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Original article

Epidemiology, clinical profile, management, and two-year risk complications among patients with chronic kidney disease in Spain

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ABSTRACT

Objectives: To describe the epidemiology, clinical profile, treatments, and to determine cardiovascular and renal outcomes after two years of follow-up in a contemporary chronic kidneay disease (CKD) population in Spain. This was also analyzed among the DAPA-CKD-like population (patients who met most inclusion criteria of DAPA-CKD trial).

Methods: Observational, retrospective, population-based study using BIG-PAC database. The CKD population was defined as patients ≥18 years, with at least one diagnostic code of CKD prior to the index date (January 1st, 2018). CKD was defined as estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 (CKD-EPI), or albuminuria >30 mg/g.

Results: We identified 56,435 CKD patients after exclusions (76.4 years, 52.2% men, urine albumin-to-creatinine ratio 390.8 mg/g, eGFR 49.7 mL/min/1.73 m^2). CKD prevalence was 4.91% and incidence 2.10 per 1000 patient-years. Regarding treatments, 69.2% were taking renin-angiotensin system inhibitors (only 4.2% at maximal doses) and 3.5% of diabetic patients SGLT-2 inhibitors. During the two years of follow-up, rates of heart failure, all-cause death, myocardial infarction, stroke, and CKD were 17.9, 12.1, 7.2, 6.3, and 5.9 events per 100 patient-years, respectively. During this period, 44% of patients were hospitalized, and 6.8% died during hospitalization. Cardiovascular outcomes were more common in the DAPA-CKD-like population.

Conclusions: In Spain, CKD population is older and comorbidities, including diabetes and heart failure, are common. Cardiovascular and renal outcomes are frequent. There is room

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for improvement in CKD management, particularly through the use of drugs with proven cardiovascular and renal benefit.

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Epidemiología, perfil clínico, manejo y riesgo de complicaciones a 2 años en pacientes con enfermedad renal crónica en España

Palabras clave:
DAPA-CKD
Muerte
Enfermedad renal crónica
Hospitalización
Medicación
Eventos

RESUMEN

Objetivos: Describir la epidemiología, el perfil clínico, los tratamientos y los eventos cardiovasculares y renales, tras 2 años de seguimiento en una población contemporánea con enfermedad renal crónica (ERC) en España. También se analizó en la población tipo DAPA-CKD (pacientes que cumplían la mayoría de criterios del estudio DAPA-CKD).

Métodos: Estudio observacional, retrospectivo, poblacional, empleando la base de datos BIG-PAC. La población con ERC se definió como pacientes ≥ 18 años, con al menos un código diagnóstico de ERC antes de la fecha índice (01/01/2018). La ERC se definió como filtrado glomerular estimado (FGe) <60 ml/min/1,73 m^2 (CKD-EPI) o albuminuria > 30 mg/g.

Resultados: Se identificaron 56.435 pacientes con ERC, tras exclusiones (76,4 años, 52,2% varones, cociente albúmina-creatinina 390,8 mg/g, FGe 49,7 ml/min/1,73 m^2). La prevalencia fue del 4,91% y la incidencia 2,10/1.000 pacientes/año. El 69,2% tomaba inhibidores del sistema renina-angiotensina (solo el 4,2% a dosis máximas) y el 3,5% de los diabéticos inhibidores SGLT-2. Tras 2 años, las tasas de insuficiencia cardiaca, muerte, infarto de miocardio, ictus y ERC fueron 17,9; 12,1; 7,2; 6,3; 5,9 eventos/100 pacientes/año, respectivamente. Además, el 44% hospitalizaron y el 6,8% murieron durante la hospitalización. Los eventos cardiovasculares fueron más frecuentes en la población tipo DAPA-CKD.

Conclusiones: En España, la población con ERC es mayor, y las comorbilidades, incluyendo diabetes e insuficiencia cardiaca, comunes. Los eventos cardiovasculares y renales son frecuentes. Hay margen de mejora en el manejo de la ERC, especialmente a través del empleo de fármacos con beneficio cardiovascular y renal.

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Introduction

Chronic kidney disease (CKD) has a major effect on global health, increasing both, morbidity and mortality.[1] CKD significantly reduces lifespan, increases the risk of cardiovascular disease and may evolve into end-stage renal disease.[2] In addition, it has been estimated that in 2017, nearly 700 million persons had CKD, 1.2 million people died from CKD, and CKD resulted in 35.8 million DALYs (disability-adjusted life-years) worldwide, being diabetic nephropathy responsible for almost a third of DALYs.[1,3] Overall, life expectancy is markedly reduced as renal function declines or albuminuria develops.[1–4] Of note, it is expected that these numbers will increase in the following years due to the aging of population, and the increased prevalence of hypertension and diabetes.[5] Despite all these data, the awareness about the impact of CKD in real-world is low among patients and health-care providers.[6]

Fortunately, the development of CKD complications can be delayed or prevented with the apropriate treatment.[7] Until recently, the only classes of drugs with proven benefit on slowing the decline of renal function were renin angiotensin system inhibitors, including angiotensin-converting enzyme inhibitors (ACEi) and angiotensin-receptor blockers (ARBs).[8,9] However, in the last years, several sodium-glucose cotransporter-2 (SGLT-2) inhibitors have shown a positive impact on renal outcomes among patients with CKD,[10,11] even in the absence of type 2 diabetes (T2D).[10] In DAPA-CKD trial, patients with and without T2D, an eGFR of 25 to 75 mL/min/1.73 m^2 and a urinary albumin-to-creatinine ratio (UACR) of 200 to 5000 mg/g were included.[10] As a result, this is an unique population in which nephroprotection with SGLT-2 inhibitors has been demonstrated, regardless the presence with T2D.

Despite the fact that healthcare system planning requires careful assessment of CKD epidemiology,[1] and some data from Spain were published some years ago,[12–14] current data for prevalence, morbidity, mortality and management of CKD are scarce, and more information is warranted.

The aims of this study were to describe the epidemiology, clinical characteristics and the therapeutic management of the CKD population in a recent cohort of patients in Spain, stratified by the presence of T2D and CKD stage, and to determine cardiovascular and renal outcomes during two years of follow-up. This was also analyzed in a population who met the most relevant inclusion criteria of the DAPA-CKD (Dapagliflozin and Prevention of Adverse Outcomes in Chronic

Kidney Disease) trial[10] (DAPA-CKD like population) with the aim of understanding the study population in real-world settings, in terms of baseline characteristics and cardiorenal events.

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, from the BIG-PAC® database. BIG-PAC® database included information from non-selected 1.8 million persons of primary health centers and referral hospitals within the Spanish national health system. Before export to BIG-PAC®, data were rigorously anonymized and dissociated, making not possible individual identification. Previous studies have demonstrated its representativeness of the Spanish population.[15] The 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.

The study population was defined as all patients ≥18 years of age with at least one diagnostic code of CKD (Supplementary sidewaystable* 1) or having laboratory results meeting the definition of any stage of CKD prior to the index date (January 1st, 2018). CKD stages 1–5 were defined according to the eGFR (calculated by the CKD-Epidemiology Collaboration equation) and the urine albumin-to-creatinine ratio (UACR) criteria: CKD stage 1: eGFR ≥90 mL/min/1.73 m^2 and UACR ≥30 mg/g (3–30 mg/mmol) or ICD (International Classification of Diseases)-10 N18.1; CKD stage 2 (mild): eGFR 60–89 mL/min/1.73 m^2 and UACR ≥30 mg/g (3–30 mg/mmol) or ICD-10 N18.2; CKD stage 3a (mild to moderate): eGFR 45–59 mL/min/1.73 m^2 or ICD-10 N18.3; CKD stage 3b (moderate to severe): eGFR 30–44 mL/min/1.73 m^2 or ICD-10 N18.3; CKD stage 4 (severe): eGFR 15–29 mL/min/1.73 m^2 or ICD-10 N18.4; CKD stage 5 (kidney failure): eGFR <15 mL/min/1.73 m^2 or ICD-10 N18.1; CKD unspecified: no eGFR data available and ICD code N18.9.[16] In addition, CKD was classified as hypertensive and diabetic CKD.

T2D was defined as all patients filling a prescription of any antidiabetic medication, T2D diagnostic code or HbA1c > 7% prior to index date, excluding type 1 diabetes. The DAPA-CKD like population included those patients ≥18 years, with or without T2D, but not type 1 diabetes, who had an eGFR of 25 to 75 mL/min/1.73 m^2 and a UACR of 200 to 5000 mg/g, on stable treatment with ACEi or ARBs for at least 4 weeks.[10]

Comorbidities were searched for in all available data prior to index date, and a minimum of 1 year of data before index date was required. The main comorbidities included myocardial infarction (MI), heart failure (HF), atrial fibrillation (AF), stroke, peripheral artery disease (PAD), diabetes, hyperkalemia, and gout. ICD-9 and ICD-10 codes (https://eciemaps.mscbs.gob.es) were considered for the diagnosis of comorbidities (Supplementary sidewaystable* 1).

The information about treatment was recorded from the registries for dispensing medicines, according to the Anatomical Therapeutic Chemical Classification System (Supplementary sidewaystable* 1).[17] Treatment for hypertension (ACEi, ARBs, direct renin inhibitors, aldosterone antagonists, sacubitril/valsartan, beta blockers, diuretics, calcium channel blockers), antidiabetic medications (SGLT-2 inhibitors, metformin, sulfonylureas, DPP-4 [dipeptidyl peptidase 4] inhibitors, GLP-1 [glucagon-like peptide-1] receptor agonists, meglitinides, glitazones, acarbose, miglitol, insulin), antithrombotic therapy (warfarin, aspirin, P2Y12 receptor antagonists) and statins were recorded. The prescription of a drug in a specific patient was based only on medical criteria (routine practice).

Baseline characteristics (total CKD population and by T2D status and CKD stage), including demographics, comorbidities and medications were determined at index date (January 1st, 2018). In addition, prevalence and incidence of CKD was calculated in the overall population and according to T2D status. Incidence was calculated as all newly diagnosed patients during 2018 divided by the number of patients without CKD in the population at the beginning of 2018 and expressed in cases per 1000 patient-years. Prevalence was calculated as all patients with a CKD diagnosis at the end of 2018, divided by all individuals in the total population covered by the database at that time.

