European Journal of Heart Failure. 2017; 19(1): 54-65

In-hospital and 1-year mortality associated with diabetes in patients with acute heart failure: results from the ESC-HFA Heart Failure Long-Term Registry

Giovanni Targher[1], Marco Dauriz1, Cécile Laroche[2], Pier Luigi Temporelli[3], Mahmoud Hassanein[4], Petar M. Seferovic[5], Jaroslaw Drozdz[6], Roberto Ferrari[7], Stephan Anker[8], Andrew Coats[9], Gerasimos Filippatos[10], Maria G. Crespo-Leiro[11], Alexandre Mebazaa[12], Massimo F. Piepoli[13], Aldo Pietro Maggioni[2,14], and Luigi Tavazzi[15], on behalf of the ESC-HFA HF Long-Term Registry investigators

[1] Division of Endocrinology, Diabetes and Metabolism, Department of Medicine, University and Azienda Ospedaliera Universitaria Integrata of Verona, Verona, Italy; [2] EURObservational Research Programme, European Society of Cardiology, Sophia-Antipolis, France; [3] Cardiology Division, IRCCS Fondazione Salvatore Maugeri, Veruno, NO, Italy; [4] Alexandria University, Alexandria, Egypt; [5] Department of Cardiology, Clinical Centre of Serbia, Belgrade, Serbia; [6] Department of Cardiology, Medical University, Lodz, Poland; [7] Department of Cardiology and LTTA Centre, University Hospital of Ferrara and Maria Cecilia Hospital, GVM Care & Research, E.S: Health Science Foundation, Cotignola, Italy; [8] Innovative Clinical Trials, Department of Cardiology & Pneumology, University Medical Center Göttingen (UMG), Göttingen, Germany; [9] Monash University, Australia and University of Warwick, Coventry, UK; [10] Cardiology Department, University Hospital; 12 de Octubre, Madrid, Spain; [11] Unidad de Insuficiencia Cardiaca Avanzada y Trasplante Cardiaco, Complexo Hospitalario, Universitario A Coruna, CHUAC, La Coruna, Spain; [12] Inserm 942, Hôpital Lariboisière, Université Paris Diderot, Paris, France; [13] Department of Cardiology, Polichirurgico Hospital G. da Saliceto, Piacenza, Italy; [14] ANMCO Research Center, Florence, Italy; and [15] Maria Cecilia Hospital, GVM Care & Research, E.S. Health Science Foundation, Cotignola, Italy

Abstract

Aims. The aim of this study was to evaluate the in-hospital and 1-year prognostic impact of diabetes and elevated blood glucose levels at hospital admission in patients with acute heart failure (HF).

Methods and results. We studied a multinational cohort of 6926 hospitalized patients with acute HF enrolled in the European Society of Cardiology (ESC) and Heart Failure Association (HFA) Long-Term Registry, of whom 49.4% (n = 3422) had known or previously undiagnosed diabetes (defined as self-reported history, or medication use, or fasting glucose levels ≥7.0 mmol/L or haemoglobin A_{1c} ≥6.5%). Compared with those without diabetes, patients with known or previously undiagnosed diabetes had higher cumulative rates of in-hospital mortality, 1-year mortality, and 1-year HF re-hospitalization that occurred independently of multiple clinical risk factors: in-hospital mortality [6.8 vs. 4.4%; adjusted hazard ratio (HR) 1.774; 95% confidence interval (CI) 1.282–2.456, $P < 0.001$], 1-year all-cause mortality (27.5 vs. 24%; adjusted HR 1.162; 95% CI 1.020–1.325, $P = 0.024$), and 1-year hospital re-admissions for HF (23.2 vs. 18.5%; adjusted HR 1.320; 95% CI 1.139–1.530, $P < 0.001$). Moreover, elevated admission blood glucose concentrations were powerfully prognostic for in-hospital mortality, but not for 1-year mortality or re-hospitalizations, in both patients with and without diabetes.

Conclusions. Among patients hospitalized for acute HF, the presence of diabetes is independently associated with an increased risk of in-hospital mortality, 1-year all-cause mortality, and 1-year re-hospitalizations for HF, underscoring the need for more effective and personalized treatments of diabetes in this particularly high-risk patient population.

Keywords
Co-morbidities; Diabetes; Acute heart failure; Observational outcome study

Introduction

Diabetes mellitus and heart failure (HF) are two common diseases that often co-exist. The prevalence of diabetes among patients with HF is extremely high, and it has been estimated as between 30% and 50%.[1-3] More than 40 years ago, the Framingham Heart study first reported that the risk for new-onset HF in patients with diabetes was about two-fold higher in men and five-fold in women compared with individuals without diabetes.[4] The pathogenesis of HF in diabetes is multifactorial, but can be largely attributed to ischaemic heart disease, hypertension, diabetic cardiomyopathy, and extracellular fluid volume expansion.[1, 2] Remarkably, diabetes *per se* is a significant risk factor for new-onset HF, independent of hypertension and ischaemic heart disease, suggesting that glycaemic control may influence the development of new-onset HF.[5] Recently, in response to concerns about the cardiovascular safety of rosiglitazone, a number of large randomized clinical trials have been designed to evaluate the cardiovascular safety of the newer drugs for the treatment of type 2 diabetes. To date, no new sound adverse cardiovascular safety signal (including the risk for HF) has arisen from the trials with incretin-based therapies (i.e. dipeptidyl peptidase 4 inhibitors and glucagon-like peptide 1 receptor agonists), and there is now evidence of benefit from the EMPA-REG trial with empagliflozin, a sodium–glucose co-transporter 2 inhibitor.[5, 6]

Despite the known high prevalence of diabetes among patients with HF, there are few contemporary, comparative data on the in-hospital and post-discharge survival outcomes from multinational cohorts of patients with and without diabetes who have been acutely admitted to the hospital for HF, out of the context of randomized clinical trials. Additionally, while diabetes is associated with increased mortality and morbidity in ambulatory patients with chronic systolic HF,[1, 2] its influence as an independent predictor of in-hospital and post-discharge adverse outcomes after hospitalization for acute HF is not consistently apparent. In fact, the published studies of patients hospitalized for HF that have explored the impact of diabetes *per se* on in-hospital and post-discharge clinical outcomes in patients hospitalized for acute HF have reported conflicting results, suggesting the need for further studies.

Indeed, as will be discussed in detail below, some large registry databases and clinical trials have shown that diabetes was associated with either poorer in-hospital and post-discharge survival outcomes or higher 1-year re-hospitalization rates in patients hospitalized for acute HF.[7-10] In contrast, a number of other recent studies did not find any significant and independent association between diabetes status and mortality risk in this patient population.[11-16]

Thus, all these findings clearly suggest that the prognostic value of diabetes *per se* on in-hospital and post-discharge survival outcomes in patients hospitalized for acute HF is still controversial. Currently, there is continued debate on this topic and, therefore, it warrants in-depth investigation.

The major aim of this study was to explore the rates of in-hospital mortality, 1-year all-cause mortality, and 1-year HF re-hospitalization among the patients with and without diabetes, who were admitted to the hospital for acute HF, enrolled in the General Long-term HF Registry that belongs to the EURObservational Research Programme (EORP) of the European Society of Cardiology (ESC) and the ESC-Heart Failure Association (HFA).[17]

Methods

Study design

The principles and procedures of the EORP of the ESC have been previously described.[17, 18] Briefly, the ESC-HF Long-Term Registry is a prospective, multicentre, observational study of patients at 211 Cardiology Centres in 21 European and Mediterranean countries, which are members of the ESC. The ESC-HFA endorsed the study, which was conducted by an ad-hoc Executive Committee.

The national cardiology societies of each country agreed to participate in the programme and were asked to select hospitals of different levels of complexity from which patients could be recruited. The aim was to include a broad spectrum of cardiology and/or HF units following outpatients with HF and admitting patients with acute, worsening, or *de novo* HF to develop a network of centres that would be reasonably representative of the European reality. The number of participating centres for each country was decided according to the number of inhabitants in that country, i.e. one centre per 2 million people, but no more than 25 and no less than 6 per country. To the extent that it was possible, the centres were also chosen to fulfil geographical criteria within each country. In this way, the registry included a balanced proportion of centres with a range of cardiology facilities.

The EORP Department at the ESC European Heart House was appointed to co-ordinate the project's operations, to provide support to the committees, national co-ordinators, and participating centres, and to oversee the methodological aspects of the survey. The database was established at the European Heart House, according to the requirements defined by the appointed Executive Committee with the support of the EORP Department.

Patient population

From May 2011 to April 2013, all outpatients seen at the clinics and all patients acutely admitted to the hospital for acute, worsening, or *de novo* HF were included in this registry during the enrolment period (on 1 day per week for 12 consecutive months). Therefore, on the screening day, the following patients were entered in the registry: (i) all outpatients with chronic HF diagnosed according to the clinical judgement of the responsible cardiologist at the participating centres; and (ii) all inpatients admitted to the hospital's cardiology ward or intensive cardiac care unit for acute HF, for whom an intravenous therapy (inotropes, vasodilators, or diuretics) was needed.

There were no specific exclusion criteria, except for age ≤18 years. The registry was approved by each local Institutional Review Board according to the rules of each participating country. No data were collected before detailed information was provided to the patient and a signed informed consent was obtained.

