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Changes over time in the association between type 2 diabetes and post-discharge outcomes in decompensated chronic heart failure patients: Findings from the RICA Registry*

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KEYWORDS
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Abstract
Aims: Heart failure (HF) and diabetes are 2 strongly associated diseases. The main objective of this work was to analyze changes in the prognosis of patients with diabetes who were admitted for heart failure in 2 time periods.
Methods: This work is a prospective study comparing prognosis at one year of follow-up among patients with diabetes who were hospitalized for HF in either 2008–2011 or 2018. The patients are from the Spanish Society of Internal Medicine's National Heart Failure Registry (RICA, for its initials in Spanish). The primary endpoint was to analyze the composite outcome of total mortality and/or readmission due to HF in 12 months. A multivariate Cox regression model was used to evaluate the strength of association (hazard ratio [HR]) between diabetes and the outcomes between both periods.

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[1] The names of the components of the RICA Registry are listed in Appendix A.

Results: A total of 936 patients were included in the 2018 cohort, of which 446 (48%) had diabetes. The baseline characteristics of the populations from the 2 periods were similar. In patients with diabetes, the composite outcome was observed in 233 (47.5%) in the 2008–2011 cohort and 162 (36%) in the 2018 cohort [HR 1.48; 95% confidence interval (95%CI) 1.18–1.85; $p < .001$]. The proportion of readmissions (HR 1.39; 95%CI 1.07–1.80; $p = .015$) and total mortality (HR 1.60; 95%CI 1.20–2.14; $p < .001$) were also significantly higher in patients with diabetes from the 2008-2011 cohort compared to the 2018 cohort.
Conclusions: In 2018, an improvement was observed in the prognosis for all-cause mortality and readmissions over one year of follow-up in patients with diabetes hospitalized for HF compared to the 2008–2011 period.

PALABRAS CLAVE
Diabetes mellitus;
Insuficiencia cardíaca;
Mortalidad;
Hospitalización;
Reingresos;
Pronóstico

Evolución de la asociación de diabetes y eventos posalta en pacientes con insuficiencia cardíaca crónica descompensada: hallazgos del registro RICA

Resumen
Objetivos: La insuficiencia cardíaca (IC) y la diabetes son 2 procesos fuertemente asociados. El objetivo principal fue analizar la evolución del pronóstico de los pacientes con diabetes que ingresan por IC a lo largo de 2 períodos.
Métodos: Estudio prospectivo para comparar el pronóstico a un año de seguimiento entre los pacientes con diabetes que ingresan por IC en 2008–2011 y 2018. Los pacientes proceden del Registro Nacional de Insuficiencia Cardíaca (RICA) de la Sociedad Española de Medicina Interna. El objetivo primario fue analizar el desenlace combinado de mortalidad total o ingreso por IC durante 12 meses. Se utilizó una regresión multivariante de Cox para evaluar la fuerza de asociación (hazard ratio [HR]) de la diabetes y los desenlaces entre ambos períodos.
Resultados: Se incluyó a un total de 936 pacientes en la cohorte de 2018, de los que 446 (48%) tenían diabetes. Las características basales de la población de los 2 períodos fueron similares. En los pacientes con diabetes se observó el desenlace combinado en 233 (47,5%) en la cohorte de 2008—2011 y 162 (36%) en la cohorte de 2018 (HR 1,48; intervalo de confianza del 95% [IC95%] 1,18–1,85; p < 0,001). La proporción de ingresos (HR 1,39; IC95% 1,07–1,80; p = 0,015) y la mortalidad total (HR 1,60; IC95% 1,20–2,14; p < 0,001) también fueron significativamente mayores en los pacientes con diabetes de la cohorte de 2008–2011 con respecto a la del 2018.
Conclusiones: En 2018 se observa una mejoría del pronóstico de la mortalidad total y los reingresos durante un año de seguimiento en pacientes con diabetes hospitalizados por IC con respecto al período de 2008–2011.

Introduction

The prevalence of heart failure (HF) and type 2 diabetes mellitus (DM2) has increased in the past decade and continues to do so[1]. The presence of DM2 in patients with HF is rising, especially among elderly patients, and is considered one of the main health problems society must face[2]. DM2 is an independent factor for developing HF[3] and, in turn, is associated with a worse prognosis in patients with established HF[4,5].

Diabetes is associated with longer hospital stays and higher readmission rates[6,7]. In addition, diabetes entails higher cardiovascular morbidity and mortality in patients with HF[8]. However, the prognostic value of diabetes for in-hospital and long-term mortality among patients with HF remains controversial[9,10].

