Effect of insulin on readmission for heart failure following a hospitalization for acute heart failure

Vicente Bertomeu-González1,2,3†, Lorenzo Fáñeca4†, Patricia Palau5,6, Gema Miñana5, Gonzalo Núñez5, Rafael de la Espriella5, Enrique Santas5, Eduardo Núñez5, Vicent Boði5,6, Francisco Javier Chorro5,6,3, Alberto Cordero1,3, Juan Sanchis5,6,3, Josep Lupón7,8,3, Antoni Bayés-Genís7,8,3 and Julio Núñez5,6,3**

1Cardiology Service, Hospital Universitario San Juan de Alicante, Alicante, Spain; 2Clinical Medicine Department, Universidad Miguel Hernández, Alicante, Spain; 3Centro de Investigación Biomédica en Red Enfermedades Cardiovasculares (CIBERCV), Madrid, Spain; 4Cardiology Service, Hospital General Universitario de Valencia, Valencia, Spain; 5Cardiology Service, Hospital Clínico Universitario, INCLIVA, Valencia, Spain; 6Department of Medicine, Universitat de València, Valencia, Spain; 7Heart Failure Unit, Cardiology Service, Hospital Universitari Germans Trias i Pujol, Barcelona, Spain; 8Department of Medicine, Autonomous University of Barcelona, Barcelona, Spain

Abstract

Aims Type 2 diabetes mellitus (T2DM) is common in patients with heart failure (HF) and is related with worse outcomes. Insulin treatment is associated with sodium and water retention, weight gain, and hypoglycaemia—all pathophysiological mechanisms related to HF decompensation. This study aimed to evaluate the association between insulin treatment and the risk of 1 year readmission for HF in patients discharged for acute HF.

Methods and results We prospectively included 2895 consecutive patients discharged after an episode of acute HF in a single tertiary hospital. Multivariable Cox regression, adapted for competing events, was used to assess the association between insulin treatment and 1 year readmission for HF in patients discharged after acute HF. Participants’ mean age was 73.4 ± 11.2 years, 50.8% were women, 44.7% had T2DM [including 527 (18.2%) on insulin therapy], and 52.7% had preserved ejection fraction. At 1 year follow-up, 518 (17.9%) patients had died and 693 (23.9%) were readmitted for HF. The crude risk of readmission for HF was higher in patients on insulin, with no differences in 1 year mortality. After multivariable adjustment, patients on insulin were at significantly higher risk of 1 year readmission for HF than patients with diabetes who were not on insulin (hazard ratio 1.28; 95% confidence interval 1.04–1.59, P = 0.022) and patients without diabetes (hazard ratio 1.26; 95% confidence interval 1.02–1.55, P = 0.035).

Conclusion Following acute HF, patients with T2DM on insulin therapy are at increased risk of readmission for HF. Further studies unravelling the mechanisms behind this association are warranted.

Keywords Insulin therapy; Type 2 diabetes mellitus; Acute heart failure; Hospital readmission

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Introduction

After hospitalization for acute heart failure (AHF), readmissions are associated with increased mortality and constitute a heavy healthcare burden. Current heart failure (HF) programmes and institutional initiatives thus prioritize efforts to reduce readmissions rates. Unfortunately, risk factors for identifying patients at higher risk of this outcome are not well established.

Type 2 diabetes mellitus (T2DM) is a known risk factor for developing HF and is highly prevalent among these patients; moreover, it is associated with a higher risk of adverse outcomes. Recent evidence points to the potential benefits of sodium–glucose cotransporter 2 inhibitors for reducing the risk of hospitalizations for HF. Although strict glycaemic control is not recommended in patients with HF, insulin remains one of the most common therapies in those who do not achieve optimal metabolic control. This therapy is still recommended for patients with T2DM and HF, and 30–50% of these patients receive it. However, insulin is an anabolizing hormone that causes sodium and fluid retention, weight gain, and hypoglycaemia,
with resulting sympathetic nervous system activation. Some observational studies have found an increased risk of adverse outcomes in patients with HF and on insulin therapy, although most of the evidence of this connection comes from post hoc analyses in select patients with chronic HF enrolled in randomized clinical trials. Little is known about the influence of insulin treatment on the risk of hospitalizations for HF, especially in subgroups at higher risk of readmission, such as patients with a recent HF decompensation. We therefore aimed to evaluate the impact of insulin treatment on the risk of readmissions and all-cause mortality after an episode of AHF.

