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Original Article

ORIGINAL ARTICLE

Risk of outcomes in a Spanish population with chronic kidney disease

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ABSTRACT

Objectives. To assess mortality and cardiovascular and renal outcomes among patients with chronic kidney disease (CKD) (primary objective), with a particular focus on heart failure (HF) risk following diagnosis of CKD (secondary objective) in Spain.

Methods. We conducted an observational study comprising cross-sectional and longitudinal retrospective analyses using secondary data from electronic health records. For the primary objective, adults with prevalent CKD [estimated glomerular filtration rate (eGFR) <60 or ≥60 mL/min/1.73 m^2 with a urine albumin:creatinine ratio (UACR) ≥30 mg/g at the index date (1 January 2017)] were included. For the secondary objective, adults with incident CKD in 2017 were enrolled.

Results. In the prevalent population, 46 786 patients with CKD without HF [75.8 ± 14.4 years, eGFR 51.4 ± 10.1 mL/min/1.73 m^2; 75.1% on renin–angiotensin system inhibitors (RASis)] and 8391 with CKD and HF (79.4 ± 10.9 years, eGFR 46.4 ± 9.8 mL/min/1.73 m^2) were included. In the prevalent population, the risk of all-cause death {hazard ratio [HR] 1.107 [95% confidence interval (CI) 1.064–1.153]}, HF hospitalization [HR 1.439 (95% CI 1.387–1.493)] and UACR progression [HR 1.323 (95% CI 1.182–1.481)] was greater in those patients with CKD and HF versus CKD only. For the incident population, 1594 patients with CKD without HF and 727 with CKD and HF were included. Within 24 months from the CKD diagnosis (with/without HF at baseline), 6.5% of patients developed their first HF hospitalization. Although 60.7% were taking RASis, only 3.4% were at maximal doses and among diabetics, 1.3% were taking sodium-glucose cotransporter-2 inhibitors.

Conclusions. The presence of HF among CKD patients markedly increases the risk of outcomes. CKD patients have a high risk of HF, which could be partially related to insufficient treatment.

Keywords: cardiovascular, chronic kidney disease, death, renal, SGLT2 inhibitors

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INTRODUCTION

Chronic kidney disease (CKD) is very common in clinical practice, accounting for ~850 million persons with this condition around the world [1, 2]. Importantly, CKD substantially increases the risk of cardiovascular and all-cause death as well as the risk of developing cardiovascular and renal complications, including heart failure (HF), ischaemic heart disease and end-stage renal disease (ESRD) [2, 3]. In fact, CKD is expected to become the second leading cause of death before the end of the century in Spain [4]. Of note, the risk of adverse outcomes increases with renal function impairment and the presence of albuminuria progress [5]. In addition, CKD is associated with substantial healthcare costs, with cardiovascular hospitalizations being the main determinant [6, 7].

Although it is expected that the prevalence of CKD will rise in the coming years due to the ageing of the population as well as the increase in the prevalence of some related conditions such as hypertension, diabetes and chronic cardiovascular disease [1, 2], some authors have suggested that the use of cardioprotective and nephroprotective agents, such as renin–angiotensin system inhibitors (RASis) could decrease these numbers [8–11]. In addition, it has been demonstrated that the use of sodium-glucose cotransporter-2 (SGLT-2) inhibitors with proven renal benefits might change the prognosis of patients with CKD. In this line, the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial showed that in patients with type 2 diabetes mellitus (T2D), CKD and albuminuria, treatment with canagliflozin co-administered with RAS blockade significantly reduced the risk of kidney failure and cardiovascular events [12]. Furthermore, the Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) trial demonstrated that in patients with CKD and albuminuria, dapagliflozin reduced the risk of renal and cardiovascular complications, including cardiovascular mortality and HF hospitalizations, as well as the risk of all-cause mortality, regardless of the presence of T2D [13]. More recently, the Effect of Sotagliflozin on Cardiovascular and Renal Events in Patients with Type 2 Diabetes and Moderate Renal Impairment Who Are at Cardiovascular Risk (SCORED) trial showed that in patients with T2D and CKD, with or without albuminuria, sotagliflozin reduced the risk of the composite of cardiovascular death, HF hospitalizations and urgent visits for HF compared with placebo, but with a higher risk of side effects [14].

As a result, it is important to determine the impact of cardiovascular and nephroprotective treatments on outcomes in patients with CKD. Unfortunately, current data are scarce [1–3] and more information is needed. The objective of this study was to assess all-cause mortality and cardiovascular and renal outcomes among patients with CKD (primary objective), with a particular focus on the risk of developing HF following diagnosis of CKD (secondary objective) in Spain.

MATERIALS AND METHODS

This was an observational cohort study comprising cross-sectional and longitudinal retrospective analyses using secondary data captured in electronic health records from seven Spanish regions, using the BIG-PAC database. The BIG-PAC database includes anonymized and dissociated data from 1.7 million non-selected persons from primary health centres and referral hospitals within the Spanish national health system, including information from routine practice, without requiring manual input. Previous studies have demonstrated the representativeness of the Spanish population's clinical profile and management in the BIG-PAC database [15]. The database 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.