In the current analysis, we presented the 1-year data from the ESC-HF Long-Term registry concerning the rates of in-hospital mortality, 1-year all-cause and cardiac mortality, and 1-year HF re-hospitalization of patients who were admitted to hospital for acute, worsening, or *de novo* HF. Data on mortality were available for the whole cohort ($n = 6926$), whereas data on 1-year HF re-hospitalization were available in 6540 (94.4%) participants.

Diagnosis of diabetes

Previously known diabetes was defined as self-reported physician-diagnosed diabetes, or use of medications for diabetes (insulin or oral hypoglycaemic agents). In the absence of previously known diabetes, the diagnosis of new-onset diabetes was based on a fasting plasma glucose level ≥7.0 mmol/L (≥126 mg/dL) and/or a haemoglobin A_{1c} (HbA_{1c}) level ≥6.5%, respectively. In accord with the American

Diabetes Association diagnostic criteria,[19] only a plasma glucose level ≥200 mg/dL (≥11.1 mmol/L), in the presence of classical hyperglycaemic symptoms, is sufficient for the diagnosis of new-onset diabetes without confirmation, whereas fasting glucose levels between 126 and 199 mg/dL (or an HbA_{1c} ≥6.5%) are considered diagnostic for diabetes only if confirmed by at least two separate testings.

Other clinical and laboratory data

Body mass index (BMI) was calculated by dividing weight in kilograms by height in metres squared. Patients were considered as having hypertension if their blood pressure was ≥140/90 mmHg or if they were taking antihypertensive drugs. Serum creatinine, glucose, HbA_{1c}, and other biochemical blood measurements were determined using local standard laboratory procedures. Estimated glomerular filtration rate (eGFR) was estimated using the four-variable Modification of Diet in Renal Disease (MDRD) study equation.[20] The presence of chronic kidney disease (CKD) was defined as an $eGFR_{MDRD}$ <60 mL/min/1.73 m^2.[20] Conventional trans-thoracic echocardiography was used to measure the LV diameter, wall thickness, and EF according to international standard criteria.

Statistical analysis

The statistical analyses were performed at the ESC European Heart House. Categorical variables were reported and compared using a χ^2 test or a Fisher's exact test if any expected cell count was <5. For categorical variables with more than two possible values, exact *P*-values were estimated according to the Monte Carlo method. Continuous variables were reported either as means ± SD or as medians and interquartile range (IQR). Among-group comparisons were made using a non-parametric test (the Kruskal–Wallis test). Two multivariable regression models (model 1, adjusted for age, sex, systolic blood pressure, $eGFR_{MDRD}$, LVEF, HF aetiology, and HF clinical presentation; and model 2, the same covariates included in model 1 plus BMI, smoking, hypertension, statin use, previous histories of stroke and COPD, sodium levels, and haemoglobin levels) were applied to estimate the risk associated with diabetes status at hospital admission in terms of in-hospital mortality (by logistic regression analysis), 1-year all-cause mortality, and 1-year re-hospitalization for HF (by Cox regression analysis). The covariates included in these multivariable regression models were chosen as potential confounding factors based on their significance in univariable analyses or their biological plausibility. We also examined the association between admission plasma glucose levels and the risk of adverse clinical outcomes after simultaneously stratifying the entire cohort of patients by quintiles of plasma glucose concentrations (i.e. ~1200 patients were included in each quintile) and by diabetes status. A two-sided *P*-value <0.05 was considered to be statistically significant. All analyses were performed with SAS statistical software version 9.4 (SAS Institute, Inc., Cary, NC, USA).

Results

As shown in *Table* 1, the study cohort included 6926 (63.0% men, mean age 69 years) hospitalized patients with acute HF, largely composed of overweight or obese individuals of Caucasian ancestry (~83%). The prevalence of diabetes in the study cohort was high (*n* = 3422; 49.4%); 80.5% (*n* = 2755) of these patients had previously known diabetes (i.e. self-reported history or use of hypoglycaemic drugs), whereas the remaining 667 (19.5%) patients had previously undiagnosed diabetes (as defined in the Methods). Among those with previously undiagnosed diabetes, 116 patients had a fasting glucose level ≥200 mg/dL (i.e. a criterion sufficient for the diagnosis of diabetes without confirmation), whereas the remaining 549 patients had a fasting glucose level between 126 and 199 mg/dL, about one-third of whom also had an HbA_{1c} level ≥6.5%. So, similarly to other large registry databases like this, since repeat glucose testings were not available, we could not distinguish in a subgroup of ~400 patients the exact number of those with a 'true' new diagnosis of diabetes from those with (non-diabetic) transient stress hyperglycaemia during hospitalization. We were also unable to distinguish between type 1 and type 2 diabetes mellitus, although the vast majority of our diabetic cases were likely to be type 2.

Table 1. Baseline characteristics of the whole cohort of patients with acute heart failure stratified by diabetes status

	Diabetic patients ($n = 3422$)	Non-diabetic patients ($n = 3504$)	*P*-value
Males	61.1%	64.8%	0.002
Age (years)	70.0 ± 11.4	68.0 ± 14.4	<0.001
Ethnic origin (Caucasian)	82.9%	82.2%	0.498
BMI (kg/m^2)	29.3 ± 5.4	27.7 ± 5.3	<0.001
Systolic BP (mmHg)	134.9 ± 29.6	130.1 ± 27.3	<0.001
Diastolic BP (mmHg)	79.2 ± 16.1	78.1 ± 15.4	0.002
Total cholesterol (mg/dL)	164.6 ± 54.6	164.7 ± 50.8	0.400
Heart rate (b.p.m,)	82.0 ± 20.6	80.5 ± 20.7	<0.001
Plasma glucose (mg/dL)	168.8 ± 75.3	96.2 ± 14.2	<0.001
Haemoglobin A_{1c}	7.4 ± 3.8	5.6 ± 0.5	<0.001
Hypertension	71.4%	57.6%	<0.001
Smoking status	15.7%	18.1%	0.007
Diabetes medicationsa			
Insulin	52.5%	0.0%	NA
Oral hypoglycaemic drugs only	47.5%	0.0%	NA
Diet only	0.0%	0.0%	NA
Cardiovascular medications			
Statins	47.3%	36.8%	<0.001
ACE inhibitors or ARBs	73.4%	69.7%	0.002
Beta-blockers	62.8%	62.5%	0.809
Aldosterone antagonists	36.6%	41.4%	<0.001
Diuretics	73.7%	71.5%	0.055
Digitalis	20.0%	23.1%	0.005
Calcium channel blockers	20.7%	14.0%	<0.001
Antiplatelets or anticoagulants	78.8%	75.7%	0.004
Nitrates	30.6%	23.2%	<0.001
Amiodarone	10.0%	11.7%	0.037
$eGFR_{MDRD}$ (mL/min/1.73 m^2)	54.9 ± 25.2	62.6 ± 34.7	<0.001
$eGFR_{MDRD}$ <60 mL/min/1.73 m^2	61.3%	50.0%	<0.001
Haemoglobin (g/dL)	12.4 ± 2.2	12.7 ± 2.2	<0.001
Sodium (mEq/L)	137.6 ± 5.4	138.3 ± 5.1	<0.001
NT-proBNP (pg/dL)	3900.0 (1674–9300)	3791.0 (1619–8878)	0.321
LVEF (%)	39.2 ± 14.2	39.2 ± 14.5	0.971
LVEF >45%	28.3%	31.2%	0.025
NYHA class III–IV	86.8%	83.0%	<0.001
HF aetiology (ischaemic)	63.7%	49.0%	<0.001
HF (*de novo*)	28.5%	30.2%	0.118
Atrial fibrillation	42.2%	45.0%	0.020
COPD	21.8%	16.8%	<0.001
Previous stroke	13.7%	10.6%	<0.001

Data are expressed as means ± SD, medians (IQR), or percentages.
Plasma glucose measurements were available in 5727 patients ($n = 2969$ and 2758 patients, respectively), whereas HbA_{1c} and NT-proBNP measurements were available in a smaller group of patients ($n = 1001$ and 1499 patients, respectively).
BMI, body mass index; BP, blood pressure; $eGFR_{MDRD}$, estimated glomerular filtration rate (as calculated by the Modification of Diet in Renal Disease study equation); HF, heart failure; NA, not applicable.
[a] Data on diabetes treatment were available for 3321 (97.1%) patients with diabetes.

Table 1 shows the baseline characteristics of patients stratified by diabetes status at hospital admission. Mean plasma glucose levels were 168.8 ± 75 mg/dL in patients with diabetes and 96.2 ± 14 mg/dL in those without diabetes, respectively. Mean HbA_{1c} levels (available only in 1001 participants; see footnote of *Table* 1) were 7.4 ± 3.8% in patients with diabetes and 5.6 ± 0.5% in those without. Patients with diabetes were more likely to be female, older, non-smokers, obese, and hypertensive compared with those without diabetes. They also had a greater likelihood of ischaemic aetiology of HF, NYHA class III–V, CKD, prior stroke or COPD, but a lower prevalence of AF, and LVEF >45%. Moreover, patients with diabetes had lower levels of $eGFR_{MDRD}$, haemoglobin, and sodium, and were more likely to be treated with statins, renin–angiotensin system blockers, calcium channel blockers, nitrates, antiplatelets or anticoagulants, and less likely to be treated with aldosterone antagonists, digitalis or amiodarone compared with those without diabetes. Most patients with diabetes were treated with insulin, oral hypoglycaemic drugs, or both. There were no significant differences in terms of ethnic origin, *de novo* HF presentation, beta-blocker drug use, total cholesterol, and NT-proBNP levels (available only in a subgroup of 1499 patients) between the two groups.