**Methods**

**Study design and patients**

This prospective observational cohort study included 3054 consecutive patients admitted with AHF in the cardiology department of a tertiary referral hospital from 1 January 2007 to 1 August 2017. AHF was defined according to clinical practice guidelines. Patients with new-onset or acutely decompensated HF were included in the registry. Patients who died during the index hospitalization and those with type 1 diabetes were excluded from the final analysis (n = 159), leaving a final sample of 2895 patients. T2DM diagnosis was defined according to international guidelines: receiving medical treatment for T2DM, confirmed fasting glucose levels of more than 125 mg/dL, non-fasting glucose levels of more than 140 mg/dL, or glycated haemoglobin of more than 6.5%. Dyslipidaemia was defined as a concentration of total cholesterol of 200 mg/dL or more, a concentration of triglycerides of 150 mg/dL or more, a registered diagnosis of hypercholesterolaemia or hypertriglyceridaemia, or the use of lipid-lowering treatment.

During the index hospitalization, data on demographics, medical history, vital signs, 12-lead electrocardiogram, laboratory and echocardiographic parameters, and drug use were routinely recorded using pre-established registry questionnaires. Left ventricular ejection fraction (LVEF) was assessed by two-dimensional echocardiography and calculated using the biplane Simpson method (96 ± 24 h after admission). HF and anti-diabetic pharmacological treatments were recorded at discharge.

**Ethical considerations**

The local institutional ethics committee (Hospital Clínico Universitario de Valencia) approved the study, which conformed to the principles outlined in the Declaration of Helsinki. All patients gave informed consent.

**Endpoints and follow-up**

The primary endpoint was readmissions for HF at 1 year. Readmission for AHF was defined as an unplanned hospitalization requiring >24 h stay and caused by substantive worsening of HF symptoms and/or signs requiring new administration of intravenous HF therapies, including inotropes, diuretics, or vasodilators. Electronic clinical records are shared by all public hospitals in the area and by all general practitioners. Clinical records were reviewed to ensure the capture of eventual hospitalizations in other hospitals. The secondary endpoint was all-cause mortality at 1 year. The personnel in charge of endpoint adjudications during follow-up were blinded to T2DM status and treatment.

**Statistical analysis**

Continuous variables are presented as mean (± standard deviation) or median (inter-quartile range), as appropriate. Categorical variables are expressed as absolute and relative frequencies. Baseline continuous variables were compared according to T2DM status (no T2DM, no-insulin T2DM, and T2DM on insulin therapy) with the ANOVA or Wilcoxon test, as appropriate; discrete variables were compared with the \( \chi^2 \) test.

Cox regression analysis was used for evaluating the risk of 1 year mortality. An adapted Cox regression model, which took into account the effect of all-cause mortality (method of Fine and Gray), was used to examine the independent association between T2DM status and HF readmissions. All covariates shown in Table 1 were evaluated in regression models for prognostic purposes. In an attempt to minimize the residual confounding and indication bias, the covariates included in the multivariable models were selected based on the biological/clinical plausibility, regardless of the P-value. The linearity assumption for all continuous variables was simultaneously tested and the variable transformed, if appropriate, with fractional polynomials. Several multivariate models were built. The first one included age and sex (Model 1). Model 2 included age, sex, prior admission for AHF, last New York Heart Association (NYHA) class under stable condition, aetiology, dyslipidaemia, Charlson co-morbidity index, peripheral oedemas on admission, left bundle branch block, systolic and diastolic blood pressures, atrial fibrillation, heart rate, glomerular filtration rate, haemoglobin, sodium, N-terminal pro-B-type natriuretic peptide (NT-proBNP), left ventricular ejection fraction categories (>40%, 40–49%, and ≥50%), severe tricuspid regurgitation, and left atrial diameter. Model 3 included the same covariates. Of Model 2 and also HF and T2DM medications prescribed on discharge (furosemide equivalent doses, angiotensin-converting
Table 1 Participant characteristics at baseline and outcomes at 12 months

