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Association between diabetes and 1-year adverse clinical outcomes in a multinational cohort of ambulatory patients with chronic heart failure: results from the ESC-HFA Heart Failure Long-Term Registry

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Abstract
OBJECTIVE. Diabetes mellitus is associated with an increased risk of cardiovascular disease (CVD) and death. Because the prevalence of diabetes is rising worldwide and chronic heart failure (CHF) is becoming increasingly common with the aging population, it is timely to examine the impact of diabetes per se on 1-year adverse outcomes in patients with CHF.
RESEARCH DESIGN AND METHODS. We prospectively assessed whether diabetes status independently affected the 1-year risk of all-cause and CVD mortality and first hospitalization for worsening heart failure (HF) in a multinational cohort of 9,428 outpatients with CHF enrolled in the European Society of Cardiology and Heart Failure Association Long-Term Registry.
RESULTS. Compared with those patients without diabetes, patients with diabetes (n = 3,440, 36.5%) had higher cumulative rates of 1-year all-cause death (9.4% vs. 7.2%; adjusted hazard ratio [HR] 1.28; 95% CI 1.07–1.54), CVD death (4.8% vs. 3.8%; adjusted HR 1.28; 95% CI 0.99–1.66), and HF hospitalization (13.8% vs. 9.3%; adjusted HR 1.37; 95% CI 1.17–1.60), all independent of age, sex, BMI, smoking, systolic blood pressure, estimated glomerular filtration rate, hemoglobin, HF etiology, left ventricular ejection fraction, hypertension, statin use, and prior stroke or chronic obstructive pulmonary disease. Among CHF patients with HbA_{1c} measurements available at baseline (n = 2,567), there was a significant and independent association between increasing HbA_{1c} levels and the risk of 1-year survival outcomes.
CONCLUSIONS. The presence of diabetes markedly increases the risk of 1-year adverse clinical outcomes in outpatients with CHF independent of multiple common risk factors. More effective and personalized treatment for diabetes should be considered in this particularly high-risk patient population.

INTRODUCTION

The prevalence of type 2 diabetes has steadily increased in many parts of the world and is expected to continue increasing as obesity and other clinical risk factors for diabetes become more common (1–3). Overt diabetes and prediabetes states are often associated with an increased risk of cardiovascular disease (CVD) (4,5), which remains the leading cause of mortality worldwide, despite a striking reduction in age-adjusted CVD mortality rates over the last 30 years (6). This means that CVD mortality has been delayed but not solved.

Chronic heart failure (CHF) is a progressive, complex clinical syndrome of the elderly (7), and the prognostic impact of diabetes itself in patients with CHF may be clinically relevant as these two pathologic conditions often coexist and share common risk factors and comorbidities that lead to early death, including unhealthy lifestyles and multiple cardiometabolic disorders, such as hypertension, chronic kidney disease (CKD), dyslipidemia, and hypercoagulability (7). CHF itself also worsens systemic insulin resistance and may make diabetes more prevalent with a poorer quality of glycemic control. Currently, a large proportion of CVD hospital admissions comprise patients affected by a worsening of CHF, a disease often associated with type 2 diabetes and poor short- and long-term survival outcomes (7,8).

The relationship between type 2 diabetes and survival outcomes in the context of multimorbidity in patients with CHF (e.g., ischemic heart disease, hypertension, and CKD) has been known for more than a decade (7–10), but there are very few contemporary, comparative data on the midterm/long-term survival outcomes from large European cohorts of ambulatory patients with CHF. In addition, as will be discussed in detail below, the observational registries and randomized clinical trials that have explored the independent prognostic impact of diabetes on survival outcomes in patients with CHF have reported conflicting or inconclusive results, suggesting the need for further studies. Currently, there is continued debate on this topic and, therefore, it warrants in-depth investigation.

Thus, in the current study we sought to explore the prognostic impact of diabetes per se on the 1-year rates of all-cause death, CVD death, and first hospitalization for worsening heart failure (HF) among outpatients with CHF who are enrolled in the General Long-Term Registry of the EURObservational Research Programme (EORP) of the European Society of Cardiology (ESC) and the ESC-Heart Failure Association (HFA).

RESEARCH DESIGN AND METHODS

Study Design

The principles and procedures of the EORP of the ESC have previously been described (11,12). Briefly, the ESC-HFA Heart Failure Long-Term Registry is a prospective, multicenter, observational study of patients at 211 cardiology centers in 21 European and Mediterranean countries that 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 program 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 centers that would be reasonably representative of the European reality. The number of participating centers from each country was decided according to the number of inhabitants in that country (i.e., 1 center per 2 million people, but no more than 25 and no less than 6 per country). To the extent that it was possible, the centers were also chosen to fulfill geographical criteria within each country. In this way, the registry included a balanced proportion of centers with a range of cardiology facilities.

