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Association Between Elevated Blood Glucose and Outcome in Acute Heart Failure

Results From an International Observational Cohort

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Objective The aim of this analysis was to assess the association between elevated blood glucose level and mortality in acute heart failure (AHF).

Background Elevated blood glucose has been reported to be prognostically meaningful in patients with cardiac diagnoses, such as coronary artery disease. The short-term prognostic impact of hyperglycemia in AHF is unknown, however.

Methods In a multinational cohort of AHF, we examined the ability of blood glucose concentrations at presentation to predict all-cause mortality by 30 days. Fully adjusted models for prognosis included a previous diagnosis of diabetes mellitus as a covariate.

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Results A total of 6,212 subjects with AHF (mean age, 72 years; 52.5% male) were studied; the median blood glucose concentration on arrival at the hospital was 7.5 mmol/l (135 mg/dl), and 41% had a previous diagnosis of diabetes mellitus (DM). After 30 days, 618 patients (10%) had died. Compared with survivors, decedents had significantly higher median blood glucose concentrations (8.9 mmol/l vs. 7.4 mmol/l; $p < 0.0001$). In the fully adjusted model, an elevated blood glucose level was an independent predictor of 30-day mortality in AHF (odds ratio: 2.19; 95% confidence interval: 1.69 to 2.83; $p < 0.001$). The risk associated with an elevated blood glucose level appeared consistent across all subgroups of patients, including patients with preserved (hazard ratio: 5.41; 95% confidence interval: 2.44 to 12.0; $p < 0.0001$) and impaired systolic function (hazard ratio: 2.37; 95% confidence interval: 1.57 to 3.59; $p < 0.0001$). Furthermore, in reclassification analyses, elevated blood glucose added significant prognostic information to clinical parameters alone (4.4% net reclassification improvement; $p = 0.01$).

Conclusions Among patients with AHF, blood glucose concentrations at presentation are powerfully prognostic for 30-day mortality, independent of a diagnosis of diabetes mellitus or other clinical variables. Because blood glucose is easily modifiable, it may represent a valid target for therapeutic intervention. (J Am Coll Cardiol 2013;61: 820–9) © 2013 by the American College of Cardiology Foundation

Acute heart failure (AHF) is a highly prevalent condition, representing one of the most frequent diagnoses in the emergency department setting (1). In addition to being common, AHF represents a pivotal moment in the course of the disease, characterized by a poor short-term prognosis; in many studies, AHF has a 30-day mortality approaching 10% in patients without shock and a similarly grim intermediate and longer term prognosis (2).

Factors associated with short-term mortality in AHF typically include altered cardiovascular parameters and/or organ dysfunction; reported variables predictive of death in AHF include hypotension, impaired ventricular function, altered renal function, and marked elevation of biomarkers such as natriuretic peptides (3). However, it remains unclear whether abnormal metabolic parameters commonly found in serious illness are associated with an altered short-term outcome in AHF. As an example, altered glycemic control is common during critical illness, occurs in patients with or without a history of diabetes mellitus (DM), and may be associated with adverse outcome in this setting (3). In cardiovascular diseases, abnormalities of glycemic control have been shown to be prognostic of a higher mortality rate in those with an acute myocardial infarction (AMI) (4–6). However, although well established in AMI, the association between elevated glucose concentration and increased mortality in other acute cardiovascular conditions such as AHF remains controversial (7–9). There are few studies on AHF, and each has variable designs, with some studying only patients without DM (10,11) and others only examining more elderly patients (12). Moreover, the definition of cutoff value to define hyperglycemia varies among the studies, and the length of follow-up varied.

For these reasons and because hyperglycemia is a potentially modifiable risk factor, we examined the prognostic importance of elevated blood glucose in a large, multicenter, international analysis of several prospective cohorts of patients with AHF. We examined the factors associated with altered glycemic control in this setting and explored the association between hospital admission glucose levels and 30-day mortality.

Subjects and Methods

All study procedures were approved by local institutional review boards/ethics committees.

The dataset consisted of 12 cohorts: 6 were based in Western Europe (2 in Italy and 1 in each of the following countries: France, Finland, Switzerland, and Spain), 2 in Central Europe (Austria, Czech Republic), 2 in the United States, 1 in Asia (Japan), and 1 in Africa (Tunisia) (13–21). The principal investigators of each study submitted the original data collected for each patient, including glucose concentrations on admission. We defined patients as eligible if they were identified as presenting with AHF and had their blood glucose level measured on arrival at the emergency department. All patients had AHF according to the European Society of Cardiology guidelines (22). Both patients with new-onset (i.e., no history) heart failure (HF) and with decompensated chronic HF were included. For the sake of simplicity, we used AHF to designate all studied patients. Owing to a lack of blood glucose concentrations in a select few, the number of patients in the other publications may differ from those reported here. Of note, even if in all cases data were collected prospectively, the current study is a retrospective analysis of those data.

