Prognostic impact of in-hospital hyperglycemia in hospitalized patients with acute heart failure: Results of the IN-HF (Italian Network on Heart Failure) Outcome registry

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ABSTRACT

Objectives: Although diabetes mellitus is frequently associated with heart failure (HF), the association between elevated admission glucose levels and adverse outcomes has not been well established in hospitalized patients with acute HF.

Methods: We prospectively evaluated in-hospital mortality, post-discharge 1-year mortality and 1-year re-hospitalization rates in the Italian Network on Heart Failure (IN-HF) Outcome registry cohort of 1776 patients hospitalized with acute HF and stratified by their admission glucose levels (*i.e.*, known diabetes, newly diagnosed hyperglycemia, no diabetes).

Results: Compared with those without diabetes ($n = 586$), patients with either known diabetes ($n = 749$) (unadjusted-odds ratio [OR] 1.64, 95%CI 0.99–2.70) or newly diagnosed hyperglycemia ($n = 441$) (unadjusted-OR 2.34, 95%CI 1.39–3.94) had higher in-hospital mortality, but comparable post-discharge 1-year mortality rates. After adjustment for age, sex, systolic blood pressure, estimated glomerular filtration rate, left ventricular ejection fraction, HF etiology and HF worsening/*de novo* presentation, the results remained unchanged in patients with known diabetes (adjusted-OR 1.86, 95%CI 1.01–3.42), while achieved borderline significance in those with newly diagnosed hyperglycemia (adjusted-OR 1.81, 95%CI 0.95–3.45). One-year re-hospitalization rates were lower in patients with newly diagnosed hyperglycemia (adjusted-hazard ratio 0.74, 95%CI 0.56–0.96) than in other groups.

Conclusions: Elevated admission blood glucose levels are associated with poorer in-hospital survival outcomes in patients with acute HF, especially in those with previously known diabetes. This finding further highlights the importance of tight glycemic control during hospital stay and address the need of dedicated intervention studies to identify customized clinical protocols to improve in-hospital survival of these high-risk patients.

1. Introduction

The occurrence of diabetes mellitus comorbid with heart failure (HF) is a common clinical experience and its prevalence is increasing at fast pace together with accompanying costs and morbidity [1–4]. Some studies [5–8], although not all [9,10], reported that the presence of known diabetes is associated with poorer short- and long-term prognosis and higher re-hospitalization rates among patients hospitalized with acute HF. However, to date few studies have explored the impact of the entire hyperglycemic spectrum on the short- and long-term adverse outcomes, and have reported discrepant results [11–14]. Indeed, the entire hyperglycemic spectrum comprises a number of clinical presentations, spanning from sub-diabetic or stress-induced

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hyperglycemia to overt diabetes (either known or previously undiagnosed) [15].

Higher in-hospital mortality rates have been associated with elevated admission blood glucose levels (especially among patients with abnormal glucose tolerance at presentation) [11], and recent data from a multicenter observational cohort study showed that among patients with acute HF blood glucose concentrations at hospital admission were a significant predictor of 30-day mortality, independent of a diagnosis of diabetes or other clinical variables [12]. Recently, Sud et al. reported similar results in a population-based cohort of 16,524 patients with acute HF presenting to the Emergency department in Ontario, Canada [13]. However, no significant relationship was observed between admission glucose levels and the risk of all-cause mortality at 30 days and 1 year, independently of pre-existing diabetes, in a nationally representative cohort of 50,532 elderly patients hospitalized with HF in the United States [14]. Recently, other investigators reported that elevated admission blood glucose levels or diabetes status did not significantly predict any post-discharge adverse outcomes (*i.e.*, 30-day and 1-year mortality and/or re-hospitalization) in patients admitted with acute HF [9,16]. All these findings suggest that the relationship between admission glucose levels and adverse outcomes in patients with acute HF is still controversial, and that the appropriate glycemic targets in this group of patients remain to be yet clearly defined.

Thus, while the prognostic relevance of known diabetes on HF-related survival outcomes has some supportive evidence, further studies are needed to elucidate the role of admission hyperglycemia on both the short- and long-term survival outcomes and the re-hospitalization rates in patients hospitalized with acute HF.

In this context, the present study aimed to prospectively explore the rates of in-hospital death, post-discharge 1-year death and 1-year re-hospitalization among the Italian Network on Heart Failure (IN-HF) Outcome study participants, who were stratified by different glycemic categories at hospital admission, *i.e.*, no diabetes, newly diagnosed hyperglycemia and known diabetes.

