Epidemiology and resource use in Spanish type 2 diabetes patients without previous cardiorenal disease: CaReMe Spain study

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Abstract

Background.

To determine baseline characteristics, the first manifestation of cardiovascular or kidney disease (CVKD) and associated resource use in type 2 diabetes mellitus (T2DM) patients during 7 years of follow up.

Methods.

Observational-retrospective secondary data study using medical records of patients aged ≥18 years with T2DM and without prior CVKD during 2013-2019. The index date was 01/01/2013 (fixed date). The manifestation of CVKD was defined by the first diagnosis of heart failure (HF), chronic kidney disease (CKD), myocardial infarction (MI), stroke or peripheral artery disease (PAD). The main variables were baseline characteristics, manifestation of CVKD, mortality, resource use and costs (health, indirect related). Descriptive analyses and Cox model were applied to the data.

Results.

26,542 patients were selected (mean age: 66.6 years, women: 47.8%, mean duration of T2DM: 17.1 years). 18.7% (N=4974) developed a first CVKD manifestation during the 7 years [distribution: HF (22.4%), CKD (36.6%), MI (14.5%), stroke (15.3%) and PAD (11.3%)]. Overall mortality was 8.3% (N=2,214). The mortality risk of the group that developed HF or CKD as the first manifestation compared to the CVKD-free cohort was higher [HR: 2.5 (CI95%: 1.8-3.4) and 1.8 (95%CI: 1.4-2,3)], respectively. The cumulative costs per patient of HF (€50,942.8) and CKD (€48,979.2) were higher than MI (€47.343.2) and stroke (€47,070.3) and similar to PAD (€51,240,0) vs. €13,098.9 in patients who did not develop CVKD, p<0.001.

Conclusions.

In T2DM patients, HF and CKD were the first most common manifestations over the 7 years of follow up and had higher mortality and re-hospitalization rates. HF and CKD were associated with the highest resource use and costs for the Spanish National Health System.

Highlights

- Type 2 diabetes mellitus (T2DM) is a disease with a large social and health impact due to its high prevalence, the chronic macro and microvascular complications, and, mainly, due to cardiovascular manifestations.
- In T2DM patients, HF and CKD were the first most common manifestations over the 7 years of follow up and had higher mortality and re-hospitalization rates.
- HF and CKD were associated with the highest resource use and costs for the Spanish National Health System.

Background

Type 2 diabetes mellitus (T2DM) is a disease with a large social and health impact due to its high prevalence, the chronic macro and microvascular complications, and, mainly, due to cardiovascular manifestations [1–2]. The prevalence is about 6–10% in the general population [3] and is estimated to be 13.8% in Spain [4]. Around 11.3% of all cause-deaths are associated with diabetes, and half these deaths occur in persons aged < 60 years [5].

A diagnosis of T2DM is often accompanied by heart failure (HF,13–47%), chronic kidney disease (CKD, 30–40%) or both, in a high proportion of patients [2]. In fact, HF is more frequent, earlier, more recurrent and has a worse prognosis in people with diabetes than ischemic heart disease [6–7]. It has recently been reported that a diagnosis of HF at any time after the diagnosis of diabetes is associated with the highest risk of relative and absolute mortality at 5 years, and with a decrease in life expectancy at 5 years, when compared with any other cardiovascular or renal diagnosis [8].

In T2DM, myocardial involvement presents very early, and it is not easily recognized by usual tests. Up to two-thirds of patients present systolic and/or diastolic dysfunction within a few years of diagnosis [9] and even when cardiovascular risk factors (blood glucose, blood pressure, cholesterol, smoking, albuminuria) are controlled, the incidence of HF is not reduced, unlike that of ischemic heart disease or stroke [10].

The onset of CKD is a determining factor in the increased risk of HF [10]. Through a series of complex mechanisms (confluence of hemodynamic, neurohormonal and inflammatory interactions), the heart and kidney are intimately connected and contribute to the onset of HF. When presented together, they create a disorder known as cardiorenal syndrome [11–13]. Cardiovascular and renal disease (CVKD) in T2DM is a significant source of morbidity and contribute to continuing increases in health expenditure [6]. Real-life data show that, in patients with T2DM, cardiorenal events (HF or CKD) are the most common first manifestation of cardiovascular disease (four times more frequent than stroke and myocardial infarction (MI) and six times more frequent than peripheral artery disease (PAD) and are associated with a high risk of mortality and other cardiovascular risks.