The EORP Department at the ESC European Heart House was appointed to coordinate the operations of the project; to provide support to the committees, national coordinators, and participating centers; 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.

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 signed informed consent had been obtained.

Patient Population

From May 2011 to April 2013, all outpatients with CHF who were observed at the clinics and those admitted to the hospital for acute HF were included in the registry during the enrollment period (on 1 day per week for 12 consecutive months) (11,12). There were no specific exclusion criteria, except for age ≤18 years. For the clinical diagnosis of HF, we applied the 2012 ESC-HF guidelines, as the registry was conducted in the European population (13). As specified above, the participating centers enrolled patients in the registry on a 1 day-per-week basis. Therefore, the following patients were entered in our registry: *1*) all outpatients with CHF (n = 9,428) diagnosed according to the clinical judgment of the responsible cardiologist at the participating centers; and *2*) all inpatients (n = 6,926) admitted to the hospital cardiology ward or intensive cardiac care unit for acute HF for whom an intravenous therapy (inotropes, vasodilators, or diuretics) was needed.

The 1-year follow-up data concerning the clinical outcomes of all inpatients hospitalized with HF have been published previously (12). In the current analysis, we present the 1-year follow-up data from the registry concerning the rates of all-cause death, CVD death (i.e., due either to cardiac or vascular reasons) and first hospitalization for worsening HF of outpatients with CHF (n = 9,428). No detailed information on specific causes of non-CVD mortality was available in the registry.

The Diagnosis of Diabetes and Other Clinical and Laboratory Data

Previously known diabetes was defined as self-reported physician-diagnosed diabetes, or use of hypoglycemic medications (insulin or oral 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 hemoglobin A_{1c} (HbA_{1c}) level ≥6.5% (≥48 mmol/mol), respectively. We were unable to distinguish between type 1 and type 2 diabetes, although the vast majority of our patients with diabetes were likely to have type 2 diabetes.

BMI was calculated by dividing patients' weight in kilograms by their height in meters squared. Blood pressure was measured with a mercury sphygmomanometer at the right upper arm using an appropriate cuff size after the patient had been seated quietly for at least 5 min. The presence of hypertension was defined as blood pressure values ≥140/90 mmHg or a self-reported history of physician-diagnosed hypertension. Venous blood samples were drawn in the morning after an overnight fast. Serum creatinine, glucose, and HbA_{1c} measurements (which were available in 2,567 patients: 1,603 with diabetes and 964 without diabetes) and other biochemical blood measurements were determined using standard laboratory procedures. The estimated glomerular filtration rate (eGFR) was estimated by the four-variable Modification of Diet in Renal Disease (MDRD) study equation (14). The presence of CKD was defined as an $eGFR_{MDRD}$ value of <60 mL/min/1.73 m^2 (14); measurements of albuminuria or proteinuria were not available. Conventional transthoracic echocardiography was used to measure the left ventricular (LV) diameter, LV wall thickness, and LV ejection fraction (LVEF) according to international standard criteria.

Statistical Analysis

The statistical analyses were performed at the ESC European Heart House. Univariate analysis was applied to both continuous and categorical variables. Categorical variables were reported and compared using the χ^2 test or the Fisher 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 the mean ± SD or as the median (interquartile range). Among-group comparisons were made using a nonparametric test (the Kruskal-Wallis test). A multivariable Cox regression analysis (Table 2), adjusted for age, sex, systolic blood pressure, $eGFR_{MDRD}$, hemoglobin, BMI, smoking, hypertension status, LVEF, HF etiology, statin use, and history of stroke and chronic obstructive pulmonary disease (COPD), was applied to estimate the 1-year risk associated with diabetes status in terms of 1-year all-cause death, CVD death, and first hospitalization for worsening HF. Interaction terms were also generated between diabetes status and sex for each clinical outcome. Because the diabetes × sex interaction term (P > 0.40) was not statistically significant, a sex-pooled multivariable regression analysis was used to assess the independence of the association between diabetes status and each clinical outcome. The covariates included in these forced-entry Cox multivariable regression models were selected as potential confounding factors on the basis of their significance in univariate regression analyses or on the basis of their biological plausibility. We also examined the association between increasing HbA_{1c} levels at baseline and the risk of 1-year clinical outcomes. For each outcome, a restricted cubic-spline Cox regression plot has been realized without adjustment and with adjustment for age, sex, systolic blood pressure, $eGFR_{MDRD}$, HF etiology, LVEF, and hemoglobin values. A two-sided P value <0.05 was considered statistically significant. All analyses were performed with SAS statistical software version 9.4 (SAS Institute, Inc., Cary, NC).