For the primary objective of the study, patients ≥18 years of age and with prevalent CKD, defined as an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 by Chronic Kidney Disease Epidemiology Collaboration equation or ≥60 mL/min/1.73 m^2 with a urine albumin:creatinine ratio (UACR) ≥30 mg/g at the index date (1 January 2017) (prevalent population) were included. For the secondary objective, patients ≥18 years of age with incident CKD, defined as at least one diagnosis of CKD or meeting the above eGFR or UACR definitions in 2017 were included (incident population). The index date was the first CKD diagnosis date in 2017. In both populations, at the index date, CKD stages were classified as follows: stage 1: eGFR ≥90 mL/min/1.73 m^2 and UACR ≥30 mg/g or International Classification of Diseases, Tenth Revision (ICD-10) code N18.1; stage 2 (mild): eGFR 60–89 mL/min/1.73 m^2 and UACR ≥30 mg/g or ICD-10 code N18.2; stage 3a (mild–moderate): eGFR 45–59 mL/min/1.73 m^2 or ICD-10 code N18.3; stage 3b (moderate–severe): eGFR 30–44 mL/min/1.73 m^2 or ICD-10 code N18.3; stage 4 (severe): eGFR 15–29 mL/min/1.73 m^2 or ICD-10 code N18.4; stage 5 (kidney failure): eGFR <15 mL/min/1.73 m^2 or ICD-10 code N18.1 or dialysis or ICD-10 code Z49 or Z99.2; CKD unspecified: no eGFR data available and ICD-10 code N18.9. In addition, to be included in the study, patients should have been registered on the database at least 12 months before the initiation of the study period, should have been included in the prescription programme (with verified records of daily doses, interdose intervals and treatment duration for each drug and at least two prescriptions during the follow-up period) and also should be traceable through certified regular follow-up (at least two recorded consultations in the electronic records). In contrast, patients who had moved or were located outside the included healthcare areas or were permanent elderly care home residents were excluded from the study.

In the prevalent population, all baseline characteristics, including biodemographic data (age, sex), physical examination data (blood pressure, body mass index), laboratory data [haemoglobin A1c (HbA1c), eGFR, UACR, serum potassium, left ventricular ejection fraction], comorbidities [stroke, myocardial infarction, peripheral artery disease, atrial fibrillation, HF with reduced ejection fraction (left ventricular ejection fraction ≤40%) and HF with preserved ejection fraction (left ventricular ejection fraction >40%), CKD stages, T2D, hyperkalaemia (defined as serum potassium >5.5 mmol/L)] and medications (antihypertensives, antidiabetic, statins, digoxin, anticoagulants and antiplatelets) were described in relation to the index date (1 January 2017). Diagnostic codes are presented in Supplementary data, Table S1. Maximal doses of angiotensin-converting enzyme inhibitors (ACEis) and angiotensin receptor blockers (ARBs) were defined as 'maximal labelled daily doses'. In the incident population, all baseline characteristics, including comorbidities and medications were described in relation to the index date, defined as the first CKD diagnosis date in 2017. Data were presented according to diabetes status and CKD stage.

With regard to the primary objective (prevalent population), for all-cause mortality, patient follow-up began on the 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 (i.e. 31

December 2019). For other outcomes, patient follow-up began on the index date and continued until the specified cardiorenal event (hospitalization for HF, CKD, or acute kidney failure or albuminuria transitions measured by UACR) 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 (i.e. 31 December 2019). Within each event category, except for albuminuria transitions, patients were censored after the first event for the category but not for events from other categories. CKD outcome referred to the first hospitalization secondary to CKD after the index date. For albuminuria transitions, all events for each patient were considered without censoring. Therefore the same patient could be listed in several categories. For the secondary objective of the study, patients were followed for 24 months from CKD diagnosis (by diagnostic code or laboratory criteria) in 2017.

Statistical analysis

Categorical variables were described by their absolute (*n*) and relative frequencies (%) and continuous variables by the mean and standard deviation. Event rates were calculated as the number of new cases from the 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 the event was analysed descriptively. Follow-up was censored at the observation period or study end unless an event occurred. The corresponding adjusted hazard ratios (HRs) and 95% confidence intervals (CIa) to estimate the risk of outcomes in the prevalent population after 3 years of follow-up were calculated. In contrast, the pathway to developing HF in patients with CKD and its types was evaluated for 24 months from the index. Categorical variables were compared with the chi-squared test or the Fisher's exact test when appropriate. When two means were compared, the Student's *t*-test was used. A level of statistical significance of 0.05 was applied in all the statistical tests. The data were analysed using SPSS version 25.0 (IBM, Armonk, NY, USA).

RESULTS

For the prevalent population, a total of 46 786 patients with CKD without HF and 8391 patients with CKD and HF were included (Supplementary data, Figure S1). The clinical characteristics and treatments in the prevalent CKD population at baseline are described in Table 1. Among patients with CKD without HF, the mean age was 75.8 ± 14.4 years, 52.4% were men, mean eGFR was 51.4 ± 10.1 mL/min/1.73 m^2, 47.5% of patients had T2D and 12.5% had previous myocardial infarction. Regarding treatments, 89.5% were taking antihypertensive drugs, particularly RASis (75.1%). Among patients with T2D, the most common antidiabetic drugs prescribed were metformin (54.5%) and dipeptidyl peptidase 4 (DPP4) inhibitors (31.5%). When compared with the CKD population, those patients with CKD and HF were older and had higher systolic blood pressure, HbA1c and UACR. In contrast, eGFR was lower in this population. In addition, all comorbidities, such as T2D, stroke, myocardial infarction, peripheral artery disease and atrial fibrillation, were more frequent in those patients with CKD and HF.

In Table 2 and in Supplementary data, Figures S2–S10, the risk of outcomes [all-cause mortality and first hospitalization for cardiorenal events (HF, CKD, acute kidney failure) or albuminuria transitions during follow-up] between CKD compared with CKD and HF patients in the prevalent population after 3 years of follow-up is reported. The risk of all-cause death, hospitalization for HF and UACR progression from 30–300 to >300 mg/g was greater in those patients with CKD and HF compared with CKD-only patients.

