REC: CardioClinics

www.reccardioclinics.org

Original article

Risk of outcomes in a Spanish population with heart failure

Nicolás Manito[a], *Carlos Escobar*[b,*], *Beatriz Palacios*[c], *Luis Varela*[c], *Unai Aranda*[c], *Margarita Capel*[c], *Antoni Sicras*[d], *Aram Sicras*[d], *Antonio Hormigo*[e], *Roberto Alcázar*[f], *Manuel Botana*[g]

[a] *Servicio de Cardiología, Hospital de Bellvitge, Hospitalet de Llobregat, Barcelona, Spain*
[b] *Servicio de Cardiología, Hospital Universitario La Paz, Madrid, Spain*
[c] *AstraZeneca, Spain*
[d] *Investigación Sobre Economía y Resultados de la Salud, Atrys Health, Barcelona, Spain*
[e] *Centro de Salud Puerta Blanca, Málaga, Spain*
[f] *Servicio de Nefrología, Hospital Universitario Infanta Leonor, Madrid, Spain*
[g] *Servicio de Endocrinología, Hospital Universitario Lucus Augusti, Lugo, Spain*

ARTICLE INFO

Article history:
Received 7 October 2021
Accepted 29 November 2021
Available online 12 February 2022

Keywords:
Cardiovascular
Chronic kidney disease
Death
Heart failure
Sacubitril/valsartan
Renal
SGLT2 inhibitors

ABSTRACT

Introduction and objectives: To assess mortality, cardiovascular and renal outcomes among patients with heart failure (HF) (primary objective), with a particular focus on the risk of developing chronic kidney disease (CKD) (secondary).

Methods: Observational cohort study, comprising cross-sectional and longitudinal retrospective analyses using secondary data from electronic health records. For the primary objective, adults with prevalent HF, defined as at least one diagnosis of HF prior to the index date (1 January 2017) were included. For the secondary objective, adults with incident HF in 2017 were enrolled.

Results: A total of 21 575 patients had HF in the prevalent population (8391 with CKD at baseline), whereas 3045 patients were included in the incident population. In the prevalent population, the risk of all-cause death (HR, 1.227; 95%CI, 1.172–1.285), CKD hospitalization (HR, 1.427; 95%CI, 1.379–1.479) and acute kidney failure (HR, 1.377; 95%CI, 1.222–1.524) was greater in those patients with HF and CKD vs HF only after 3 years of follow-up. For the incident population, within 24 months from HF diagnosis, 5.9% of patients developed CKD. Overall, 23.4% were taking angiotensin-converting enzyme inhibitors, 26.3% angiotensin receptor blockers, 7.9% sacubitril/valsartan, 64.2% beta blockers, 11.5% aldosterone antagonists and 4.5% sodium-glucose Cotransporter-2 inhibitors.

Abbreviations: CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; HF: heart failure; UACR: urine albumin-to-creatinine ratio; SGLT-2: sodium-glucose cotransporter-2.

* *Corresponding author*.
E-mail address: escobar_cervantes_carlos@hotmail.com (C. Escobar).

https://doi.org/10.1016/j.rccl.2021.11.005

Conclusions: In Spain, patients with HF have a high risk of developing cardiovascular and renal complications. Despite that, there is a substantial proportion of patients that are not taking guideline recommended drugs. A higher use of these drugs could reduce HF burden and complications in clinical practice.

Riesgo de eventos en una población española con insuficiencia cardiaca

Palabras clave:
Cardiovascular
Enfermedad renal crónica
Muerte
Insuficiencia cardiaca
Sacubitrilo/valsartán
Renal
Inhibidores SGLT-2

RESUMEN

Introducción y objetivos: Determinar la mortalidad y los eventos cardiovasculares y renales en pacientes con insuficiencia cardiaca (IC) (objetivo primario), en particular sobre el desarrollo de enfermedad renal crónica (ERC) (secundario).

Métodos: Estudio observacional, con análisis transversal y retrospectivo, empleando datos secundarios de registros electrónicos de salud. Para el objetivo primario se incluyeron adultos con IC prevalente, definida como al menos un diagnóstico de IC antes de la fecha índice (1 de enero de 2017). Para el secundario se incluyeron adultos con IC incidente en 2017.

Resultados: Se incluyeron 21.575 pacientes con IC en la población prevalente (8.391 con ERC basal) y 3.045 en la población incidente. En la población prevalente el riesgo de muerte (HR = 1,227; IC 95%, 1,172-1,285), hospitalización por ERC (HR = 1,427; IC 95%, 1,379-1,479) y fallo renal agudo (HR = 1,377; IC 95%, 1,222-1,524) fue mayor en los pacientes con IC y ERC frente a IC sola, tras 3 años de seguimiento. En la población incidente, a los 24 meses del diagnóstico el 5,9% desarrollaron ERC. Globalmente, el 23,4% tomaban inhibidores de la enzima convertidora de angiotensina, el 26,3% antagonistas de los receptores de angiotensina II, el 7,9% sacubitrilo/valsartán, el 64,2% bloqueadores beta, el 11,5% antialdosterónicos y el 4,5% inhibidores del cotransportador sodio-glucosa tipo 2.

Conclusiones: En España, los pacientes con IC tienen un riesgo elevado de desarrollar complicaciones cardiovasculares y renales. Sin embargo, existe una proporción importante de pacientes que no toman los fármacos recomendados por las guías. Un mayor uso podría reducir la carga de IC y las complicaciones en la práctica clínica.

Introduction

Heart failure (HF) is a common condition. It has been estimated that the current prevalence reaches 2% in developed countries, but will increase in the following years due to the ageing of the population, better management of acute cardiovascular conditions and new HF treatments.[1–4] Despite traditional HF therapies, HF is associated with a poor prognosis and high cost burden.[5,6] In fact, in 2013, the MAGGIC meta-analysis reported that around 40% of HF patients died after only 2.5 years of follow-up.[7] Hospitalizations are the most common complication in patients with chronic HF, mainly due to acute HF decompensation, but also because other conditions, such as chronic kidney disease (CKD).[4,8–10]

The 2021 European HF guidelines recommend the use of angiotensin-converting enzyme inhibitors or sacubitril/valsartan, beta blockers, aldosterone antagonists, and sodium-glucose Cotransporter-2 (SGLT-2) inhibitors as first-line therapies in patients with reduced HF and should be early used in this population.[1] However, according to the available evidence,[11,12] the 2016 HF guidelines recommended a step by step approach, starting with the use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers and beta blockers as a first-line approach, adding aldosterone antagonists if symptoms persisted and then changing to sacubitril/valsartan from angiotensin-converting enzyme inhibitors/angiotensin receptor blockers or adding ivabradine if patients remained symptomatic.[13] Of note, although clinical trials performed in diabetic population had suggested a positive effect on HF incidence with the use of some SGLT-2 inhibitors,[12] their beneficial effects in patients with reduced HF, regardless diabetes status, has recently been demonstrated.[14,15] Unfortunately, data regarding the impact of these new therapies on morbidity and mortality in real-life patients are lacking. On the other hand, patients with reduced ejection fraction exhibit relevant disparities in the clinical profile, treatment and prognosis compared to patients with preserved ejection fraction.[16–18] However, current data about differences in the management and outcomes of both entities are scarce.

The objectives of this study were to assess all-cause mortality, and cardiovascular and renal outcomes among patients with HF (primary objective), with a particular focus on the

risk of developing CKD following diagnosis of HF (secondary objective).

Methods

Observational and cohort study, using secondary data collected from the electronic health records of 7 Spanish Autonomous Communities within the validated BIG PAC database.[19] This study was approved by the Investigation Ethics Committee of Consorci Sanitari from Terrassa. No informed consent was provided, as this was a secondary data study and data were fully anonymized and dissociated from patients.