In recent years, new drugs have become available that have improved the prognosis of patients with HF with reduced ejection fraction (EF) in addition to new glucose-lowering drugs with cardiovascular and HF benefits. Despite these advances, the long-term prognosis of patients with HF and diabetes continues to be worse compared to their peers without diabetes. Nevertheless, it seems the prognosis is progressively improving in both groups[11].

Data from Spanish centers reveal the close relationship between diabetes and hospitalizations due to HF in recent years. Although total mortality or readmissions for HF have increased in patients with DM2[4], in-hospital mortality appears to have declined[12].

The aims of this study were to evaluate to what extent DM2 continues to influence the prognosis of patients hospitalized due to HF in 2018 and compare it to the results

obtained in a previous study (2008–2011), analyzing how this association has changed in the past decade.

Materials and methods

Design and data source

This work is a prospective cohort study based on patients in the National Heart Failure Registry (RICA, for its initials in Spanish), which belongs to the Heart Failure and Atrial Fibrillation Working Group of the Spanish Society of Internal Medicine (SEMI, for its initials in Spanish). It is a multicenter, prospective registry that has been active since 2008. It includes unique consecutive patients >50 years of age with a HF diagnosis upon hospital discharge following an episode of decompensation or new onset HF, according to current European cardiology guidelines[13].

The registry protocol was initially approved by the Reina Sofía University Hospital Ethics Committee, in Córdoba, Spain. The data are gathered via a website (www.registrorica.org) that contains an anonymized database each researcher can access using a personal user name and password. As it is an observational cohort study, the STROBE guidelines for this method were followed.

Study population

All patients included in the registry in 2018 were studied. Patients were included in the diabetes group when there was a previous diagnosis, if they took glucose-lowering drugs, as well as those who were not recorded in the diabetes group but who had a glycosylated hemoglobin (HbA1c) level $\geq$6.5%. Patients with primary pulmonary hypertension, type 1 diabetes mellitus, an indication for heart surgery, those for whom outpatient follow-up was not possible, and those who did not consent to participate were excluded from this study's analysis.

All patients were followed-up on at 12 months as well as every time it was necessary according to clinical criteria.

Study variables

Demographic variables, comorbidities (hypertension, dyslipidemia, chronic kidney disease, peripheral artery disease, stroke, dementia, chronic obstructive pulmonary disease, coronary disease, anemia, and atrial fibrillation), clinical data, and prescriptions upon hospital discharge were evaluated.

Hypertension was defined as presence of a prior diagnosis, active treatment with hypotensive drugs, or patients who repeatedly presented with systolic blood pressure measurements >140 mmHg or diastolic blood pressure measurements >90 mmHg. Anemia was considered to be hemoglobin <12 g/dL in women or <13 g/dL in men. Patients with preserved and reduced EF were included.

The laboratory variables were measured in a fasting sample in the first 24 h of hospitalization. The usual measurements were taken: creatinine, urea, glomerular filtration rate (GFR) according to the MDRD (Modification of Diet in Renal Disease) equation, hemoglobin, lipids, glucose, sodium, and N-terminal pro b-type natriuretic peptide (NT-proBNP). Hyponatremia was defined as sodium <135 mEq/L.

The primary dependent (outcome) variable was the combination of total mortality or readmission due to HF during the 12-month follow-up period. Treatment decisions were made according to the investigator's judgment.

Data analysis

Continuous quantitative variables are shown as mean (standard deviation) and discrete and nominal categorical variables are shown as number (%).

The categorical variables were compared using the chi-square test. To evaluate if a continuous variable followed a normal distribution, the Kolmogorov–Smirnov test was used and to compare means, Student's t test was used.

A multivariate stepwise Cox regression was performed to evaluate the strength of an association, or hazard ratio (HR), of diabetes to total mortality or readmissions. All variables with $p < .1$ were included in the model. The relationship between antidiabetic treatment upon discharge and the dependent variable was evaluated using the chi-square test.

For the analysis of patients with type 2 diabetes, baseline characteristics and events are shown, using the corresponding tests depending on the type of variable in order to compare them. Likewise, the independent relationship to total mortality or readmissions in the current cohort with respect to the initial cohort was evaluated by means of a Kaplan–Meier survival curve (log-rank). Lastly, a multivariate stepwise Cox regression evaluated the variables which independently influenced mortality/readmissions between the two periods.