Clinical data, including anthropometric measures, comorbidities, precipitating factors, the most recent echocardiographic findings, clinical presentation, and medication at baseline were recorded. A previous diagnosis of DM was based on self-report by the patient, ongoing antidiabetic therapy, or documentation in the patient's medical records.

Blood glucose was measured with enzymatic methods. Estimated glomerular filtration rate (eGFR) was calculated from creatinine values using the Modified Diet in Renal Disease formula (23).

Outcomes. Vital status follow-up was completed at 30 days. The endpoint of interest was death from any cause; cardiovascular death was also evaluated.

Statistical analysis. The results are expressed as median and first to third quartile or number and percentage. The study outcome was defined as all-cause 30-day mortality.

Abbreviations and Acronyms

AHF = acute heart failure
AMI = acute myocardial infarction
CAD = coronary artery disease
CI = confidence interval
DM = diabetes mellitus
eGFR = estimated glomerular filtration rate
HF = heart failure
LVEF = left ventricular ejection fraction
SBP = systolic blood pressure

The log-linearity of the effect of blood glucose was studied for all patients and for diabetic and nondiabetic patients separately. The effect was found to be not log-linear for both groups with an inflection of the smoothing splines at 7 mmol/l (126 mg/dl) for nondiabetic patients and at 10 mmol/l (180 mg/dl) for diabetic patients (Online supplementary Fig. 1). Thus, hyperglycemia was defined as a glucose level of ≥7 mmol/l for nondiabetic subjects and ≥10 mmol/l for those with previous DM. Because patients from various countries were included, a potential cluster effect was taken into account using a generalized linear model with random intercept where the cluster of interest was the country. The effect of hyperglycemia on all-cause 30-day mortality was studied without and with adjustment for potential confounding factors. The confounders included in the multiple model were age, sex, comorbidities (history of chronic HF, history of coronary artery disease [CAD], diabetes mellitus), systolic blood pressure (SBP) or diastolic blood pressure, heart rate, impaired renal function (eGFR <60 ml/min/1.73 m^2) (24) and sodium <136 mmol/l. Moreover, the effect of hyperglycemia on all-cause 30-day mortality was studied in various pairs of subgroups (including diabetic, nondiabetic, no anemia, anemia, de novo HF, decompensation of chronic HF, no history of CAD, history of CAD, ≤age 80 years, >80 years, no history of hypertension, history of hypertension, eGFR ≥60 ml/min/1.73 m^2, eGFR <60 ml/min/1.73 m^2, male, female, left ventricular ejection fraction [LVEF] ≥40%, LVEF <40%, LVEF ≥50%, LVEF <50%, median or lower B-type natriuretic peptide, B-type natriuretic peptide greater than median, SBP ≤140 mm Hg, and SBP >140 mm Hg). For each pair of subgroups, an interaction test was performed, indicating whether the difference of effect between the 2 subgroups was significant.

The clinical benefit in risk prediction of adding hyperglycemia status to the clinical model was further assessed by reclassification analysis, including both the net reclassification improvement and the integrated discrimination index (25,26). Clinical variables used to build the baseline model for mortality risk prediction were the same as those used to adjust the main analysis (i.e., age, sex, comorbidities [history of chronic HF, CAD, and DM; SBP or diastolic blood pressure; heart rate; eGFR <60 ml/min/1.73 m^2; and sodium <136 mmol/l). In the reclassification analysis, cutoffs for low-, intermediate- and high-risk classes were defined based on the observed overall mortality in the study cohort. Patients were regarded as at high risk if the predicted risk of death was approximately 2-fold the observed mortality, whereas a predicted risk around half the observed mortality was considered the low-risk category. For 30-day mortality, cutoffs were defined as a predicted risk of <5%, 5% to 15%, and >15% for low-, intermediate-, and high-risk categories.

Statistical analyses were performed using R statistical software (R foundation for Statistical Computing, Vienna, Austria). A 2-sided p value <0.05 was considered statistically significant.

Results

Baseline characteristics. Among 8,213 patients with AHF included in the registry, 6,212 met the inclusion criteria for

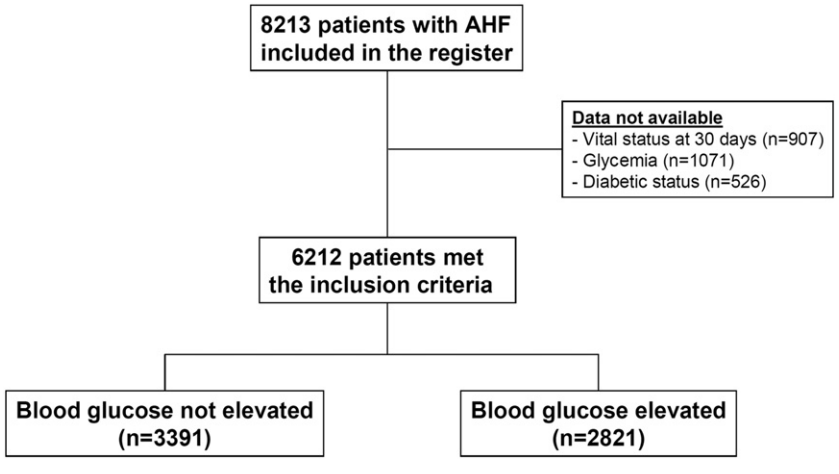

Figure 1 Flow Chart of the Study

All acute heart failure (AHF) patients for whom 30-day outcome, blood glucose level at admission, and diabetic status were available were included in the study.