In Spain, there is little evidence on the type and time to the first manifestation of CVKD after diagnosis of T2DM and subsequent impact on health resource use in usual clinical practice [14]. The aim of this study was to determine the first manifestation requiring hospital admission due to a CVKD manifestation in initially CVKD-free T2DM patients during a 7-year follow up and quantify the use of health and non-health related resources and costs in these patients.

Patients And Methods

Design and study population

This was a retrospective, observational study based on electronic medical records from BIG-PAC [15] administrative database (secondary data source; owner: Atrys Health-RLD) which includes 1.8 million patients *(*http://www.encepp.eu/encepp/viewResource.htm?id=29236#*).* Primary data came from the computerized medical records of seven integrated Spanish public healthcare areas (primary care centers and hospitals) from seven Spanish Autonomous Communities. Before exporting to the BIG-PAC database [15] all electronic records were rigorously anonymized by the centers/hospitals of origin, in compliance with Organic Law 3/2018, of December 5, on the Protection of Personal Data and Guarantee of Digital Rights *(*https://www.boe.es/doue/2016/119/*L00001-00088.pdf*). Atrys Health-RLD has no access to primary data sources.

Study population and follow up

All patients with a diagnosis of T2DM (CIE-09-MC: 250) and without prior CVKD on January 1, 2013 (fixed index date) were selected. During the 7-year follow up (2013–2019), the first CVKD manifestation (a diagnosis of HF, CKD, MI, stroke, or PAD) with hospital admission was evaluated and the percentage of new cases, or cumulative incidence, was determined. Angina and transient ischemic accident were not counted as CVKD during the follow up. In addition, all-cause mortality was determined. Codes for CVD and CKD were as follows: HF (428, 404.90), CKD (583–585), acute MI (410, 412), unstable angina (411), stroke (430–432, 433–434, 436) and PAD (440–441, 444).

Inclusion and exclusion criteria

Inclusion criteria were: (a) age ≥ 18 years, b) patients active in the database for ≥ 12 months before study inclusion, c) inclusion in the prescription program (≥ 2 prescriptions during follow up), d) regular monitoring of patients (≥ 2 health records in the computer system) and e) without CVKD on or before the index date. Exclusion criteria were a) patients displaced or out of area, b) permanently institutionalized (geriatric residences), and (c) patients with severe mental illness or terminal illness.

Other variables of interest

Demographic variables, comorbidities, biochemical/anthropometric parameters, and baseline treatment were obtained (Table 1). Medication was obtained according to records from the pharmacological dispensing of medicinal products according to the Anatomical Therapeutic Chemical Classification System (ATC) [16]. The choice of drug in a specific patient was at the discretion of the physician (clinical practice).

Table 1
Baseline characteristics

Description	Group who stayed CVKD-free during follow up*	Group who developed CVKD during follow up	Total	p
N, (%)	**21568 (81.3 %)**	**4974 (18.7 %)**	**26542 (100%)**	
CLINICAL CHARACTERISTICS				
Age, mean (SD)	65.7 (12.1)	70.8 (11.7)	66.6 (12.2)	< 0.001
Gender, n (%); female	10088 (46.8 %)	2600 (52.3 %)	12688 (47.8 %)	< 0.001
Diabetes duration (years)	16.1 (15.2)	21.6 (19.5)	17.1 (16.2)	< 0.001
BMI (Kg/m^2)	28.5 (4.5)	28.1 (4.3)	28.4 (4.5)	0.524
COMORBIDITIES, n (%)				
Hypertension	10698 (49.6 %)	4288 (86.2 %)	14986 (56.5 %)	< 0.001
Hyperlipidemia	9958 (46.2 %)	4168 (83.8 %)	14126 (53.2 %)	< 0.001
Smoking status, n (%)	1910 (8.9 %)	508 (10.2 %)	2418 (9.1 %)	< 0.001
CLINICAL TESTS, mean (SD)				
HbA1c	7.0 (1.4)	7.1 (1.3)	7.1 (1.4)	0.002
eGFR (mL/min/1.73 m2)	83.5 (16.2)	79.9 (16.2)	82.9 (16.3)	< 0.001
SBP (mmHg)	137.9 (19.4)	139.2 (19.5)	138.1 (19.4)	< 0.001
DBP (mmHg)	80.4 (11.3)	79.7 (11.5)	80.3 (11.3)	0.121
HDL (mg/dL)	49.6 (11.2)	49.9 (11.2)	49.6 (11.2)	0.687

