Original Article

Type 2 diabetes increases the risk of hospital admission for heart failure and reduces the risk of in hospital mortality in Spain (2001–2015)

Nuria Muñoz-Rivas[a], Rodrigo Jiménez-García[b,*], Manuel Méndez-Bailón[c],
Valentín Hernández-Barrera[b], Javier de Miguel-Díez[d], Noel Lorenzo-Villalba[e],
José M. de Miguel-Yanes[f], Ana López-de-Andrés[b]

[a] Medicine Department, Hospital Universitario Infanta Leonor, Madrid, Spain
[b] Preventive Medicine and Public Health Teaching and Research Unit, Rey Juan Carlos University, Alcorcón, Madrid, Spain
[c] Internal Medicine Department, Clínico San Carlos University Hospital, Medicine Department, Complutense University of Madrid (UCM), Clínico San Carlos Hospital Biomedical Research Institute (IdISSC), Madrid, Spain
[d] Respiratory Department, Hospital General Universitario Gregorio Marañón, Facultad de Medicina, Universidad Complutense de Madrid (UCM), Instituto de Investigación Sanitaria Gregorio Marañón (IiSGM), Madrid, Spain
[e] Service de Medicine Interne, Centre Hospitalier Chretien, Liege, Belgium
[f] Internal Medicine Department, Hospital General Universitario Gregorio Marañón, Facultad de Medicina, Universidad Complutense de Madrid (UCM), Madrid, Spain

ARTICLE INFO

ABSTRACT

Background: To compare trends in incidence, clinical characteristics and outcomes of heart failure (HF) hospitalizations among patients with or without type 2 diabetes (T2DM) in Spain (2001–2015).
Methods: We used national hospital discharge data to select hospital admissions for HF as primary diagnosis. Incidence, comorbidities, diagnostic and therapeutic procedures, and in hospital mortality (IHM) were analyzed.
Results: We identified a total of 1,501,811 admissions for HF (36.87% with T2DM). Incidences were higher among those with T2DM than those without diabetes. The adjusted incidence of HF among T2DM patients was 4.93 higher than for non-diabetic subjects (IRR 4.93;95%CI 4.91–4.95). Jointpoint analysis showed that sex-age-adjusted admissions in T2DM patients with HF increased by 7.12% per year from 2001 to 2007 and stabilized afterwards. For non-diabetic patients a constant increase overtime of around 1% was found.

Patients with T2DM were significantly younger than patients without diabetes (77.22 vs. 79.36 years) and had more coexisting medical conditions according to the Charlson Comorbidity Index (mean CCI 1.99 ± 0.88 vs. 1.90 ± 0.86). For the total time period, crude IHM was lower for T2DM patients than for non-diabetic people (8.35% vs, 10.57%; p < 0.05) and the association remained significant after multivariable adjustment ((OR, 0.84; 95%CI 0.83–0.86).). Female sex, older age and multiple comorbidities were significant risk factors for IHM.
Conclusions: T2DM increases the risk of admission for HF by five-fold. Our study demonstrates an increase in hospitalization for HF in diabetic patients from 2001 to 2007 and stabilization afterwards. T2DM was associated with a lower IHM after hospitalization for HF.

1. Introduction

Heart failure (HF) is currently one of the most prevalent cardiovascular diseases in the world. Advance age, hypertension, obesity, dyslipidemia, and type 2 diabetes mellitus (T2DM) are considered to be the most important risk factors related to HF [1,2].

T2DM represents a frequent comorbid condition in patients with HF. Its prevalence in HF is ranging between 15 and 50% according to the series studied [3]. The coexistence of T2DM and HF determines the prognosis and treatment of both entities [4]. This fact is especially

---

important in elderly individuals who present higher risk to develop a T2DM and also HF [5]. In a study, patients with T2DM aged 75 and older were 2 folds more at risk to develop HF [6]. In a recent HF clinical trials such as Prospective Comparison of ARNI (Angiotensin Receptor–Neprilysin Inhibitor) with ACEI (Angiotensin-Converting–Enzyme Inhibitor) to determine impact on global mortality and morbidity in heart failure trial (PARADIGM-HF), prevalence of T2DM reached 35% [7]. Data from patients hospitalized for HF in the U.S. and Europe show a T2DM prevalence of 40–45% and this seems to be progressively increasing over the last years [8,9].

In Spain, the situation is similar with an increase incidence of hospitalizations in patients with both HF and T2DM. An investigation conducted in Spain showed an increase of hospitalizations from 38% in 1997 to 45% in 2002 [10]. However, there are, presently, no studies evaluating the impact of T2DM on hospitalizations for HF during the last 15 years in this country. For these reasons, we considered it important to conduct this research.

Using the Spanish National Hospital Discharge Database (SNHDD), we aim to: i) examine trends in the incidence, characteristics, and in-hospital outcomes of HF as the primary diagnosis among patients with or without T2DM from 2001 to 2015; and ii) identify factors associated with in-hospital mortality (IHM) among patients with HF as the primary diagnosis.

2. Methods

2.1. Data source

This retrospective observational study was performed using the SNHDD. Details of the design and description of the SNHDD are available online [11]. Briefly, this nationally representative database, which compiles all public hospital data, covers > 95% of hospital admissions in Spain. The SNHDD includes patient variables (sex, date of birth), admission and discharge dates, up to 14 discharge diagnoses, and up to 20 procedures performed during the hospital stay [11].

