Effect of Elevated Blood Glucose on Outcome in Acutely Decompensated Heart Failure: Results from an international observational cohort

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Running title: Hyperglycaemia and outcome in acutely decompensated heart failure

Abstract

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 hyperglycaemia in the setting of acutely decompensated heart failure (ADHF) is unknown, however.

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

Results: 6212 subjects with ADHF (mean age 72 years, 52.5% male) were studied; the median blood glucose concentration on arrival was 7.5 mmol/L, and 41% had prior diabetes mellitus (DM). After 30 days, 618 patients (10%) had died. Compared to survivors, decedents had significantly higher median blood glucose concentrations (8.9 versus 7.4; p<0.0001). In a fully-adjusted model including prevalent DM, an elevated blood glucose was a strong independent predictor of 30 day mortality in ADHF (OR = 2.19; 95% CI = 1.69-2.83; P <0.001). In time-to-event analyses, the risk associated with hyperglycaemia appeared early, was sustained to 30 days (HR = 1.97, 95% CI = 1.55-2.49, p<0.0001) independent of prevalent DM. The risk associated with hyperglycaemia appeared consistent across patient with preserved (HR = 5.41, 95% CI = 2.44 – 12.0; p<.0001) and impaired systolic function (HR = 2.37, 95% CI = 1.57 - 3.59; p <.0001) as well as with and without diabetes mellitus. In reclassification analyses, elevated blood glucose added significant prognostic information to clinical parameters alone (net reclassification improvement = 4.4%; p = 0.01; integrated discrimination improvement = 0.011; p < 0.001).

Conclusions: Among patients with ADHF, blood glucose concentrations at presentation are powerfully prognostic for death by 30 days, independent of a diagnosis of DM or other

clinical variables. As blood glucose is easily modifiable, it may represent a valid target for therapeutic intervention.

Acutely decompensated heart failure (ADHF) is a highly prevalent condition, representing one of the most frequent diagnoses in emergency department setting (1). In addition to being common, ADHF represents a pivotal moment in the course of the diagnosis, characterized by a poor short-term prognosis; in many studies, ADHF 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 ADHF typically include altered cardiovascular parameters and/or organ dysfunction; reported variables predictive of death in ADHF 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 ADHF. As an example, altered glycaemic control is common during critical illness, occurs in patients with or without a previous history of diabetes mellitus (DM), and may be associated with adverse outcome in this setting (3). In cardiovascular diseases, abnormalities of glycaemic control have been shown to be prognostic of a higher mortality in those with an acute myocardial infarction (AMI) (4-6), however, while well-established in AMI, the association between elevated glucose concentration and increased mortality in other acute cardiovascular conditions such as ADHF remains controversial (7-9). In ADHF, few studies exist and each has variable designs, with some studying only patients without DM while others only examined more elderly patients. Moreover the definition of cut-off value to define hyperglycaemia varies among the studies, and the follow up time horizon varied.

For these reasons and because hyperglycaemia 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 ADHF. We examined

the factors associated with altered glycaemic control in this setting, and explored the association between 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; 8 were based in Europe, 2 in the United States, one in Japan and one in Africa (10-12). 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 ADHF and had a measurement of blood glucose at arrival to the emergency department. All patients had ADHF according to the European Society of Cardiology guidelines (13). Both patients with new onset (i.e. no previous history) of HF and with acute decompensation of chronic HF were included. Owing to lack of blood glucose concentrations in a select few, the number of patients in the other publications may differ from those reported here.

Clinical data, including anthropometric measures, comorbidities, precipitating factors, the most recent echocardiography findings, clinical presentation and medication at baseline were recorded. A diagnosis of prior DM was based on-self report by the patient or by documentation in the patient's medical records. Hyperglycaemia was defined as blood glucose $\geq$ 7 mmol/L in those without prior DM and $\geq$ 10 mmol/L in those with prevalent DM.

Plasma glucose was measured with enzymatic methods. Estimated glomerular filtration rate (eGFR) was calculated from creatinine values using the Modified Diet in Renal Disease formula (14).

Outcomes

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

Statistical analysis

The results are expressed as means and standard deviation (SD), median and first to third quartile or counts and percent. The study outcome was defined as all cause 30-day mortality.

The log-linearity of blood glucose was studied for all patients and for diabetic and non-diabetic separately. The effect was found to be not log-linear for both groups with an inflexion of the smoothing splines at 7 mmol/L for non-diabetic patients and at 10 mmol/L for diabetic patients (Supplementary figure 1). Thus, hyperglycaemia was defined as glucose ≥ 7 mmol/L for non-diabetic subjects and ≥ 10 mmol/L for those with prevalent DM. As patients were included from various countries, a potential cluster effect was taking into account using generalized linear model with random intercept where the cluster of interest was the country. The effect of hyperglycaemia 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, gender, co-morbidities (history of chronic heart failure; history of CAD, diabete melitus), systolic [SBP] or diastolic [DBP] blood pressure, heart rate, impaired renal function (estimated glomerular filtration rate [eGFR] <60 mL/minute/1.73m^2) (15) and sodium < 136 mmol/L.

The clinical benefit in risk prediction of adding hyperglycaemia status to the clinical model was further assessed by reclassification analysis, including both the net reclassification improvement (NRI) and the integrated discrimination index (IDI) (16, 17). Clinical variables used to build the baseline model for mortality risk prediction were the same than those used to adjust the main analysis (namely age, gender, co-morbidities (history of chronic heart failure; history of CAD, DM, systolic [SBP] or diastolic [DBP] blood pressure, heart rate, eGFR <60 mL/minute/1.73 m^2 and sodium <136 mmol/L) . In the reclassification analysis, cut-offs for low-, intermediate- and high-

risk classes were defined based on the observed overall mortality in the study cohort. Patients were regarded to be at high-risk if the predicted risk of death was approximately two-fold the observed mortality, whereas a predicted risk around half the observed mortality was considered low-risk category. For 30-day mortality, cut-offs were defined as a predicted risk of <5%, 5-15%, and >15% for low-, intermediate-, and high-risk categories.

Statistical analyses were performed using R-statistical software (http://www.r-project.org/). A two-sided pvalue<0.05 was considered statistically significant.

Results

Baseline characteristics

Baseline characteristics of these 6212 studied patients are described in Table 1. The study subjects were typical of a population of patients with ADHF, with a mean age of nearly 72 years, a slight male predominance (52.5%) and 41% had a prior history of DM. Half of studied patients had *de novo* HF (also reflected in the use of HF medications at presentation), and the mean left ventricular ejection fraction was approximately 40%, indicating a slight predominance of HF due to left ventricular systolic dysfunction (LVSD), but a substantial percentage with HF and preserved ejection fraction (HFpEF). Laboratory investigations in the study population were consistent with other studies of ADHF, with an eGFR and natriuretic peptide concentration typical of a generally higher-risk population. Characteristics of the study population as a function of center of origin are detailed in Supplemental Table 1.

