Original article

Differential Effect of Glycosylated Hemoglobin Value and Antidiabetic Treatment on the Risk of 30-day Readmission Following a Hospitalization for Acute Heart Failure

Julio Núñez, a,* Clara Bonanad, a Juan Paulo Navarro, a Lourdes Bondanza, a Ana Artero, b Silvia Ventura, a Eduardo Núñez, a Cema Miñana, a Juan Sanchis, a and José Real a

a Servicio de Cardiología, Hospital Clínico Universitario, INCLIVA, Universitat de València, València, Spain
b Servicio de Endocrinología y Nutrición, Hospital Clínico Universitario, INCLIVA, CIBERDEM and Universitat de València, València, Spain

A B S T R A C T

Introduction and objectives: In patients with heart failure and type 2 diabetes, low glycosylated hemoglobin has been related with higher risk of mortality but information regarding morbidity is scarce. We sought to evaluate the association between glycosylated hemoglobin and 30-day readmission in patients with type 2 diabetes and acute heart failure.

Methods: Glycosylated hemoglobin was measured before discharge in 835 consecutive patients with acute heart failure and type 2 diabetes. Cox regression analysis adapted for competing events was used.

Results: Mean (standard deviation) age was 72.9 (9.6) years and median glycosylated hemoglobin was 7.2% (6.5%-8.0%). Patients treated with insulin or insulin/sulfonylurea/meglitinides were 41.1% and 63.2% of the cohort, respectively. At 30 days post-discharge, 109 (13.1%) patients were readmitted. A multivariate analysis revealed that the effect of glycosylated hemoglobin on the risk of 30-day readmission was differentially affected by the type of treatment (P for interaction < .01). Glycosylated hemoglobin (per 1% decrease) was inversely associated with higher risk in those receiving insulin (hazard ratio = 1.45; 95% confidence interval, 1.13-1.86; P = .002) or insulin/sulfonylurea/meglitinides (hazard ratio = 1.44; 95% confidence interval, 1.16-1.80; P = .007). Conversely, glycosylated hemoglobin (per 1% increase) had no effect in non-insulin dependent diabetes (hazard ratio = 1.01; 95% confidence interval, 0.87-1.17; P = .897) or even a positive effect in patients not receiving insulin/sulfonylurea/meglitinides (hazard ratio = 1.12; 95% confidence interval, 1.03-1.22; P = .011).

Conclusions: In acute heart failure, glycosylated hemoglobin showed to be inversely associated to higher risk of 30-day readmission in insulin-dependent or those treated with insulin/sulfonylurea/meglitinides. A marginal effect was found in the rest. Whether this association reflects a treatment-related effect or a surrogate of more advanced disease should be clarified in further studies.

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Efecto diferencial de la glucohemoglobina y el tratamiento antidiabético sobre el riesgo de reingreso a 30 días después de un ingreso por insuficiencia cardiaca aguda

R E S U M E N

Introducción y objetivos: En los pacientes con insuficiencia cardiaca y diabetes tipo 2, las cifras bajas de glucohemoglobina se han relacionado con un riesgo más elevado de mortalidad, pero la información relativa a la morbimidad es escasa. El objetivo de este estudio fue evaluar la asociación existente entre la glucohemoglobina y el reingreso en un plazo de 30 días en los pacientes con diabetes tipo 2 e insuficiencia cardiaca aguda.

Métodos: Se determinó la glucohemoglobina antes del alta en 835 pacientes consecutivos con insuficiencia cardiaca aguda y diabetes tipo 2. Se utilizó un análisis de regresión de Cox adaptado para eventos competitivos.

Resultados: La media de edad fue de 72,9 ± 9,6 años y la mediana de la glucohemoglobina fue de 7,2% (6,5%-8,0%). Los pacientes tratados con insulina o con insulina/sulfonylurea/meglitinidas constituieron un 41,1% y un 63,2% de la cohorte, respectivamente. A los 30 días del alta, 109 (13,1%) pacientes habían tenido un reingreso en el hospital. El análisis multivariante reveló que el efecto de la glucohemoglobina sobre el riesgo de reingreso en 30 días se veía afectado de manera diferente según el tipo de tratamiento (p para la
interacción < 0,01). La glucohemoglobina (por cada 1% de disminución) presentaba una asociación inversa con un mayor riesgo en los pacientes tratados con insulina [hazard ratio = 1,45; intervalo de confianza del 95%, 1,13-1,86; p = 0,003] o con insulina/sulfonilurea/meglitinidas [hazard ratio = 1,44; intervalo de confianza del 95%, 1,16-1,80; p = 0,001]. En cambio, la glucohemoglobina (por cada 1% de aumento) no tenía efecto alguno en la diabetes no insulinodependiente [hazard ratio = 1,01; intervalo de confianza del 95%, 0,87-1,17; p = 0,897] o mostraba incluso un efecto positivo en los pacientes no tratados con insulina/sulfonilurea/meglitinidas [hazard ratio = 1,12; intervalo de confianza del 95%, 1,03-1,22; p = 0,011].