RESULTS

As shown in Table 1, the study cohort included 9,428 (71.5% male) outpatients with CHF, largely composed of overweight or obese individuals of Caucasian ancestry (~95%). The prevalence of diabetes in the study cohort was high (*n* = 3,440; 36.5%); 80.9% (*n* = 2,782) of these patients had previously known diabetes (i.e., self-reported history or use of hypoglycemic drugs), whereas the remaining 658 patients (19.1%) had previously undiagnosed diabetes. Among those patients with previously undiagnosed diabetes, 187 had a fasting glucose level ≥200 mg/dL, whereas the remaining 471 patients had a fasting glucose level between 126 and 199 mg/dL and/or an HbA_{1c} level ≥6.5% (≥48 mmol/mol).

Table 1 Baseline demographic, clinical, and biochemical characteristics of outpatients with CHF, enrolled in the ESC-HFA Heart Failure Long-Term Registry, stratified by diabetes status

	N/N	Patients with diabetes (*n* = 3,440)	Patients without diabetes (*n* = 5,988)	*P* value
Male sex (%)	3,440/5,988	74.7	69.7	<0.001
Age (years)	3,440/5,988	67.1 ± 10.9	63.7 ± 14.4	<0.001
Caucasian ethnicity (%)	3,300/5,654	95.3	94.3	0.033
BMI (kg/m^2)	3,349/5,755	29.5 ± 5.3	27.3 ± 4.9	<0.001
BMI ≥30 kg/m^2 (%)	3,349/5,755	41.8	25.0	<0.001
Systolic blood pressure (mmHg)	3,439/5,968	126.5 ± 21.4	123.2 ± 20.6	<0.001
Diastolic blood pressure (mmHg)	3,433/5,988	73.7 ± 12.2	73.9 ± 12.2	0.572
Total cholesterol (mg/dL)	2,347/3,611	161.5 ± 78.5	173.1 ± 44.3	<0.001
Heart rate (bpm)	3,163/5,381	74.3 ± 15.9	72.7 ± 16.4	<0.001
Diabetes medications (%)	3,368/5,770	71.8	0.0	<0.001
Insulin		44.6		
Oral hypoglycemic drugs only		55.4		
Plasma glucose (mg/dL)	2,645/3,933	143.3 ± 60.4	94.4 ± 12.8	<0.001
HbA_{1c} (%)	1,603/964	7.3 ± 1.5	5.7 ± 0.4	<0.001
HbA_{1c} (mmol/mol)	1,603/964	56.1 ± 16	38.6 ± 5	<0.001
Hypertension (%)	3,390/5,808	75.5	58.1	<0.001
Current smoking (%)	3,440/5,988	9.2	12.5	<0.001
Lipid-lowering medications (%)	3,369/5,782	69.3	50.2	<0.001
Cardiovascular medications (%)	3,312/5,655			
ACE inhibitors or ARBs		87.6	85.6	0.009
β-Blockers		86.0	85.7	0.698
Aldosterone antagonists		54.1	54.0	0.901
Diuretics		87.0	77.6	<0.001
Digitalis		24.0	20.4	<0.001
Calcium channel blockers		14.4	9.9	<0.001
Antiplatelets or anticoagulants		85.8	74.8	<0.001
Nitrates		23.6	15.5	<0.001
Amiodarone		14.1	13.8	0.708
Creatinine (mg/dL)	3,202/5,335	1.2 (0.9–1.5)	1.1 (0.9–1.3)	<0.001
$eGFR_{MDRD}$ (mL/min/1.73 m^2)	3,202/5,335	58.3 (42.1–75.7)	66.3 (50.6–82.7)	<0.001
$eGFR_{MDRD}$ <60 mL/min/1.73 m^2 (%)	3,202/5,335	52.4	39.5	<0.001
Hemoglobin (g/dL)	2,976/4,906	13.1 ± 1.8	13.5 ± 1.9	<0.001
NT-proBNP (pg/dL)	1,194/1,970	1,324 (546–3,470)	1,240 (467–3,373)	0.131
LVEF (%)	2,969/5,099	37.1 ± 13.1	37.9 ± 13.7	0.010
LVEF >45% (%)	2,969/5,099	22.6	24.7	0.040
NYHA functional class (%)	3,433/5,970			<0.001

