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Hypoglycaemia in hospitalized patients with or without heart failure

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Abstract

Hospitalized patients with heart failure (HF) undergoing bedside glucose monitoring with subcutaneous insulin orders were retrospectively identified over 2 years. Hypoglycaemia was defined as any glucose value <3.9 mmol/L (70 mg/dL) within 24 hours of admission (Hypo_{1day}) or throughout the hospitalization (Hypo_T) or any glucose value <2.2 mmol/L (40 mg/dL) throughout the hospitalization (Hypo_{Severe}). A total of 13 424 patients were included, of whom 2484 had HF. Patients with HF were more likely to have Hypo_{1day} (9.1% vs 7.0%, $P = .0003$), Hypo_T (28% vs 18.5%, $P < .0001$), or Hypo_{Severe} (3.4% vs 2.1%, $P = .0001$). After controlling for other variables, the odds of Hypo_{1day} were similar between the HF and non-HF groups (odds ratio [OR] 1.14, 95% CI 0.94–1.39, $P = .18$, fully adjusted model), slightly lower for Hypo_T (OR 0.85, 95% CI 0.73–0.99, $P = .03$, fully adjusted model), and similar for Hypo_{Severe} (OR 1.25, 95% CI 0.91–1.70, $P = .17$). Hypo_{1day}, Hypo_T and Hypo_{Severe} were all associated with increased mortality; there was no evidence of an interaction by HF status. Hypoglycaemia occurred at a similar or lower frequency in hospitalized patients with HF compared to those without HF. Hypoglycaemia was associated with increased hospital mortality, regardless of HF status.

Keywords

cardiovascular disease; cohort study; hypoglycaemia

1 | INTRODUCTION

Heart failure (HF) is a frequent comorbidity of diabetes mellitus (DM) that poses an enormous medical, societal and financial burden. DM is an independent predictor of mortality in patients with HF.¹ Hypoglycaemia is a complication of DM that may lead to adverse cardiovascular events, including abnormalities in coagulation and inflammation, hypokalaemia, repolarization abnormalities, endothelial dysfunction and activation of sympathoadrenal responses.^{2–4} Hypo-glycaemia is particularly concerning in patients with

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Author contributions

JM performed the research and wrote the manuscript. KD wrote the protocol, performed the research, and wrote the manuscript.

Conflict of interest

J. M. has no conflicts of interest to disclose.

HF because they are predisposed to arrhythmias and ischaemic events. Experts recommend relaxed glucose targets for patients with significant comorbidities and an individualized approach based on the perceived risk of hypoglycaemia.⁵ These efforts are complicated by the fact that glucose control has not been well characterized in this population.

Hypoglycaemia is common in hospitalized patients with DM, particularly in those treated with insulin.⁶ Many factors contribute to hypoglycaemia among hospitalized patients, including increasing age, higher insulin doses, basal insulin, mistiming of insulin administration, lower body weight, decreased renal function, and changes in diet or medications.⁷ Hypoglycaemia in the hospital is associated with longer length of stay, increased inpatient and 1-year mortality, and increased costs.⁸ In ambulatory settings, HF is associated with increased risk of severe hypoglycaemia.⁹ It is unclear whether HF plays a direct role in the incidence of hypoglycaemia or whether hypoglycaemia confers risk of poor outcomes in patients with HF.

The objective of the present study was to assess whether the risk of iatrogenic hypoglycaemia and relationship with mortality differed among a large population of hospitalized patients with or without HF exacerbation.

2 | METHODS

2.1 | Patient selection

Hospital admissions between January 1, 2014 and December 31, 2015 were retrospectively identified from the study institution's Information Warehouse, a data analysis tool that validates patient information from multiple sources. Hospitalized patients aged >18 years undergoing bedside glucose monitoring with ≥ 2 available blood glucose values per day and an order for subcutaneous insulin were considered. A diagnosis code for diabetes was not an inclusion criterion; the population could include both patients with and without DM. Patients receiving insulin via intravenous infusion, admitted directly to the intensive care unit, and pregnant women were excluded. Each hospitalization is assigned a random number by the electronic medical record (developed by Epic Systems, Madison, Wisconsin). For repeat admissions, these numbers were used to identify an encounter for inclusion. HF was identified when a primary International Classification of Diseases (ICD)-9 diagnosis code of 428.xx or an ICD-10 diagnosis code of I50.xx was listed on the active problem list. The Ohio State University's institutional review board approved all procedures.