Collectively, over the follow-up period, there were 386 (5.6%) cases of in-hospital mortality, 1781 (25.7%) cases of 1-year all-cause mortality, 1001 (14.5%) cases of 1-year cardiac mortality and 1361 (20.8%) cases of 1-year hospital re-admission due to HF.

As shown in *Figure* 1, the cumulative rates of in-hospital mortality and 1-year adverse clinical outcomes were markedly higher in patients with diabetes than in those without diabetes ($P < 0.001$ for all between-group differences).

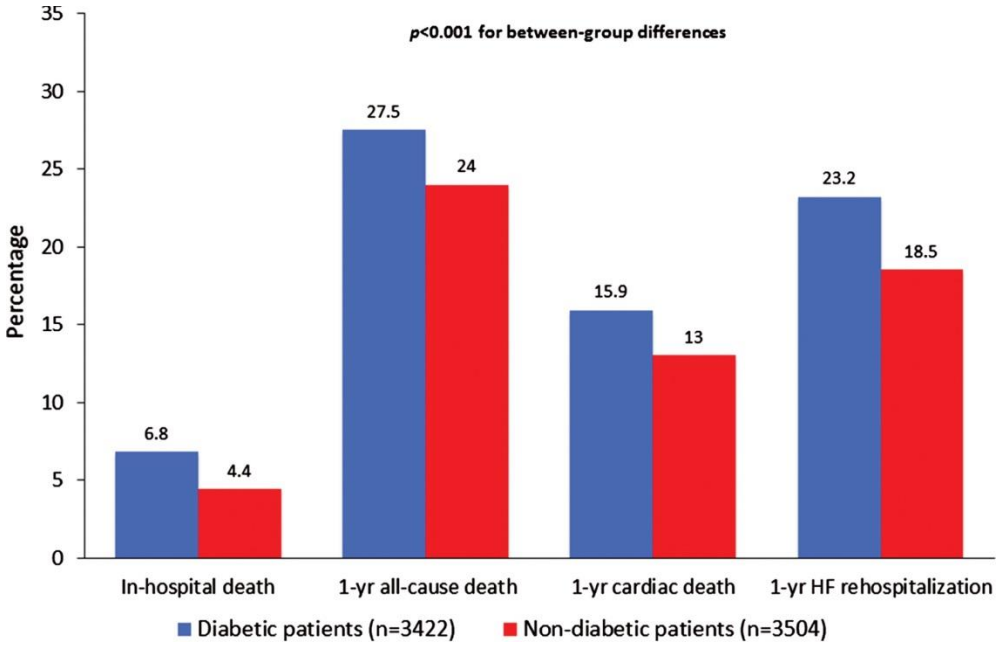

Figure 1. Cumulative incidence rates of in-hospital mortality, 1-year all-cause mortality, 1-year cardiac mortality and 1-year heart failure (HF) re-hospitalization among patients admitted to the hospital for acute HF stratified by diabetes status.

Table 2 shows the association between quintiles of plasma glucose levels at hospital admission and adverse clinical outcomes in the whole cohort of patients stratified by diabetes status. The rates per 100 patient-years of all considered clinical outcomes were almost always higher in patients with diabetes in each quintile of plasma glucose levels (i.e. at the same range of plasma glucose levels) than in those without diabetes. Elevated blood glucose levels at admission were associated with a significantly higher risk of in-hospital mortality in both diabetic and non-diabetic patients even after adjusting for age, sex, systolic blood pressure, $eGFR_{MDRD}$, LVEF, HF aetiology, and HF presentation. In contrast, no significant associations were observed between admission blood glucose levels and 1-year mortality or re-hospitalization rates in both groups of patients.

Table 2. Association between plasma glucose quintiles at hospital admission and adverse outcomes in the whole cohort of patients stratified by diabetes status

Group	Outcome	Plasma glucose (mg/dL)	Events/patients	Rate per 100 patient-years (95% CI)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)[a]
Diabetic patients	1-year all-cause death	≤90	72/231	31.2 (25.3–37.6)	Reference	Reference
		>90–103	59/207	28.5 (22.5–35.2)	0.92 (0.65–1.30)	0.90 (0.59–1.40)
		>103–122	91/339	26.8 (22.2–31.9)	0.82 (0.61–1.12)	0.91 (0.63–1.32)
		>122–165	264/1048	25.2 (22.6–27.9)	0.81 (0.63–1.06)	0.81 (0.59–1.12)
		>165	335/1144	29.3 (26.7–32.0)	0.96 (0.75–1.24)	1.10 (0.81–1.49)
	1-year cardiovascular death	≤90	43/231	18.6 (13.8–24.2)	Reference	Reference
		>90–103	37/207	17.9 (12.9–23.8)	0.97 (0.62–1.50)	0.74 (0.42–1.32)
		>103–122	49/339	14.5 (10.9–18.7)	0.75 (0.50–1.13)	0.76 (0.47–1.23)
		>122–165	151/1048	14.4 (12.3–16.7)	0.78 (0.56–1.10)	0.69 (0.46–1.03)
		>165	205/1144	17.9 (15.7–20.3)	0.99 (0.71–1.37)	0.99 (0.68–1.45)
	In-hospital death	≤90	7/231	3.0 (1.2–6.1)	Reference	Reference
		>90–103	15/207	7.2 (4.1–11.7)	2.50 (1.00–6.25)	2.93 (0.84–10.19)
		>103–122	15/339	4.4 (2.5–7.2)	1.48 (0.59–3.69)	2.40 (0.74–7.75)
		>122–165	78/1048	7.4 (5.9–9.2)	2.57 (1.17–5.65)	3.08 (1.07–8.84)
		>165	94/1144	8.2 (6.7–10.0)	2.86 (1.31–6.25)	3.79 (1.33–10.78)
	1-year HF re-hospitalization	≤90	67/224	29.9 (24.0–36.4)	Reference	Reference
		>90–103	57/192	29.7 (23.3–36.7)	0.99 (0.69–1.42)	1.01 (0.70–1.45)
		>103–122	77/324	23.8 (19.2–28.8)	0.73 (0.52–1.02)	0.73 (0.52–1.03)
		>122–165	230/970	23.7 (21.1–26.5)	0.77 (0.58–1.02)	0.82 (0.62–1.08)
		>165	242/1050	23.0 (20.5–25.7)	0.75 (0.57–0.98)	0.85 (0.64–1.12)
Non-diabetic patients	1-year all-cause death	≤90	218/981	22.2 (19.7–25.0)	Reference	Reference
		>90–103	184/903	20.4 (17.8–23.2)	0.89 (0.73–1.08)	0.78 (0.62–0.98)
		>103–122	205/796	25.8 (22.7–28.9)	1.18 (0.97–1.42)	1.04 (0.83–1.30)
		>122–165[b]	25/78	32.1 (21.9–43.6)	1.65 (1.09–2.49)	1.38 (0.82–2.30)
		>165	0/0	NA	NA	NA
	1-year cardiovascular death	≤90	125/981	12.7 (10.7–15.0)	Reference	Reference
		>90–103	103/903	11.4 (9.4–13.7)	0.86 (0.67–1.12)	0.81 (0.60–1.08)

Table 2. Association between plasma glucose quintiles at hospital admission and adverse outcomes in the whole cohort of patients stratified by diabetes status

Group	Outcome	Plasma glucose (mg/dL)	Events/patients	Rate per 100 patient-years (95% CI)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)[a]
		>103–122	106/796	13.3 (11.0–15.9)	1.06 (0.82–1.37)	0.93 (0.69–1.25)
		>122–165[b]	12/78	15.4 (8.2–25.3)	1.37 (0.76–2.47)	1.09 (0.53–2.24)
		>165	0/0	NA	NA	NA
	In-hospital death	≤90	31/981	3.2 (2.2–4.5)	Reference	Reference
		>90–103	26/903	2.9 (1.9–4.2)	0.91 (0.54–1.54)	0.90 (0.52–1.55)
		>103–122	38/796	4.8 (3.4–6.5)	1.54 (0.95–2.49)	1.41 (0.86–2.31)
		>122–165*	7/78	9.0 (3.7–17.6)	3.02 (1.29–7.10)	2.82 (1.15–6.89)
		>165	0/0	NA	NA	NA
	1-year HF re-hospitalization	≤90	201/950	21.2 (18.6–23.9)	Reference	Reference
		>90–103	174/877	19.8 (17.2–22.6)	0.91 (0.73–1.12)	0.80 (0.62–1.03)
		>103–122	154/758	20.3 (17.5–23.4)	0.97 (0.78–1.21)	0.82 (0.63–1.07)
		>122–165[b]	11/71	15.5 (8.0–26.0)	0.71 (0.36–1.38)	0.75 (0.33–1.71)
		>165	0/0	NA	NA	NA

Cohort size for this analysis, $n = 5727$.
Cox regression analyses for 1-year all-cause death, 1-year cardiovascular death, and 1-year HF re-hospitalization, and logistic regression analyses for in-hospital death have been performed. CI, confidence interval; HF, heart failure; HR, hazard ratio; NA, not applicable.
[a] Covariates considered for adjustment: age, sex, systolic blood pressure, estimated glomerular filtration rate (as calculated by the Modification of Diet in Renal Disease study equation), LVEF, HF aetiology and HF presentation.
[b] Note that for non-diabetic patients the maximum of plasma glucose levels in the fourth quintile was 125 mg/dL.

