Cardiovascular and all-cause mortality in patients with type 2 diabetes mellitus in the MADIABETES Cohort Study: Association with chronic kidney disease

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ABSTRACT

Aims: To assess the prevalence of stage 3–5 chronic kidney disease (CKD) at baseline and to identify associated risk factors. To determine the effect of CKD and CKD stage according to estimated glomerular filtration rate (eGFR) and albuminuria categories on all-cause and cardiovascular mortality after a 5-year follow-up.
Methods: Prospective cohort study of 3443 outpatients with type 2 diabetes mellitus.
Results: The prevalence of CKD was 28.32% (95% CI, 26.84–29.86); and variables most strongly associated were: age >74 years (OR, 19.88; 95% CI, 12.89–30.68) and albuminuria (OR, 2.27; 95% CI, 1.72–3.00). During follow-up, 221 CKD patients (22.90%) died compared with 203 non-CKD patients (8.31%) (p < 0.01). The adjusted HR of CKD for cardiovascular and all-cause mortality was 1.82 (95% CI, 1.36–2.44) and 2.11 (95% CI, 1.61–2.76) for those with LDL cholesterol = 135 mg/dl, respectively. The adjusted HR of very-high-risk CKD for all-cause mortality was 4.44 (95% CI, 2.31–8.53) in aged <75 years and 1.80 (95% CI, 1.19–2.72) in aged ≥75 years.
Conclusions: CKD at baseline is an independent risk factor for all-cause and cardiovascular mortality in the overall cohort, men and women, or in primary and secondary prevention of coronary heart disease. Albuminuria is an independent risk factor for all-cause and cardiovascular mortality only in primary prevention.

1. Introduction

Chronic kidney disease (CKD) is defined as the presence of kidney damage (i.e., albuminuria) or decreased kidney function for at least 3 months, irrespective of clinical diagnosis (National Kidney Foundation, 2002). CKD is a worldwide public health problem and a well-known epidemiologic risk factor that can be used to predict cardiovascular morbidity (Sarnak et al., 2003) and long-term mortality (Coladonato, Klassen, & Owen, 2002). The prevalence of CKD is growing worldwide owing to the increased frequency of associated chronic diseases such as type 2 diabetes mellitus (T2DM) and hypertension (Haroun et al., 2003).

The Kidney Disease Improving Global Outcomes (KDIGO) organization has developed a clinical practice guideline for the evaluation and management of CKD (KDIGO, 2013) that includes a prognostic classification of CKD based on glomerular filtration rate (GFR) and albuminuria. The guideline also takes into account epidemiological

data associated with adverse outcomes of CKD (end-stage renal disease, acute kidney injury, progression of CKD, all-cause mortality, and cardiovascular mortality) from 45 cohorts. The classification includes 4 risk categories for adverse outcome: low, moderate, high, and very high.

To our knowledge, very few cohort studies have analyzed the prevalence of CKD measured at baseline in southern European patients diagnosed with T2DM (Targher et al., 2012). Similarly, few authors have investigated mortality risk in a prognostic classification of CKD by albuminuria categories and estimated glomerular filtration rate (eGFR) in Mediterranean countries (Toyama et al., 2013).

We studied a cohort of Spanish T2DM patients attending primary care centers in order to assess the prevalence of stage 3–5 CKD at baseline and to identify associated risk factors. We also determined the effect of CKD and risk categories of an adverse outcome on all-cause and cardiovascular mortality after a 5-year follow-up period.

2. Subjects

The MADrid DIABETES Study (MADIABETES Study) is a prospective cohort study of 3443 T2DM outpatients that has been described in detail elsewhere (Salinero-Fort et al., 2013). Briefly, the study participants were selected using simple random sampling by participating general practitioners (n = 131) from 56 primary health care centers in the metropolitan area of Madrid (Spain) based on the list of patients with a diagnosis of T2DM in their computerized clinical records.

3. Material and methods

General practitioners collected data at the baseline visit (2007) and annually during the follow-up period (2008–2012). The data were recorded on electronic case report forms hosted on the website www. madiabetes.com. The inclusion criteria were age ≥30 years, a previous diagnosis of T2DM, and written informed consent to participate in the study. The exclusion criteria were type 1 DM and being homebound. For this analysis, 36 patients were excluded owing to missing serum creatinine values; the remaining 3407 patients constituted the MADIABETES CKD Cohort.

3.1. Outcomes: definition and measurement

The CKD stages were classified according to the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (K/DOQI) (National Kidney Foundation, 2002). For the purposes of this study, CKD was defined as K/DOQI stage 3–5 CKD.

Patients were classified according to the risk of adverse outcomes. Four categories of risk were established (low, moderate, high and very high) based on values of albuminuria and eGFR, as indicated elsewhere [see Figure 2 from Levey et al. (2011) that provides the definitions of the categories].

eGFR was calculated using the CKD-EPI equation, which has proven to be a more accurate predictor of the risk of death in patients with T2DM (Targher et al., 2012), and is recommended by the 2012 KDIGO Clinical Practice Guidelines (Inker et al., 2014). The equation is especially suitable for elderly patients (Kilbride et al., 2013).

3.1.1. Clinical examination and biochemistry

A clinical history was taken, and patients underwent a physical examination and biochemical tests. The variables collected at baseline were age, gender, duration of DM (years), fasting plasma glucose, glycated hemoglobin (HbA1c), systolic blood pressure (SBP) and diastolic blood pressure (DBP), total cholesterol, triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), albuminuria, smoking status (current smoker, former smoker, non-smoker), use of hypoglycemic and cardiovascular medications (antihypertensive agents, statins, aspirin), body mass index

(BMI), and history of cardiovascular events (myocardial infarction, peripheral artery disease or stroke) and hypertension.

BMI was calculated as weight/height^2 (kg/m^2). Blood pressure was measured using a calibrated sphygmomanometer. Hypertension was defined as SBP 140 mmHg or more, and/or diastolic blood pressure 90 mmHg or more; or prior diagnosis of arterial hypertension and/or use of antihypertensive medication. After a 5-min rest period, the first reading was taken, followed by a second reading 5 min later.

Dyslipidemia was defined as either of the following lipid alterations: 1) total cholesterol concentration ≥190 mg/dl in patients with a history of cardiovascular disease (CVD) and ≥240 mg/dl or more in patients without a history of CVD, and/or TG > 200 mg/dl; or 2) LDL-C > 130 mg/dl and/or HDL-C < 35/45 mg/dl (male/female, respectively), or prior diagnosis of dyslipemia and/or use of lipid-lowering drugs.