2. Materials and methods

2.1. Study population

The IN-HF Outcome study is a prospective, observational, nationwide study that involved 61 cardiology centers in Italy. The geographical distribution of hospitals across the country and the overall profile of the participating cardiology institutions (defined according to standard criteria) were representative of the national setting of cardiovascular care in Italy. Enrollment could occur during a routine ambulatory visit (patients with chronic HF) or at the time of admission to a cardiology ward (patients with worsening or *de novo* acute HF). Patients were enrolled from 23 November 2007 to 31 December 2009 and followed up for 1 year. Outpatient visits were performed at 3, 6 and 12 months after enrollment/discharge. Clinical status was ascertained by a telephone interview for patients who did not visit the clinic. Causes of death were ascertained by hospital records, death certificates, and autopsy records or by contacting the patients' physician or referring cardiologist. Consecutiveness of enrollment was recommended but not checked with an admission log. There were no specific exclusion criteria, with the exception of age < 18 years and patient unwillingness to participate. Patients with acute HF were enrolled only if treated with intravenous therapy (diuretics, vasodilators or inotropes). For the purpose of this study, we included the whole cohort of the IN-HF Outcome participants admitted to the hospital for acute HF in which blood glucose levels at admission were available ($n = 1776$ out of 1855). More details on the study design and methods have been published elsewhere [17,18].

The local Institutional Review Boards at each participating center approved the study protocol, and all study participants signed a written informed consent upon recruitment. Data were collected using a web-based system and stored in a central database.

2.2. Heart failure definition

Presence of HF was classified as "*de novo* HF" in the absence of a HF history and as "worsening HF" in the presence of a previously documented HF diagnosis or hospital admission for HF with a recent worsening of HF symptoms reported by the patient and confirmed by the physician. If not documented, a prior hospitalization was accepted as patient-reported. Being the study observational, no specific protocols or recommendations for the management of HF were imposed. Participating physicians were invited to be adherent to the 2008 European Society of Cardiology guidelines [19], which were diffused and discussed along with the HF diagnostic criteria, during the investigators' meetings performed at the beginning and during the course of the study.

2.3. Classification of glycemic categories

Known diabetes was defined as self-reported physician-diagnosed diabetes, or use of any medication for diabetes (insulin or oral hypoglycemic agents). In the absence of a previous diagnosis of diabetes, the non-diabetes and the newly diagnosed hyperglycemia categories were defined as a plasma glucose level < 7.0 mmol/l or ≥7.0 mmol/l, respectively.

2.4. Other clinical and laboratory data

Body mass index (BMI) was calculated by dividing weight in kilograms by height in meters squared. Patients were considered to have hypertension if their blood pressure was ≥140/90 mmHg or if they were taking any anti-hypertensive drugs.

Venous blood samples were drawn in the morning after an overnight fast. Serum creatinine, glucose and other biochemical blood measurements were determined using standard laboratory procedures. Glomerular filtration rate (e-GFR) was estimated by the four-variable Modification of Diet in Renal Disease (MDRD) study equation [20].

Conventional transthoracic echocardiography was used to measure left ventricular (LV) diameters, wall thickness according to international standard criteria. LV end-diastolic and end-systolic volumes and ejection fraction (EF) at rest were measured at the apical 4-chamber and 2-chamber views. More details have been published elsewhere [17].

2.5. Statistical analysis

Data are presented as means ± SD or percentages. Categorical variables were compared by the chi-square test and continuous variables by the Kruskal–Wallis test. Two multivariable regression models (model 1: unadjusted; model 2: adjusted for age, sex, systolic blood pressure, e-GFR_{MDRD}, LV-EF, HF etiology and HF worsening *vs. de novo* presentation) were applied to estimate the risks associated with different glycemic categories at hospital admittance in terms of all-cause in-hospital mortality (logistic regression model), post-discharge 1-year mortality and 1-year re-hospitalization rates (Cox regression model). In addition, the effect of *de novo vs.* worsening HF presentation on the relationship between admission blood glucose levels and mortality risk was tested by introducing the interaction term 'glucose group × HF presentation' in the above multivariable regression models. The covariates for these multivariable regression analyses were chosen as potential confounding factors based on their significance in univariable analyses or based on their biological plausibility. All statistical analyses were carried out with R Development Core Team 2014 and the package "rms": R package version 4.3-0 (http://CRAN.R-project.org/package=rms). *P*-values < 0.05 were considered to be statistically significant.

3. Result

Among the 1776 hospitalized patients with acute HF enrolled in the IN-HF Outcome study, 749 (42.2%) had known diabetes, 441 (24.8%)

had newly diagnosed hyperglycemia and the remaining 586 (33.0%) patients had no diabetes. The mean age of the whole cohort of patients with acute HF was 72 ± 12 years (range: 21–98 years) and 60% were men. The median duration of hospital stay was 10 days (interquartile range: 7–15 days).