2.2 | Clinical and laboratory variables

Each patient's demographics, including age, gender, race and body mass index (BMI), were identified. Data on glycated haemoglobin (HbA1c) level during the admission or within the preceding 30 days, β blockade at admission, and initial serum creatinine level were collected. The admitting service was characterized as medical or surgical. Basal insulin administration was defined as any order for glargine, detemir, NPH, 70/30, 75/25, or degludec. Glucose measures included admission point-of-care glucose and mean glucose within the first 24 and 72 hours. All occurrences of hypoglycaemia (glucose <3.9 mmol/L) and severe hypoglycaemia (glucose <2.2 mmol/L) in the first 24 hours or during the

hospitalization were identified. Hypoglycaemia was defined as any glucose value <3.9 mmol/L (70 mg/dL) within 24 hours of admission (Hypo_{1day}), or throughout the hospitalization (Hypo_T). Glucose <2.2 mmol/L (40 mg/dL) throughout the hospitalization was defined as Hypo_{Severe} and Hypo_{Mild} was defined as any glucose value 2.28 to 3.9 mmol/L (41–70 mg/dL).

In-hospital mortality and DM-related diagnoses (ICD-9 codes of 250.xx) for each patient were collected.

2.3 | Glucose management

At the study institution, patients with DM and hyperglycaemia are managed with subcutaneous basal-bolus insulin. Orders for capillary glucose monitoring four times daily accompany all subcutaneous insulin orders. Meters are downloaded with exact time stamps at least daily to the electronic medical record.

2.4 | Analysis

Continuous variables were reported as mean (SD) for normally distributed variables and median (interquartile range) for non-normally distributed variables. Differences between groups were determined with the unpaired Student's *t* test for normally distributed variables or Wilcoxon rank-sum for non-normal distributions. Dichotomous variables were reported as number (percentage) and differences between groups were determined using Fisher's exact test. *P* values $<.05$ were considered statistically significant.

Multivariable backward logistic regression was performed for hypoglycaemia occurrence, with glucose <3.9 mmol/L [1] at 24 hours or [2] during hospitalization and <2.2 mmol/L during hospitalization as the dependent variables (cut-offs used in previous studies)¹⁰ and HF as the primary independent variable. Initial models adjusting for available covariates were created and backward logistic regression was used to form a final model. The initial covariates were age, gender, race, BMI, surgery service, admission glucose, admission creatinine, β blockade and basal insulin use. Clinical covariates were selected based on clinical knowledge and analyses found in the literature with consideration for what variables were reliably extractable.⁹ Additional models analysing hospital mortality as dependent variables and hypoglycaemia as the primary independent variable were created, and interactions between HF and hypoglycaemia were assessed. Analyses were performed using JMP 10.0 software.

3 | RESULTS

3.1 | Patient characteristics

A total of 21 105 admissions met the inclusion criteria. After elimination of 7681 repeat hospitalizations, 13 424 unique admissions were analysed. Study population demographics are detailed in Table S1, Supporting Information.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Admission glucose and mean glucose at 24 and 72 hours were lower in the HF than in the non-HF group (Table S2, Supporting Information). Hypo_{1day} and Hypo_T were more common in the HF group than in the non-HF group (Hypo_{1day} 9.1 vs 7.0%, $P = .0003$; Hypo_T 28.0 vs 18.5%, $P < .0001$). Hypo_{Severe} was more common for those in the HF group (3.4 vs 2.1%, $P = .0001$).

3.2 | Relationship between HF and hypoglycaemia

Univariable predictors of hypoglycaemia are shown in Table S3, Supporting Information. For patients without HF, the unadjusted odds ratio (OR) for Hypo_T was 2.02 (CI 1.52–2.70). For patients with HF, the unadjusted OR for Hypo_T was 1.71 (CI 1.19–2.45). In the initial logistic regression model (adjusting for age, gender, race, BMI, surgery service, admission glucose, admission creatinine, β blockade, basal insulin), the odds of Hypo_{1day}, Hypo_T and Hypo_{Severe} were similar in patients with or without HF (OR 1.14, 95% CI 0.94–1.39, $P = .18$; Table 1). This remained unchanged in the final adjusted model. Sensitivity analyses assessing Hypo_{Mild} and excluding patients without a diagnosis code for diabetes were consistent with these results. In models incorporating mean 72-hour glucose as opposed to admission glucose, HF did not predict any definition of hypoglycaemia.

