Characteristics, Mortality and Cardiovascular Events in Chronic Kidney Disease According To Previous Type 2 Diabetes Mellitus and/or Hypertension. A Population-Based Epidemiological Study (KIDNEES)

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Research Article

Keywords: Chronic kidney disease, mortality, cardiovascular risk, type 2 Diabetes Mellitus, Hypertension

Posted Date: July 7th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-658979/v1

Abstract

Introduction and objectives.

Chronic Kidney Disease (CKD) entails a considerable burden of adverse outcomes. Identifying the cause is recommended but data on its prognostic value are scarce. We aimed to estimate how the clinical, cardiovascular events (CVE) and all-cause mortality (ACM) of CKD patients differs according to previous Type 2 Diabetes Mellitus (2TD) and/or Hypertension (HTN).

Methods.

We conducted a retrospective cohort study based on electronic health records of subjects aged 18–90 years old, with incident CKD between 1st January 2007 and 31st December 2017. The association between CKD groups according to previous T2D and/or HTN, and risk of ACM and CVE at follow-up were determined with Cox and Fine-Gray regressions, respectively.

Results.

398,477 subjects were included. Median age was 74years, 55.2% were women. Individuals were distributed to HTN-CKD (51.9%), T2D-CKD (3.87%), HTN/T2D-CKD (31.4%) and unspecified-CKD (12.9%). In the multivariate analysis, with the T2D-CKD group as reference, the ACM Hazard Ratio (HR) was 0.645 (95%CI 0.624–0.667) in HTN-CKD, 0.704 (95%CI 0.682–0.728) in HTN/T2D-CKD and 0.875 (95%CI 0.844–0.908) in Unspecified-CKD group. The respective sub distribution HRs for CVE were 1.006 (CI95% 0.946–1.069), 1.238 (CI95% 1.164–1.316) and 0.722 (CI95% 0.665–0.785).

Conclusion.

In individuals with CKD, the risk of ACM and CVE differed according to previous HTN or/and T2D. These characteristics can help identifying individuals at higher risk of adverse outcomes, and improving the management of CKD patients in primary care.

Introduction

Chronic kidney disease (CKD) entails a considerable burden of adverse outcomes, including higher risk of cardiovascular events (CVE) and death [1–3]. To predict risk of unfavourable outcomes, CKD is classified based on estimated glomerular filtration rate (eGFR) and albuminuria categories [4]. Identifying the cause of CKD is also recommended. However, the data on the independent prognostic role of the cause of CKD are scarce [5]. Recently, the high cardiovascular event rates in dialysis patients has been shown to vary considerably by cause of end-stage renal disease (ESRD) among six glomerular disease subtypes,

diabetic nephropathy or polycystic kidney disease being diabetic nephropathy the one associated with the highest risk [6].

Type 2 Diabetes mellitus (T2D) and Hypertension (HTN), the main causes of CKD in adults [7], are frequent conditions and two of the main cardiovascular risk factors. A large percentage of patients with T2D and CKD also have HTN [8], and when both conditions are present CKD prognosis may worsen [9].

As a primary cause of CKD, HTN has been less studied than T2D [10]. The increased risk of CVE in patients with HTN, T2D or CKD is well-known [11], but there is still a gap on the comparison and characterization of the interaction between T2D and HTN in the cardiovascular prognosis of CKD patients. Understanding differences in characteristics and risk factors for prognosis in diabetic and/or hypertensive patients with CKD can improve cardiovascular risk stratification and be crucial for the management of these patients in routine clinical practices.

The objective of the present study is to know how the clinical, demographic, prognosis and cardiovascular risk of CKD patients without previous CVE differs according to a previous diagnosis of T2D and/or HTN.

Research Design And Methods

Data source

SIDIAP is a well-established, large primary care electronic health record from Catalonia, North-East Spain with information from centers managed by the Institut Català de la Salut (80% of the population), including demographics, lifestyle factors, clinical diagnoses coded using the International Classification of Diseases- 10th revision (ICD-10), lab values, diagnostic procedures, specialist referrals, drug prescription and hospital data discharge. SIDIAP database is hosted by the IDIAP Jordi Gol, a long-standing primary care research institution affiliated with the Catalan Government.

SIDIAP has been validated for its use in cardiovascular risk factors and disease research [12,13].

Study design and participants

We conducted a retrospective cohort study based on electronic health records of subjects aged 18–90 years old with incident CKD between 1st January 2007 and 31st December 2017, whose disease was managed in a primary health care centers belonging to the Institut Català de la Salut in Catalonia (covered population 5,564,292 million).

Cohort entry was defined as first CKD evidence during study period ascertained as: 1) Two measures of eGFR < 60 mL/min/1.73m^2 present for more than 90 days, 2) abnormal urine albumin (albumin to creatinine ratio –ACR- values ≥ 3.4 g/mmol or albumin ≥ 20 mg/L or ≥ 30 mg/day) present for more than 90 days, or 3) ICD-10 codes indicative for CKD (Supplementary Table 1). Exclusion criteria applied to

persons with any CKD evidence prior to cohort entry as defined above. Individuals with previous atherosclerotic cardiovascular disease (angina and myocardial infarction [ICD-10: I20 - I24], ischemic or hemorrhagic stroke [I63, I64, I67] or transient ischemic attack [G45, G46], and peripheral arterial disease [I70]) were excluded in the present analysis.

Subjects were followed up for outcomes until transference out of the SIDIAP or end of the study period on 31st December 2018.

Exposure, outcomes and covariates

Patients were classified according to previous T2D and HTN evidence into four mutually exclusive groups: HTN-CKD, T2D-CKD, HTN/T2D-CKD and Unspecified-CKD (U-CKD). T2D was defined according to an algorithm using ICD-10 codes [E10, E11, E12, E14 and subcategories], treatment patterns, age at diagnosis and lab values (two fasting plasma glucose ≥ 126 mg/dL (7.0 mmol/L) or glycosylated haemoglobin (HbA1c) ≥ 6.5%) (Supplementary Fig. 1). HTN was based on ICD-10 codes [I10, I11and subcategories], or mean blood pressure (BP) on two consecutive measurements with systolic BP (SBP) ≥ 140 and/or diastolic BP (DBP) ≥ 90 mmHg separated at least 1 week.