2.2. Patient population

We selected admissions of patients (aged ≥40 years) with a primary diagnosis of HF in the SNHDD database. A primary HF diagnosis refers to hospitalizations mainly attributable to HF. These were identified via the following International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis codes, as recommended by the ACC/AHA task force on performance measures: 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, and 428.12 [12]. HF was classified as a primary diagnosis if any of the codes appear as the first diagnosis in the SNHDD database. We collected data between January 1, 2001 and December 31, 2015.

We grouped admissions by diabetes status as follows: T2DM (ICD-9-CM codes 250.x0 and 250.x2) or no-diabetes in any diagnostic position. We excluded people with type 1 diabetes mellitus (codes 250.x1 and 250.x3).

2.3. Covariates

Clinical characteristics included information on overall comorbidity at the time of discharge, which was assessed by calculating the Charlson comorbidity index (CCI) [13]. In addition to those conditions included in the CCI, the following were analyzed as described by Quan et al. [14] using the enhanced ICD-9-CM: ischemic coronary disease (codes 410.x, 412.x, 413.x, 414.0, 414, 414.00, 414.01, and 414.2–9), atrial fibrillation (code 427.31), anemia (codes 285.2, 285.2x and 285.9), pneumonia (codes 480–488 and 507.0–507.8), pulmonary embolism (codes 415.11 and 415.19), hypertension (codes 401, 401.0, 401.1 and 401.9), acute renal failure (codes 584.x), and chronic obstructive pulmonary disease (COPD) (codes 490, 491, 491.0, 491.1, 491.2x, 491.8,

491.9, 492, 492.0, 492.8, and 496).

Regardless of the position in the procedures coding list, we retrieved data about following in-hospital procedures: echocardiogram (code 88.72), non-invasive mechanical ventilation (code 93.90), invasive mechanical ventilation (codes 96.7, 96.70, 96.71 and 96.72), heart catheterization (codes 37.21–37.23 and 88.52–88.57), pacemaker (codes 37.70–37.74 and 37.80–37.83), and red cell transfusion (codes 99.00 and 99.01–99.08).

We evaluated the proportion of admissions through the emergency room (ER) and the readmissions rate (patients that had been discharged from the same hospital within the previous 30 days) and the mean of length of hospital stay (LOHS).

We also calculated costs. Costs were calculated using Diagnosis-Related Groups (DRG) for the disease. DRG represents a medical economic entity concerning a set of diseases requiring analogous management resources [15]. All costs shown were adjusted for the inflation in the same period in Spain.

2.4. End points

The main end points in our investigation were trends in incidence rates of hospitalizations and IHM in patients admitted with a primary diagnosis of HF. IHM was defined by the proportion of patients who died during admission for each year of study.

2.5. Statistical analysis

We considered five time periods that included three consecutive years each (2001–03; 2004–06; 2007–09; 2010–12; 2013–15).

In order to assess time trends we estimated the incidence rates of admission with a primary diagnosis of HF in patients with T2DM and non-diabetic patients calculated per 100,000 inhabitants. We calculated T2DM-specific incidence rates by dividing the number of admissions per year, sex, and age group by the corresponding number of people in that population group using the age-adjusted, sex-adjusted estimated prevalence of T2DM obtained from National Health Surveys (NHS) conducted in 2001/02, 2003/04, 2006/07, 2009/10, 2011/12, and 2014/15, and based on data from the Diabet.es Study, which estimated the prevalence of diabetes in the Spanish population [16,17]. Data for the diabetic population for missing years (2005, 2008 and 2013) was estimated assuming that the growth rate was the same through the period 2004–2014. We estimated rates by fitting a linear regression model with population from years when NHS was available, and we used this model to impute population data for 2005, 2008, and 2013. We also calculated incidence rates for non-diabetic patients by dividing the number of cases per year, sex, and age group by the corresponding number of people in that population group (excluding those with T2DM), according to the data from the Spanish National Institute of Statistics, as reported on 31 December of each year [18].

In our study we used log linear joinpoint regression to identify the period in which trend changes occurred in annual HF incidence rates by diabetes status. The incidence rates included in the joinpoint regression were adjusted by age and sex, when appropriate, using the direct standardization method and the 2015 population as the reference. We also estimated the annual percentage of change (APC) in each of the periods delimited by the points of change. The analysis started with the minimum number of joinpoints and tested whether the inclusion of one or more joinpoints was statistically significant [19]. In the final model, each joinpoint indicated a significant trend change, and the APC was obtained in each of the segments delimited by the joinpoints, using the weighted least squares technique. The Joinpoint Regression Program, version 4.0.4, was used for the analysis [20].

A descriptive statistical analysis was performed for all continuous variables and categories. Variables are expressed as proportions as means with standard deviations. A bivariable analysis according to year was performed using the χ^2 test for linear trend (proportions) and

ANOVA (means), as appropriate.

To assess differences between those patients with and without T2DM, for each year and for the total sample, the statistical tests conducted for continuous variables were the *t*-test for normal distributions and the Mann–Whitney test for non-normal distributions; categorical variables were compared using the Chi-square test and incidences were compared using Poisson regression. Estimates correspond to Incidence Rate Ratios (IRR) with their 95% confidence intervals (95%CI).

To identify variables associated with IHM as a binary outcome among patients with HF, we performed three multivariable logistic regression analyses (T2DM, non-T2DM, both). The variables included in the models were those with significant results in the bivariable analysis and those considered relevant in other investigations. Estimates were Odds Ratio (OR) with their 95%CI.