Table 1 shows the baseline clinical and biochemical characteristics of the IN-HF Outcome participants stratified by glycemic categories at hospital admission. Compared with those without established diabetes, patients with newly diagnosed hyperglycemia or known diabetes were more likely to be female, older, obese and hypertensive. Both these groups also had a lower e-GFR value and a higher prevalence of acute HF clinical presentation (either shock or acute pulmonary oedema) at hospital admission compared with the no-diabetes group. Patients with newly diagnosed hyperglycemia also had a higher prevalence of *de novo* HF presentation than both the no-diabetes and the known-diabetes groups. Compared with those without diabetes, patients with either known diabetes or newly diagnosed hyperglycemia had a greater likelihood of ischemic etiology of HF; patients with known diabetes also had a higher prevalence of prior myocardial infarction or coronary revascularization. Finally, most patients with known diabetes had type 2 diabetes and were treated with hypoglycemic drugs (insulin or oral hypoglycemic agents) and anti-hypertensive medications (mainly ACE-inhibitors, angiotensin receptor blockers, diuretics or beta-blockers).

During the follow-up period 113 (6.4%) cases of all-cause in-hospital mortality (almost 90% of cardiac etiology), 315 (17.7%) cases of post-discharge 1-year all-cause mortality and 505 (28.4%) cases of 1-year re-hospitalization occurred.

As shown in Fig. 1 and Table 2, patients with acute HF pertaining to the two "hyperglycemic" phenotypes (either newly diagnosed hyperglycemia or known diabetes) had significantly higher all-cause in-hospital mortality rates than patients without diabetes. After adjustment for multiple HF risk factors, the association with higher in-hospital mortality was confirmed in patients with known diabetes (adjusted-OR 1.86, 95%CI 1.01–3.42), but was only of borderline significance in those with newly diagnosed hyperglycemia (adjusted-OR 1.81, 95%CI 0.95–3.45). While the post-discharge 1-year mortality rates were essentially comparable among the three groups of patients (as also shown in Fig. 1), the 1-year re-hospitalization rates were lower in patients with newly diagnosed hyperglycemia than in those without diabetes (Table 2 and Supplemental Fig. 1).

As shown in Table 3, we performed further statistical analyses adding to the fully adjusted regression models the terms of interaction between HF presentation at hospital admittance and glycemic groups. Though the overall interaction terms were not statistically significant, these results showed that worsening of pre-existing HF, rather than *de novo* presentation of HF, was significantly associated with higher in-hospital mortality rates in patients with known diabetes (adjusted-OR 2.56, 95%CI 1.16–5.62) and with lower 1-year re-hospitalization rates in those with newly diagnosed hyperglycemia (adjusted-HR 0.60, 95%CI 0.43–0.85). A non-significant trend towards higher 1-year re-hospitalization rates was observed in *de novo* HF patients with

Table 1
Baseline clinical and biochemical characteristics of the IN-HF Outcome study participants stratified by glycemic status at admission ($n = 1776$).