Table 1 Baseline demographic, clinical, and biochemical characteristics of outpatients with CHF, enrolled in the ESC-HFA Heart Failure Long-Term Registry, stratified by diabetes status

	N/N	Patients with diabetes (*n* = 3,440)	Patients without diabetes (*n* = 5,988)	*P* value
Class I		13.5	19.4	
Class I		57.6	56.1	
Class III		26.3	22.8	
Class IV		2.6	1.7	
HF etiology (%)	3,430/5,942			<0.001
Ischemic		53.4	36.8	
Dilatative		23.8	32.3	
Hypertensive		8.5	8.1	
Other		14.3	22.7	
Atrial fibrillation (%)	3,440/5,987	39.2	36.5	0.009
Implantable cardioverter defibrillator (%)	3,429/5,970	16.4	15.3	0.127
COPD (%)	3,435/5,974	16.6	12.6	<0.001
Previous stroke (%)	3,436/5,983	10.8	8.5	<0.001

Data are presented as the mean ± SD or median (interquartile range), unless otherwise indicated. ARB, angiotensin receptor blocker; *N*/*N*, number of patients with and without diabetes who had measurements available for each single variable at the study entry; NT-proBNP, N-terminal of the prohormone brain natriuretic peptide.

As also shown in Table 1, compared with those patients without diabetes, those with known or previously undiagnosed diabetes were older and were more likely to be obese, have hypertension, and be treated with antihypertensive drugs (i.e., angiotensin-converting enzyme inhibitors, angiotension receptor blockers, diuretic agents, or calcium channel blockers) or "cardiovascular" medications (i.e., digitalis, nitrates, antiplatelet drugs, or anticoagulant agents). Additionally, they were less often smokers and had a more severe New York Heart Association (NYHA) functional class, lower values of $eGFR_{MDRD}$ and hemoglobin, and a higher prevalence of ischemic HF etiology, atrial fibrillation, and a history of stroke or COPD. Notably, no significant differences were found in circulating levels of N-terminal of prohormone brain natriuretic peptide, which were measured in 3,164 patients; the presence of implantable cardioverter defibrillators; and current use of β-blockers or aldosterone antagonists between the two groups of patients.

Over the 1-year follow-up period, there were a total of 757 deaths (8.0%), 394 of them due to CVD causes, and 1,030 (10.9%) first hospitalizations for worsening HF.

As shown in Fig. 1, patients with diabetes had substantially higher cumulative incidence rates of 1-year all-cause death (9.4% vs. 7.2%), CVD death (4.8% vs. 3.8%), and first hospitalization for worsening HF (13.8% vs. 9.3%) compared with their counterparts without diabetes (P = 0.017 to <0.001 for differences between the groups).

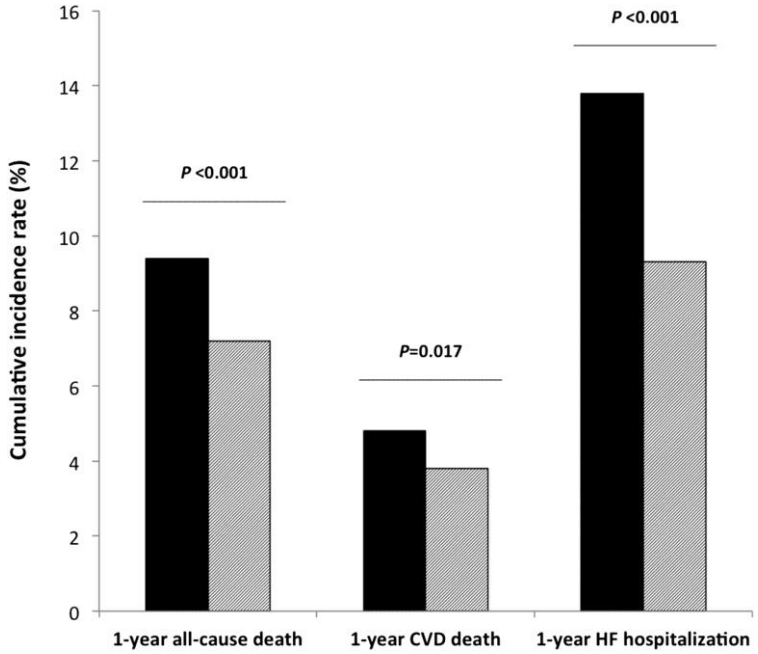

Figure 1 One-year cumulative incidence rates of adverse clinical outcomes in 9,428 outpatients with CHF stratified by diabetes status at baseline. The figure shows the 1-year rates of all-cause death, CVD death, and first hospitalization for worsening HF in 3,440 CHF outpatients with diabetes (black bars) and 5,988 CHF outpatients without diabetes (dashed bars) who were enrolled in the ESC-HFA Heart Failure Long-Term Registry.