Cardiovascular events were defined as a main diagnosis during a hospital visit or stay occurred during 2 years after index date (i.e. at any time during 2018 or 2019) (Supplementary sidewaystable* 1). Outcomes included all-cause death and hospitalizations due to MI, stroke, HF, CKD, and PAD, or CKD complications. In the case of CKD, these were hospitalizations due to CKD complications that were defined as decline of eGFR ≥50% at any time during follow-up, kidney transplantation or dialysis. All-cause death was defined as death of any cause. Since the cause of death was not available in the database, cardiovascular death was not reported. Outcomes were calculated in the overall CKD population and in the DAPA-CKD-like population, according to the presence of T2D, and were stratified by CKD stage. In addition, the following variables were also assessed for the total CKD group and by the presence of T2D: hospitalization rates, hospital readmission rates, mortality rates during hospitalization and mortality rates after first hospitalization.

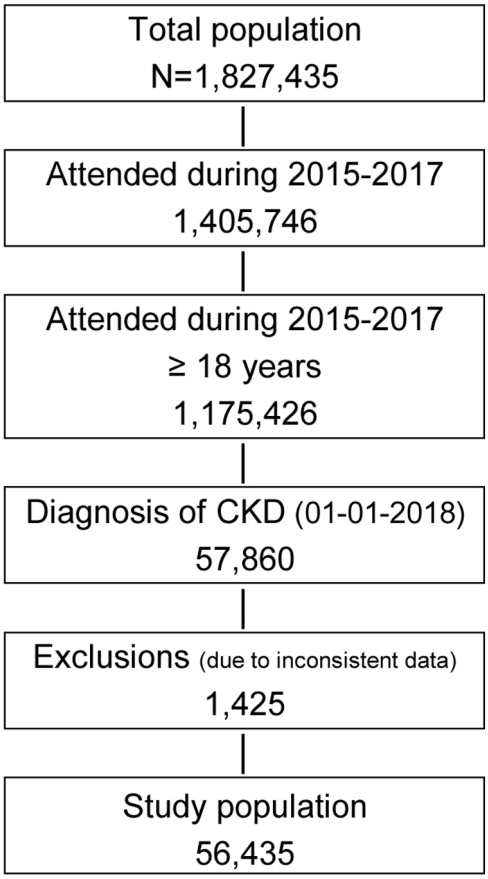
Statistical analysis

Categorical variables were described by their absolute (*n*) and relative frequencies (%). Continuous variables were described using the mean and standard deviation. Event rates were presented as events and events per 100 patient-years. Categorical variables were compared with the Chi-square test or the Fisher exact test when appropriate. When two means were compared, the t-student test was used. Analyses of events were performed for the index date of 1st January 2018 with 2 years of follow-up. Time to first event was analyzed with the contrast t-student test for independent samples. Follow-up was censored at observation period, or death end unless an event has occurred. A level of statistical significance of 0.05 was applied in all the statistical tests. The data were analyzed using the statistical package SPSS v25.0 (SPSS Inc., Chicago, Illinois, USA).

Results

Out of 1.827.435 persons included in the BIG-PAC® database in 2018, 1,405,746 people were attended during the 2015–2017 period, of whom 1,175,426 were 18 years or older. At index date, 57,860 patients had CKD. As 1425 patients were excluded due to inconsistent data, 56,435 patients (97.6%) comprised the CKD study population (75% with a diagnostic code, 25% based on laboratory values, Fig. 1). The incidence of CKD in 2018 was 2.10 per 1000 patient-years and the prevalence was 4.91%. T2D patients had a CKD prevalence about 19 fold that of those without T2D (55.3% vs. 2.9%).

The baseline clinical characteristics of the CKD population according to the presence of T2D and CKD stage are presented in Table 1. Overall, mean age was 76.4 years, 52.2% of patients were men, mean UACR was 390.8 mg/g and mean eGFR 49.7 mL/min/1.73 m^2. Overall, 20.6% of patients had a history of HF, 14.3% MI, and 10.6% stroke. With regard to treatments, 69.2% were taking renin angiotensin system inhibitors, but only 4.2% of patients at maximal doses. A total of 25,770 (45.7%) patients had T2D. Patients with T2D were younger (75.9 vs. 76.9 years; $P<0.001$), but UACR (390.8 vs. 345.2 mg/g, $P<0.001$), and HbA1c (7.6 vs. 6.1%; $P<0.001$) were higher and eGFR lower (47.6 vs. 49.8 mL/min/1.73 m^2, $P<0.001$) compared to those without T2D. In addition, comorbidities were more common among patients with T2D. Moreover, more T2D patients were taking renin-angiotensin system inhibitors (76.9% vs. 62.7%; $P<0.001$) (Table 1).



CKD: chronic kidney disease.

Fig. 1 – Flowchart modern population (2018).

Overall, 70.8% of patients had stage ≥3 CKD. Age increased as renal function worsened (from 71.3 years in patients with stage 1 CKD to 80.3 years among stage 5 CKD patients; $P<0.001$), as well as UACR (from 107.1 mg/g to 1640.0 mg/g; $P<0.001$) and the proportion of patients treated with renin-angiotensin system inhibitors (from 67.5% to 71.6%; $P<0.001$). Similarly, comorbidities increased as renal function decreased (Table 1).

After 2 years of follow-up, eGFR was 49.5 ± 12.4 mL/min/1.73 m^2 and UACR 401.8 ± 195.6 mg/g, 1.1% of patients underwent dialysis and 0.5% kidney transplantation. During this period, rates of hospitalizations due to HF, all-cause death, MI, stroke, CKD and PAD were 17.9, 12.1, 7.2, 6.3, 5.9 and 3.1 events per 100 patient-years, respectively. With regard to CKD endpoints, rates of decline of eGFR ≥50%, end-stage kidney disease, dialysis, and kidney transplantation were 3.8, 1.7, 1.1 and 0.5 events per 100 patient-years, respectively. Rates of the combined endpoint of CKD and/or HF were 20.8 events per 100 patient-years. Rates of all-cause death, cardiovascular and renal outcomes were significantly higher, and time to first HF hospitalization shorter, among patients with T2D, compared to those without T2D. Similarly, rates of all-cause death, cardiovascular and renal outcomes increased as CKD stage worsened. For instance, rates of combined endpoint of CKD and/or HF increased from 13.3 events per 100 patient-years in patients with stage 1 CKD to 26.4 events per 100 patient-years among stage 5 CKD patients (Table 2).

After 2 years of follow-up, 44% of patients were hospitalized, of whom 37.1% were hospitalized due to heart failure, 32.7% were re-hospitalized and 15.4% of patients died during hospitalization (Table 3). The proportion of patients who were hospitalized and that of patients requiring re-hospitalization were higher in T2D patients than in patients without T2D (47.7% vs. 40.8%; $P<0.001$, and 16.6% vs. 12.5%; $P<0.001$, respectively). However, mortality during hospitalization was slightly lower among patients with T2D (6.6% vs. 6.9%; $P<0.001$) (Table 3).

A specific analysis was performed in the DAPA-CKD like population ($n=7224$). In this subpopulation, mean age was 77.0 years, 52.6% were men, mean UACR was 391.5 mg/g and mean eGFR 49.8 mL/min/1.73 m^2. Overall, 21.1% of patients had a history of HF, 12.4% MI, and 11.3% prior stroke. With regard to treatments, all patients were taking renin-angiotensin system inhibitors, but only 13.5% of patients at maximal doses. A total of 3426 (47.4%) patients had T2D. Patients with T2D were older (77.1 vs. 76.3 years; $P=0.045$), and had higher UACR (423.8 vs. 352.4 mg/g), and HbA1c (7.6 vs. 5.9%; $P<0.001$), but without significant differences in eGFR (49.5 vs. 50.0 mL/min/1.73 m^2). In addition, comorbidities were more common among patients with T2D compared to those without T2D. Overall, in the DAPA-CKD like population, 95.6% had stage 3 or 4 CKD. UACR increased as renal function worsened (from 129.3 in patients with stage 2 CKD to 1713.4 mg/g among stage 4 CKD patients; $P<0.001$), as well as comorbidities. In addition, the proportion of patients at maximal doses of ACEi or ARBs also increased as stage CKD worsened (from 9.8% in patients with stage 2 CKD to 17.1% among stage 4 CKD patients; $P<0.001$) (Table 4).

Table 1 – Baseline clinical characteristics of the CKD population at index date (1st January 2018) and according to the presence of type 2 diabetes and CKD stage.