Table 1 Baseline Characteristics of the Study Subjects

	Available Data, No. (%)	Patients Studied, (N = 6,212)
Age	6,207 (99.9)	74.1 (65.0–80.8)
Male sex	6,212 (100.0)	3,258 (52.4)
Body mass index, kg/m^2	3,394 (54.6)	27.1 (24.0–31.1)
Medical history		
Diabetes mellitus	6,212 (100.0)	2,543 (40.9)
Chronic obstructive pulmonary disease	5,679 (91.4)	1,161 (20.4)
Hypertension	6,064 (97.6)	4,146 (68.4)
History of heart failure	6,187 (99.6)	3,071 (49.6)
Atrial fibrillation	5,686 (91.5)	1,760 (31.0)
Coronary artery disease	6,053 (97.4)	2,946 (48.7)
Medication before admission		
Beta-blocker	4,773 (76.8)	2,258 (47.3)
Angiotensin-converting enzyme inhibitor	4,590 (73.9)	2,095 (45.6)
Angiotensin receptor blocker	4,580 (73.7)	880 (19.2)
Diuretic	4,590 (73.9)	2,661 (58.0)
Nitrate	4,567 (73.5)	1,041 (22.8)
Aspirin	4,592 (73.9)	1,903 (41.4)
Statin	4,491 (72.3)	1,335 (29.7)
Hemodynamic status at admission		
Systolic blood pressure, mm Hg	6,118 (98.2)	136 (115–160)
Diastolic blood pressure, mm Hg	6,117 (98.5)	80 (69–90)
Heart rate, beats/min	6,117 (98.5)	89 (74–107)
Left ventricular ejection fraction, %	3,446 (55.5)	40 (27–55)
Laboratory test results		
Hemoglobin, g/dl	5,262 (84.7)	12.9 (11.4–14.3)
Sodium, mmol/l	3,587 (57.7)	139 (136–141)
Potassium, mmol/l	6,124 (98.6)	4.2 (3.8–4.6)
Glomerular filtration rate, ml/min/1.73 m^2	6,132 (98.7)	54.2 (38.6–72.0)
Creatinine, μmol/l	6,141 (98.9)	102 (79.7–137.0)
Glucose, mmol/l	6,212 (100)	7.5 (5.9–10.7)
C-reactive protein, mg/l	1,306 (21)	13 (4.5–37.0)
B-type natriuretic peptide, pg/ml	2,070 (33.3)	895.5 (444–1,710)

Values are n (%) or median (interquartile range).

the study and were included. The population was then divided into to 2 groups: nonelevated blood glucose level (n = 3,391) and elevated blood glucose level (n = 2,821) according to the definition described previously (Fig. 1). The baseline characteristics of these 6,212 studied patients are given in Table 1.

The study subjects were typical of a population of patients with AHF, with a mean age of nearly 72 years, a slight male predominance (52.5%), and 41% having a history of DM. Half of the studied patients had de novo HF (also reflected by the clinical history and in the use of HF medications at presentation), and the mean LVEF was ~40%, indicating a slight predominance of HF due to left ventricular systolic dysfunction, but a substantial percentage with HF and preserved ejection fraction. Laboratory investigations in the study population were consistent with other studies of AHF, with an eGFR and natriuretic peptide concentration typical of a generally higher risk population. Characteristics of the study population as a function of the center of origin are detailed in Online Table 1.

Glucose concentrations at presentation. The median blood glucose level at admission was 7.5 mmol/l (135 mg/dl). In nondiabetic patients, the blood glucose level was elevated (≥7 mmol/l) in 42%, whereas in DM patients, it was elevated (≥10 mmol/l) in 50%.

We first sought to identify predictors of an elevated blood glucose level using variables available on presentation, which are detailed in Table 2; numerous cardiometabolic risk factors as well as prevalent CAD and HF were associated directly or inversely with the likelihood of hyperglycemia. Compared with a nonelevated blood glucose level, an elevated blood glucose level was not associated with a clinically significant alteration in hemodynamic parameters, heart function, or renal function.