Description	Group who stayed CVKD-free during follow up*	Group who developed CVKD during follow up	Total	p
N, (%)	**21568 (81.3 %)**	**4974 (18.7 %)**	**26542 (100%)**	
LDL (mg/dL)	112.1 (32.8)	110.1 (32.0)	111.8 (32.6)	0.001
Triglycerides (mg/dL)	172.3 (123.7)	169.1 (111.6)	171.8 (121.7)	< 0.001
Albumin (g/dL)	4.8 (1.0)	4.7 (0.9)	4.8 (9.5)	0.1 98
Creatinine (mg/dL)	0.8 (0.2)	0.8 (0.3)	0.8 (0.2)	0.7 46
MEDICATION				
CVD risk treatment. n (%)	17492 (81.1 %)	4330 (87.1 %)	21822 (82.2 %)	< 0.001
Lipid lowering drugs	9738 (45.2 %)	2226 (44.8 %)	13536 (51.1 %)	0.2 17
Antihypertensives. n (%)	13880 (64.4 %)	3858 (77.6 %)	17738 (66.8 %)	< 0.001
Anticoagulant/antiplatelet	3450 (16.0 %)	670 (13.5 %)	5255 (19.8 %)	< 0.001
Glucose lowering drugs. n (%)	18444 (85.5 %)	4064 (81.7 %)	22508 (84.8 %)	< 0.001
Metformin	14664 (68.0 %)	3106 (62.4 %)	17770 (67.0 %)	< 0.001
SU	7092 (32.9 %)	1454 (29.2 %)	8546 (32.2 %)	< 0.001
DPP-4 inhibitors	5028 (23.3 %)	1050 (21.1 %)	6078 (22.9 %)	< 0.001
GLP-1 RA	354 (1.6 %)	20 (0.4 %)	374 (1.4 %)	< 0.001
Meglitinides	552 (2.6 %)	530 (10.7 %)	1082 (4.1 %)	< 0.001

Description	Group who stayed CVKD-free during follow up*	Group who developed CVKD during follow up	Total	p
N, (%)	**21568 (81.3 %)**	**4974 (18.7 %)**	**26542 (100%)**	
Glitazones	184 (0.9 %)	38 (0.8 %)	222 (0.8 %)	0.469
Acarbose (miglitol)	248 (1.1 %)	68 (1.4 %)	316 (1.2 %)	0.183
Insulin	4388 (20.3 %)	770 (15.5 %)	5158 (19.4 %)	< 0.001
CVKD: cardiovascular or kidney disease (heart failure, kidney disease, myocardial infarction, stroke, peripheral artery disease); * includes angina and transient ischemic accident.				
BMI: Body mass index				
HbA1c: Glycated hemoglobin				
eGFR: Estimated glomerular filtration rate				
SBP: Systolic blood pressure				
DBP: Diastolic blood pressure				
HDL: High-density lipoprotein				
LDL: Low-density lipoprotein				
SU: Sulfonylureas				
GLP-1 RA: Glucagon-like peptide-1 receptor agonists				
DPP-4: Inhibitors of dipeptidyl peptidase 4				

Resource use and costs during follow up (2013–2019)

We analyzed: (a) direct healthcare costs, defined as costs related to care (primary care medical visits, specialist visits, days of hospitalization (hospital admissions), hospital emergency room admissions, diagnostic or therapeutic requests and medication; and b) indirect costs, defined as days of productivity lost due to disability. Costs were expressed as the mean cost per patient and absolute cumulative cost. Rates were obtained from hospital accounting, except for the costs of medication and indirect costs (Table S1). Medical prescriptions were quantified according to the retail price per package at the time of dispensing (according to the General Council of Official Pharmacists' Colleges of Spain *(*https://botplusweb.portalfarma.com*)*. Indirect costs were considered as days of lost productivity due to disability according to the mean interprofessional wage (source: NEI) [17]. Use of resources and costs

were calculated only for cardiovascular or renal disease. Total costs were obtained for the first manifestation of CVKD and for each hospitalization due to CVKD.