To assess the objectives of the study, cross-sectional and longitudinal retrospective analyses were performed. For the primary objective of the study, adults with prevalent HF, defined as at least one diagnosis of HF prior to the index date (1 January 2017) (prevalent population) were included. CKD was defined as an estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2 by CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) or ≥60 mL/min/1.73 m^2 with a urine albumin-to-creatinine ratio (UACR) ≥30 mg/g at index date. For the secondary objective, adults with incident HF, defined as new diagnosis of HF in 2017 were included (incident population). Index date was the first HF diagnosis date in 2017. According to DAPA-HF and DELIVER trials,[14,20] HF with reduced o preserved left ventricular ejection fraction was defined as those patients with HF and a left ventricular ejection fraction ≤ 40% or >40%, respectively. In both populations, CKD stages were classified, as follows: CKD stage 1: eGFR ≥ 90 mL/min/1.73 m^2 and UACR ≥ 30 mg/g; CKD stage 2: eGFR 60–89 mL/min/1.73 m^2 and UACR ≥ 30 mg/g; CKD stage 3a: eGFR 45–59 mL/min/1.73 m^2; CKD stage 3b: eGFR 30–44 mL/min/1.73 m^2; CKD stage 4: eGFR 15–29 mL/min/1.73 m^2; CKD stage 5: eGFR < 15 mL/min/1.73 m^2; CKD unspecified: no eGFR data available.

In the prevalent population, at baseline (index date 1 January 2017), biodemographic data, physical examination, HF data, laboratory data, comorbidities and concomitant drugs were recorded. In the incident population, baseline clinical characteristics, including comorbidities, laboratory data and concomitant medications were reported in relation to the index date (the first HF diagnosis date in 2017). Data were presented according to the HF type and CKD stage.

Regarding the primary objective (prevalent population), for overall mortality, patient follow-up began at index date (1 January 2017) and continued until the death date or censored at the earliest of the end of enrolment for the latest available linked data or observational study period end date (31 December 2019, 3 years of follow-up). For other outcomes, patient follow-up began on the index date and continued until the specified cardiorenal event (hospitalization for HF, CKD, albuminuria transition from UACR < 30 to 30–300 mg/g and acute kidney failure) occurred or was censored at the earliest of the end of enrolment for the latest available linked data, death date or observational study period end date (31 December 2019, 3 years of follow-up). Within each event category, patients were censored after the first event for the category but not for events from other categories. For the secondary objective of the study, patients were followed from HF diagnosis in 2017, for 24 months.

Statistical analysis

Absolute and relative frequency distributions were used to describe the qualitative variables and mean and standard deviation for quantitative variables. Event rates were calculated as the number of new cases from index date in the 24 months of follow up divided by the total time at risk of the event. Event rates were presented as events and events per 100 patient-years for all-cause death, HF, CKD, and albuminuria. Time to first hospitalization due to event was analyzed descriptively. Follow-up was censored at observation period, or death end unless an event had occurred. The corresponding adjusted hazard ratios and 95% confidence intervals to estimate the risk of outcomes in the prevalent population after 3 years of follow-up were calculated. The pathway to develop CKD in patients with incident HF was evaluated for 24 months from index date. Categorical variables were compared using the chi-square test or the Fisher exact test when appropriate. When 2 means were compared, the t test or the Mann–Whitney test was used, as applicable. The data were analyzed using the statistical package SPSS v25.0 (SPSS Inc., Chicago, United States).

Results

Overall, 21 575 patients had HF in the prevalent population (13 184 without CKD at baseline and 8391 with CKD at baseline), whereas 3045 patients were included in the incident population (Fig. 1 of the supplementary data).

Among patients with HF but without CKD at baseline, mean age was 77.8 ± 13.7 years, 52.7% were men, 31.9% type 2 diabetes, and 21.4% prior myocardial infarction. With regard to the type of HF, 51.7% had HF with reduced left ventricular ejection fraction and 48.3% HF with preserved left ventricular ejection fraction. With respect to treatments, 30.6%, 32.4% and 7.7% were taking angiotensin-converting enzyme inhibitors, angiotensin receptor blockers and sacubitril/valsartan, respectively, and 4.3% SGLT-2 inhibitors. Compared with patients with HF without CKD, those with CKD were older, more commonly women, had higher levels of systolic blood pressure, body mass index, glycosylated hemoglobin (HbA1c), UACR and serum potassium levels. Comorbidities, including diabetes, atrial fibrillation, myocardial infarction, stroke, and peripheral artery disease were more common in those patients with CKD and HF (vs HF alone). In addition, more patients in the HF and CKD population (vs HF alone) were taking more angiotensin-converting enzyme inhibitors, angiotensin receptor blockers and beta blockers, with a similar proportion of aldosterone antagonists and SGLT-2 inhibitors (Table 1).

Regarding outcomes between HF vs HF and CKD patients in the prevalent population after 3 years of follow-up, the risk of all-cause death (HR, 1.227; 95%CI, 1.172–1.285; $P < .001$), hospitalization for CKD (HR, 1.427; 95%CI, 1.379–1.479; $P < .001$), and acute kidney failure (HR, 1.377; 95%CI, 1.222–1.524; $P < .001$)

Table 1 – Clinical characteristics and treatments in the prevalent HF population at index date.

	Only HF (*n* = 13 184; 61.1%)	HF + CKD (*n* = 8391; 38.9%)	$P_{HF+CKD\ vs\ CKD}$
Biodemographic data			
Age, years	77.8 ± 13.7	79.4 ± 10.9	<.001
Gender, male, (%)	6949 (52.7)	4237 (50.5)	<.001
Physical examination			
Systolic blood pressure, mmHg	130.7 ± 21.3	133.9 ± 20.5	<.001
Diastolic blood pressure, mmHg	83.8 ± 7.2	83.7 ± 6.9	.312
BMI, kg/m²	28.4 ± 5.0	28.9 ± 5.2	<.001
BMI > 30 kg/m², *n* (%)	2914 (22.1)	2013 (24.0)	<.001
Laboratory data			
HbA1c, %	7.3 ± 1.8	7.7 ± 2.0	<.001
<7%, *n* (%)	6895 (52.3)	4256 (50.7)	<.001
7 to <8%, *n* (%)	2278 (17.3)	1680 (20.0)	<.001
8 to <9%, *n* (%)	1185 (9.0)	867 (10.3)	<.001
≥9%, *n* (%)	936 (7.1)	769 (9.2)	<.001
*eGFR**	85.5 ± 7.2	46.4 ± 9.8	<.001
UACR, mg/g	16.7 ± 9.8	361.2 ± 148.5	<.001
Serum potassium levels, mmol/L	4.5 ± 0.5	5.7 ± 1.6	<.001
Left ventricular ejection fraction, %	44.2 ± 10.2	43.4 ± 10.1	.235
Comorbidities, *n* (%)			
CVD	5415 (41.1)	5180 (61.7)	<.001
Stroke	1364 (10.3)	1030 (12.3)	<.001
Myocardial infarction	2824 (21.4)	2154 (25.7)	<.001
PAD	681 (5.2)	564 (6.7)	<.001
Atrial fibrillation	4379 (33.2)	2970 (35.4)	<.001
HF	13 184 (100)	8391 (100)	–
HF-reduced ejection fraction	6810 (51.7)	4465 (53.2)	<.001
HF-preserved ejection fraction	6374 (48.3)	3926 (46.8)	<.001
CKD	–	8391 (100)	–
Stage 1	–	977 (11.6)	–
Stage 2	–	1584 (18.9)	–
Stage 3a	–	1753 (20.9)	–
Stage 3b	–	1961 (23.4)	–
Stage 4	–	1127 (13.4)	–
Stage 5	–	296 (3.5)	–
Type 2 diabetes	4200 (31.9)	5034 (60.0)	<.001
Hyperkalemia	6 (0)	851 (10.1)	–
Medications, n (%)			
CVD risk treatment	13 184 (100)	8391 (100)	–
Antihypertensives	12 230 (92.8)	7960 (94.9)	<.001
ACEi	4034 (30.6)	2716 (32.4)	<.001
ARBs	4269 (32.4)	3548 (42.3)	<.001
ARNI	1017 (7.7)	743 (8.9)	.142
Beta blockers	9107 (69.1)	5998 (71.5)	<.001
Loop diuretics	9263 (70.3)	5978 (71.2)	.186
Aldosterone antagonists	4258 (32.3)	2781 (33.1)	.130
Calcium channel blockers	1234 (9.4)	658 (7.8)	<.001
Thiazide diuretics	665 (5.0)	433 (5.2)	.747
Antidiabetics	3823 (29.0)	3571 (42.6)	<.001
Metformin	2739 (20.8)	2021 (24.1)	<.001
Sulfonylurea	1571 (11.9)	969 (11.5)	.761
DPP4 inhibitors	1371 (10.4)	962 (11.5)	.098
SGLT-2 inhibitors	571 (4.3)	333 (4.0)	.933
GLP-1 receptor agonists	141 (1.1)	221 (2.6)	<.001
Metiglinides	190 (1.4)	375 (4.5)	<.001
Thiazolidinediones	25 (0.2)	27 (0.3)	.977
Acarbose	22 (0.2)	20 (0.2)	.849
Insulin	950 (7.2)	1255 (15.0)	<.001
Statins	7846 (59.5)	5327 (63.5)	<.001
Digoxin	878 (6.7)	524 (6.2)	.891
Nitrates	1442 (10.9)	1267 (15.1)	<.001