All statistical analyses were performed with Stata version 10.1 (Stata, College Station, Texas, USA). Statistical significance was set at $p < 0.05$ (2-tailed).

2.6. Ethical aspects

The study maintains data confidentiality at all times. Given the anonymous and mandatory nature of the database, it was not necessary to obtain informed consent or approval by an ethics committee in accordance with Spanish legislation.

3. Results

In our study we identified a total of 1,501,811 hospitalizations of patients aged 40 years or more with a primary diagnosis of HF in Spain (2001–2015). Patients with T2DM accounted for 36.87% of total (308,380 women and 245,395 men).

Table 1 shows the incidence, clinical characteristics and in-hospital outcomes in patients with or without T2DM who were admitted with a primary diagnosis of HF. Among patients with T2DM, we found that the incidence of HF coding increased significantly from 1185.44 cases per 100,000 T2DM population in 2001–03 to 1740.27 in 2013–15. In patients without T2DM the incidence of admissions also increased significantly over the study period from 296.52 to 356.5 cases per 100,000 non-T2DM population (Table 1). Incidence was significantly higher in people with T2DM than in non-diabetic people for all years analyzed.

Using the Poisson regression model, adjusting by age and sex, we found that the incidence for a primary diagnosis of HF admission was 4.93-times higher among patients with T2DM than those without diabetes (IRR 4.93; 95%CI 4.91–4.95).

Shown in Supplementary Fig. 1 are the age adjusted annual incidences rates among T2DM diabetic patients according to gender.

The results of the joinpoint analysis showed that sex and age-adjusted admissions in T2DM patients with HF increased by 7.12% per year from 2001 to 2007 and from 2007 to 2015, it decreased by 0.09% per year, but not significantly. According to sex admissions increased by 5.16% per year, from 2001 to 2008, and by 1.18% per year, from 2008 to 2015, among men, with no different significance. In women, admissions increased by 9.95% per year from 2001 to 2006 and decreased by 0.73% from 2006 to 2015, with no significant difference too.

For non-diabetic patients, men and women, the age adjusted incidences are shown in Supplementary Fig. 2. According to joint point regression there are no significant points of change in any of the groups studied with significant and constant increase overtime with APC of around 1%.

In patients who had an admission for HF there was a significant female predominance (55.69% for T2DM and 54.45% for no diabetes). Overall, patients with T2DM were younger (77.22; SD = 9.32 years) than patients without diabetes (79.30; SD = 10.44 years) and had more coexisting medical conditions (mean CCI index 1.99 ± 0.88 vs. 1.90 ± 0.86) (all P values < 0.001). Age and mean CCI index increased significantly over time in both people with T2DM and without diabetes, however female sex decreased in those with T2DM and increased in those without (59.52% and 53.48% in 2001–03 vs. 53.01% and 54.67% in 2013–15, respectively, p < 0.001).

Admission by ER and readmission rates were significantly higher in patients with T2DM (95.38% and 18.81% vs. 94.71% and 16.07%, respectively: p < 0.001). Readmissions and admission by ER increased in both groups during the study period (Table 1).

Overall mean LOHS was significantly higher in patients with T2DM (9.19 SD = 8.02 days vs. 9.06 SD = 8.65 days). Over time, LOHS fell significantly in both patients with T2DM and without diabetes.

For the total time period, crude IHM was 8.35% for T2DM patients and 10.57% for non-diabetic people (p < 0.05). IHM decreased significantly over time in people with T2DM (from 8.63% in 2001–03 to 8.15% in 2013–15) (Table 1). No changes were found in non-T2DM

Table 1

Characteristics of Hospital Admissions with Primary Diagnosis of HF in Spain (2001–2015) according to the presence of Type 2 Diabetes Mellitus (T2DM).

Variable	T2DM	2001–03	2004–06	2007–09	2010–12	2013–15	Total	P trend
Number of hospital admissions	Yes	68467	92322	114374	132645	145967	553775	
	No	155327	168916	190230	208971	224592	948036	
Crude incidence per 100.000 population	Yes	1185.44	1476.72	1688.47	1762.34	1740.27	1595.18	< 0.001
	No	296.52	298.5	315.2	336.39	356.5	321.97	< 0.001
Female. N (%)*	Yes	40754(59.52)	53530(57.98)	64351(56.26)	72375(54.56)	77370(53.01)	308380(55.69)	< 0.001
	No	83069(53.48)	90957(53.85)	104051(54.70)	115329(55.19)	122787(54.67)	516193(54.45)	< 0.001
Age in years. Mean(SD)*	Yes	75.44(9.19)	76.15(9.21)	77.00(9.18)	77.76(9.26)	78.42(9.41)	77.22(9.32)	< 0.001
	No	77.14(10.52)	78.21(10.44)	79.23(10.36)	80.21(10.25)	80.81(10.28)	79.30(10.44)	< 0.001
CCI. Mean (SD)*	Yes	1.84(0.85)	1.92(0.87)	1.96(0.87)	2.02(0.88)	2.10(0.88)	1.99(0.88)	< 0.001
	No	1.75(0.81)	1.83(0.85)	1.89(0.86)	1.95(0.87)	2.01(0.88)	1.90(0.86)	< 0.001
Readmission. N(%)*	Yes	11947(17.45)	17096(18.52)	21519(18.81)	25275(19.05)	28327(19.41)	104164(18.81)	< 0.001
	No	22236(14.32)	25652(15.19)	30335(15.95)	35127(16.81)	38989(17.36)	152339(16.07)	< 0.001
ER admission. N(%)*	Yes	65160(95.17)	87853(95.16)	108528(94.89)	126608(95.45)	140015(95.92)	528164(95.38)	< 0.001
	No	146642(94.41)	159664(94.52)	178364(93.76)	198690(95.08)	214479(95.50)	897839(94.71)	< 0.001
LOHS. Mean(SD)*	Yes	10.21(9.28)	9.79(8.39)	9.48(8.38)	8.83(7.57)	8.43(7.12)	9.19(8.02)	< 0.001
	No	9.65(9.54)	9.43(8.77)	9.27(8.73)	8.74(8.25)	8.48(8.13)	9.06(8.65)	< 0.001
Cost. Mean (SD)	Yes	4193.11(2706.27)	4210.44(2669.68)	4205.40(2677.02)	4196.40(2681.67)	4184.17(2575.51)	4196.97(2654.21)	0.132
	No	4193.75(2654.90)	4211.31(2744.61)	4204.23(2659.46)	4201.25(2713.87)	4209.34(2822.70)	4204.33(2725.29)	0.346
IHM. N (%)*	Yes	5912(8.63)	7863(8.52)	9655(8.44)	10902(8.22)	11899(8.15)	46231(8.35)	< 0.001
	No	16432(10.58)	17872(10.58)	20037(10.53)	22192(10.62)	23663(10.54)	100196(10.57)	0.890