Confidentiality of information/ ethical aspects

Confidentiality of the anonymous records was respected in accordance with the Organic Law on the Protection of Personal Data. The study was classified and approved by local regulatory authorities and a Research Ethics Committee (ERC: *Consorci Sanitari de Terrassa*). In the participating centers, the informed consent of the patients is obtained. The study methods were carried out in accordance with the Declaration of Helsinki.

Statistical analysis

The presented data were initially validated to ensure the quality of the results. A descriptive, univariate analysis of the variables of interest was made. Qualitative data were expressed as absolute and relative frequencies and quantitative data as means and standard deviation (SD). The 95% ratios and confidence intervals (CI) were analyzed according to the total number of subjects with non-missing values. A bivariate analysis was made using the Chi-square test and the ANOVA test for independent groups. A Cox proportional risk model was constructed to estimate the time-to-first manifestation and the mortality risk according to the different CVKD. The dependent variable was time (manifestation or death) and the covariates (confounding factors) were age, sex, and time from diagnosis (procedure: enter; method: maximum likelihood 2). A value of $p < 0.05$ was considered statistically significant. The analysis was made using SPSSWIN version 23 statistical program.

Results

Baseline characteristics

Of an initial population of 731,759 patients aged ≥ 18 years on index date 01/01/2013, 43,596 had a diagnosis of T2DM (prevalence in the population attended: 6%; 95%CI: 5.8–6.2%). Of the 38,691 T2DM patients who met the inclusion/exclusion criteria on the index date, 31.4% (N = 12,149) had prior CVKD and were excluded from the study population, while 68.6% (N = 26,542) were free from CVKD and were selected for the study (Fig. 1). Table 1 shows baseline participant characteristics. The mean age was 66.6 years (70.7% aged ≥ 65 years), 47.8% were female and the mean duration of T2DM was 17.1 years. Hypertension (56.5%) and dyslipidemia (53.2%) were the most frequent comorbidities.

CVKD manifestation during follow up

A total of 4,974 (18.7%) patients developed a first CVKD manifestation during the 7-year follow up (Fig. 1). The percentage of events/manifestations was HF (N = 1,112; 22.4%), CKD (N = 1,820; 36.6%), MI (N = 720; 14.5%), stroke (N = 760; 15.3%) and PAD (N = 562; 11.3%) (Fig. 2A). The mean time to the first manifestation was HF 0.52 years (median: 0.56), CKD 0.53 years (median: 0.54), MI 0.57 years (median. 0.58), stroke 0.58 years (median: 0.63) and PAD 0.57 years (median: 0.64), respectively. The number of

patients who had any CVKD as first manifestation increased over the 7 years of follow up (2013 = 536, 2014 = 658, 2015 = 622, 2016 = 676, 2017 = 757, 2018 = 850 and 2019 = 875 patients; $p < 0.001$) (Fig. 2B).

The cumulative incidence rates of HF, CKD, MI, stroke, and PAD were 51.6, 84.4, 33.4, 35.2 and 26.1 new events per 1000 patient/years, respectively. Mortality rates were 10.6, 16.9, 5.4, 6.4 and 3.5 deaths per 1000 patient-years, respectively.

Figure S1 shows the percentage of patients who had additional CVKD events/diagnoses different from the first event/diagnosis. Patients with HF or CKD as the first event had the greatest number of events due to other CVKD. In fact, in these two groups, 10% of the patients had three or more additional events/diagnoses different from the first one (HF, CKD, MI, stroke and/or PAD; Fig. S1).

Patients who had HF or CKD as first CVKD manifestation had an increased mortality risk vs. CVKD-free patients (HF; HR: 2.5; 95% CI: 1.8–3.4; CKD; HR: 1.8; 95% CI: 1.4-2,3). This risk was higher than that in patients who had MI (HR:1.6; 95% CI: 1.1–2.3), stroke (HR:1.5; 95% CI: 1.0-2.1) or PAD (HR: 1.2; 95% CI:0.8–1.9) as their first CVKD manifestation. Additionally, the risk of having HF or CKD as the first event was higher than that of having MI, stroke or PAD (HR: 2.1: 95% CI: 1.8–2.4).

Overall mortality was 8.3% (N = 2,214) and was more common in patients who developed HF (N = 280 patients; 25.2% mortality; median [time]: 666 days) and/or CKD (N = 451; 24.8%; median: 811 days) as the first CVKD manifestation than in those with MI (N = 143; 19.8%; 1,099 days) stroke (N = 169; 22.3%; 1,074 days) and PAD (N = 93;16.5%; 1,184 days). Mortality was lower in patients who remained without CVKD (N = 1079; 5%; 1,259 days).