The outcomes were time from CKD evidence to death and CVE (myocardial infarction, unstable angina or angina, non-hemorrhagic cerebrovascular disease or transient ischemic attack) (see Supplementary Table 2 for detailed definition).

The covariate definition included baseline data on age, sex, socio-economic index quintiles [14], urban or rural area, T2D or HTN years of evolution and complications, CKD severity based on eGFR and albuminuria categories [4], any primary renal disease diagnosis, autoimmune disease with CKD risk, heart failure, Charlson score, smoking status, body mass index (BMI), SBP, DBP, total cholesterol, HbA1c, anemia and drugs of frequent use with cardiovascular or renal effect (statins, platelet aggregation inhibitors and anticoagulants, aldosterone antagonists, angiotensin-converting enzyme inhibitors –ACEIs- and angiotensin II receptor antagonists –ARBs-) (Supplementary Table 2).

Statistical analysis

Continuous variables were summarized as median and interquartile range, and categorical variables as absolute and relative frequencies.

The association of risk factors with ACM was evaluated by Cox proportional hazards model, with estimation of the hazard ratio of ACM for the HTN/T2D -CKD, HTN-CKD or U-CKD groups compared to the T2D -CKD, adjusted for all described co-variables. For the CVE outcome analysis sub distribution hazard ratios were estimated from Fine-Gray models considering death as a competitive risk. For both models, transference out of the SIDIAP or end of the study period were sources of right censoring, and final multivariate models were constructed from backward stepwise processes of selection of variables (based on the Akaike information criterion).

Multiple imputation of missing values of co-variables was performed with the Markov Chains Multiple Imputation approach – 5 imputations, 10 iterations; interactions included in the process. Imputed variables were explored to check for quality of the imputation process. To observe the effect of data imputation, a sensitivity analysis was performed replicating the resulting models with complete case analysis.

All analyses were performed using R-software V3.5.1 (R Foundation for Statistical Computing, Vienna, Austria).

Ethical approval was obtained from the Ethics Committee for Clinical Research IDIAPJGol (19/082-P).

Results

A total of 398,477 individuals with incident CKD aged 18–90 years old were identified (Fig. 1). Median age was 74 years [IQR 65–81] and 55.2% were women. HTN was present in 83.3% of individuals and T2D in 35.3%, of whom 89.0% had also HTN. Individuals were distributed by previous HTN or/and T2D diagnosis as follows: HTN-CKD (51.9%), T2D-CKD (3.87%), HTN/T2D-CKD (31.4%) and unspecified-CKD (12.9%).

Individuals in the HTN-CKD group were the oldest and had the highest proportion of women (76 years [IQR 68–82] and 59.03% respectively). It was the opposite in the T2D-CKD (69 years [IQR 57–78]; 38.9% women) (Table 1). The HTN/T2D-CKD and the T2D-CKD groups presented a higher proportion of lower socioeconomic quintiles and higher Charlson Index score. Active smokers were more prevalent in T2D-CKD.

Table 1
Baseline characteristics of the KIDNEES cohort free of Atherosclerotic Cardiovascular Disease at baseline (n = 398,477) (pooled imputed data).

	Unspecific-CKD	HTN-CKD	T2D-CKD	HTN/T2D-CKD	p value
Age (years)	70 [58, 80]	76 [68, 82]	69 [57, 78]	74 [65, 80]	< 0.001
Age (years, cat.) *< 65*	39.74	20.61	42.61	25.30	< 0.001
[65, 80)	37.01	47.97	38.19	51.22	
≥ 80	23.24	31.42	19.20	23.48	
Sex (Female)	56.55	59.03	38.94	50.27	< 0.001
MEDEA deprivation index *Rural*	24.43	25.52	23.40	24.53	< 0.001
Least deprived quintile	18.13	16.07	13.35	12.91	
Second quintile	16.05	15.34	15.11	14.27	
Third quintile	14.95	15.36	14.57	15.53	
Forth quintile	13.90	14.57	15.87	16.27	
Most deprived quintile	12.54	13.14	17.70	16.49	
Expanded CHARLSON INDEX SCORE					< 0.001
Non comorbidity	64.57	68.31	54.05	51.05	
Low	29.38	26.47	34.88	37.08	
High	6.05	5.21	11.08	11.87	
Opht/ neur complications	0.07	0.27	10.33	13.53	< 0.001
Hypertensive heart disease	0.00	2.71	0.00	3.16	< 0.001
Primary Renal Disease Diagnosis	3.43	2.28	2.32	2.09	< 0.001
Autoimmune Disease with CKD risk	0.59	0.34	0.38	0.20	< 0.001
Smoking status *Non smoker*	66.20	72.30	53.90	65.28	< 0.001
Smoker	17.10	11.37	23.47	13.54	

	Unspecific-CKD	HTN-CKD	T2D-CKD	HTN/T2D-CKD	p value
Former smoker	16.70	16.34	22.63	21.18	
Obesity *Underweight*	1.53	0.42	0.63	0.16	< 0.001
Normal	31.64	17.78	20.22	11.85	
Overweight	43.64	43.31	43.21	38.72	
Class 1 obesity	17.96	27.41	25.16	31.29	
Class 2/3 obesity	5.23	11.08	10.78	17.98	
Heart failure	4.60	6.02	6.42	7.83	< 0.001
Atrial Fibrillation	6.97	9.83	8.10	10.49	< 0.001
Hypercholesterolemia	44.20	43.29	29.23	27.36	< 0.001
Systolic blood pressure ≥ 140 mm Hg	14.93	37.03	16.78	42.95	< 0.001
Diastolic blood pressure ≥ 90 mm Hg	4.83	9.81	4.06	9.74	< 0.001
Anemia	17.10	18.04	20.66	24.29	< 0.001
Statins	30.91	41.49	49.50	59.70	< 0.001
Platelet / Anticoagulant	22.64	32.40	38.54	51.57	< 0.001
Angiotensin-converting enzyme inh.	12.63	57.18	23.42	63.59	< 0.001
Angiotensin II receptor antagonists	7.09	36.01	11.84	43.37	< 0.001
Aldosterone antagonists	4.21	4.06	6.82	5.89	< 0.001

Primary renal disease and autoimmune disease with CKD risk diagnosis were more frequent in the U-CKD group. Patients in the HTN/T2D-CKD group were more likely to present complications due to T2D and HTN, obesity, HF and atrial fibrillation. All these conditions were less frequent in the U-CKD group.