Glucose concentrations at presentation and 30-day mortality in AHF. Overall, 618 patients (10%) died during the 30 days of follow-up; clinical characteristics of survivors versus decedents at 30 days are depicted in Table 3. Notably, median glucose concentrations were higher in those dying by 30 days compared with survivors (median [interquartile range], 8.9 [6.7 to 13.2] vs. 7.4 [5.8 to 10.3] mmol/l, respectively; $p < 0.0001$). Likewise, consistent with this association between glucose values and death, we found a direct association between glucose concentrations on admission and 30-day mortality. When divided by the glucose level at admission, 30-day mortality increased by 2-fold when glycemia was between 7 and 14 mmol/l and >3-fold when glycemia was >14 mmol/l (Fig. 2).

In a fully adjusted model for death by 30 days after presentation with AHF, an elevated blood glucose level was a powerfully significant predictor of risk (odds ratio: 2.19; 95% confidence interval [CI] = 1.69 to 2.83; $p < 0.001$) (Table 4); those patients with an elevated blood glucose level at hospital presentation had an early and sustained risk of death at 30 days (Fig. 3).

The area under the receiver-operating characteristic curve for an elevated blood glucose level to predict short-term outcome was 0.61 when used alone; an elevated blood glucose level added to a base model of clinical parameters (those used above for adjustment), changed the area under the curve from the clinical parameters alone (0.769 vs. 0.753, respectively; $p = 0.0001$). The net reclassification improvement for death at 30 days from adding elevated blood glucose level to clinical parameters versus clinical parameters alone was 4.4% (95% CI: 0.99 to 7.78, $p = 0.016$). As the net reclassification improvement is influenced by the probability cut points selected, the integrated discrimination improvement was also calculated, and an integrated discrimination improvement of 0.011 (95% CI: 0.007 to 0.0155, $p < 0.001$) was found.

Subgroup analyses. When examined by source of data, the association between elevated glucose level and risk of 30-day mortality was compellingly consistent with the exception of outcomes in patients from Africa (Tunisia) (Fig. 4).

Table 2 Characteristics of Study Subjects as a Function of Blood Glucose Concentration on Presentation

	Blood Glucose Not Elevated (n = 3,391)	Blood Glucose Elevated (n = 2,821)	p Value
Age, yrs	74 (64–80.1)	74.8 (65.6–81.2)	<0.0001
Male sex	1,773 (52.3)	1,485 (52.6)	0.78
Body mass index, kg/m^2	27.3 (23.9–31.2)	27 (24.2–30.9)	0.13
Medical history			
Diabetes mellitus	1,276 (37.6)	1,267 (44.9)	<0.0001
Chronic obstructive pulmonary disease	701 (22.2)	460 (18.2)	0.00018
Hypertension	2,215 (66.9)	1,931 (70.1)	0.0086
History of heart failure	1,853 (54.8)	1,218 (43.4)	<0.0001
Atrial fibrillation	1,059 (33.7)	701 (27.6)	<0.0001
Coronary artery disease	1,493 (45.1)	1,453 (53)	<0.0001
Medication before admission			
Beta-blocker	1,212 (47.9)	1,046 (46.7)	0.41
Angiotensin-converting enzyme inhibitor	1,093 (45.1)	1,002 (46.3)	0.41
Angiotensin receptor blocker	481 (19.9)	399 (18.5)	0.23
Diuretic	1,519 (62.7)	1,142 (52.7)	<0.0001
Nitrate	532 (21.9)	509 (23.8)	0.15
Aspirin	989 (40.6)	914 (42.4)	0.23
Statin	704 (29.7)	631 (29.7)	0.98
Hemodynamic status at admission			
Systolic blood pressure, mm Hg	135 (115–156)	140 (115–164)	0.00019
Diastolic blood pressure, mm Hg	80 (70–90)	80 (68–90)	0.077
Heart rate, beats/min	85 (70–102)	93 (78–110)	<0.0001
Left ventricular ejection fraction, %	40 (25–55)	40 (30–52)	0.95
Laboratory test results			
Hemoglobin, g/dl	12.8 (11.2–14.2)	13 (11.5–14.4)	0.00011
Sodium, mmol/l	139 (136–142)	138 (135–141)	<0.0001
Potassium, mmol/l	4.2 (3.8–4.6)	4.2 (3.8–4.6)	0.37
Glomerular filtration rate, ml/min/1.73 m^2	55.9 (39.3–73.8)	52.5 (37.5–68.7)	<0.0001
Creatinine, μmol/l	99 (79–134)	105 (82–140.2)	0.032
Glucose, mmol/l	6 (5.3–6.9)	11.2 (8.4–14.4)	<0.0001
C-reactive protein, mg/l	12 (4.1–33.2)	15 (5–41)	0.18
B-type natriuretic peptide, pg/ml	877 (430.9–1,680.6)	924 (473.7–1,777.5)	0.053

Values are median (interquartile range) or n (%).