| Variables                                      | No diabetes (N = 1600) | No-insulin T2DM (N = 768) | T2DM on insulin (N = 527) | P  |
|------------------------------------------------|------------------------|---------------------------|---------------------------|----|
| Demographic and medical history                |                        |                           |                           |    |
| Age (years), mean ± SD                         | 73.1 ± 12.5            | 73.6 ± 9.8                | 73.7 ± 9.1                | 0.486 |
| Men, n (%)                                     | 785 (50.9)             | 339 (44.1)                | 269 (51.0)                | 0.005 |
| ≥2 prior admissions for AHF, n (%)             | 685 (42.8)             | 365 (47.5)                | 298 (56.5)                | <0.001 |
| Last stable NYHA class ≥III, n (%)             | 215 (13.4)             | 120 (15.6)                | 118 (22.4)                | <0.001 |
| Hypertension, n (%)                            | 1149 (71.8)            | 649 (84.5)                | 478 (90.7)                | <0.001 |
| Dyslipidaemia, n (%)                            | 710 (44.4)             | 484 (63.0)                | 357 (67.7)                | <0.001 |
| Current smoker, n (%)                          | 213 (13.3)             | 96 (12.5)                 | 50 (9.5)                  | 0.069 |
| History of CHD, n (%)                          | 437 (27.3)             | 309 (40.2)                | 271 (51.4)                | <0.001 |
| History of atrial fibrillation, n (%)          | 774 (48.4)             | 336 (43.8)                | 170 (32.3)                | <0.001 |
| Charlson index, mean ± SD                      | 1.4 ± 1.4              | 2.4 ± 1.7                 | 3.3 ± 1.9                 | <0.001 |
| Physical examination at admission              |                        |                           |                           |    |
| Heart rate (b.p.m.), mean ± SD                | 101 ± 30               | 98 ± 28                   | 93 ± 24                   | <0.001 |
| Systolic BP (mmHg), mean ± SD                  | 146 ± 33               | 148 ± 33                  | 149 ± 33                  | 0.215 |
| Diastolic BP (mmHg), mean ± SD                 | 83 ± 20                | 81 ± 20                   | 78 ± 18                   | <0.001 |
| Peripheral oedema, n (%)                       | 908 (56.8)             | 487 (63.4)                | 356 (67.6)                | <0.001 |
| Pleural effusion, n (%)                        | 774 (46.5)             | 366 (47.7)                | 255 (48.4)                | 0.714 |
| Laboratory parameters                          |                        |                           |                           |    |
| Haemoglobin (g/dL), mean ± SD                  | 12.8 ± 1.9             | 12.4 ± 1.9                | 11.8 ± 1.9                | <0.001 |
| Creatinine (mg/dL), mean ± SD                  | 1.2 ± 0.6              | 1.2 ± 0.5                 | 1.4 ± 0.7                 | <0.001 |
| eGFR (mL/min/1.73 m²), mean ± SD               | 64.3 ± 29.3            | 63.7 ± 24.3               | 54.3 ± 24.4               | <0.001 |
| Serum sodium (mEq/L), mean ± SD                | 138.8 ± 4.4            | 138.4 ± 4.5               | 138.1 ± 4.5               | 0.005 |
| NT-proBNP (pg/mL), median (IQR)                | 4721 (2012–8855)       | 3992 (1889–7769)          | 4154 (1937–8012)          | 0.066 |
| CA 125 (U/mL), median (IQR)                    | 55 (25–126)            | 54 (25–120)               | 58 (26–127)               | 0.900 |
| Echocardiography                               |                        |                           |                           |    |
| LVEF categories, n (%)                         |                        |                           |                           |    |
| ≤40%                                           | 512 (32.0)             | 253 (32.9)                | 148 (28.1)                | 0.002 |
| 41–4%                                          | 217 (13.6)             | 140 (18.2)                | 100 (19.0)                | 0.788 |
| ≥50%                                           | 871 (54.0)             | 375 (48.8)                | 279 (52.9)                | 0.976 |
| LVEF (%), mean ± SD                            | 49.7 ± 15.7            | 49.0 ± 14.8               | 50.0 ± 14.7               | 0.436 |
| LA diameter (mm), mean ± SD                    | 44.2 ± 8.6             | 43.5 ± 7.3                | 42.9 ± 7.2                | 0.002 |
| Tricuspid regurgitation ≥II, mean ± SD         | 167 (10.4)             | 64 (8.3)                  | 41 (7.8)                  | 0.097 |
| Treatment at discharge                         |                        |                           |                           |    |
| Loop diuretics, n (%)                          | 1584 (99.0)            | 757 (98.6)                | 524 (99.4)                | 0.314 |
| Furosemide dose (mg/day), mean ± SD            | 61.9 ± 43.3            | 66.5 ± 43.7               | 78.6 ± 42.9               | <0.001 |
| Beta-blockers, n (%)                           | 1123 (70.2)            | 522 (68.0)                | 348 (66.2)                | 0.169 |
| ACEI/ARB, n (%)                                | 1014 (63.41)           | 533 (69.4)                | 355 (67.4)                | 0.010 |
| MRAs, n (%)                                    | 473 (29.6)             | 271 (35.3)                | 149 (28.3)                | 0.007 |
| Statins, n (%)                                 | 670 (41.9)             | 427 (55.6)                | 303 (57.5)                | <0.001 |
| Events at 12 month follow-up, n (%)            |                        |                           |                           |    |
| Death                                          | 279 (17.4)             | 130 (16.9)                | 109 (20.7)                | <0.001 |
| HF readmissions                                | 332 (20.8)             | 181 (23.6)                | 180 (34.2)                | <0.001 |
| Death or HF readmission                       | 497 (31.1)             | 253 (32.9)                | 243 (46.1)                | <0.001 |

ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; AHF, acute heart failure; BP, blood pressure; CA 125, antigen carbohydrate 125; CHD, coronary heart disease; eGFR, estimated glomerular filtration rate; HF, heart failure; IQR, inter-quartile range; LA, left atrial; LVEF, left ventricular ejection fraction; MRAs, mineralocorticoid receptor antagonists; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; SD, standard deviation; T2DM, type 2 diabetes mellitus.

Comparisons were made among the three categories (no T2DM, no-insulin T2DM, and T2DM on insulin therapy). Continuous variables were compared with the ANOVA or Kruskal–Wallis test, as appropriate; discrete variables were compared with the χ² test. Comparison between continuous variables between no-insulin T2DM and T2DM on insulin was tested with t-test or Mann–Whitney–Wilcoxon, as appropriate.

Significant differences (P < 0.05) in an additional analysis comparing patients with T2DM with and without insulin therapy.

Enzyme inhibitors/angiotensin receptor blockers, mineralocorticoid receptor antagonists, beta-blockers, metformin, sulfonylureas, and dipeptidyl peptidase-4 inhibitors. The proportionality assumption for the hazard function over time was tested by means of the Schoenfeld residuals. The discriminatory ability of the multivariable models was evaluated with Harrell’s C-statistic.

We set a two-sided P-value of <0.05 as the threshold for statistical significance. Stata 15.1 [Stata Statistical Software, Release 15 (2017); StataCorp LP, College Station, TX, USA] was used for the analysis.

Results

The mean age of the sample was 73.4 ± 11.2 years, 50.8% were women, 52.7% showed LVEF of at least 50%, and...
44.7% had T2DM. Of the 1295 participants with T2DM, 40.7% (n = 527) were on insulin.

**Baseline characteristics across type 2 diabetes mellitus status**

*Table 1* shows participants’ characteristics according to T2DM categories. People receiving insulin for their diabetes exhibited a worse HF risk profile, with a higher proportion of prior hypertension, dyslipidaemia, prior admission for AHF, ischaemic heart disease, worse baseline functional NYHA class, greater signs of congestion, and more Charlson co-morbidity. Likewise, haemoglobin, glomerular filtration rate, and serum sodium values were lower in this group. At discharge, they were more frequently treated with statins and higher loop diuretic doses. In contrast, a lower proportion were prescribed sulfonylurea prescription rates. There were no differences in the differential effect across the levels of glycated haemoglobin, regardless of whether the variable was analysed continuously (P-value for interaction = 0.365) or dichotomized at the median (P-value for interaction = 0.446).