BP control was lower in association with HTN, with or without T2D, and cholesterol control was higher in patients with T2D diagnosis. Statins, platelet aggregation inhibitors (PAI) and/or anticoagulant drugs,

and ACEis and ARBs use was higher in the HTN/T2D-CKD group (Table 1). Aldosterone antagonists were more frequent in the T2D-CKD group.

The median time span from T2D and/or HTN diagnosis to renal disease evidence was shorter for T2D-CKD (4.38 years; IQR 1.89–8.14) than HTN-CKD (5.62 years; IQR 2.32–9.87) (Table 2). The HTN/T2D-CKD group was exposed to both conditions for 4.31 [1.72–7.82] (separately, 5.90 years [2.94–9.74] of exposition to T2D and 6.77 years [3.18–11.03] exposed to HTN).

Table 2
Time span from T2DM and/or HTN diagnosis to renal disease evidence and renal function parameters in the KIDNEES cohort free of Atherosclerotic Cardiovascular Disease at baseline (n = 398,477)

	Unspecific-CKD	HTN-CKD	T2D-CKD	HTN/T2D-CKD	p value
Time Span from T2D and/or HTN diagnosis (years of evolution)					
T2D	-	-	4.38 [1.89, 8.14]	5.90 [2.94, 9.74]	< 0.001
HTN	-	5.62 [2.32, 9.87]	-	6.77 [3.18, 11.03]	< 0.001
T2D and HTN	-	5.62 [2.32, 9.87]	4.38 [1.89, 8.14]	4.31 [1.72, 7.82]	< 0.001
T2D < 5 years (%)	-		54.8	43.1	
HTN < 5 years (%)		45.7		38.0	
T2D < 10 years (%)	-		83.7	76.3	
HTN < 10 years (%)	-	75.6		69.7	
Renal function parameters (pooled imputed data)					
eGFR severity (mL/min/1.63m^2)					< 0.001
< 15	0.56	0.34	0.33	0.25	
15–29	2.15	2.69	2.02	2.19	
30–44	10.69	16.07	8.82	12.40	
45–59	65.69	63.01	37.63	46.47	
60–89	11.33	11.86	22.45	23.75	
≥ 90	9.58	6.03	28.76	14.94	
Albuminuria severity (%)					< 0.001
normal to mildly increased	72.98	70.04	39.11	48.09	
moderately increased	23.37	26.87	54.99	45.52	
severely increased	3.65	3.10	5.90	6.38	

The majority of patients had less than 10 years of evolution from HTN or DM diagnosis until CKD (73.4% and 77.1% respectively), and 42.8% and 44.4%, respectively, less than 5 years. Percentages were higher in those with isolated HTN or T2D, where 45.7% and 54.8% had CKD evidence within 5 years (Table 2). The

phenotypic characteristics of CKD differed by specified groups (Table 2). The proportion of patients with eGFR < 60 was higher in the HTN-CKD group (82.1%) and U-CKD group (79.1%) than in the HTN/T2D-CKD (61.3%) and T2D-CKD (48.8%). Those with T2D were more likely to have moderately and severely increased albuminuria (60.9% in T2D-CKD, 51.9% in HTN/T2D-CKD, 30.0% in HTN-CKD and 27.0% in U-CKD).

Only a small percentage of patients were referred to nephrologists: 1.89% in unspecified-CKD, 1.17% HTN-CKD, 0.81% T2D-CKD and 0.89% HTN/T2D-CKD.

All-cause mortality by CKD group

Over a mean follow-up of 5.82 years, 105,782 (26.6%) patients died. The overall crude mortality rate was 4,561.23 deaths/100,000 persons per year (Table 3), being highest in the T2D-CKD group, followed by HTN/T2D-CKD, U-CKD and finally the HTN-CKD group.

Table 3
Crude mortality and Cardiovascular Events (CVE) rates at follow-up in the KIDNEES cohort free of Atherosclerotic Cardiovascular Disease at baseline (n = 398,477)

		Mortality		CVE	
		CR[1]	Mean follow-up[2]	CR[1]	Mean follow-up[2]
Overall		4561.23	5.82	1145.87	5.61
Group	Unspecific-CKD	4330.06	5.40	653.41	5.29
	HTN-CKD	4227.72	6.05	1019.56	5.86
	T2D-CKD	5823.84	5.05	1198.90	4.87
	HTN/T2D-CKD	5096.77	5.71	1560.90	5.44
1. Crude rate: number of events per 100,000 persons per year					
2. Years					

The Kaplan-Meier curves on mortality by CKD-group are shown in Fig. 2. The higher mortality in the T2D-CKD group was clear at the beginning but closer to the HTN/T2D at the end of follow-up.

Bivariate association of factors with ACM can be consulted in Supplementary Table 4. Apart from T2D and HTN/T2D-CKD group, the proportion of death was slightly higher in those with T2D and HTN complications and non-controlled BP and HbA1c, and higher in those with eGFR < 45, anemia, autoimmune disease with CKD risk and severe albuminuria. Inversely, patients with primary renal diseases presented a lower proportion of mortality. Those who died presented shorter T2D and/or HTN years of evolution at the time of CKD diagnosis, especially when both T2D and HTN were present (Sup table 5).

In the multivariate analysis, using the T2D-CKD group as reference, the mortality risk was lower in U-CKD (HR 0.875; 95%CI 0.844–0.908), HTN/T2D-CKD (HR 0.704; 95%CI 0.682–0.728) and, the lowest, in the HTN-CKD group (HR 0.645; 95%CI 0.624–0.667) (Table 4).