The risk associated with an elevated blood glucose level appeared consistent across patients with preserved (hazard ratio: 5.41; 95% CI; 2.44 to 12.0; $p < 0.0001$) and impaired (hazard ratio: 2.37; 95% CI: 1.57 to 3.59; $p < 0.0001$) systolic function (Table 5). When considering patients as a function of incident DM, interestingly, the predictive value of elevated blood glucose appeared consistent if not stronger in nondiabetic patients (Table 5, Fig. 5). All interactions were found significant in all considered subgroups.

Sensitivity analyses. Sensitivity analyses (Table 6) showed that adjustment with the level of LVEF or plasma natriuretic peptides on hospital admission, using a fixed-center effect or excluding patients with hypoglycemia (blood glucose <4 mmol/l [72 mg/dl] at presentation, n = 112), as well as excluding patients from the Czech Republic, the largest cohort of patients) did not alter study findings. As such, when glucose concentrations were examined continuously, we found an absolute increase in 30-day mortality of 9% for each 1-mmol/l (18-mg/dl) increase in blood glucose (odds ratio: 1.09; 95% CI: 1.05 to 1.12; $p < 0.0001$). Last, using an alternative definition of diabetes status (i.e., known diabetes or unknown diabetes but blood glucose level at admission >14 mmol/l [250 mg/dl]), consistent results were found.

Discussion

Among a large multinational cohort of patients with AHF, we found abnormal plasma glucose levels in more than half of the studied patients and a strong prognostic importance associated with elevated blood glucose concentrations at presentation. The prognostic importance of elevated blood glucose level was present in multiple subgroups analyzed, independent of traditional covariates of risk in AHF in adjusted analyses, and contributed to reclassification for risk stratification above a clinical model with robust perfor-

Table 3 Characteristics of Study Subjects Surviving Versus Dying by 30 Days

	Survivors (n = 5,594)	Nonsurvivors (n = 618)	p Value
Age, yrs	73.8 (64.4–80.2)	78 (69.9–84.2)	<0.0001
Male sex	2,928 (52.3)	330 (53.4)	0.62
Body mass index, kg/m^2	27.2 (24.1–31.1)	26.1 (23.4–30.3)	0.00028
Medical history			
Diabetes mellitus	2,277 (40.7)	266 (43)	0.26
Chronic obstructive pulmonary disease	1,045 (20.5)	116 (20.3)	0.94
Hypertension	3,727 (68.3)	419 (68.6)	0.91
History of heart failure	2,807 (50.4)	264 (42.8)	0.00034
Atrial fibrillation	1,592 (31.2)	168 (29)	0.27
Coronary artery disease	2,612 (48)	334 (54.7)	0.0018
Medication before admission			
Beta-blocker	2,043 (47.9)	215 (42.1)	0.012
Angiotensin-converting enzyme inhibitor	1,872 (45.8)	223 (44.6)	0.62
Angiotensin receptor blocker	804 (19.7)	76 (15.2)	0.016
Diuretic	2,375 (58.1)	286 (57.1)	0.67
Nitrate	916 (22.5)	125 (25.2)	0.18
Aspirin	1,667 (40.7)	236 (47.3)	0.0049
Statin	1,223 (30.6)	112 (22.9)	0.00047
Hemodynamic status at admission			
Systolic blood pressure, mm Hg	140 (120–160)	116 (100–140)	<0.0001
Diastolic blood pressure, mm Hg	80 (70–90)	70 (60–80)	<0.0001
Heart rate, beats/min	88 (73–107)	90 (75–105)	0.99
Left ventricular ejection fraction, %	40 (28–55)	35 (25–48)	0.00046
Laboratory test results			
Hemoglobin, g/dl	12.9 (11.4–14.3)	12.5 (10.9–14.0)	<0.0001
Sodium, mmol/l	139 (136–141)	137 (134–140)	<0.0001
Potassium, mmol/l	4.2 (3.8–4.6)	4.3 (3.8–4.8)	0.091
Glomerular filtration rate, ml/min/1.73 m^2	55.5 (40.2–73.1)	39.1 (26.0–56.5)	<0.0001
Creatinine, μmol/l	99 (79.6–132.8)	127 (96.0–186.6)	<0.0001
Glycemia, mmol/l	7.4 (5.8–10.3)	8.9 (6.7–13.2)	<0.0001
C-reactive protein, mg/l	12 (4–33)	32.4 (13.0–79.8)	0.0002
B-type natriuretic peptide, pg/ml	878.2 (434.2–1,651.3)	1,300 (679.1–2,441.6)	0.013

Values are median (interquartile range) or n (%).