Table 1 (*Continued*)

	Only HF (*n* = 13 184; 61.1%)	HF + CKD (*n* = 8391; 38.9%)	$P_{HF+CKD\ vs\ CKD}$
Warfarin/acenocoumarol	2506 (19.0)	1887 (22.5)	<.001
Low dose aspirin	2819 (21.4)	2518 (30.0)	<.001
Receptor $P2Y_{12}$ antagonists	1041 (7.9)	880 (10.5)	<.001

ACEi, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; ARNI, angiotensin receptor and neprilysin inhibition; BMI, body mass index; CVD, cardiovascular disease; CKD, chronic kidney disease; CVD, cardiovascular disease; DPP4, dipeptidyl peptidase 4; eGFR, estimated glomerular filtration rate; *, mL/min/1.73 m^2; GLP-1, glucagon-like peptide-1; HF, heart failure; PAD, peripheral artery disease; SGLT-2, sodium-glucose Cotransporter-2; UACR, Urine albumin-to-creatinine ratio; hyperkalemia: serum potassium > 5.5 mmol/L.

Table 2 – Risk of outcomes* between HF vs CKD and HF patients in the prevalent population after 3 years of follow-up.

Group	Endpoint	Follow-up (median, days)	Events, N	%	$HR_{CKD\ and\ HF\ vs\ HF}$	95%CI	P
CKD and HF	All-cause death	428	3132	37.3%	1.227	1.172–1.285	<.001
HF		552	4579	34.7%			
CKD and HF	HF	447	3994	47.6%	1.013	0.973–1.056	.526
HF		458	5416	41.1%			
CKD and HF	CKD	545	2097	25.0%	1.427	1.379–1.479	<.001
HF		538	3070	23.3%			
CKD and HF	UACR progression:	504	43	0.5%	1.309	0.956–1.770	.094
HF	<30 to 30–300 mg/g	548	725	5.5%			
CKD and HF	Acute kidney failure	592	164	2.0%	1.377	1.222–1.524	<.001
HF	(ICD N17)	642	49	0.4%			

95%CI, confidence interval; CKD, chronic kidney disease; HF, heart failure; UACR, urine albumin-to-creatinine ratio.
* All-cause mortality and first hospitalization for cardiorenal events (HF, CKD, acute kidney failure) or albuminuria transitions during follow-up.

was greater in those patients with HF and CKD compared to HF only patients (Table 2, and Fig. 2 of the supplementary data).

In the incident population, 3045 patients with HF (2435 [79.6%] without CKD at baseline) were included (Table 3). Overall, mean age was 65.4 ± 23.2 years, 51.4% men, left ventricular ejection fraction 45.4 ± 11%, eGFR 85.8 ± 7.9 mL/min/1.73 m^2 and UACR 96.5 ± 44.4 mg/g. One third of patients had diabetes, 20.0% CKD and 14.1% prior myocardial infarction. Patients without CKD at baseline were younger and suffered less from prior myocardial infarction, atrial fibrillation or stroke. Data according to the type of HF (reduced and preserved left ventricular ejection fraction) are shown in Tables 1 and 2 of the supplementary data. Despite patients with preserved HF were older than those with reduced HF, both had many comorbidities. With regard to HF treatments, in the overall incident HF population, 23.4% were taking angiotensin-converting enzyme inhibitors, 26.3% angiotensin receptor blockers, 7.9% sacubitril/valsartan (total 57.6%), 64.2% beta blockers, 11.5% aldosterone antagonists and 4.5% SGLT-2 inhibitors.

Within 24 months from HF diagnosis, eGFR progressively decreased from 85.8 ± 7.5 to 75.9 ± 7.3 mL/min/1.73 m^2; $P < .001$ (from 96.2 ± 3.2 to 85.9 ± 7.8 mL/min/1.73 m^2 among those patients without CKD at baseline), whereas UACR increased from 96.5 ± 44.4 to 103.4 ± 42.4 mg/g; $P < .001$ (from 14.8 ± 6.7 to 15.4 ± 7.2 mg/g; $P = .003$ among those patients without CKD at baseline). The same trend towards worsening was observed in all stages for patients with CKD at baseline (Table 3 of the supplementary data). Thus, during this period, 5.9% of patients developed CKD, regardless of left ventricular ejection fraction (Table 4). In the overall study population, all-cause death, and hospitalization for HF and CKD were 17.2, 20.6 and 9.4 per 100 patient-year, after 24 months of follow-up, respectively. These numbers were 16.1, 20.2 and 9.3 per 100 patient-year in those patients without CKD at baseline and 21.9, 23.8 and 11.0 per 100 patient-year, in those with CKD at baseline, respectively. In general, outcome rates increased and time to first event shortened as renal function worsened (Table 5). These figures were higher in those patients with HF and reduced left ventricular ejection fraction than in those with HF and preserved left ventricular ejection fraction, both in patients with or without CKD at index date, consistent with the slightly higher percentage of patients with reduced ejection fraction HF who developed CKD at the end of the 24-month follow up period (6.0% vs 5.8%, respectively) (Tables 4 and 5 of the supplementary data). In addition, in the overall study population, 6.4 per 100 patient-year developed type 2 diabetes during this period (Table 5), slightly more common in those patients with HF and reduced left ventricular ejection fraction than in those with HF and preserved left ventricular ejection fraction (Tables 4 and 5 of the supplementary data).

Discussion

Our study showed in a wide sample of patients representative of the Spanish population, that both prevalent and incident HF patients have many comorbidities and high risk of presenting cardiovascular and renal complications that could be partially related with an underuse of HF guidelines recommended therapies in a substantial proportion of patients.

Table 3 – Clinical characteristics and treatments in the incident HF population at baseline.