Table S1 in the Supplementary material online shows the same associations between admission blood glucose levels and adverse clinical outcomes of those reported in *Table* 2. However, in this table, patients with diabetes were stratified by clinically chosen cut-off levels (i.e. ≤125, 126–180, and >180 mg/dL), whereas patients without diabetes were stratified by tertiles of plasma glucose levels of the whole cohort of patients (i.e. ≤98, 98–132, and >132 mg/dL) at hospital admission. It is important to remark that, as expected, for patients without diabetes, the maximum plasma glucose level was 125 mg/dL. Also in this case, the rates per 100 patient-years of all considered clinical outcomes were almost always higher in patients with diabetes than in those without diabetes in each cut-off of admission plasma glucose levels. Similarly, elevated admission blood glucose levels were significantly associated with a higher in-hospital mortality in patients with diabetes (and only marginally in patients without diabetes) after adjusting for age, sex, systolic blood pressure, $eGFR_{MDRD}$, LVEF, HF aetiology, and HF presentation. No significant associations were observed between admission blood glucose levels and 1-year follow-up outcomes in both groups of patients.

Table S2 in the Supplementary material online shows the age- and sex-adjusted associations between diabetes treatment (insulin vs. diet/oral drugs) at hospital admission and adverse clinical outcomes in the subgroup of patients with diabetes. As expected, diabetic patients treated with insulin showed a worse prognosis than those treated with oral hypoglycaemic drugs or diet alone.

Table 3 shows the effect of the adjustment for multiple potential confounding variables on the relationship between diabetes and in-hospital mortality. Presence of diabetes was associated with an ~1.6-fold increased risk of in-hospital mortality after adjusting for age, sex, systolic blood pressure, $eGFR_{MDRD}$, LVEF, HF aetiology, and HF presentation (model 1). Additional adjustment for other

potential confounding variables (model 2) did not weaken the significant association between diabetes and in-hospital mortality. Notably, other variables that were independently associated with in-hospital mortality were older age, *de novo* HF presentation, lower BMI, lower systolic blood pressure (or a pre-existing non-hypertensive status), lower LVEF, and lower levels of $eGFR_{MDRD}$, haemoglobin, and sodium.

Table 3. Multivariable logistic regression analysis for in-hospital mortality in the whole cohort of patients

Variables	Regression model 1		Regression model 2	
	OR (95% CI)	P-value	OR (95%CI)	*P*-value
Diabetes status, yes vs. no	1.580 (1.177–2.120)	0.002	1.774 (1.282–2.456)	<0.001
Age, years	1.016 (1.003–1.028)	0.013	1.022 (1.008–1.036)	0.002
Sex, male vs. female	0.910 (0.670–1.236)	0.545	0.868 (0.623–1.211)	0.406
Systolic blood pressure, mmHg	0.974 (0.968–0.980)	<0.001	0.980 (0.974–0.987)	<0.001
$eGFR_{MDRD}$, mL/min/1.73 m^2	0.977 (0.971–0.984)	<0.001	0.981 (0.973–0.988)	<0.001
LVEF, %	0.987 (0.976–0.998)	0.018	0.988 (0.977–1.000)	0.048
HF aetiology, ischaemic vs. non-ischaemic	0.814 (0.605–1.095)	0.173	0.926 (0.667–1.287)	0.648
HF presentation, worsening vs. *de novo*	0.542 (0.401–0.733)	<0.001	0.593 (0.422–0.833)	0.003
BMI, kg/m^2	NC		0.951 (0.919–0.984)	0.004
Smoking status, yes vs. no	NC		1.228 (0.796–1.895)	0.354
Hypertension status, yes vs. no	NC		0.645 (0.454–0.915)	0.014
Statin use, yes vs. no	NC		0.775 (0.556–1.082)	0.135
Previous stroke, yes vs. no	NC		1.472 (0.970–2.232)	0.069
Previous COPD, yes vs. no	NC		1.286 (0.894–1.850)	0.176
Haemoglobin, g/dL	NC		0.902 (0.841–0.968)	0.004
Sodium, mEq/L	NC		0.946 (0.925–0.967)	<0.001

Model 1: adjusted for age, sex, systolic blood pressure, $eGFR_{MDRD}$, LVEF, HF aetiology, and HF presentation.
Model 2: the same covariates included in model 1 plus BMI, smoking history, hypertension, statin use, previous stroke and COPD, haemoglobin, and sodium levels.
BMI, body mass index; CI, confidence interval; $eGFR_{MDRD}$, estimated glomerular filtration rate (as calculated by the Modification of Diet in Renal Disease study equation); HF, heart failure; NC, not considered; OR, odds ratio.

Table 4 shows the effect of the adjustment for potential confounding variables on the relationship between diabetes and 1-year all-cause mortality. In regression model 2, the presence of diabetes was associated with a 1.16-fold increased risk of 1-year all-cause mortality. Other variables that were independently associated with 1-year all-cause mortality were older age, male sex, prior stroke, non-use of statins, lower systolic blood pressure (or a pre-existing non-hypertensive status), lower levels of $eGFR_{MDRD}$, haemoglobin, and sodium, and lower LVEF. Similar findings were also observed for 1-year cardiac mortality (data not shown).

Table 4. Multivariable Cox regression analysis for 1-year all-cause mortality in the whole cohort of patients

Variables	Regression model 1		Regression model 2	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Diabetes status, yes vs. no	1.133 (1.006–1.277)	0.040	1.162 (1.020–1.325)	0.024
Age, years	1.029 (1.023–1.035)	<0.001	1.030 (1.024–1.036)	<0.001
Sex, male vs. female	1.125 (0.988–1.280)	0.076	1.216 (1.058–1.399)	0.006
Systolic blood pressure, mmHg	0.991 (0.989–0.993)	<0.001	0.995 (0.992–0.997)	<0.001
$eGFR_{MDRD}$, mL/min/1.73 m^2	0.986 (0.984–0.989)	<0.001	0.989 (0.986–0.992)	<0.001
LVEF, %	0.985 (0.980–0.989)	<0.001	0.984 (0.979–0.989)	<0.001
HF aetiology, ischaemic vs. non-ischaemic	0.848 (0.750–0.958)	<0.008	0.928 (0.812–1.060)	0.271
HF presentation, worsening vs. *de novo*	1.027 (0.898–1.176)	0.695	1.106 (0.952–1.286)	0.189
BMI, kg/m^2	NC		0.987 (0.974–1.001)	0.061
Smoking status, yes vs. no	NC		0.926 (0.763–1.123)	0.432
Hypertension status, yes *vs*. no	NC		0.742 (0.636–0.866)	<0.001
Statin use, yes vs. no	NC		0.733 (0.640–0.840)	<0.001
Previous stroke, yes vs. no	NC		1.260 (1.059–1.498)	0.009
Previous COPD, yes vs. no	NC		1.157 (0.994–1.348)	0.060
Haemoglobin, g/dL	NC		0.897 (0.871–0.923)	<0.001
Sodium, mEq/L	NC		0.970 (0.961–0.980)	<0.001

Model 1: adjusted for age, sex, systolic blood pressure, $eGFR_{MDRD}$, LVEF, HF aetiology, and HF presentation.
Model 2: the same covariates included in model 1 plus BMI, smoking history, hypertension, statin use, previous stroke and COPD, haemoglobin, and sodium levels.
BMI, body mass index; CI, confidence interval; $eGFR_{MDRD}$, estimated glomerular filtration rate (as calculated by the Modification of Diet in Renal Disease study equation); HF, heart failure; HR, hazard ratio; NC, not considered.

Table 5 shows the effect of the adjustment for multiple potential confounding variables on the relationship between diabetes and 1-year re-hospitalization for HF. Also in this case, the presence of diabetes was associated with a 1.32-fold increased risk of 1-year hospital re-admission due to HF, independently of multiple potential confounders (model 2). Other variables that were independently associated with HF hospital re-admissions were prior stroke, COPD, non-ischaemic HF aetiology, lower systolic blood pressure, lower $eGFR_{MDRD}$, lower haemoglobin, lower LVEF, and worsening HF presentation.

Table 5. Multivariable Cox regression analysis for 1-year heart failure re-hospitalization in the whole cohort of patients

Variables	Regression model 1		Regression model 2	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Diabetes status, yes vs. no	1.348 (1.175–1.548)	<0.001	1.320 (1.139–1.530)	<0.001
Age, years	1.002 (0.996–1.008)	0.519	1.000 (0.993–1.006)	0.904
Sex, male vs. female	1.082 (0.931–1.257)	0.306	1.067 (0.911–1.251)	0.422
Systolic blood pressure, mmHg	0.996 (0.993–0.998)	0.001	0.997 (0.994–0.999)	0.020
$eGFR_{MDRD}$, mL/min/1.73 m^2	0.991 (0.988–0.994)	<0.001	0.991 (0.988–0.994)	<0.001
LVEF, %	0.991 (0.985–0.996)	<0.001	0.989 (0.983–0.994)	<0.001
HF aetiology, ischaemic vs. non-ischaemic	0.828 (0.720–0.953)	0.008	0.803 (0.691–0.933)	0.004
HF presentation, worsening vs. *de novo*	2.070 (1.737–2.467)	<0.001	1.854 (1.536–2.239)	<0.001
BMI, kg/m^2	NC		0.996 (0.982–1.010)	0.589
Smoking status, yes vs. no	NC		0.940 (0.766–1.154)	0.554
Hypertension status, yes vs. no	NC		0.885 (0.740–1.059)	0.182
Statin use, yes vs. no	NC		1.163 (1.002–1.349)	0.046
Previous stroke, yes vs. no	NC		1.343 (1.105–1.632)	0.003
Previous COPD, yes vs. no	NC		1.333 (1.128–1.575)	<0.001
Haemoglobin, g/dL	NC		0.961 (0.931–0.993)	0.018
Sodium, mEq/L	NC		1.001 (0.988–1.015)	0.853

Model 1: adjusted for age, sex, systolic blood pressure, $eGFR_{MDRD}$, LVEF, HF aetiology, and HF presentation.
Model 2: the same covariates included in model 1 plus BMI, smoking history, hypertension, statin use, previous stroke and COPD, haemoglobin, and sodium levels.
BMI, body mass index; CI, confidence interval; $eGFR_{MDRD}$, estimated glomerular filtration rate (as calculated by the Modification of Diet in Renal Disease study equation); HF, heart failure; NC, not considered.