Conclusions: En la insuficiencia cardíaca aguda, la glucohemoglobina mostró una asociación inversa con el riesgo de reingreso en 30 días en los pacientes insulinodependientes o en los tratados con insulina/sulfonilurea/meglitinidas. En el resto de pacientes se observó un efecto marginal. En futuros estudios deberá esclarecerse si esa asociación refleja un efecto relacionado con el tratamiento o bien es un indicador indirecto de una enfermedad más avanzada.

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Outcomes

The primary endpoint was 30-day all-cause unplanned readmission after discharge. Secondary endpoints were 30-day CV cause and AHF readmission. Readmission definition included unplanned in-hospital stay longer than 24 h and was classified as CV and non-CV causes (including AHF hospitalizations). These endpoints were ascertained by a physician blinded to the exposures (HbA1c values and antidiabetic treatment) through a review of hospital records. This study conforms to the principles outlined in the Declaration of Helsinki and was approved by an institutional review committee. All patients gave informed consent.

Statistical Analysis

Continuous variables were expressed as mean (1 standard deviation) or median [interquartile range] when appropriate. Discrete variables were summarized as percentages. Baseline characteristics were compared among the quartiles (Q1, Q2, Q3, and Q4) of HbA1c. An adapted version of Cox regression that takes into account the effect of all-cause mortality and other causes of readmission as competing events (method of Fine and Gray) was used to examine the independent association between HbA1c and 30-day unplanned all-cause, CV, and AHF readmissions. For any regression model, all covariates shown in Table 1 were evaluated for prognostic purposes. Reduced and parsimonious models were derived by using backward stepwise selection with a p-value of 0.157 (AIC criterion) for variable inclusion. During this selection process, the linearity assumption for all continuous variables was simultaneously tested and the variable transformed, if appropriate, with fractional polynomials. Covariates included in the final multivariate model for 30-day all-cause readmission were age, prior admission for AHF, Charlson comorbidity index, the interaction between atrial fibrillation and heart rate, the interaction between left ventricular ejection fraction ≤ 35% and systolic blood pressure, plasma antigen carbohydrate 125, urea, and the dose of furosemide equivalent prescribed at discharge. Covariates included in the final multivariate model for 30-day CV readmission were prior admission for AHF, etiology, Charlson comorbidity index, the interaction between atrial fibrillation and heart rate, the interaction between left ventricular ejection fraction ≤ 35% and systolic blood pressure, high sensitivity troponin, and furosemide dose at discharge. Covariates included in the final multivariate model for AHF readmission were prior admission for AHF, Charlson comorbidity index, the interaction between atrial fibrillation and heart rate, the interaction between left ventricular ejection fraction ≤ 35% and systolic blood pressure, antigen carbohydrate 125, and urea. Proportionality assumption for the hazard function over time was tested by means of the Schoenfeld residuals. Discriminative ability of the multivariate models was evaluated with Harrell’s C-statistics.

A 2-sided P-value of < .05 was considered statistically significant for all analyses. All survival analyses were performed using STATA 13.1 (StataCorp. 2013. Stata Statistical Software: Release 13.1. College Station, Texas: StataCorp LP).

RESULTS

Mean age was 72.9 (9.6) years, 49.2% were females, 48.7% showed left ventricular ejection fraction < 50% and the median HbA1c value was 7.2% (6.5%-8.0%). The antidiabetic treatment was insulin (41.1%), metformin (32.9%), sulfonylureas (22.5%), meglitinides (5.3%), inhibitors of dipeptidyl peptidase 4 (4.5%), alpha glucosidase inhibitors (2.9%), and thiazolidinediones (0.5%). Patients treated with at least one hypoglycemic agent (Ins/SU/MG) accounted for 63.2% of the sample.