	All HF (*n* = 3045; 100%)	HF without CKD (*n* = 2435; 79.6%)	$P_{HF\ without\ CKD\ vs\ HF\ CKD}$	HF + CKD at index date												Total with CKD (*n* = 610; 20.4%)
				Stage 1 (*n* = 19; 3.1%)	Stage 2 (*n* = 115; 18.9%)	$P_{Stage\ 2\ vs\ 1}$	Stage 3a (*n* = 201; 33.0%)	$P_{Stage\ 3a\ vs\ 1}$	Stage 3b (*n* = 148; 24.3%)	$P_{Stage\ 3b\ vs\ 1}$	Stage 4 (*n* = 44; 7.2%)	$P_{Stage\ 4\ vs\ 1}$	Stage 5 (*n* = 37; 6.1%)	$P_{Stage\ 5\ vs\ 1}$	Unspecified (*n* = 46; 7.5%)	$P_{Unsp\ vs\ 1}$	
Biodemographic data																
Age, years	65.4 ± 23.2	60.6 ± 20.4	<.001	58.4 ± 24.5	59.8 ± 24.4	.817	61.1 ± 23.6	.635	65.2 ± 22.7	.225	68.7 ± 21.4	.099	69.8 ± 20.3	.069	59.1 ± 20.8	.907	67.8 ± 22.1
Gender, male, *n* (%)	1565 (51.4)	1259 (51.7)	.116	5 (26.3)	58 (50.4)	<.001	103 (51.2)	<.001	74 (50.0)	<.001	23 (52.3)	<.001	19 (51.4)	<.001	24 (52.2)	<.001	306 (50.2)
Physical examination																	
Systolic blood pressure, mmHg	129.8 ± 19.8	129.6 ± 20.4	.595	128.6 ± 21.2	128.7 ± 21.3	.798	129.2 ± 20.5	.759	129.1 ± 20.6	.845	129.8 ± 20.8	.756	130.2 ± 22.1	.845	128.7 ± 19.7	.657	130.1 ± 22.1
Diastolic blood pressure, mmHg	83.5 ± 6.9	83.4 ± 7.1	<.001	82.9 ± 7.0	82.8 ± 6.8	.854	82.9 ± 6.9	.985	83.2 ± 7.0	.756	83.1 ± 7.2	.654	84.1 ± 7.1	.761	82.9 ± 7.0	.758	82.2 ± 6.9
BMI, kg/m^2	28.7 ± 5.1	28.6 ± 5.0	<.001	28.5 ± 4.9	28.7 ± 4.8	.867	28.6 ± 4.9	.854	28.8 ± 5.1	.654	28.9 ± 5.0	.754	28.9 ± 4.9	.752	28.7 ± 5.1	.861	27.8 ± 5.0
HF data																	
Left ventricular ejection fraction, %	45.4 ± 11	45.8 ± 9	<.001	45.7 ± 10.6	45.5 ± 9.9	.789	45.5 ± 9.1	.845	45.4 ± 10.6	.745	45.3 ± 11	.845	44.9 ± 10.5	.456	45.8 ± 10.6	.769	43.3 ± 9.4
LVEF ≤ 40%, n (%)	1542 (50.6)	1223 (50.2)	.155	10 (52.6)	58 (50.4)	.7	106 (52.7)	.997	79 (53.4)	.829	23 (52.3)	.974	19 (51.4)	.982	24 (52.2)	.8	319 (52.3)
LVEF > 40%, n (%)	1496 (49.1)	1205 (49.5)	.159	9 (47.4)	57 (49.6)	.936	95 (47.3)	.993	69 (46.6)	.762	21 (47.7)	.795	18 (48.6)	.804	22 (47.8)	.796	291 (47.7)
NYHA functional class, n (%)																	
I	386 (12.7)	311 (12.8)	.829	3 (15.8)	15 (13.0)	.987	26 (12.9)	.715	17 (11.5)	.717	4 (9.1)	.63	3 (8.1)	.848	7 (15.2)	.933	75 (12.3)
II	1391 (45.7)	1130 (46.4)	<.001	8 (42.1)	48 (41.7)	.996	87 (43.3)	.873	63 (42.6)	.982	19 (43.2)	.872	16 (43.2)	.765	20 (43.5)	.802	261 (42.8)
III	1134 (37.2)	890 (36.6)	<.001	7 (36.8)	44 (38.3)	.797	80 (39.8)	.85	61 (41.2)	.862	19 (43.2)	.837	16 (43.2)	.79	17 (37.0)	.84	244 (40.0)
IV	124 (4.1)	97 (4.0)	.798	1 (5.3)	4 (3.5)	.801	9 (4.5)	.912	7 (4.7)	.706	2 (4.5)	.777	2 (5.4)	.954	2 (4.3)	.842	27 (4.4)
Laboratory data																	
*eGFR**	85.8 ± 7.9	96.2 ± 4.9	<.001	94.3 ± 3.7	74.7 ± 8.6	<.001	52.1 ± 10.8	<.001	36.8 ± 10.6	<.001	21.9 ± 10.5	<.001	8.8 ± 7.4	<.001	–	–	43.4 ± 8.8
UACR, mg/g	96.5 ± 44.4	14.8 ± 6.8	<.001	105.8 ± 43.4	128.1 ± 64.1	<.001	249.8 ± 122.4	<.001	261.3 ± 109.7	<.001	1631.4 ± 750.4	<.001	1651.3 ± 726.6	<.001	122.3 ± 51.4	<.001	384.2 ± 180.6

Table 3 (*Continued*)