	Diabetes status			CKD stage												Total
	Non T2D (*n* = 30,665; 54.3%)	T2D (*n* = 25,770; 45.7%)	*P*	Stage 1 (*n* = ;2755; 4.9%)	Stage 2 (*n* = ;9650; 17.1%)	$P_{2\ vs.\ 1}$	Stage 3a (*n* = 17,865; 31.7%)	$P_{3a\ vs.\ 1}$	Stage 3b (*n* = 15,415; 27.3%)	$P_{3b\ vs\ 1}$	Stage 4 (*n* = 4620; 8.2%)	$P_{4\ vs.\ 1}$	Stage 5 (n= 2,060;3.7%)	$P_{5\ vs.\ 1}$	Unspe-cified (*n* = 4070; 7.2%)	$P_{Unsp.\ vs.\ 1}$	
Age, years	76.9	75.9	<0.001	71.3	75.1	<0.001	77.6	<0.001	78.6	<0.001	79.5	<0.001	80.3	<0.001	64.2	<0.001	76.4
≥85 years, *n* (%)	9455 (30.8)	5450 (21.1)	<0.001	540 (19.6)	1990 (20.6)	0.250	5045 (28.2)	<0.001	4635 (30.1)	<0.001	1395 (30.2)	<0.001	1090 (52.9)	<0.001	210 (5.2)	<0.001	14,905 (26.4)
Sex, female, n (%)	15,461 (50.4)	11,956 (46.4)	<0.001	1275 (46.3)	4620 (47.9)	0.138	8534 (47.8)	<0.001	7586 (49.2)	<0.001	2197 (47.6)	0.279	1120 (54.4)	<0.001	2085 (51.2)	<0.001	26,957 (47.8)
Physical examination and laboratory tests																	
BMI, kg/m²	28.3	29.4		29.1	29.3		28.7		28.5		28.2		27.9		29.6		28.8
SBP, mmHg	136.7	138.7	0.003	136.2	138.1	0.379	138.2	0.222	138.5	0.165	136.2	0.999	134.8	0.548	138.6		137.6
UACR	345.2	390.8	<0.001	107.1	126.7	<0.001	249.6	<0.001	252.2	<0.001	1623.1	<0.001	1640.0	<0.001	121.2		390.8
UACR A1	139 (0.5)	123 (0.5)	0.999	0	0	–	0	–	0	–	0		–	0	–	262 (6.4)	<0.001
UACR A2	20,838 (68.0)	12,682 (49.2)	<0.001	2755 (100)	9650 (100)		11,014 (61.7)	<0.001	9412 (61.1)	<0.001	523 (11.3)	<0.001	50 (2.4)	<0.001	116 (2.9)	<0.001	33,520 (59.4)
UACR A3	9688 (31.6)	12,965 (50.3)	<0.001	0	0		6851 (38.4)	<0.001	6003 (38.9)	<0.001	4097 (88.7)	<0.001	2010 (97.6)	<0.001	3692 (90.7)	<0.001	22,653 (40.1)
*eGFR**	49.8	47.6	<0.001	94.5	74.8	<0.001	52.0	<0.001	36.9	<0.001	22.1	<0.001	8.9	<0.001	0	<0.001	49.7
eGFR ≥90*, *n* (%)	1549 (5.1)	1206 (4.7)	<0.001	2755 (100)	0	–	0	–	0	–	0	–	0	–	0	–	2755 (4.9)
eGFR 60–89*, *n* (%)	5341 (17.4)	4309 (16.7)	<0.001	0	9650 (100)	–	0	–	0	–	0	–	0	–	0	–	9650 (17.1)
eGFR 45–59*, *n* (%)	9947 (32.4)	7918 (30.7)	<0.001	0	0	–	17,865 (100)	–	0	–	0	–	0	–	0	–	17,865 (31.7)
eGFR 30–44*, *n* (%)	8240 (26.9)	7175 (27.8)	<0.001	0	0	–	0	–	15,415 (100)	–	0	–	0	–	0	–	15,414 (27.3)
eGFR 15–29*, *n* (%)	2379 (7.8)	2241 (8.7)	<0.001	0	0	–	0	–	0	–	4620 (100)	–	0	–	0	–	4621 (8.2)
eGFR <15*, *n* (%)	936 (3.1)	1124 (4.4)	<0.001	0	0	–	0	–	0	–	0	–	2060 (100)	–	0	–	2060 (3.7)

Table 1 (*Continued*)

	Diabetes status			CKD stage												Total
	Non T2D (*n* = 30,665; 54.3%)	T2D (*n* = 25,770; 45.7%)	*P*	Stage 1 (*n* = ;2755; 4.9%)	Stage 2 (*n* = ;9650; 17.1%)	$P_{2\ vs.\ 1}$	Stage 3a (*n* = 17,865; 31.7%)	$P_{3a\ vs.\ 1}$	Stage 3b (*n* = 15,415; 27.3%)	$P_{3b\ vs\ 1}$	Stage 4 (*n* = 4620; 8.2%)	$P_{4\ vs.\ 1}$	Stage 5 (n= 2,060;3.7%)	$P_{5\ vs.\ 1}$	Unspe-cified (*n* = 4070; 7.2%)	$P_{Unsp.\ vs.\ 1}$	
HbA1c, %	6.1	7.6	<0.001	6.7	6.7	0.999	6.8	0.224	6.8	0.227	6.8	0.299	6.9	0.170	6.9	0.170	6.8
Creatinine, mg/dL	1.3	1.3	0.887	0.7	1.0	<0.001	1.2	<0.001	1.6	<0.001	2.1	<0.001	0.5	<0.001	0.9	<0.001	1.3
Uric acid, g/dL	6.1	7.2	<0.001	6.5	6.7	0.123	6.6	0.225	6.6	0.225	6.7	0.038	6.5	0.895	6.6	0.253	6.6
Comorbidities, *n* (%)																	
CKD – Chronic	30,665 (100)	25,770 (100)	–	2755 (100)	9650 (100)	–	17,865 (100)	–	15,415 (100)	–	4620 (100)	–	2060 (100)	–	4070 (100)	–	56,435 (100)
Stage 1	1549 (5.1)	1206 (4.7)	<0.001	2755 (100)	0	–	0	–	0	–	0	–	0	–	0	–	2755 (4.9)
Stage 2	5341 (17.4)	4309 (16.7)	<0.001	0	9650 (100)	–	0	–	0	–	0	–	0	–	0	–	9650 (17.1)
Stage 3a	9947 (32.4)	7918 (30.7)	<0.001	0	0	–	17,865 (100)	–	0	–	0	–	0	–	0	–	17,865 (31.7)
Stage 3b	8240 (26.9)	7175 (27.8)	<0.001	0	0	–	0	–	15,415 (100)	–	0	–	0	–	0	–	15,415 (27.3)
Stage 4	2379 (7.8)	2241 (8.7)	<0.001	0	0	–	0	–	0	–	4620 (100)	–	0	–	0	–	4620 (8.2)
Stage 5	936 (3.1)	1124 (4.4)	<0.001	0	0	–	0	–	0	–	0	–	2060 (100)	–	0	–	2060 (3.7)
Not staged	2273 (7.4)	1797 (7.0)	<0.001	0	0	–	0	–	0	–	0	–	0	–	4070 (100)	–	4070 (7.2)
Unspecified	8979 (28.4)	912 (3.5)	<0.001	380 (13.8)	1410 (14.6)	0.205	3241 (18.1)	<0.001	2745 (17.8)	<0.001	710 (15.4)	0.061	265 (12.9)	0.365	1140 (28.0)	<0.001	9891 (17.5)
CKD – Diabetic	531 (1.7)	15,759 (61.2)	<0.001	820 (29.8)	2925 (30.3)	0.614	4770 (26.7)	<0.001	4315 (28.0)	0.053	1380 (29.9)	0.928	635 (30.8)	0.455	1445 (35.5)	<0.001	16,290 (28.9)
CKD – Hypertensive	21,155 (69.9)	9099 (35.3)	<0.001	1555 (56.4)	5315 (55.1)	0.226	9854 (55.2)	0.238	8355 (54.2)	0.033	2530 (54.8)	0.181	1160 (56.3)	0.945	1485 (36.5)	<0.001	30,254 (53.6)
Dialysis	371 (1.2)	554 (2.2)	<0.001	0	0	–	0	–	0		0	–	870 (42.2)	<0.001	55 (1.4)	–	925 (1.6)

Table 1 (*Continued*)

	Diabetes status			CKD stage								Total				
	Non T2D (*n* = 30,665; 54.3%)	T2D (*n* = 25,770; 45.7%)	*P*	Stage 1 (*n* = ;2755; 4.9%)	Stage 2 (*n* = ;9650; 17.1%)	$P_{2 \text{ vs. } 1}$	Stage 3a (*n* = 17,865; 31.7%)	$P_{3a \text{ vs. } 1}$	Stage 3b (*n* = 15,415; 27.3%)	$P_{3b \text{ vs } 1}$	Stage 4 (*n* = 4620; 8.2%)	$P_{4 \text{ vs. } 1}$	Stage 5 (n= 2,060;3.7%)	$P_{5 \text{ vs. } 1}$	Unspe-cified (*n* = 4070; 7.2%)	$P_{Unsp. \text{ vs. } 1}$	
CVD	4616 (15.1)	5904 (22.9)	<0.001	405 (14.7)	1510 (15.7)	0.201	3535 (19.8)	<0.001	2900 (18.8)	<0.001	780 (16.9)	<0.001	500 (24.3)	<0.001	890 (21.9)	<0.001	10,519 (18.6)
Myocardial infarction	3590 (11.7)	4476 (17.4)	<0.001	295 (10.7)	1100 (11.4)	0.305	2685 (15.0)	<0.001	2271 (14.7)	<0.001	705 (15.3)	<0.001	355 (17.2)	<0.001	655 (16.1)	<0.001	8067 (14.3)
Heart failure	5701 (18.6)	5908 (22.9)	<0.001	350 (12.7)	1400 (14.5)	0.017	3694 (20.7)	<0.001	3285 (21.3)	<0.001	1085 (23.5)	<0.001	565 (27.4)	<0.001	1230 (30.2)	<0.001	11,610 (20.6)
Stroke	3011 (9.8)	2956 (11.5)	<0.001	170 (6.2)	840 (8.7)	<0.001	1726 (9.7)	<0.001	1941 (12.6)	<0.001	520 (11.3)	<0.001	300 (14.6)	<0.001	470 (11.6)	<0.001	5967 (10.6)
Atrial fibrillation	4917 (16.0)	4005 (15.5)	<0.001	295 (10.7)	1365 (14.2)	<0.001	3016 (16.9)	<0.001	2681 (17.4)	<0.001	795 (17.2)	<0.001	360 (17.5)	<0.001	410 (10.1)	0.425	8921 (15.8)
PAD	1254 (4.1)	1446 (5.6)	<0.001	120 (4.4)	385 (4.0)	0.350	790 (4.4)	0.924	825 (5.4)	0.030	270 (5.8)	0.009	125 (6.1)	0.008	185 (4.6)	0.696	2700 (4.8)
Diabetic CKD	531 (1.7)	15,759 (63.0)	<0.001	820 (29.8)	2925 (30.3)	0.614	4770 (26.7)	<0.001	4315 (28.0)	0.053	1380 (29.9)	0.928	635 (30.8)	0.455	1445 (35.5)	<0.001	16,245 (28.8)
Diabetes	0	27,394 (100)	<0.001	1265 (45.9)	4655 (48.2)	0.033	8565 (47.9)	0.050	7581 (49.2)	<0.001	2281 (49.4)	<0.001	1038 (50.4)	<0.001	2009 (49.4)	<0.001	27,394 (48.5)
Hyperkalemia	1316 (4.3)	1923 (7.5)	<0.001	115 (4.2)	520 (5.4)	0.012	915 (5.1)	0.024	849 (5.5)	0.001	320 (6.9)	<0.001	150 (7.3)	<0.001	370 (9.1)	<0.001	3241 (5.7)
Gout	9644 (31.5)	8277 (32.1)	<0.001	770 (28.0)	2855 (29.6)	0.104	5801 (32.5)	0.001	5135 (33.3)	<0.001	1545 (33.4)	<0.001	700 (34.0)	<0.001	1115 (27.4)	0.587	17,919 (31.8)
Medications, *n* (%)																	
Antihypertensives	22,017 (71.8)	22,446 (87.1)		2108 (76.5)	7469 (77.4)	0.321	14,292 (80.0)	<0.001	12,517 (81.2)	<0.001	3802 (82.3)	<0.001	1784 (86.6)	<0.001	3111 (76.4)	0.924	43,562 (77.2)
RAAS inhibitors	19,221 (62.7)	19,825 (76.9)	<0.001	1860 (67.5)	6830 (67.5)	0.999	12,506 (70.0)	<0.001	10,570 (68.6)	0.253	3305 (71.5)	<0.001	1475 (71.6)	<0.001	2500 (61.4)	<0.001	39,046 (69.2)
ACEi	9108 (29.7)	8221 (31.9)	<0.001	880 (31.9)	3220 (33.4)	0.140	5265 (29.5)	0.001	4379 (28.4)	<0.001	1560 (33.8)	0.093	745 (36.2)	<0.001	1280 (31.5)	0.727	17,332 (30.7)
ACEi at maximal doses	473 (1.6)	611 (2.4)	<0.001	30 (1.1)	60 (0.6)	0.001	409 (2.3)	0.001	445 (2.9)	<0.001	85 (1.8)	0.018	55 (2.7)	0.003	0	–	1086 (1.9)
ARBs	11,076 (36.1)	12,790 (49.6)	<0.001	1115 (40.5)	3955 (41.0)	0.001	7830 (43.8)	<0.001	6726 (43.6)	<0.001	2050 (44.4)	0.001	885 (43.0)	<0.001	1305 (32.1)	<0.001	23,866 (42.3)
ARBs at maximal doses	593 (1.9)	729 (2.8)	<0.001	0	0	–	481 (2.7)	<0.001	651 (4.2)	<0.001	190 (4.1)	<0.001	0	–	0	–	1318 (2.3)