**Outcomes at 1 year**

At 1 year follow-up, 518 (17.9%) of our participants died, 693 (23.9%) were readmitted for HF, and 993 (34.3%) experienced at least one of these two outcomes.

The 1 year HF readmission rates were higher in patients with T2DM on insulin compared with patients with T2DM not on insulin and non-diabetic patients (*Table 1*). Cumulative incidence curves showed a marked separation from the first month after discharge (*Figure 1*). After a comprehensive and progressive multivariable adjustment, those patients receiving insulin were at higher risk for 1 year HF readmissions (*Table 2*). Compared with non-T2DM, T2DM on insulin showed and increased risk [hazard ratio (HR) 1.26, 95% confidence interval (CI) 1.02–1.59, *P* = 0.035]. Likewise, the excess of risk was also present when compared with T2DM not on insulin (HR 1.28, 95% CI 1.04–1.59, *P* = 0.022). The risk of HF readmission did not differ significantly between the no-insulin T2DM and no-T2DM groups (HR 1.02, 95% CI 0.84–1.25, *P* = 0.829). Harrell’s C-statistic of the fully adjusted model was 0.773.

The excess risk attributable to insulin did not differ significantly by sex or HF treatment nor did it vary across key patient subgroups, including those aged 75 years or more, those with LVEF of 50% or more, and those with higher than median NT-proBNP values (*Figure 2*). When the analysis was restricted to patients with T2DM, there was no differential effect across the levels of glycated haemoglobin, regardless of whether the variable was analysed continuously (P-value for interaction = 0.365) or dichotomized at the median (P-value for interaction = 0.446).

**All-cause mortality**

Kaplan–Meier curves did not differ significantly among the T2DM categories (*Figure 3*). Likewise, multivariable analysis did not show differences between these groups (HR 1.03,
Table 2  Insulin treatment and risk of 1 year HF readmission

|                | HR (95% CI) Omnibus P-value |
|----------------|----------------------------|
| Univariate     |                            |
| No diabetes    | 1                          |
| No-insulin T2DM| 1.14 (0.95–1.37)            |
| T2DM on insulin| 1.72 (1.44–2.06)            |
| Multivariate   |                            |
| Model 1        |                            |
| No diabetes    | 1                          |
| No-insulin T2DM| 1.15 (0.95–1.37)            |
| T2DM on insulin| 1.73 (1.44–2.07)            |
| Model 2        |                            |
| No diabetes    | 1                          |
| No-insulin T2DM| 0.99 (0.82–1.20)            |
| T2DM on insulin| 1.27 (1.03–1.56)            |
| Model 3        |                            |
| No diabetes    | 1                          |
| No-insulin T2DM| 0.98 (0.80–1.19)            |
| T2DM on insulin| 1.26 (1.02–1.55)            |

Cl, confidence interval; HF, heart failure; HR, hazard ratio; T2DM, type 2 diabetes mellitus.

Model 1: adjusted for age and sex.
Model 2: adjusted for age, sex, prior admission for acute heart failure, New York Heart Association class under stable condition, aetiology, dyslipidaemia, Charlson comorbidity index, peripheral oedemas on admission, left bundle branch block, systolic and diastolic blood pressures, atrial fibrillation, heart rate, glomerular filtration rate, haemoglobin, sodium, N-terminal pro-brain natriuretic peptide, left ventricular ejection fraction, severe tricuspid regurgitation, and left atrial diameter.
Model 3: adjusted for age, sex, prior admission for acute heart failure, New York Heart Association class under stable condition, aetiology, dyslipidaemia, Charlson comorbidity index, peripheral oedemas on admission, left bundle branch block, systolic and diastolic blood pressures, atrial fibrillation, heart rate, glomerular filtration rate, haemoglobin, sodium, N-terminal pro-brain natriuretic peptide, left ventricular ejection fraction, severe tricuspid regurgitation, left atrial diameter, and discharge treatments (furosemide equivalent doses, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, mineralocorticoid receptor antagonists, beta-blockers, metformin, sulfonylureas, and dipeptidyl peptidase-4 inhibitors). Harrell’s C-statistic of Model 3 = 0.773.