	No diabetes ($n = 586$)	Newly diagnosed hyperglycemia ($n = 441$)	Known diabetes ($n = 749$)	*P* value
Male sex (%)	64.2	55.6	59.8	0.02
Age (years)	71 ± 14	74 ± 11	72 ± 9	0.0012
Body weight (kg)	73 ± 16	74 ± 17	80 ± 17	<0.0001
Body mass index (kg/m^2)	26.6 ± 5	27.2 ± 6	29.1 ± 7	<0.0001
Systolic blood pressure (mm Hg)	128 ± 27	137 ± 38	137 ± 32	<0.0001
Diastolic blood pressure (mm Hg)	77 ± 16	80 ± 21	78 ± 17	0.11
Heart rate (bpm)	91 ± 26	98 ± 27	91 ± 25	<0.0001
Hemoglobin (g/dl)	12.7 ± 2.0	13.0 ± 2.1	12.1 ± 2.0	<0.0001
Creatinine (mg/dl)	1.4 ± 0.9	1.4 ± 0.8	1.6 ± 1.2	<0.001
e-GFR$_{MDRD}$ (ml/min/1.73 m^2)	58.9 ± 25.2	54.3 ± 21.5	51.9 ± 23.3	<0.0001
Glucose (mmol/l)	5.61 ± 0.8	9.94 ± 3.2	11.22 ± 5.1	<0.0001
Worsening/*de novo* presentation (%)				
De novo HF	40.6	51.5	39.2	<0.0001
Worsening HF	59.4	48.5	60.8	
HF etiology (%)				
Ischemic	33.5	36.3	54.6	<0.0001
Non-ischemic	66.5	63.7	45.5	
Clinical presentation (%)				
Shock	1.4	8.2	4.0	<0.0001
Acute pulmonary oedema	18.9	47.6	38.2	
NYHA-IV	25.4	16.8	23.0	
NYHA-III	54.3	27.4	34.8	
LV ejection fraction (%)	36.8 ± 14.2	37.2 ± 14.2	38.7 ± 13.8	0.02
Treated hypertension (%)	49.5	55.1	66.2	<0.0001
History of atrial fibrillation (%)	39.3	40.6	34.1	0.04
Previous myocardial infarction (%)	29.2	26.8	44.1	<0.0001
Previous coronary revascularization (%)	20.7	17.9	34.3	<0.0001
Previous stroke (%)	5.0	4.5	6.0	0.49
History of COPD (%)	28.2	28.6	33.4	0.07
Previous malignancy (%)	7.8	4.5	5.7	0.08
ACE-I/ARB users (%)	56.1	54.7	64.6	<0.001
Beta-blocker users (%)	38.4	36.3	45.5	<0.005
Digital users (%)	19.1	15.9	14.8	0.10
Diuretic users (%)	67.4	54.7	68.9	<0.001
Aldosterone blocker users (%)	18.9	12.7	16.6	0.03
Insulin users (%)	–	–	39.5	ND
Oral hypoglycemic users (%)	–	–	42.7	ND
Diabetes mellitus type (%)				
Type 1 diabetes	–	–	6.2	ND
Type 2 diabetes	–	–	93.8	

e-GFR$_{MDRD}$, estimated glomerular filtration rate; HF, heart failure; NYHA, New York Heart Association classification; LV, left ventricular; COPD, chronic obstructive pulmonary disease; ACE-I, angiotensin-converting-enzyme inhibitors; ARB, angiotensin receptor blocker; ND, not determined.

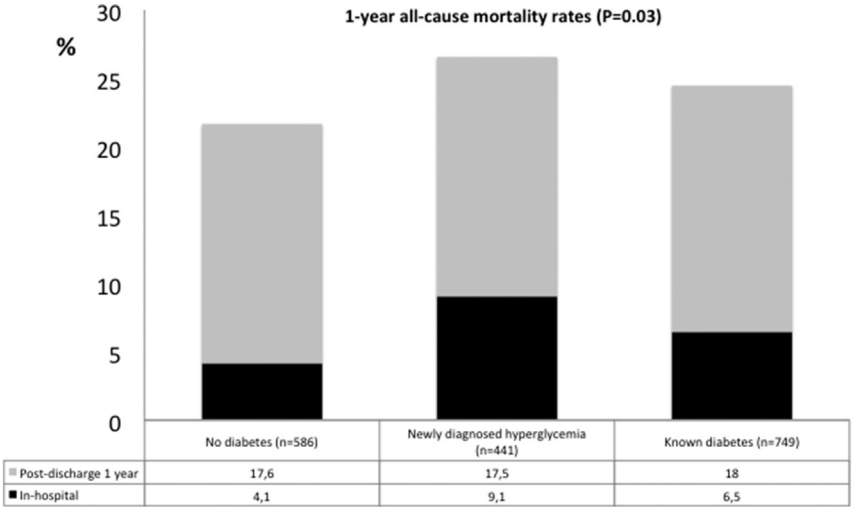

Fig. 1. Rates of 1-year all-cause mortality (both in-hospital and post-discharge 1-year mortality) in patients with acute HF stratified by glycemic status at hospital admission.

known diabetes (adjusted-HR 1.41, 95%CI 0.93–2.12). Similarly, a trend towards higher in-hospital death rates was also observed in *de novo* HF patients with newly diagnosed hyperglycemia (adjusted-HR 2.14, 95%CI 0.85–5.34). On the contrary, there was no significant association between HF presentation (*de novo vs.* worsening) and the three groups of patients in terms of post-discharge 1-year mortality rates (data not shown).

4. Discussion

The major finding of the IN-HF Outcome registry, involving a large number of elderly patients hospitalized with acute HF, was that compared with those without diabetes, patients with either known diabetes or newly diagnosed hyperglycemia had significantly higher in-hospital mortality rates. After adjustment for multiple risk factors for HF, the results remained statistically significant in patients with known diabetes, but achieved borderline significance in those with newly diagnosed hyperglycemia. No significant differences in post-discharge 1-year all-cause mortality were observed among the three groups of patients, whereas 1-year re-hospitalization rates were lower in patients with newly diagnosed hyperglycemia.