Table 1 (*Continued*)

	Diabetes status			CKD stage												Total
	Non T2D (*n* = 30,665; 54.3%)	T2D (*n* = 25,770; 45.7%)	*P*	Stage 1 (*n* = ;2755; 4.9%)	Stage 2 (*n* = ;9650; 17.1%)	$P_{2\ vs.\ 1}$	Stage 3a (*n* = 17,865; 31.7%)	$P_{3a\ vs.\ 1}$	Stage 3b (*n* = 15,415; 27.3%)	$P_{3b\ vs\ 1}$	Stage 4 (*n* = 4620; 8.2%)	$P_{4\ vs.\ 1}$	Stage 5 (n= 2,060;3.7%)	$P_{5\ vs.\ 1}$	Unspe-cified (*n* = 4070; 7.2%)	$P_{Unsp.\ vs.\ 1}$	
Aldosterone antagonists	1553 (5.1)	1781 (6.9)	<0.001	115 (4.2)	425 (4.4)	0.798	1090 (6.1)	0.001	994 (6.5)	<0.001	330 (7.1)	<0.001	175 (8.5)	<0.001	205 (5.0)	0.125	3336 (5.9)
Direct renin inhibitors	84 (0.3)	41 (0.2)	0.001	5 (0.2)	10 (0.1)	0.379	50 (0.3)	0.361	5 (0.0)	0.002	20 (0.4)	0.145	20 (1.0)	<0.001	15 (0.4)	0.151	127 (0.2)
ARNI	1729 (5.6)	1850 (7.2)	<0.001	175 (6.4)	535 (5.5)	0.072	1209 (6.8)	0.436	1000 (6.5)	0.844	255 (5.5)	0.111	185 (9.0)	<0.001	220 (5.4)	0.083	3580 (6.3)
Beta blockers	10,929 (35.6)	10,731 (41.6)	<0.001	790 (28.7)	3000 (31.1)	<0.001	6765 (37.9)	<0.001	5915 (38.4)	<0.001	1735 (37.6)	<0.001	825 (40.1)	<0.001	1305 (32.1)	<0.001	20,335 (36.0)
Diuretics	11,030 (36.0)	11,430 (44.4)	<0.001	780 (28.3)	3310 (34.3)	<0.001	7370 (41.3)	<0.001	6620 (42.9)	<0.001	2080 (45.0)	<0.001	975 (47.3)	<0.001	1325 (32.6)	<0.001	22,460 (39.8)
Thiazide diuretics	839 (2.7)	876 (3.4)	<0.001	70 (2.5)	355 (3.7)	0.002	550 (3.1)	0.087	475 (3.1)	0.090	135 (2.9)	0.309	50 (2.4)	0.825	80 (2.0)	0.167	1716 (3.0)
Loop diuretics	9799 (32.0)	10,321 (40.1)	<0.001	680 (24.7)	2815 (29.2)	<0.001	6610 (37.0)	<0.001	5975 (38.8)	<0.001	1935 (41.9)	<0.001	895 (43.5)	<0.001	1210 (29.7)	<0.001	20,122 (35.7)
Potassium sparing diuretics	1718 (5.6)	1979 (7.7)	<0.001	140 (5.1)	510 (5.3)	0.798	1226 (6.9)	<0.001	1141 (7.4)	<0.001	320 (6.9)	0.002	165 (8.0)	<0.001	195 (4.8)	0.574	3693 (6.6)
CCB	8255 (26.9)	9305 (36.1)	<0.001	760 (27.6)	2920 (30.3)	<0.001	5545 (31.0)	<0.001	4905 (31.8)	<0.001	1475 (31.9)	<0.001	695 (33.7)	<0.001	1260 (31.0)	<0.001	17,560 (31.1)
Dihydropyridines	7666 (25.0)	8659 (33.6)	<0.001	700 (25.4)	2715 (28.1)	<0.001	5145 (28.8)	<0.001	4540 (29.5)	<0.001	1390 (30.1)	<0.001	655 (31.8)	<0.001	1180 (29.0)	<0.001	16,325 (28.9)
Non-dihydropyridines	684 (2.2)	739 (2.9)	<0.001	70 (2.5)	225 (2.3)	0.798	439 (2.5)	0.985	419 (2.7)	0.549	120 (2.6)	0.793	50 (2.4)	0.825	100 (2.5)	0.999	1426 (2.5)
Antidiabetics	322 (1.0)	21,050 (81.7)	<0.001	1071 (38.9)	3925 (40.7)	0.089	6570 (36.8)	<0.001	6073 (39.4)	0.621	2054 (44.5)	<0.001	1057 (51.3)	<0.001	1497 (33.4)	<0.001	21,372 (37.9)
Metformin	0	12,375 (48.0)	<0.001	541 (19.6)	2356 (24.4)	<0.001	3526 (19.7)	0.902	3240 (21.0)	0.095	1497 (32.4)	<0.001	718 (34.9)	<0.001	497 (12.2)	<0.001	12,375 (21.9)
Sulfonylurea	0	2962 (11.5)	<0.001	178 (6.5)	691 (7.2)	0.205	850 (4.8)	<0.001	701 (4.5)	0.001	256 (5.5)	0.078	169 (8.2)	0.024	117 (2.9)	<0.001	2962 (5.2)

Table 1 (*Continued*)

	Diabetes status			CKD stage												Total
	Non T2D (*n* = 30,665; 54.3%)	T2D (*n* = 25,770; 45.7%)	P	Stage 1 (*n* = ;2755; 4.9%)	Stage 2 (*n* = ;9650; 17.1%)	$P_{2\ vs.\ 1}$	Stage 3a (*n* = 17,865; 31.7%)	$P_{3a\ vs.\ 1}$	Stage 3b (*n* = 15,415; 27.3%)	$P_{3b\ vs\ 1}$	Stage 4 (*n* = 4620; 8.2%)	$P_{4\ vs.\ 1}$	Stage 5 (n= 2,060;3.7%)	$P_{5\ vs.\ 1}$	Unspecified (*n* = 4070; 7.2%)	$P_{Unsp.\ vs.\ 1}$	
DPP4 inhibitors	0	9864 (38.3)	<0.001	437 (15.9)	1711 (17.7)	0.028	2856 (16.0)	0.894	2823 (18.3)	<0.001	905 (19.6)	<0.001	465 (22.6)	<0.001	667 (16.4)	0.582	9864 (17.5)
SGLT-2 inhibitors	0	889 (3.5)	<0.001	55 (2.0)	163 (1.7)	0.292	201 (1.1)	0.001	205 (1.3)	0.004	163 (3.5)	0.002	65 (3.2)	0.009	37 (0.9)	<0.001	889 (1.6)
GLP-1 receptor agonists	0	750 (2.9)	<0.001	44 (1.6)	116 (1.2)	0.101	224 (1.3)	0.202	157 (1.0)	0.005	123 (2.7)	0.002	72 (3.5)	<0.001	14 (0.3)	<0.001	750 (1.3)
Metiglinides	0	3551 (13.8)	<0.001	127 (4.6)	529 (5.5)	0.063	1188 (6.6)	<0.001	1087 (7.1)	0.001	124 (2.7)	<0.001	132 (6.4)	0.006	364 (8.9)	<0.001	3551 (6.3)
Glitazones	0	430 (1.7)	<0.001	38 (1.4)	39 (0.4)	<0.001	84 (0.5)	<0.001	143 (0.9)	1.000	54 (1.2)	0.459	48 (2.3)	0.020	24 (0.6)	0.001	430 (0.8)
Acarbose	0	549 (2.1)	<0.001	31 (1.1)	58 (0.6)	0.010	130 (0.7)	0.238	175 (1.1)	0.999	62 (1.3)	0.459	51 (2.5)	0.350	42 (1.0)	0.690	549 (1.0)
Insulin	322 (1.0)	5154 (20.0)	<0.001	223 (8.1)	852 (8.8)	0.249	1631 (9.1)	0.087	1525 (9.9)	0.003	509 (11.0)	<0.001	259 (12.6)	<0.001	477 (11.7)	<0.001	5476 (9.7)
Statins	14,187 (46.3)	16,189 (62.8)	<0.001	1430 (51.9)	5245 (54.4)	<0.001	9770 (54.7)	<0.001	8306 (53.9)	<0.001	2485 (53.8)	0.114	1125 (54.6)	<0.001	2015 (49.5)	<0.001	30,375 (53.8)
Warfarin	3789 (12.4)	3551 (26.9)	<0.001	260 (9.4)	1155 (12.0)	<0.001	2415 (13.5)	<0.001	2090 (13.6)	<0.001	645 (14.0)	<0.001	275 (13.4)	<0.001	500 (12.3)	<0.001	7341 (13.0)
Low dose aspirin	7775 (25.4)	6924 (26.9)	<0.001	580 (21.1)	2380 (24.7)	<0.001	4815 (27.0)	<0.001	4009 (26.0)	<0.001	1335 (28.9)	<0.001	565 (27.4)	<0.001	1015 (24.9)	<0.001	14,698 (26.1)
Receptor P2Y12 antagonists	1380 (4.5)	2265 (8.8)	<0.001	140 (5.1)	555 (5.8)	0.225	1090 (6.1)	0.039	1115 (7.2)	<0.001	330 (7.1)	<0.001	200 (9.7)	<0.001	215 (5.3)	0.716	3645 (6.5)