3.3 | Relationship between hypoglycaemia and hospital mortality

Univariable predictors of mortality are shown in Table S3, Supporting Information. The odds of in-hospital mortality were increased in patients with Hypo_{1day} and Hypo_T after adjusting for multiple variables (Hypo_{1day} OR 1.81, 95% CI 1.15–2.74, $P = .01$; Hypo_T adjusted OR 2.41, 95% CI 1.72–3.36, $P < .0001$; Table 2). The relationship was not affected by HF status (P value for Hypo_{1day} $\times$ HF interaction = .82; P value for Hypo_T interaction = .19), and remained significant in the final reduced models. The odds of mortality were increased in patients with Hypo_{Severe} (adjusted OR 4.70, 95% CI 2.75–7.76, $P < .0001$; Table 2). There was no evidence of heterogeneity by HF status (P value for interaction = .72); the relationship remained highly significant in the final reduced model. Sensitivity analyses revealed increased odds of mortality for Hypo_{Mild}, although the magnitude of risk appeared smaller (Table 2). Sensitivity analyses incorporating mean 72-hour glucose yielded similar results, although Hypo_{Mild} was no longer a significant predictor of mortality. Sensitivity analyses excluding patients without a diagnosis code for diabetes were similar. There was no interaction by HF status for any of these analyses.

4 | DISCUSSION

In this manuscript, the odds of hypoglycaemia within the first 24 hours of admission and severe hypoglycaemia throughout the admission were similar between patients with and without HF. The odds of overall hypoglycaemia were lower in the HF group after controlling for other variables; thus, the risk of hypoglycaemia in hospitalized patients with HF seems more likely to be attributable to other known risk factors.

Heart failure is characterized by profound neuroendocrine and autonomic disturbances,¹¹ and it is possible that this affects the incidence or manifestations of hypoglycaemia¹²; however, the autonomic responses to hypoglycaemia in the setting of HF are unknown. The

present findings are consistent with those of a small study that included hospitalized patients, in which HF was associated with a lower risk of hypoglycaemia, captured using continuous glucose monitoring during algorithmic adjustment of basal bolus insulin.¹³ The lack of increased risk of hypoglycaemia attributable to HF may have important implications for targeting prevention, recognition and treatment strategies.

Importantly, it is unknown whether hypoglycaemia risk translates to outcomes in patients with HF. In the present study, the association between hypoglycaemia and mortality was similar in the HF and non-HF groups, supporting a more generalized hypoglycaemia mitigation strategy, although this study is unable to prove causation. In the ADVANCE study, there was no clear direct relationship between hypo-glycaemia and mortality and therefore it was unclear whether hypoglycaemia was a marker of severe illness or a causal factor.³ In the ACCORD trial, severe hypoglycaemia did not explain the excess risk of mortality observed with tight glycaemic control.⁴ In patients with HF, higher HbA1c level has been associated with increased mortality,¹⁴ while other data support a paradoxical relationship between HbA1c and outcomes,¹⁵ indicating that the risk of hypoglycaemia may mitigate benefits of lower HbA1c. These studies could not determine whether the low HbA1c is harmful, or even whether hypoglycaemia plays a role.

The present study has several limitations, owing to its retrospective nature. The population was defined via electronic medical record data and thus the aetiology and severity of HF and cause of death were unknown. A diagnosis of diabetes was not an inclusion criterion because of the limitations of using diagnosis codes for identifying at-risk patients and because patients undergoing glucose monitoring with insulin orders were considered a more relevant population. HbA1c values were not available in most patients. Interventions for HF or DM were not standardized and the details of management were unavailable. Medication classes that may affect risks of hypoglycaemia or mortality, such as inotropes, diuretics, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers were not analysed, as the doses of these medications change frequently during a hospitalization for HF. In the present analysis, we included established clinical factors used by other authors.⁹ It might be worthwhile for future studies to investigate the effects of these medication classes on hypoglycaemia and mortality during HF admissions. The exact insulin doses for each patient could not be analysed because they could not be adequately extracted from the dataset. In addition, we were unable to assess episodes of hypoglycaemia prior to admission. Despite these limitations, the present analysis is consistent with other inpatient data, and is the most comprehensive study of hypoglycaemia in hospitalized patients with HF to date.

In summary, the present study indicates that HF is associated with similar or lower risk of hypoglycaemia in hospitalized patients after controlling for other variables. Moreover, hypoglycaemia is associated with increased hospital mortality, regardless of HF.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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TABLE 1