Finally, we also performed some sensitivity analyses to assess the robustness of our observations. Supplementary material online, *Table S3* shows the age- and sex-adjusted associations between patients with reduced LVEF ≤45% or with LVEF >45% at hospital admission and the risk of adverse clinical outcomes stratified by diabetic status. Conversely, Supplementary material online, *Table S4* shows the associations between patients with ischaemic or non-ischaemic HF aetiology and the risk of adverse clinical outcomes stratified by diabetic status.

As expected, patients with LVEF >45% at hospital admission had better clinical outcomes than those with reduced LVEF ≤45%, irrespective of pre-existing diabetes. In contrast, there were no significant age- and sex-adjusted associations between patients with ischaemic or non-ischaemic HF aetiology and risk of adverse outcomes stratified by diabetic status. Notably, in both of these sensitivity analyses, the rates per 100 patient-years of adverse clinical outcomes were almost always higher in patients with diabetes than in those without diabetes, irrespective of either HF aetiology or the level of LVEF at hospital admission.

Discussion

In this prospective, observational registry of a large unselected European population of consecutive patients admitted to the hospital for acute HF, we observed: (i) a very high prevalence of known and previously undiagnosed diabetes among these patients (49.4%); (ii) higher rates of in-hospital mortality, 1-year all-cause and cardiac mortality, and 1-year hospital readmission due to HF in patients with diabetes (especially in those treated with insulin that may reflect a greater disease severity) compared with those without diabetes; (iii) a significant association between diabetes and in-hospital mortality and 1-year follow-up outcomes even after adjusting for multiple established risk factors and potential confounding variables (including also HF aetiology, HF presentation, LVEF, haemoglobin, and $eGFR_{MDRD}$); and (iv) a significant and independent association between high blood glucose levels at hospital admission and the risk of in-hospital mortality in both patients with and without diabetes.

Our findings provide a contemporary picture on short- and mid-term adverse clinical outcomes of a large European cohort of acute HF patients with and without diabetes, outside the context of randomized clinical trials. In addition, our findings also shed light on the previously reported discrepant results (as discussed below) regarding the prognostic impact of diabetes *per se* on adverse clinical outcomes among inpatients with acute HF. In fact, to date, despite the high prevalence of diabetes among patients with acute HF (ranging from 30% to 50%),[1-3] the association between diabetes and HF often remains under-recognized by clinicians, and there are conflicting data regarding the prognostic impact of diabetes *per se* on the risk of mortality and re-hospitalizations, both in the short and mid term, among patients hospitalized for acute HF.

Our findings expand previous observations supporting that patients with acute HF and diabetes have poor in-hospital mortality and/or post-discharge adverse outcomes compared with those without diabetes.[7, 9, 10] However, our findings also contrast with those from other previously published studies. For instance, in a large retrospective cohort study of Scottish patients discharged from hospital with a diagnosis of acute HF between 1986 and 2003, the presence of diabetes was associated with a lower mortality at 30 days, but it was an independent predictor of higher mortality at 1 year.[8] Similarly, the presence of diabetes did not independently predict in-hospital mortality in the cohort of patients from the Acute Decompensated Heart Failure National Registry (ADHERE).[11] However, the ADHERE registry did not address the impact of diabetes on post-discharge outcomes as these data were not collected. The Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF) registry showed that the presence of diabetes did not independently predict in-hospital mortality, 60- to 90-day post-discharge mortality, or re-hospitalizations.[15] Moreover, Kosiborod *et al.* did not find any association between diabetes and 30-day and 1-year all-cause mortality in elderly patients hospitalized with acute HF.[12] Finally, the presence of diabetes was strongly associated with higher rates of in-hospital mortality but it did not significantly predict 1-year post-discharge mortality or re-hospitalization rates in the cohort of 1176 inpatients from the Italian Network on HF (IN-HF) Outcome registry.[16]

To date, studies of patients with acute HF that have also specifically examined the association between admission blood glucose levels and the rates of mortality and hospital readmission are limited and discrepant. Some studies did not find any association between elevated admission blood glucose levels and mortality, both in the short and long term.[12, 14, 21] Our results are consistent with other observations suggesting that elevated admission blood glucose levels are a prognostic marker for in-hospital mortality in both patients with and without diabetes.[10, 22, 23] For example, Sud *et al.*[22] demonstrated that mildly elevated hyperglycaemia was significantly associated with increased rates of 30-day all-cause mortality and re-hospitalizations in patients with acute HF. However, similarly to our findings, the association between admission blood glucose levels and mortality was no longer significant at 1 year among these patients, regardless of pre-existing diabetes.[22] Although additional studies are certainly needed, our findings further suggest that in-hospital hyperglycaemia is a reliable marker of poor short-term outcomes and mortality in patients with and without diabetes.[24, 25]

Unfortunately, as specified in the Results, we cannot exactly distinguish in a certain number of our patients between those with newly diagnosed diabetes and those with non-diabetic stress hyperglycaemia, as repeat glucose testings or extensive HbA_{1c} measurements were not performed. However, it is known that a significant association between transient stress hyperglycaemia and adverse clinical outcomes does exist in the short term (e.g. a longer length of hospital stay, a higher admission rate to an intensive care unit, and a higher rate of in-hospital mortality), but not in the longer term.[24, 25] Thus, it is important to underline that some misclassification of new-onset diabetes based on a single blood glucose measurement was likely in our clinical setting (i.e. some of our newly diagnosed diabetic inpatients might have transient stress hyperglycaemia). If so, this misclassification could have partly affected the assessment of the 'true' prevalence of diabetes and its prognostic effect on in-hospital mortality; in contrast, given that in the literature, transient stress hyperglycaemia has not been reported to be significantly associated with adverse clinical outcomes in the longer term,[24, 25] our results are most likely to be a conservative estimate of the impact of diabetes on 1-year clinical outcomes.

The major strengths of our study are intrinsic to the design of the ESC-HF Long-Term Registry, which is one of the largest, multinational, and nationally representative systematic collections of contemporary European patients with HF. The sample size of our registry provides an adequate statistical power to keep the possible occurrence of both type I and type II errors to a minimum. Thus, we believe that the added value of our registry to the existing literature is that it provides solid and updated data regarding in-hospital and 1-year survival rates in a large unselected cohort of acute HF patients followed by cardiologists, thus providing a picture of European patients, who were not included in controlled trials but were currently being treated in general cardiology clinical practice. In addition, our registry also provides clear evidence of the impact of diabetes *per se* on the risk of both in-hospital mortality and 1-year follow-up outcomes as well as the possible impact of elevated blood glucose levels at hospital admission on the risk of in-hospital mortality, regardless of pre-existing diabetes. Finally, in our registry, thorough sensitivity analyses that accounted for a reasonably large number of established risk factors were also possible because of the availability of systematically collected clinical data, laboratory measures, and instrumental data (including echocardiographic functional measures, i.e. LVEF) for a large number of patients.

Some important limitations of this registry should also be mentioned. First, although we sought to balance the methodological need for consecutiveness of enrolment with the practical feasibility, thereby decreasing the workload for centres by limiting recruitment to 1 day per week for 12 months, we cannot prove definitely the consecutiveness of patient enrolment. However, local audits were performed to verify the quality of data and the consecutiveness of enrolment. Secondly, representativeness is often recognized as a limitation in all observational studies. To lessen this problem, the centres were selected in proportion to the population size of participating countries, taking into account the different technological levels of the invited centres. Thirdly, all patients were enrolled in cardiology wards and clinics, and they do not represent those acutely admitted to other hospital facilities. Accordingly, our patient cohort does not represent the whole gamut of patients with acute HF. Fourthly, as discussed above, this study cannot exactly distinguish between a new diagnosis of diabetes and transient stress hyperglycaemia in a subgroup of patients. However, we would like to note that this is an intrinsic limitation of most epidemiological studies or registry databases, like this, in which the confirmation of diabetes diagnosis, on at least two separate occasions, in patients with previously undiagnosed diabetes has never been made. Finally, we lacked detailed information about the use of different classes of oral hypoglycaemic agents, the hypoglycaemic events, and the extra-cardiac causes of mortality and re-hospitalization, and also follow-up data on plasma glucose and HbA_{1c} levels were not available.