Serum creatinine was measured using an enzymatic creatinine assay that was not traceable to isotope dilution mass spectrometry (ID-MS), and the value was included in the equation used to estimate GFR as follows: serum creatinine (Jaffe's method) = 1.0302 × serum creatinine (enzymatic method) + 0.2648 [r = 0.999, p < 0.001].

Persistent microalbuminuria was defined as a urinary albumin excretion rate ≥30 mg/g and <300 mg/g in at least 2 of 3 consecutive samples; macroalbuminuria was defined as a urinary albumin excretion rate ≥300 mg/g. HbA1c was measured using high-performance liquid chromatography (Diabetes Control and Complications Trial-aligned) (Selvin, Coresh, Zhu, Folsom, & Steffes, 2010).

Cardiovascular risk was calculated following the REGICOR formula (a calibration of the Framingham algorithm adapted for Spain) (Marrugat et al., 2003) for each patient free of CVD at the baseline examination in 2007 (n = 1869). Patients with a cardiovascular risk of 10% over 10 years were considered moderate- or high-risk (Bosomworth, 2011).

Retinopathy was diagnosed as the presence of any of the following lesions: microaneurysm, intraretinal hemorrhage, venous beading, neovascularization, vitreous/preretinal hemorrhage, cotton wool spots, retinal thickening, and hard exudates. The stage of retinopathy was based on the severity scale proposed by Wilkinson et al. (2003). In the absence of photographic records, it was difficult to determine the number of microaneurysms per quadrant; therefore, we simplified categorization of nonproliferative diabetic retinopathy to 2 categories, namely, mild and moderate/severe.

After the 5-year follow-up, the vital status of the diabetic cohort was ascertained on 31 December 2012 from the mortality records of the Spanish National Institute of Statistics (*Instituto Nacional de Estadística*, http://www.ine.es). The underlying cause of death stated on the death certificates was coded according to the International Classification of Diseases, Tenth Revision (World Health Organization, 2004) and cardiovascular mortality was defined as death due to myocardial infarction, heart failure, stroke, or sudden cardiac death.

4. Statistical analysis

Descriptive data were expressed as mean and standard deviation and median and IQR. Continuous variables were compared between the 2 groups using the *t* test for normal distributions and the Mann–Whitney test for non-normal distributions; categorical variables were compared using the chi-square test. The multivariable analysis of variables associated with CKD at baseline was by logistic regression. The variables for the adjustment were selected on the basis of significant bivariate relationships or clinical relevance. Statistical significance was set at ≤0.05, with a 95% confidence interval (95% CI).

Mortality was expressed in terms of cumulative incidence and incidence density (cases per 1000 person-years of follow-up). Life tables (actuarial method) were used to calculate death and survival rates. In the bivariate analysis, survival curves were constructed, and the statistical significance of survival differences for each variable (CKD vs. non-CKD and 4 categories of risk of developing adverse outcomes according to eGFR and albuminuria level) was determined

Table 1
Baseline characteristics of the MADIABETES CKD Cohort (N = 3407), stratified by CKD at baseline.

	N = 3407	95% CI	CKD (n = 965)	Non-CKD (n = 2442)	p value
Sociodemographic variables					
Female gender (%)	49.7	48.0–51.4	61.3	45.1	<0.001
Age (yr), mean (SD)	69 (10.8)	68.7–69.4	75.7 (8.2)	66.4 (10.6)	<0.001
Duration of DM (yr), mean (SD)	9.1 (7.7)	8.8–9.3	10.9 (8.7)	8.3 (7.2)	<0.001
Duration of DM (yr), median (IQR)	7 (8)	7–7	8 (10)	6 (7)	<0.001
Current smoker, (%)	15.8	14.6–17.1	9	18.6	<0.001
Former smoker, (%)	25.4	23.9–26.9	18.9	27.9	<0.001
Non-smoker, (%)	58.8	57.1–60.4	72.1	53.5	<0.001
Medication Profile (%)					
Oral antidiabetic alone	60.4	58.8–62.1	52.3	63.6	<0.001
Insulin alone	6.9	6.1–7.8	11.4	5.1	<0.001
Oral antidiabetic + Insulin	13.6	12.5–14.8	17.9	11.9	<0.001
Antihypertensive agents	84.9	83.7–86.1	95.4	80.8	<0.001
Aspirin	51	49.3–52.7	58.2	48.2	<0.001
Statins	71.7	70.1–73.2	72.7	71.2	0.393
History of (%)					
Hypertension	74.1	72.6–75.5	86.6	69.1	<0.001
Myocardial Infarction	12.7	11.6–13.8	17.6	10.7	<0.001
Stroke	8.3	7.5–9.3	12.6	6.6	<0.001
Peripheral artery disease	7.3	6.5–8.2	10.6	5.9	<0.001
Congestive heart failure	6.9	6.1–7.8	11.1	5.2	<0.001
Number of Cardiovascular events					
0 (%)	74.6	72.7–75.7	69.8	76.5	<0.001
1 (%)	17.8	16.5–19.1	23.7	15.4	<0.001
2 (%)	6.8	6.0–7.6	10.8	5.2	<0.001
>2 (%)	1.32	0.9–1.7	2.2	0.9	<0.001
Neuropathy	7.2	6.4–8.1	9	6.5	0.011
Retinopathy	8.8	7.9–9.8	12.6	7.3	<0.001
Neuropathy + Retinopathy	1.9	1.5–2.4	3.2	1.4	<0.001
Risk of developing coronary events					
Number of Patients free CVD at baseline (%)	2543 (74.6)		674 (69.8)	1869 (76.5)	
Adjusted REGICOR function 10-year risk, mean (SD)	5.8 (2.9)	5.7–5.9	5.8 (2.9)	5.9 (2.9)	0.465
Percentage of patients with risk <5%	53.3	51.5–55.1	55	52.6	0.445
Percentage of patients with risk 5%–10%	37.6	35.9–39.3	36.6	37.7	
Percentage of patients with risk >10%	9.1	8.1–10.1	8.3	9.6	
Anthropometric variables					
BMI (kg/m^2), mean (SD)	30.1 (4.9)	29.9–30.3	30.1 (5)	30.1 (4.9)	0.949
SBP (mmHg), mean (SD)	133.8 (13.5)	133.3–134.2	134.7 (13)	133.4 (13.6)	0.013
DBP (mmHg), mean (SD)	76.8 (7.9)	76.5–77.1	75.2 (7.3)	77.5 (8.1)	<0.001
Laboratory variables					
eGFR (mL/min/1.73 m^2), mean (SD)	70.5 (17.8)	69.9–71.1	48.9 (9.4)	79.1 (12.2)	<0.001
eGFR (mL/min/1.73 m^2), median (IQR)	70.7 (25.5)	69.8–71.5	51.4 (12.2)	78.1 (18.9)	<0.001
FPG (mg/dl), mean (SD)	143.4 (41.4)	141.9–144.9	139.8 (41.1)	144.8 (41.5)	0.002
FPG (mg/dl), median (IQR)	135 (43)	134–137	133 (44)	136 (42)	0.001
Patients with HbA1c level <7, (%)	53.8	52.1–55.5	55.2	53.2	0.313
HbA1c (%), mean (SD)	7.1 (1.2)	7.1–7.2	7.05 (1.1)	7.1 (1.2)	0.188
HbA1c (%), median (IQR)	6.9 (1.4)	6.8–6.9	6.9 (1.3)	6.9 (1.4)	0.265
Dyslipidemia, (%)	56.3	54.6–57.9	52.7	57.7	0.009
Total cholesterol (mg/dl), mean (SD)	192 (36.1)	190.8–193.2	188.8 (37.1)	193.2 (35.6)	0.001
LDL-C (mg/dl), mean (SD)	115.1 (29.9)	114.1–116.2	112.3 (30.3)	116.2 (26.9)	0.001
HDL-C (mg/dl), mean (SD)	48.9 (12.9)	48.5–49.4	48.7 (14)	49 (12.5)	0.562
Triglycerides (mg/dl), mean (SD)	145.3 (91.4)	142.2–148.5	144.3 (78)	145.8 (96)	0.687
Triglycerides (mg/dl), median (IQR)	123 (78)	121–125	127 (75)	122 (80)	0.037
Albuminuria^2 (%)	10.9	9.9–11.9			
Microalbuminuria	10.1	9.1–11.1	15.6	7.8	<0.001
Macroalbuminuria	0.8	0.6–1.2	1.8	0.5	<0.001