CCI Charlson Comorbidity Index. ER Emergency room. LOHS Length of hospital stay. IHM In-hospital mortality. P value trend: P < 0.05 to assess time trend from 2001 to 2015.

Test used: Poisson regression (incidences), the χ2 test (proportions) and T student (means), as appropriate.

* Significant differences (p < 0.05) when comparing patients with and without T2DM for total figures.

Table 2

Selected Comorbidities and procedures of Hospital Admissions With Primary Diagnosis of HF in Spain (2001–2015) according to the presence of type 2 diabetes mellitus (T2DM).

Variable	T2DM	2001–03	2004–06	2007–09	2010–12	2013–15	Total	P trend
Ischemic coronary. N(%)*	Yes	24138(35.25)	32534(35.24)	38623(33.77)	43079(32.48)	46652(31.96)	185026(33.41)	< 0.001
	No	38233(24.61)	41891(24.80)	45894(24.13)	48141(23.04)	51238(22.81)	225397(23.78)	< 0.001
Atrial fibrillation. N(%)*	Yes	24651(36.00)	37499(40.62)	49746(43.49)	59902(45.16)	69018(47.28)	240661(43.49)	< 0.001
	No	66343(42.71)	79099(46.83)	94673(49.77)	108500(51.92)	121626(54.15)	470241(49.60)	< 0.001
Anemia. N(%)*	Yes	179(0.26)	257(0.28)	390(0.34)	462(0.35)	491(0.34)	1779(0.32)	0.001
	No	366(0.24)	477(0.28)	515(0.27)	638(0.31)	703(0.31)	2699(0.28)	< 0.001
Pneumonia. N(%)*	Yes	1555(2.27)	2221(2.41)	3077(2.69)	4051(3.05)	4905(3.36)	15809(2.85)	< 0.001
	No	4014(2.58)	4834(2.86)	6475(3.40)	8062(3.86)	8898(3.96)	32283(3.41)	< 0.001
Pulmonary embolism. N(%)*	Yes	196(0.29)	231(0.25)	275(0.24)	304(0.23)	363(0.25)	1369(0.25)	0.182
	No	606(0.39)	669(0.40)	745(0.39)	935(0.45)	891(0.40)	3846(0.41)	0.020
Hypertension. N(%)*	Yes	27492(40.15)	42550(46.09)	52312(45.74)	58859(44.37)	60289(41.30)	241502(43.61)	< 0.001
	No	44562(28.69)	59217(35.06)	69105(36.33)	78735(37.68)	81956(36.49)	333575(35.19)	< 0.001
Acute renal failure. N(%)*	Yes	7617(11.13)	10559(11.44)	24888(21.76)	43233(32.59)	56915(38.99)	143212(25.86)	< 0.001
	No	13211(8.51)	14786(8.75)	31582(16.60)	51906(24.84)	65949(29.36)	177434(18.72)	< 0.001
COPD. N(%)*	Yes	13752(20.09)	18485(20.02)	22820(19.95)	26654(20.09)	29047(19.90)	110758(20.00)	0.706
	No	29795(19.18)	32643(19.32)	36773(19.33)	40523(19.39)	43087(19.18)	182821(19.28)	0.346
Echocardiogram. N(%)*	Yes	19364(28.28)	26863(29.10)	35456(31.00)	41400(31.21)	46812(32.07)	169895(30.68)	< 0.001
	No	42370(27.28)	48834(28.91)	58651(30.83)	65388(31.29)	71677(31.91)	286920(30.26)	< 0.001
Non invasive mechanical ventilation. N(%) *	Yes	375(0.55)	906(0.98)	2183(1.91)	5415(4.08)	7998(5.48)	16877(3.05)	< 0.001
	No	778(0.50)	1325(0.78)	3057(1.61)	7413(3.55)	10483(4.67)	23056(2.43)	< 0.001
Invasive mechanical ventilation. N(%)*	Yes	860(1.26)	1101(1.19)	1155(1.01)	1120(0.84)	1045(0.72)	5281(0.95)	< 0.001
	No	2061(1.33)	2180(1.29)	2060(1.08)	1918(0.92)	1925(0.86)	10144(1.07)	< 0.001
Catheterization. N(%)*	Yes	1505(2.20)	2687(2.91)	3889(3.40)	5145(3.88)	6524(4.47)	19750(3.57)	< 0.001
	No	3271(2.11)	4567(2.70)	6250(3.29)	7723(3.70)	9725(4.33)	31536(3.33)	< 0.001
Pacemaker. N(%)*	Yes	307(0.45)	433(0.47)	453(0.40)	635(0.48)	617(0.42)	2445(0.44)	0.015
	No	785(0.51)	855(0.51)	898(0.47)	1000(0.48)	1035(0.46)	4573(0.48)	0.174
Red cell transfusion. N(%)*	Yes	2748(4.01)	4292(4.65)	6449(5.64)	8120(6.12)	9060(6.21)	30669(5.54)	< 0.001
	No	5677(3.65)	7512(4.45)	9859(5.18)	11967(5.73)	12830(5.71)	47845(5.05)	< 0.001