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; PAD: peripheral artery disease; RAAS: renin angiotensin system; SBP: systolic blood pressure; SGLT-2: sodium-glucose Cotransporter-2; UACR: Urine albumin-to-Creatinine Ratio.

Table 2 – Event rates after 2 years of follow-up in the overall population and according to the presence of type 2 diabetes and CKD stage.

	Diabetes status			CKD stage												Total (n = 56,435)
	Non T2D (n = 30,665)	T2D (n = 25,770)	P	Stage 1 (n = 2755)	Stage 2 (n = 9650)	$P_{2\ vs.\ 1}$	Stage 3a (n = 17,865)	$P_{3a\ vs.\ 1}$	Stage 3b (n = 15,415)	$P_{3b\ vs.\ 1}$	Stage 4 (n = 4620)	$P_{4\ vs.\ 1}$	Stage 5 (n = 2060)	$P_{5\ vs.\ 1}$	Unspecified (n = 4070)	$P_{Unsp.\ vs.\ 1}$	
All-cause death																	
Events	2998	3022		35	605		2120		1985		660		310		305		6020
Events per 100 patient-year	10.3	12.6	<0.001	1.3	6.5	<0.001	12.7	<0.001	13.8	<0.001	15.6	<0.001	16.6	<0.001	7.8	<0.001	12.1
Time to first event, days	397 ± 159	357 ± 143	<0.001	489.5 ± 196	414 ± 166	<0.001	377 ± 151	<0.001	339 ± 136	<0.001	264 ± 105	<0.001	225.9 ± 90	<0.001	527 ± 211	<0.001	377 ± 148
Myocardial infarction																	
Events	2015	1835		175	650		1190		1040		315		205		275		3850
Events per 100 patient-year	6.7	7.2	<0.001	6.4	6.8	0.459	6.8	0.436	6.8	0.441	6.9	0.401	10.3	0.001	6.9	0.418	7.2
Time to first event, days	308 ± 148	291 ± 140	<0.001	390.2 ± 187	330 ± 158	<0.001	300 ± 144	<0.001	270 ± 130	<0.001	210 ± 101	<0.001	180.1 ± 86	<0.001	420 ± 202	<0.001	300 ± 144
Stroke																	
Events	1640	1690		115	475		1025		1005		320		170		220		3330
Events per 100 patient-year	5.5	6.8	<0.001	4.3	5.1	0.087	5.9	0.001	6.8	0.001	7.2	0.001	8.7	<0.001	5.6	0.016	6.3
Time to first event, days	309 ± 217	298 ± 209	<0.001	397.2 ± 278	336 ± 235	<0.001	306 ± 214	<0.001	275 ± 192	<0.001	214 ± 150	<0.001	183 ± 128	<0.001	428 ± 299	<0.001	306 ± 214
Heart failure																	
Events	4723	4497		295	1240		3040		2805		860		430		550		9220
Events per 100 patient-year	16.9	19.5	<0.001	11.4	13.8	<0.001	18.9	<0.001	20.4	<0.001	20.9	<0.001	24.0	<0.001	14.7	0.001	17.9
Time to first event, days	264 ± 123	242 ± 135	<0.001	351 ± 193	297 ± 163	<0.001	270 ± 148	<0.001	243 ± 134	<0.001	189 ± 104	<0.001	162 ± 89	<0.001	378 ± 208	0.001	261 ± 148
CKD																	
Events	1390	1247		65	210		665		555		200		802		140		2637
Events per 100 patient-year	6.1	5.3	<0.001	3.2	2.9	0.413	4.3	0.001	4.3	0.001	4.9	0.001	41.2	<0.001	42	0.034	5.9
Time to first event, days	356 ± 145	274 ± 178	<0.001	414 ± 211	350 ± 179	<0.001	318 ± 162	<0.001	287 ± 146	<0.001	223 ± 114	<0.001	191 ± 97	<0.001	446 ± 227	<0.001	318 ± 166

Table 2 (Continued)

	Diabetes status			CKD stage												Total (*n* = 56,435)
	Non T2D (*n* = 30,665)	T2D (*n* = 25,770)	P	Stage 1 (*n* = 2755)	Stage 2 (*n* = 9650)	$P_{2\ vs.\ 1}$	Stage 3a (*n* = 17,865)	$P_{3a\ vs.\ 1}$	Stage 3b (*n* = 15,415)	$P_{3b\ vs.\ 1}$	Stage 4 (*n* = 4620)	$P_{4\ vs.\ 1}$	Stage 5 (*n* = 2060)	$P_{5\ vs.\ 1}$	Unspecified (*n* = 4070)	$P_{Unsp.\ vs.\ 1}$	
Decline of eGFR ≥50%[*]																	
Events	1068	907		69	211		669		558		208		115		145		1975
Events per 100 patient-year	3.6	3.6	0.904	2.5	2.3	0.541	4.0	<0.001	3.7	0.002	4.7	<0.001	5.6	<0.001	3.6	0.011	3.8
ESKD (kidney transplantation or dialysis)																	
Events	340	352		0	0	–	0	–	0	–	0	–	692	–	0	–	692
Events per 100 patient-year	1.1	1.4	<0.001	0	0		0		0		0		38.1		0		1.65
Dialysis																	
Events	245	235		0	0	–	0	–	0	–	0	–	480	–	0	–	480
Events per 100 patient-year	0.8	0.9	0.013	0	0		0		0		0		26.9		0		1.1
Time to first event, days	285 ± 137	269 ± 124	–	–	–		–		–		–		271 ± 126		–		271 ± 126
Kidney transplantation																	
Events	95	117		0	0	–	0	–	0	–	0	–	212	–	0	–	212
Events per 100 patient-year	0.3	0.5	0.001	0	0		0		0		0		11.2		0		0.5
Time to first event, days	366 ± 162	306 ± 144	–	–	–		–		–		–		328 ± 147		–		328 ± 147
PAD																	
Events	737	828		55	245		530		440		155		75		65		1565
Events per 100 patient-year	2.5	3.3	<0.001	2.0	2.6	0.07	3.0	0.003	2.9	0.008	3.4	0.001	3.8	<0.001	1.6	0.218	3.1
Time to first event, days	282 ± 141	232 ± 116	<0.001	339 ± 169	286 ± 143	<0.001	260 ± 130	<0.001	234 ± 117	<0.001	182 ± 91	<0.001	156 ± 78	<0.001	365 ± 182	<0.001	260 ± 130
Cardiorenal disease (CKD and/or HF)																	
Events	5405	5180		345	1385		3445		3165		1055		505		685		10,585
Events per 100 patient-year	19.2	22.1	<0.001	13.3	15.5	<0.001	21.5	<0.001	23.2	<0.001	24.5	<0.001	26.4	<0.001	18.6	<0.001	20.8
Time to first event, days	358 ± 163	276 ± 171	<0.001	382 ± 198	324 ± 180	<0.001	294 ± 165	<0.001	2893 ± 147	<0.001	225 ± 101	<0.001	194 ± 84	<0.001	446 ± 206	<0.001	321 ± 142

[*] From baseline to the lowest available during follow up; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; ESKD: end stage kidney disease; HF: heart failure; PAD: peripheral artery disease.

Table 3 – Hospitalization and mortality rates after 2 years of follow-up in the overall CKD population and according to the presence of type 2 diabetes.

	No T2D (*n* = 30,665;54.3%)	T2D (*n* = 25,770;45.7%)	Total (*n* = 56,435;100%)	P
Percentage of patients on maximal doses of ACE-I or ARB, *n* (%)	1064 (3.5)	1326 (5.2)	2390 (4.2)	<0.001
Hospitalization, *n* (%)	12,514 (40.8)	12,287 (47.7)	24,801 (44.0)	<0.001
Hospitalization due to heart failure, *n* (%)	4723 (15.4)	4497 (17.5)	9220 (16.3)	<0.001
Hospital readmission, *n* (%)	3836 (12.5)	4284 (16.6)	8120 (14.4)	<0.001
Mortality during hospitalization, *n* (%)	2115 (6.9)	1700 (6.6)	3815 (6.8)	<0.001
Mortality after first hospitalization, *n* (%)	885 (2.9)	1320 (5.1)	2205 (3.9)	<0.001

ACEi: angiotensin-converting enzyme inhibitors; ARBs: angiotensin receptor blockers; CKD: chronic kidney disease; T2D: type 2 diabetes.