Glucose concentrations at arrival

The median admitting blood glucose was 7.5 mmol/L. Blood glucose was <7 mmol/L in 34 % of the studied ADHF patients, and frankly elevated in more than half.

We first sought to identify predictors of an elevated blood glucose using variables available on presentation which are detailed in Table 2; numerous cardiometabolic risk factors

as well as prevalent coronary artery disease and HF were associated directly or inversely with the likelihood for hyperglycaemia. Compared to normoglycaemia, hyperglycaemia was not associated with clinically significant alteration in hemodynamic parameters, heart function or renal function

Glucose concentrations at arrival and 30-day mortality in ADHF

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 to survivors (7.4 (5.8 to 10.3) versus 8.9 (6.7 to 13.2), p<0.0001).

Consistent with this association between values of glucose and death, we then found a direct association between glucose concentrations on admission and 30-day mortality (Figure 1). The incremental increase in 30-day mortality ranged from 6.4% in patients with normal glucose (≤7 mmol/L) to 10.8% in patients with moderately altered glycaemic control (7 to 10 mmol/L) and up to 14.5% in patients with seriously elevated glucose (≥10 mmol/L). As such, when glucose concentrations were examined continuously, we found an absolute increase in 30-day mortality of 9% for each 1 mmol/L increase in blood glucose (OR = 1.09; 95% CI = 1.05-1.12, p<0.0001). When divided by level of glucose at admission, 30-day mortality increased by 2-fold when glycemia was between 7 and 14 mmol/L and more than 3-fold when glycemia was > 14 mmol/L (figure 1).

In a fully-adjusted model for death by 30 days following presentation with ADHF, elevated blood glucose was a powerfully significant predictor of risk (OR = 2.19; 95% CI = 1.69-2.83; P <.001) (Table 4); those patients with hyperglycaemia on arrival had an early and sustained risk for death to 30 days (Figure 2).

In C-statistic analysis, the area under the curve for elevated blood glucose to predict short term outcome was 0.61, when used alone; elevated glucose added to a base model of clinical parameters (those used above for adjustment), changed the AUC from the clinical parameters alone (0.769 vs 0.753 respectively, p=0.0001). The net reclassification improvement for 30 day death from adding elevated blood glucose 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 and risk for 30 day mortality was compellingly consistent with the exception of outcomes in patients from Africa (Figure3). Sensitivity analyses (Table 5) showed that adjustment with the level of LV ejection fraction or plasma natriuretic peptides on admission (using a fixed center effect or performing a complete case study, as well as excluding patients from the Czech Republic, the largest cohort of patients) did not alter study findings.

The risk associated with hyperglycaemia appeared consistent across patients with preserved (HR = 5.41, 95% CI = 2.44 – 12.0; p<.0001) and impaired systolic function (HR = 2.37, 95% CI = 1.57 - 3.59; p <.0001) (Table 6). When considering patients as a function of incident DM, interestingly, the predictive value of elevated blood glucose appeared consistent if not stronger in non-diabetic patients (Table 6 & Figure 4).

DISCUSSION

Among a large multinational cohort of patients with ADHF, we have found an abnormal plasma glucose in more than half of the studied patients and a strong prognostic importance associated with elevated blood glucose concentrations at presentation. Blood glucose

concentrations were associated with death by 30 days in a linear fashion, such that for every 1 mmol/L of glucose a nearly 10% increase in death rates was observed. The prognostic importance of hyperglycaemia was present in multiple subgroups analysed, independent of traditional covariates of risk in ADHF in adjusted analyses, and contributed to reclassification for risk stratification above a clinical model with robust performance. Notably, the risk associated with elevated blood glucose was seen in both patients with and without prior diabetes mellitus.

The negative effect of hyperglycaemia on outcomes in a number of medical states such as AMI (18), stroke (19), pulmonary diseases (20) and critical illness (21-23) 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 non-endocrinologic outcomes (24), despite mixed results regarding this approach (25). However, risks related to glucose concentrations in the context of ADHF are not well-established. For example, one very large study of elderly and medically complex patients with ADHF found no link between blood glucose levels and outcome (9), while other smaller studies of generally younger and less medically complex patients did find glucose concentrations associated with adverse outcome, particularly while in the hospital or soon after discharge (7, 8, 26). In our large international cohort of subjects with a profile rather representative of a "real world" sample of ADHF patients from a demographics and medical profile perspective (27, 28), we found a clear and significant adverse prognostic impact related to hyperglycaemia, a risk that was present in patients with or without incident DM, and across a wide range of ethnicities and left ventricular function.

It is not entirely clear whether elevated blood glucose in ADHF is a marker for risk or a mediator of adverse outcomes. In the present study, hyperglycaemia 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 (23, 29), and mechanistically, elevated blood glucose has been repeatedly shown to be directly deleterious to cardiac performance. Chronically elevated glucose levels (as evidenced by an elevated HbA1c) have been shown to be associated with myocardial injury (reflected in elevated highly sensitive troponin concentrations) in patients free of HF (30), while intensive glycemic control may reduce cardiovascular events likely through coronary and non-coronary mechanisms (31). Furthermore, higher glucose levels may lead to abnormally elevated concentration of circulating free fatty acid, increased myocardial uptake of free fatty acid (which in turn may promote arrhythmogenesis) (32) and decreased myocardial uptake of glucose (33); hyperglycaemia may also directly promotes a number of negative effects at the myocyte level, including deranged calcium metabolism (23), apopotosis, and progressive remodeling. This latter observation may be due to the fact that elevated glucose increases concentrations of nuclear factor-κB, with consequent upregulation of matrix metalloproteinases (34). Indeed, elevated glucose levels in the context of AMI clinically predict the onset of symptomatic HF (35). As well, hyperglycaemia may lead to other untoward effects on the cardiovascular system, including endothelial dysfunction, vascular inflammation, and accelerated atherogenesis (36). Thus, one can envision numerous reasons why hyperglycaemia might lead to adverse outcome in patients with ADHF; in our cohort, the early and substantial risk associated with elevated glucose concentrations argues most compellingly for a direct myocardial effect, either related to reduced pump function or arrhythmia promotion. Considerably more data are needed to answer whether hyperglycaemia is a marker or mediator, but our compelling data suggest the latter, rather than the former.

Clinical implications of our study are numerous. Firstly, as blood glucose is widely measured, easily interpreted and inexpensive, its use for risk assessment in ADHF is worthy of consideration. Secondly, our data suggests that stress-induced impaired glucose tolerance and/or occult diabetes mellitus among patients with ADHF 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 hyperglycaemia likely predicts future issues with glycaemic control and monitor and manage accordingly. Lastly, as 30 day outcomes are a very relevant endpoint in ADHF, and driven largely by early treatment decision-making, the robust associations between serum glucose levels and fatal outcomes in this population immediately conjure the need for consideration of a treatment trial comparing aggressive versus permissive glycaemic management in patients presenting with ADHF. Given the tight associations between hyperglycaemia and myocardial performance discussed above, it is reasonable to consider not only expect superior clinical outcomes from aggressive glycaemic control, but also improved myocardial performance and remodeling.