P value trend: P < 0.05 to assess time trend from 2001 to 2015.

  * Significant differences (p < 0.05) when comparing patients with and without T2DM for total figures.

patients over time.

The mean cost per patient was slightly, but not significantly, higher in non-diabetic patients (4204.33€ vs. 4196.97€) and no changes were found in both groups over the study period (Table 1).

As can been seen in Table 2, among patients with T2DM, the most common comorbidities were hypertension (43.61%), atrial fibrillation (43.49%), ischemic coronary disease (33.41%), acute renal failure (25.86%), and COPD (20.00%). Hypertension, ischemic coronary disease, acute renal failure, COPD, and anemia were significantly more frequently coded as comorbidities in patients with T2DM than in non-diabetic patients. All comorbidities coded, except ischemic coronary disease which showed a significant decrease, increased significantly over time in both groups. COPD and pulmonary embolism have not changed over time (Table 2).

In T2DM patients, echocardiogram (30.68%), followed by transfusion (5.54%) and heart catheterization (3.57%), were the most frequently used. All procedures, except invasive mechanical ventilation and pacemaker implantation, were significantly higher in T2DM patients than in non-diabetic patients. The use of all procedures (except invasive mechanical ventilation which showed a significant decrease) significantly increased over the study period in diabetic and non-diabetic patients. No change was detected in the use of pacemaker implantation over time (Table 2).

Table 3 shows the characteristics of hospital admissions for HF in patients with and without T2DM according to IHM during the study period. As pointed out before, for the entire period, IHM was significantly higher among those without diabetes (10.57%vs. 8.35%) and these differences were significant in all studyperios and all age groups of patients. Patients with T2DM who died during their hospitalization were significantly younger (80.93 ± 8.28 vs. 83.02 ± 8.97), had more comorbidity (2.18 ± 0.92 vs. 2.05 ± 0.91), lower ER admission rates (8.36% vs. 10.63%), lower readmission rates (11.89% vs. 14.97%), and higher LOHS (10.12 days vs. 9.88 days) than non-T2DM patients.

Table 3

In-hospital mortality among hospitalization with a primary diagnosis of Heart failure according to the presence of type 2 diabetes mellitus (T2DM).

		T2DM	non T2DM	P
Year. N (%)	2001–03	5912(8.63)	16432(10.58)	< 0.001
	2004–06	7863(8.52)	17872(10.58)	< 0.001
	2007–09	9655(8.44)	20037(10.53)	< 0.001
	2010–12	10902(8.22)	22192(10.62)	< 0.001
	2013–15	11899(8.15)	23663(10.54)	< 0.001
Sex. N (%)	Female	26925(8.73)	57039(11.05)	< 0.001
	Male	19306(7.87)	43157(9.99)	< 0.001
Age in years. Mean (SD)		80.93(8.28)	83.02(8.97)	< 0.001
Age groups in years. N (%)	40–64 years	1912(3.47)	4102(4.59)	< 0.001
	65–74 years	7089(5.43)	10,328(6.69)	< 0.001
	75–84 years	20605(8.36)	36377(9.57)	< 0.001
	85 or over	16625(13.67)	49389(15.23)	< 0.001
Readmission N (%)	Yes	12390(11.89)	22806(14.97)	< 0.001
	No	33841(7.53)	77390(9.73)	< 0.001
CCI. Mean (SD)		2.18(0.92)	2.05(0.91)	< 0.001
CCI. N (%)	1	11275(6.30)	30496(8.66)	< 0.001
	2	19623(8.38)	41582(10.70)	< 0.001
	3 +	15333(10.90)	28118(13.59)	< 0.001
ER admission. N (%)	Yes	44175(8.36)	95413(10.63)	< 0.001
	No	2056(8.03)	4783(9.53)	< 0.001
LOHS. Mean (SD)		10.12(12.11)	9.88(12.59)	< 0.001
Cost. Mean (SD)		4430.28(2954.80)	4429.78(2928.68)	0.827

The P value for the difference between patients with type 2 diabetes non diabetic patients was calculated with the bivariate logistic regression model adjusted by age and sex when appropriate. CCI Charlson Comorbidity Index. ER Emergency room. LOHS Length of hospital stay.