Baseline Characteristics Across Glycosylated Hemoglobin

Overall, lower HbA1c values were associated with a worse baseline risk profile. A monotonic increase in age, N-terminal pro-brain natriuretic peptide, serum creatinine, left atrial diameter, and Charlson comorbidity index was observed when moving from HbA1c-Q4 to HbA1c-Q1 (Table 1); the same was true for the prevalence of hypertension, dyslipidemia, previous smoker, significant valvular disease, and prior known renal failure. Likewise, lower values of systolic/diastolic blood pressure, hemoglobin, total cholesterol, leukocyte count, and glomerular filtration rate predominated at the lower quartiles (Table 1). In regard to medications, those patients belonging to the lower quartiles of HbA1c had higher prevalence in the prescription of aldosterone receptor blockers and lower for insulin, alpha glucosidase inhibitors, and angiotensin-converted enzyme inhibitors/angiotensin receptor blockers. No significant differences were found for variables including other HF-drugs and other oral antidiabetic agents when tested across quartiles of HbA1c (Table 2).

Baseline Characteristics Across Antidiabetic Treatment

Patients treated with insulin or Ins/SU/MG exhibited worse baseline risk profile. Briefly, these patients exhibited greater comorbidity (peripheral artery disease, renal failure and prior admission for AHF). Likewise, these patients showed higher prevalence of ischemic heart disease, lower mean hemoglobin, and higher glycemic profile. No significant differences were observed between HF-treatment groups (Tables 1 and 2 of the supplementary material).

Glycosylated Hemoglobin Antidiabetic Agents and Risk of 30-day Readmission

At 30 days after discharge, 17 (2.0%) patients had died (3 of them without readmission) and 109 (13.1%) were readmitted, mostly for CV causes ([n = 80 [73.4%]]. Among CV causes, AHF was the most frequent diagnosis (n = 52 [65% CV]) Figure 1 summarizes the most common causes of readmission.

In the whole sample, 30-day readmission rates differed across HbA1c-Q. There was a monoton ic increase of rate of readmission from Q4 to Q1 (10.5%, 11.0%, 12.0% and 18.8%, respectively; P for trend = .016). Further analysis revealed a divergent association between HbA1c quartiles and rates of 30-day readmission according to the type of antidiabetic therapy. Thus, in patients receiving Ins/SU/MG, an inverse relationship was found between HbA1c quartiles and 30-day rates of readmission (26.5%, 15.3%, 10.5%, and 7.2%, for Q1, Q2, Q3 and Q4, respectively; P for trend < .001). This inverse relationship was found for both insulin-DM2 (26.2%, 14.6%, 12.4% and 7.1%, for Q1, Q2, Q3 and Q4, respectively; P for trend < .001) and sulfonylureas treatment (30.2%, 17.7%, 10.5%, and 9.5%, respectively; P for trend < .001), analyzed as single agents. Conversely, in those not treated with Ins/SU/MG, a borderline significant increase in readmission rate was found from lower to upper quartiles (8.8%, 7.1%, 12.0% and 19.6% for Q1, Q2, Q3 and Q4, respectively; P for trend = .087). No differences, however, were found for HbA1c quartiles
(15.4%, 10.2%, 9.8% and 13.6%, respectively; P for trend = .443) in those patients not receiving insulin.

In a multivariate setting, after adjusting for risk factors and accounting for the effect of 30-day mortality as a competing event, this differential prognostic effect persisted (P-value for interaction < .05). Glycosylated hemoglobin value was inverse and linearly associated to higher risk of readmission in patients treated with insulin (hazard: ratio = 1.45; 95% confidence interval, 1.13-1.86; p = .003, per 1% decrease) or Ins/SU/MG (hazard ratio = 1.44; 95% confidence interval, 1.16-1.80; P = .001, per 1% decrease) (Figures 2 and 3). For instance, insulin-treated patients and those receiving Ins/SU/MG, HbA1c-Q1 (≤ 6.5%) exhibited a 3.5 and 3.4-fold adjusted increase risk vs HbA1c-Q2-Q4 (P = .010 and P = .001, respectively). Likewise, and using a reference HbA1c threshold of
7%, those Ins/SU/MG and DM2 patients with values of HbA1c between 6.9% and 5.0% exhibited an increased risk ranging from 4% to 210% (Figures 2 and 3).

In contrast, HbA1c value was not related with the outcome in patients not receiving insulin treatment (hazard ratio = 1.01; 95% confidence interval, 0.87-1.17; P = .897, per 1% increase) and was positively associated with an increased risk in patients not treated with Ins/SU/MG (hazard ratio = 1.12; 95 confidence interval, 1.03-1.22; P = .011, per 1% increase) (Figures 2 and 3). A similar differential prognostic effect was observed for CV-readmission or AHF-readmission when evaluated as endpoints (Table 3).

### DISCUSSION

Early rehospitalization rates after an admission for HF decompensation remain unacceptably high, and represent a substantial problem to both patients and the healthcare system. Recent institutional initiatives recognize the need to decrease 30-day readmission as a health care priority. Unfortunately, accurate readmission risk stratification remains an unmet challenge and several interventions during the past decade did not decrease the rates of HF-related hospitalizations.