Table 2 shows the results after adjusting for multiple risk factors regarding the association between diabetes status and the risk of 1-year clinical outcomes. Patients with diabetes had an ~30% increased risk of all-cause death (adjusted hazard ratio [HR] 1.28; 95% CI 1.07–1.54) and CVD death (adjusted HR 1.28; 95% CI 0.99–1.66), and an even higher risk of first hospitalization for worsening HF (adjusted HR 1.37; 95% CI 1.17–1.60) compared with patients without diabetes. Notably, the 1-year risk associated with diabetes comorbid with CHF for each of these clinical outcomes was essentially on the same order as that of having a history of stroke or COPD. Other variables that were independently associated with poorer clinical outcomes were older age, lower systolic blood pressure, lower $eGFR_{MDRD}$, lower hemoglobin level, lower LVEF, not receiving statins, and prior stroke or COPD. Almost identical results were found even when $eGFR_{MDRD}$ was replaced by eGFR estimated by the CKD Epidemiology Collaboration equation or when hypertension status was removed from the list of covariates (data not shown).

Table 2 Multivariable Cox regression analysis of 1-year adverse clinical outcomes in the cohort of outpatients with CHF

Variables	All-cause death		CVD death		HF hospitalization	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Diabetes status (yes vs. no)	1.28 (1.07–1.54)	0.008	1.28 (0.99–1.66]	0.060	1.37 (1.17–1.60)	<0.001
Age (years)	1.03 (1.02–1.03)	<0.001	1.03 (1.02–1.04)	<0.001	1.01 (1.00–1.02)	0.006
Sex (male vs. female)	1.41 (1.14–1.75)	0.002	1.32 (0.98–1.78)	0.065	1.18 (0.99–1.41)	0.073
Systolic blood pressure (mmHg)	0.99 (0.98–0.99)	<0.001	0.98 (0.97–0.98)	<0.001	0.99 (0.98–0.99)	<0.001
$eGFR_{MDRD}$ (mL/min/1.73 m^2)	0.99 (0.98–0.99)	<0.001	0.98 (0.98–0.99)	<0.001	0.99 (0.98–0.99)	<0.001
LVEF (%)	0.99 (0.98–0.99)	<0.001	0.99 (0.98–1.00)	0.002	0.98 (0.97–0.99)	<0.001
HF etiology (ischemic vs. nonischemic)	1.20 (0.99–1.46)	0.063	1.21 (0.92–1.58)	0.177	0.83 (0.71–0.98)	0.026
BMI (kg/m^2)	0.98 (0.96–1.00)	0.037	0.96 (0.94–0.99)	0.010	1.00 (0.99–1.02)	0.395
Smoking (yes vs. no)	0.90 (0.67–1.21)	0.470	0.95 (0.64–1.42)	0.816	1.00 (0.79–1.28)	0.989
Hypertension (yes vs. no)	1.06 (0.86–1.30)	0.585	1.03 (0.79–1.36)	0.809	1.21 (1.01–1.44)	0.036
Statin use (yes vs. no)	0.77 (0.63–0.93)	0.007	0.69 (0.52–0.90)	0.006	1.00 (0.85–1.18)	0.958
Previous stroke (yes vs. no)	1.36 (1.06–1.76)	0.016	1.46 (1.03–2.06)	0.033	1.42 (1.15–1.76)	0.001
Previous COPD (yes vs. no)	1.37 (1.10–1.71)	0.005	1.42 (1.05–1.94)	0.024	1.42 (1.18–1.71)	<0.001
Hemoglobin (g/dL)	0.81 (0.77–0.85)	<0.001	0.82 (0.77–0.87)	<0.001	0.89 (0.85–0.93)	<0.001

Cohort sizes: n = 6,463 for regression models with 1-year all-cause or CVD mortality as outcome; n = 6,446 for regression model with 1-year HF hospitalization as outcome. The values of HRs and 95% CIs were rounded to the second decimal place.