All statistical analyses were conducted using SPSS 26.0 (SPSS, version 26.0, IBM, Chicago, IL). Statistical significance was established as $p < .05$.

Results

Results from the 2018 cohort

A total of 936 patients were included in the 2018 cohort, of which 446 (48%) had diabetes. The baseline characteristics of patients with diabetes compared to patients without diabetes are summarized in Table 1. The patients with diabetes were younger, but had a greater number of comorbidities. Regarding HF treatment, the proportion of patients treated with beta-blockers and antialdosterones was higher among patients with diabetes.

A total of 309 (33%) patients developed the combined event of all-cause death or hospital readmission due to HF. The differences between patients with and without diabetes did not reach statistical significance: 162 (36%) of patients with diabetes versus 147 (30%) patients without diabetes, $p = .051$, died or were readmitted due to HF in the year of follow-up (hazard ratio (HR) 1.25; 95% confidence interval (95%CI) 1.0–1.57; $p = .048$).

On the analysis of each event individually, 202 (22%) patients died: 101 (23%) patients with diabetes and 101 (21%) without diabetes ($p = .475$), HR 1.11 (95%CI 0.84—1.46; $p = .478$), and 178 (19%) patients required readmission: 98

Table 1 Baseline characteristics of the 2018 cohort population according to diabetes and comparison to patients with diabetes from the 2008 to 2011 cohort.

	Total 2018 N = 934	DM (2018) N = 446 (48%)	No DM (2018) N = 488 (52%)	*p* 2018	DM (2008–2011) N = 490	*p* DM
Age (years), mean (SD)	80.2 (9.3%)	78.9 (9.2%)	81.3 (9.3%)	<.001	76.5 (8.4%)	**.001**
Sex (male), n (%)	487 (52%)	245 (55%)	242 (50%)	.116	217 (44%)	**.001**
BMI (kg/m^2), mean (SD)	29.3 (5.6)	29.9 (6.1)	28.6 (5.1)	<.001	31.1 (6.0)	.267
Medical history, n (%)						
Hypertension	817 (87%)	416 (93%)	401 (82%)	<.001	424 (86%)	1.000
Hyperlipidemia	503 (54%)	311 (70%)	192 (39%)	<.001	285 (58%)	**<.001**
CKD	383 (41%)	211 (47%)	172 (35%)	<.001	235 (48%)	.845
PAD	76 (8%)	56 (13%)	20 (4.1%)	<.001	84 (17%)	.054
AF	607 (65%)	276 (62%)	331 (68%)	.064	286 (58%)	.285
Stroke	124 (13%)	67 (15%)	57 (12%)	.148	71 (14%)	.854
Dementia	46 (4.9%)	17 (3.8%)	29 (5.9%)	.173	32 (6.5%)	.077
COPD	205 (22%)	101 (23%)	104 (21%)	.636	123 (25%)	.399
Anemia	148 (17%)	80 (20%)	68 (15%)	.124	320 (65%)	.983
HHD	362 (41%)	162 (38%)	200 (44%)	.075	201 (41%)	.344
IHD	245 (28%)	151 (35%)	94 (21%)	<.001	172 (35%)	1.000
Charlson Comorbidity Index, mean (SD)	3.1 (2.5)	4.3 (2.6)	2.0 (1.8)	<.001	4.0 (2.5)	.113
NYHA, n (%)						
I	35 (3.9%)	17 (3.9%)	18 (3.8%)	1.000	29 (5.9%)	.174
II	498 (55%)	239 (55%)	259 (55%)	.947	242 (49%)	.130
III	348 (38%)	171 (39%)	177 (38%)	.682	203 (41%)	.462
IV	28 (3.1%)	11 (2.5%)	17 (3.6%)	.443	16 (3.3%)	.560
Laboratory variables, mean (SD)						
Hemoglobin (g/dL)	12.0 (2.0)	11.6 (1.9)	12.4 (2.0)	<.001	11.7 (2.0)	.486
Creatinine (mg/dL)	1.4 (4.0)	1.6 (5.7)	1.2 (0.6)	.152	1.4 (0.7)	.445

Table 1 (*Continued*)