For the incident population, a total of 2321 patients with CKD (1594 without HF and 727 patients with CKD and HF) were included (Supplementary data, Figure S1). Clinical characteristics and treatments in the incident CKD population at baseline are presented in Table 3 and Supplementary data, Table S2. Overall, the mean age was 64.9 ± 23.4 years, 52.4% were men, mean eGFR was 60.6 ± 20.5 mL/min/1.73 m^2 and mean UACR was 317.7 ± 168.4 mg/g. Although 60.7% of patients were taking RASis, only 3.4% of them were taking them at maximal doses. The use of RASis according to UACR and blood pressure levels according to treatment with RASis are reported in Supplementary data, Tables S3 and S4, respectively. Among diabetics, only 2.8% of patients were taking SGLT2 inhibitors and 2.5% were taking glucagon-like peptide-1 (GLP-1) receptor agonists. Age increased as renal function worsened, as well as comorbidities. Within 24 months from CKD diagnosis (with/without HF at baseline), 6.5% of patients developed their first HF hospitalization, regardless of renal function (Figure 1 and Supplementary data, Table S5). Among patients with CKD without HF at the index date, all-cause death, myocardial infarction, hospitalization for HF and stroke rates were 4.9, 3.4, 3.2 and 2.9 per 100 patient-years, respectively, after 24 months of follow-up (Table 4). Among patients with CKD with HF, all-cause death, myocardial infarction, hospitalization for HF and stroke rates were 5.0, 3.6, 3.2 and 3.0 per 100 patient-years, respectively, after 24 months of follow-up (Table 5). In both patients with and without HF, outcomes rates increased and the time to the first event decreased as renal function worsened (Tables 4 and 5).

DISCUSSION

Our study showed in a large sample of patients representative of the Spanish population that both prevalent and incident patients with CKD are predominantly at stage 3, have many comorbidities and, with regard to cardio- and nephroprotective medications, there is much room for improvement. This undertreatment may consequently be translated into a higher risk of cardiovascular and renal complications.

Different studies performed in different clinical settings have reported the same clinical profile, with a high risk of developing cardiovascular complications [16–18]. Of note, our data were collected from the BIG-PAC database, which has been previously validated. In addition, data included in this database are representative of the Spanish population attended in primary health centres and referral hospitals within the Spanish national health system [15].

There is a bidirectional relationship between CKD and HF. The presence of one condition promotes the development of the other and vice versa [19]. Our study showed that patients with both conditions were older and had a worse clinical profile and poorer cardiovascular risk factor control rates, with more comorbidities, lower renal function and more albuminuria. As a result, these patients have a marked risk of developing outcomes during the follow-up. In fact, our data in the prevalent population showed that compared with CKD-only patients, the concomitance of both conditions substantially increased the risk of all-cause death, HF hospitalizations and UACR progression. In addition, outcomes increased as renal function worsened. This was more evident when CKD and HF occurred concomitantly. As a

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

Characteristics	Only CKD [*n* = 46.786 (84.8%)]	HF and CKD [*n* = 8.391 (15.2%)]	P-value (HF and CKD versus CKD)
Biodemographic data			
Age (years)	75.8 ± 14.4	79.4 ± 10.9	<0.001
Gender (male), *n* (%)	24 493 (52.4)	4 237 (50.5)	<0.001
Physical examination			
Systolic blood pressure (mmHg)	131.3 ± 19.2	133.9 ± 20.5	<0.001
Diastolic blood pressure (mmHg)	84.6 ± 7.3	83.7 ± 6.9	<0.001
BMI (kg/m^2)	28.2 ± 4.9	28.9 ± 5.2	<0.001
BMI >30 kg/m^2, *n* (%)	10 941 (23.4)	2013 (24.0)	0.332
Laboratory data			
HbA1c (%)	7.0 ± 1.9	7.7 ± 2.0	<0.001
<7%, *n* (%)	24 256 (51.8)	4256 (50.7)	0.177
7–<8%, *n* (%)	7733 (16.5)	1680 (20.0)	<0.001
8–<9%, *n* (%)	4056 (8.7)	867 (10.3)	<0.001
≥9%, *n* (%)	3439 (7.4)	769 (9.2)	<0.001
eGFR (mL/min/1.73 m^2)	51.4 ± 10.1	46.4 ± 9.8	<0.001
UACR (mg/g)	329.1 ± 145.3	361.2 ± 148.5	<0.001
Median (25th–75th percentile)	276.4 (159.7–384.9)	280.0 (130.3–444.1)	
<30 mg/g (stage 1), *n* (%)	255 (0.5)	366 (4.4)	<0.001
30–300 mg/g (stage 2), *n* (%)	29 234 (62.5)	4077 (48.6)	<0.001
>300 mg/g (stage 3), *n* (%)	17 297 (37.0)	3948 (47.1)	<0.001
Serum potassium (mmol/L)	5.2 ± 1.5	5.7 ± 1.6	<0.001
Left ventricular ejection fraction (%)	–	43.4 ± 10.1	–
Comorbidities, *n* (%)			
CVD	14 578 (31.2)	5180 (61.7)	<0.001
Stroke	3480 (7.4)	1030 (12.3)	<0.001
Myocardial infarction	5861 (12.5)	2154 (25.7)	<0.001
PAD	2303 (4.9)	564 (6.7)	<0.001
Atrial fibrillation	5630 (12.0)	2970 (35.4)	<0.001
HF	–	8391 (100)	–
HFrEF	–	4465 (53.2)	–
HFpEF	–	3926 (46.8)	–
CKD	46 786 (100)	8391 (100)	0.908
Stage 1	1370 (2.9)	977 (11.6)	<0.001
Stage 2	8403 (18.0)	1584 (18.9)	0.192
Stage 3a	15 578 (33.3)	1753 (20.9)	<0.001
Stage 3b	12 266 (26.2)	1961 (23.4)	<0.001
Stage 4	3389 (7.2)	1127 (13.4)	<0.001
Stage 5	2433 (5.2)	296 (3.5)	<0.001
T2D	22 229 (47.5)	5034 (60.0)	<0.001
Hyperkalaemia	15 252 (32.6)	3104 (37.0)	<0.001
Medications, *n* (%)			
CVD risk treatment	38 116 (81.5)	8391 (100)	-
Antihypertensives	41 869 (89.5)	7960 (94.9)	<0.001
ACEi	15 754 (33.7)	2716 (32.4)	<0.001
ARB	19 377 (41.4)	3548 (42.3)	0.246
ARNI	0	743 (8.9)	<0.001
Beta-blocker	22 854 (48.8)	5998 (71.5)	<0.001
Loop diuretic	22 499 (48.1)	5978 (71.2)	<0.001
Aldosterone antagonist	3133 (6.7)	2781 (33.1)	<0.001
Calcium channel blocker	2536 (5.4)	658 (7.8)	<0.001
Thiazide diuretic	15 018 (32.1)	3037 (36.2)	<0.001
Antidiabetics	17 456 (37.3)	3571 (42.6)	<0.001
Metformin	12 806 (27.4)	2021 (24.1)	<0.001
Sulfonylurea	3799 (8.1)	969 (11.5)	<0.001
DPP4 inhibitor	5025 (10.7)	962 (11.5)	0.285
SGLT2 inhibitor	1700 (3.6)	333 (4.0)	0.75
GLP-1 receptor agonist	1108 (2.4)	221 (2.6)	0.786
Metiglinides	1401 (3.0)	375 (4.5)	<0.001
Thiazolidinediones	115 (0.2)	27 (0.3)	0.962
Acarbose	98 (0.2)	20 (0.2)	0.711
Insulin	5194 (11.1)	1255 (15.0)	<0.001