In the DAPA-CKD-like population, after 2 years of follow-up, rates of HF, all-cause death, MI, stroke, CKD and PAD were 21.4, 15.3, 8.2, 8.3, 4.2 and 3.2 events per 100 patient-years, respectively. With regard to CKD endpoints, rates of decline of eGFR ≥50% were 4.4 events per 100 patient-years, but no cases of end-stage kidney disease, dialysis, and kidney transplantation were reported. Rates of the combined endpoint of CKD and/or HF were 26.4 events per 100 patient-years. Except for MI, rates of all-cause death, cardiovascular and renal outcomes were significantly higher among patients with T2D, compared to those without T2D. Similarly, rates of all-cause death, cardiovascular and renal outcomes increased as CKD stage worsened. For example, rates of combined endpoint of CKD and/or HF increased from 18.1 events per 100 patient-years in patients with stage 2 CKD to 29.0 events per 100 patient-years among stage 4 CKD patients (Table 5).

Discussion

In our study, the prevalence of CKD was nearly 5% with an older population than in previous studies. Comorbidities such as HF and T2D were common, meaning that these greatly increase the risk of having CKD. In the last years, a number of studies have analyzed the prevalence of CKD worldwide. For instance, a study that estimated CKD prevalence in the European adult general population showed considerable differences between countries, from 3% to 17%, when considering CKD stages 1–5 and from 1% to 6%, when considering CKD stages 3–5. It is important to emphasize that the CKD prevalence stratified by diabetes, hypertension, and obesity status followed the same pattern as the overall prevalence.[2] As a result, to understand differences in CKD prevalence between countries, not only age, but also the distribution of risk factors should be considered. In Spain, the Hortega study was a cross-sectional study that collected data from 1997 to 2000 and showed that the prevalence of stage 2 CKD affected at least one third of the general population whereas stage 3 CKD ranged from 3% to almost 9% of individuals.[12] The EPIRCE study was an epidemiologic, general population-based, cross-sectional study that included a randomly selected Spanish sample aged 20 years or older from January 2004 to January 2008. In this study, the overall prevalence of CKD stages 3–5 was 6.8%, but when the UACR was added to the diagnostic criteria, the prevalence rose to 9.2%.[13] A more recent study performed in 11,505 individuals representative of the Spanish adult population and recruited from June 2008 to October 2010, showed a prevalence of CKD of 15%. The prevalence of CKD increased with age, and the presence of previous cardiovascular disease of cardiovascular risk factors.[14] On the other hand, underdiagnosis is a commonly observed issue in the early detection of CKD, as shown in a cross-sectional study performed in the Basic Health Area of Balaguer (Lleida), in which an initial prevalence of 3.98% was increased up to 6.00% after performing a review of CKD diagnostic criteria, denoting the existence of diagnostic and coding errors.[4]

Our data were provided by BIG-PAC®. This electronic database has been validated as an information source for studies of epidemiology, therapeutic adaptation and health/non-healthcare resource use and it has been demonstrated its representativeness of the Spanish population.[15,18] As a result, our data suggest that the prevalence of CKD could have changed in the last years in Spain. However, there are many reasons that may explain these differences beyond a real change in the CKD prevalence. Among these reasons, differences in the methodology of the studies, not only for the inclusion of patients (i.e. population based study vs. database studies), but also in the way CKD prevalence was determined (i.e. the use of one-off testing for assessment of eGFR or albuminuria to define the prevalence of CKD, the use of CKD-EPI equation vs. other formula, population based study [i.e. EPIRCE] vs. database-based study, etc.) could have played a role.[12–14,19–21] Moreover, in our study, due to its retrospective design, some relevant data (i.e. albuminuria) could not be documented in all patients, leading to an underdiagnosis of CKD. In fact, previous studies have also shown an underdiagnosis of CKD of database studies compared to population based studies.[4] On the other hand, it is likely that the higher use of CKD prevention treatments have had some impact on changes in CKD prevalence.[1] In the EPIRCE study, 11% of patients had diabetes and 5% ischemic heart disease.[13] In the work of Gorostidi et al., 17% had diabetes and 6% previous cardiovascular disease.[14] In our study, approximately half of patients had T2D, 21% a history of HF, and 14% prior MI. Around 70% of patients were taking renin-angiotensin system inhibitors and this proportion increased as renal function worsened. Different guidelines recommend the use of renin-angiotensin system inhibitors for the prevention or delay of cardiovascular and renal diseases.[22–24] Despite the high use of renin angiotensin system inhibitors, only 4% of patients were taking them at maximal doses. It is likely that the risk of hyperkalemia, particularly in those patients with advanced CKD

Table 4 – Baseline clinical characteristics of the DAPA-CKD population at index date (1st January 2018) and according to the presence of type 2 diabetes and CKD stage.

	Diabetes status			CKD stage										Total
	Non T2D (*n* = 3798; 52.6%)	T2D (*n* = 3426; 47.4%)	*P*	Stage 1 (*n* = 0)	Stage 2 (*n* = 315; 4.4%)	Stage 3a (*n* = 3242; 44.9%)	$P_{3a\ vs.\ 2}$	Stage 3b (*n* = 2771; 38.4%)	$P_{3b\ s\ 2}$	Stage 4 (n= 896; 12.4%)	$P_{4\ vs.\ 2}$	Stage 5 (*n* = 0)	Unspecified (*n* = 0)	(n = 7224%)
Age, years	76.3	77.1		NA	77.0	76.8		80.5		79.4		NA	NA	77.0
≥85 years, *n* (%)	1162 (30.6)	893 (26.1)	0.045	NA	64 (20.3)	889 (27.4)	0.007	828 (29.9)	0.001	274 (30.6)	0.001	NA	NA	2055 (26.3)
Sex, female, n (%)	1894 (49.9)	1606 (46.9)	0.011	NA	153 (48.6)	1545 (47.7)	0.760	1376 (49.7)	0.711	426 (47.5)	0.737	NA	NA	3424 (47.4)
Physical examination and laboratory tests														
SBP, mmHg	136.5	139.9	<0.001	NA	138.5	138.1		138.7		136.4		NA	NA	138.1
UACR	352.4	423.8	<0.001	NA	129.3	256.3		258.1		1713.4		NA	NA	391.5
UACR A1	0	0	–	NA	0	0		0		0		NA	NA	0
UACR A2	2386 (62.8)	2245 (61.4)	0.221	NA	315 (100)	2150 (66.3)	<0.001	1826 (65.9)		340 (38.0)		NA	NA	4631 (64.1)
UACR A3	1312 (37.2)	1281 (38.6)	0.221	NA	0	1092 (33.7)		945 (34.1)		556 (62.1)		NA	NA	2593 (35.9)
*eGFR**	50.0	49.5	0.724	NA	75.0	51.9		37.1		22.2		NA	NA	49.8
eGFR ≥90*, *n* (%)	0	0	–	NA	0	0		0		0		NA	NA	0
eGFR 60–89*, *n* (%)	177 (4.7)	138 (4.0)	0.146	NA	315 (100)	0		0		0		NA	NA	315 (4.4)
eGFR 45–59*, *n* (%)	1810 (47.7)	1432 (41.8)	<0.001	NA	0	3242 (100)		0		0		NA	NA	3242 (44.9)
eGFR 30–44*, *n* (%)	1358 (35.8)	1413 (41.2)	<0.001	NA	0	0		2771 (100)		0		NA	NA	2771 (38.4)
eGFR 15–29*, *n* (%)	453 (11.9)	443 (12.9)	0.197	NA	0	0		0		896 (100)		NA	NA	896 (12.4)
eGFR <15*, *n* (%)	0	0	–	NA	0	0		0		0		NA	NA	0
HbA1c, %	5.9	7.6	<0.001	NA	6.6	6.6	0.999	6.6	0.999	7.1	0.764	NA	NA	7.0
Creatinine, mg/dL	1.1	1.2	<0.001	NA	1.0	1.3	0.650	1.6	0.685	2.2	0.178	NA	NA	1.1
Uric acid, g/dL	5.9	6.9	<0.001	NA	7.0	6.8	0.893	6.3	0.730	7.0	0.999	NA	NA	6.4
Comorbidities, N (%)														
CKD – Chronic	3798 (100)	3426 (100)	–	NA	315 (100)	3242 (100)		2771 (100)		896 (100)		NA	NA	7224 (100)
Stage 1	0	0	–	NA	0	0		0		0		NA	NA	0
Stage 2	177 (4.7)	138 (4.0)	0.146	NA	315 (100)	0		0		0		NA	NA	315 (17.2)
Stage 3a	1810 (47.7)	1432 (41.8)	<0.001	NA	0	3242 (100)		0		0		NA	NA	3242 (31.8)
Stage 3b	1358 (35.8)	1413 (41.2)	<0.001	NA	0	0		2771 (100)		0		NA	NA	2771 (27.5)
Stage 4	453 (11.9)	443 (12.9)	0.197	NA	0	0		0		896 (100)		NA	NA	896 (7.9)
Stage 5	0	0	–	NA	0	0		0		0		NA	NA	0

Table 4 (*Continued*)