Limitations of our study include the fact that we lack data regarding HbA1c at admission and serial measurement of glucose during hospital stay, and whether this provides superior risk stratification beyond presenting values of blood sugar. We similarly lack data regarding in-hospital treatment for diabetes mellitus and/or hyperglycaemia. Despite these facts, the powerful association between presenting glucose and risk for death is unmistakable, and implies need for further study. Future analyses should consider serial measurements of blood glucose after presentation, with an effort to define the trajectory of hyperglycaemia in those destined for adverse outcome. While our study was a large multinational analysis, it is intriguing to note that the association between glucose and outcomes was not seen in subjects from African sites. Whether this reflects an ethnic or racial resistance to the effects of

hyperglycaemia or merely a difference in clinical management following presentation remains unclear, and more data regarding this finding are needed.

In conclusion, in a large multinational cohort of patients with ADHF, we have shown that elevated blood glucose is common and is a powerful risk marker, predicting death within 30 days. Our results are consistent with basic and clinical science data linking hyperglycaemia with myocardial injury, impaired myocardial performance, arrhythmia and risk for ventricular remodeling. Given the relative paucity of specific therapeutic options for this high risk population of patients with ADHF, together with the wide availability of monitoring tools and treatment strategies to safely lower blood glucose, our results imply the need for consideration of a prospective randomized treatment trial designed with the goal to improve the considerable risk associated with hyperglycaemia in this setting.

Table 1: Baseline characteristics of the study subjects.

	Studied patients (n=6212)
Age	74.1 (65 to 80.8)
Male sex	3258 (52.4)
Body-mass index (kg/m^2)	27.1 (24 to 31.1)
Medical history	
NYHA class	
I	557 (15.2)
II	914 (24.9)
III	1385 (37.8)
IV	812 (22.1)
Diabetes mellitus	2543 (40.9)
Chronic obstructive pulmonary disease	1161 (20.4)
Hypertension	4146 (68.4)
History of HF	3071 (49.6)
Atrial fibrillation	1760 (31)
Coronary artery disease	2946 (48.7)
Medication before admission	
β-blocker	2258 (47.3)
Angiotensin converting enzyme inhibitor	2095 (45.6)
Angiotensin receptor blocker	880 (19.2)
Diuretic	2661 (58)
Nitrate	1041 (22.8)
Aspirin	1903 (41.4)
Statin	1335 (29.7)
Hemodynamic status at admission	
Systolic blood pressure (mmHg)	136 (115 to 160)
Diastolic blood pressure (mmHg)	80 (69 to 90)
Heart rate (bpm)	89 (74 to 107)
Left ventricular ejection fraction (%)	40 (27 to 55)
Lab results (medians, interquartile range)	
Haemoglobin (g/dL)	12.9 (11.4 to 14.3)
Sodium (mmol/L)	139 (136 to 141)
Potassium (mmol/L)	4.2 (3.8 to 4.6)
Glomerular filtration (mL/min)	54.2 (38.6 to 72)
Creatinine (µmol/L)	102 (79.7 to 137)
Glucose (mmol/L)	7.5 (5.9 to 10.7)
C-reactive protein (mg/L)	13 (4.5 to 37)
B-type natriuretic peptide (pg/mL)	895.5 (444 to 1710)

Unless otherwise specified, results are expressed as mean (standard deviation) or count (percentage)

Table 2: Characteristics of study subjects as a function of baseline glucose concentration.

	No hyperglycaemia (n=3391)	Hyperglycaemia (n=2821)	p value
Age	74 (64 to 80.1)	74.8 (65.6 to 81.2)	<0.0001
Male sex	1773 (52.3)	1485 (52.6)	0.78
Body-mass index (kg/m^2)	27.3 (23.9 to 31.2)	27 (24.2 to 30.9)	0.13
Medical history			
NYHA class			<0.0001
I	204 (10.9)	353 (19.7)	
II	462 (24.6)	452 (25.3)	
III	817 (43.5)	568 (31.7)	
IV	395 (21)	417 (23.3)	
Diabetes mellitus	1276 (37.6)	1267 (44.9)	<0.0001
Chronic obstructive pulmonary disease	701 (22.2)	460 (18.2)	0.00018
Hypertension	2215 (66.9)	1931 (70.1)	0.0086
History of HF	1853 (54.8)	1218 (43.4)	<0.0001
Atrial fibrillation	1059 (33.7)	701 (27.6)	<0.0001
Coronary artery disease	1493 (45.1)	1453 (53)	<0.0001
Medication before admission			
β-blocker	1212 (47.9)	1046 (46.7)	0.41
Angiotensin converting enzyme inhibitor	1093 (45.1)	1002 (46.3)	0.41
Angiotensin receptor blocker	481 (19.9)	399 (18.5)	0.23
Diuretic	1519 (62.7)	1142 (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 (mmHg)	135 (115 to 156)	140 (115 to 164)	0.00019
Diastolic blood pressure (mmHg)	80 (70 to 90)	80 (68 to 90)	0.077
Heart rate (bpm)	85 (70 to 102)	93 (78 to 110)	<0.0001
Left ventricular ejection fraction (%)	40 (25 to 55)	40 (30 to 52)	0.95
Lab results (medians, interquartile range)			
Haemoglobin (g/dL)	12.8 (11.2 to 14.2)	13 (11.5 to 14.4)	0.00011
Sodium (mmol/L)	139 (136 to 142)	138 (135 to 141)	<0.0001
Potassium (mmol/L)	4.2 (3.8 to 4.6)	4.2 (3.8 to 4.6)	0.37
Glomerular filtration (mL/min)	55.9 (39.3 to 73.8)	52.5 (37.5 to 68.7)	<0.0001
Creatinine (µmol/L)	99 (79 to 134)	105 (82 to 140.2)	0.032
Glucose (mmol/L)	6 (5.3 to 6.9)	11.2 (8.4 to 14.4)	<0.0001
C-reactive protein (mg/L)	12 (4.1 to 33.2)	15 (5 to 41)	0.18
B-type natriuretic peptide (pg/mL)	877 (430.9 to 1680.6)	924 (473.7 to 1777.5)	0.053

Table 3: Characteristics of study subjects surviving versus dying by 30 days.