Table 1. Continued.

	Only CKD (n = 46.786; 84.8%)	HF + CKD (n = 8.391; 15.2%)	$P_{HF+CKD\ vs\ CKD}$
Statins	20 714 (44.3)	5327 (63.5)	<0.001
Digoxin	378 (0.8)	524 (6.2)	<0.001
Warfarin/acenocoumarol[a]	4176 (8.9)	1887 (22.5)	<0.001
Low-dose aspirin	11 245 (24.0)	2518 (30.0)	<0.001
Receptor P2Y12 antagonist	3459 (7.4)	880 (10.5)	<0.001

Values presented as mean ± standard deviation unless stated otherwise. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor and neprilysin inhibition; BMI, body mass index; CVD, cardiovascular disease; DBP, diastolic blood pressure; HFrEF, heart failure with reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; PAD, peripheral artery disease; SBP, systolic blood pressure; hyperkalaemia, serum potassium >5.5 mmol/L.
[a]Use of direct oral anticoagulants was not collected.

Table 2. Risk of outcomes[a] between CKD versus CKD and HF patients in the prevalent population after 3 years of follow-up

Group	Endpoint	Follow-up (median, days)	Events, n	%	Event rates per 100 patient-years	HR[b] (CKD and HF versus CKD)	95% CI	P-value
CKD and HF	All-cause death	428	3132	37.3	17.1	1.107	1.064–1.153	<.001
CKD		506	10 701	22.9	10.1			
CKD and HF	Heart failure	447	3994	47.6	21.7	1.439	1.387–1.493	<.001
CKD		541	8293	17.7	7.1			
CKD and HF	CKD	545	2097	25.0	10.2	1.019	0.964–1.078	.505
CKD		408	4114	8.8	3.6			
CKD and HF	UACR Progression: <30 to 30–300 mg/g	504	43	0.5	0.2	1.300	0.961–1.761	.089
CKD		551	1865	4.0	1.6			
CKD and HF	UACR Progression: 30–300 to >300 mg/g	490	1158	13.8	5.5	1.323	1.182–1.481	<.001
CKD		558	451	1.0	0.4			
CKD and HF	UACR Regression: ≥30 to <30 mg/g	522	85	1.0	0.4	1.147	0.854–1.538	.363
CKD		601	109	0.2	0.1			
CKD and HF	UACR Regression: ≥300 to <300 mg/g	493	40	0.5	0.2	1.166	0.789–1.721	.441
CKD		552	80	0.2	0.1			
CKD and HF	Acute kidney failure (ICD-10 code N17)	592	164	2.0	0.7	1.082	0.784–1.493	.633
CKD		532	686	1.5	0.6			

[a]All-cause mortality and first hospitalization for cardiorenal events (HF, CKD, acute kidney failure) or albuminuria transitions during follow-up.
[b]HR was adjusted according to age, sex, eGFR and the number of associated clinical conditions.

result, a comprehensive therapeutic approach is warranted to reduce the risk of cardiovascular and renal complications in this population.