In order to elucidate whether HF clinical presentation at hospital admission had any effect on the observed results, we also analyzed the interaction between HF presentation and glycemic groups. Notably, we found that, within the two clinical 'hyperglycemic' phenotypes, there was a trend towards higher in-hospital mortality both in known diabetes with worsening HF and in newly diagnosed hyperglycemia with *de novo* HF, though the results were statistically significant only in patients with known diabetes. Moreover, patients with newly diagnosed hyperglycemia admitted to the hospital for worsening HF experienced lower 1-year re-hospitalization rates, while the presence of *de novo* HF in known diabetes was associated with marginally higher 1-year re-hospitalization rates.

Our findings are consistent with previous observations that HF patients with known diabetes have higher in-hospital mortality rates than those without diabetes [8,11,21]. Some studies also showed a significant association between known diabetes and post-discharge adverse outcomes in patients with acute HF [5,7,22]. Conversely, in the analysis of short-term clinical outcomes in the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF) registry, Greenberg et al. found that HF patients with known diabetes had similar in-hospital and post-discharge mortality rates compared with patients without diabetes, but had higher risk of re-hospitalization [10].

Published studies examining the association between elevated admission blood glucose levels and adverse outcomes in patients with acute HF have been limited and have reported discrepant results. For instance, Mebazaa et al. showed that among patients with acute HF blood glucose levels at hospital admission were powerfully prognostic for 30-day mortality, independently of pre-existing diabetes, in a multinational cohort of patients with acute HF [12]. Similarly, in a large, population-based cohort of patients presenting to an Emergency Department with acute HF, Sud et al. have recently shown that presentation blood glucose levels were significantly associated with an increased risk of 30-day all-cause mortality both in patients without diabetes and in those with

Table 2
Univariable and multivariable logistic or Cox regression analyses for all-cause in-hospital mortality, post-discharge 1-year mortality and 1-year re-hospitalization rates in patients with acute HF stratified by glycemic status at admission.

	In–hospital mortality		Post–discharge 1–year mortality		1–Year re–hospitalization	
	Unadjusted OR	Adjusted OR[a]	Unadjusted HR	Adjusted HR[a]	Unadjusted HR	Adjusted HR[a]
No diabetes (n = 586)	1.0 (Ref.)	1.0 (Ref.)	1.0 (Ref.)	1.0 (Ref.)	1.0 (Ref.)	1.0 (Ref.)
Newly diagnosed hyperglycemia (n = 441)	2.34 (1.39–3.94)	1.81 (0.95–3.45)	1.07 (0.80–1.44)	1.10 (0.8–1.5)	0.70 (0.55–0.90)	0.74 (0.56–0.96)
Known diabetes (n = 749)	1.64 (0.99–2.70)	1.86** (1.01–3.42)	1.08 (0.84–1.40)	0.98 (0.74–1.31)	0.95 (0.78–1.16)	0.99 (0.79–1.23)

Data are expressed as odds ratio (OR) or hazard ratios (HR) and 95% confidence intervals (CI). Ref. = Reference category.
[a]Data are adjusted for age, sex, systolic blood pressure, e-GFR_{MDRD}, LV-EF, HF etiology and HF worsening/*de novo* presentation. For clarity, significant values are highlighted in gray.
**Wald statistics of glycemic group n.s. ($P = 0.11$).

Table 3
Multivariable logistic or Cox regression analyses for all-cause in-hospital mortality, and 1-year re-hospitalization rates in patients with acute HF stratified by glycemic categories and HF presentation (*de novo vs.* worsening).

	In–hospital mortality	1–Year re–hospitalization
	Adjusted OR*	Adjusted HR**
No diabetes (n = 586)	1.0 (Ref.)	1.0 (Ref.)
Newly diagnosed hyperglycemia (n = 441)		
Worsening HF group	1.29 (0.49–3.38)	0.60 (0.43–0.85)
De novo HF group	2.14 (0.85–5.34)	1.09 (0.70–1.71)
Known diabetes (n = 749)		
Worsening HF group	2.56 (1.16–5.62)	0.86 (0.67–1.10)
De novo HF group	1.15 (0.44–3.01)	1.41 (0.93–2.12)

Data are expressed as odds ratio (OR) or hazard ratios (HR) and 95% confidence intervals (CI). Ref. = Reference category. All data are adjusted for age, sex, systolic blood pressure, e-GFR_{MDRD}, LV-EF, HF etiology and HF worsening/*de novo* presentation with the interaction terms HF worsening/*de novo* presentation × glycemic status at hospital admission. For clarity, significant values are highlighted in gray.
*P of group = 0.038, P of HF presentation = 0.013, and P of the interaction term = 0.072.
**P of group = 0.021, P of HF presentation < 0.001, and P of the interaction term = 0.061.

established diabetes; quite surprisingly, however, patients with diabetes had lower mortality rates (expressed per 100 person-years) compared with those in patients without diabetes [13]. Along this line of evidence, among the diabetic and non-diabetic patients with chronic HF, who were enrolled in the Candesartan in Heart failure—Assessment of Reduction in Mortality and Morbidity (CHARM) trial, baseline HbA1c levels were independently associated with higher re-hospitalization rates and with a progressively increased risk of long-term all-cause mortality [23].