Figure 2 shows a restricted cubic-spline Cox regression plot of the unadjusted and adjusted associations between increasing HbA_{1c} levels (i.e., the reference category used in the Fig. 2 was an HbA_{1c} level of 6.5% [48 mmol/mol]) and the risk of all-cause death, CVD death, and first hospitalization for worsening HF among the 2,567 CHF patients with HbA_{1c} measurements at baseline. We found a significant association of increasing HbA_{1c} levels with the risk of 1-year survival outcomes, but not with HF hospitalization, after adjustment for age, sex, systolic blood pressure, $eGFR_{MDRD}$, LVEF, HF etiology, and hemoglobin values. These results should be interpreted with some caution, given that baseline HbA_{1c} measurements were available only in a subgroup of CHF patients. However, we believe that this subgroup of 2,567 patients was sufficiently representative of the whole cohort of patients, given that the main clinical variables (also including LVEF and HF etiology), and especially the rates of 1-year clinical outcomes, were essentially comparable between patients with and without HbA_{1c} measurements available at baseline, irrespective of pre-existing diabetes (Supplementary Tables 1 and 2).

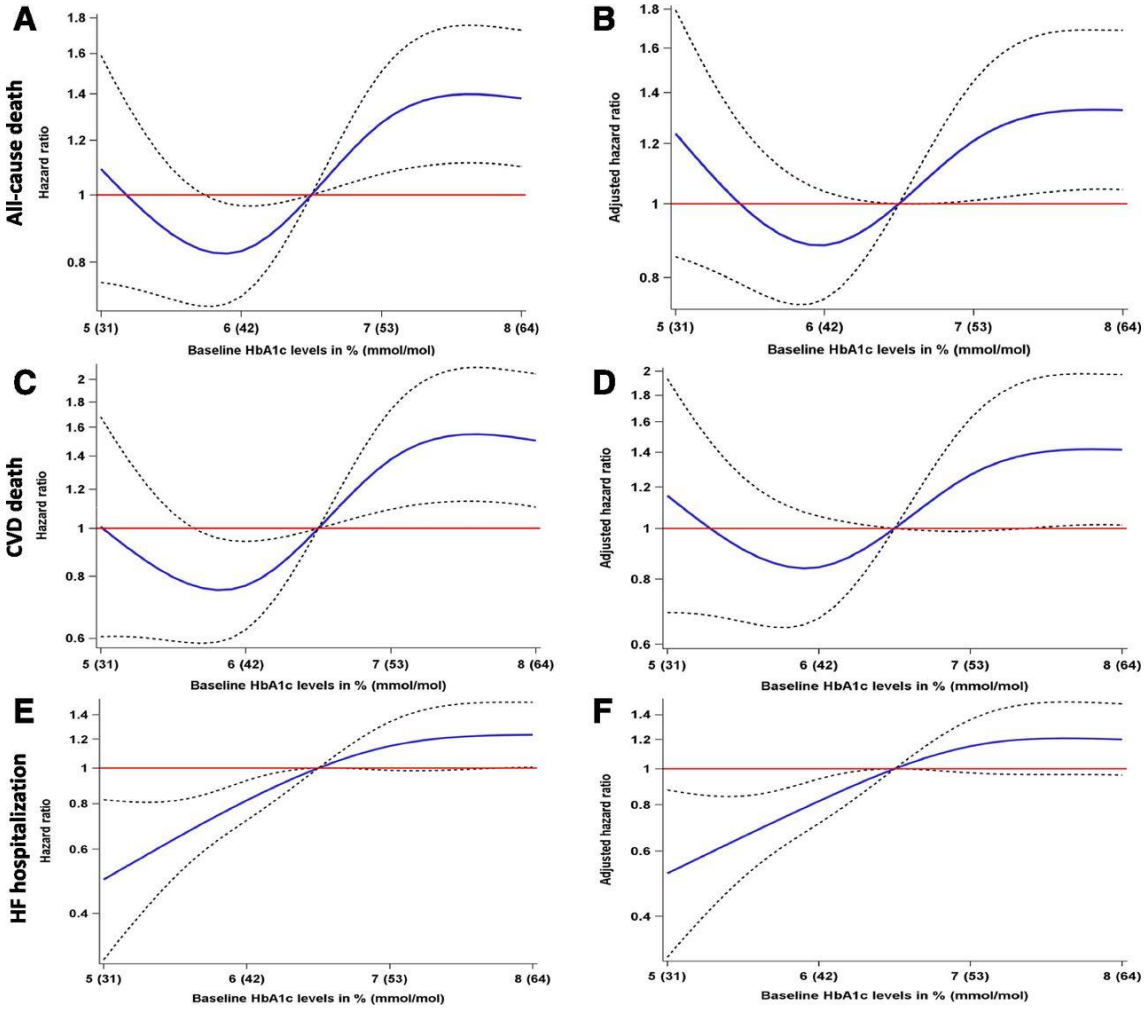

Figure 2. Unadjusted and adjusted HRs (±95% CIs, presented with dotted lines) of 1-year all-cause death (panel *A* [unadjusted HR] and panel *B* [adjusted HR]), CVD death (panel *C* [unadjusted HR] and panel *D* [adjusted HR]), and first hospitalization for worsening HF (panel *E* [unadjusted HR] and panel *F* [adjusted HR]) according to increasing HbA_{1c} levels in a subgroup of 2,567 CHF patients with HbA_{1c} measurements available at baseline. The reference category used in the figure was an HbA_{1c} level of 6.5% (or 48 mmol/mol; on the *x*-axis, the HbA_{1c} values were dually reported as percentage and mmol/mol). Data are adjusted for age, sex, systolic blood pressure, $eGFR_{MDRD}$, LVEF, HF etiology, and hemoglobin values.

Finally, we also performed a series of sensitivity analyses (subgroup analyses) to assess the robustness of our observations. Supplementary Table 3 shows the unadjusted and adjusted associations between patients with preserved LVEF versus those with reduced LVEF at baseline and the risk of 1-year clinical outcomes stratified by diabetes status. Supplementary Table 4 shows the unadjusted and adjusted associations between those patients with ischemic HF versus those with nonischemic HF etiology and the risk of 1-year clinical outcomes stratified by diabetes status. Notably, in both of these sensitivity analyses, the rates per 100 patient-years of each clinical outcome were almost always higher in patients with diabetes than in those without diabetes, irrespective of HF etiology or LVEF at baseline. Both in patients with and without diabetes, there was a significant adjusted association between the presence of baseline LVEF ≤45% and increased risk of 1-year survival outcomes (CVD death for patients with diabetes and all-cause death for those without diabetes, respectively) and 1-year HF hospitalization. In contrast, no significant associations were found between those patients with ischemic versus nonischemic HF at the study entry and the risk of 1-year survival outcomes or HF hospitalization after adjusting for potential

confounders. Finally, as shown in Supplementary Table 5, there were no significant adjusted associations between diabetes treatment at baseline and the risk of 1-year clinical outcomes in the subgroup of patients with diabetes. However, these results should be interpreted with (some) caution, given the lack of any detailed information about the different classes of oral hypoglycemic agents.