	All HF (*n* = 3045; 100%)	HF without CKD (*n* = 2435; 79.6%)	$P_{HF\ without\ CKD\ vs\ HF\ CKD}$	HF + CKD at index date												Total with CKD (*n* = 610; 20.4%)
				Stage 1 (*n* = 19; 3.1%)	Stage 2 (*n* = 115; 18.9%)	$P_{Stage\ 2\ vs\ 1}$	Stage 3a (*n* = 201; 33.0%)	$P_{Stage\ 3a\ vs\ 1}$	Stage 3b (*n* = 148; 24.3%)	$P_{Stage\ 3b\ vs\ 1}$	Stage 4 (*n* = 44; 7.2%)	$P_{Stage\ 4\ vs\ 1}$	Stage 5 (*n* = 37; 6.1%)	$P_{Stage\ 5\ vs\ 1}$	Unspecified (*n* = 46; 7.5%)	$P_{Unsp\ vs\ 1}$	
HbA1c. %	7.1 ± 1.9	5.3 ± 1.4	<.001	6.1 ± 1.7	6.8 ± 2	.152	6.9 ± 1.9	<.001	7.1 ± 2	.421	7.3 ± 2.1	.345	7.5 ± 2	.453	6.9 ± 2	.453	6.7 ± 1.9
<7%, *n* (%)	1574 (51.7)	1256 (51.6)	.924	10 (52.6)	60 (52.2)	.949	105 (52.2)	.907	77 (52.0)	.986	23 (52.3)	.912	19 (51.4)	.703	24 (52.2)	.779	318 (52.1)
7–<8%, *n* (%)	535 (17.6)	433 (17.8)	.627	0	19 (16.5)	–	35 (17.4)	–	26 (17.6)	–	7 (15.9)	.279	7 (18.9)	.075	8 (17.4)	.183	102 (16.7)
8–<9%, *n* (%)	270 (8.9)	205 (8.4)	<.001	2 (10.5)	11 (9.6)	.893	20 (10.0)	.784	18 (12.2)	.815	5 (11.4)	.84	5 (13.5)	.844	4 (8.7)	.851	65 (10.7)
≥9%, *n* (%)	231 (7.6)	174 (7.1)	.074	1 (5.3)	9 (7.8)	.82	19 (9.5)	.989	16 (10.8)	.566	5 (11.4)	.78	4 (10.8)	.946	3 (6.5)	.761	57 (9.3)
Comorbidities, *n* (%)																	
CVD	2246 (73.8)	1801 (74.0)	.374	14 (73.7)	85 (73.9)	.927	148 (73.6)	.81	105 (70.9)	.890	32 (72.7)	.72	28 (75.7)	.907	33 (71.7)	.927	445 (73.0)
Myocardial infarction	429 (14.1)	307 (12.6)	<.001	3 (15.8)	23 (20.0)	.98	41 (20.4)	.998	29 (19.6)	.959	9 (20.5)	.765	8 (21.6)	.818	9 (19.6)	.812	122 (20.0)
Stroke	183 (6.0)	101 (4.1)	<.001	2 (10.5)	14 (12.2)	.988	27 (13.4)	.9	23 (15.5)	.488	6 (13.6)	.968	5 (13.5)	.769	5 (10.9)	.751	82 (13.4)
Atrial fibrillation	836 (27.5)	626 (25.7)	<.001	7 (36.8)	39 (33.9)	.891	69 (34.3)	.961	52 (35.1)	.925	15 (34.1)	.995	13 (35.1)	.942	15 (32.6)	.871	210 (34.4)
Peripheral artery disease	137 (4.5)	102 (4.2)	.243	1 (5.3)	6 (5.2)	.923	11 (5.5)	.729	10 (6.8)	.965	3 (6.8)	.94	2 (5.4)	.849	2 (4.3)	.916	35 (5.7)
CKD	610 (20.0)	0	–	19 (100)	115 (100)	–	201 (100)	–	148 (100)	–	44 (100)	–	37 (100)	–	46 (100)	–	610 (100)
Diabetes	1010 (33.2)	801 (32.9)	.241	7 (36.8)	38 (33.0)	.766	70 (34.8)	.953	51 (34.5)	.894	15 (34.1)	.754	13 (35.1)	.873	15 (32.6)	.898	209 (34.3)
Medications, *n* (%)																	
HF medication	3001 (98.6)	2391 (98.2)	.206	19 (100)	115 (100)	–	201 (100)	–	148 (100)	–	44 (100)	–	37 (100)	–	46 (100)	–	610 (100)
RAAS inhibitors	1493 (49.0)	1205 (49.5)	<.001	10 (52.6)	51 (44.3)	.205	93 (46.3)	.506	70 (47.3)	.492	21 (47.7)	.933	19 (51.4)	.98	24 (52.2)	.919	288 (47.2)
ACEi	712 (23.4)	558 (22.9)	<.001	5 (26.3)	27 (23.5)	.986	50 (24.9)	.847	37 (25.0)	.892	12 (27.3)	.77	11 (29.7)	.986	12 (26.1)	.911	154 (25.2)
ARBs	801 (26.3)	632 (26.0)	.128	6 (31.6)	30 (26.1)	.629	54 (26.9)	.729	42 (28.4)	.843	12 (27.3)	.785	11 (29.7)	.968	14 (30.4)	.74	169 (27.7)
Beta blockers	1954 (64.2)	1531 (62.9)	<.001	13 (68.4)	80 (69.6)	.733	138 (68.7)	.74	103 (69.6)	.934	31 (70.5)	.894	26 (70.3)	.958	32 (69.6)	.767	423 (69.3)
Loop-diuretics	2090 (68.6)	1655 (68.0)	<.001	13 (68.4)	83 (72.2)	.937	145 (72.1)	.885	105 (70.9)	.99	31 (70.5)	.774	27 (73.0)	.793	31 (67.4)	.923	435 (71.3)
Aldosterone antagonists	349 (11.5)	273 (11.2)	.231	2 (10.5)	14 (12.2)	.823	25 (12.4)	.828	20 (13.5)	.97	5 (11.4)	.865	4 (10.8)	.891	6 (13.0)	.966	76 (12.5)
ARNI	242 (7.9)	187 (7.7)	.275	1 (5.3)	10 (8.7)	.754	18 (9.0)	.833	15 (10.1)	.946	4 (9.1)	.956	3 (8.1)	.972	4 (8.7)	.791	55 (9.0)
Digoxin	213 (7.0)	169 (6.9)	.866	1 (5.3)	8 (7.0)	.955	15 (7.5)	.909	11 (7.4)	.73	3 (6.8)	.947	3 (8.1)	.716	3 (6.5)	.722	44 (7.2)

Table 3 (*Continued*)

	All HF (*n* = 3045; 100%)	HF without CKD (*n* = 2435; 79.6%)	$P_{HF\ without\ CKD\ vs\ HF\ CKD}$	HF + CKD at index date													Total with CKD (*n* = 610; 20.4%)
				Stage 1 (*n* = 19; 3.1%)	Stage 2 (*n* = 115; 18.9%)	$P_{Stage\ 2\ vs\ 1}$	Stage 3a (*n* = 201; 33.0%)	$P_{Stage\ 3a\ vs\ 1}$	Stage 3b (*n* = 148; 24.3%)	$P_{Stage\ 3b\ vs\ 1}$	Stage 4 (*n* = 44; 7.2%)	$P_{Stage\ 4\ vs\ 1}$	Stage 5 (*n* = 37; 6.1%)	$P_{Stage\ 5\ vs\ 1}$	Unspecified (*n* = 46; 7.5%)	$P_{Unsp\ vs\ 1}$	
Antidiabetics	867 (28.5)	682 (28.0)	<.001	6 (31.6)	35 (30.4)	.808	60 (29.9)	.799	45 (30.4)	.962	14 (31.8)	.814	12 (32.4)	.954	13 (28.3)	.838	185 (30.3)
Metformin	594 (19.5)	462 (19.0)	<.001	5 (26.3)	24 (20.9)	.542	43 (21.4)	.904	32 (21.6)	.865	9 (20.5)	.77	9 (24.3)	.738	10 (21.7)	.987	132 (21.6)
Sulfonylurea	367 (12.1)	295 (12.1)	.774	2 (10.5)	15 (13.0)	.714	23 (11.4)	.833	17 (11.5)	.892	5 (11.4)	.746	4 (10.8)	.723	6 (13.0)	.746	72 (11.8)
DPP4 inhibitors	339 (11.1)	273 (11.2)	.862	2 (10.5)	12 (10.4)	.703	22 (10.9)	.984	16 (10.8)	.932	5 (11.4)	.909	4 (10.8)	.981	5 (10.9)	.723	66 (10.8)
SGLT-2 inhibitors	138 (4.5)	101 (4.1)	.236	1 (5.3)	6 (5.2)	.994	13 (6.5)	.967	10 (6.8)	.832	3 (6.8)	.967	2 (5.4)	.932	2 (4.3)	.87	37 (6.1)
GLP-1 receptor agonists	29 (1.0)	23 (0.9)	.913	0	0	–	1 (0.5)	–	2 (1.4)	–	1 (2.3)	–	1 (2.7)	–	1 (2.2)	–	6 (1.0)
Metiglinides	43 (1.4)	35 (1.4)	.963	0	1 (0.9)	–	2 (1.0)	–	2 (1.4)	–	1 (2.3)	–	1 (2.7)	–	1 (2.2)	–	8 (1.3)
Thiazolidinedione	10 (0.3)	5 (0.2)	.714	0	0	–	1 (0.5)	–	2 (1.4)	–	1 (2.3)	–	1 (2.7)	–	0	–	5 (0.8)
Acarbose	6 (0.2)	5 (0.2)	.973	0	0	–	0	–	1 (0.7)	–	0	–	0	–	0	–	1 (0.2)
Insulin	222 (7.3)	176 (7.2)	.813	1 (5.3)	8 (7.0)	.763	15 (7.5)	.861	12 (8.1)	.881	4 (9.1)	.823	3 (8.1)	.839	3 (6.5)	.761	46 (7.5)
Statins	1763 (57.9)	1396 (57.3)	<.001	11 (57.9)	68 (59.1)	.928	122 (60.7)	.848	90 (60.8)	.786	27 (61.4)	.962	23 (62.2)	.886	26 (56.5)	.735	367 (60.2)
Antihypertensives	626 (20.6)	490 (20.1)	.212	4 (21.1)	24 (20.9)	.900	45 (22.4)	.91	34 (23.0)	.928	10 (22.7)	.848	9 (24.3)	.71	10 (21.7)	.853	136 (22.3)
Dihydropyridine CCB	439 (14.4)	352 (14.5)	.91	2 (10.5)	17 (14.8)	.997	29 (14.4)	.805	21 (14.2)	.903	6 (13.6)	.898	5 (13.5)	.881	7 (15.2)	.998	87 (14.3)
Thiazide diuretics	185 (6.1)	143 (5.9)	.421	1 (5.3)	7 (6.1)	.737	14 (7.0)	.8	11 (7.4)	.896	3 (6.8)	.922	3 (8.1)	.83	3 (6.5)	.747	42 (6.9)
Non-dihydropyridine CCB	92 (3.0)	68 (2.8)	.606	1 (5.3)	4 (3.5)	.945	8 (4.0)	.749	6 (4.1)	.965	2 (4.5)	.763	2 (5.4)	.962	1 (2.2)	.873	24 (3.9)
Nitrates	312 (10.2)	236 (9.7)	<.001	2 (10.5)	13 (11.3)	.917	25 (12.4)	.74	19 (12.8)	.968	6 (13.6)	.92	6 (16.2)	.802	5 (10.9)	.831	76 (12.5)
Warfarin/ acenocoumarol	618 (20.3)	496 (20.4)	.859	3 (15.8)	22 (19.1)	.902	41 (20.4)	.722	30 (20.3)	.794	9 (20.5)	.836	8 (21.6)	.949	9 (19.6)	.981	122 (20.0)
Low dose aspirin	632 (20.8)	492 (20.2)	<.001	4 (21.1)	25 (21.7)	.740	47 (23.4)	.741	35 (23.6)	.831	10 (22.7)	.783	9 (24.3)	.909	10 (21.7)	.803	140 (23.0)
Receptor $P2Y_{12}$ antagonists	232 (7.6)	176 (7.2)	.208	1 (5.3)	9 (7.8)	.813	19 (9.5)	.837	15 (10.1)	.964	4 (9.1)	.835	4 (10.8)	.808	4 (8.7)	.702	56 (9.2)