	Survivors (n=5594)	Non-survivors (n=618)	p value
Age	73.8 (64.4 to 80.2)	78 (69.9 to 84.2)	<0.0001
Male sex	2928 (52.3)	330 (53.4)	0.62
Body-mass index (kg/m^2)	27.2 (24.1 to 31.1)	26.1 (23.4 to 30.3)	0.00028
Medical history			
NYHA class			<0.0001
I	451 (14.1)	106 (23.1)	
II	790 (24.6)	124 (27)	
III	1247 (38.9)	138 (30.1)	
IV	721 (22.5)	91 (19.8)	
Diabetes mellitus	2277 (40.7)	266 (43)	0.26
Chronic obstructive pulmonary disease	1045 (20.5)	116 (20.3)	0.94
Hypertension	3727 (68.3)	419 (68.6)	0.91
History of HF	2807 (50.4)	264 (42.8)	0.00034
Atrial fibrillation	1592 (31.2)	168 (29)	0.27
Coronary artery disease	2612 (48)	334 (54.7)	0.0018
Medication before admission			
β-blocker	2043 (47.9)	215 (42.1)	0.012
Angiotensin converting enzyme inhibitor	1872 (45.8)	223 (44.6)	0.62
Angiotensin receptor blocker	804 (19.7)	76 (15.2)	0.016
Diuretic	2375 (58.1)	286 (57.1)	0.67
Nitrate	916 (22.5)	125 (25.2)	0.18
Aspirin	1667 (40.7)	236 (47.3)	0.0049
Statin	1223 (30.6)	112 (22.9)	0.00047
Hemodynamic status at admission			
Systolic blood pressure (mmHg)	140 (120 to 160)	116 (100 to 140)	<0.0001
Diastolic blood pressure (mmHg)	80 (70 to 90)	70 (60 to 80)	<0.0001
Heart rate (bpm)	88 (73 to 107)	90 (75 to 105)	0.99
Left ventricular ejection fraction (%)	40 (28 to 55)	35 (25 to 48)	0.00046
Lab results (medians, interquartile range)			
Haemoglobin (g/dL)	12.9 (11.4 to 14.3)	12.5 (10.9 to 14)	<0.0001
Sodium (mmol/L)	139 (136 to 141)	137 (134 to 140)	<0.0001
Potassium (mmol/L)	4.2 (3.8 to 4.6)	4.3 (3.8 to 4.8)	0.091
Glomerular filtration (mL/min)	55.5 (40.2 to 73.1)	39.1 (26 to 56.5)	<0.0001
Creatinine (µmol/L)	99 (79.6 to 132.8)	127 (96 to 186.6)	<0.0001
Glycaemia (mmol/L)	7.4 (5.8 to 10.3)	8.9 (6.7 to 13.2)	<0.0001
C-reactive protein (mg/L)	12 (4 to 33)	32.4 (13 to 79.8)	0.0002
B-type natriuretic peptide (pg/mL)	878.2 (434.2 to 1651.3)	1300 (679.1 to 2441.6)	0.013

Table 4: Multivariate analysis of the factors associated with 30-day mortality in a fully adjusted model.

	OR [95% CI]	p value
Hyperglycaemia	2.19 [1.69-2.83]	< 0.0001
Gender	1.16 [0.96-1.41]	0.121
Age (for 10 years)	1.54 [1.40-1.70]	< 0.0001
Prior diabetes mellitus	1.42 [1.05-1.91]	0.0225
Prior HF	0.77 [0.63-0.93]	0.0084
Prior coronary artery disease	0.88 [0.72-1.07]	0.21
Systolic blood pressure (for each 20 mmHg)	0.73 [0.67-0.80]	< 0.0001
Diastolic blood pressure (for each 10 mmHg)	0.89 [0.82-0.96]	0.0041
Heart rate (for each 10 bpm)	1.01 [0.98-1.05]	0.541
Sodium < 136 mmol/l	1.73 [1.41-2.12]	< 0.0001
Estimated glomerular filtration rate <60 ml/min	1.82 [1.46-2.28]	< 0.0001

Table 5: Sensitivity analyses.

	Adjusted OR [95% CI]
Without Central Europa	1.85 [1.32 - 2.60]
Fixed cluster effect	2.34 [1.82 - 3.01]
Without patient with hypoglycaemia	2.28 [1.76 - 2.96]
After adjustment on LVEF*	2.83 [1.97 - 4.07]
After adjustement on BNP*	2.00 [1.23 - 3.27]

* in addition of the other variables already used for adjustment

Table 6: Thirty-day mortality hazard ratio in various clinically relevant subgroups.

	Risk for death in patients with hyperglycaemia OR [95% CI]	*p interaction*
Diabetic	2.18 [1.67 - 2.83]	
Non Diabetic	1.65 [1.23 - 2.22]	< 0.0001
NYHA I or II	2.44 [1.53 - 3.87]	
NYHA III or IV	1.78 [1.18 - 2.7]	0.97
No anemia	2.87 [1.95 - 4.23]	
Anemia	1.61 [1.09 - 2.38]	< 0.0001
De novo HF	2.23 [1.58 - 3.16]	
Decompensation of Chronic HF	2.1 [1.42 - 3.11]	0.005
No history of CAD	2.27 [1.58 - 3.25]	
History of CAD	2.1 [1.45 - 3.06]	< 0.0001
Age ≤ 80 years	2.34 [1.67 - 3.28]	
Age > 80 years	2.04 [1.38 - 3.03]	<0.0001
No history of hypertension	2.12 [1.4 - 3.2]	
History of hypertension	2.19 [1.58 - 3.06]	0.005
eGFR > or = 60 ml/min	2.36 [1.4 - 3.98]	
eGFR < 60 ml/min	2.12 [1.58 - 2.86]	<0.0001
Male	2.53 [1.72 - 3.71]	
Female	2.02 [1.42 - 2.86]	< 0.0001
LVEF ≥ 40%	3.3 [1.92 - 5.67]	
LVEF < 40%	2.54 [1.55 - 4.18]	< 0.0001
LVEF ≥ 50%	5.41 [2.44 – 12]	
LVEF < 50%	2.37 [1.57 - 3.59]	< 0.0001
NT-proBNP ≤ median*	1.63 [0.79 - 3.38]	
NT-proBNP > median*	2.54 [1.3 - 4.96]	<0.0001
SBP < or = 140 mmHg	1.9 [1.42 - 2.54]	
SBP > 140 mmHg	3.25 [1.78 - 5.93]	<0.0001

* median value of NT-proBNP in our population was 3999 pg/ml (data were available in 1101 patients)

Figure 1: 30-day mortality rates according to the level of glucose at admission.