Table 4
Multivariable analysis of factors associated with in-hospital mortality among patients with heart failure according to presence of type 2 diabetes (T2DM).

		T2DM	non T2DM	Both
		OR (95%CI)	OR (95%CI)	OR (95%CI)
Year	2001–03	1	1	1
	2004–06	0.94(0.9–0.97)	0.94(0.92–0.96)	0.94(0.92–0.96)
	2007–09	0.88(0.85–0.91)	0.88(0.86–0.9)	0.88(0.86–0.9)
	2010–12	0.81(0.78–0.84)	0.84(0.82–0.86)	0.83(0.81–0.84)
	2013–15	0.76(0.74–0.79)	0.8(0.78–0.82)	0.79(0.77–0.8)
Sex	Female	1.02(1–1.04)	1.02(1–1.03)	1.02(1.01–1.03)
Age groups in years.	40–64 years	1	1	1
	65–74 years	1.55(1.47–1.63)	1.43(1.38–1.49)	1.46(1.42–1.51)
	75–84 years	2.54(2.42–2.67)	2.16(2.09–2.24)	2.28(2.22–2.35)
	85 or over	4.67(4.44–4.9)	3.86(3.74–3.99)	4.1(3.99–4.22)
Readmission	Yes	1.6(1.57–1.64)	1.6(1.57–1.62)	1.6(1.58–1.62)
CCI	1	1	1	1
	2	1.35(1.31–1.38)	1.24(1.22–1.26)	1.27(1.25–1.29)
	3 +	1.81(1.76–1.86)	1.61(1.59–1.64)	1.67(1.65–1.7)
ER admission	Yes	1.00(0.95–1.05)	1.06(1.02–1.09)	1.04(1.01–1.07)
LOHS		1.01(1.00–1.03)	1.01(1.00–1.02)	1.01(1.00–1.02)
T2DM	Yes	NA	NA	0.84(0.83–86)

CCI Charlson Comorbidity Index.ER Emergency room. LOHS Length of hospital stay.
OR Odds ratio obtained using logistic regression models. 95%CI; 95% confidence intervals.
Only those variable that showed a significant association are showed.
NA. Not applicable.
T2DM increases the risk of admission for heart failure (HF) by five-fold.
Hospitalization for HF in T2DM patients raised from 2001 to 7 and stabilized afterwards.
In hospital mortality was lower among T2DM patients after hospitalization for HF.
Female gender increased the risk of hospital mortality among T2DM patients with HF.

Table 4 shows the result of the logistic regression analysis of the factors independently associated with IHM according to the presence of T2DM. Over time, the IHM decreased significantly regardless of the presence of T2DM. Female sex was a significant risk factor for IHM in the three populations analyzed.

Among T2DM patients with HF, IHM was significantly higher in older subjects (OR 4.67, 95%CI 4.44–4.90 for ≥85 years old vs. < 40–64 years old), in those with more comorbidities according to the CCI (OR 1.81, 95%CI 1.76–1.86 in those with 3 or more comorbidities vs. no comorbidities), and in those with readmissions (OR 1.6, 95%CI 1.57–1.64). Older age, comorbidities, and being readmitted were risk factors for IHM among patients without diabetes hospitalized with HF.

Finally, in our study, diabetes was associated with a lower IHM (OR, 0.84; 95%CI 0.83–0.86).

4. Discussion

This research shows an increasing incidence of hospitalizations for HF as the principal diagnosis during the period 2001–2015 in Spain. This increase seems to be more relevant in T2DM individuals. T2DM in Spain was noted to have five times more risk of hospitalization for HF compared to non-T2DM patients (IRR 4.93; 95%CI 4.91–4.95). These results were different with those of others authors reported in the literature. Win et al. [21] described a decrease of admissions for HF as the principal diagnosis in the US. Important advances in the therapy of HF have been achieved over the past decades. Several pharmacological treatments such as angiotensin-converting enzyme inhibitors, beta blockers, spironolactone or more recently of ARNI have demonstrated in clinical trials improvement in outcomes of patients living with HF, especially with reduced ejection fraction [7].

The prevalence of T2DM as a comorbid condition in HF has been progressively increasing in in US [21]. The prevalence of T2DM in our series was of 37% in contrast to 49% observed in the *ESC HFA Heart Failure LongTerm Registry* [8]. These differences in prevalence of T2DM in HF may vary according to the definition of T2DM and the study design [22]. In this respect, it is known that the coding of T2DM in our investigation could be diminished by several factors: no determination

of glycosylated hemoglobin during hospitalization and low registration of T2DM diagnosis in the SNHDD [22]. In spite of the limitations the prevalence of T2DM in HF in our study was high. This finding could be due to several factors such as advanced age, obesity, and high index of co-morbidities leading to an increase risk of hospitalization for HF and T2DM [23].