using the Gehan–Wilcoxon test. Finally, a multivariable Cox proportional hazard analysis including age, gender, and history of cardiovascular events (myocardial infarction, stroke, peripheral artery disease) was used to estimate the adjusted hazard ratio (aHR) and corresponding 95% CI for incident all-cause mortality associated with both CKD (model 1) and CKD prognosis stage (model 2), respectively.

If the CIs of the mortality rates overlapped, we considered that the differences were not statistically significant.

In order to analyze the effect of CKD on cardiovascular and all-cause mortality, a multivariable Cox regression analysis with each mortality outcome was conducted for the overall sample, and stratified by gender and prior CVD. The adjustment variables, when it was necessary, were: gender, age, history of CVD or heart failure, body mass index, SBP, total cholesterol, LDL cholesterol, tryglycerides, albuminuria, insulin, statins,

antiplatelet therapy, and renin–angiotensin system inhibitors. The procedure was repeated to analyze the effect of CKD prognosis stage. Finally, effect modification was tested by an analysis of 2-way interaction terms between CKD and several variables (blood pressure, gender, age, history of CVD or heart failure, total cholesterol, and LDL cholesterol). Interactions between CKD prognosis stage and the variables were also tested.

The statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS for Windows, version 19.0; IBM Corp, Armonk, New York, USA) and STATA 11.0 (STATA 11.0 for Windows, Stata, College Station, TX, USA).

The study was approved by the Institutional Review Board of the Ramón y Cajal Hospital (Madrid), and conducted in accordance with the principles of the Declaration of Helsinki. All

Table 2
Distribution of eGFR stages stratified by albuminuria stage.

			Albuminuria stage			
			A1 Optimum and high–normal <30 mg/g	A2 High 30–299 mg/g	A3 Very high and nephrotic ≥300 mg/g	All
eGFR stages (mL/min/ 1.73 m²)	G1	>105	45 (1.32)	6 (0.18)	1 (0.03)	52 (1.52)
		90–104	395 (11.59)	35 (1.03)	2 (0.06)	432 (12.67)
	G2	75–89	855 (25.10)	66 (1.94)	5 (0.15)	926 (27.17)
		60–74	945 (27.74)	84 (2.47)	3 (0.09)	1,032 (30.29)
	G3a	45–59	623 (18.29)	67 (1.97)	8 (0.23)	698 (20.48)
	G3b	30–44	152 (4.46)	57 (1.67)	7 (0.21)	216 (6.34)
	G4	15	22 (0.65)	24 (0.70)	2 (0.06)	48 (1.41)
	G5	<15	0 (0.00)	3 (0.09)	0 (0.00)	3 (0.09)
	All		3,037 (89.14)	342 (10.04)	28 (0.82)	3,407 (100)

eGFR: estimated glomerular filtration rate. Values in cells show absolute frequency (relative frequency).

patients gave their written informed consent to participate in the study.

5. Results

Table 1 shows the baseline sociodemographic and clinical characteristics of the MADIABETES CKD Cohort. Mean age was 69 years (SD = 10.8), and the average of duration of DM was 9.1 years (SD = 7.7). The vast majority of patients (90.9%) had a low risk (≤10%) of developing coronary events within 10 years. However, 28.3% had prior cardiovascular disease (12.7% myocardial infarction, 8.3% stroke, and 7.3% peripheral artery disease).

The baseline prevalence of CKD was 28.32% (95% CI, 26.84–29.86) and that of albuminuria was 10.9% (95% CI, 9.9–11.9), with a predominance of microalbuminuria (10.1%; 95% CI, 9.1–11.1).

Among CKD patients, men had a higher cardiovascular risk than women; 25.5% had history of myocardial infarction compared with 12.7% in women (p < 0.01). In addition, 18.7% of men had had ≥2

cardiovascular events (myocardial infarction, stroke or peripheral artery disease) compared with 9.3% of women (p < 0.01).

There were significant differences for most of the study variables between patients with and without CKD (Table 1). The only variables for which differences were not statistically significant were use of statins, REGICOR score, BMI, HbA1c, HDL-C, and TG.

When eGFR and stage of albuminuria were taken into account (Table 2), 23.89% of patients (95% CI, 22.46–25.32) had a moderate risk of developing adverse outcomes, 6.75% (95% CI, 5.91–7.59) had a high risk, and 3.61% (95% CI, 2.98–4.24) had a very high risk.