Unfortunately, our data also indicated that a substantial number of patients with CKD were not taking those drugs that have been shown to be cardio- and nephroprotective in the CKD population. For instance, ~25–40% of patients were not taking RASis and only a small proportion at maximal doses. This undertreatment was not justified by differences in UACR, renal function or blood pressure levels. In addition, among diabetics, the use of SGLT2 inhibitors was marginal. However, it should be taken into account that during the study period, treatment with SGLT2 inhibitors was not to be initiated to improve glycaemic control in patients with an eGFR <60 mL/min and was to be discontinued at a GFR persistently <45 mL/min, and also that penetration was low since the completion of pivotal clinical trials was close to or after index date [19–21]. For years, RASis have been considered a cornerstone in the management of patients with CKD and are recommended by clinical practice guidelines for the prevention of cardiovascular and renal complications [22, 23]. In this regard, more efforts are needed to increase the proportion of patients taking RASis [24]. In addition, it is important to achieve the maximal tolerated doses of RASis, as their beneficial effects are greater at maximal doses compared with lower doses [25]. However, our study showed that despite the fact that hyperkalaemia was reported in only a small proportion of

Table 3. Clinical characteristics and treatments in the incident CKD population at baseline in the overall population and according to T2D and HF status

	T2D status			HF status			
Characteristics	Non-T2D [*n* = 1216 (52.40%)]	T2D [*n* = 1105 (47.60%)]	P-value (T2D versus no T2D)	Non-HF [*n* = 1594 (68.7%)]	HF [*n* = 727 (31.3%)]	P-value (HF versus no HF)	Total [N = 2321 (100%)]
Biodemographic data							
Age (years)	65.0 ± 23.4	64.8 ± 23.5	0.837	63.8 ± 23.5	66.3 ± 23.2	<0.001	64.9 ± 23.4
Gender (male), *n* (%)	614 (50.5)	603 (54.6)	<0.001	832 (52.2)	385 (53.0)	0.720	1217 (52.4)
Physical examination							
Systolic blood pressure (mmHg)	129.8 ± 20.7	131.8 ± 19.3	0.016	129.7 ± 20.1	131.2 ± 19.6	0.093	130.8 ± 19.7
Diastolic blood pressure (mmHg)	83.9 ± 7	84.5 ± 7	0.039	84.2 ± 7.0	84.6 ± 7.1	0.204	84.3 ± 7
BMI (kg/m^2)	29 ± 5	27.7 ± 5.1	0.001	27.8 ± 5.2	29.7 ± 5.2	<0.001	28.7 ± 5
Laboratory data							
HbA1c (%)	6.2 ± 1.8	7.7 ± 1.8	<0.001	6.8 ± 1.7	7.0 ± 1.7	0.001	6.9 ± 1.7
<7%, *n* (%)	834 (68.6)	401 (36.3)	<0.001	852 (53.5)	383 (52.7)	0.720	1235 (53.2)
7–<8%, *n* (%)	10 (0.8)	344 (31.1)	<0.001	239 (15.0)	115 (15.8)	0.619	354 (15.3)
8–<9%, *n* (%)	3 (0.2)	215 (19.5)	<0.001	140 (8.8)	78 (10.7)	0146	218 (9.4)
≥9%, *n* (%)	2 (0.2)	145 (13.1)	<0.001	97 (6.1)	50 (6.9)	0.437	147 (6.3)
eGFR (mL/min/1.73 m^2)	60.7 ± 18.9	60.5 ± 20.2	0.436				60.6 ± 20.5
UACR (mg/g)	298.1 ± 155	381.9 ± 198.6	<0.001	305.4 ± 169.2	330.1 ± 167.5	0.001	317.7 ± 168.4
UACR (mg/g), median (IQR)	261 (148.3–372.4)	295.3 (142.3–438.6)					255.6 (153.8–376.5)
<30 mg/g (stage 1), *n* (%)	7 (0.6)	2 (0.2)	0.971	6 (0.4)	3 (0.4)	0.999	9 (0.4)
30–300 mg/g (stage 2), *n* (%)	838 (68.9)	585 (52.9)	<0.001	976 (58.3)	447 (61.5)	0.146	1423 (61.3)
>300 mg/g (stage 3), *n* (%)	371 (30.5)	518 (46.9)	<0.001	612 (35.7)	277 (38.1)	0.265	889 (38.3)
Serum potassium, (mmol/L)	5.2 ± 1.5	5.3 ± 1.5	0.532	4.8 ± 1.7	5.3 ± 1.8	<0.001	5.0 ± 1.4
Left ventricular ejection fraction (%)	44.1 ± 12.8	42.6 ± 12.4		–	43.5 ± 12.2	–	43.5 ± 12.2
Comorbidities, *n* (%)							
CVD	159 (13.1)	220 (19.9)	<0.001	178 (11.2)	201 (27.6)	<0.001	379 (16.3)
Stroke	95 (7.8)	111 (10.0)	0.054	91 (5.7)	115 (15.8)	<0.001	206 (8.9)
Myocardial infarction	122 (10.0)	162 (14.7)	<0.001	136 (8.5)	148 (20.4)	<0.001	284 (12.2)
PAD	43 (3.5)	56 (5.1)	0.081	64 (4.0)	35 (4.8)	0.376	99 (4.3)
Atrial Fibrillation	164 (13.5)	151 (13.7)	0.97	151 (9.5)	164 (22.6)	<0.001	315 (13.6)
Heart failure	354 (29.1)	373 (33.8)	<0.001	0	727 (100)	–	727 (31.2)
HFrEF	180 (14.8)	192 (17.4)	<0.001	0	372 (51.2)	–	372 (16.0)
HFpEF	174 (14.3)	181 (16.4)	0.23	0	355 (48.8)	–	355 (15.3)
T2D	48 (3.9)	1105 (100)	–	783 (49.1)	370 (50.9)	0.421	1153 (49.7)
Hyperkalaemia (potassium >5.5 mmol/L)	318 (26.6)	299 (27.1)	0.786	420 (26.3)	197 (27.1)	0.686	617 (26.6)
Medications, *n* (%)							
Antihypertensive medication	725 (59.6)	827 (74.8)	<0.001	973 (61.0)	579 (79.6)	<0.001	1552 (66.9)
RASi	633 (52.1)	775 (70.1)	<0.001	920 (57.7)	488 (67.1)	<0.001	1408 (60.7)
ACEi	311 (25.6)	294 (26.6)	0.309	383 (24.0)	222 (30.5)	0.002	605 (26.1)
ACEi at maximal dose	15 (1.2)	23 (2.1)	0.623	24 (1.5)	14 (1.9)	0.367	38 (1.6)
ARB	347 (28.5)	516 (46.7)	<0.001	564 (35.4)	299 (41.1)	0008	863 (37.2)
ARB at maximal dose	18 (1.5)	23 (2.1)	0.818	26 (1.6)	15 (2.1)	0.395	41 (1.8)
Aldosterone antagonist	49 (4.0)	67 (6.1)	0.265	77 (4.8)	39 (5.4)	0.538	116 (5.0)
Direct renin inhibitor	3 (0.2)	1 (0.1)	0.84	3 (0.2)	1 (0.1)	0.586	4 (0.2)
ARNI	51 (4.2)	67 (6.1)	0.059	78 (4.9)	40 (5.5)	0.542	118 (5.1)
Beta-blocker	342 (28.1)	363 (32.9)	<0.001	456 (28.6)	249 (34.3)	0.001	705 (30.4)
Diuretics	376 (30.9)	397 (35.9)	<0.001	484 (30.4)	289 (39.8)	0.001	773 (33.3)
Thiazide diuretic	257 (21.1)	239 (21.6)	0.769	332 (20.8)	164 (22.6)	0.224	496 (21.4)
Loop diuretic	311 (25.6)	365 (33.0)	<0.001	433 (27.2)	243 (33.4)	0.002	676 (29.1)
Potassium-sparing diuretic	57 (4.7)	68 (6.2)	0.18	79 (5.0)	46 (6.3)	0.199	125 (5.4)
Calcium channel blocker	301 (24.8)	312 (28.2)	<0.001	384 (24.1)	229 (31.5)	<0.001	613 (26.4)
Dihydropyridines	289 (23.8)	262 (23.7)	0.963	345 (21.6)	206 (28.3)	<0.001	551 (23.7)
Non-dihydropyridines	22 (1.8)	26 (2.4)	0.982	30 (1.9)	18 (2.5)	0.348	48 (2.1)