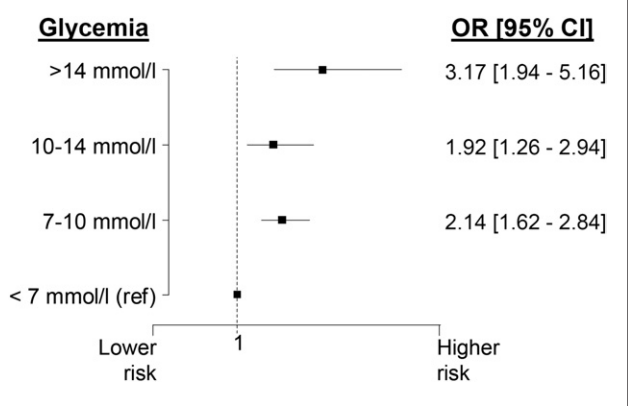

Figure 2 30-Day Mortality Rates According to the Level of Glucose at Admission

Blood glucose level at admission >14 mmol/l was associated with a 3-fold higher risk of death compared with patient with a normal glycemia level. CI = confidence interval; OR = odds ratio.

mance. Notably, the risk associated with an elevated blood glucose level was seen in both patients with and without previous diabetes mellitus.

Table 4 Multivariate Analysis of the Factors Associated With 30-Day Mortality in a Fully Adjusted Model

	OR (95% CI)	p Value
Elevated blood glucose	2.19 (1.69–2.83)	<0.0001
Estimated glomerular filtration rate <60 ml/min/1.73 m^2	1.82 (1.46–2.28)	<0.0001
Sodium <136 mmol/l	1.73 (1.41–2.12)	<0.0001
Age (for 10 yrs)	1.54 (1.40–1.70)	<0.0001
Previous diabetes mellitus	1.42 (1.05–1.91)	0.0225
Sex	1.16 (0.96–1.41)	0.121
Heart rate (for each 10 beats/min)	1.01 (0.98–1.05)	0.541
Diastolic blood pressure (for each 10 mm Hg)	0.89 (0.82–0.96)	0.0041
Previous coronary artery disease	0.88 (0.72–1.07)	0.21
Previous heart failure	0.77 (0.63–0.93)	0.0084
Systolic blood pressure (for each 20 mm Hg)	0.73 (0.67–0.80)	<0.0001

Elevated blood glucose showed the highest odds ratio.
CI = confidence interval; OR = odds ratio.

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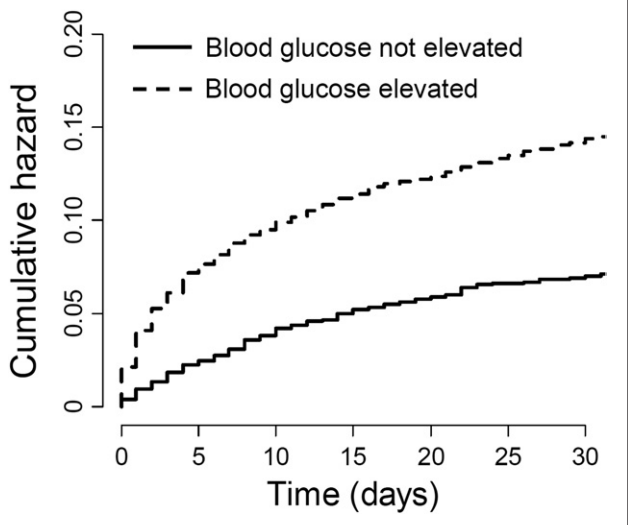

Figure 3 Cumulative Hazard for Death Associated With Hyperglycemia on Arrival at Hospital With AHF

Mortality was higher within few days in acute heart failure patients with elevated blood glucose levels.

The negative effect of hyperglycemia on the outcomes in a number of medical states such as AMI (27), stroke (28), pulmonary diseases (29), and critical illness (30–32) is well recognized. Indeed, multiple clinical practice guidelines recommend careful monitoring of blood glucose for this reason, with some recommending treatment with a goal to improve nonendocrinological outcomes (33), despite mixed results regarding this approach (34). However, risks related to glucose concentrations in the context of AHF are not well established. For example, 1 very large study of elderly and medically complex patients with AHF found no link between blood glucose levels and outcome (9), whereas other smaller studies of generally younger and less medically complex patients did find glucose concentrations associated with adverse outcomes, particularly while in the hospital or soon after discharge (7,8,35). In our large international cohort of subjects with a profile rather representative of a real-world sample of AHF patients from a demographics and medical profile perspective (36,37), we found a clear and significant adverse prognostic impact related to hyperglycemia, a risk that was present in patients with or without incident DM and across a wide range of ethnicities and left ventricular function.

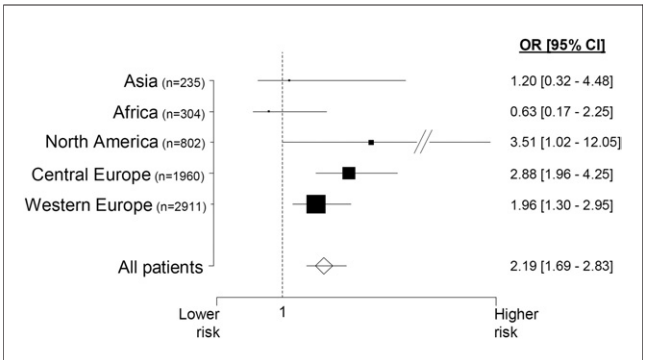

Figure 4 30-Day Mortality Odds Ratio for Death Associated With Hyperglycemia: Comparison Among Various Continents

There are important variations in the risk of death among the continents. Although elevated blood glucose level was independently associated with 30-day mortality in North America, in Central and Western Europe, the association was not significant in Africa and in Asia.