The variables most strongly associated with the presence of CKD at baseline were age > 74 years (OR, 19.88; 95% CI, 12.89–30.68), age 60–74 years (OR, 6.22; 95% CI, 4.06–9.53), and albuminuria (OR, 2.27; 95% CI, 1.72–3.00). Other positively associated variables were female gender (OR, 1.82; 95% CI, 1.49–2.21), hypertension (OR, 1.97; 95% CI, 1.54–2.52), history of myocardial infarction (OR, 1.37; 95% CI, 1.05–1.78), retinopathy (OR, 1.38; 95% CI, 1.02–1.87), TG ≥150 mg/dl (OR, 1.47; 95% CI, 1.20–1.80), and use of insulin (OR, 1.77; 95% CI 1.40–2.25) and antiplatelet medication (OR, 1.26; 95% CI, 1.04–1.52). Finally, DBP <80 mmHg (OR, 0.77; 95% CI, 0.63–0.93), HbA1c <7% (OR, 0.73; 95 CI, 0.60–0.88), and HDL-C ≥45 mg/dl (OR, 0.73; 95% CI, 0.60–0.89) were inversely associated with CKD.

5.1. Mortality

During the 5-year follow-up, the mortality rate was 26.38 cases per 1000 patient-years (95% CI, 23.92–29.01), with higher rates in men (28.43 per 1000 patient-years; 95% CI, 24.87–32.36) than in women (24.31 per 1000 patient-years; 95% CI, 21.02–27.98). As for the cause of mortality, 51.9% of deaths were of cardiovascular origin: 13.69 per 1000 patient-years (95% CI, 11.94–15.62), with no statistically significant predominance of males (15.02 per 1000 patient-years; 95% CI, 12.47–17.95) or females (12.34 per 1000 patient-years; 95% CI, 10.03–15.03).

Of the 965 patients with CKD, 221 died (22.90%; 95% CI, 20.36–25.66) compared with 203 of 2442 patients without CKD (8.31%; 95% CI, 7.28–9.47) (p < 0.01) (Table 3). The incidence density was 51.47 cases per 1000 patient-years (95% CI, 44.91–58.72) in CKD patients compared with 17.23 cases per 1000 patient-years (95% CI, 14.94–

Table 3
Mortality rates according CKD and CKD prognosis stages.

		All-causes mortality	95% CI	Cardiovascular mortality	95% CI
CKD					
Yes	CI	22.90	20.36–25.66	12.85	10.88–15.11
	DI	51.47	44.91–58.72	28.88	24.02–34.43
No	CI	8.31	7.28–9.47	3.93	3.23–4.78
	DI	17.23	14.94–19.77	8.15	6.60–9.95
CKD Prognosis stage					
Low	CI	7.95	6.90–9.14	3.75	3.04–4.62
	DI	16.44	14.11–19.04	7.76	6.19–9.60
Moderate	CI	17.08	14.65–19.81	8.97	7.19–11.13
	DI	37.15	31.23–43.87	19.51	15.29–24.53
High	CI	26.96	21.64–33.04	14.35	10.40–19.46
	DI	61.90	47.46–79.35	32.95	22.68–46.27
Very high	CI	36.59	28.60–45.38	24.39	17.65–32.68
	DI	89.61	65.37–119.91	59.74	40.31–85.29

CI: Cumulative incidence (%).
DI: Density incidence (per 1000 person-years).

Table 4
Hazard ratios for all-cause mortality for CKD at baseline and albuminuria (Model 1) and CKD risk (Model 2).

A. For the overall sample (n = 3407).				
	Variables		**aHR[a] (95% CI)**	**p value**
Model 1	**CKD at baseline**, *Yes*	*With LDL C = 114 mg/dl (p50)*	1.72 (1.39–2.13)	<0.01
		With LDL C = 135 mg/dl (p75)	2.11 (1.61–2.76)	<0.01
		With LDL C = 153 mg/dl (p90)	3.59 (2.03–6.36)	<0.01
	Albuminuria, *Yes (ref. no)*		1.23 (0.94–1.61)	0.13
Model 2	**Moderate-risk,** *Yes (ref. Low-risk)*	*With Age <75 y*	2.32 (1.58–3.39)	<0.01
		With Age ≥75 y	1.27 (0.95–1.69)	0.11
	High-risk, *Yes (ref. Low-risk)*	*With Age <75 y*	2.78 (1.46–5.3)	<0.01
		With Age ≥75 y	1.78 (1.26–2.52)	<0.01
	Very-high-risk, *Yes (ref. Low-risk)*	*With Age <75 y*	4.44 (2.31–8.53)	<0.01
		With Age ≥75 y	1.80 (1.19–2.72)	<0.01

B. Stratified by gender (men, n = 1713; women, n = 1694).				
Model 1		**Men**		
	CKD at baseline, *Yes (ref. no)*		1.44 (1.07–1.93)	0.02
	Albuminuria, *Yes (ref. no)*		1.28 (0.91–1.81)	0.16
		Women		
	CKD at baseline, *Yes (ref. no)*		1.95 (1.43–2.67)	<0.01
	Albuminuria, *Yes (ref. no)*		1.14 (0.73–1.80)	0.56
Model 2		**Men**		
	Moderate-risk, *Yes (ref. Low-risk)*	Without Insulin	1.25 (0.86–1.83)	0.24
		With Insulin	1.41 (0.77–2.59)	0.27
	High-risk, *Yes (ref. Low-risk)*	Without Insulin	1.53 (0.82–2.85)	0.18
		With Insulin	2.50 (1.02–4.10)	0.04
	Very-high-risk, *Yes (ref. Low-risk)*	Without Insulin	5.09 (2.81–9.22)	<0.01
		With Insulin	0.94 (0.46–1.92)	0.86
		Women		
	Moderate-risk, *Yes (ref. Low-risk)*		1.82 (1.28–2.58)	<0.01
	High-risk, *Yes (ref. Low-risk)*		2.30 (1.49–3.54)	<0.01
	Very-high-risk, *Yes (ref. Low-risk)*		2.73 (1.56–4.77)	<0.01