Table 3. Continued.

	T2D status			HF status			
	Non T2D (n = 1216; 52.40%)	T2D (n = 1105; 47.60%)	$P_{T2D\ vs\ no\ T2D}$	Non-HF (n = 1594; 68.7%)	HF (n = 727; 31.3%)	$P_{HF\ vs\ no\ HF}$	Total (n = 2321; 100%)
Antidiabetics	11 (0.9)	957 (86.6)	<0.001	607 (38.1)	361 (49.7)	<0.001	968 (41.7)
Metformin	0	602 (54.5)	–	385 (24.2)	217 (29.8)	0.004	602 (25.9)
Sulfonylurea	0	108 (9.8)	–	69 (4.3)	39 (5.4)	0.243	108 (4.7)
DPP4 inhibitor	0	348 (31.5)	–	225 (14.1)	123 (16.9)	0.079	348 (15.0)
SGLT2 inhibitor	0	31 (2.8)	–	20 (1.3)	11 (1.5)	0.699	31 (1.3)
GLP-1 receptor agonist	0	28 (2.5)	–	18 (1.1)	10 (1.4)	0.537	28 (1.2)
Metiglinides	0	123 (11.1)	–	81 (5.1)	42 (5.8)	0.486	123 (5.3)
Glitazones	0	14 (1.3)	–	9 (0.6)	5 (0.7)	0.778	14 (0.6)
Acarbose	0	19 (1.7)	–	12 (0.8)	7 (1.0)	0.629	19 (0.8)
Insulin	11 (0.9)	184 (16.7)	<0.001	123 (7.7)	72 (9.9)	0.076	195 (8.4)
Statins	506 (41.6)	491 (44.4)	<0.001	625 (39.2)	372 (512)	<0.001	997 (43.0)
Warfarin/acenocoumarol[a]	131 (10.8)	121 (11.0)	0.992	161 (10.1)	91 (12.5)	0.085	252 (10.9)
Low-dose aspirin	237 (19.5)	274 (24.8)	<0.001	334 (21.0)	177 (24.3)	0.075	511 (22.0)
Receptor P2Y12 antagonist	45 (3.7)	75 (6.8)	<0.001	76 (4.8)	44 (6.1)	0.191	120 (5.2)

Values presented as mean ± standard deviation unless stated otherwise. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor and neprilysin inhibition; BMI, body mass index; HFrEF, heart failure with reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; PAD, peripheral artery disease; SBP, systolic blood pressure; hyperkalaemia, serum potassium >5.5 mmol/L.
[a]Use of direct oral anticoagulants was not collected