Relationship between heart failure and hypoglycaemia

	OR	95% CI	P
OR for Hypo_{1day} in HF group vs non-HF group			
Unadjusted model	1.33	1.14 to 1.55	.0003
Model 1	1.14	0.94 to 1.39	.18
Model 2	1.14	0.94 to 1.39	.18
Model 3	1.14	0.94 to 1.39	.19
Model 4	1.07	0.89 to 1.30	.46
OR for Hypo_T in HF group vs non-HF group			
Unadjusted model	2.69	2.16 to 3.35	<.0001
Model 5	0.85	0.73 to 0.99	.03
Model 6	0.86	0.74 to 1.00	.05
Model 7	0.91	0.77 to 1.07	.25
Model 8	0.91	0.79 to 1.05	.22
OR for Hypo_{Severe} in HF group vs non-HF group			
Unadjusted model	1.63	1.26 to 2.10	.0001
Model 9	1.25	0.91 to 1.70	.17
Model 10	1.27	0.92 to 1.72	.14
Model 11	1.32	0.96 to 1.83	.09
Model 12	1.22	0.90 to 1.68	.20
OR for Hypo_{Mild} in HF group vs non-HF group			
Unadjusted model	1.69	1.52 to 1.88	<.0001
Model 13	0.83	0.71 to 0.96	.02
Model 14	0.84	0.71 to 0.98	.02
Model 15	0.86	0.73 to 1.02	.08
Model 16	0.89	0.73 to 0.99	.03

Abbreviations: BMI, body mass index; HF, heart failure; Hypo_{1day}, glucose <3.9 mmol/L within 24 hours of admission; Hypo_{Mild}, glucose 2.28 to 3.9 mmol/L; Hypo_{Severe}, glucose value <2.2 mmol/L; Hypo_T, glucose value <3.9 mmol/L throughout the hospitalization; OR, odds ratio.

Model 1 (initial model): includes age, gender, race, BMI*, surgery service, admission glucose*, admission creatinine*, β blockade, basal insulin.

Model 2 (final model): includes age, gender, BMI*, surgery service, admission glucose*, admission creatinine*, β blockade, basal insulin.

Model 3: includes age, gender, race, BMI*, surgery service, mean glucose at 24 hours*, admission creatinine*, β blockade, basal insulin.

Model 4 (restricted to patients with a diabetes diagnosis code): includes age, gender, race, BMI*, surgery service, length of stay*, admission glucose*, admission creatinine*, β blockade, basal insulin.

Model 5 (initial model): includes age, gender, race, BMI*, surgery service, length of stay*, admission glucose*, admission creatinine*, β blockade, basal insulin.

Model 6 (final model): includes age, gender, BMI*, length of stay*, creatinine, admission glucose*, β blockade, basal insulin.

Model 7: includes age, gender, race, BMI*, surgery service, length of stay*, mean glucose at 72 hours*, admission creatinine*, β blockade, basal insulin.

Model 8 (restricted to patients with a diabetes diagnosis code): includes age, gender, race, BMI*, surgery service, length of stay*, admission glucose*, admission creatinine*, β blockade, basal insulin.

Model 9 (initial model): includes age, gender, race, BMI, surgery service, admission glucose*, admission creatinine*, β blockade, basal insulin.

Model 10 (final model): includes age, gender, BMI*, admission glucose*, admission creatinine*, basal insulin.

Model 11: includes age, gender, race, BMI, surgery service, mean glucose at 72 hours*, admission creatinine*, β blockade, basal insulin.

Model 12 (restricted to patients with a diabetes diagnosis code): includes age, gender, race, BMI*, surgery service, length of stay*, admission glucose*, admission creatinine*, β blockade, basal insulin.

Model 13 (initial model): includes age, gender, race, BMI*, surgery service, length of stay*, admission glucose*, admission creatinine*, β blockade, basal insulin.

Model 14 (final model): includes age, gender, BMI*, length of stay*, admission glucose*, admission creatinine*, β blockade, basal insulin.

Model 15: includes age, gender, race, BMI*, surgery service, length of stay*, mean glucose at 72 hours*, admission creatinine*, β blockade, basal insulin.

Model 16 (restricted to patients with a diabetes diagnosis code): includes age, gender, race, BMI*, surgery service, length of stay*, admission glucose*, admission creatinine*, β blockade, basal insulin.

* denotes log-transformed values.