C. Stratified by history of Cardiovascular disease (Primary Prevention, n = 2646; Secondary Prevention, n = 761).				
	Primary Prevention			
Model 1	**CKD at baseline,** *Yes (ref. no)*	With cholest. = 172 mg/dl (p25)	1.59 (1.18–2.16)	<0.01
		With cholest. = 194 mg/dl (p50)	1.99 (1.51–2.63)	<0.01
		With cholest. = 217 mg/dl (p75)	2.50 (1.78–3.53)	<0.01
	Albuminuria, *Yes (ref. no)*		1.51 (1.03–2.21)	0.04
	Secondary Prevention			
	CKD at baseline, *Yes (ref. no)*		1.62 (1.16–2.27)	<0.01
	Albuminuria, *Yes (ref. no)*		1.16 (0.79–1.70)	0.46
Model 2	**Primary Prevention**			
	Moderate-risk, *Yes (ref. Low-risk)*	With cholest. = 172 mg/dl (p25)	1.41 (1.01–1.97)	0.04
		With cholest. = 217 mg/dl (p75)	1.68 (1.13–2.51)	0.01
	High-risk, *Yes (ref. Low-risk)*	With cholest. = 172 mg/dl (p25)	2.29 (1.45–3.62)	<0.01
		With cholest. = 217 mg/dl (p75)	3.23 (2.06–5.07)	<0.01
	Very-high-risk, *Yes (ref. Low-risk)*	With cholest. = 172 mg/dl (p25)	2.22 (1.19–4.13)	0.01
		With cholest. = 217 mg/dl (p75)	5.73 (3.02–10.9)	<0.01
	Secondary Prevention			
	Moderate-risk, *Yes (ref. Low-risk)*	Without Statins	1.42 (0.69–2.91)	0.34
		With Statins	1.69 (1.11–2.60)	0.02
	High-risk, *Yes (ref. Low-risk)*	Without Statins	2.36 (1.06–5.24)	0.04
		With Statins	0.94 (0.49–1.80)	0.85
	Very-high-risk, *Yes (ref. Low-risk)*	Without Statins	0.98 (0.34–2.78)	0.97
		With Statins	2.62 (1.52–4.49)	<0.01

CKD: Chronic Kidney Disease; aHR: adjusted hazard ratio; CI: Confidence Interval; Cardiovascular disease (Myocardial Infarction, Stroke, Peripheral Arterial Disease, Heart failure); p25: 25th percentile; p50: 50th percentile; p75: 75th percentile; y: years.

[a] Adjusting for Body Mass Index, Systolic Blood Pressure, Neuropathy, Cholesterol, LDL Cholesterol, Triglycerides, Insulin, Statins, Platelet Antiaggregant drugs, Inhibitors of renin–angiotensin system.

19.77) in non-CKD patients. These differences were statistically significant. The remaining mortality rates according to prognosis stage are shown in Table 3. There were no statistically significant differences between a high and a very high risk of developing adverse outcomes with respect to all-cause and cardiovascular mortality, respectively. However, statistically significant differences were observed between the other categories.

The 5-year actuarial survival rate and cardiovascular mortality-free survival rate for non-CKD patients were significantly higher than for CKD patients (Supplementary 1, A and C). Stratifying by prognosis stage, low-risk patients had the highest all-cause mortality-free survival rate

(Supplementary 1, B) and cardiovascular mortality-free survival rate (Supplementary 1, D).

5.2. Factors associated with all-cause mortality

The unadjusted HR for all-cause mortality in patients with CKD at baseline was 3.02 (95% CI, 2.50–3.66), and the aHR was 1.72 in those with LDL cholesterol levels of 114 mg/dl (50th percentile of the distribution of LDL cholesterol values) and 3.59 in those with LDL cholesterol levels of 153 mg/dl (90th percentile), owing to the effect of modification by LDL cholesterol values (p < 0.01) (Table 4A, model 1).

Table 5

Hazard ratios for cardiovascular mortality for CKD at baseline and albuminuria (Model 1) and CKD risk (Model 2).

A. For the overall sample (n = 3407)				
Variables			aHR[a] (95% CI)	p value
Model 1	**CKD at baseline** *yes (ref. no)*		1.82 (1.36–2.44)	<0.01
	Albuminuria *yes (ref. no)*		1.15 (0.80–1.66)	0.45
Model 2	**Moderate-risk** *yes (ref. Low-risk)*	With Cholesterol = 168 mg/dl (p25)	1.52 (1.08–2.15)	<0.01
		With Cholesterol = 214 mg/dl (p75)	1.55 (1.05–2.60)	0.03
	High-risk *yes (ref. Low-risk)*	With Cholesterol = 168 mg/dl (p25)	1.58 (0.97–2.57)	0.06
		With Cholesterol = 214 mg/dl (p75)	2.78 (1.68–4.60)	<0.01
	Very-high-risk *yes (ref. Low-risk)*	With Cholesterol = 168 mg/dl (p25)	2.03 (1.19–3.46)	0.01
		With Cholesterol = 214 mg/dl (p75)	3.89 (2.28–6.67)	<0.01

B. Stratified by gender (men, n = 1713; women, n = 1694).				
Model 1		**Men**		
	CKD at baseline *yes (ref. no)*		1.90 (1.27–2.84)	<0.01
	Albuminuria *yes (ref. no)*		0.99 (0.62–1.59)	0.98
		Women		
	CKD at baseline *yes (ref. no))*	With SBP <150 mmHg	1.59 (0.99–2.54)	0.06
		With SBP ≥150 mmHg	5.98 (1.71–20.97)	<0.01
	Albuminuria *yes (ref. no)*		1.34 (0.75–2.39)	0.33
Model 2		**Men**		
	Moderate-risk *yes (ref. Low-risk)*	Without Insulin	1.51 (0.89–2.56)	0.13
		With Insulin	1.48 (0.69–3.19)	0.31
	High-risk *yes (ref. Low-risk)*	Without Insulin	1.84 (0.80–4.19)	0.15
		With Insulin	1.76 (0.73–4.26)	0.21
	Very-high-risk *yes (ref. Low-risk)*	Without Insulin	5.54 (2.52–12.18)	<0.01
		With Insulin	1.06 (0.45–2.51)	0.90
		Women		
	Moderate-risk *yes (ref. Low-risk)*	With LDL C = 97 mg/dl (p25)	1.81 (1.04–3.16)	0.04
		With LDL C = 138 mg/dl (p75)	1.41 (0.73–2.74)	0.31
	High-risk *yes (ref. Low-risk)*	With LDL C = 97 mg/dl (p25)	1.42 (0.65–3.09)	0.38
		With LDL C = 138 mg/dl (p75)	2.96 (1.49–5.87)	<0.01
	Very-high-risk *yes (ref. Low-risk)*	With LDL C = 97 mg/dl (p25)	2.59 (1.08–6.18)	0.03
		With LDL C = 138 mg/dl (p75)	5.15 (2.41–10.98)	<0.01