HF and CKD were associated with a higher frequency of hospitalizations than classic CV complications (MI, stroke, or PAD). Days of occupational disability were low, as might be expected, since the mean patient age was ≥ 65 years (Table S2).

There were important baseline differences between patients who remained without CVKD compared with those who developed any CVKD manifestation during the follow up (Table 1). Patients without CVKD were younger (65.7 vs. 70.8 years; $p < 0.001$), with fewer comorbidities (hypertension: 49.6% vs. 86.2%, $p < 0.001$; hyperlipidemia: 46.2% vs. 83.8%, $p < 0.001$), better preserved kidney function (eGFR: 83.5 vs. 79.9 mL/min/1.73 m^2; $p < 0.001$), greater use of antidiabetic agents (85.5% vs. 81.7%; $p < 0.001$) and better glycemic control (HbA1c: 7.0% vs. 7.1%; $p = 0.002$).

Use of resources in CVKD

Total healthcare and indirect related costs for the population studied during the 7-year follow were € 527 million, of which 96.0% were for direct healthcare costs and 4.0% for indirect costs. The main cost components were hospital admissions (39%), cardiovascular and antidiabetic medication (19%), specialist visits (14%) and primary care visits (13%) (Table 2). According to the first manifestation of CVKD the cost was HF: € 50,943, CKD: € 48, 979, MI: € 47,343, stroke: € 47,070 and PAD: € 51,240. The mean cost in patients without CVKD was € 13,099 (Table 2).

Table 2
Costs per patient during the follow up period (2013–2019) according to first cardiorenal manifestation in Euros

Description	Group who stayed CVKD-free during follow up*	HF	CKD	MI	Stroke	PAD
N, (%)	21568 (81.3%)	1112 (4.2%)	1820(6.9%)	720 (2.7%)	760 (2.9%)	562 (2.1%)
Primary care visits	2533.4 (2025.7)	2439.8 (1998).9)	2529.6 (2241.8)	1941.4 (1763.4)	2473.4 (1943).6)	2531.9 (2028.1)
Laboratory requests	419.7 (278.1)	398 (273.2)	391.1 (291.9)	310 (252.8)	402.6 (251.9)	408.2 (283.9)
Radiology requests	139.3 (69.5)	119.7 (65.9)	130.6 (70.5)	181 (61.4)	149.9 (68.9)	166.6 (54.6)
Computed tomographies	380.4 (174.8)	334.1 (161.6)	385.3 (186.9)	572.5 (114)	398.7 (167.5)	364.5 (162.7)
Magnetic nuclear resonance	682.7 (171.4)	682.5 (159)	708.8 (168.3)	710.5 (196.5)	645.1 (166.8)	543.6 (165.3)
Other tests	229.4 (200.6)	218.9 (186.9)	208.4 (214.2)	144.7 (183.2)	186.7 (194.3)	228.3 (217.4)
Specialized visits	2896 (1900.2)	2939 (2158.1)	2872.1 (2073)	2156.7 (1713)	2753.4 (1922.8)	2623.8 (1863.3)
Emergency rooms visits	1372.3 (417.5)	1462.9 (386.9)	1460.2 (418.2)	1457.6 (417.6)	1366.2 (327.8)	1252.1 (348.1)
Hospitalization, days	686.1 (2201.9)	39608.5 (23081.7)	37220.6 (23210.7)	37740 (26722.1)	35749.9 (28596.7)	39875.3 (24077.4)
Cardiovascular medication	812.2 (1127.1)	715 (874.9)	768.7 (1049.6)	557.3 (787.1)	790 (1087.5)	869.3 (1001.2)
Antidiabetic medication	2200 (3232.7)	1480 (2748.5)	1751.7 (2887)	1175.9 (2207.9)	1723.3 (2632.2)	1766.3 (2984)

CVKD: cardiovascular or kidney disease (heart failure, kidney disease, myocardial infarction, stroke, peripheral artery disease); * includes angina and transient ischemic accident.