In the present study, we found that HbA1c value predicted 30-day unplanned rehospitalization in DM2 patients recently admitted for AHF. However, this effect was not uniform among the population as a whole. In fact, the predictive ability of HbA1c varied according to the treatment received for glycemic control in T2DM. Interestingly, low values of HbA1c strongly predicted higher risk of readmission in patients treated with insulin, sulfonylureas, or meglintinides, with a slight protector effect in the rest of patients. To the best of our knowledge, these results are novel in suggesting a treatment-related hypoglycemia as a main factor explaining the inverse relationship between HbA1c and early readmission in DM2 patients or in those receiving Ins/SU/MG. In the subgroup of patients not receiving Ins/SU/MG, the slight excess of risk attributable to higher HbA1c might be due to a higher risk of metabolic-related complications but also to a better baseline risk profile. Importantly, if reproduced in further studies, these results may have potential clinical implications, such as the following: a) need to monitor glycemic control during an episode of HF decompensation for short-term risk stratification, and b) avoidance of intensive glycemic control strategies (stringent glycemic targets) following an episode of AHF.

### Glycemic control in diabetes mellitus with heart failure

Current guidelines for the treatment of hyperglycemia in patients with DM2 highlight the importance of individualization of therapy based on patient needs, comorbid conditions, and potential adverse effects of hyperglycemic treatments. Intensive glycemic control, obtaining low HbA1c values prone to higher risk of hypoglycemic events, has been related to higher morbidity and mortality, especially in certain subgroups of comorbid and frail diabetics. In this regard, recent observational studies done in patients with diabetes and established HF have revealed a paradoxical effect between glycemic control and adverse outcomes. Most of these studies have found either a U-shaped pattern

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### Table 2

<table>
<thead>
<tr>
<th>Variables</th>
<th>All (n=835)</th>
<th>HbA1c quartiles</th>
<th>P-value for trend</th>
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<tr>
<td></td>
<td>Q1 (4.8%-6.5%)</td>
<td>Q2 (6.5%-7.2%)</td>
<td>Q3 (7.2%-8.0%)</td>
</tr>
<tr>
<td></td>
<td>n=208</td>
<td>n=209</td>
<td>n=209</td>
</tr>
<tr>
<td>Medical treatment at discharge</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>508 (60.8)</td>
<td>125 (60.1)</td>
<td>129 (61.7)</td>
</tr>
<tr>
<td>ACE inhibitors or ARB</td>
<td>588 (70.4)</td>
<td>139 (66.8)</td>
<td>138 (66.0)</td>
</tr>
<tr>
<td>Aldosterone antagonist blockers</td>
<td>290 (34.7)</td>
<td>86 (41.3)</td>
<td>74 (35.4)</td>
</tr>
<tr>
<td>Furosemide equivalent dose, mg/day</td>
<td>80 [80]</td>
<td>80 [40]</td>
<td>80 [80]</td>
</tr>
<tr>
<td>Insulin</td>
<td>343 (41.1)</td>
<td>65 (31.2)</td>
<td>82 (39.2)</td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td>188 (22.5)</td>
<td>53 (25.5)</td>
<td>34 (16.3)</td>
</tr>
<tr>
<td>Meglitinides</td>
<td>44 (5.3)</td>
<td>12 (5.8)</td>
<td>17 (8.1)</td>
</tr>
<tr>
<td>Metformin</td>
<td>275 (32.9)</td>
<td>68 (32.7)</td>
<td>68 (32.5)</td>
</tr>
<tr>
<td>DPP-4 inhibitors</td>
<td>34 (4.5)</td>
<td>11 (5.3)</td>
<td>9 (4.3)</td>
</tr>
</tbody>
</table>

### Notes:

- Ins/SU/MG: insulin, sulfonylureas, meglitinides
- DPP-4: Dipeptidyl peptidase 4
- HbA1c: glycated hemoglobin

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**Figure 1.** Causes of 30-day readmission. AHF, acute heart failure; CV, cardiovascular.
Figure 2. Adjusted effect of glycosylated hemoglobin on the risk of 30-day readmission according to antidiabetic treatment. HbA1c, glycosylated hemoglobin; Ins/SU/MG, insulin/sulfonylurea/meglitinides. Interaction \( P \)-value = .001.