IHM was lower in T2DM patients compared to non-T2DM patients in our study. These results were different with those of others authors reported in the literature. In the ALARM registry (six European countries, Mexico and Australia), and in the European Society of Cardiology, HF Long Term Registry, T2DM was associated with an increase in mortality [8,24]. However as observed, in our Spanish registry, data from other studies conducted in the US such as the *OPTIMIZE HF, ADHERE, and Get With the Guidelines* HF did not show an increase of IHM in patients with HF and T2DM [2,25,26]. A recent published meta-analysis demonstrated that mortality associated to both acute and chronic HF is higher compared to non-T2DM patients [27]. These results may be due to the different populations and types of studies that have been carried out to evaluate the prognosis of T2DM in HF. It is well known that T2DM increases the risk of cardiovascular events such coronary heart disease, renal failure, stroke and HF. These clinical conditions are associated to an increase of risk of long term complications and worsening of prognosis in patients with diabetes [28]. In our study, patients with T2DM had a higher degree of hypertension, renal impairment, coronary heart disease compared to non-diabetic patients. However, we did not observe an increase in mortality in the series. This finding could be the result of better metabolic control in T2DM patients during hospitalization. Fasting glycemia and glycosylated hemoglobin were not known, and thus the impact on in-hospital HF prognosis could not be evaluated. Left ventricular ejection fraction and natriuretic peptides levels in HF patients with and without T2DM were not available. All these factors might have an impact on short- and medium-term prognosis of HF [29]. Unfortunately, data on out-of-hospital mortality in both groups was not known. It is well-known that patients with HF present a higher risk of sudden death [30]. This is particularly important in patients with T2DM as they develop silent ischemic disease and systolic ventricular dysfunction [2]. On the other hand, obese

patients are considered to have lower IHM during acute events such as myocardial infarction or acute HF [31]. This finding, known as the paradox of obesity, may have affected the subjects with T2DM included in our investigation.

We have observed that patients with HF and T2DM presented a higher incidence of hospital readmissions compared to patients with HF and non-T2DM. This may be due to several factors: glycemic control in patients with T2DM can influence hospitalizations for HF [32]. In addition, patients with HF and comorbidities present a higher risk of hospital readmissions and require better outpatient follow-up as part of their care. Management programs and HF units for patients with HF after discharged hospitalization have demonstrated to reduce health care costs and the need of readmissions [33]. In 2007, in Spain a study showed that 41% of hospitals had a HF unit [34]. Although incidence of hospitalization for HF has increased during the study period, the second half (2008–2015) show a non significant decrease of around 1% per year in T2DM patients. We could expect that all these strategies could be successful in the prevention of HF in the future and this could explain a change of trend in the last years of our study.

In our investigations T2DM subject with HF had more comorbidities than non-T2DM individuals. Treatment for metabolic control in T2DM was not known in the study. This could be of importance when analyzing early readmissions in HF and T2DM [35]. The study period ended in 2015 so some drugs for the treatment of T2DM such as SGLT2 inhibitors were not still available. This group of drugs has been shown to decreased admissions for HF in T2DM patients [36].

In conclusion T2DM increases the risk of admission for HF four to five-fold. Our study demonstrates an increase in hospitalization for HF in diabetic patients, from 2001 to 2007 and it has been stabilized in the second half of the study period. Female sex, older age and multiple comorbidities were significant risk factors for IHM. T2DM was associated with a lower IHM for HF.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejim.2018.08.011.

Competing interests

The authors declare that they have no competing interests.

Funding

References

[1] Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, et al. 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 Heart J 2016;37:2129–200.

[2] Seferović PM, Petrie MC, Filippatos GS, Anker SD, Rosano G, Bauersachs J, et al. Type 2 diabetes mellitus and heart failure: a position statement from the heart failure association of the European society of cardiology. Eur J Heart Fail 2018;20:853–72.

[3] Nichols GA, Hillier TA, Erbey JR, Brown JB. Congestive heart failure in type 2 diabetes: prevalence, incidence, and risk factors. Diabetes Care 2001;24:1614–9.

[4] Castagno D, Baird-Gunning J, Jhund PS, Biondi-Zoccai G, MacDonald MR, Petrie MC, et al. Intensive glycemic control has no impact on the risk of heart failure in type 2 diabetic patients: evidence from a 37,229 patient meta-analysis. Am Heart J 2011;162:938. [48.e2].

[5] Sleiman I, Rozzini R, Giordano A, Trabucchi M. Short-term survival in elderly patients hospitalized for heart failure: the role of diabetes mellitus and newly recognized hyperglycemia. J Am Geriatr Soc 2009;57:1313–6.

[6] MacDonald MR, Petrie MC, Varyani F, Ostergren J, Michelson EL, Young JB, et al. Impact of diabetes on outcomes in patients with low and preserved ejection fraction heart failure: an analysis of the candesartan in heart failure: assessment of reduction in mortality and morbidity (CHARM) programme. Eur Heart J 2008;29:1377–85.

[7] McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med 2014;371:993–1004.

[8] Targher G, Dauriz M, Laroche C, Temporelli PL, Hassanein M, Seferovic PM, et al. 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. Eur J Heart Fail 2017;19:54–65.

[9] Echouffo-Tcheugui JB, Xu H, Devore AD, Schulte PJ, Butler J, Yancy CW, et al. Temporal trends and factors associated with diabetes mellitus among patients hospitalized with heart failure: findings from get with the guidelines-heart failure registry. Am Heart J 2016;182:9–20.

[10] Pérez-Belmonte LM, Lara-Rojas CM, López-Carmona MD, Guijarro-Merino R, Bernal-López MR, Gómez-Huelgas R. National trends in heart failure hospitalization rates in patients with diabetes mellitus: 1997-2010. Rev Esp Cardiol (Engl Ed) 2018;71(5):408–41.

[11] Instituto Nacional de Gestión Sanitaria, Ministerio de Sanidad, Servicios Sociales e Igualdad. Conjunto Mínimo Básico de Datos, Hospitales del INSALUD. http://www.ingesa.msssi.gob.es/estadEstudios/documPublica/CMBD-2001.htm, Accessed date: 16 January 2018.