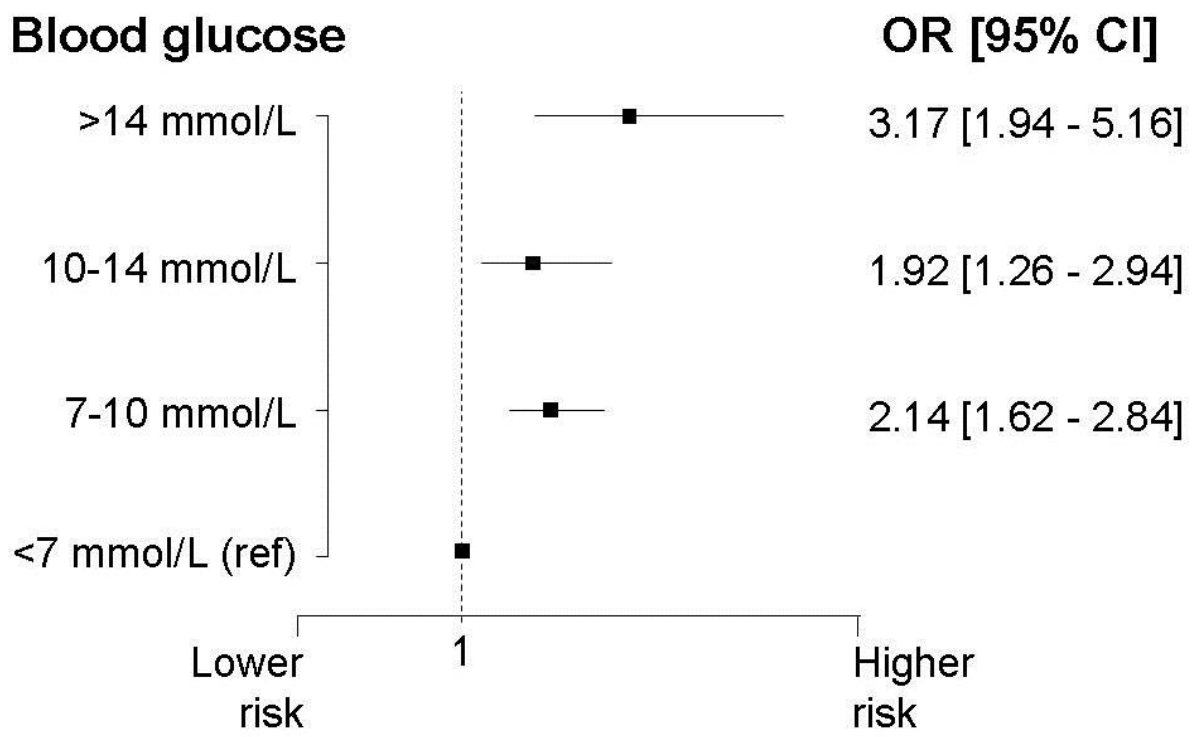


Figure 2: Cumulative hazard for death associated with hyperglycaemia on arrival with ADHF.

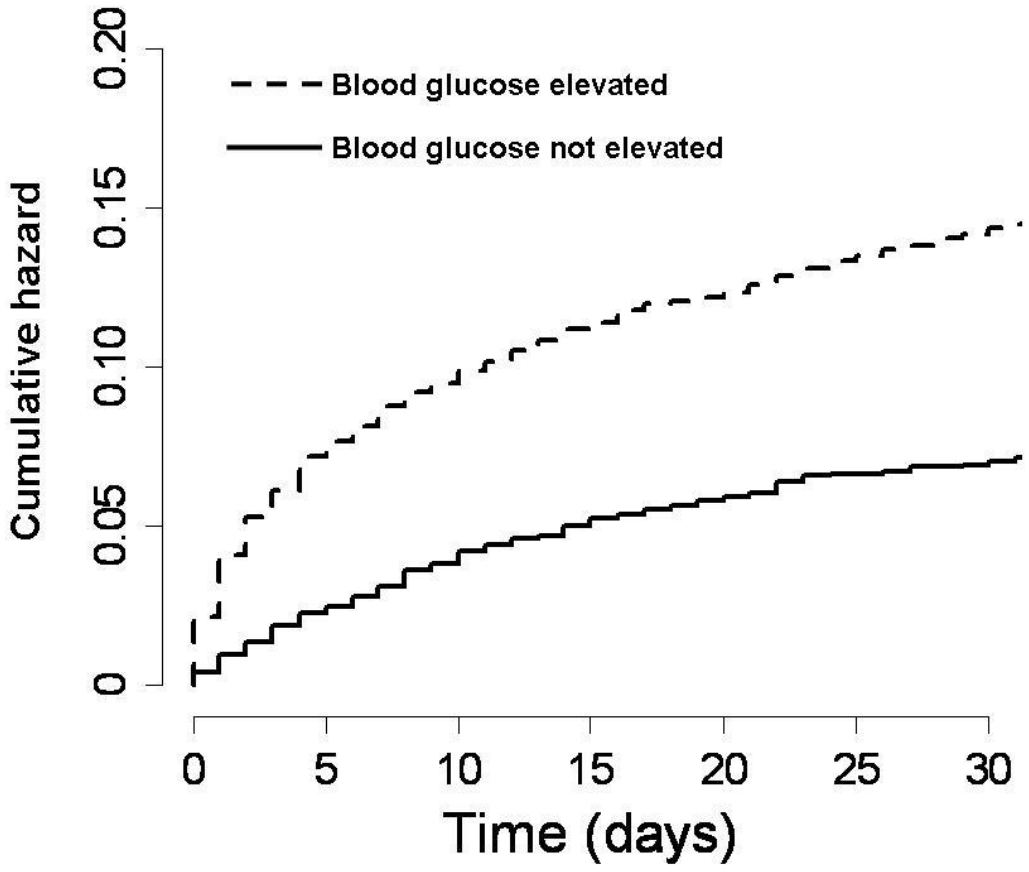


Figure 3: 30 day mortality odds ratio for death associated with hyperglycaemia: comparison among various continents