In conclusion, our contemporary results from the ESC-HF Long-Term Registry show that the presence of diabetes is associated with substantially increased rates of in-hospital mortality, 1-year all-cause mortality, and 1-year HF re-hospitalization in patients hospitalized for acute HF. Notably, these associations remain statistically significant after adjusting for multiple clinical risk factors and potential confounding variables (including also HF aetiology, HF presentation, LVEF, and kidney function parameters). Furthermore, elevated admission blood glucose concentrations are powerfully prognostic for in-hospital mortality in patients both with and without established diabetes. In an era where there is

increasing emphasis on chronic disease management as a strategy to contain healthcare costs, these findings further highlight the prognostic value of diabetes and the need for therapies that improve survival outcomes in this particularly high-risk patient population.[26]

Supplementary information

Additional Supporting Information may be found in the online version of this article:

Table S1. Associations between plasma glucose levels at hospital admission and adverse clinical outcomes stratified by diabetes status.
Table S2. Associations between diabetes treatment (insulin vs. diet/oral drugs) at hospital admission and adverse clinical outcomes in the subgroup of diabetic patients.
Table S3. Associations between patients with either reduced LVEF ≤45% or with LVEF >45% at hospital admission and adverse clinical outcomes stratified by diabetes status.
Table S4. Associations between patients with ischaemic or non-ischaemic HF aetiology at hospital admission and adverse clinical outcomes stratified by diabetes status.

Acknowledgements

The Executive Committee of the study had full access to the data and takes complete responsibility for the integrity and the accuracy of the data analysis.

Funding

Since the start of EORP, the following companies have supported the programme: Abbott Vascular Int. (2011–2014), Amgen Cardiovascular (2012–2018), AstraZeneca (2014–2017), Bayer (2013–2018), Boehringer Ingelheim (2013–2016), Boston Scientific (2010–2012), The Bristol Myers Squibb and Pfizer Alliance (2014–2016), The Alliance Daiichi Sankyo Europe GmbH and Eli Lilly and Company (2014–2017), Edwards (2016–2019), Gedeon Richter Plc. (2014–2017), Menarini Int. Op. (2010–2012), MSD-Merck & Co. (2011–2014), Novartis Pharma AG (2014–2017), ResMed (2014–2016), Sanofi (2010–2011), SERVIER (2012–2015).

Conflicts of interest: R.F. reported that he received a honorarium from Servier for steering committee membership consulting and speaking, and support for travel to study meetings from Servier. In addition, he received personal fees from Boehringer-Ingelheim, Novartis, Merck Serono, and Irbtech. Finally, he is a stockholder in Medical Trials Analyis. L.T. reports personal fees from Servier, St Jude Medical, CVIE Therapeutics, Cardiorentis, Medtronic, and from Boston Scientific, outside the submitted work. A.P.M. reports grants from Novartis, Bayer, and Cardiorentis, outside the submitted work. All other authors have no conflicts to declare.

Appendix 1: Committees and Investigators

Executive Committee: M.G. Crespo-Leiro, S.D. Anker, A.J. Coats, R. Ferrari, G. Filippatos, A.P. Maggioni, A. Mebazaa, M.F. Piepoli
Steering Committee (National Co-ordinators): O. Amir, O. Chioncel, U. Dahlström, J.F. Delgado Jimenez, J. Drozdz, A. Erglis, E. Fazlibegovic, C. Fonseca, F. Fruhwald, P. Gatzov, E. Goncalvesova, M. Hassanein, J. Hradec, A. Kavoliuniene, M. Lainscak, D. Logeart, B. Merkely, M. Metra, M. Otljanska, P.M. Seferovic, E. Srbinovska Kostovska, A. Temizhan, D. Tousoulis
EORP Team: M. Andarala, T. Ferreira, E. Fiorucci, G. Gracia, C. Laroche, C. Pommier, C.Taylor
Local monitors: A. Cuculici (Republic of Moldova, Romania), C. Gaulhofer (Austria), E. Perez Casado (Portugal, Spain), E. Szymczyk (Poland), F. Ramani (Italy), G. Mulak (France, Switzerland), IL. Schou (Denmark), J. Semenka (Bulgaria, Czech Republic, Hungary, Poland, Slovakia), J. Stojkovic (Bosnia Herzegovina, Croatia, Serbia, Slovenia), R. Mehanna (Egypt), V. Mizarienne (Latvia).

Investigators from the participating centres

AUSTRIA **Braunau**: J. Auer; **Graz**: K. Ablasser, F. Fruhwald, T. Dolze, K. Brandner; **Innsbruck**: S. Gstrein, G. Poelzl; **Sankt Poelten**: D. Moertl; **Vienna**: S. Reiter, A. Podczeck-Schweighofer; *BOSNIA HERZEGOVINA* **Mostar**: A. Muslibegovic, M. Vasilj, E. Fazlibegovic, M. Cesko, D. Zelenika, B. Palic, D. Pravdic, D. Cuk; *BULGARIA* **Sofia**: K. Vitlianova, T. Katova, T. Velikov, T. Kurteva, P. Gatzov, **Vidin**: D. Kamenova; **Varna**: M. Antova, V. Sirakova; *CZECH REPUBLIC* **Brno**: J. Krejci, M. Mikolaskova, J. Spinar; **Prague**: J. Krupicka, F. Malek, M. Hegarova; **Olomouc**: M. Lazarova; **Znojmo**: Z. Monhart; *EGYPT* **Alexandria**: M. Hassanein, M. Sobhy, F. El Messiry, A.H. El Shazly, Y. Elrakshy; **Assiut**: A. Youssef; **Benha**: A.A. Moneim; **Cairo**: M. Noamany, A. Reda, T.K. Abdel Dayem, N. Farag, S. Ibrahim Halawa, M. Abdel Hamid, K. Said, A. Saleh; **Damanhour, El Beheira**: H. Ebeid; **Giza Cairo**: R. Hanna, R. Aziz, O. Louis, M.A. Enen, B.S. Ibrahim; **Ismailya**: G. Nasr; **Port Said**: A. Elbahry; **Tanta**: H. Sobhy, M. Ashmawy; **Zagazig**: M. Gouda, W. Aboleineen; *FRANCE* **Besançon**: Y. Bernard, P. Luporsi, N. Meneveau, M. Pillot, M. Morel, M-F. Seronde, F. Schiele, F. Briand; **Bron – Lyon**: F. Delahaye; **Créteil**: T. Damy; **Dijon**: J-C. Eicher; **Lille**: P. de Groote, M. Fertin, N. Lamblin; **Paris**: R. Isnard, C. Lefol, S. Thevenin, A. Hagege, G. Jondeau, D. Logeart; **Poitiers**: V. Le Marcis, J-F. Ly, D. Coisne, B. Lequeux; **Rennes**: V. Le Moal, S. Mascle, P. Lotton, N. Behar, E. Donal, C. Thebault, C. Ridard, A. Reynaud, A. Basquin; **Rouen**: F. Bauer; **Senlis**: R. Codjia; **Toulouse**: M. Galinier; *GREECE* **Athens**: P. Tourikis, M. Stavroula, D. Tousoulis, C. Stefanadis, C. Chrysohoou, I. Kotrogiannis, V. Matzaraki, T. Dimitroula, A. Karavidas, G. Tsitsinakis, C. Kapelios, J. Nanas, H. Kampouri, E. Nana, E. Kaldara, A. Eugenidou; **Heraklion, Crete**: P. Vardas, I. Saloustros, A. Patrianakos; **Volos**: T. Tsaknakis, S. Evangelou, N. Nikoloulis, H. Tziourganou, A. Tsaroucha, A. Papadopoulou, A. Douras; *HUNGARY* **Budapest**: L. Polgar, B. Merkely, A. Kosztin, N. Nyolczas, A. Csaba Nagy; **Pecs (Baranya)**: R. Halmosi; *ISRAEL* **Hadera**: J. Elber, I. Alony, A. Shotan, A. Vazan Fuhrmann; **Haifa**: O. Amir; *ITALY* **Atri**: S. Romano, S. Marcon, M. Penco, M. Di Mauro, E. Lemme; **Brescia**: V. Carubelli, R. Rovetta, M. Metra, M. Bulgari, F. Quinzani, C. Lombardi; **Cotignola**: S. Bosi, G. Schiavina, A. Squeri, A. Barbieri; **Cremona**: G. Di Tano, S. Pirelli; **Ferrara**: R. Ferrari, A. Fucili; **Foggia**: T. Passero, S. Musio, M. Di Biase, M. Correale, G. Salvemini; **Lumezzane**: S. Brognoli, E. Zanelli, A. Giordano; **Milano**: P. Agostoni, G. Italiano, E. Salvioni; **Modena**: S. Copelli, M.G. Modena, L. Reggianini, C. Valenti, A. Olaru; **Monserrato**: S. Bandino, M. Deidda, G. Mercuro, C. Cadeddu Dessalvi; **Novara**: P.N. Marino, M.V. Di Ruocco, C. Sartori, C. Piccinino; **Palermo**: G. Parrinello, G. Licata, D. Torres, S. Giambanco, S. Busalacchi, S. Arrotti, S. Novo, R.M. Inciardi, P. Pieri, P.R. Chirco, M. Ausilia Galifi, G. Teresi, D. Buccheri, A. Minacapelli; **Passirana di rho (Milano)**: M. Veniani, A. Frisinghelli; **Pavia**: S.G. Priori, S. Cattaneo, C. Opasich, A. Gualco; **Roma**: M. Pagliaro, M. Mancone, F. Fedele, A. Cinque, M. Vellini, I. Scarfo, F. Romeo, F. Ferraiuolo, D. Sergi; **San Bonifacio (Verona)**: M. Anselmi; **Sassuolo**: F. Melandri, E. Leci, E. Iori; **Torino**: V. Bovolo, S. Pidello, S. Frea, S. Bergerone, M. Botta, F.G. Canavosio, F. Gaita; **Trieste**: M. Merlo, M. Cinquetti, G. Sinagra, F. Ramani, E. Fabris, D. Stolfo; **Udine**: J. Artico, D. Miani, C. Fresco, C. Daneluzzi, A. Proclemer; **Verona**: M. Cicoira, L. Zanolla, G. Marchese, F. Torelli, C. Vassanelli; *LATVIA* **Jelgava**: N. Voronina; **Riga**: A. Erglis; *LITHUANIA* **Kaunas**: V. Tamakauskas, V. Smalinskas, R. Karaliute, I. Petraskiene, E. Kazakauskaite, E. Rumbinaite, A. Kavoliuniene;