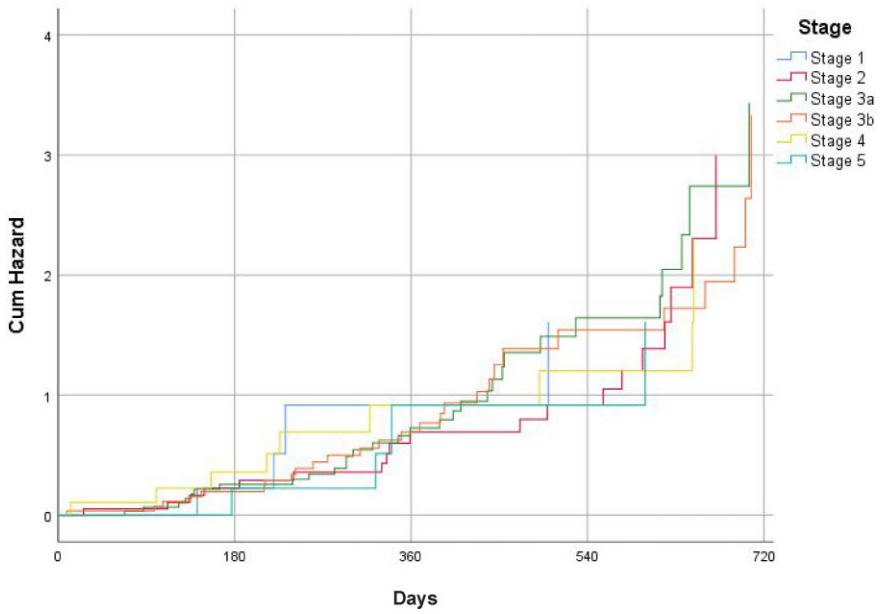

FIGURE 1: Kaplan–Meier survival curves for patients with/without HF at baseline who developed first HF hospitalization within 24 months from CKD diagnosis.

patients, regardless of CKD stage, the great majority of patients were not taking RASis at maximal doses, leading to inappropriate use of these drugs and consequently to a higher risk of developing cardiovascular and renal complications. Moreover, the use of drugs that reduce potassium levels, such as patiromer and sodium zirconium cyclosilicate, could allow optimizing the use of RASis [26, 27].

In our study, after only 2 years from CKD diagnosis, 6.5% of patients developed HF. In addition, in the incident population, the risk of myocardial infarction and HF was equally high in patients with CKD. This means that the aim of the therapeutic approach in patients with CKD should not be limited to the prevention of atherosclerotic cardiovascular outcomes, but also HF and renal complications [22, 23]. Similarly, this has been observed in previous studies [28]. For instance, in a DAPA-CKD-like cohort of real-life patients, the number of adverse renal and cardiovascular outcomes was substantial [28]. In the DAPA-CKD trial, treatment with dapagliflozin was associated with significant reductions in the risk of major adverse kidney and cardiovascular events, including HF hospitalizations, as well as all-cause mortality in both diabetic and non-diabetic CKD patients. In addition, these beneficial effects were consistent across all eGFR

Table 4. Event rates per 100 patient-years for CKD patients diagnosed in 2017 without HF at baseline and followed for 24 months

Events	Stage 1 (*n* = 95)	Stage 2 (*n* = 335)	Stage 3a (*n* = 522)	Stage 3b (*n* = 402)	Stage 4 (*n* = 116)	Stage 5 (*n* = 49)	Unspecified (*n* = 75)	Total CKD (*N* = 1594)
All-cause death, *n* (event rate)	7 (3.9)	26 (4.2)	44 (4.5)	36 (4.9)	11 (5.3)	5 (5.7)	6 (4.0)	135 (4.9)
Time to first event (days)	516.0	482.2	450.7	405.6	369.1	343.3	484.2	429.2
Heart failure, *n* (event rate)	5 (2.6)	18 (2.8)	29 (3.0)	24 (3.3)	8 (3.5)	3 (3.8)	4 (2.6)	91 (3.2)
Time to first event (days)	317.5	288.7	269.8	248.2	223.4	203.3	309.1	287.0
CKD, *n* (event rate)	3 (1.8)	12 (2.0)	20 (2.1)	18 (2.3)	5 (2.5)	3 (2.8)	3 (2.0)	64 (2.6)
Time to first event (days)	479.1	447.7	426.4	396.6	356.9	324.8	463.4	394.8
Myocardial infarction, *n* (event rate)	5 (2.6)	17 (2.8)	28 (2.9)	23 (3.2)	7 (3.4)	3 (3.7)	4 (2.6)	87 (3.4)
Time to first event (days)	423.3	403.1	366.5	337.1	316.9	288.4	396.7	336.2
Stroke, *n* (event rate)	4 (2.1)	14 (2.3)	24 (2.5)	21 (2.8)	7 (3.0)	3 (3.2)	3 (2.1)	76 (2.9)
Time to first event (days)	390.7	368.6	338.2	314.5	292.5	272.0	364.5	363.6
PAD, *n* (event rate)	2 (1.1)	8 (1.2)	13 (1.3)	10 (1.4)	3 (1.6)	2 (1.7)	2 (1.2)	40 (1.3)
Time to first event (days)	359.9	342.8	320.4	304.3	277.0	249.3	358.4	299.4
Albuminuria (UACR ≥30 mg/g), *n* (event rate)	2 (1.0)	7 (1.1)	11 (1.2)	10 (1.3)	3 (1.4)	1 (1.4)	1 (1.1)	35 (1.3)
Time to first event (days)	521.5	492.0	455.6	410.0	389.5	350.6	496.6	429.8
Albuminuria (UACR ≥300 mg/g), *n* (event rate)	1 (0.5)	3 (0.5)	6 (0.6)	5 (0.6)	1 (0.6)	1 (0.7)	1 (0.5)	18 (0.7)
Time to first event (days)	562.2	525.4	491.0	446.8	411.1	386.4	516.6	446.4

PAD, peripheral artery disease.