Table 4

Mortality Cox proportional hazard model, with estimation of adjusted hazard ratio of the presence of T2D, HTN/T2D, HTN or none free in the KIDNEES cohort of Atherosclerotic Cardiovascular Disease at baseline, adjusted for co-variables with variates selection process (n = 398,477)

		HR	Low CI	Up. CI	p value
Group	*Unspecific*	0.875	0.844	0.908	< 0.001
	HTN-CKD	0.645	0.624	0.667	< 0.001
	T2D-CKD		(Ref.)		
	HTN/T2D-CKD	0.704	0.682	0.728	< 0.001
Age (years)	*< 65*		(Ref.)		
	65–79	3.068	2.985	3.152	< 0.001
	≥ 80	8.291	8.056	8.532	< 0.001
Sex	*Female*		(Ref.)		
	Male	1.219	1.201	1.238	< 0.001
MEDEA Deprivation index	*Rural*	1.342	1.314	1.370	< 0.001
	Least deprived quintile	0.883	0.861	0.906	< 0.001
	Second quintile	0.968	0.943	0.993	0.012
	Third quintile		(Ref.)		
	Forth quintile	0.973	0.949	0.998	0.031
	Most deprived quintile	1.023	0.997	1.050	0.078
Any primary renal disease		0.879	0.836	0.924	< 0.001
Autoimmune Disease with CKD risk		1.731	1.580	1.898	< 0.001
Smoking status *Non smoker*			(Ref.)		
	Smoker	1.272	1.236	1.309	< 0.001
	Former Smoker	1.161	1.135	1.187	< 0.001
Obesity	*Underweight*	1.454	1.333	1.585	< 0.001
	Normal		(Ref.)		
	Overweight	0.812	0.798	0.826	< 0.001
	Class 1 Obesity	0.775	0.761	0.789	< 0.001

HR: Pooled Hazard Ratios.

		HR	Low CI	Up. CI	p value
	Class 2–3 obesity	0.838	0.818	0.859	< 0.001
Heart failure		1.420	1.390	1.451	< 0.001
Non controlled HbA1c		1.148	1.124	1.173	< 0.001
eGFR severity (mL/min/1.63m^2)	*< 15*	2.389	2.186	2.610	< 0.001
	15–29	1.794	1.727	1.865	< 0.001
	30–44	1.506	1.462	1.551	< 0.001
	45–59	1.129	1.099	1.159	< 0.001
	60–89		(Ref.)		
	≥ 90	0.815	0.783	0.849	< 0.001
Albuminuria severity *normal to mildly increased*			(Ref.)		
	moderately increased	1.404	1.366	1.442	< 0.001
	severely increased	1.828	1.745	1.915	< 0.001
Anemia		1.582	1.560	1.604	< 0.001
Hypercholesterolemia		0.873	0.861	0.886	< 0.001
Statins		0.866	0.855	0.877	< 0.001
Platelet / Anticoagulant		1.356	1.338	1.374	< 0.001
Aldosterone antagonists		1.613	1.575	1.651	< 0.001
Angiotensin converting enzyme inhibidors		1.080	1.066	1.094	< 0.001
Charlson	*No comorbidity*		(Ref.)		
	Low comorbidity	1.340	1.321	1.359	< 0.001
	High comorbidity	1.960	1.918	2.004	< 0.001
HR: Pooled Hazard Ratios.					

Persons of older age, and with eGFR < 15 presented the highest hazards of death, followed by albuminuria and less severe eGFR categories, high comorbidity, autoimmune disease with CKD risk, anemia, heart failure and aldosterone antagonist treatment. On the contrary, the risk was lower in less deprived quintiles, and when primary renal diseases diagnosis, overweight, obesity or hypercholesterolemia was present.

Non controlled HbA1c further increased the risk of death.

In sensitivity analyses including only individuals without any missing data (complete-case analysis), the relation between CKD-groups was not modified (Supplementary table 6).

Cardiovascular events by CKD group

During a mean follow-up of 5.61 years, 25,635 (6.43%) patients developed a CVE and 94,737 (23.8%) died before reaching a CVE.

The global crude rate for CVE was 1,145.87/100,000 persons per year (Table 3), and was highest in the HTN/T2D-CKD group followed by T2D-CKD, HTN-CKD, and finally the U-CKD group.

The Kaplan-Meier curves on CVE are shown in Fig. 3. The HTN/T2D-CKD and T2D-CKD curves diverged from the beginning of follow-up.

The proportion of individuals presenting a CVE ranged from 3.46% in the U-CKD group to 8.49% in the HTN/T2D-CKD, with similar percentages in the HTN-CKD and T2D-CKD groups (around 5.9%; Supl Table 4). Bivariately, some classifications resulted in higher CVE percentages than the HTN/T2D-CKD group as T2D complications, albuminuria severity or non-controlled HbA1c. Timespans between HTN or T2D and CKD diagnoses in the group developing CVE were longer than for death, except for T2D-CKD group, and shorter than for the no-event group (Supl Table 5).

Table 5

Multivariate adjusted subdistributional hazard ratios (sHR) for Cardiovascular Event (CVE) adjusted for co-variables with imputed data, considering death as a competitive risk in the KIDNEES cohort free of Atherosclerotic Cardiovascular Disease at baseline (n = 398,477).