Marijampole: V. Vysniauskas, R. Brazyte-Ramanauskiene, D. Petraskiene; *POLAND* **Biala**: S. Stankala, P. Switala, Z. Juszczyk; **Bydgoszcz**: W. Sinkiewicz, W. Gilewski, J. Pietrzak; **Chelmza**: T. Orzel, P. Kasztelowicz; **Czestochowa**: P. Kardaszewicz, M. Lazorko-Piega, J. Gabryel; **Gdansk**: K. Mosakowska, J. Bellwon, A. Rynkiewicz, G. Raczak, E. Lewicka, A. Dabrowska-Kugacka; **Kielce**: R. Bartkowiak, B. Sosnowska-Pasiarska, B. Wozakowska-Kaplon; **Kluczbork**: A. Krzeminski; **Krakow**: M. Zabojszcz, E. Mirek-Bryniarska, A. Grzegorzko, K. Bury, J. Nessler, J. Zalewski, A. Furman; **Lodz**: M. Broncel, A. Poliwczak, A. Bala, P. Zycinski, M. Rudzinska, L. Jankowski, J.D. Kasprzak, L. Michalak, K. Wojtczak Soska, J. Drozdz, I. Huziuk, A. Retwinski; **Lublin**: P. Flis, J. Weglarz, A. Bodys; **Poznan**: S. Grajek, M. Kaluzna-Oleksy, E. Straburzynska-Migaj, R. Dankowski, K. Szymanowska, J. Grabia, A. Szyszka, A. Nowicka; **Pruszkow**: M. Samcik, L. Wolniewicz, K. Baczynska, K. Komorowska, I. Poprawa, E. Komorowska, D. Sajnaga, A. Zolbach, A. Dudzik-Plocica, A-F. Abdulkarim, A. Lauko-Rachocka; **Przeworsk**: L. Kaminski, A. Kostka, A. Cichy; **Sieradz**: P. Ruszkowski, M. Splawski; **Starachowice**: G. Fitas, A. Szymczyk, A. Serwicka, A. Fiega; **Strzegom**: D. Zysko; **Szczecin**: W. Krysiak, S. Szabowski, E. Skorek; **Warszawa**: P. Pruszczyk, P. Bienias, M. Ciurzynski, M. Welnicki, A. Mamcarz, A. Folga, T. Zielinski, T. Rywik, P. Leszek, M. Sobieszczanska-Malek, M. Piotrowska, K. Kozar-Kaminska, K. Komuda, J. Wisniewska, A. Tarnowska, P. Balsam, M. Marchel, G. Opolski, A. Kaplon-Cieslicka, R.J. Gil, O. Mozenska, K. Byczkowska, K. Gil, A. Pawlak, A. Michalek, P. Krzesinski, K. Piotrowicz, B. Uzieblo-Zyczkowska, A. Stanczyk, A. Skrobowski; **Wroclaw**: P. Ponikowski, E. Jankowska; **Zabrze**: P. Rozentryt, L. Polonski, E. Gadula-Gacek, E. Nowalany-Kozielska, A. Kuczaj, Z. Kalarus, M. Szulik, K. Przybylska, J. Klys; **Zamosc**: G. Prokop-Lewicka, A. Kleinrok; *PORTUGAL* **Carnaxide**: C. Tavares Aguiar, A. Ventosa; **Faro**: S. Pereira, R. Faria, J. Chin, I. De Jesus; **Guilhufe-Penafiel**: R. Santos, P. Silva, N. Moreno, C. Queirós, C. Lourenço, A. Pereira, A. Castro, A. Andrade; **Lisboa**: T. Oliveira Guimaraes, S. Martins, R. Placido, G. Lima, D. Brito, A.R. Francisco, R. Cardiga, M. Proenca, I. Araujo, F. Marques, C. Fonseca; **Porto**: B. Moura, S. Leite, M. Campelo, J. Silva-Cardoso, J. Rodrigues, I. Rangel, E. Martins, A. Sofia Correia; **Santarem**: M. Peres, L. Marta, G. Ferreira da Silva, D. Severino, D. Durao; **Vila Real**: S. Leao, P. Magalhaes, I. Moreira, A. Filipa Cordeiro, C. Ferreira, C. Araujo, A. Ferreira, A. Baptista; *ROMANIA* **Brasov**: M. Radoi; **Bucharest**: G. Bicescu, D. Vinereanu, C-J. Sinescu, C. Macarie, R. Popescu, I. Daha, G-A. Dan, C. Stanescu, A. Dan; **Constanta**: E. Craiu; **Galati**: E. Nechita; **Iasi**: V. Aursulesei; **Timisoara**: R. Christodorescu; *SERBIA* **Belgrade**: P. Otasevic, P.M. Seferovic, D. Simeunovic, A.D. Ristic, V. Celic, M. Pavlovic-Kleut, J. Suzic Lazic, B. Stojcevski, B. Pencic, A. Stevanovic, A. Andric; **Kragujevac**: V. Iric-Cupic, M. Jovic, G. Davidovic, S. Milanov; **Nis**: V. Mitic, V. Atanaskovic, S. Antic, M. Pavlovic, D. Stanojevic; **Niska Banja**: V. Stoickov, S. Ilic, M. Deljanin Ilic, D. Petrovic; **Sremska Kamenica (Vojvodina)**: S. Stojsic, S. Kecojevic, S. Dodic, N. Cemerlic Adic, M. Cankovic, J. Stojiljkovic, B. Mihajlovic, A. Radin; **Zemun, Belgrade**: S. Radovanovic, M. Krotin; *SLOVAKIA* **Banovce nad Bebravou**: A. Klabnik; **Bratislava**: E. Goncalvesova, M. Pernicky, J. Murin; **Martin**: F. Kovar; **Presov**: J. Kmec, H. Semjanova; *SLOVENIA* **Brezice**: M. Strasek, M. Savnik Iskra; **Izola**: T. Ravnikar, N. Cernic Suligoj, J. Komel; **Ljubljana**: Z. Fras, B. Jug; **Maribor**: T. Glavic, R. Losic, M. Bombek, I. Krajnc, B. Krunic; **Murska Sobota**: S. Horvat, D. Kovac, D. Rajtman; **Ptuj**: V. Cencic, M. Letonja; **Sempeter pri Novi Gorici**: R. Winkler, M. Valentincic, C. Melihen-Bartolic, A. Bartolic; **Slovenj Gradec**: M. Pusnik Vrckovnik, M. Kladnik, C. Slemenik Pusnik, A. Marolt; **Trbovlje**: J. Klen, B. Drnovsek, B. Leskovar; *SPAIN* **Albacete**: M.J. Fernandez Anguita, J.C. Gallego Page, F.M. Salmeron Martinez; **Barakaldo (Vizcaya)**: J. Andres; **Barcelona**: A.B. Genis, S. Mirabet, A. Mendez, L. Garcia-Cosio, E. Roig, V. Leon, J. Gonzalez-Costello, G. Muntane, A. Garay; **Granada**: V. Alcade-Martinez, S. Lopez Fernandez, R. Rivera-Lopez, M. Puga-Martinez, M. Fernandez-Alvarez, J.L. Serrano-Martinez; **La Coruna**: M.G. Crespo-Leiro, Z. Grille-Cancela, R. Marzoa-Rivas, P. Blanco-Canosa, M.J. Paniagua-Martin, E. Barge-Caballero; **La Laguna – Santa Cruz de Tenerife (Canary Islands)**: I. Laynez Cerdena, I. Famara Hernandez Baldomero, A. Lara Padron; **Madrid**: S. Ofelia Rosillo, R. Dalmau Gonzalez-Gallarza, O. Salvador Montanes, A.M. Iniesta Manjavacas, A. Castro Conde, A. Araujo, T. Soria, P. Garcia-Pavia, M. Gomez-Bueno, M. Cobo-Marcos, L. Alonso-Pulpon, J. Segovia Cubero, I. Sayago, A. Gonzalez-Segovia, A. Briceno, P. Escribano Subias, M. Vicente Hernandez, M.J. Ruiz Cano, M.A. Gomez Sanchez, J.F. Delgado Jimenez, E. Barrios Garrido-Lestache; **Malaga**: J.M. Garcia Pinilla; **Manacor (Mallorca)**: B. Garcia de la Villa, A. Sahuquillo; **Marbella (Malaga)**: R. Bravo Marques, F. Torres Calvo; **Murcia**: M.T. Perez-Martinez, M.R. Gracia-Rodenas, I. P. Garrido-Bravo, F. Pastor-Perez, D.A. Pascual-Figal; **Oviedo**: B. Diaz Molina; **Sabadell (Barcelona)**: J. Orus, F. Epelde Gonzalo; **San Juan de Alicante**: V. Bertomeu, R. Valero, R. Martinez-Abellan, J.