[12] Bonow RO, Bennett S, Casey Jr. DE, Ganiats TG, Hlatky MA, Konstam MA, et al. ACC/AHA clinical performance measures for adults with chronic heart failure: a report of the American College of Cardiology/American Heart Association Task Force on performance measures (writing committee to develop heart failure clinical performance measures): endorsed by the Heart Failure Society of America. Circulation 2005;112:1853–1887.2.

[13] Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373–83.

[14] Quan H, Sundararajan V, Halfon P, Fong A, Burnand B, Luthi JC, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. Med Care 2005;43:1130–9.

[15] Instituto Nacional de la Salud. CMBD Insalud. Análisis de los GRDs Año www.ingesa.msc.es/estadEstudios/documPublica/cmbd2000.htm; 2000, Accessed date: 16 January 2018.

[16] Ministerio de Sanidad, Servicios Sociales e Igualdad. [Encuesta Nacional de Salud de España]. http://www.msssi.gob.es/estadEstudios/estadisticas/encuestaNacional/, Accessed date: 16 January 2018.

[17] Soriguer F, Goday A, Bosch-Comas A, Bordiú E, Calle-Pascual A, Carmena R, et al. Prevalence of diabetes mellitus and impaired glucose regulation in Spain: the Di@bet.es study. Diabetologia 2012;55:88–93.

[18] Instituto Nacional de Estadística. Population estimates. http://www.ine.es; 2010, Accessed date: 1 December 2015.

[19] Kim HJ, Fay MP, Feuer EJ, Midthune DN. Permutation tests for joinpoint regression with applications to cancer rates. Stat Med 2000;19:335–51.

[20] Joinpoint regression program, version 4.0.4. Statistical Methodology and Applications Branch, Surveillance Research Program, National Cancer Institute; May 2013.

[21] Win TT, Davis HT, Laskey WK. Mortality among patients hospitalized with heart failure and diabetes mellitus: results from the national inpatient sample 2000 to 2010. Circ Heart Fail 2016;9:e003023.

[22] Presley CA, Min JY, Chipman J, Greevy RA, Grijalva CG, Griffin MR, et al. Validation of an algorithm to identify heart failure hospitalisations in patients with diabetes within the veterans health administration. BMJ Open 2018;8(3):e020455.

[23] Dai S, Walsh P, Wielgosz A, Gurevich Y, Bancej C, Morrison H. Comorbidities and mortality associated with hospitalized heart failure in Canada. Can J Cardiol 2012;28:74–9.

[24] Parissis JT, Rafouli-Stergiou P, Mebazaa A, Ikonomidis I, Bistola V, Nikolaou M, et al. Acute heart failure in patients with diabetes mellitus: clinical characteristics and predictors of in-hospital mortality. Int J Cardiol 2012;157:108–13.

[25] Greenberg BH, Abraham WT, Albert NM, Chiswell K, Clare R, Stough WG, et al. 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.e1–8].

[26] 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.

[27] Dauriz M, Mantovani A, Bonapace S, Verlato G, Zoppini G, Bonora E, et al. Prognostic impact of diabetes on long-term survival outcomes in patients with heart failure: a meta-analysis. Diabetes Care 2017;40:1597–605.

[28] de Miguel-Yanes JM, Jiménez-García R, Hernández-Barrera V, Méndez-Bailón M, de Miguel-Díez J, Lopez-De-Andrés A. Impact of type 2 diabetes mellitus on in-hospital-mortality after major cardiovascular events in Spain (2002–2014). Cardiovasc Diabetol 2017;16:126.

[29] Yancy CW, Jessup M, Bozkurt B, Butler J, Casey Jr. DE, Colvin MM, et al. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of cardiology/American heart association task force on clinical practice guidelines and the heart failure society of America. J Am Coll Cardiol 2017;70(6):776–803.

[30] Vaduganathan M, Claggett BL, Chatterjee NA, Anand IS, Sweitzer NK, Fang JC, et al. Sudden death in heart failure with preserved ejection fraction: a competing risks analysis from the TOPCAT trial. JACC 2018. https://doi.org/10.1016/j.jchf.2018.02.014.

[31] Nagarajan V, Kohan L, Holland E, Keeley EC, Mazimba S. Obesity paradox in heart

failure: a heavy matter. ESC Heart Fail 2016;3:227–34.

[32] van Melle JP, Bot M, de Jonge P, de Boer RA, van Veldhuisen DJ, Whooley MA. Diabetes, glycemic control, and new-onset heart failure in patients with stable coronary artery disease: data from the heart and soul study. Diabetes Care 2010;33:2084–9.

[33] Blue L, Lang E, McMurray JJ, Davie AP, McDonagh TA, Murdoch DR, et al. Randomised controlled trial of specialist nurse intervention in heart failure. BMJ 2001;323:715–8.

[34] Zamora E, Lupon J. Unidades de insuficiencia cardiaca en España: situación actual. Rev Esp Cardiol 2007;60:874–7.

[35] Rosano GM, Vitale C, Seferovic P. Heart failure in patients with diabetes mellitus. Card Fail Rev 2017;3:52–5.

[36] Abdul-Ghani M, Del Prato S, Chilton R, Defronzo RA. SGLT2 inhibitors and cardiovascular risk: lessons learned from the EMPA-REG OUTCOME Study. Diabetes Care 2016;39:717–25.