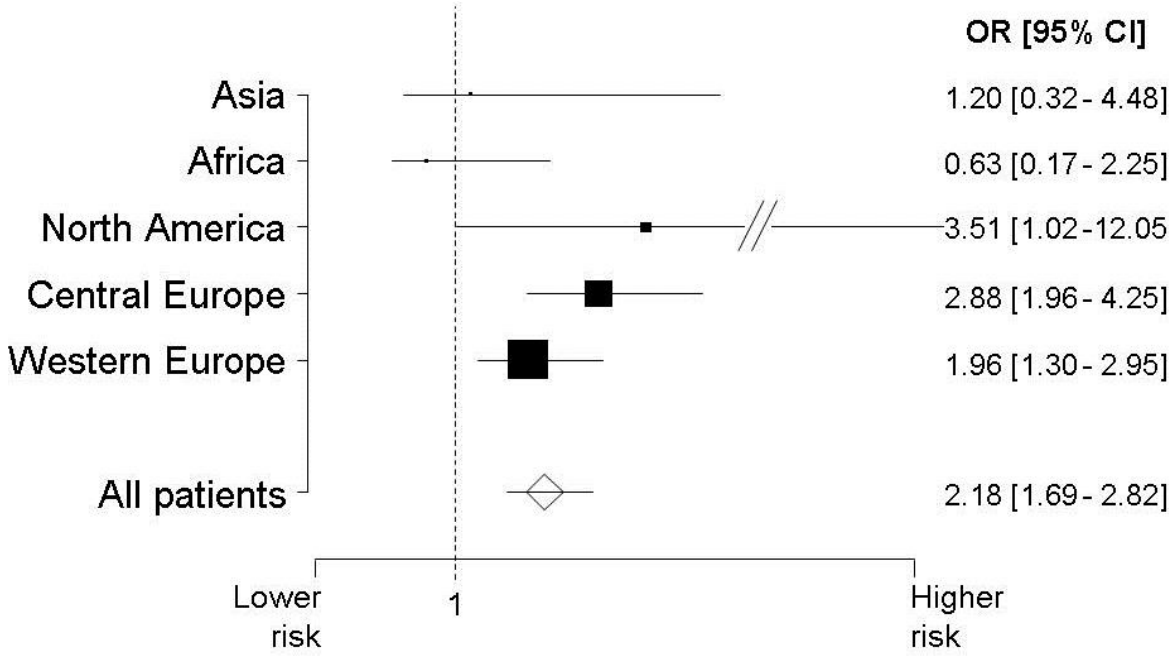
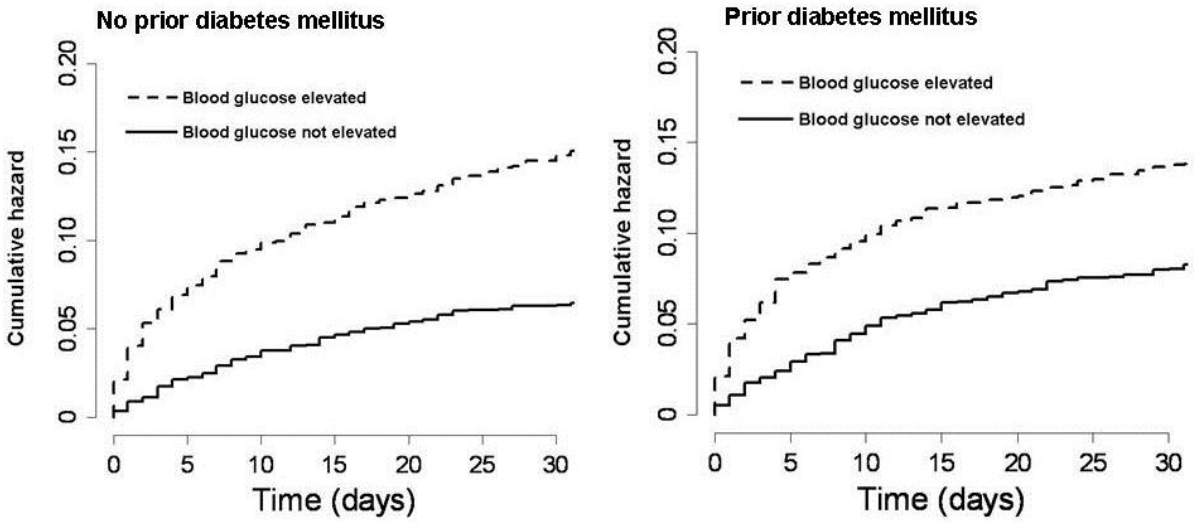


Figure 4: Risk of death associated with elevated blood glucose as a function of the presence or absence of diabetes mellitus on admission.



References

1. Nieminen MS, Harjola VP. Definition and epidemiology of acute heart failure syndromes. Am J Cardiol. 2005 Sep 19;96(6A):5G-10G.

2. Goldberg RJ, Ciampa J, Lessard D, Meyer TE, Spencer FA. Long-term survival after heart failure: a contemporary population-based perspective. Arch Intern Med. 2007 Mar 12;167(5):490-6.

3. Januzzi JL, Jr., Rehman S, Mueller T, van Kimmenade RR, Lloyd-Jones DM. Importance of biomarkers for long-term mortality prediction in acutely dyspneic patients. Clin Chem. 2010 Dec;56(12):1814-21.

4. Kosiborod M, Inzucchi SE, Goyal A, Krumholz HM, Masoudi FA, Xiao L, et al. Relationship between spontaneous and iatrogenic hypoglycemia and mortality in patients hospitalized with acute myocardial infarction. JAMA. 2009 Apr 15;301(15):1556-64.

5. Kosiborod M, Inzucchi SE, Krumholz HM, Masoudi FA, Goyal A, Xiao L, et al. Glucose normalization and outcomes in patients with acute myocardial infarction. Arch Intern Med. 2009 Mar 9;169(5):438-46.

6. Kosiborod M, Rathore SS, Inzucchi SE, Masoudi FA, Wang Y, Havranek EP, et al. Admission glucose and mortality in elderly patients hospitalized with acute myocardial infarction: implications for patients with and without recognized diabetes. Circulation. 2005 Jun 14;111(23):3078-86.

7. Barsheshet A, Garty M, Grossman E, Sandach A, Lewis BS, Gottlieb S, et al. Admission blood glucose level and mortality among hospitalized nondiabetic patients with heart failure. Arch Intern Med. 2006 Aug 14-28;166(15):1613-9.

8. Berry C, Brett M, Stevenson K, McMurray JJ, Norrie J. Nature and prognostic importance of abnormal glucose tolerance and diabetes in acute heart failure. Heart. 2008 Mar;94(3):296-304.

9. Kosiborod M, Inzucchi SE, Spertus JA, Wang Y, Masoudi FA, Havranek EP, et al. Elevated admission glucose and mortality in elderly patients hospitalized with heart failure. Circulation. 2009 Apr 14;119(14):1899-907.

10. Januzzi JL, Jr., Camargo CA, Anwaruddin S, Baggish AL, Chen AA, Krauser DG, et al. The N-terminal Pro-BNP investigation of dyspnea in the emergency department (PRIDE) study. Am J Cardiol. 2005 Apr 15;95(8):948-54.

11. Mueller T, Gegenhuber A, Poelz W, Haltmayer M. Diagnostic accuracy of B type natriuretic peptide and amino terminal proBNP in the emergency diagnosis of heart failure. Heart. 2005 May;91(5):606-12.

12. Manzano-Fernandez S, Januzzi JL, Jr., Boronat-Garcia M, Bonaque-Gonzalez JC, Truong QA, Pastor-Perez FJ, et al. beta-trace protein and cystatin C as predictors of long-term outcomes in patients with acute heart failure. J Am Coll Cardiol. 2011 Feb 15;57(7):849-58.

13. Nieminen MS, Bohm M, Cowie MR, Drexler H, Filippatos GS, Jondeau G, et al. Executive summary of the guidelines on the diagnosis and treatment of acute heart failure: the Task Force on Acute Heart Failure of the European Society of Cardiology. Eur Heart J. 2005 Feb;26(4):384-416.

14. Levey AS, Coresh J, Greene T, Stevens LA, Zhang YL, Hendriksen S, et al. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. Ann Intern Med. 2006 Aug 15;145(4):247-54.

15. Sarnak MJ, Levey AS, Schoolwerth AC, Coresh J, Culleton B, Hamm LL, et al. Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. Circulation. 2003 Oct 28;108(17):2154-69.

16. Pencina MJ, D'Agostino RB, Sr., D'Agostino RB, Jr., Vasan RS. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. Stat Med. 2008 Jan 30;27(2):157-72; discussion 207-12.

17. Cook NR. Statistical evaluation of prognostic versus diagnostic models: beyond the ROC curve. Clin Chem. 2008 Jan;54(1):17-23.