C. Stratified by History of Cardiovascular disease (Primary Prevention, n = 2646; Secondary Prevention, n = 761).			
Model 1	**Primary Prevention**		
	CKD at baseline *yes (ref. no)*	1.82 (1.20–2.75)	<0.01
	Albuminuria *yes (ref. no)*	1.92 (1.11–3.30)	0.02
	Secondary Prevention		
	CKD at baseline *yes (ref. no)*	2.03 (1.34–3.08)	<0.01
	Albuminuria *yes (ref. no)*	0.85 (0.52–1.39)	0.52
Model 2	**Primary Prevention**		
	Moderate-risk *yes (ref. Low-risk)*	1.46 (0.91–2.35)	0.12
	High-risk *yes (ref. Low-risk)*	2.57 (1.43–4.65)	<0.01
	Very-high-risk *yes (ref. Low-risk)*	4.48 (2.18–9.24)	<0.01
	Secondary Prevention		
	Moderate-risk *yes (ref. Low-risk)*	1.78 (1.13–2.81)	0.01
	High-risk *yes (ref. Low-risk)*	1.44 (0.78–2.67)	0.25
	Very-high-risk *yes (ref. Low-risk)*	2.21 (1.22–4.02)	<0.01

CKD: Chronic Kidney Disease; aHR: adjusted hazard ratio; CI: Confidence Interval; Cardiovascular disease (Myocardial Infarction, Stroke, Peripheral Arterial Disease, Heart failure); p25: 25th percentile; p50: 50th percentile; p75: 75th percentile; y: years.

[a] Adjusting for Body Mass Index, Systolic Blood Pressure, Neuropathy, Cholesterol, LDL Cholesterol, Triglycerides, Insulin, Statins, Platelet Antiaggregant drugs, Inhibitors of renin–angiotensin system.

When prognosis stage was taken into account (model 2), the highest aHR was 4.44 for patients aged <75 years, the very-high-risk group and 1.80 in patients aged ≥75 years (Table 4A, model 2).

Men with CKD at baseline showed an aHR of 1.44, whereas women showed an aHR of 1.95 (Table 4B, model 1). However, the men from the very-high-risk group had a higher risk (aHR, 5.09) than women (aHR, 2.73), although the differences were not statistically significant because the confidence intervals were over-lapping (Table 4B, model 2).

In primary prevention, the highest risk of CKD at baseline for all-cause mortality was found in patients with cholesterol levels of 217 mg/dl (75th percentile). In secondary prevention, the risk of CKD at baseline was similar to that of patients without a history of CVD and with total cholesterol levels of 172 mg/dl (25th percentile) (Table 4C, model 1).

5.3. Factors associated with cardiovascular mortality

Patients with CKD at baseline had an increased risk of cardiovascular mortality (aHR 1.82; 95% CI, 1.36–2.44) (Table 5A, model 1). We detected an interaction between CKD at baseline and SBP in women (p = 0.049); data on CKD at baseline revealed a lower risk of cardiovascular mortality in women with SBP <150 mmHg (aHR, 1.59) than in men (aHR 1.90) regardless of the blood pressure reading (aHR 1.90; 95% CI, 1.27–2.84). However, the CKD at baseline in women with SBP ≥150 mmHg showed a higher risk of cardiovascular mortality than in men (aHR 5.98) (Table 5B, model 1).

Moreover, CKD at baseline implied a lower risk in patients without a history of CVD (aHR 1.82) than in patients with prior CVD (aHR 2.03), although the differences were small, and the confidence intervals were over-lapping (Table 5C, model 1).

Analysis of the effect of each prognosis risk group on cardiovascular mortality (model 2) revealed that an interaction with the total cholesterol value was detected (p < 0.01). The lower risk of cardiovascular mortality was seen in the moderate-risk group with cholesterol levels of 168 mg/dl (25th percentile) and the highest risk was seen for those included in the very-high-risk group with cholesterol levels of 214 mg/dl (75th percentile). The differences between both groups were statistically significant because the confidence intervals did not overlap (Table 5A, model 2).

In men, we detected an interaction between CKD prognosis risk group and insulin use (p = 0.03), whereas in women an interaction was observed between prognosis risk group and LDL cholesterol level (p = 0.02). In men, the highest risk was seen in the very-high-risk group without use of insulin; in women the highest risk was seen in the very-high-risk group with LDL cholesterol levels of 138 mg/dl (75th percentile) (Table 5B, model 2).

The risk of cardiovascular mortality in the very-high-risk group was higher in patients without history of CVD (aHR, 4.48) than in those with prior CVD (aHR, 2.21), although the differences were not statistically significant (Table 5C, model 2).

6. Discussion

6.1. Prevalence of CKD

Since the publication of the K/DOQI clinical practice guidelines for the classification of CKD in 2002 (National Kidney Foundation, 2002), several studies based on this classification system have shown high prevalence estimates for CKD in the general population and in patients with T2DM. The results of our study show that approximately a quarter of patients with T2DM have an eGFR below 60 mL/min/ 1.73 m^2. This result is concordant with those of previous studies in T2DM performed in Spain (Coll-de-Tuero et al., 2012; Mur Martí, Villaró Gabarrós, Porta Martínez, & Jaén Manzanera, 2013) and southern Europe (Targher et al., 2012). However, studies in Italian hospitals revealed lower figures, around 19% (Penno et al., 2012). Patients with DM participating in NHANES III, NHANES 1999–2004, and NHANES 2005–2008 had a <20% prevalence of stage 3–5 CKD (CKD-EPI equation) (14.9%, 16.7%, and 17.7%, respectively). The discrepancy in the prevalence data might be due to the difference in mean age between the studies (58 vs. 69 years). In addition, in their study of 2798 DM patients aged 20 years or older from NHANES 2001–2008, Mottl et al. (2013) reported the prevalence of normoal-buminuric CKD to be 9.7% and that of albuminuria to be 7.6% (CKD-EPI equation).

Previous data from the first epidemiological investigation of the prevalence of CKD (stages 3–5) in Spanish patients aged ≥20 years revealed an overall prevalence of 6.8% and a prevalence of 21.42% for patients aged >64 years. In addition, the prevalence ratio was 2.0 (95% CI, 1.4–2.8) among participants with DM (Otero, de Francisco, Gayoso, García, & EPIRCE Study Group, 2010).