Values expressed as mean (SD: standard deviation) in euros

HF: heart failure

CKD: chronic kidney disease

MI: myocardial infarction

PAD: peripheral artery disease

Description	Group who stayed CVKD-free during follow up*	HF	CKD	MI	Stroke	PAD
Health costs	12351.5 (6299.3)	50398.5 (24064.9)	48427 (23569.9)	46947.4 (27112.1)	46639 (29748.5)	50629.9 (25131.1)
Indirect costs (disability)	747.4 (3235.7)	544.3 (2593.9)	552.2 (2879.1)	395.8 (2056.5)	431.2 (1599.2)	610.1 (2179.5)
Total cost	13098.9 (7309.5)	50942.8 (24327.7)	48979.2 (23666.3)	47343.2 (27269.9)	47070.3 (29846.3)	51240 (25183.2)
CVKD: cardiovascular or kidney disease (heart failure, kidney disease, myocardial infarction, stroke, peripheral artery disease); * includes angina and transient ischemic accident.						
Values expressed as mean (SD: standard deviation) in euros						
HF: heart failure						
CKD: chronic kidney disease						
MI: myocardial infarction						
PAD: peripheral artery disease						

The total cumulative hospital absolute cost (N = 4,974) of CVKD in T2DM patients per year of follow up (2013–2019) is showed in Fig. 3 and Table S3. The total hospital cost for the population over the 7 years of the study studied was €188.5 million, equivalent to a mean per patient of € 37,905. The total hospital cost due to HF (€ 58,258,479) and CKD (€ 51,471,084) as the first complications of T2DM was significantly higher than that for MI (€ 28,092,277), stroke (€ 32,051,591) and PAD (€18,665,338); $p < 0.001$. Moreover, a significantly higher expenditure was observed when comparing the mean cost per patient/year before the first event versus that after (Table S4) for the groups presenting HF (N = 1,112) or CKD (N = 1,820) as first manifestation: a) HF (€ 1,509 vs. € 10,063; $p < 0.001$) and b) CKD € 2.162 vs. € 9,508; $p < 0.001$).

Discussion

The results of this population-based study show that two-thirds of T2DM patients were free of CVDK on the index date. During the follow up (2013–2019), HF and CKD were the most frequent first manifestations compared with MI, stroke, and PAD, and also had higher mortality rates. In addition, both were associated with a higher incidence of rehospitalization when compared with MI, stroke, and PAD, increasing the use of healthcare and indirect resources, and increasing Spanish National Health System expenditure. These two diseases also resulted in a worse prognosis because, as described in our study, both HF and CKD are accompanied by a higher incidence of subsequent diagnoses that worsen the evolution. It should be noted that the 6% prevalence that we found corresponds approximately to the 50% of known diabetes that is described in the usual prevalence studies [4].

Winell [18], in a 1996–2012 study in Finland, found that diabetic patients have a higher incidence rate of HF, with a worse prognosis, than non-diabetic patients. Sukkar [19] studied 9,313 diabetic patients and found that 22.6% developed CKD during a mean follow up of 5.7 years. Advanced age and cardiovascular comorbidity, among other factors, were associated with an increased incidence. Our results are in line with these studies, with HF and CKD being the two most common manifestations of T2DM, and these two complications presented earlier than other CVD analyzed [20].

Albuminuria increases the cardiovascular risk, and its association with reduced glomerular filtration increases mortality [21]. Based on the results of the study, which show the importance of CKD and HF as serious and early complications in T2DM, strategies should be established to prevent and treat these patients early. Among them, the use of albuminuria and the albumin / creatinine ratio as early markers are of special importance. Koye [22] found an annual incidence rate of microalbuminuria of 7–8% in T2DM patients. Until recently, the treatments used for preventing kidney disease (renin angiotensin system inhibitors) were of very limited efficacy and there was no optimal tool to prevent HF development or its progression in any way. Our data are not surprising and show one of the therapeutic areas with unmet needs. Therefore, current data on SGLT-2 inhibitors are encouraging since they have demonstrated a capacity to both prevent and slow the progression of HF and CKD in diabetic patients and reduce hospitalization rate due to HF which is the most important cause of increase healthcare expenditure [23–31]. HF of ischemic etiology is associated with a higher risk of death compared with non-ischemic HF among patients with T2DM [32], however, this has not been confirmed in more recent data [33]. We had no access to the etiology of HF in our sample and therefore cannot analyze this aspect, which is a limitation of the study.