ACEi, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; ARNI, angiotensin receptor and neprilysin inhibition; BMI, body mass index; CCB, calcium channel blockers; CVD, cardiovascular disease; CKD, chronic kidney disease; DPP4, dipeptidyl peptidase 4; eGFR, estimated glomerular filtration rate; * mL/min/1.73 m^2; GLP-1: glucagon-like peptide-1; HF: heart failure; LVEF: left ventricular ejection fraction; RAAS: renin–angiotensin system; SBP: systolic blood pressure; SGLT-2: sodium-glucose cotransporter-2; UACR: urine albumin-to-creatinine ratio.

Table 4 – Percentage of patients who developed CKD within 24 months from HF diagnosis.

		3 months	6 months	12 months	24 months	Total
All HF patients who develop CKD according to CKD grade, n (%)	Stage 1	1 (20.0)	3 (10.7)	2 (6.3)	4 (5.1)	10 (7.0)
	Stage 2	0	4 (14.3)	4 (12.5)	14 (17.9)	22 (15.4)
	Stage 3a	2 (40.0)	8 (28.6)	10 (31.3)	22 (28.2)	42 (29.4)
	Stage 3b	2 (40.0)	5 (17.9)	8 (25.0)	18 (23.1)	33 (23.1)
	Stage 4	0	3 (10.7)	5 (15.6)	8 (10.3)	16 (11.2)
	Stage 5	0	3 (10.7)	0	4 (5.1)	7 (4.9)
	Unspecified	0	2 (7.1)	3 (9.4)	8 (10.3)	13 (9.1)
	Total CKD	5 (100)	28 (100)	32 (100)	78 (100)	143 (100)
HF who stay without CKD, n (%)	Baseline					
All HF	2435	2430 (99.8)	2404 (98.7)	2375 (97.5)	2302 (94.5)	2292 (94.1)
HF-rEF	1223	1221 (99.8)	1207 (87.7)	1193 (97.5)	1155 (94.4)	1150 (94.0)
HF-pEF	1212	1209 (99.8)	1197 (98.7)	1182 (97.5)	1147 (94.6)	1142 (94.2)

CKD: chronic kidney disease; HF: heart failure; HF-rEF: heart failure with reduced ejection fraction; HF-pEF: heart failure with preserved ejection fraction.

At baseline, HF patients were old and had many comorbidities. Of note, the clinical profile of patients worsened with the presence of CKD. This is in line with previous studies performed in Spain and in other developed countries.[21,22] In fact, our data were collected from the BIG-PAC database that comprised nearly 1.8 million persons daily attended in clinical practice and has been demonstrated its validity for observational studies and its representativeness of the Spanish population.[19]

On the other hand, approximately 52% of prevalent or incident patients had HF with reduced left ventricular ejection fraction and the remaining 48% preserved HF. First, it should be emphasized that in our study, in line with the DAPA-HF and DELIVER trials,[14,20] preserved HF was defined as those patients with HF and a left ventricular ejection fraction > 40%. However, current European guidelines define preserved HF with an ejection fraction ≥ 50% and mildly reduced HF with an ejection fraction 41%–49%,[1] and this could partially limit the interpretation of the data.

Previous studies have shown that HF with preserved ejection fraction accounts for at least half of the cases of HF, but reaches almost three-quarters of all HF patients among those subjects aged 65 years or older.[17,18,23] Although previous studies have shown relevant differences in the clinical profile of patients with both entities, with more comorbidities in those patients with preserved HF,[24,25] in our study baseline characteristics were quite similar. Although the definition of preserved HF was different in our study, these data suggest that the type of HF cannot be based solely on the presence of some particular conditions, but on an adequate diagnostic approach.[1] In any case, although more evidences exist about treatments with reduced HF, overall, the management of HF patients is complex and requires a comprehensive approach.[1]

With regard to HF treatments, in the overall study population, around 30%–40% of patients were not taking angiotensin-converting enzyme inhibitors, angiotensin receptor blockers or sacubitril/valsartan, 30%–35% beta blockers, 70%–90% aldosterone antagonists and 95% SGLT-2 inhibitors (85% among patients with type 2 diabetes). In those patients with HF and reduced left ventricular ejection fraction, these numbers were 19%, 35%, 88% and 95% (83%), respectively. Although the prevalence of renal dysfunction was important, partially explained by the elderly population, some with hyperkalemia, and this could have had an impact on the management of these patients, overall, there was a substantial proportion of patients that were not taking those drugs that have demonstrated clinical benefits on reduced HF patients. It is likely that the use of oral potassium-binding agents in some cases could increase the use of renin–angiotensin system inhibitors.[26] On the other hand, in the case of SGLT-2 inhibitors this low use could be explained because the DAPA-HF and the EMPEROR-Reduced trials were published in 2019 and 2020, respectively.[14,15] However, the use of other HF guideline-directed medical therapies was too low, despite the clear recommendations performed by 2016 European guidelines, the current recommendations at the moment of the study.[13] Although data provided from specific HF units show better numbers, studies performed in other clinical settings report similar figures than those observed in our study.[27–30] As a result, more efforts are necessary to reduce the gap between guidelines recommendations and clinical practice.[31,32] Of note, the 2021 European guidelines recommend the use of angiotensin-converting enzyme inhibitors/sacubitril-valsartan, beta blockers, aldosterone antagonists and SGLT-2 inhibitors as first line-therapy in the treatment of reduced HF patients,[1] as this approach has been shown to significantly reduce mortality and HF hospitalization compared to standard HF therapy.[33]

Our study showed that the risk of outcomes in patients with HF remains unacceptably high. Thus, after only two years, rate of overall mortality was 17.2/100 patient-year and rates of hospitalization for HF and CKD were 20.6 and 9.4/100 patient-year. In a meta-analysis of 60 studies with data from 1.5 million people with HF, although the 5-year survival rates have improved in the last years (from 29.1% between 1970–1979 to 59.7% in 2000–2009), these remain very high.[34] A recent study showed in patients with HF that 3 out of every 5 patients had died within 5 years of follow-up, with a median survival of 3 years.[35] However, the elevated risk of outcomes in this population, particularly as renal function worsens, many patients do not receive evidence-based medical therapies, what worsens the prognosis.[36] These data emphasize the need of prescribing recommended drugs as soon as possible to get the maximum

Table 5 – Event rates per 100 patient-year for HF patients diagnosed in 2017 with or without CKD at baseline and followed for 24 months.