In contrast, other published studies did not find any significant association between elevated admission glucose levels and mortality, both in the short- and long-term, in patients with acute HF. For instance, a recent large study showed that plasma glucose levels at hospital admission were not significantly associated with an increased risk of all-cause mortality at 30 days and 1 year, independently of pre-existing diabetes, in a nationally representative cohort of 50,532 United States elderly patients with acute HF [14]. Additionally, Barsheshet et al. reported that elevated admission blood glucose levels were associated with increased in-hospital and 60-day mortality, but not with 6-month or 1-year mortality, in a cohort of 1122 hospitalized patients with acute HF [24]. Two other studies recently reported similar results [9,16].

Overall, therefore, our results confirm that known diabetes is extremely common (>40%) in patients hospitalized with acute HF, and that the in-hospital mortality rates are very high (cumulative incidence of 6.4%) in this patient population. In addition, our study sets a step forward on the existing literature as it provides both short- and long-term predictability estimates of the HF-related survival and functional outcomes across the entire spectrum of glycemic status at hospital admission, with a reasonably comprehensive adjustment for potential confounding variables, including also HF etiology, HF presentation, kidney function parameters and LV-EF.

However, as noted above, to date there is limited and conflicting information about the role of admission hyperglycemia on adverse outcomes in patients hospitalized with acute HF. As reported by other investigators, it is possible to speculate that the relationship between in-hospital hyperglycemia and adverse outcomes seen in acute myocardial infarction cannot be automatically extrapolated to patients hospitalized with acute HF [14,25]. Furthermore, it should be noted that most of the existing literature stands upon crude estimates of mortality rates in often quite heterogeneous study populations, comprising patients with different demographic characteristics and varying degrees of baseline cardiovascular risk. Therefore, the interpretation and comparison of published results necessarily face with a variety of confounding or mediating factors, such as population age, HF etiology and presentation, residual cardiac performance or other accompanying cardio-metabolic risk proxies, like systolic blood pressure or residual kidney function. Finally, it should also be pointed out that under the umbrella of in-hospital hyperglycemia there is a quite heterogeneous representation of clinical glycemic phenotypes, not ultimately the so-called "stress-induced hyperglycemia". This is a frequent occurrence at hospital admittance among patients with acute HF, it is characterized by an abrupt and transient increase in blood glucose levels [15], and is significantly associated with higher mortality rates and lower functional outcomes than either previously known diabetes or normal glucose regulation [26,27]. Unfortunately, we could not differentiate precisely stress-induced hyperglycemia from newly diagnosed diabetes because measurements of HbA1c were not available and blood glucose levels at the hospital discharge were available only in a subgroup of patients.

Interestingly, we observed a significant, inverse, association between admission blood glucose levels and 1-year re-hospitalization rates among patients with newly diagnosed hyperglycemia. The higher rates of shock and acute pulmonary oedema at hospital admission in this subgroup of patients might have accounted for higher in-hospital mortality, and as a consequence, for a lower rate of post-discharge adverse outcomes compared with patients without diabetes. In this context, it is also possible to assume that cardiovascular complications due to long-lasting uncontrolled diabetes did not already take place in this group of patients and a customized therapy (with hypoglycemic agents, statins, diuretics, anti-hypertensive drugs or a combination of them) was promptly started with proper timing at the earliest occurrence. Unfortunately, we have no robust data supporting this hypothesis, which would be however worth pursuing further in dedicated intervention trials. Another possibility is that the population pool undergoing 1-year re-hospitalization was actually enriched of "survivors" with an overall cardiac risk profile (considerably) better than the original pool of patients who died during the first hospitalization. According to these lines of reasoning, it is perhaps not surprising that the known-diabetes group with *de novo* HF also had marginally higher rates of 1-year re-hospitalization, given its veteran exposure to elevated blood glucose levels.

4.1. Study limitations

The most important limitations of the IN-HF Outcome registry include the lack of data regarding different hypoglycemic treatment regimens both at admission and during the hospital stay; the lack of follow-up information regarding hypoglycemic medications both in patients with known diabetes and in those with newly diagnosed hyperglycemia; and, finally, the unavailability of both baseline and follow-up data on HbA1c levels.