		sHR	Low CI	Up. CI	p value
Group	*Unspecific*	0.722	0.665	0.785	< 0.001
	HTN-CKD	1.006	0.946	1.069	0.861
	T2D-CKD	(ref.)			
	HTN/T2D-CKD	1.238	1.164	1.316	< 0.001
Age (years)	*< 65*	(ref.)			
	65–79	1.645	1.578	1.716	< 0.001
	≥ 80	2.020	1.927	2.118	< 0.001
Sex	*Female*	(ref.)			
	Male	1.285	1.254	1.317	< 0.001
MEDEA Deprivation Index *Rural*		1.044	0.996	1.095	0.077
Least deprived quintile		0.927	0.880	0.977	0.005
Second quintile		0.960	0.912	1.009	0.111
Third quintile		(ref.)			
Forth quintile		1.001	0.949	1.056	0.969
Most deprived quintile		0.980	0.935	1.028	0.410
Oft /neur. complications		1.139	1.088	1.192	< 0.001
Hypertensive heart disease		1.058	0.975	1.148	0.175
Renal Disease Diagnosis		0.906	0.818	1.004	0.059
Autoimmune Disease with CKD risk		0.920	0.718	1.178	0.507
Smoking status *Non smoker*		(ref.)			
	Smoker	1.195	1.148	1.244	< 0.001
	Former Smoker	0.976	0.940	1.013	0.208
Obesity	*Underweight*	0.918	0.701	1.202	0.535
	Normal	(ref.)			
	Overweight	1.034	0.993	1.076	0.105

		sHR	Low CI	Up. CI	p value
	Class 1 Obesity	1.027	0.986	1.069	0.203
	Class 2–3 obesity	0.953	0.906	1.002	0.059
Heart failure		1.039	0.985	1.095	0.159
Systolic blood pressure	*≥ 140 mm Hg*	1.148	1.117	1.180	< 0.001
Diastolic blood pressure	*≥ 90 mm Hg*	1.096	1.054	1.139	< 0.001
Non controlled HbA1c		1.343	1.294	1.394	< 0.001
eGFR severity (mL/min/1.63m^2)	*<15*	0.955	0.708	1.288	0.763
	15–29	1.048	0.948	1.158	0.363
	30–44	1.201	1.121	1.286	< 0.001
	45–59	1.056	0.996	1.120	0.080
	60–89	(ref.)			
	≥ 90	0.925	0.876	0.977	0.006
Albuminuria severity *normal to mildly increased*		(ref.)			
moderately increased		1.190	1.094	1.294	0.001
	severely increased	1.377	1.241	1.528	< 0.001
Anemia		0.931	0.901	0.963	< 0.001
Hypercholesterolemia		1.085	1.056	1.115	< 0.001
Statins		1.015	0.987	1.045	0.297
Platelet inh. / anticoagulants		1.425	1.386	1.465	< 0.001
Aldosterone antagonists		0.849	0.799	0.903	< 0.001
Angiotensin-converting enzyme inh.		0.935	0.910	0.962	< 0.001
Angiotensin II receptor antagonists		1.047	1.019	1.075	< 0.001
Charlson Index Score	*No comorbidity*	(ref.)			
	Low comorbidity	0.948	0.920	0.978	< 0.001
	High comorbidity	0.846	0.802	0.894	< 0.001

In the multivariate analysis, there were no differences in the risk of CVE between the reference T2D-CKD group and the HTN-CKD group (sHR 1.006; CI95% 0.946–1.069), which increased in the HTN/T2D-CKD

group (sHR 1.238; CI95% 1.164–1.316) and decreased in the U-CKD group (sHR 0.722; CI95% 0.665–0.785) (Table 5).

Age, severe albuminuria, non-controlled HbA1c and treatment with platelet inhibitors/anticoagulants presented higher sHR associated with CVE than the HTN/T2D-CKD group.

Sensitivity complete-case analysis did not alter the relation between CKD-groups (Sup table 7).

Discussion

In this primary care cohort of incident CKD, the risk of CVE and mortality differed according to previous HTN or/and T2D diagnosis. After adjusting for multiple factors associated with HTN, T2D and CKD, the risk of death was higher in the T2D group than in the HTN-CKD group, and it was in-between for HTN/T2D-CKD. For CVE, the risk was similar in HTN and T2D-CKD, and increased when both were present.

The prevalence of HTN in T2D patients in the cohort was high (89.0%), and therefore the percentage of patients in the T2D-CKD group was low (3.87%). This is within the range of similar cohorts in primary care; in patients with T2D and CKD, a prevalence of HTN of 85.4% [15] and 88.6% has been described [16].

The characteristics of individuals differed according to CKD groups. Those with isolated T2D were the youngest, with higher prevalence of male sex and smokers, and lower prevalence of obesity compared to the HTN/T2D-CKD group. Both groups presented a high prevalence of comorbidities, HF and anaemia. On the contrary, individuals in the HTN-CKD were the oldest, more frequently female and had the lower prevalence of smokers and comorbidity.

Although the risk of CKD increases notably with a T2D duration of 10 years or more [15], renal disease evidence was found in approximately three quarters of this cohort < 10 years from HTN or T2D diagnosis, and in more than a third within 5 years. The time span was shorter when T2D presented without evidence of HTN. This could suggest a more aggressive clinical course or reflect a distinctive patient profile for isolated T2D which presents in younger patients. Moreover, individuals who died or developed a CVE had a shorter time of T2D and HTN evolution. Therefore, a shorter time to CKD appearance could identify individuals at higher risk of unfavourable outcomes, and further analysis should be performed.

The higher mortality risk associated with CKD is well known [1,3] and has been confirmed in this population [17,18].

Mortality risk in CKD individuals with/without T2D has been specifically compared. In a previous study, both moderate CKD (eGFR 30–50 mL/min), and T2D similarly increased the risk of death (HR 1.40 [95%CI 1.25–1.56] in CKD, 1.49 [95%CI 1.37–1.62] in T2D), especially when both were present (2.19 [95%CI.91-2.51]) [19]. In the Kaiser Permanente cohort, T2D patients were 1.5-3 times more likely to die from any cause than patients without T2D in all categories of eGFR and for all levels of albuminuria [20].

Although all-cause and cardiovascular mortality is higher in individuals with HTN than in those without [21], the associations of eGFR and ACR with mortality outcomes were found to be stronger in individuals without hypertension than in those with hypertension [21].

Several studies have reported the higher risk of death associated with HTN and T2D in individuals with CKD, either similar (HR 1.25 [95%CI 1.12–1.39] and 1.57 [95%CI 1.29–1.92] respectively, CHS) or higher for T2D than HTN (HR 1.11 [95%CI 1.02–1.21] and 1.61 [95%CI 1.52–1.70] respectively [22].