Table 5 30-Day Mortality Hazard Ratio in Various Clinically Relevant Subgroups

	Risk of Death in Patients With Elevated Blood Glucose		p Value Interaction
	No.	OR (95% CI)	
Diabetic	2,543	2.18 (1.67–2.83)	< 0.0001
Nondiabetic	3,669	1.65 (1.23–2.22)	
No anemia	3,059	2.87 (1.95–4.23)	< 0.0001
Anemia	2,203	1.61 (1.09–2.38)	
De novo HF	3,116	2.23 (1.58–3.16)	0.005
Decompensation of chronic HF	3,071	2.10 (1.42–3.11)	
No history of CAD	3,107	2.27 (1.58–3.25)	< 0.0001
History of CAD	2,946	2.1 (1.45–3.06)	
Age, yrs			
≤80	4,537	2.34 (1.67–3.28)	<0.0001
>80	1,670	2.04 (1.38–3.03)	
No history of hypertension	1,918	2.12 (1.40–3.20)	0.005
History of hypertension	4,146	2.19 (1.58–3.06)	
eGFR, ml/min/1.73 m^2			
≥60	2,516	2.36 (1.4–3.98)	<0.0001
<60	3,616	2.12 (1.58–2.86)	
Male	3,258	2.53 (1.72–3.71)	< 0.0001
Female	2,954	2.02 (1.42–2.86)	
LVEF, %			
≥40	1,764	3.30 (1.92–5.67)	< 0.0001
<40	1,682	2.54 (1.55–4.18)	
≥50	1,156	5.41 (2.44–12)	< 0.0001
<50	2,290	2.37 (1.57–3.59)	
BNP			
Median or lower*	1,035	1.63 (0.79–3.38)	<0.0001
Greater than median*	1,035	2.54 (1.30–4.96)	
SBP, mm Hg			
≤140	3,613	1.90 (1.42–2.54)	<0.0001
>140	2,505	3.25 (1.78–5.93)	

BNP = B-type natriuretic peptide; CAD = coronary artery disease; eGFR = estimated glomerular filtration rate; HF = heart failure; LVEF = left ventricular ejection fraction; SBP = systolic blood pressure; other abbreviations as in Table 4.

It is not entirely clear whether elevated blood glucose level in AHF is a marker for risk or a mediator of adverse outcomes. In the present study, hyperglycemia did not seem overtly associated with signs of altered hemodynamic, heart, or renal function. Nonetheless, severe systemic stress may lead to higher glucose levels due to effects of the sympathetic nervous system or from excessive release of adrenally derived hormones such as cortisol (32,38), and mechanistically, elevated blood glucose has been repeatedly shown to be directly deleterious to cardiac performance. Chronically

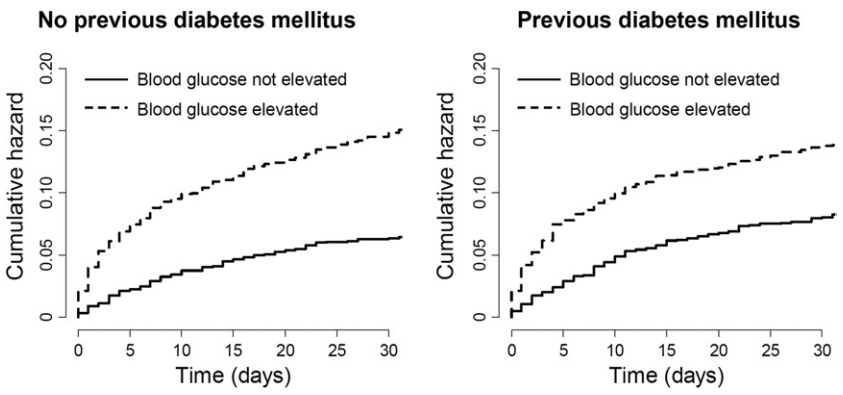

Figure 5 **Risk of Death Associated With Elevated Blood Glucose Level as a Function of the Presence or Absence of Diabetes Mellitus on Admission**

Although the risk of death seemed higher for acute heart failure patients with previous diabetes mellitus compared with others, the association between elevated blood glucose level and 30-day mortality existed in both patients without and with this comorbidity.