CONCLUSIONS

In this prospective, observational registry of a large unselected European population of consecutive outpatients with CHF (*n* = 9,428), we observed the following: *1*) known or previously undiagnosed diabetes was highly prevalent among ambulatory patients with CHF (occurring in up to 37% of these patients); *2*) CHF patients with known or previously undiagnosed diabetes had substantially higher 1-year rates of all-cause death, CVD death, and first hospitalization for worsening HF than those without diabetes; *3*) the association between diabetes and 1-year clinical outcomes remained statistically significant even after adjustment for multiple established risk factors and potential confounding variables (including also hypertension, $eGFR_{MDRD,}$ hemoglobin, HF etiology, and LVEF); and *4*) there was a significant and independent association between increasing HbA_{1c} levels and elevated risk of 1-year survival outcomes in the subset of 2,567 CHF patients with available HbA_{1c} measurements at baseline.

Our findings provide a contemporary picture of midterm (1-year) adverse clinical outcomes of a large European cohort of CHF outpatients with and without diabetes, outside the context of randomized clinical trials. Additionally, our findings also shed light on the previously reported discrepant results (as discussed below) regarding the independent prognostic impact of diabetes on 1-year clinical outcomes among outpatients with CHF. To date, despite the extremely high prevalence of diabetes among patients with acute or chronic HF (ranging from 30% to 50%) (10), the association between diabetes and HF often remains under-recognized by clinicians, and there are inconclusive or conflicting results regarding the independent prognostic impact of diabetes on the risk of mortality and hospitalization, both in the short term and in the midterm, among ambulatory patients with CHF.

Collectively, our data confirm and expand previous findings from observational registries and randomized clinical trials of patients with CHF supporting the existence of a significant and independent association between diabetes status and risk of adverse clinical outcomes (15–19). For instance, the Candesartan in Heart Failure: Assessment of Reduction in Mortality and morbidity (CHARM) trial, involving 7,599 patients with symptomatic CHF observed for a median period of ~3 years, reported that pre-existing diabetes was a powerful predictor of all-cause death and of a composite of cardiovascular death or HF hospitalization (15). A prospective analysis of the Norwegian Heart Failure Registry, involving ~4,000 patients with CHF (mean follow-up time of 13 months), also highlighted the independent prognostic role of diabetes in the risk of all-cause mortality (16). Similar results were also found in the Gruppo Italiano per lo Studio della Sopravvivenza nella Insufficienza Cardiaca (GISSI-HF) trial (mean follow-up time of 3.9 years) (17). A recent post hoc analysis of the Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial found that the presence of diabetes was independently associated with an increased risk of the composite of cardiovascular death or HF hospitalization in 8,399 CHF patients with LVEF <35%, who were randomly assigned to receive sacubitril/valsartan treatment or enalapril and followed up for 3 years (18). Finally, in the Swedish Heart Failure Registry, involving 35,163 patients with HF, diabetes status independently predicted mortality risk, regardless of the coexistence of ischemic heart disease (19).