TABLE 2

Relationship between hypoglycaemia and mortality

Mortality	OR	95% CI	P
OR for mortality in patients with vs those without Hypo_{1day}			
Unadjusted model	1.83	1.33 to 2.52	.0005
Model 1	1.81	1.15 to 2.74	.01
Model 2	1.70	1.16 to 2.42	.007
Model 3	2.05	1.33 to 3.16	.0012
Model 4	1.88	1.20 to 2.94	.006
OR for mortality in patients with vs those without Hypo_T			
Unadjusted model	2.08	1.67 to 2.61	<.0001
Model 5	2.41	1.72 to 3.36	<.0001
Model 6	2.43	1.79 to 3.29	<.0001
Model 7	2.34	1.61 to 3.42	<.0001
Model 8	1.77	1.25 to 2.51	.0012
OR for mortality in patients with vs those without Hypo_{Severe}			
Unadjusted model	4.28	2.91 to 6.30	<.0001
Model 9	4.70	2.75 to 7.76	<.0001
Model 10	3.93	2.41 to 6.19	<.0001
Model 11	3.36	1.86 to 6.06	<.0001
Model 12	3.97	2.33 to 6.77	<.0001
OR for mortality in patients with vs those without Hypo_{Mild}			
Unadjusted model	1.75	1.36 to 2.23	<.0001
Model 13	1.54	1.12 to 2.11	.009
Model 14	1.61	1.23 to 2.11	.005
Model 15	1.42	0.999 to 2.000	.05
Model 16	1.49	1.02 to 2.17	.04

Abbreviations: BMI, body mass index; HF, heart failure; Hypo_{1day}, glucose <3.9 mmol/L within 24 hours of admission; Hypo_{Mild}, glucose 2.28 to 3.9 mmol/L; Hypo_{Severe}, glucose value <2.2 mmol/L; Hypo_T, glucose value <3.9 mmol/L throughout the hospitalization; OR, odds ratio.

Model 1 (initial model with interaction for HF and hypoglycemia): includes HF, age, gender, race, BMI*, surgery service, admission glucose*, admission creatinine*, β blockade, length of hospital stay*, basal insulin. Interaction *P* value = .81.

Model 2 (final model): includes HF, age, race, admission creatinine*, length of hospital stay*, basal insulin.

Model 3 (initial model with interaction for HF and hypoglycemia): includes HF, age, gender, race, BMI*, surgery service, mean glucose at 24 hours*, admission creatinine*, β blockade, length of hospital stay*, basal insulin. Interaction *P* value = .87.

Model 4 (restricted to patients with a diabetes diagnosis code): includes HF, age, gender, race, BMI*, surgery service, length of stay*, admission glucose*, admission creatinine*, β blockade, basal insulin. Interaction *P* value = .77.

Model 5 (with interaction for HF and hypoglycemia): includes HF, age, gender, race, BMI*, surgery service, admission glucose*, admission creatinine*, β blockade, length of hospital stay*, basal insulin. Interaction *P* value = .90.

Model 6: HF, age, race, admission creatinine*, admission glucose*, length of hospital stay*, basal insulin, β blocker.

Model 7 (with interaction for HF and hypoglycemia): model includes HF, age, gender, race, BMI*, surgery service, mean glucose over the first 72 hours of hospitalization*, admission creatinine*, β blockade, length of hospital stay*, basal insulin. Interaction *P* value = .33.

Model 8 (restricted to patients with a diabetes diagnosis code): includes HF, age, gender, race, BMI*, surgery service, length of stay*, admission glucose*, admission creatinine*, β blockade, basal insulin. Interaction P value = .22.

Model 9 (with interaction for HF and hypoglycemia): includes HF, age, gender, race, BMI*, surgery service, admission glucose*, admission creatinine*, length of hospital stay*, β blockade, basal insulin. Interaction P value = .72.

Model 10: includes HF, age, race, admission creatinine*, length of hospital stay*, basal insulin.

Model 11 (with interaction for HF and hypoglycemia): includes HF, age, gender, race, BMI*, surgery service, mean glucose over the first 72 hours of hospitalization*, admission creatinine*, β blockade, length of hospital stay*, basal insulin. Interaction P value = 0.85.

Model 12 (restricted to patients with a diabetes diagnosis code): includes HF, age, gender, race, BMI*, surgery service, length of stay*, admission glucose*, admission creatinine*, β blockade, basal insulin. Interaction P value = .40.

Model 13 (initial model with interaction for HF and hypoglycemia): includes HF, age, gender, race, BMI*, surgery service, admission glucose*, admission creatinine*, β blockade, length of hospital stay*, basal insulin. Interaction P value = .14.

Model 14 (final model): includes HF, age, race, hypoglycaemia 41 to 70 mg/dL, admission glucose*, admission creatinine*, β blockade, length of hospital stay*, basal insulin.

Model 15 (with interaction for HF and hypoglycemia): model includes HF, age, gender, race, BMI*, surgery service, mean glucose over the first 72 hours of hospitalization*, admission creatinine*, β blockade, length of hospital stay*, basal insulin. Interaction P value = .31.

Model 16 (restricted to patients with a diabetes diagnosis code): model includes HF, age, gender, race, BMI*, surgery service, length of stay*, admission glucose*, admission creatinine*, β blockade, basal insulin. Interaction P value = .24.

* denotes log transformed values.