elevated glucose levels (as evidenced by an elevated HbA_{1c}) have been shown to be associated with myocardial injury (reflected in elevated, highly sensitive troponin concentrations) in patients free of HF (39), whereas intensive glycemic control may reduce cardiovascular events likely through coronary and noncoronary mechanisms (40). Furthermore, higher glucose levels may lead to an abnormally elevated concentration of circulating free fatty acids, increased myocardial uptake of free fatty acids (which in turn may promote arrhythmogenesis) (41), and decreased myocardial uptake of glucose (42). Hyperglycemia may also directly promote a number of negative effects at the myocyte level, including deranged calcium metabolism (23), apoptosis, and progressive remodeling. This latter observation may be due to the fact that elevated glucose increases concentrations of nuclear factor κB, with consequent up-regulation of matrix metalloproteinases (43). Indeed, elevated glucose levels in the context of AMI clinically predict the onset of symptomatic HF (44). As well, hyperglycemia may lead to other untoward effects on the cardiovascular system, including endothelial dysfunction, vascular inflammation, and accelerated atherogenesis (45). Thus, one can envision numerous reasons why hyperglycemia might lead to an adverse outcome in patients with AHF; in our cohort, the early and substantial risk associated with elevated glucose concentrations argues most compellingly for a direct myocardial effect, related to either reduced pump function or arrhythmia promotion. Considerably more data are needed to answer whether hyperglycemia is a marker or mediator, but our compelling data suggest the latter rather than the former.

Table 6 **Sensitivity Analyses**

Without Central Europe	1.85 (1.32–2.60)
Fixed cluster effect	2.34 (1.82–3.01)
Without patient with hypoglycemia	2.28 (1.76–2.96)
After adjustment of LVEF*	2.83 (1.97–4.07)
After adjustment of BNP*	2.00 (1.23–3.27)
Using alternative definition of diabetes†	2.07 (1.59–2.70)

Values are adjusted odds ratios (95% confidence interval).
*In addition of the other variables already used for adjustment.
†Diabetes was defined here either as known diabetes at admission or unknown diabetes but glycemia >14 mmol/l (250 mg/dl) at admission.
Abbreviations as in Tables 4 and 5.

The clinical implications of our study are numerous. First, because blood glucose is widely measured, easily interpreted, and inexpensive to measure, its use for risk assessment in AHF is worthy of consideration. Second, our data suggest that stress-induced impaired glucose tolerance and/or occult diabetes mellitus among patients with AHF is common and deserves further study, especially with respect to efforts at follow-up care and longer term management. Clinicians should recognize the fact that in-hospital hyperglycemia likely predicts future issues with glycemic control and monitor and manage accordingly. Last, because 30-day outcomes are a very relevant endpoint in AHF and driven largely by early treatment decision making, the robust associations between serum glucose levels and fatal outcomes in this population immediately conjure up the need for consideration of a treatment trial comparing aggressive and permissive glycemic management in patients presenting with AHF. Given the tight associations between hyperglycemia and myocardial performance discussed earlier, it is reasonable to consider not only expected superior clinical outcomes from aggressive glycemic control, but also improved myocardial performance and remodeling.

The differences observed among the continents and especially the lack of association in Asia and Africa are intriguing. Several explanations could be considered. First, these 2 continents were associated with the lowest sample size; thus, the results are probably underpowered, and it seems difficult to draw a conclusion. Second, ethnic blood glucose variations have recently been described (46). In this study, the authors found that South Asian individuals had

higher blood glucose levels, even after taking into account risk factors that influence sugar levels, compared with white European individuals. Whether this reflects an ethnic or racial resistance to the effects of hyperglycemia or merely a difference in clinical management after presentation remains unclear, and more data regarding this finding are needed.

Study limitations. Limitations include the fact that we lack data regarding HbA_{1c} at admission and serial measurement of glucose during the hospital stay and whether this provides superior risk stratification beyond presenting values of blood glucose. We similarly lack data regarding in-hospital treatment of DM and/or hyperglycemia. Despite these facts, the powerful association between presenting glucose level and risk of death is unmistakable and implies the need for further study. Future analyses should consider serial measurements of blood glucose after presentation, with an effort to define the trajectory of hyperglycemia in those destined for an adverse outcome. The question of whether patients with hyperglycemia in the nondiabetic group were in fact underdiagnosed diabetic patients and whether this potential misclassification would have altered final results remained unanswered. However, this is unlikely to be true because we showed that hyperglycemia is consistently associated with poor short-term outcome in all studied subgroups including in the subgroup of diabetic patients and in all sensitivity analyses.

Conclusions

In this large multinational cohort of patients with AHF, we showed that an elevated blood glucose level is common and is a powerful risk marker, predicting death within 30 days. Our results are consistent with basic and clinical science data linking an elevated blood glucose level with myocardial injury, impaired myocardial performance, arrhythmia, and risk of ventricular remodeling. Furthers studies are needed to understand more thoroughly the physiopathology of hyperglycemia in AHF.

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Key Words: acute heart failure ■ blood glucose ■ 30-day mortality ■ hyperglycemia.

APPENDIX

For supplemental tables and figure, please see the online version of this article.