18. Capes SE, Hunt D, Malmberg K, Gerstein HC. Stress hyperglycaemia and increased risk of death after myocardial infarction in patients with and without diabetes: a systematic overview. Lancet. 2000 Mar 4;355(9206):773-8.

19. Capes SE, Hunt D, Malmberg K, Pathak P, Gerstein HC. Stress hyperglycemia and prognosis of stroke in nondiabetic and diabetic patients: a systematic overview. Stroke. 2001 Oct;32(10):2426-32.

20. Baker EH, Janaway CH, Philips BJ, Brennan AL, Baines DL, Wood DM, et al. Hyperglycaemia is associated with poor outcomes in patients admitted to hospital with acute exacerbations of chronic obstructive pulmonary disease. Thorax. 2006 Apr;61(4):284-9.

21. Egi M, Bellomo R, Stachowski E, French CJ, Hart GK, Hegarty C, et al. Blood glucose concentration and outcome of critical illness: the impact of diabetes. Crit Care Med. 2008 Aug;36(8):2249-55.

22. Fahy BG, Sheehy AM, Coursin DB. Glucose control in the intensive care unit. Crit Care Med. 2009 May;37(5):1769-76.

23. Kavanagh BP, McCowen KC. Clinical practice. Glycemic control in the ICU. N Engl J Med. 2010 Dec 23;363(26):2540-6.

24. Antman EM, Anbe DT, Armstrong PW, Bates ER, Green LA, Hand M, et al. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction; A report of the American College of Cardiology/American Heart Association Task

Force on Practice Guidelines (Committee to Revise the 1999 Guidelines for the Management of patients with acute myocardial infarction). J Am Coll Cardiol. 2004 Aug 4;44(3):E1-E211.

25. Wiener RS, Wiener DC, Larson RJ. Benefits and risks of tight glucose control in critically ill adults: a meta-analysis. JAMA. 2008 Aug 27;300(8):933-44.

26. Newton JD, Squire IB. Glucose and haemoglobin in the assessment of prognosis after first hospitalisation for heart failure. Heart. 2006 Oct;92(10):1441-6.

27. Adams KF, Jr., Fonarow GC, Emerman CL, LeJemtel TH, Costanzo MR, Abraham WT, et al. Characteristics and outcomes of patients hospitalized for heart failure in the United States: rationale, design, and preliminary observations from the first 100,000 cases in the Acute Decompensated Heart Failure National Registry (ADHERE). Am Heart J. 2005 Feb;149(2):209-16.

28. Nieminen MS, Brutsaert D, Dickstein K, Drexler H, Follath F, Harjola VP, et al. EuroHeart Failure Survey II (EHFS II): a survey on hospitalized acute heart failure patients: description of population. Eur Heart J. 2006 Nov;27(22):2725-36.

29. Carmen Wong KY, Wong V, Ho JT, Torpy DJ, McLean M, Cheung NW. High cortisol levels in hyperglycaemic myocardial infarct patients signify stress hyperglycaemia and predict subsequent normalization of glucose tolerance. Clin Endocrinol (Oxf). 2010 Feb;72(2):189-95.

30. Rubin J, Matsushita K, Ballantyne CM, Hoogeveen R, Coresh J, Selvin E. Chronic hyperglycemia and subclinical myocardial injury. J Am Coll Cardiol. 2012 Jan 31;59(5):484-9.

31. Ray KK, Seshasai SR, Wijesuriya S, Sivakumaran R, Nethercott S, Preiss D, et al. Effect of intensive control of glucose on cardiovascular outcomes and death in patients with diabetes mellitus: a meta-analysis of randomised controlled trials. Lancet. 2009 May 23;373(9677):1765-72.

32. Coronel R, Wilms-Schopman FJ, Den Ruijter HM, Belterman CN, Schumacher CA, Opthof T, et al. Dietary n-3 fatty acids promote arrhythmias during acute regional myocardial ischemia in isolated pig hearts. Cardiovasc Res. 2007 Jan 15;73(2):386-94.

33. Herrero P, Peterson LR, McGill JB, Matthew S, Lesniak D, Dence C, et al. Increased myocardial fatty acid metabolism in patients with type 1 diabetes mellitus. J Am Coll Cardiol. 2006 Feb 7;47(3):598-604.

34. Uemura S, Matsushita H, Li W, Glassford AJ, Asagami T, Lee KH, et al. Diabetes mellitus enhances vascular matrix metalloproteinase activity: role of oxidative stress. Circ Res. 2001 Jun 22;88(12):1291-8.

35. Mansour AA, Wanoose HL. Acute Phase Hyperglycemia among Patients Hospitalized with Acute Coronary Syndrome: Prevalence and Prognostic Significance. Oman Med J. 2011 Mar;26(2):85-90.

36. Xu J, Zou MH. Molecular insights and therapeutic targets for diabetic endothelial dysfunction. Circulation. 2009 Sep 29;120(13):1266-86.

Supplementary material

Supplemental Table 1: Clinical characteristics as a function of country of origin.

	Japan	Spain	USA II	France	Austria	Tunisia	Czech Republic	Italy II
Male gender	141 (60)	60 (56.1)	107 (51.7)	112 (64)	128 (93.4)	131 (43.1)	1070 (58.7)	692 (39.9)
Age (years)	77 (68 to 84)	74 (67.5 to 79.5)	76 (65 to 83)	75 (64.5 to 82)	76.1 (69.1 to 81.8)	72 (64 to 78)	72.9 (63 to 79.6)	74.3 (65.9 to 80.7)
Glucose (mmol/l)	8.6 (6.9 to 12.7)	8.4 (6.2 to 12.2)	7.2 (6 to 8.7)	8.2 (6.1 to 11.9)	6.3 (5.3 to 7.9)	8.1 (6.1 to 11.5)	8.1 (6.3 to 11.7)	7.5 (5.8 to 10.7)
Diabetes mellitus	93 (39.6)	60 (56.1)	88 (42.5)	93 (53.1)	39 (28.5)	138 (45.4)	772 (42.3)	706 (40.7)
History of HF	91 (38.9)	63 (58.9)	111 (53.6)	75 (49.7)	65 (47.4)	85 (28)	707 (38.8)	989 (57.1)
Coronary artery disease	97 (41.3)	42 (39.3)	87 (42)	70 (51.5)	81 (59.1)	66 (21.7)	1223 (67.1)	600 (34.6)
Haemoglobin	-	12.2 (11.1 to 13.7)	12.3 (10.6 to 13.9)	12.5 (11 to 13.9)	13.6 (12.3 to 15)	11.9 (10 to 13.2)	13.4 (12 to 14.7)	12.6 (11 to 14)
eGFR (ml/min)	61.3 (36.9 to 83.1)	45.2 (33.7 to 62.3)	50.7 (39.2 to 73.4)	45.8 (34.1 to 60.4)	84.3 (56.7 to 114.2)	49.7 (33.8 to 64.6)	53.4 (39 to 68.7)	53.9 (37.9 to 71.7)
Sodium (mmol/l)	140 (136.5 to 142)	138 (135 to 140.5)	138 (135 to 140)	137 (134 to 139)	138 (135 to 140)	137 (134 to 140.2)	139 (136 to 141)	139 (136 to 142)
SBP (mmHg)	150 (114 to 180)	148 (124.5 to 175)	138.5 (119.8 to 155)	131 (110 to 154)	135 (115 to 160)	143 (120 to 170)	136.5 (115 to 160)	130 (110 to 150)
DBP (mmHg)	80 (66 to 92.5)	80 (68 to 96)	74 (65.5 to 86)	74 (60 to 84.2)	80 (70 to 90)	82 (70 to 95)	80 (70 to 90)	80 (66.2 to 90)
HR (bpm)	100 (84 to 120)	97 (79.5 to 126)	82 (70 to 100)	86 (70 to 105)	86 (75 to 110)	92.5 (79 to 108.5)	90 (75 to 108)	90 (73 to 110)
30-day mortality	21 (8.9)	6 (5.6)	13 (6.3)	11 (6.3)	11 (8)	24 (7.9)	320 (17.6)	124 (7.2)