6.2. Prevalence of albuminuria

The proportion of T2DM patients with albuminuria is lower in our study than that reported in previous studies in Spain (Coll-de-Tuero et al., 2012). Other DM cohort studies also showed a wide variation in the prevalence of albuminuria, ranging from 6% to 89% (Fox et al., 2012). For example, Rodriguez-Poncelas et al. (2014) recently reported a prevalence of albuminuria of 13.5% in a Spanish cross-sectional study of 1141 participants with T2DM (aged >40 years).

6.3. Prevalence of risk of adverse outcomes

A high or very high risk of adverse outcomes was recorded in 10.36% of participants, that is, higher than the 5.5% reported in the

NHANES III study (Levey et al., 2011). This difference might be because the NHANES study was a nationally representative sample of 15,625 adults aged ≥20 years with and without DM (Coresh, Astor, Greene, Eknoyan, & Levey, 2003). Results from 45 cohorts (1,555,332 people) included in a meta-analysis (Levey et al., 2011) indicate that the risk of lower eGFR and higher levels of albuminuria is well established for various outcomes: all-cause mortality, cardiovascular mortality, end-stage renal disease, acute kidney injury, and progressive CKD. The adjusted relative risk is usually higher for kidney outcomes than for mortality outcomes. Since 2006, the unadjusted relative risk for mortality in participants with reduced kidney function compared with those without has ranged from 0.94 to 5.0 (Tonelli et al., 2006).

6.4. CKD-associated factors

The classic factors associated with the presence of CKD are older age, gender, smoking, black race, low income or education, cardiovascular disease, hypertension, DM, duration of DM, and obesity (Afghahi et al., 2011; Levey et al., 2003); the factors associated with progression of CKD are poor glycemic control (Bash, Selvin, Steffes, Coresh, & Astor, 2008), higher blood pressure, lower HDL cholesterol levels (Zoppini et al., 2009), and higher proteinuria levels (Levey et al., 2003). Male gender has been associated with CKD in the general population (Cueto-Manzano et al., 2014) and in patients with DM (Gall, Hougaard, Borch-Johnsen, & Parving, 1997). However, in our study, as in other reports, we found an association with female gender (Afghahi et al., 2011; De Pablos-Velasco et al., 2010), possibly owing to the higher mortality rate in men (survival bias) as a consequence of their higher cardiovascular risk.

Our findings revealed other associated factors such as TG ≥150 mg/dl and use of antiplatelet medication and insulin, as we found in a previous study of predictors of retinopathy after a 4-year follow-up (Salinero-Fort et al., 2013). Insulin may be associated with CKD because it is strongly recommended as first-line treatment if eGFR is <30 mL/min/1.73 m^2 and HbA1c is 6.5%–8.5% (Gómez-Huelgas, Martínez-Castelao, Artola, Górriz, & Menéndez, 2014).

The factors most closely associated with CKD at baseline in the adjusted multivariable analysis were age 60–74 years and age >74 years (OR, 5.89 and 13.10, respectively) and albuminuria (OR, 2.61). Other studies in our setting revealed an association with heart failure, atrial fibrillation, peripheral arteriopathy, stroke (Salvador González et al., 2015), and hyperuricemia (De Pablos-Velasco et al., 2010).

Finally, our study showed an association between CKD and retinopathy, as reported elsewhere (Colhoun et al., 2001). This finding is congruent with previous findings showing that both entities are microvascular complications in DM patients (Girach & Vignati, 2006). Therefore, it has been demonstrated that retinal arterioles and venules are narrowed in renal failure and that the narrowing worsens as kidney function declines (Ooi et al., 2011). However, to the best of our knowledge, this is the first study to examine the relationship between CKD and retinopathy among T2DM patients in Spain.

6.5. Mortality

6.5.1. All-cause mortality

Our report shows that the unadjusted HR for all-cause mortality in patients with eGFR <60 mL/min/1.73 m^2 was 3.02 (95% CI, 2.50–3.66) after 5 years of follow-up. This finding is consistent with those of other studies in patients with DM (Patel, Young, Ojo, & Hayward, 2005). After adjusting for gender, age, prior cardiovascular disease, albuminuria, SBP, BMI, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, neuropathy, insulin, statins, antiplatelet drugs, and inhibitors of the renin–angiotensin system inhibitors, the HR was 1.72 (95% CI, 1.39–2.13) in patients with LDL cholesterol levels of 114 mg/dl (50th percentile), which is higher than in other studies

performed with 4 community-based, longitudinal public use datasets, where the adjusted HR was around 1.20 (Weiner et al., 2004). A possible explanation for this difference is that our study did not exclude patients with prior cardiovascular disease.

CKD at baseline tended to indicate a lower risk for all-cause mortality in men (aHR, 1.44; 95% CI, 1.07–1.93) than in women (aHR 1.95; 95% CI, 1.43–2.67), in contrast with other reported studies (Fried et al., 2005). When at baseline, albuminuria and eGFR were analyzed, men who did not use insulin and were in the very-high-risk group (eGFR <60 mL/min/1.73 m² and macroalbuminuria, or eGFR <45 mL/min/1.73 m² and albuminuria 30–299 mg/g, or eGFR <30 mL/min/m² and albuminuria <30 mg/g) had an almost 2-fold higher risk of all-cause mortality than women in the same group (aHR 5.09; 95% CI, 2.81–9.22, vs. aHR, 2.73; 95% CI, 1.56–4.77). However, these results should be interpreted with caution because the small sample size limited the ability to detect differences between both groups.

High total cholesterol levels influenced the risk for all-cause mortality in CKD patients with no history of CVD, to the extent that risk was equal to or greater than that recorded in patients with a prior history of CVD. These data contrast with those reported by Kovesdy, Anderson, and Kalantar-Zadeh (2007), who showed that lower lipid levels were associated with higher mortality in patients who have moderate and advanced CKD and are not yet on dialysis.

Consistent with our findings, several studies observed a synergistic interaction between albuminuria and eGFR that affected all-cause mortality. For example, in the Kidney Early Evaluation program (KEEP) (Amin et al., 2013), participants with eGFR <30 mL/min/1.73 m² and macroalbuminuria were 5 times more likely to die than participants with eGFR ≥105 mL/min/m2 and normoalbuminuria (HR, 4.84; 95% CI 3.33–7.04). In participants with eGFR <30 mL/min/1.73 m², no differences were observed between microalbuminuria and macroalbuminuria in all-cause mortality, but it seems that differences were observed in patients with eGFR > =30 and <60 mL/min/1.73 m². A recent 10-year cohort study carried out in Taipei (Taiwan) with 646 DM2 patients showed similar results (Yu et al., 2013) for all-cause mortality with both proteinuria and eGFR < 60 mL/min/1.73 m² (HR, 4.01; 95% CI 2.42–6.67).