Quiles, J.A. Rodrigez-Ortega, I. Mateo, A. ElAmrani; **Sevilla**: C. Fernandez-Vivancos; **Tortosa**: D. Bierge Valero; **Valencia**: L. Almenar-Bonet, I.J. Sanchez-Lazaro, E. Marques-Sule, L. Facila-Rubio, J. Perez-Silvestre, P. Garcia-Gonzalez, F. Ridocci-Soriano, D. Garcia-Escriva, A. Pellicer-Cabo; **Valladolid**: L. de la Fuente Galan, J. Lopez Diaz, A. Recio Platero; **Vigo**: J.C. Arias; **Zaragoza**: T. Blasco-Peiro, M. Sanz Julve, E. Sanchez-Insa, C. Aured-Guallar, A. Portoles-Ocampo; *SWEDEN* **Stockholm**: M. Melin, E. Hägglund; **Lindesberg**: A. Stenberg, I-M. Lindahl; **Varberg**: B. Asserlund, L. Olsson; **Linköping**: U. Dahlström, M. Afzelius; **Jönköping**: P. Karlström, L. Tengvall; **Kristianstad**: P-A.Wiklund, B. Olsson; *TURKEY* **Ankara**: S. Kalayci, A. Temizhan; **Eskisehir**: Y. Cavusoglu; **Kilis**: E. Gencer; **Sivas**: M.B. Yilmaz, H. Gunes

References

1. Nichols GA, Gullion CM, Koro CE, Ephross SA, Brown JB. The incidence of congestive heart failure in type 2 diabetes: an update. *Diabetes Care* 2004;27:1879–1884.
2. Dei Cas A, Khan SS, Butler J, Mentz RJ, Bonow RO, Avogaro A, Tschoepe D, Doehner W, Greene SJ, Senni M, Gheorghiade M, Fonarow GC. Impact of diabetes on epidemiology, treatment, and outcomes of patients with heart failure. *JACC Heart Fail* 2015;3:136–145.
3. Thomas MC. Type 2 diabetes and heart failure: challenges and solutions. *Curr Cardiol Rev* 2016;12:249–255.
4. Kannel WB, Hjortland M, Castelli WP. Role of diabetes in congestive heart failure: the Framingham study. *Am J Cardiol* 1974;34:29–34.
5. Gilbert RE, Krum H. Heart failure in diabetes: effects of anti-hyperglycaemic drug therapy. *Lancet* 2015;385:2107–2017.
6. Zannad F, Stough WG, Lipicky RJ, Tamargo J, Bakris GL, Borer JS, Alonso García ML, Hadjadj S, Koenig W, Kupfer S, McCullough PA, Mosenzon O, Pocock S, Scheen AJ, Sourij H, Van der Schueren B, Stahre C, White WB, Calvo G. Assessment of cardiovascular risk of new drugs for the treatment of diabetes mellitus: risk assessment vs. risk aversion. *Eur Heart J Cardiovasc Pharmacother* 2016;2:200–205.
7. Gustafsson I, Brendorp B, Seibaek M, Burchardt H, Hildebrandt P, Køber L, Torp-Pedersen C; Danish Investigations of Arrhythmia and Mortality on Dofetilde Study Group. Influence of diabetes and diabetes–gender interaction on the risk of death in patients hospitalized with congestive heart failure. *J Am Coll Cardiol* 2004;43:771–777.
8. MacDonald MR, Jhund PS, Petrie MC, Lewsey JD, Hawkins NM, Bhagra S, Munoz N, Varyani F, Redpath A, Chalmers J, MacIntyre K, McMurray JJ. 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* 2008;1:234–241.
9. Mebazaa A, Gayat E, Lassus J, Meas T, Mueller C, Maggioni A, Peacock F, Spinar J, Harjola VP, van Kimmenade R, Pathak A, Mueller T, Tavazzi L, Disomma S, Metra M, Pascual-Figal D, Laribi S, Logeart D, Nouira S, Sato N, Parenica J, Deye N, Boukef R, Collet C, Van den Berghe G, Cohen-Solal A, Januzzi JL Jr; GREAT Network. Association between elevated blood glucose and outcome in acute heart failure: results from an international observational cohort. *J Am Coll Cardiol* 2013;61:820–829.
10. Sarma S, Mentz RJ, Kwasny MJ, Fought AJ, Huffman M, Subacius H, Nodari S, Konstam M, Swedberg K, Maggioni AP Zannad F, Bonow RO, Gheorghiade M; 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* 2013;15:194–202.
11. Yancy CW, Lopatin M, Stevenson LW, De Marco T, Fonarow GC; ADHERE Scientific Advisory Committee and Investigators. Clinical presentation, management, and in-hospital outcomes of patients admitted with acute decompensated heart failure with preserved systolic function: a report from the Acute Decompensated Heart Failure National Registry (ADHERE) Database. *J Am Coll Cardiol* 2006;47:76–84.
12. Kosiborod M, Inzucchi SE, Spertus JA, Wang Y, Masoudi FA, Havranek EP, Krumholz HM. Elevated admission glucose and mortality in elderly patients hospitalized with heart failure. *Circulation* 2009;119:1899–1907.
13. Parissis JT, Ikonomidis I, Rafouli-Stergiou P, Mebazaa A, Delgado J, Farmakis D, Vilas-Boas F, Paraskevaidis I, Anastasiou-Nana M, Follath F. Clinical characteristics and predictors of in-hospital mortality in acute heart failure with preserved left ventricular ejection fraction. *Am J Cardiol* 2011;107:79–84.

14. Cleland JG, Chiswell K, Teerlink JR, Stevens S, Fiuzat M, Givertz MM, Davison BA, Mansoor GA, Ponikowski P, Voors AA, Cotter G, Metra M, Massie BM, O'Connor CM. 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* 2014;7:76–87.
15. Greenberg BH, Abraham WT, Albert NM, Chiswell K, Clare R, Stough WG, Gheorghiade M, O'Connor CM, Sun JL, Yancy CW, Young JB, Fonarow GC. 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* 2007;154:277.e1–e8.
16. Targher G, Dauriz M, Tavazzi L, Temporelli PL, Lucci D, Urso R, Lecchi G, Bellanti G, Merlo M, Rossi A, Maggioni AP; IN-HF Outcome Investigators. 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. *Int J Cardiol* 2016;203**:**587–593.
17. Maggioni AP, Anker SD, Dahlström U, Filippatos G, Ponikowski P, Zannad F, Amir O, Chioncel O, Leiro MC, Drozdz J, Erglis A, Fazlibegovic E, Fonseca C, Fruhwald F, Gatzov P, Goncalvesova E, Hassanein M, Hradec J, Kavoliuniene A, Lainscak M, Logeart D, Merkely B, Metra M, Persson H, Seferovic P, Temizhan A, Tousoulis D, Tavazzi L; Heart Failure Association of the ESC. Are hospitalized or ambulatory patients with heart failure treated in accordance with European Society of Cardiology guidelines? Evidence from 12,440 patients of the ESC Heart Failure Long-Term Registry. *Eur J Heart Fail* 2013;15:1173–1184.
18. Crespo-Leiro MG, Anker SD, Maggioni AP, Coats AJ, Filippatos G, Ruschitzka F, Ferrari R, Piepoli MF, Delgado Jimenez JF, Metra M, Fonseca C, Hradec J, Amir O, Logeart D, Dahlström U, Merkely B, Drozdz J, Goncalvesova E, Hassanein M, Chioncel O, Lainscak M, Seferovic PM, Tousoulis D, Kavoliuniene A, Fruhwald F, Fazlibegovic E, Temizhan A, Gatzov P, Erglis A, Laroche C, Mebazaa A; Heart Failure Association (HFA) of the European Society of Cardiology (ESC). European Society of Cardiology Heart Failure Long-Term Registry (ESC-HF-LT): 1-year follow-up outcomes and differences across regions. *Eur J Heart Fail* 2016;18:613–625.
19. American Diabetes Association. Classification and diagnosis of diabetes. *Diabetes Care* 2016;39(suppl 1):S13–S22.
20. Stevens LA, Coresh J, Greene T, Levey AS. Assessing kidney function—measured and estimated glomerular filtration rate. *N Engl J Med* 2006;354:2473–2483.
21. Novack V, Pencina M, Zahger D, Fuchs L, Nevzorov R, Jotkowitz A, Porath A. Routine laboratory results and thirty day and one-year mortality risk following hospitalization with acute decompensated heart failure. *PLoS One* 2010;5:e12184.
22. Sud M, Wang X, Austin PC, Lipscombe LL, Newton GE, Tu JV, Vasan RS, Lee DS. Presentation blood glucose and death, hospitalization, and future diabetes risk in patients with acute heart failure syndromes. *Eur Heart J* 2015;36:924–931.
23. Barsheshet A, Garty M, Grossman E, Sandach A, Lewis BS, Gottlieb S, Shotan A, Behar S, Caspi A, Schwartz R, Tenenbaum A, Leor J. Admission blood glucose level and mortality among hospitalized nondiabetic patients with heart failure. *Arch Intern Med* 2006;166:1613–1619.
24. Umpierrez GE, Isaacs SD, Bazargan N, You X, Thaler LM, Kitabchi AE. Hyperglycemia: an independent marker of in-hospital mortality in patients with undiagnosed diabetes. *J Clin Endocrinol Metab* 2002;87:978–982.
25. Dungan KM, Braithwaite SS, Preiser JC. Stress hyperglycaemia. *Lancet* 2009;373:1798–1807.
26. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, González-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2016;18:891–975.