	Diabetes status			CKD stage										Total
	Non T2D (*n* = 3798; 52.6%)	T2D (*n* = 3426; 47.4%)	P	Stage 1 (*n* = 0)	Stage 2 (*n* = 315; 4.4%)	Stage 3a (*n* = 3242; 44.9%)	$P_{3a\ vs.\ 2}$	Stage 3b (*n* = 2771; 38.4%)	$P_{3b\ s\ 2}$	Stage 4 (n= 896; 12.4%)	$P_{4\ vs.\ 2}$	Stage 5 (*n* = 0)	Unspecified (*n* = 0)	(n = 7224%)
Not staged	0	0	–	NA	0	0		0		0		NA	NA	0
Unspecified	1122 (29.5)	166 (4.8)	<0.001	NA	46 (14.6)	587 (18.1)	0.121	510 (18.4)	0.096	145 (16.2)	0.503	NA	NA	1288 (17.8)
CKD – Diabetic	8 (0.2)	1991 (58.1)	<0.001	NA	98 (31.1)	878 (27.1)	0.129	756 (27.3)	0.153	267 (29.8)	0.665	NA	NA	1999 (27.7)
CKD – Hypertensive	2668 (70.2)	1269 (37.0)	<0.001	NA	171 (54.3)	1777 (54.8)	0.865	1505 (54.3)	0.999	484 (54.0)	0.927	NA	NA	3937 (54.5)
Dialysis	0	0	–	NA	0	0	–	0	–	0	–	NA	NA	0
CVD	633 (16.7)	714 (20.8)	0.001	NA	50 (15.9)	621 (19.2)	0.153	527 (19.0)	0.181	149 (16.6)	0.773	NA	NA	1347 (20.5)
Myocardial infarction	423 (11.1)	524 (15.3)	0.001	NA	38 (12.1)	408 (12.6)	0.798	367 (13.2)	0.583	134 (15.0)	0.205	NA	NA	947 (12.4)
Heart failure	713 (18.8)	814 (23.8)	<0.001	NA	43 (13.7)	664 (20.5)	0.004	609 (22.0)	0.001	211 (23.5)	<0.001	NA	NA	1527 (21.1)
Stroke	384 (10.1)	401 (11.7)	0.029	NA	27 (8.6)	322 (9.9)	0.459	342 (12.3)	0.055	94 (10.5)	0.334	NA	NA	785 (11.3)
Atrial Fibrillation	674 (17.8)	588 (17.2)	0.503	NA	44 (14.0)	560 (17.3)	0.137	500 (18.0)	0.077	158 (17.6)	0.140	NA	NA	1262 (17.0)
PAD	162 (4.3)	208 (6.1)	0.001	NA	15 (4.8)	169 (5.2)	0.759	136 (4.9)	0.938	50 (5.6)	0.589	NA	NA	370 (6.1)
Diabetic CKD	8 (0.2)	1991 (58.1)	<0.001	NA	98 (31.1)	878 (27.1)	0.129	756 (27.3)	0.153	267 (29.8)	0.665	NA	NA	1999 (36.9)
Diabetes	0	3658 (100)	<0.001	NA	162 (51.4)	1611 (49.7)	0.565	1383 (49.9)	0.614	502 (56.0)	0.158	NA	NA	3658 (50.6)
Hyperkalemia	153 (4.0)	204 (6.0)	<0.001	NA	15 (4.8)	142 (4.4)	0.742	138 (5.0)	0.877	62 (6.9)	0.189	NA	NA	357 (7.3)
Gout	1227 (32.3)	1127 (32.9)	0.587	NA	91 (28.9)	1045 (32.2)	0.230	916 (33.1)	0.132	302 (33.7)	0.118	NA	NA	2354 (32.7)
Medications, *n* (%)														
Antihypertensives	2881 (75.9)	3035 (88.6)	<0.001	NA	240 (76.3)	2577 (79.5)	0.182	2317 (83.6)	0.001	782 (87.3)	<0.001	NA	NA	5916 (81.9)
RAAS inhibitors	3798 (100)	3426 (100)	–	NA	315 (100)	3242 (100)	–	2771 (100)	–	896 (100)	–	NA	NA	7224 (100)
ACEi	1607 (42.3)	1394 (40.7)	0.168	NA	101 (32.1)	1199 (37.0)	0.085	1255 (45.3)	<0.001	446 (49.8)	<0.001	NA	NA	3001 (41.5)
ACEi at maximal doses	220 (5.8)	216 (6.3)	0.373	NA	14 (4.4)	182 (5.6)	0.372	172 (6.2)	0.203	68 (7.6)	0.052	NA	NA	436 (6.0)
ARBs	2191 (57.7)	2032 (59.3)	0.168	NA	145 (46.0)	1687 (52.0)	0.042	1587 (57.3)	<0.001	804 (89.7)	<0.001	NA	NA	4223 (58.5)
ARBs at maximal doses	273 (7.2)	271 (7.9)	0.260	NA	17 (5.4)	215 (6.6)	0.409	227 (8.2)	0.081	85 (9.5)	0.024	NA	NA	544 (7.5)
Aldoster one antagonists	212 (5.6)	281 (8.2)	<0.001	NA	17 (5.4)	192 (5.9)	0.718	200 (7.2)	0.236	84 (9.4)	0.027	NA	NA	493 (6.8)
Direct renin inhibitors	45 (1.2)	53 (1.6)	0.147	NA	3 (1.0)	40 (1.2)	0.754	41 (1.5)	0.482	14 (1.6)	0.443	NA	NA	98 (1.4)
ARNI	241 (6.4)	267 (7.8)	0.020	NA	16 (5.1)	201 (6.2)	0.436	209 (7.5)	0.120	82 (9.2)	0.022	NA	NA	508 (7.0)
Beta blockers	1216 (32.0)	1485 (43.4)	<0.001	NA	91 (28.9)	1139 (35.1)	0.027	1119 (40.4)	<0.001	352 (39.3)	<0.001	NA	NA	2701 (37.4)

Table 4 (*Continued*)

	Diabetes status			CKD stage										Total
	Non T2D (*n* = 3798; 52.6%)	T2D (*n* = 3426; 47.4%)	*P*	Stage 1 (*n* = 0)	Stage 2 (*n* = 315; 4.4%)	Stage 3a (*n* = 3242; 44.9%)	$P_{3a\ vs.\ 2}$	Stage 3b (*n* = 2771; 38.4%)	$P_{3b\ s\ 2}$	Stage 4 (n= 896; 12.4%)	$P_{4\ vs.\ 2}$	Stage 5 (*n* = 0)	Unspecified (*n* = 0)	(n = 7224%)
Diuretics	1385 (36.5)	1571 (45.9)	<0.001	NA	94 (29.8)	1167 (36.0)	0.028	1202 (43.4)	<0.001	493 (55.0)	<0.001	NA	NA	2956 (40.9)
Thiazide diuretics	153 (4.0)	171 (5.0)	0.040	NA	11 (3.5)	125 (3.9)	0.725	124 (4.5)	0.412	64 (7.1)	0.022	NA	NA	324 (4.5)
Loop diuretics	1237 (32.6)	1400 (40.9)	<0.001	NA	84 (26.7)	1089 (33.6)	0.013	1062 (38.3)	<0.001	402 (44.9)	<0.001	NA	NA	2637 (36.5)
Potassium sparing diuretics	265 (7.0)	318 (9.3)	<0.001	NA	19 (6.0)	222 (6.9)	0.545	230 (8.3)	0.155	112 (12.5)	0.001	NA	NA	583 (8.1)
CCB	1064 (28.0)	1292 (37.7)	<0.001	NA	84 (26.7)	909 (28.0)	0.623	994 (35.9)	0.001	369 (41.2)	<0.001	NA	NA	2356 (32.6)
Dihydropyridines	972 (25.6)	1203 (35.1)	<0.001	NA	74 (23.5)	849 (26.2)	0.297	909 (32.8)	0.001	343 (38.3)	<0.001	NA	NA	2175 (30.1)
Non-dihydropyridines	134 (3.5)	120 (3.5)	0.999	NA	8 (2.5)	100 (3.1)	0.554	98 (3.5)	0.353	48 (5.4)	0.035	NA	NA	254 (3.5)
Antidiabetics	106 (2.8)	2846 (83.1)	<0.001	NA	91 (28.9)	1156 (35.7)	0.016	1258 (45.4)	<0.001	447 (49.9)	<0.001	NA	NA	2952 (40.9)
Metformin	0	1676 (48.9)	<0.001	NA	45 (14.3)	686 (21.2)	0.004	689 (24.9)	<0.001	256 (28.6)	<0.001	NA	NA	1676 (23.2)
Sulfonylurea	0	448 (13.1)	<0.001	NA	12 (3.8)	184 (5.7)	0.159	185 (6.7)	0.005	67 (7.5)	0.022	NA	NA	448 (6.2)
DPP4 inhibitors	0	1359 (39.7)	<0.001	NA	51 (16.2)	543 (16.7)	0.820	531 (19.2)	0.197	234 (26.1)	<0.001	NA	NA	1359 (18.8)
SGLT-2 inhibitors	0	163 (4.8)	<0.001	NA	6 (1.9)	64 (2.0)	0.904	69 (2.5)	0.513	24 (2.7)	0.433	NA	NA	163 (2.3)
GLP-1 receptor agonists	0	127 (3.7)	<0.001	NA	4 (1.3)	55 (1.7)	0.596	49 (1.8)	0.521	19 (2.1)	0.370	NA	NA	127 (1.8)
Metiglinides	0	496 (14.5)	<0.001	NA	16 (5.1)	198 (6.1)	0.476	205 (7.4)	0.134	77 (8.6)	0.045	NA	NA	496 (6.9)
Glitazones	0	105 (3.1)	<0.001	NA	3 (1.0)	44 (1.4)	0.559	37 (1.3)	0.652	21 (2.3)	0.152	NA	NA	105 (1.5)
Acarbose	0	111 (3.2)	<0.001	NA	6 (1.9)	42 (1.3)	0.379	39 (1.4)	0.482	24 (2.7)	0.433	NA	NA	111 (1.5)
Insulin	106 (2.8)	723 (21.1)	<0.001	NA	28 (8.9)	335 (10.3)	0.433	312 (11.3)	0.198	154 (17.2)	<0.001	NA	NA	829 (11.5)
Statins	1791 (47.2)	2183 (63.7)	<0.001	NA	118 (37.5)	1694 (52.3)	<0.001	1570 (56.7)	<0.001	592 (66.1)	<0.001	NA	NA	3974 (55.0)
Warfarin	504 (13.3)	496 (14.5)	0.141	NA	36 (11.4)	386 (11.9)	0.793	422 (15.2)	0.072	156 (17.4)	0.012	NA	NA	1000 (13.8)
Low dose aspirin	982 (25.9)	969 (28.3)	<0.001	NA	63 (20.0)	806 (24.9)	0.053	801 (28.9)	0.001	281 (31.4)	<0.001	NA	NA	1951 (27.0)
Receptor P2Y12 antagonists	46 (1.2)	79 (2.3)	<0.001	NA	4 (1.3)	48 (1.5)	0.779	50 (1.8)	0.521	23 (2.6)	0.182	NA	NA	125 (1.7)

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; NA: not applicable; PAD: peripheral artery disease; RAAS: renin angiotensin system; SBP: systolic blood pressure; SGLT-2: sodium-glucose Cotransporter-2; UACR: Urine albumin-to-Creatinine Ratio.