The cumulative hospital costs per patient of HF (€ 50,942.8) and CKD (€ 48,979.2) were higher than those for MI (€ 47,343.2) and stroke (€ 47,070.3) and similar to those for PAD (€ 51,240.0), compared with € 13,098.9 in patients without CVKD. Rehospitalization is common in this type of patients (HF and CKD), and results in high health resource use and costs. The most striking cost components were hospital admissions (39%) and medication (19%). A review by Einarson [34] described high comorbidity in T2DM patients with a mean annual cost per patient according to the absence or presence of CVD of $3,418 and $9,705, respectively. Wan [35], in a large cohort of patients (1.6 million patient-years) and with an 8.5 year follow up, found that the effect of CVD, cerebrovascular accidents, CKD and the combination of these factors has an additive impact to health costs, with special emphasis on CKD on T2DM patients. A Spanish study also highlighted a higher cost in patients with CKD + HF (€ 14,868) compared with those with HF (€ 9,365). The comorbidity associated with HF was high [14]. Goncalves [36] described the associated cost of HF and CKD attributable to diabetes in 2010–2016 in Brazil, which was $ 180 million per year for HF, with an upward trend. The presence of CKD increased the cost ($ 475 million). The authors emphasized that the economic burden of CKD will gradually increase in coming years, with serious implications for the financial sustainability of the Brazilian public health system. McQueen [37] found that costs increase as kidney function decreases in T2DM patients (phase 1: $1,732 vs. phase 5: $6,949). Other authors highlighted the effect of prevention and self-care in the early stages of HF, reviewing the medical record and symptoms with the aim of reducing the economic burden of HF + T2DM

on hospital admissions [38]. All these studies conclude that the cost of hospitalization and the presence of HF and/or CKD increases health costs in T2DM patients.

The study had some limitations: (a) the main limitation was the bias regarding the time of evolution of T2DM, as a single fixed index date was used for patient selection; (b) the inherent limitations of retrospective, observational studies using databases, such as disease underreporting or possible variations in the recording of information by health professionals; the database was constructed in 2012, and therefore, for some patients it was not possible to determine with certainty whether patients were CVKD-free on or before the index date, even though the obtention of records from both primary and hospital care may have minimized this bias; c) the possible inaccuracy of disease coding in the diagnosis of CVKD and other comorbidities; d) the absence of specific variables, such as socioeconomic level, adherence and variations in the dose of the medication administered, comorbidities, healthy lifestyle, variations in blood pressure or cholesterol, among other unmeasured factors which could have influenced the results; e) only hospitalizations due to CVKD were considered, so there could be an underestimate of less serious conditions; f) the lack of information from the private healthcare sector, which although much less relevant in Spain, could have had a certain influence on the results.

Conclusions

In T2DM patients, HF and CKD were the first and most common manifestations during a 7-year follow up, with a significantly higher impact on mortality and rehospitalization rates. This resulted in increased healthcare resource use and related costs for HF and CKD, respectively, in the Spanish National Health System.

Abbreviations

Abbreviation	Description
ATC	Anatomical Therapeutic Chemical Classification System
CKD	Chronic kidney disease
CVD	Cardiovascular disease
CVKD	Cardiovascular or kidney disease
HF	Heart failure
SGLT-2	Sodium-glucose cotransporter 2
MI	Myocardial infarction
NSI	National Statistical Institute
PAD	Peripheral artery disease
T2DM	Type 2 diabetes mellitus

Declarations

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CONFLICT OF INTEREST

ASM and ASN are independent consultants in relation to the development of this manuscript.

BP, MS and JB are employees of AstraZeneca. AH has carried out paid activities for AstraZeneca Laboratories as a speaker at national meetings. MABL have no conflict of interest for the subject of the work. I have received honoraria for lectures, consultancies and collaborations for research and attendance at conferences from Almirall, AstraZeneca, Boehringer, Esteve, FAES, Ferrer, Fresenius, Janssen, Lilly, MSD, Nestlé, NovoNordisk, Novartis, Nutricia, Rovi, Sanofi. NM, conferences and advisory boards for AstraZeneca. RAA reports personal fees from AstraZeneca, during the conduct of the study; personal fees from AstraZeneca, personal fees from Vifor-Fresenius, personal fees from Otsuka, personal fees from Boehringer IngelHeim, personal fees from Fresenius Medical Care, outside the submitted work.

DATA AVAILABILITY

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

CONSENT TO PUBLICATION

Not applicable.

ETHICAL ASPECTS

The study was classified and approved by local regulatory authorities and a Research Ethics Committee (ERC: Consorci Sanitari de Terrassa). In the participating centers, the informed consent of the patients is obtained. The study methods were carried out in accordance with the Declaration of Helsinki.