Table 5. Event rates per 100 patient-years for CKD patients diagnosed in 2017 with HF at baseline and followed for 24 months

Events	Stage 1 (*n* = 23)	Stage 2 (*n* = 98)	Stage 3a (*n* = 242)	Stage 3b (*n* = 194)	Stage 4 (*n* = 66)	Stage 5 (*n* = 36)	Unspecified (*n* = 68)	Total CKD (*N* = 727)	P-value (Total CKD + HF versus total CKD without HF)	Total CKD with and without HF in 2017 (*N* = 2321)
All-cause death, *n* (event rate)	2 (4.2)	9 (4.7)	22 (4.9)	18 (5.2)	6 (5.4)	4 (5.8)	5 (4.3)	66 (5.0)	0.889	201 (5.0)
Time to first event (days)	500.5	477.4	428.2	373.2	339.6	315.8	440.6	424.9	0.647	423.6
Heart failure, *n* (event rate)	1 (2.6)	5 (3.0)	14 (3.2)	13 (3.6)	5 (3.9)	3 (4.1)	3 (2.7)	44 (3.2)	0.999	135 (3.2)
Time to first event (days)	304.8	282.9	256.3	223.4	221.1	189.0	296.8	278.4	0.078	272.9
CKD, *n* (event rate)	1 (1.9)	4 (2.1)	9 (2.1)	9 (2.5)	3 (2.7)	2 (2.9)	3 (2.1)	31 (2.7)	0.772	95 (2.5)
Time to first event (days)	445.5	411.9	396.6	384.7	353.3	308.5	421.7	386.9	0.356	396.3
Myocardial infarction, *n* (event rate)	1 (2.7)	5 (2.9)	14 (3.0)	12 (3.4)	4 (3.7)	3 (4.0)	3 (2.6)	42 (3.6)	0.671	129 (3.6)
Time to first event (days)	419.0	383.0	362.8	330.4	307.4	268.2	380.8	319.4	0.013	327.6
Stroke, *n* (event rate)	1 (2.1)	4 (2.5)	12 (2.7)	10 (2.9)	4 (3.3)	2 (3.2)	3 (2.1)	36 (3.0)	0.858	112 (3.0)
Time to first event (days)	351.6	335.4	304.3	289.3	266.2	266.6	360.8	341.8	0.060	374.6
PAD, *n* (event rate)	1 (1.2)	2 (1.2)	7 (1.4)	5 (1.5)	2 (1.7)	1 (1.8)	2 (1.3)	20 (1.4)	0.893	60 (1.3)
Time to first event (days)	338.3	325.6	307.5	289.1	257.6	236.8	329.7	272.5	<0.001	285.2
Albuminuria (UACR ≥30 mg/g), *n* (event rate)	0 (1.0)	2 (1.1)	5 (1.2)	5 (1.5)	2 (1.4)	1 (1.5)	1 (1.1)	16 (1.3)	0.894	51 (1.3)
Time to first event (days)	479.8	457.6	423.7	405.9	373.9	326.0	466.8	395.4	<0.001	423.2
Albuminuria (UACR ≥300 mg/g), *n* (event rate)	0	1 (0.6)	3 (0.6)	2 (0.6)	1 (0.7)	0	1 (0.5)	8 (0.7)	0.999	26 (0.7)
Time to first event (days)	528.5	488.6	456.7	433.4	370.0	371.0	480.4	401.8	<0.001	449.8

PAD, peripheral artery disease.

and UACR stages [29–32]. Moreover, in the Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58 trial, dapagliflozin not only prevented and reduced the progression of renal disease among patients with T2D at high risk for cardiovascular events, but also HF hospitalizations in patients with normal and impaired renal function [19, 33]. Furthermore, a recent meta-analysis in patients with T2D and CKD showed that treatment with SGLT2 inhibitors was associated with a decreased risk of cardiovascular and renal events [34], indicating the protective effects of SGLT2 inhibitors across the cardiorenal continuum, even regardless of T2D status [35]. In fact, a recent study has shown that following the 2020 Kidney Disease:

Improving Global Outcomes guidelines, more than one-third of patients with T2D in the USA should be treated with SGLT2 inhibitors, as all patients with CKD would obtain a cardiovascular benefit with such drugs [36]. Unfortunately, in our study, the use of SGLT2 inhibitors was marginal in patients with T2D, even in those patients with CKD and HF. As a result, greater use of these types of drugs would be desirable to reduce the cardiovascular and renal burden in patients with CKD.

Limitations

Due to the design of the study (observational and retrospective cohort study), without a control group, only indirect causality can be suggested that should be confirmed in specific studies. As this was a retrospective study, taking data from secondary healthcare resources, some relevant variables, such as UACR, could not be reported in all patients, leading to an underdiagnosis of CKD. However, the high number of patients included, with prevalent and incident CKD, as well as the robustness of the data, may provide an accurate picture of the current management and cardiovascular/renal risk in the Spanish population with CKD. On the other hand, although the ICD-10 code N-17 may underestimate AKI, this code was used, as it is widely used in electronic health records in Spain.

CONCLUSIONS

In Spain, patients with CKD are predominantly at stage 3 and have many comorbidities and there is a marked underuse of cardio- and nephroprotective medications. Patients with CKD have a substantial risk of developing HF, as well as atherosclerotic cardiovascular outcomes, renal progression disease and all-cause mortality. Therefore it is expected that greater use of guideline-recommended therapy could translate into a reduction of cardiovascular and renal burden in patients with CKD.

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SUPPLEMENTARY DATA

Supplementary data are available at *CKJ* online.

CONFLICT OF INTEREST STATEMENT

None declared.

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