	HF without CKD at index (*n* = 2435)	HF + CKD at index								Total HF (*n* = 3045)
		Stage 1 (*n* = 19)	Stage 2 (*n* = 115)	Stage 3a (*n* = 201)	Stage 3b (*n* = 148)	Stage 4 (*n* = 44)	Stage 5 (*n* = 37)	Unspecified (*n* = 46)	Total CKD (*n* = 610)	$P_{HF\ without\ CKD\ vs\ HF+CKD}$	
All-cause death, n (event rates)	382 (16.1)	2 (10.5)	16 (14.9)	35 (17.0)	32 (21.3)	11 (25.5)	9 (27.6)	6 (14.4)	111 (21.9)	<.001	493 (17.2)
Time to first event, days	426.9	446.4	429.9	396.8	330.7	264.6	231.5	438.2	348.1	<.001	410.8
HF, n (event rates)	480 (20.2)	2 (10.5)	18 (16.2)	37 (18.5)	35 (23.1)	12 (27.7)	10 (30.0)	7 (15.6)	121 (23.8)	<.001	601 (20.6)
Time to first event, days	393.9	499.8	481.3	444.2	370.2	296.2	259.1	490.5	366.5	<.001	396.1
CKD, n (event rates)	214 (9.3)	1 (5.3)	8 (7.8)	18 (9.0)	17 (11.2)	5 (13.4)	5 (14.6)	3 (7.6)	57 (11.0)	.203	271 (9.4)
Time to first event, days	441.2	626.5	603.3	556.9	464.0	371.2	324.8	614.9	450.5	.359	447.5
Albuminuria, n (event rates)	238 (10.3)	1 (5.3)	9 (8.8)	20 (10.0)	20 (12.6)	6 (15.1)	5 (16.4)	4 (8.5)	65 (12.1)	<.001	303 (10.6)
Time to first event, days	424.1	532.9	513.2	473.7	394.7	315.8	276.3	523.0	372.4	<.001	421.8
T2D development, n (event rates)	149 (6.4)	1 (5.3)	6 (6.0)	14 (6.9)	13 (8.6)	4 (10.3)	4 (11.1)	3 (5.8)	45 (8.4)	<.001	194 (6.4)
Time to TD2 development, days	413.1	515.9	496.8	458.6	382.1	305.7	267.5	506.3	376.7	<.001	405.7

CKD: chronic kidney disease; HF: heart failure; T2D: type 2 diabetes.

benefit, as HF is a progressive condition without the appropriate treatment.[37]

Our study showed that among HF patients, renal function progressively decreased and albuminuria increased (11.5% and 7.2%, respectively) and 5.9% of patients developed CKD after only 2 years of follow-up. In addition, the risk of outcomes was higher in those patients with HF and CKD and time to first event was shorter (vs only HF alone) and worsened as CKD stage increased. Remarkably, although patients with HF and CKD were taking more angiotensin-converting enzyme inhibitors and angiotensin receptor blockers than those without CKD at baseline, the proportion of SGLT-2 inhibitors was similar. The relationship between HF and CKD is bidirectional and one condition promotes the development of the other and vice versa.[38] Traditionally, renin–angiotensin system inhibitors have been the drugs used for the prevention and treatment of both, cardiovascular and renal complications, and their prescription should be promoted.[1,39] Remarkably, in the last years, different clinical trials have shown that some SGLT-2 inhibitors can reduce the risk of cardiovascular and renal complications in patients with CKD (dapagliflozin in DAPA-CKD and canagliflozin in CREDENCE) and also in patients with HF and reduced left ventricular ejection fraction (dapagliflozin in DAPA-HF and empagliflozin in EMPEROR-Reduced).[14,15,40,41] In addition, in patients with HF, SGLT2-inhibitors reduce the rate of kidney function decline, regardless baseline renal function.[9,10] Unfortunately, our data showed that the current use of SGLT-2 inhibitors in this population is marginal. However, these drugs should be used to a higher extent, as their use is associated with a reduction of morbidity and mortality in patients with HF and reduced left ventricular ejection fraction, regardless of the renal function.[42]

Finally, although rates of outcomes were also high in patients with HF and preserved left ventricular ejection fraction, these seemed somewhat lower than in patients with reduced HF. This is in line with previous studies that have shown a similar or lower risk of mortality and cardiovascular complications in this population when compared to patients with reduced HF.[23,24,43,44] Unfortunately, although some studies have suggested that some drugs could provide some benefits in patients with preserved HF,[45,46] the fact is that the best approach in this population is a comprehensive management, treating adequately all comorbidities and congestive symptoms.[1] However, at this moment different studies are being developed to assess the impact of SGLT-2 inhibitors on this population.[20]

Limitations

This was an observational cohort study, with cross-sectional and longitudinal retrospective analyses that used secondary data from electronic health records. Therefore, only data that were recorded in the electronic clinical history could be collected, leading to a possible underdiagnosis of some comorbidities in some patients. In addition, data regarding the department where patients were managed (ie. HF unit, cardiology, internal medicine, intensive care unit, etc.) were not available in the database. However, although only indirect causality can be provided, this is the best design to actually

represent clinical practice. In addition, the high number of patients included, as well as the robustness of the data, may reduce potential bias. On the other hand, no mildly reduced ejection fraction HF was considered as a separate entity in our study, as was included in the preserved HF cohort, what could limit the generalizability of the results.

In Spain, patients with HF are old, have many comorbidities and a high risk of developing cardiovascular and renal complications regardless of the ejection fraction group. Despite that, there is a substantial proportion of patients that are not taking guideline recommended drugs, partially due to the high prevalence of renal insufficiency. A higher use of these drugs could reduce HF burden in clinical practice.

What is known about the subject?

- Current data about the management and cardiovascular and renal outcomes of patients with preserved and reduced HF are scarce.

Does it contribute anything new?

- In Spain, patients with HF are old, have many comorbidities.
- HF patients have a high risk of developing cardiovascular and renal complications regardless of the ejection fraction group.
- Unfortunately, there is a substantial proportion of patients that are not taking guideline recommended drugs, partially due to the high prevalence of renal insufficiency.

Funding

This study was fully funded with an unrestricted grant of AstraZeneca.

Authors' contributions

All authors have contributed to the study design, result review, manuscript preparation and final approval of the manuscript.

Conflicts of interest

None.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.rccl.2021.11.005.