95% CI 0.79–1.33, P = 0.840) nor were there variations by patient subgroup (Figure 4).

Discussion

In this large observational study, there was a strong association between insulin treatment at discharge and a higher risk of 1 year readmission for HF in patients discharged for AHF. This increased risk was consistent across key patient subgroups. Most published evidence on the association between insulin therapy and adverse events (as a composite outcome) has come from a narrow selection of stable patients enrolled in clinical trials. In contrast, our sample of patients with AHF was much more representative, and we evaluated the specific association between insulin treatment and HF readmission. These findings point to the potentially harmful effect of insulin therapy for T2DM following an episode of decompensation.

Risk of readmission in patients with established heart failure: what role does type 2 diabetes mellitus play?

Reducing hospital readmissions is a major objective in managing patients with HF, as rehospitalization is strongly associated with disease progression and mortality.20 Many strategies have been proposed to reduce the burden of readmissions after an AHF episode,3,21 but predicting which patients are at higher risk remains challenging, as there are no well-established predictors for this outcome.

Most of the literature suggests that T2DM is an independent predictor of mortality in patients with HF, but this relationship is not necessarily straightforward. Some authors hold that T2DM increases the risk only in patients with coronary artery disease,22 whereas others argue that women bear a disproportionate share of the burden.23 Our group observed a higher risk of death in women with T2DM in a cohort of patients with HF and preserved ejection fraction.24 However, emerging evidence suggests that most of T2DM’s prognostic impact is mediated by insulin therapy. To date, three post hoc analyses from randomized clinical trials, plus one observational registry study, have found an independent association between insulin therapy and adverse outcomes in different phenotypes of patients with stable HF.13,25–27 Our study corroborates these findings and extends the implications to the first year following an episode of decompensation—a high-risk period for subsequent HF readmission.

Biological plausibility for the association between insulin and heart failure risk

Congestion explains most of the pathophysiology of AHF syndromes,28 and several pathophysiological mechanisms, probably interrelated, could be behind a causal relationship between insulin and greater congestion.

Sodium and water retention

Insulin treatment has well-known effects on sodium transport, resulting in sodium and water retention.29 The mechanism of insulin’s anti-natriuretic effects involves the reduction of glycosuria and, in turn, of urinary sodium excretion. In addition, insulin also directly promotes sodium and water reabsorption in the nephron.29 These anti-natriuretic effects, while widely acknowledged by the scientific...
community for over 40 years, are probably underestimated. Papers dating back to 1974 warn against insulin’s side effects: ‘In the diabetic with a long-term uncontrolled disease, it must be anticipated that sodium will be avidly retained. Excessive sodium intake might overload the vascular space and precipitate cardiopulmonary complications in the susceptible patient’. Our results are consistent with these predictions, demonstrating that patients on insulin therapy showed more symptoms and signs of congestion.

**Hypoglycaemia**

Insulin is a major determinant of hypoglycaemic episodes. The Action to Control Cardiovascular Risk in Diabetes trial was designed to evaluate the effects of intensive glucose control for preventing cardiovascular disease. Far from demonstrating a benefit, the trial found increased mortality in patients with more intensive glycaemic control, which was attributed to higher rates of hypoglycaemic events.
that group.\footnote{31} A recent post hoc analysis of the EMPA-REG OUTCOME trial has shown a strong association between hypoglycaemia and an increased risk of HF readmissions and myocardial infarction.\footnote{32} Although the statistical association between hypoglycaemia and cardiovascular mortality is strong, the mechanisms underpinning it are not well understood. The counterregulatory response stimulates the sympathetic nervous system, which can lead to increased preload, myocardial ischaemia, cardiac arrhythmias, and prothrombotic state—all factors related to HF decompensation.\footnote{33,34} In addition, some evidence suggests that in patients with chronic insulin resistance, insulin may be associated with the activation of the sympathetic nervous system, even without the mediation of hypoglycaemia.\footnote{29}