	Total 2018 N = 934	DM (2018) N = 446 (48%)	No DM (2018) N = 488 (52%)	*p* 2018	DM (2008–2011) N = 490	*p* DM
Urea (mg/dL)	70.8 (40.2)	76.3 (45.6)	65.9 (34.1)	<.001	74.0 (39.4)	.458
Sodium (mEq/L)	138.6 (7.6)	138.5 (8.4)	138.7 (6.8)	.669	138.6 (4.8)	.724
GF, (mL/min/1.73 m^2)	61.2 (28.0)	59.9 (29.7)	62.4 (26.4)	.174	53.2 (22.8)	**<.001**
NT-proBNP (ng/L)	6,466.2 (7,643.8)	6,455.0 (7,636.8)	6,476.8 (7,667.6)	.976	5,826.9 (7,035.7)	.380
LVEF (%)	50.8 (16.1)	50.4 (16.5)	51.2 (15.8)	.432	49.9 (15.1)	.662
HbA1c (%)	6.9 (1.4)	7.4 (1.3)	5.8 (0.5)	<.001	7.3 (1.6)	.620
Heart failure treatment upon discharge, n (%)						
Loop diuretics	812 (87%)	407 (91%)	405 (83%)	<.001	441 (90%)	.575
Thiazide diuretics	115 (12%)	60 (13%)	55 (11%)	.320	34 (6.9%)	**.001**
Antialdosterones	298 (32%)	157 (35%)	141 (29%)	.042	136 (28%)	**.016**
ACEI/ARB	555 (59%)	268 (60%)	287 (59%)	.739	394 (80%)	**<.001**
Beta-blockers	587 (63%)	299 (67%)	288 (59%)	.012	261 (53%)	**<.001**
Antiplatelets	299 (32%)	174 (39%)	125 (26%)	<.001	218 (44%)	.097
ARNI	61 (6.5%)	31 (7.0%)	30 (6.1%)	.678	0 (0.00%)	**<.001**

p for the differences between groups.
In bold, *p* values that were statistically significant.
ACEI/ARB: angiotensin-converting enzyme inhibitors/angiotensin 2 receptor blockers; AF: atrial fibrillation; ARNI: angiotensin receptor-neprilysin inhibitor; BMI: body mass index; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; DM: diabetes mellitus; GF: glomerular filtration; HbA1c: glycosylated hemoglobin; HHD: hypertensive heart disease; IHD: ischemic heart disease; LVEF: left ventricular ejection fraction; NT-proBNP: N-terminal pro b-type natriuretic peptide; NYHA: New York Heart Association; PAD: peripheral artery disease; SD: standard deviation.

Table 2 Percentage of events according to diabetes, time cohort, and glucose-lowering treatment. Events during follow-up among patients with diabetes in the 2018 cohort and 2008-2011 cohort (A). Total mortality or readmissions according to antidiabetic treatment upon discharge in the 2018 cohort (B).

A. Events during the follow-up period among patients with diabetes in the 2018 cohort and the 2008–2011 cohort

	Total 2018 N = 934	DM (2018) N = 446 (48%)		No DM (2018) N = 488 (52%)	*p* 2018	DM (2008–2011) N = 490	*p* DM
Death or readmission due to HF	309 (33%)	162 (36%)		147 (30%)	.051	233 (47.5%)	<.001
			HR 1.25 (1.00-1.57)		.048		
Total mortality	202 (22%)	101 (23%)		101 (21%)	.475	151 (30.8%)	.003
			HR 1.11 (0.84-1.46)		.478		
Readmission due to HF	178 (19%)	98 (22%)		80 (16%)	.037	197 (40.2%)	<.001
			HR 1.40 (1.04-1.88)		.026		

B. Total mortality and/or readmissions according to antidiabetic treatment upon discharge in the 2018 cohort

	Total N = 446	Yes N = 162	No N = 284	*p*
Metformin	154 (35%)	41 (25%)	113 (40%)	.002
Sulfonylureas	26 (5.8%)	9 (5.6%)	17 (6.0%)	1.000
DPP4i	230 (51.5%)	118 (72.8%)	112 (39.4%)	.937
Insulin	141 (32%)	55 (34%)	86 (30%)	.459
GLP-1ra	5 (1.1%)	2 (1.2%)	3 (1.1%)	1.000
SGLT2i	12 (2.69%)	1 (0.62%)	11 (3.9%)	.063

p for the differences between groups.
DM: diabetes mellitus; DPP4i: dipeptidyl peptidase-4 inhibitors; GLP-1ra: glucagon-like peptide 1 receptor agonists; HF: heart failure; HR: hazard ratio; SGLT2i: sodium/glucose cotransporter 2 inhibitors.

(22%) with diabetes and 80 (16%) without diabetes ($p = .037$), HR 1.40 (95%CI 1.04–1.88; $p = .026$) (Table 2A).