REFERENCES

1. McDonagh TA, Metra M, Adamo M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2021;42:3599–3726.
2. Bauersachs J. Heart failure drug treatment: the fantastic four. *Eur Heart J*. 2021;42:681–683.
3. van Riet EE, Hoes AW, Wagenaar KP, Limburg A, Landman MA, Rutten FH. Epidemiology of heart failure: the prevalence of heart failure and ventricular dysfunction in older adults over time. A systematic review. *Eur J Heart Fail*. 2016;18:242–252.
4. Groenewegen A, Rutten FH, Mosterd A, Hoes AW. Epidemiology of heart failure. *Eur J Heart Fail*. 2020;22:1342–1356.
5. Escobar C, Varela L, Palacios B, et al. Clinical characteristics, management, and one-year risk of complications among patients with heart failure with and without type 2 diabetes in Spain. *Rev Clin Esp*. 2021., http://doi.org/10.1016/j.rce.2021.04.008
6. Ambrosy A, Fonarow G, Butler J, et al. The global health and economic burden of hospitalizations for heart failure. Lessons learned from hospitalized heart failure registries. *J Am Coll Cardiol*. 2014;63:1123–1133.
7. Pocock SJ, Ariti CA, McMurray JJ, et al. Predicting survival in heart failure: a risk score based on 39,372 patients from 30 studies. *Eur Heart J*. 2013;34:1404–1413.
8. Chan DZ, Kerr AJ, Doughty RN. Temporal trends in the burden of heart failure: a literature review. *Intern Med J*. 2021;51:1212–1218.
9. Jhund PS, Solomon SD, Docherty KF, et al. Efficacy of dapagliflozin on renal function and outcomes in patients with heart failure with reduced ejection fraction: results of DAPA-HF. *Circulation*. 2021;143:298–309.
10. Zannad F, Ferreira JP, Pocock SJ, et al. Cardiac and kidney benefits of empagliflozin in heart failure across the spectrum of kidney function: insights from EMPEROR-reduced. *Circulation*. 2021;143:310–321.
11. McMurray JJ, Packer M, Desai AS, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med*. 2014;371:993–1004.
12. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med*. 2015;373:2117–2128.
13. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2016;37:2129–2200.
14. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med*. 2019;381:1995–2008.
15. Packer M, Anker SD, Butler J, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. *N Engl J Med*. 2020;383:1413–1424.
16. Smith DH, Thorp ML, Gurwitz JH, et al. Chronic kidney disease and outcomes in heart failure with preserved versus reduced ejection fraction: the Cardiovascular Research Network PRESERVE Study. *Circ Cardiovasc Qual Outcomes*. 2013;6:333–342.
17. Nagueh SF. Heart failure with preserved ejection fraction: insights into diagnosis and pathophysiology. *Cardiovasc Res*. 2021;117:999–1014.
18. Toth PP, Gauthier D. Heart failure with preserved ejection fraction: strategies for disease management and emerging therapeutic approaches. *Postgrad Med*. 2021;133:125–139.
19. Sicras-Mainar A, Sicras-Navarro A, Palacios B, Varela L, Delgado JF. Epidemiology and treatment of heart failure in Spain: the HF-PATHWAYS study. *Rev Esp Cardiol*. 2020., http://doi.org/10.1016/j.recesp.2020.09.014
20. Solomon SD, de Boer RA, DeMets D, et al. Dapagliflozin in heart failure with preserved and mildly reduced ejection fraction: rationale and design of the DELIVER trial. *Eur J Heart Fail*. 2021;23:1217–1225.

21. Ruiz-Laiglesia FJ, Sánchez-Marteles M, Pérez-Calvo JI, et al. Comorbidity in heart failure. Results of the Spanish RICA Registry. *QJM*. 2014;107:989–994.
22. Ziaeian B, Fonarow GC. Epidemiology and aetiology of heart failure. *Nat Rev Cardiol*. 2016;13:368–378.
23. Pagel PS, Tawil JN, Boettcher BT, et al. Heart failure with preserved ejection fraction: a comprehensive review and update of diagnosis, pathophysiology, treatment, and perioperative implications. *J Cardiothorac Vasc Anesth*. 2021;35:1839–1859.
24. Meta-analysis Global Group in Chronic Heart Failure (MAGGIC). The survival of patients with heart failure with preserved or reduced left ventricular ejection fraction: an individual patient data meta-analysis. *Eur Heart J*. 2012;33:1750–7.
25. Trullàs JC, Pérez-Calvo JI, Conde-Martel A, et al. Epidemiology of heart failure with preserved ejection fraction: results from the RICA Registry. *Med Clin (Barc)*. 2021;157:1–9.
26. Colbert GB, Patel D, Lerma EV. Patiromer for the treatment of hyperkalemia. *Expert Rev Clin Pharmacol*. 2020;13:563–570.
27. Rachamin Y, Meier R, Rosemann T, Flammer AJ, Chmiel C. Heart failure epidemiology and treatment in primary care: a retrospective cross-sectional study. *ESC Heart Fail*. 2021;8:489–497.
28. Greene SJ, Butler J, Albert NM, et al. Medical therapy for heart failure with reduced ejection fraction: the CHAMP-HF registry. *J Am Coll Cardiol*. 2018;72:351–366.
29. Allen LA, Fonarow GC, Liang L, et al. Medication initiation burden required to comply with heart failure guideline recommendations and hospital quality measures. *Circulation*. 2015;132:1347–1353.
30. Crespo-Leiro MG, Segovia-Cubero J, González-Costello J, et al. Adherence to the ESC heart failure treatment guidelines in Spain: ESC heart failure long-term registry. *Rev Esp Cardiol*. 2015;68:785–793.
31. Chioncel O, Ambrosy AP. Improving adherence to guideline-directed medical therapies and outcomes in the developing world: a call to end global inequities in heart failure. *Int J Cardiol*. 2021;329:74–76.
32. Dębska-Kozłowska A, Książczyk M, Lelonek M. Where are we in 2021 with heart failure with reduced ejection fraction? Current outlook and expectations from new promising clinical trials. *Heart Fail Rev*. 2021., http://doi.org/10.1007/s10741-021-10120-x
33. Vaduganathan M, Claggett BL, Jhund PS, et al. Estimating lifetime benefits of comprehensive disease-modifying pharmacological therapies in patients with heart failure with reduced ejection fraction: a comparative analysis of three randomised controlled trials. *Lancet*. 2020;396:121–128.
34. Jones NN, Roalfe AK, Adoki I, Hobbs FD, Taylor CJ. Survival of patients with chronic heart failure in the community: a systematic review and meta-analysis. *Eur J Heart Fail*. 2019;21:1306–1325.
35. Harikrishnan S, Jeemon P, Ganapathi S, et al. Five-year mortality and readmission rates in patients with heart failure in India: results from the Trivandrum heart failure registry. *Int J Cardiol*. 2021;326:139–143.
36. Patel RB, Fonarow GC, Greene SJ, et al. Kidney function and outcomes in patients hospitalized with heart failure. *J Am Coll Cardiol*. 2021;78:330–343.
37. Bohm M, Komajda M, Borer JS, et al. Duration of chronic heart failure affects outcomes with preserved effects of heart rate reduction with ivabradine: findings from SHIFT. *Eur J Heart Fail*. 2018;20:373–381.
38. Deferrari G, Cipriani A, La Porta E. Renal dysfunction in cardiovascular diseases and its consequences. *J Nephrol*. 2021;34:137–153.
39. de Boer IH, Caramori ML, Chan JCN, et al. Executive summary of the 2020 KDIGO Diabetes Management in CKD Guideline: evidence-based advances in monitoring and treatment. *Kidney Int*. 2020;98:839–848.
40. Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med*. 2019;380:2295–2306.
41. Heerspink HJL, Stefánsson BV, Correa-Rotter R, et al. Dapagliflozin in patients with chronic kidney disease. *N Engl J Med*. 2020;383:1436–1446.
42. O'Meara E, Verma S. When and how to use sodium-glucose cotransporter 2 inhibitors in patients with heart failure with reduced ejection fraction or chronic kidney disease. *Can J Cardiol*. 2021;37:669–673.
43. Desai RJ, Mahesri M, Chin K, et al. Epidemiologic characterization of heart failure with reduced or preserved ejection fraction populations identified using medicare claims. *Am J Med*. 2021;134:e241–e251.
44. Cho DH, Yoo BS. Current prevalence, incidence, and outcomes of heart failure with preserved ejection fraction. *Heart Fail Clin*. 2021;17:315–326.
45. Nie D, Xiong B, Qian J, Rong S, Yao Y, Huang J. The effect of sacubitril-valsartan in heart failure patients with mid-range and preserved ejection fraction: a meta-analysis. *Heart Lung Circ*. 2021;30:683–691.
46. Flather MD, Shibata MC, Coats AJ, et al. Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure (SENIORS). *Eur Heart J*. 2005;26:215–225.