\section*{Cardiac hypocontractility}

Hyperinsulinaemia has been associated with decreased myocardial contractility, despite elevated catecholamine levels. The mechanisms have yet to be fully elucidated, but some of the implicated pathophysiological pathways include dysfunctional calcium handling within cardiomyocytes, catecholamine-induced β-adrenergic receptor desensitization, and direct inhibition of cardiac adrenergic signalling. Reinforcing these findings, blocking the insulin receptor-induced adrenergic signalling has been shown to ameliorate cardiac dysfunction.\footnote{35} Despite the strong association and biological postulates that reinforce causality, we cannot rule out the possibility that this relationship is confounded by other factors. Insulin is used to treat cases of T2DM that are more severe and have a longer duration. In HF clinical trials, patients receiving insulin for T2DM were at a more advanced stage in terms of NYHA functional class, NT-proBNP values, and congestion signs compared with those without insulin treatment.\footnote{13} Despite multivariable adjustment, we cannot rule out the presence of some residual confounding. A randomized clinical trial designed specifically to assess the effects of de-intensifying insulin treatment in HF patients with T2DM would provide valuable information for better managing these patients. With the existing evidence, we propose to counteract the excess of risk associated to insulin therapy with a careful adjustment of diuretics, the use of other anti-diabetics with natriuretic effect such as sodium–glucose cotransporter 2 inhibitors, and a close monitoring of body weight and other decompensation parameters of HF.

\section*{Limitations}

Our study has several limitations. First, it is a single-centre observational study with several potential confounders. Although the analysis used rigorous multivariable adjustment, the effects of unmeasured confounders cannot be fully excluded. Some important data were not registered, including the duration of T2DM and HF, the doses and type

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure4.png}
\caption{The excess mortality risk attributable to insulin across patient subgroups [no type 2 diabetes mellitus (T2DM), no-insulin T2DM, and T2DM on insulin therapy]. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide.}
\end{figure}

\begin{table}
\centering
\begin{tabular}{|c|c|c|}
\hline
Age & & \hline
\leq75\ years & HR & 1.02 & 0.66 – 1.57 & 0.836 \\
>75\ years & HR & 1.01 & 0.73 – 1.40 & \hline
Gender & & \hline
Women & HR & 1.12 & 0.77 – 1.63 & 0.193 \\
Men & HR & 0.93 & 0.65 – 1.34 & \hline
NT-proBNP & & \hline
\leq\text{median} & HR & 1.04 & 0.67 – 1.64 & 0.471 \\
>median & HR & 0.99 & 0.72 – 1.36 & \hline
LVEF & & \hline
\geq50\% & HR & 0.95 & 0.65 – 1.38 & 0.583 \\
<50\% & HR & 1.12 & 0.70 – 1.63 & \hline
ACEI/ARB & & \hline
Yes & HR & 0.76 & 0.51 – 1.11 & 0.856 \\
No & HR & 1.07 & 0.73 – 1.58 & \hline
Beta blockers & & \hline
Yes & HR & 0.91 & 0.66 – 1.25 & 0.010 \\
No & HR & 1.28 & 0.83 – 1.99 & \hline
MRA & & \hline
Yes & HR & 1.04 & 0.61 – 1.79 & 0.935 \\
No & HR & 1.02 & 0.75 – 1.38 & \hline
\end{tabular}
\end{table}
of insulin regimen, the number of hypoglycaemic episodes, and changes over time in treatment (HF and anti-diabetes) and glycaemic control. Observational studies are likewise unable to establish causality, although they do provide real-world data, which are particularly necessary when studying patients who are under-represented in clinical trials. Another limitation was that no uniform screening for T2DM was used, raising the possibility that some borderline cases may have been misdiagnosed. Finally, given the underuse of sodium–glucose cotransporter 2 inhibitors and glucagon-like peptide-1 receptor agonists at the time of this study, we could not evaluate the influence of these pharmacological groups on the present findings.

Conclusions

Insulin therapy is associated with an increased risk of 1 year HF readmission in patients with AHF and T2DM. The present findings warrant further investigation into the relationship between insulin treatment and prognosis following an episode of AHF.

Conflict of interest

None declared.

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