Although diabetes was related to total mortality or hospital readmission on the baseline analysis, as mentioned above, it did not reach statistical significance on the multivariate analysis. The variables that were independently associated with the combined event were age (HR 1.02; 95%CI 1.00–1.03; $p = .033$), atrial fibrillation (HR 1.53; 95%CI 1.18–1.97; $p = .001$), and peripheral artery disease (HR 1.58; 95%CI 1.08–2.31; $p = .018$). Regarding laboratory variables, hemoglobin (HR 0.92; 95%CI 0.87–0.98; $p = .014$) and GF (HR 0.992; 95%CI 0.991–0.993; $p = .001$) were associated with the combined event. Treatment with beta-blockers ($p = .025$) and antialdosterones ($p = .019$) led to a reduction in events over the follow-up period (Table 3).

Metformin was the most used drug (35%). The use of SGLT2i (2.69%) and GLP-1ra (1.12%) was still very low. A non-significant trend of a reduction in events in patients treated with SGLT2i (0.62% vs. 3.9% respectively, $p = .063$) (Table 2B) was observed.

Results from 2008 to 2011 cohort

The previously published results regarding the principle outcome variable showed excess mortality and readmissions due to HF in patients with diabetes. A total of 233 (47.5%) patients with diabetes died or were readmitted for HF ($p < .001$). Of them, 151 (31.3%) patients with diabetes died versus 136 (23%) without diabetes, $p = .002$; HR 1.54 (95%CI 1.20–1.97; $p < .001$) and 197 (40.9%) patients with diabetes were readmitted versus 186 (31.4%) without diabetes, $p = .001$; HR 1.46 (95%CI 1.18–1.80; $p < .001$)[4].

Comparison of the two cohorts

Patients with diabetes in the 2018 cohort were older, had a greater prevalence of hyperlipidemia, and had higher GF. In addition, there was a higher percentage of men in this cohort. As was expected, a significant increase in the use of beta-blockers, antialdosterones, and ARNI (dual angiotensin receptor-neprilysin inhibitor) was observed, while the use of ACEI/ARB remained steady (Table 1).

After comparing patients with diabetes from the 2018 cohort (n = 446) with the 2008–2011 cohort (n = 490), a significant decrease in combined events was observed (36% vs. 47.5%; $p < .001$). On the independent analysis, both total mortality (30.8% vs. 23%; $p = .003$) and hospitalizations (22% vs. 40.2%; $p < .001$) declined significantly (Table 2A).

The multivariate analysis revealed a significant excess of combined events in the 2008–2011 cohort (HR 1.48; 95%CI 1.18–1.85; $p < .001$) with respect to the 2018 cohort. The events in the initial cohort were proportionally related to age, comorbidities measured by the Charlson Comorbidity Index, and left ventricular EF. Beta-blockers protected against events (with greater use in the 2018 cohort) (Table 4).

Fig. 1A–C shows a survival analysis by means of Kaplan–Meier curves which compared mortality or hospi-

Table 3 Independent predictors of mortality or hospital readmission at 12 months of follow-up in the 2018 cohort. Univariate and multivariate analyses via the Cox regression.

	Univariate		Multivariate	
	HR (95%CI)	*p*	HR (95%CI)	*p*
Diabetes mellitus	1.25 (1.00–1.57)	.048		
Age	1.02 (1.00–1.03)	.022	1.02 (1.00–1.03)	.033
Sex (male)	1.11 (0.89–1.39)	.370		
BMI	0.99 (0.97–1.01)	.609		
Medical history				
Hypertension	1.42 (0.98–2.07)	.067		
Hyperlipidemia	0.99 (0.79–1.23)	.900		
CKD	1.59 (1.27–1.99)	<.001		
PAD	1.52 (1.07–2.16)	.020	1.58 (1.08–2.31)	.018
AF	1.36 (1.07–1.74)	.013	1.53 (1.18–1.97)	.001
Stroke	1.11 (0.80–1.52)	.532		
Dementia	1.35 (0.86–2.13)	.190		
COPD	1.26 (0.97–1.62)	.081	1.30 (0.99–1.71)	.061
Anemia	1.29 (0.96–1.72)	.088		
HHD	1.06 (0.84–1.34)	.622		
IHD	0.90 (0.69–1.17)	.422		
Charlson Comorbidity Index	1.09 (1.05–1.13)	<.001		
Laboratory variables				
Hemoglobin	0.90 (0.85–0.95)	<.001	0.92 (0.87–0.98)	.014
Creatinine	1.00 (0.98–1.02)	.819		
Urea	1.01 (1.00–1.01)	<.001		
Sodium	0.99 (0.98–1.00)	.042		
Glomerular filtration	0.99 (0.98–0.99)	<.001	0.99 (0.99–0.99)	<.001
NT-proBNP	1.00 (1.00–1.00)	.071		
LVEF	1.00 (0.99–1.00)	.255	0.99 (0.98–0.99)	<.001
HbA1c	1.06 (0.88–1.27)	.547		
Heart failure treatment upon discharge				
Loop diuretics	1.29 (0.90–1.85)	.166		
Thiazide diuretics	1.37 (1.01–1.86)	.046		
Antialdosterones	0.81 (0.64–1.04)	.105	0.74 (0.57–0.96)	.025
ACEI/ARB	0.99 (0.79–1.25)	.940		
Beta-blockers	0.82 (0.66–1.04)	.097	0.75 (0.58–0.95)	.019
Antiplatelets	1.01 (0.79–1.28)	.942		
ARNI	1.14 (0.93–1.53)	.224		