Notwithstanding these limitations, the major strengths of the IN-HF Outcome study include a relatively long follow-up duration, which is a quite rare occurrence in the existing literature for a large HF outcome registry; a long-lasting track record of both 1-year mortality and 1-year re-hospitalization events; and the availability of a large panel of baseline confounding variables, including HF etiology and presentation, LV-EF and kidney function parameters. Finally, though we did not replicate our analyses in a separate, independent cohort of HF in-patients with comparable clinical characteristics, our study sample was fairly representative of the current Italian in-patient population admitted for acute HF. However, whether these observations can be also extended to other groups of HF patients remains to be determined.

5. Conclusion

These results indicate that elevated admission blood glucose levels are associated with poorer in-hospital survival outcomes in patients with acute HF, especially in those with previously known diabetes. No significant differences in post-discharge 1-year all-cause mortality were observed among the three groups of patients. These results provide additional support for the use of efficacious evidence-based treatment regimens in HF patients with known diabetes. However, though there is urgent need of proper clinical protocols for the management of in-hospital hyperglycemia among patients with acute HF, the impact of an aggressive treatment of admission hyperglycemia on survival outcomes in this patient population needs to be explored in much greater detail with dedicated intervention trials.

Authorship

The authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation. All authors have read and approved the manuscript.

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Conflict of interest

No potential conflicts of interest relevant to this article were reported.

Contributors

GT and MD conceived the study analysis and wrote the draft of the manuscript; PLT, GL, GB, and MM researched data and edited/reviewed the manuscript. DL and RU analyzed the data and edited/reviewed the manuscript; AR edited/reviewed the manuscript and contributed to discussion; LT and APM, designed the study, edited/reviewed the manuscript and contributed to discussion. The Steering Committee of the study is the guarantors of this work and, as such, has full access to all the data in the study and takes responsibility for the integrity and the accuracy of the data analysis.

Appendix A

A.1. Steering committee

L. Tavazzi (Chairman), G. Cacciatore, A. Chinaglia, A. Di Lenarda, A.P. Maggioni, A. Mortara, M. Metra, F. Oliva and M. Senni.

