proposed explanations include the association of lower weight and lower cholesterol with increased protein energy malnutrition and an increased inflammatory syndrome associated with cardiac cachexia (31,32). Of note, the mean body mass index was slightly lower in the lowest HbA1C quintile in this study, but the association between HbA1C and mortality remained statistically significant after adjusting for small differences in body mass index. Another potential explanation for our findings is that low HbA1C is a marker for more advanced or severe HF or a marker for older patients with more comorbid conditions. It is important to note that functional status was not available in this cohort, but patients in the lowest HbA1C quintile were more likely to have preserved LVEF than those patients with increased HbA1C levels. Finally, low HbA1C may not be an adequate marker of glycemic control and/or may be reflective of an unmeasured variable that may be contributing to adverse events.

Study limitations. The present study has several limitations. First, the study is an observational study with the inherent limitations of this type of study design. Multivariable statistical models were used to adjust for heterogeneity between HbA1C groups, but residual unmeasured confounding may remain. However, availability of data on LVEF, pharmacy data (including diabetic therapy), and laboratory data should provide robust risk-adjustment variables. In addition, these data were collected as part of a national clinical database at VA medical centers, and measurements of HbA1C were performed in a clinical setting and not in a standardized laboratory. Also, the most recent HbA1C value within 1 year before and up to 2 weeks after

the index visit were used as the baseline value. Future, appropriately designed prospective studies with standardized measurements of baseline HbA1C will be necessary to confirm our findings.

Despite these limitations, these data have several strengths. The large sample size of this study population allows stratification of the data by HbA1C levels in order to identify the complex, nonlinear relationship between HbA1C and mortality. Although this study was not a prospectively designed study to test the association between HbA1C and outcomes in HF patients, the observational study highlights an association seen in a real-world setting of clinical care. Finally, our study provides timely data in light of the recently published ACCORD results, which demonstrated a previously unrecognized harm of strategy of tight glycemic control in high-risk patients with type 2 diabetes (30).

Conclusions

In a large national cohort of patients with diabetes and established HF, we demonstrate that the association between levels of HbA1C and mortality appears U-shaped, with increased risk of death at both higher and lower HbA1C levels when compared with modest glucose control ($7.1\% < \text{HbA1C} \leq 7.8$). It is estimated that approximately 20% to 30% (8), and perhaps up to 45% (9), of the nearly 5 million individuals with HF in the U.S. have coexisting diabetes. Therefore, we feel that our data have significant public health implications. We confirm that significantly elevated HbA1C is associated with increased risk in this population and efforts should be made to treat these patients with proven HF therapies and consider glucose-lowering therapy. Importantly, we also demonstrate an unexpected hazard with normal or near-normal HbA1C levels in this high-risk population of patients with diabetes and HF. Although this study is an observational study and does not test an active treatment strategy targeting lowering HbA1C levels in diabetic patients with HF, our data are consistent with the ACCORD trial data and demonstrate that low HbA1C levels in this high-risk population are associated with increased risk of death. Future appropriately designed studies are necessary to confirm our findings and expand on potential mechanisms contributing to the increased hazard.

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Reprint requests and correspondence: Dr. David Aguilar, Cardiovascular Division, Baylor College of Medicine, 1709 Dryden Street-BCM 620, Suite 500, Box 13, Houston, Texas 77030. E-mail: daguilar@bcm.edu.

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