	Finland	USA I	Italy I	Switzerland
Male gender	199 (49.9)	313 (52.6)	108 (90)	197 (52.3)
Age (years)	76.5 (69.3 to 82.2)	72 (61 to 80)	68 (58.8 to 76)	79 (72 to 84)
Glucose (mmol/l)	7.4 (6.1 to 10.1)	6.1 (5.2 to 8.7)	7 (5.6 to 10.7)	6.9 (5.8 to 8.5)
Diabetes mellitus	150 (37.6)	254 (42.7)	41 (34.2)	109 (28.9)
History of HF	191 (47.9)	422 (70.9)	98 (81.7)	174 (46.2)
Coronary artery disease	219 (54.9)	292 (49.1)	-	169 (44.8)
Hemoglobin	12.9 (11.6 to 13.9)	-	12.6 (11.4 to 14.3)	12.9 (11.4 to 14.2)
eGFR (ml/min)	54.8 (41.7 to 69.9)	60 (41 to 81)	52 (35.8 to 70.2)	55.2 (36.9 to 76.9)
Sodium (mmol/l)	139 (136 to 141)	140 (137 to 142)	138 (135.5 to 140)	138 (135 to 140)
SBP (mmHg)	144 (124 to 170)	140 (121 to 164)	110 (100 to 130)	136 (118 to 156.2)
DBP (mmHg)	80 (70 to 95)	77 (66 to 92)	75 (65 to 80)	83 (70.8 to 96)
HR (bpm)	88 (73.2 to 106)	82 (70 to 95)	85 (70 to 100)	89 (72 to 109)
30-day mortality	29 (7.3)	14 (2.4)	5 (4.2)	40 (10.6)

Supplementary table 2: Patients included vs not included in the adjusted analysis because of the presence of missing data

	Complete cases (n=5576)	Incomplete cases (n=436)
Age	74.4 (65 to 80.9)	72 (62 to 79)
Male sex	2976 (51.5)	282 (64.7)
Body-mass index (kg/m^2)	27.1 (24 to 31.1)	27.5 (24.7 to 31.1)
Medical history		
NYHA class		
I	546 (15.9)	11 (4.7)
II	871 (25.4)	43 (18.3)
III	1281 (37.3)	104 (44.3)
IV	735 (21.4)	77 (32.8)
Diabetes mellitus	2366 (41)	177 (40.6)
Chronic obstructive pulmonary disease	1117 (20.5)	44 (18.4)
Hypertension	3949 (68.5)	197 (65.9)
History of HF	2831 (49)	240 (58.4)
Atrial fibrillation	1685 (30.8)	75 (34.9)
Coronary artery disease	2850 (49.3)	96 (34.7)
Medication before admission		
β-blocker	2146 (47.8)	112 (39.6)
Angiotensin converting enzyme inhibitor	2018 (45.5)	77 (51.3)
Angiotensin receptor blocker	827 (18.7)	53 (35.3)
Diuretic	2571 (57.9)	90 (61.2)
Nitrate	973 (22.5)	68 (28.1)
Aspirin	1797 (41.5)	106 (41.2)
Statin	1209 (28.9)	126 (40.3)
Hemodynamic status at admission		
Systolic blood pressure (mmHg)	138 (116 to 160)	130 (110 to 150)
Diastolic blood pressure (mmHg)	80 (69 to 90)	80 (65 to 88)
Heart rate (bpm)	89 (74 to 107)	88 (71 to 105)
Left ventricular ejection fraction (%)	40 (29 to 55)	29.5 (20 to 45)
Lab results (medians, interquartile range)		
Haemoglobin (g/dL)	12.9 (11.4 to 14.3)	12.5 (11.1 to 14.2)
Sodium (mmol/L)	139 (136 to 141)	138 (135 to 141)
Potassium (mmol/L)	4.2 (3.8 to 4.6)	4.1 (3.8 to 4.5)
Glomerular filtration (mL/min)	54.4 (38.7 to 72.2)	50 (35.6 to 67.1)
Creatinine (µmol/L)	101 (79.6 to 136)	116 (88.4 to 154.7)
Glucose (mmol/L)	7.5 (5.9 to 10.6)	7.9 (6 to 11.6)
C-reactive protein (mg/L)	13 (4.2 to 36.8)	13 (5.7 to 43.6)
B-type natriuretic peptide (pg/mL)	843 (425 to 1500)	1918 (748.6 to 4708.5)

Supplementary Table 3: Multivariate adjusted analysis for predictors of hyperglycaemia on arrival with ADHF.

	OR [95% CI]	P value
Age < 65 years	0.81 [0.70 - 0.95]	0.0078
Diabetes	1.22 [1.07 - 1.39]	0.0037
Chronic obstructive pulmonary disease	0.81 [0.69 - 0.94]	0.0047
History of hypertension	1.13 [0.98 - 1.3]	0.0854
Atrial fibrillation	0.80 [0.70 - 0.92]	0.0019
History of heart failure	0.73 [0.63 - 0.84]	<0.0001
History of coronary artery disease	1.51 [1.33 - 1.72]	<0.0001
Diuretic at admission	0.70 [0.61 - 0.81]	<0.0001
Systolic blood pressure		
110 - 140 mmHg (ref)	-	-
< 110 mmHg	1.41 [1.18 - 1.69]	0.0002
> 140 mmHg	1.30 [1.13 - 1.49]	0.0002
Heart rate > 70 bpm	1.71 [1.47 - 2.00]	<0.0001
Haemoglobin		
10 - 12 g/dl (ref)		
< 10 g/dl	1.10 [0.87 - 1.40]	0.4273
> 12 g/dl	1.32 [1.14 - 1.53]	0.0003
Sodium < 136 mmol/L	1.46 [1.25 - 1.71]	<0.0001
Estimated glomerular filtration rate < 60 ml/min/1.73m^2	1.41 [1.23 - 1.62]	<0.0001

Supplementary figure 1: Spline analyses for risk for death as a function of blood glucose and prior diabetes mellitus.