p for the differences between groups.
ACEI/ARB: angiotensin-converting enzyme inhibitors/angiotensin 2 receptor blockers; AF: atrial fibrillation; ARNI: angiotensin receptor-neprilysin inhibitor; BMI: body mass index; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; HbA1c: glycosylated hemoglobin; HHD: hypertensive heart disease; HR: hazard ratio; IHD: ischemic heart disease; LVEF: left ventricular ejection fraction; NT-proBNP: N-terminal pro b-type natriuretic peptide; PAD: peripheral artery disease; 95%CI: 95% confidence interval.

tal admission, total mortality, or hospital admissions at one year of follow-up between the 2018 and 2008–2011 cohorts. Patients with diabetes in the 2018 cohort had significant reductions in the three outcomes with respect to the 2008–2011 cohort.

Discussion

This study found that the prognosis of patients with DM2 hospitalized due to HF has improved in recent years, with a significant reduction in total mortality and readmissions due to HF. The main objective of this study was to compare the prognosis of patients with diabetes in both periods. It was observed that the prevalence of DM2 showed a slight, non-significant decline in recent years. Our results also confirm a significant reduction in mortality of patients with DM2 hospitalized due to HF and of readmissions due to HF. Patients with diabetes in the 2008–2011 cohort had a 1.5 times higher risk of mortality or readmission compared to patients with diabetes from the 2018 cohort.

These results come from a cohort of patients with decompensated chronic HF in real-world conditions and with a prevalence of diabetes of nearly 50%. This is similar to other registries, which also show a progressive increase in patients with both diabetes and HF in recent years[6,9,10,14]. In Spain, the situation is quite similar, with an increase in the incidence of hospitalizations of patients with HF and DM2[3]. Diabetes tends to be underestimated when measured by hospital discharges, given that the term diabetes is occasionally omitted as a secondary diagnosis[12].

Diabetes was not linked to greater mortality in the 2018 cohort, but it was related to more hospital readmissions. In registry patients recruited between 2008 and 2011, a significant association was observed between diabetes and all-cause mortality or hospitalizations due to HF[4]. Along these lines, among patients hospitalized in coronary care units due to HF between 1985 and 2008, the diabetic population presented with more adverse events, including mortality and hospitalizations; this trend improved over time in both periods of time[11]. In contrast, Muñoz-Rivas et al.[12] reported that in-hospital mortality in patients with

Table 4 Independent predictors of mortality or hospital readmission at 12 months of follow-up in patients with diabetes according to inclusion in 2008–2011 versus 2018. Multivariate analyses via the Cox regression.