However, our findings also contrast with those from other previously published large clinical trials, including the Studies Of Left Ventricular Dysfunction (SOLVD) Prevention and Treatment trial, the Digitalis Investigation Group (DIG) trial, and the Beta-Blocker Evaluation of Survival trial (BEST) (20–22), which have suggested that the prognostic impact of diabetes per se on survival outcomes, if any, might be confined only to patients with ischemic HF. Moreover, Kosiborod et al. (23) did not find any significant relationship between the presence of pre-existing diabetes (or elevated blood glucose levels at hospital admission) and the risk of 30-day or 1-year mortality in a nationally representative sample of

U.S. elderly patients hospitalized with HF. Finally, in the Surgical Treatment for Ischemic Heart Failure (STICH) trial the presence of diabetes was not independently associated with the 5-year risk of all-cause and CVD death in a sample of 1,212 patients with ischemic HF (24).

More recently, the MAGGIC (Meta-analysis Global Group in Chronic Heart Failure) meta-analysis (25), which included individual data on nearly 40,000 HF patients with preserved or reduced LVEF at baseline from 30 cohort studies (6 of which were clinical trials) has reported that pre-existing diabetes independently predicted the risk of all-cause death during a median follow-up period of 2.5 years. In this meta-analysis, other independent predictors of mortality were older age, lower LVEF, higher NYHA functional class, higher serum creatinine level, lower systolic blood pressure, lower BMI, history of COPD, and not being prescribed β-blockers, ACE inhibitors, or angiotensin receptor blockers (25).

Similar to the results of the CHARM trial (26) and the PARADIGM-HF trial (18), our findings also show that there was a significant relationship between increasing HbA_{1c} levels and the risk of 1-year survival outcomes (but not 1-year HF hospitalizations) in the subset of CHF patients with and without diabetes with HbA_{1c} measurement available at baseline.

The major strengths of our study are intrinsic to the design of the ESC-HFA Heart Failure Long-Term Registry which is one of the largest, multinational and nationally representative systematic collections of contemporary European patients with acute and chronic 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 1-year survival rates in a large unselected cohort of CHF outpatients followed by cardiologists, thus providing a picture of European patients who were not included in randomized clinical trials but were currently being treated in general cardiology clinical practice. In addition, our registry also provides clear evidence of the independent prognostic impact of diabetes on risk of 1-year survival outcomes, independent of coexisting clinical risk factors. 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.

However, some important limitations of our registry should also be mentioned, as follows: *1*) despite the methodological desirability of consecutive enrollment, consecutive enrollment cannot be fully proven to have occurred in our cohort of CHF outpatients, although local audits were performed to verify the quality of data and the consecutiveness of enrollment; *2*) the identification of diabetes subtypes was not feasible, although patients with diabetes subtypes other than type 2 probably represented a minimal proportion of our patients; *3*) all clinical outcomes were physician reported but were not adjudicated by a blinded end point committee; and *4*) information about the duration of diabetes, the use of different classes of oral hypoglycemic agents, and the extracardiac causes of mortality as well as follow-up data on HbA_{1c} measurements were not available.

In conclusion, our contemporary results from the ESC-HFA Heart Failure Long-Term Registry show that the presence of known or previously undiagnosed diabetes is associated with a substantially increased risk of 1-year all-cause death, CVD death, and first hospitalization for worsening HF in a large cohort of outpatients with CHF. Notably, this association remains statistically significant even after adjusting for established risk factors and potential confounding variables. These findings are relevant to cardiologists/practicing physicians in routine clinical practice because the early identification of an ambulatory patient with CHF and diabetes might translate into a patient-tailored, team-based clinical approach, including the timely recognition of multimorbidity, earlier referral to the clinical diabetologists, and implementation of closer follow-up schedules. In the context of the prospective global estimates for a longer life expectancy, and in an era in which there is increasing emphasis on long-term disease management to contain health care costs, these findings further highlight the prognostic value of diabetes comorbid with CHF and the need for further therapies that can improve survival outcomes in this particularly high-risk patient population.

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