A.2. Coordinating center

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References

[1] C. Iribarren, A.J. Karter, A.S. Go, et al., Glycemic control and heart failure among adult patients with diabetes, Circulation 103 (2001) 2668–2673.
[2] G.A. Nichols, C.M. Gullion, C.E. Koro, S.A. Ephross, J.B. Brown, The incidence of congestive heart failure in type 2 diabetes: an update, Diabetes Care 27 (2004) 1879–1884.
[3] M.A. Cavender, P.G. Steg, S.C. Smith Jr., et al., REACH Registry Investigators, Impact of diabetes mellitus on hospitalization for heart failure, cardiovascular events, and death: outcomes at 4 years from the reduction of atherothrombosis for continued health (REACH) registry, Circulation 132 (2015) 923–931.
[4] A. Dei Cas, S.S. Khan, J. Butler, et al., Impact of diabetes on epidemiology, treatment, and outcomes of patients with heart failure, JACC Heart Fail. 3 (2015) 136–145.
[5] M.R. MacDonald, P.S. Jhund, M.C. Petrie, et al., Discordant short- and long-term outcomes associated with diabetes in patients with heart failure: importance of age and sex: a population study of 5.1 million people in Scotland, Circ. Heart Fail. 1 (2008) 234–241.
[6] A.J. Burger, L. Tsao, D. Aronson, Prognostic impact of diabetes mellitus in patients with acute decompensated heart failure, Am. J. Cardiol. 95 (2005) 1117–1119.
[7] S. Sarma, R.J. Mentz, M.J. Kwasny, et al., EVEREST Investigators, Association between diabetes mellitus and post-discharge outcomes in patients hospitalized with heart failure: findings from the EVEREST trial, Eur. J. Heart Fail. 15 (2013) 194–202.
[8] J.P. Lassus, K. Siirilä-Waris, M.S. Nieminen, et al., FINN-AKVA study group, Long-term survival after hospitalization for acute heart failure—differences in prognosis of acutely decompensated chronic and new-onset acute heart failure, Int. J. Cardiol. 168 (2013) 458–462.
[9] J.G. Cleland, K. Chiswell, J.R. Teerlink, et al., Predictors of post-discharge outcomes from information acquired shortly after admission for acute heart failure: a report from the placebo-controlled randomized study of the selective A1 adenosine receptor antagonist rolofylline for patients hospitalized with acute decompensated heart failure and volume overload to assess treatment effect on congestion and renal function (PROTECT) study, Circ. Heart Fail. 7 (2014) 76–87.
[10] B.H. Greenberg, W.T. Abraham, N.M. Albert, et al., Influence of diabetes on characteristics and outcomes in patients hospitalized with heart failure: a report from the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF), Am. Heart J. 154 (277) (2007) e1–8.
[11] C. Berry, M. Brett, K. Stevenson, J.J. McMurray, J. Norrie, Nature and prognostic importance of abnormal glucose tolerance and diabetes in acute heart failure, Heart 94 (2008) 296–304.
[12] A. Mebazaa, E. Gayat, J. Lassus, et al., GREAT network, Association between elevated blood glucose and outcome in acute heart failure: results from an international observational cohort, J. Am. Coll. Cardiol. 61 (2013) 820–829.
[13] M. Sud, X. Wang, P.C. Austin, et al., Presentation blood glucose and death, hospitalization, and future diabetes risk in patients with acute heart failure syndromes, Eur. Heart J. 36 (2015) 924–931.
[14] M. Kosiborod, S.E. Inzucchi, J.A. Spertus, et al., Elevated admission glucose and mortality in elderly patients hospitalized with heart failure, Circulation 119 (2009) 1899–1907.
[15] K.M. Dungan, S.S. Braithwaite, J.C. Preiser, Stress hyperglycaemia, Lancet 373 (2009) 1798–1807.
[16] V. Novack, M. Pencina, D. Zahger, et al., Routine laboratory results and thirty day and one-year mortality risk following hospitalization with acute decompensated heart failure, PLoS One 5 (2010) e12184.
[17] F. Oliva, A. Mortara, G. Cacciatore, et al., IN-HF Outcome Investigators, Acute heart failure patient profiles, management and in-hospital outcome: results of the Italian Registry on Heart Failure Outcome, Eur. J. Heart Fail. 14 (2012) 1208–1217.
[18] L. Tavazzi, M. Senni, M. Metra, et al., IN-HF (Italian Network on Heart Failure) Outcome Investigators, Multicenter prospective observational study on acute and chronic heart failure: one-year follow-up results of IN-HF (Italian Network on Heart Failure) outcome registry, Circ. Heart Fail. 6 (2013) 473–481.
[19] K. Dickstein, A. Cohen-Solal, G. Filippatos, et al., ESC Committee for Practice Guidelines (CPG), ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the diagnosis and treatment of acute and chronic heart failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM), Eur. J. Heart Fail. 10 (2008) 933–989.
[20] L.A. Stevens, J. Coresh, T. Greene, A.S. Levey, Assessing kidney function—measured and estimated glomerular filtration rate, N. Engl. J. Med. 354 (2006) 2473–2483.

[21] J.T. Parissis, P. Rafouli-Stergiou, A. Mebazaa, et al., Acute heart failure in patients with diabetes mellitus: clinical characteristics and predictors of in-hospital mortality, Int. J. Cardiol. 157 (2012) 108–113.
[22] F.J. Carrasco-Sanchez, R. Gomez-Huelgas, F. Formiga, et al., RICA Investigators, Association between type 2 diabetes mellitus and post-discharge outcomes in heart failure patients: findings from the RICA registry, Diabetes Res. Clin. Pract. 104 (2014) 410–419.
[23] H.C. Gerstein, K. Swedberg, J. Carlsson, et al., CHARM Program Investigators, The hemoglobin A1c level as a progressive risk factor for cardiovascular death, hospitalization for heart failure, or death in patients with chronic heart failure: an analysis of the Candesartan in Heart failure: Assessment of Reduction in Mortality and Morbidity (CHARM) program, Arch. Intern. Med. 168 (2008) 1699–1704.
[24] A. Barsheshet, M. Garty, E. Grossman, et al., Admission blood glucose level and mortality among hospitalized nondiabetic patients with heart failure, Arch. Intern. Med. 166 (2006) 1613–1619.
[25] C. Lazzeri, S. Valente, G.F. Gensini, Hyperglycemia in acute heart failure: an opportunity to intervene? Curr. Heart Fail. Rep. 11 (2014) 241–245.
[26] G.E. Umpierrez, S.D. Isaacs, N. Bazargan, X. You, L.M. Thaler, A.E. Kitabchi, Hyperglycemia: an independent marker of in-hospital mortality in patients with undiagnosed diabetes, J. Clin. Endocrinol. Metab. 87 (2002) 978–982.
[27] S.E. Capes, D. Hunt, K. Malmberg, H.C. Gerstein, Stress hyperglycaemia and increased risk of death after myocardial infarction in patients with and without diabetes: a systematic overview, Lancet 355 (2000) 773–778.