However, the interaction between HTN and T2D, two frequently coexisting conditions in CKD, has not been fully evaluated.

According to these results, the presence of both T2D and HTN would have a higher risk of death than HTN alone, but T2D had the highest risk. On the contrary, there were no differences between HTN and T2D for CVE, and the risk increased when both were present. Moreover, the risk associated with older age, higher comorbidity, eGFR and albuminuria were higher for death than for CVE, and lower, or non-significant, with non-controlled HbA1c and SBP. Therefore, the potential impact and benefit of control, for the latter risk factors would be greater for CVE.

The known excess mortality risk in T2D has been currently described at about 15% [23,24]. When adjusting for SBP and other risk factors, the association strengthened between T2D status and ACM but not for cardiovascular mortality [24].

The results also resembles those of the meta-analysis of risk factors for CVE and death in individuals with eGFR < 30, where both diabetes (HR 1.41; 95%CI 1.30–1.53) and SBP ≥ 140 mmHg (HR 1.09; 95%CI 1.04–1.15) increased the risk of CVE, but only diabetes (HR 1.12; 95%CI 1.03–1.22) increased the risk of death [25].

In another study using electronic health records in individuals with CKD with/without diabetes and no prior CVE [26], the risk of major CVE was 4.6–2.4 times higher in those with T2D. The presence of a HTN diagnosis increased the risk a 10% in Non-Diabetes (HR 1.09; 95%CI 1.03–1.15) but was not significant in T2D (1.12; 0.99–1.27). Moreover, higher BP measures tended to increase the risk more in Non-DM than T2D. HTN is highly prevalent in T2D. In the present analysis, as for T2D, we considered HTN diagnosis and BP control separately, so this effect could appear more clearly, without differences between HTN-CKD and T2D-CKD.

The results of the study might have important clinical significance. Studies show a big room for improvement in CKD screening and management, especially for albuminuria [27, 28].. In the present CKD cohort, albuminuria was assessed in 52% of cases, more frequently when associated with T2D diagnosis. The onset of CKD in the first years after T2D and/or HTN diagnosis can identify individuals at higher risk of adverse events, and screening should be emphasized. Moreover, although the cardiovascular risk is already increased when CKD is present, the coexistence of HTN and T2D identifies individuals at even

higher risk, and should prompt a more intensive management to reduce it, including a better control of BP and HbA1c.

Only a small proportion of patients undergo biopsy, which are performed in specific circumstances usually to rule out other causes of renal disease. In a cohort followed by nephrologists, patients with T2D had a similar risk of ESRD when it was considered the primary cause of CKD according to the consulting physician (HR 1.49; 95% CI 1.18–1.88) or only as comorbidity (1.57; 95% CI 1.14–2.15) [29]. Even though a causal approximation, T2D and HTN diagnosis are easily identified and can add useful information in the management of CKD patients.

The results of the present study should be interpreted considering some limitations. Some refer to the type of study. Causal relationships can only be approached in these study, we aimed to make descriptions and report associations. Data are obtained from electronic health records which include primary care medical histories of subjects seeking care in the geographic primary care area covered by the Institut Català de la Salut and misdetection cannot be excluded. However, data for cardiovascular disease in primary health care has been shown to be of higher quality than for other diseases and suitable for epidemiological studies in our population [13].

Although models were adjusted for socioeconomic factors, cardiovascular risk factors and diseases, comorbidities and treatments, the presence of unmeasured or residual confounding cannot be ruled out. In this sense, renal disease could act as a marker of multimorbidity.

The eGFR was estimated from serum creatinine measurements using the CKD-EPI formula, and limitations of creatinine-based estimating formulas, with greater impact at higher eGFR, must be accepted. Data on race were not available and correction could not be applied, although Caucasian ethnicity is vastly predominant in the population under study. Although, creatinine was measured in different labs, and different methods may be used, all have completed standardization of creatinine calibration to be traceable to an isotope dilution mass spectrometry (IDMS) reference measurement procedure, which reduces variability [4]. Two different measures of albumin in urine were used. The multiple meta-analyses performed by the CKD Prognosis Consortium have also included different methods without modification of the results [1,2,3,21,].

The risk of stroke is higher in women and increases with age [30]. Individuals in this primary care incident CKD cohort are more frequently women and quite old and stroke may be overrepresented. Therefore, results might not apply to younger people with different patterns of cardiovascular disease. However, that is the type of population usually attended in primary care and represents the majority of CKD patients.

Despite these limitations, the study presents noteworthy strengths. To our knowledge, it includes the largest incident CKD sample, with diagnosis confirmed using not epidemiological but clinical criteria and with a considerable follow-up. Furthermore, the use of real world data is representative of the usual care. The wealth of information on drug prescription, lab parameters measurements, and complete medical

histories is also remarkable. In addition, in Catalonia,, as in other regions of Europe like in the UK or in the rest of Spain, primary care acts as a gate-keeper of patient management. Therefore, it can be considered that a primary care database like SIDIAP provides a quite complete picture of a CKD patient cohort in terms of clinical characterization.

Conclusion

The results of the present study suggest that the risk of CVE and ACM differ according to previous HTN or/and T2D diagnosis, and the outcome. The identification of this easily detected clinical characteristic can help to identify individuals at higher risk of adverse outcomes, and to improve the management of CKD patients in primary care.

List Of Abbreviations

CKD, Chronic kidney disease

eGFR, estimated glomerular filtration rate

CVE, Cardiovascular event

T2D, Type 2 Diabetes Mellitus

HTN, Hypertension

HR, Hazard ratio

Declarations

Ethics approval and consent to participate.

Ethical approval was obtained from the Ethics Committee for Clinical Research IDIAPJGol (19/082-P).

We did not seek informed consent from participants, as it was not deemed necessary by the research ethics committee.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

DV works in Bayer Pharmaceuticals.

The rest of authors declare no conflicts of interest.

Funding

The study has been founded by Bayer Pharmaceuticals. The decision to publish the results was taken previously.

Authors' contributions

BSG has contributed to the design of the work, acquisition and interpretation of data, drafting the work and approved the final version to be published.