Table 5 – Event rates after 2 years of follow-up in the DAPA-CKD population and according to the presence of type 2 diabetes and CKD stage.

	Diabetes status			CKD stage										
	Non T2D (*n* = 3798; 52.6%)	T2D (*n* = 3426; 47.4%)	P	Stage 1 (*n* = 0)	Stage 2 (*n* = 315; 4.4%)	Stage 3a (*n* = 3242; 44.9%)	$P_{3a\ vs.\ 2}$	Stage 3b (*n* = 2771; 38.4%)	$P_{3b\ vs.\ 2}$	Stage 4 (*n* = 896; 12.4%)	$P_{4\ vs.\ 2}$	Stage 5 (*n* = 0)	Unspecified (*n* = 0)	Total (*n* = 7224; 100%
All-cause death														
Events	512	530			24	459		417		142				1042
Events per 100 patient-year	14.1	15.8	<0.001	NA	7.8	14.4	0.001	15.2	<0.001	16.0	<0.001	NA	NA	15.3
Time to first event, days	411 ± 155	363 ± 148	<0.001		507 ± 201	389 ± 153	<0.001	351 ± 140	<0.001	273 ± 111	<0.001			389 ± 154
Myocardial infarction														
Events	313	251			22	251		218		73				564
Events per 100 patient-year	8.3	7.4	<0.001	NA	7.1	7.8	0.657	8.1	0.535	8.3	0.500	NA	NA	8.2
Time to first event, days	288 ± 135	262 ± 129	<0.001		359 ± 181	273 ± 138	<0.001	249 ± 124	<0.001	191 ± 96	<0.001			276 ± 139
Stroke														
Events	241	303			20	210		229		85				544
Events per 100 patient-year	6.5	9.0	<0.001	NA	6.4	6.6	0.891	8.8	0.220	10.8	0.023	NA	NA	8.3
Time to first event, days	286 ± 178	221 ± 155	<0.001		385 ± 269	297 ± 210	<0.001	268 ± 187	<0.001	208 ± 141	<0.001			297 ± 208
Heart failure														
Events	750	746			49	616		626		205				1496
Events per 100 patient-year	19.9	22.0	<0.001	NA	15.6	19.4	<0.001	23.1	0.003	23.1	<0.001	NA	NA	21.4
Time to first event, days	293 ± 161	249 ± 137	<0.001		306 ± 168	235 ± 128	<0.001	213 ± 117	<0.001	164 ± 91	<0.001			265 ± 128
CKD														
Events	127	139			8	113		105		40				266
Events per 100 patient-year	3.4	4.2	<0.001	NA	2.6	3.6	0.357	3.9	0.251	4.7	<0.001	NA	NA	4.2
Time to first event, days	362 ± 146	281 ± 178	<0.001		405 ± 196	315 ± 156	<0.001	285 ± 141	<0.001	228 ± 115	<0.001			304 ± 151
Decline of eGFR ≥50%[*]														
Events	129	142		NA	8	115		107		41		NA	NA	2710
Events per 100 patient-year	3.4	4.3	<0.001		2.6	3.6	0.357	4.0	0.220	4.7	0.016			4.4

Table 5 (*Continued*)

	Diabetes status			CKD stage										
	Non T2D (n = 3798; 52.6%)	T2D (n = 3426; 47.4%)	P	Stage 1 (n = 0)	Stage 2 (n = 315; 4.4%)	Stage 3a (n = 3242; 44.9%)	$P_{3a\ vs.\ 2}$	Stage 3b (n = 2771; 38.4%)	$P_{3b\ vs.\ 2}$	Stage 4 (n = 896; 12.4%)	$P_{4\ vs.\ 2}$	Stage 5 (n = 0)	Unspecified (n = 0)	Total (n = 7224; 100%
ESKD (kidney transplantation or dialysis)														
Events	0	0	–	NA	0	0	–	0	–	0	–	NA	NA	0
Events per 100 patient–year	0	0			0	0	–	0	–	0	–			0
Dialysis														
Events	0	0			0	0		0		0				0
Events per 100 patient-year	0	0	–	NA	0	0	–	0	–	0	–	NA	NA	0
Time to first event, days	–	–			–	–	–	–	–	–	–			–
Kidney transplantation														
Events	0	0			0	0		0		0				0
Events per 100 patient-year	0	0	–	NA	0	0	–	0	–	0	–	NA	NA	0
Time to first event, days	–	–			–	–	–	–	–	–	–			–
PAD														
Events	86	123			4	68		92		45				209
Events per 100 patient-year	2.3	3.6	<0.001	NA	1.3	2.1	0.336	3.3	0.052	5.0	0.004	NA	NA	3.2
Time to first event, days	331 ± 164	272 ± 137	<0.001		398 ± 196	304 ± 150	<0.001	275 ± 136	<0.001	210 ± 106	<0.001			304 ± 151
Cardiorenal disease (CKD and/or HF)														
Events	865	862			53	717		724		233				1727
Events per 100 patient-year	24.2	27.3	<0.001	NA	18.1	23.2	<0.001	28.6	0.001	29.0	<0.001	NA	NA	26.4
Time to first event, days	322 ± 193	264 ± 159	<0.001		385 ± 230	295 ± 178	<0.001	268 ± 160	<0.001	206 ± 124	<0.001			296 ± 177

* From baseline to the lowest available during follow up; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; ESKD: end stage kidney disease; HF: heart failure; PAD: peripheral artery disease.

could have played a role.[25] However, it is important to mention that different studies have shown that the use of higher-dose compared with lower-dose angiotensin receptor blockers or the use of neprilysin inhibitors may be associated with better cardiovascular and renal outcomes.[18,26–28] In addition, it has been reported that the use of guidelines recommended drugs is associated not only with a reduction of morbidity and mortality, but also with a reduction of healthcare costs.[18]

There is a clear relationship between CKD and HF.[24] Fortunately, a number of clinical trials have shown in the last years that among patients with T2D, SGLT-2 inhibitors are associated with a reduction in the risk of major adverse cardiovascular events, and particularly with a decrease in the risk for HF hospitalization and kidney outcomes.[29] In DECLARE-TIMI 58 trial, dapagliflozin prevented and reduced progression of kidney disease among T2D patients at high risk for cardiovascular events, in both, patients with normal or impaired renal function.[30] In our study, only 3.5% of patients with T2D were taking SGLT-2 inhibitors. As a result, it is very likely that a higher prescription of guidelines recommended drugs would translate into a higher reduction in CKD prevalence. Likewise, the DAPA-CKD trial,[10] aimed to assess the long-term efficacy and safety of the SGLT2 inhibitor dapagliflozin in patients with CKD, with or without T2D, was prematurely interrupted due to the beneficial effects on renal outcomes and the composite of death from cardiovascular causes or hospitalization for HF. In the CREDENCE (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation) trial,[11] canagliflozin reduced the risk of kidney failure and cardiovascular events in patients with T2D and CKD. Therefore, a higher use of SGLT2 inhibitors with proven efficacy among CKD population, regardless the presence of T2D, could delay the progression of renal disease and may reduce the incidence of CKD complications. In our study, cardiovascular outcomes were more common in the DAPA-CKD like subpopulation than in the general CKD population, suggesting that these patients would benefit more from this treatment.

Individuals with CKD are at increased risk of all-cause and cardiovascular premature death, and may progress to end-stage renal disease. In addition, CKD translates into increased health system costs.[31–33] In our study, after 2 years of follow-up, rates of cardiovascular and renal outcomes were high, reaching nearly 21 events per 100 patient-years in the combined endpoint of CKD and/or HF. Moreover, during the study period, 44% of patients were hospitalized, 16% were hospitalized due to heart failure, and around 7% of patients died during hospitalization. Furthermore, rates of mortality, cardiovascular, particularly HF, and renal outcomes were significantly higher in the subgroup of patients with T2D. Therefore, it is necessary to implement a comprehensive management to prevent or delay the development of CKD (primary prevention) and its complications (secondary prevention), including end-stage renal disease that implies not only improving cardiovascular risk factors control, but also the use of guidelines recommended drugs, such as renin-angiotensin system blockers and SLGT-2 inhibitors.[7–11,22] Unfortunately, our data showed that there is much room for improvement and more efforts are required to enhance the therapeutic approach of these patients.

Limitations

This was an observational retrospective cohort study that used secondary data from electronic health records. Therefore, only indirect causality may be suggested. Moreover, due to the retrospective design of the study, some relevant data (i.e. albuminuria) could not be documented in all patients, leading to an underdiagnosis of CKD. On the contrary, time of evolution of CKD was not recorded and this could lead to an overdiagnosis of CKD in some individuals, as the definition of CKD requires at least 3 months of functional or structural renal impairment.[7] However, although all these limitations could interfere with the prevalence of CKD, the high number of patients included, as well as the robustness of the data may allow to determine the value of the study. On the other hand, although data came from 7 Spanish regions, previous studies have shown that these data are representative of the Spanish population.[15]

Conclusions

Our data show that CKD in Spain is a relevant clinical condition with poor prognosis and suboptimal treatment. Population was older and comorbidities such as T2D and HF were common. Nearly 30% of patients with CKD are not taking renin angiotensin system blockers, and only 4% at maximal doses. Less than 4% of T2D patients are being treated with SGLT-2 inhibitors. Cardiovascular and renal outcomes are frequent, and markedly increase with the presence of T2D and with renal function decline. As the use of guidelines recommended treatments prevents or delays cardiovascular and renal progression, improving CKD management, particularly through the use of drugs with proven cardiovascular and renal benefit, is mandatory.

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Conflict of interests

The authors declare that they have no conflict of interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.nefro.2021.03.006.

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