	Univariate		Multivariate	
	HR (95%CI)	*p*	HR (95%CI)	*p*
Age	1.03 (1.01–1.04)	<.001	1.03 (1.02–1.04)	<.001
Sex (male)	1.02 (0.84–1.24)	.860		
BMI	0.97 (0.95–0.99)	.001		
Medical history				
Hypertension	1.13 (0.75–1.69)	.560		
Hyperlipidemia	0.90 (0.74–1.11)	.337		
Chronic kidney disease	1.55 (1.27–1.89)	<.001		
Peripheral artery disease	1.34 (1.04–1.74)	.025		
Atrial fibrillation	1.18 (0.96–1.44)	.125		
Stroke	1.31 (1.01–1.70)	.042		
Dementia	1.48 (1.00–2.21)	.053		
COPD	1.17 (0.94–1.47)	.167		
Anemia	1.09 (0.75–1.59)	.640		
HHD	0.94 (0.77–1.16)	.574		
IHD	1.13 (0.92–1.39)	.237		
Charlson comorbidity index	1.08 (1.05–1.12)	<.001	1.06 (1.02–1.10)	.006
Laboratory parameters				
Hemoglobin	0.94 (0.89–0.99)	.015		
Creatinine	1.00 (0.98–1.02)	.943		
Urea	1.01 (1.00–1.01)	<.001	1.01 (1.00–1.01)	<.001
Sodium	0.98 (0.97–1.00)	.012	0.98 (0.97–1.00)	.044
Glomerular filtration	0.99 (0.98–0.99)	<.001		
NT-proBNP[a]	1.00 (1.00–1.00)	.023		
LVEF	0.99 (0.99–1.00)	.115	0.99 (0.98–0.99)	<.001
HbA1c	1.00 (0.82–1.20)	.966		
Heart failure treatment upon discharge				
Loop diuretics	1.13 (0.79–1.61)	.510		
Thiazide diuretics	1.07 (0.78–1.47)	.678		
Antialdosterones	0.96 (0.77–1.18)	.683		
ACEI/ARB	0.98 (0.79–1.22)	.841		
Beta-blockers	0.72 (0.59–0.88)	.001	0.71 (0.57–0.89)	.003
Antiplatelets	1.14 (0.93–1.39)	.196		
ARNI	0.46 (0.22–0.96)	.039		
Patients in the 2008–2011 cohort	1.51 (1.24–1.85)	<.001	1.48 (1.18–1.85)	<.001

p for the differences between groups.
ACEI/ARB: angiotensin-converting enzyme inhibitors/angiotensin 2 receptor blockers; ARNI: angiotensin receptor-neprilysin inhibitor; BMI: body mass index; COPD: chronic obstructive pulmonary disease; HbA1c: glycosylated hemoglobin; HHD: hypertensive heart disease; HR: hazard ratio; IHD: ischemic heart disease; LVEF: left ventricular ejection fraction; NT-proBNP: N-terminal pro b-type natriuretic peptide; 95%CI: 95% confidence interval.
[a] These variables were not included in the multivariate model as more than 25% of values were missing.

DM2 was lower compared to patients without diabetes in the period from 2001 to 2015. Regarding hospitalizations due to HF, patients with diabetes had a greater probability of readmission compared to patients without diabetes, but this observation was less marked in the period from 2008 to 2015.

All evidence indicates that something is changing in the approach to patients with HF and DM2, but the explanation of this trend is not clear. The reduction in mortality may be due to better glycemic control in patients with diabetes during hospitalization[15] or the impact of specific programs for approaching HF via multidisciplinary units such as Comprehensive Management Units for Patients with Heart Failure (UMIPIC, for its initials in Spanish). The UMIPIC programs have been demonstrated to reduce hospitalizations and emergency room visits, but not mortality[16].

Other explanations could be advances in the treatment of HF with reduced EF with the incorporation of ARNI and a greater use of drugs that modify prognosis as well as the incorporation of new glucose-lowering drugs with better metabolic profiles and additional benefits in regard to mortality.

Hospitalizations due to HF continue to be more frequent among patients with diabetes, although the difference between the two periods has declined considerably. In the period from 2008 to 2011, there was a relative increase of 10% ($p = .001$); in 2018, there was a 6% increase ($p = .037$). These findings could also be explained by the progressive impact of UMIPIC programs or simply due to specialized HF clinics and the introduction of SGLT2i in DM2 treatment.

These data are in concordance with those published by Muñoz-Rivas et al.[12], which show a stabilization in hospitalizations due to HF in patients with diabetes and a downward trend in mortality over the period studied (2001–2015). Our results add to these observations with data from 2018. In-hospital mortality of patients with diabetes and HF seem to have been in decline since the last decade despite the increase in prevalence of diabetes[5].