However, of the 31 studies included in the meta-analysis by Toyama et al. (2013)), who investigated the impact of albuminuria and/or low eGFR on the risk of mortality, only 2 reported about the combined influence of low eGFR (<60 mL/min/1.73 m²) and albuminuria in terms of the risk for the outcomes. Patients with both albuminuria and eGFR <60 mL/min/1.73 m² had a 4.20-fold (95% CI 3.11–5.68) higher risk of cardiovascular mortality than those with neither of these risk factors. In this respect, de Boer et al. (2009) analyzed a cohort of the Cardiovascular Health Study that included 691 participants with DM. The participants with a normal urine albumin-to-creatinine-ratio (ACR) and low eGFR had an aHR for mortality of 1.69, and those with elevated urine ACR and normal eGFR had an aHR of 1.67. In addition, the aHR was 2.54 if the patients had both low eGFR and elevated urine ACR.

With regard to studies conducted in the southern Europe, 2 were included in the meta-analysis of Toyama et al. (2013). Firstly, the Casale Monferrato study (Bruno et al., 2007) analyzed 1538 participants with DM2 of whom 670 died over an 11-year follow-up period. In patients with eGFR <60 ml/min/1.73 m² and microalbuminuria the aHR (adjusted for age and sex) for all-cause mortality was 1.40 (95% CI, 1.05–1.87); in patients with eGFR <60 mL/min/1.73 m² and macroalbuminuria it was of 1.79 (95% CI, 1.28–2.50). The aHRs for cardiovascular mortality were 1.41 (95% CI, 0.91–2.21) and 1.81 (95% CI, 1.17–2.82), respectively, in the same groups. Secondly, the study of Casiglia et al. (2000) which was carried out in the Pordenone Diabetic Care Centre (Italy) followed 683 participants with DM2 for 6 years. A total of 132 died (19.3%), 10% of cardiovascular causes. Although the combined effect of impaired renal function and albuminuria was not analyzed, data showed for cardiovascular mortality an HR of 2.97 for

macroalbuminuria (95% CI, 1.56–5.12) and of 2.01 for microalbuminuria (95% CI, 1.15–3.68). The values we recorded were higher when total cholesterol was high (aHR, 3.89; 95% CI, 2.28–6.67), but similar when total cholesterol was under 170 mg/dl.

6.5.2. Cardiovascular mortality

With regard to the risk of cardiovascular mortality in patients with CKD, our results (aHR, 1.82; 95% CI, 1.36–2.44) are similar to those of the ADVANCE study for eGFR <60 mL/min/1.73 m² and normoalbuminuria (HR, 1.85; 95% CI, 1.17–2.92) (Ninomiya et al., 2009). Furthermore, the ADVANCE study showed a multivariable aHR for cardiovascular mortality of 3.26 (95% CI, 2.46–4.32) for T2DM patients with a urinary albumin creatinine ratio ≥30 and eGFR 30–59 mL/min/1.73 m². Our aHR for patients at very high risk of adverse outcomes and total cholesterol levels of 214 mg/dl (75th percentile) was higher, with no clear explanation, except that patients at very high risk also included those who had an eGFR <15 mL/min/1.73 m².

These findings support current recommendations to regularly assess both albuminuria and GFR in the clinical care of patients with diabetes, especially in primary health care (Martínez-Castelao et al., 2014).

The strengths of our study include the use of a population-based cohort, prospective ascertainment of end points, and assessment of information on potentially confounding variables, which reduces potential selection and confusion bias. We believe our results are applicable to other patients with T2DM. Our dataset included patients from many primary health care centers in Madrid. The range of patients was broad, namely, men and women aged from 30 years to >65 years, and the major exposure categories were well represented. The severity of T2DM at baseline ranged from low (no complications) to very severe (micro and macrovascular complications). In addition, in Spain, it is mandatory to register deaths in registries. Registry information is then submitted to the National Institute of Statistics (*Instituto Nacional de Estadística*). Therefore, data about vital status, and date and cause of death are available for all patients, with no loss of data during follow-up.

Our study is also subject to a series of limitations. First, the laboratory data were measured at different primary health care centers and using different devices; however, all laboratories used standard methods. Second, as noted by other authors (Carter, Stevens, Irving, & Lamb, 2011), the use of the CKD-EPI equation may have led us to overestimate the prevalence of CKD in the elderly, which could be a limitation of our study given the characteristics of the cohort. Third, serum creatinine was measured using an enzymatic creatinine assay that was not traceable to isotope dilution mass spectrometry (ID-MS). This is a limitation given that gas chromatography ID-MS is considered the method of choice for establishing the true concentration of creatinine in serum (Myers et al., 2006). Fourth, the determination of microalbuminuria could be affected by the concomitant use of ACE inhibitors or Angiotensin receptor blockers and by the presence of urinary tract infections. Therefore, albuminuria was only considered in the analysis if it was persistent (at least 2 of 3 consecutive samples). However, false negatives can arise because of medication. Finally, we used the result of a single creatinine determination to calculate the CKD-EPI equation and estimate GFR.

7. Conclusions

We found a high prevalence of CKD and a low prevalence of albuminuria in a Spanish cohort of T2DM patients attended in the primary care setting. The prevalence of CKD at baseline was significantly higher in women than in men, but CKD-associated mortality was higher in men than in women. Approximately half of the deaths were due to cardiovascular causes. Baseline CKD is an independent risk factor for all-cause and cardiovascular mortality in the overall cohort, as well in separate subsamples of men and women

and in subsamples of primary and secondary prevention of coronary heart disease. Albuminuria is an independent risk factor for all-cause and cardiovascular mortality only in primary prevention.

Classifying patients by prognosis stage based on eGFR and albuminuria revealed that low-risk patients had the highest all-cause mortality-free survival rate and cardiovascular mortality-free survival rate.

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Authors' contributions

MASF and CBL conceived and designed the experiments. MASF, CBL, FJSR, PGC, and RCM performed the experiments. FJSR, CBL, and MASF analyzed the data. MASF, CBL, PGC, ALA, RJG, RCM, JCAH, and ECS provided reagents, materials, and analysis tools. MASF, FJSR RJG, and ALA drafted the manuscript.

Acknowledgments

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