OCP has contributed to the design of the work, acquisition, analysis and interpretation of data, drafting the work and approved the final version to be published.

DV has contributed to the conception and design of the work, interpretation of data, revised the work critically and approved the final version to be published.

MJCH has contributed to the interpretation of data, drafting the work and approved the final version to be published.

NGT has contributed to the interpretation of data, drafting the work and approved the final version to be published.

SCG has contributed to the interpretation of data, drafting the work and approved the final version to be published.

Acknowledgements

To the Foundation University Institute for Primary Health Care Research Jordi Gol i Gurina (IDIAPJGol) and the SIDIAP Information System for Research in Primary Care (SIDIAP) for the support through the process.

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Figures

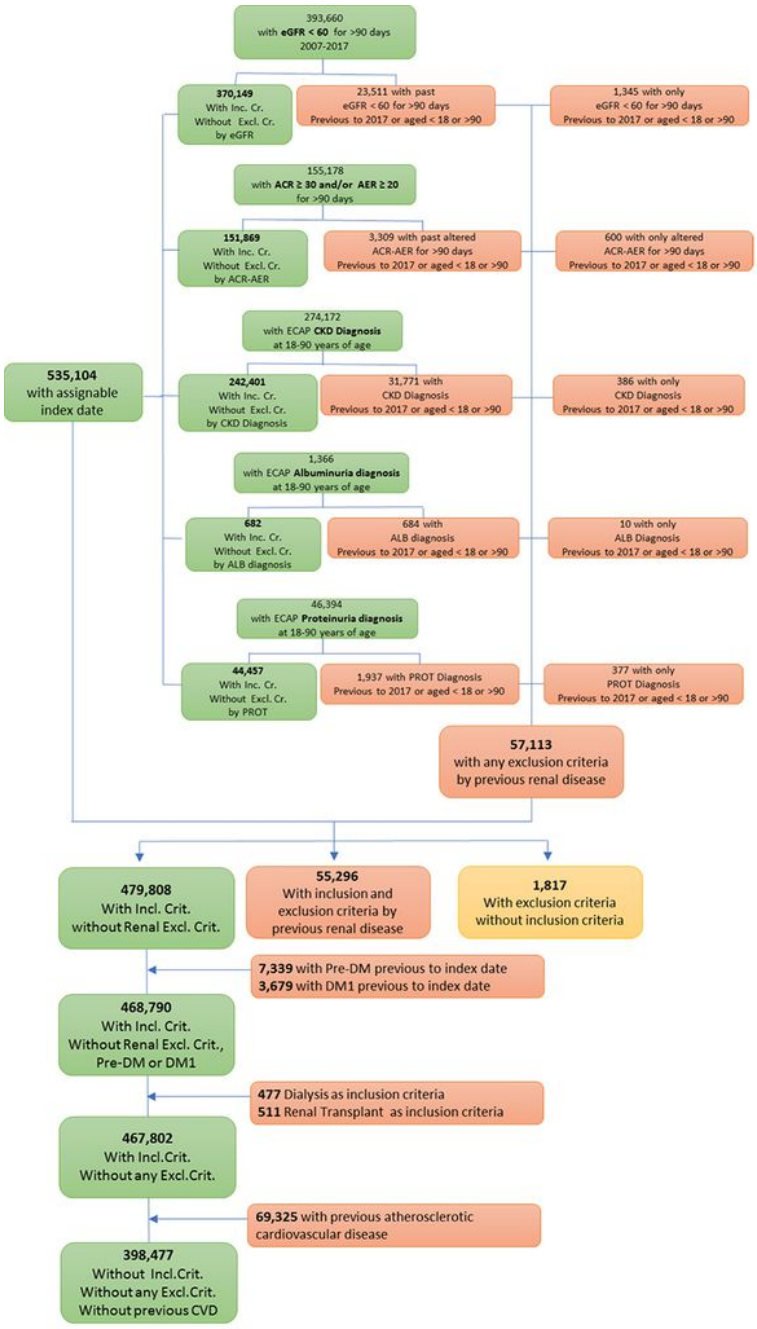

Figure 1

KIDNEES cohort flow-chart.