Patients with diabetes continue to have a greater number of comorbidities than patients without diabetes; this find-

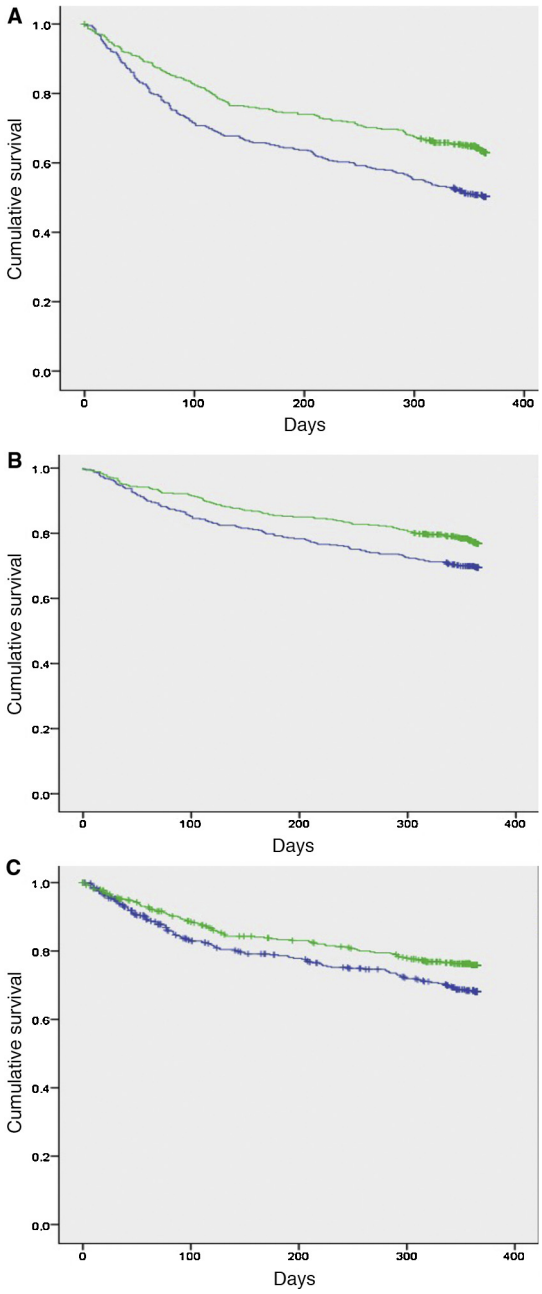

Figure 1 Kaplan–Meier curves comparing event-free follow-up at one year between the two cohorts: patients with diabetes from the 2018 cohort (upper curve, green) and patients with diabetes from the 2008 to 2011 cohort (lower curve, blue). Total mortality or hospitalizations due to heart failure, log-rank <0.001 (A). Total mortality, log-rank 0.007 (B). Readmissions due to heart failure, log-rank 0.015 (C).

ing is reported in all published studies[17]. The independent variables associated with the outcome variables of all-cause mortality or readmissions due to HF are what are to be expected in a cohort of patients with a high level of external validity, given that it represents the real situation in our hospital wards. Advanced age as well as presence of comorbidities such as atrial fibrillation, chronic kidney disease, peripheral artery disease, and anemia are variables which have classically been associated with poor prognosis in these patients[4,6].

As stated above, the emergence of new drugs for HF treatment could help explain the changes observed. However, the use of ARNI was not sufficiently widespread in 2018 so as to have had a substantial influence on our results[18,19]. The increase in the use of beta-blockers and aldosterone receptor antagonists was associated with a reduction in events despite the fact that the majority of patients had preserved EF. This fact is difficult to explain, but it could be related to better treatment optimization. Regarding DM2 treatment, the use of SGLT2i was quite low in 2018; they were only used in 12 patients (2.7%) out of the total cohort of patients with diabetes. However, only one of these patients was readmitted versus 11 patients who were not readmitted ($p = .067$). Although this is not sufficient to explain the reduction in hospitalizations due to HF in our cohort, it is in line with observations from similar studies on SGLT2i[20,21].

Therefore, our observational study demonstrates a downward trend in total mortality and hospitalization due to HF, but it cannot explain its cause.

These results must be interpreted taking into account the study's limitations. First, in addition to new diagnoses, the definition of DM2 is based on the medical records and the record of antidiabetic drugs. Second, the measurement of HbA1c was not done systematically. Third, the results can only be extrapolated to patients with chronic HF after an acute episode. Fourth, the use of drugs with benefits regarding the progress of HF and DM2 was still very anecdotal. Lastly, though the analysis has been adjusted with various clinically-relevant covariates, unmeasured variables that could have modified the results cannot be ruled out.

Conclusions

Diabetes continues to be related to a greater rate of readmission due to HF, but mortality become more similar to that of patients without diabetes. Total mortality and hospitalizations in patients with diabetes and chronic HF has significantly declined in the last decade. The explanation for this finding is likely multifactorial and specific studies are needed to further clarify it.

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Conflicts of interest

The authors declare that they do not have any conflicts of interest.

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Appendix A. RICA Registry members

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