Figure 3. Adjusted effect of glycosylated hemoglobin on the risk of 30-day readmission according to insulin treatment. HbA1c, glycosylated hemoglobin. Interaction \( P \)-value = .001.
or an inverse relationship between HbA1c value and mortality.11–13 For instance, in a study of 5815 ambulatory HF diabetic patients, individuals with modest glycemic control (HbA1c > 7.1%–7.8%) had a lower mortality compared with HbA1c levels that were either higher or lower.11 An inverse association between HbA1c values and adverse outcomes also has been documented in smaller cohorts of patients with diabetes and advanced systolic HF.12,13 In the setting of interventional studies, the evidence about this dual-effect of HbA1c in HF is even scarcer. Recent randomized clinical trials of patients with established DM2 and either CV disease or high risk for CV disease have failed to demonstrate significant reduction in major CV outcomes with more intensive glycemic control (HbA1c < 6.0%–6.5%), despite significant improvements of glycemic control.7–10 In these trials, HF patients have been excluded or underrepresented. Only in a subgroup analysis of the ACCORD trial, a 5% (n = 494) of individuals enrolled had a previous diagnosis of HF.9,22 In this HF subgroup, a significant (25%) increase in mortality risk was reported in those patients randomized to intensive glycemic control strategy.22 Unfortunately, to date no controlled trials addressing the optimal treatment and glycemic targets, specifically in HF patients with diabetes, have been performed.

### Hypoglycemia and Adverse Events

There is evidence endorsing a theory that hypoglycemia, mainly through activation of the sympathoadrenal system, increases systolic blood pressure, heart rate, risk of arrhythmias, myocardial ischemia, and fluid accumulation/redistribution, all factors linked to HF decompensations.8,14,15 In addition, it has been reported that when glycemic values are low, muscle cells shift to free fatty acids as the principal fuel. Long-term use of free fatty acids increases beta-oxidation and mitochondrial-derived H2O2, oxidative stress, and signals that contribute to muscle cell dysfunction and apoptosis.23 This can be another relevant pathophysiological mechanism endorsing the relationship between low HbA1c and adverse events in HF.

#### Low Glycosylated Hemoglobin and Adverse Events: An Epiphenomenon or a Treatment-related Effect?

Factors involved in the paradoxical association between low HbA1c and adverse outcome remains a matter of debate. On one side are data endorsing hypoglycemia as a confounder of other surrogates of disease severity, rather than as having a causal relationship with treatment success.8,9,24 On the other, some findings suggest a treatment-related effect. For instance, a contemporary systematic review of observational studies, including 903 510 diabetic patients, found that severe hypoglycemia was associated with approximately twice the risk of CV disease. A bias analysis revealed that the observed association between severe hypoglycemia and CV disease may not be entirely due to confounding by comorbid severe illness.7

In the setting of patients with diabetes and HF, this controversy is especially relevant, for two reasons: a) these patients usually exhibit a high-risk profile for hypoglycemic episodes (longer history of diabetes, extensive comorbidity, and frailty), and b) the available data on this topic are scarce and heterogeneous. For
instance, diabetic patients with HF enrolled in CHARM (Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity) who were treated with insulin had about two-fold increased risk of morbidity and mortality, compared to those who were not treated with insulin.25 Conversely, in a cohort from the United States of 16 000 Medicare patients with diabetes recently discharged with HF, treatment with sulfonylureas or insulin were not independently associated with higher risk of 1-year mortality and readmission.26 Unfortunately, treatment was evaluating and present.24 Present and future randomized trials are needed to elucidate the optimal diabetes control in patients with a recent admission for AHF.

Limitations

This is a single-center observational study. Important risk factors for hypoglycemia such as evolution of diabetes, frailty, and treatment dosage were not available in the registry, which precludes their inclusion as covariates in the multivariable models. Diabetes treatments were grouped into categories; this impedes evaluating the contribution of each pharmacological agent to the present findings. In addition, hypoglycemic episodes were not monitored during the observation period, precluding any establishment of a temporal relationship between hypoglycemia and rehospitalization. Finally, information regarding metabolic control and therapeutic history prior this hospitalization was not assessed in this study.

CONCLUSIONS

In summary, in DM2 patients recently discharged for AHF, we found that Glycosylated hemoglobin value was differentially associated with the risk of 30-day readmission. HbA1c was inversely related to higher risk of 30-day readmission in patients discharged with insulin or Ins/SU/MG. A marginal effect was found in the rest of diabetics. Whether this association reflects a treatment-related effect or merely a surrogate of more advanced disease should be clarified in further studies.

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CONFLICTS OF INTEREST

None declared.

SUPPLEMENTARY MATERIAL

Supplementary material associated with this article can be found in the online version available at doi:10.1016/j.rec.2014.10.019.

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