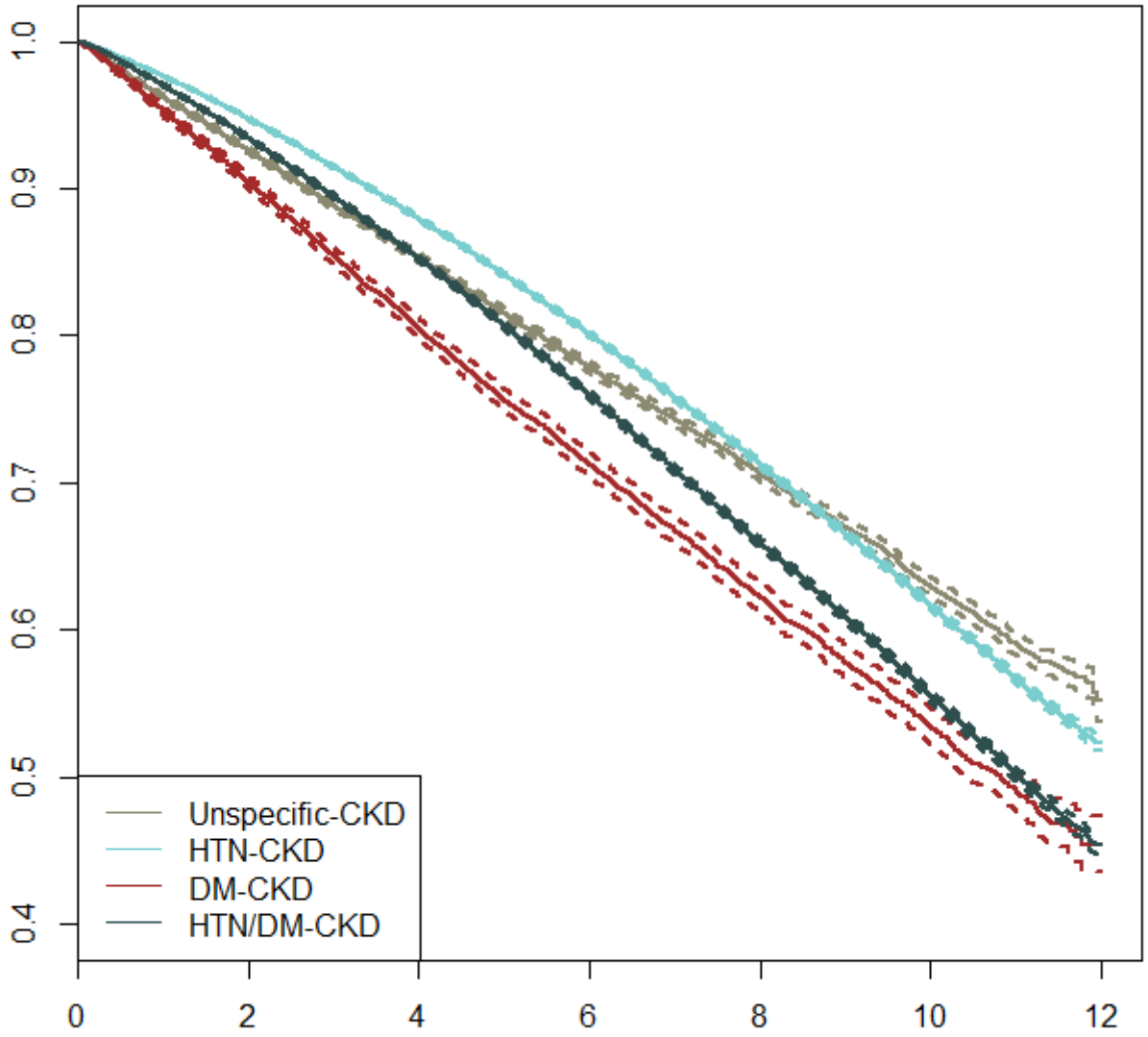

Figure 2

Kaplan-Meier Curves on mortality by CKD-group

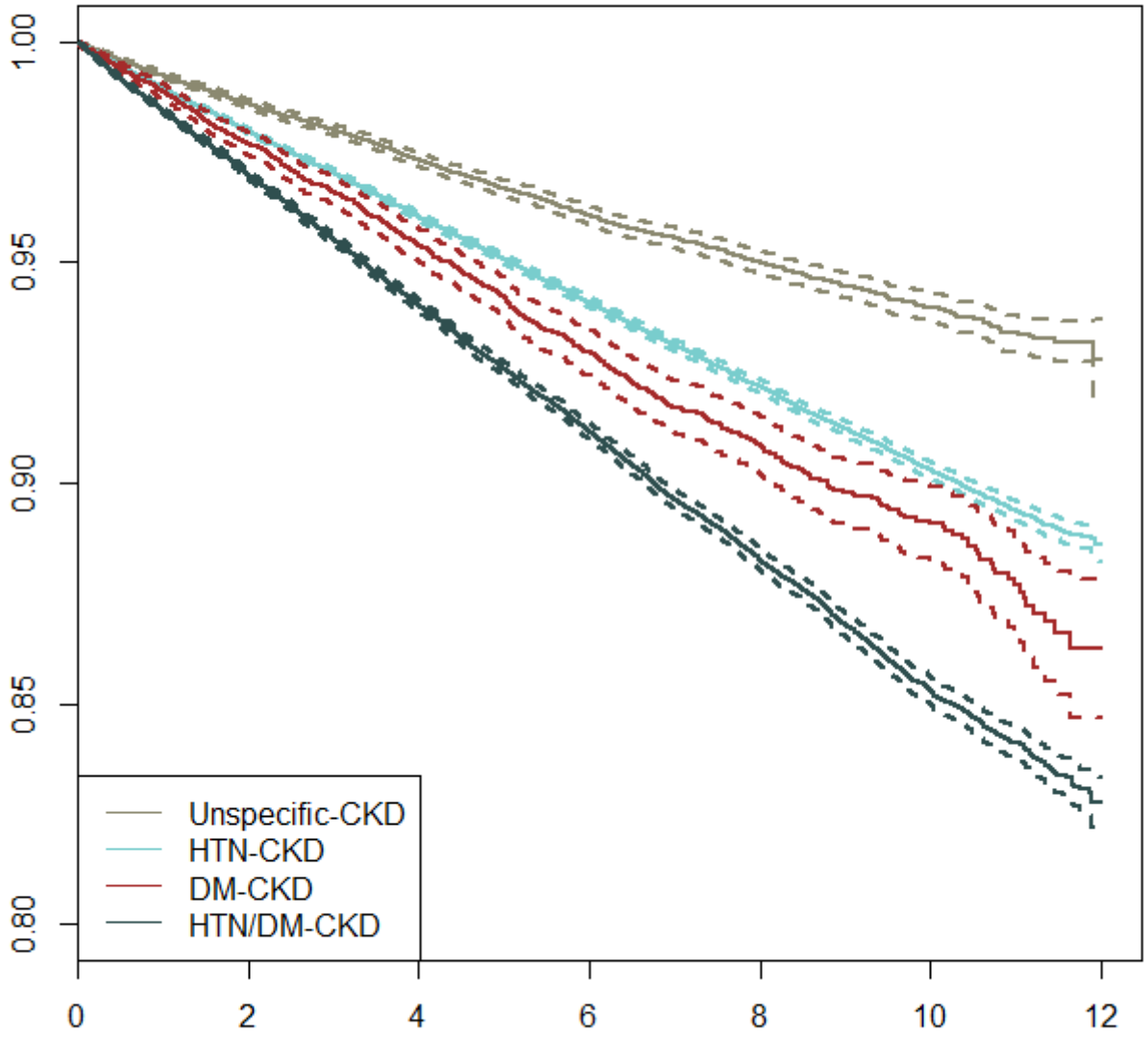

Figure 3

Kaplan-Meier Curves on Cardiovascular Events by CKD-group