The study authors declare that they have no competing conflicts of interest for the remaining authors.

AUTHOR CONTRIBUTIONS

The conception and design of the manuscript were made by all authors. The collection of data and statistical analysis by ASN, and the interpretation of the data, drafting, revision and approval of the manuscript submitted, by all authors.

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Figures

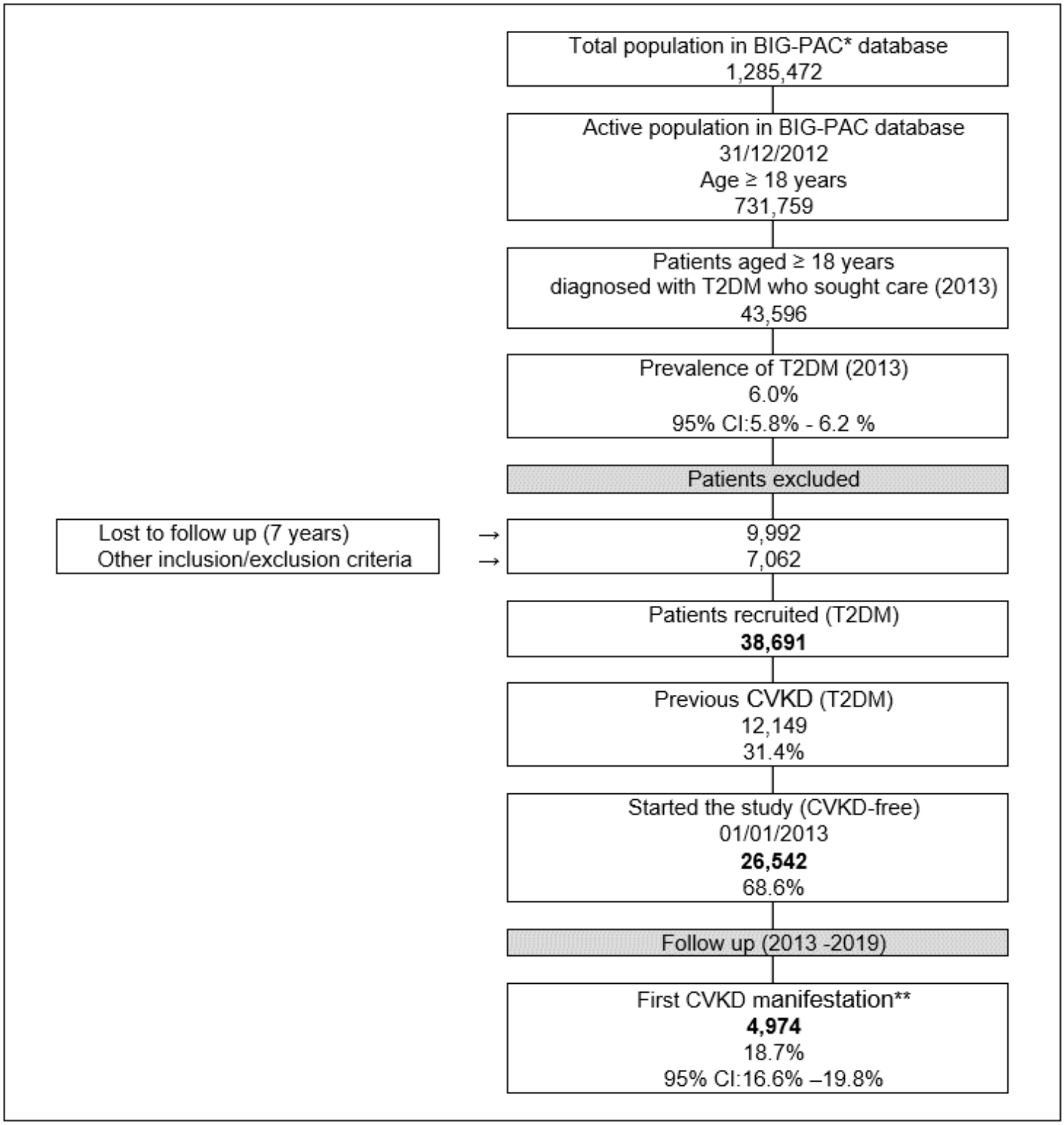

Figure 1

Study flow chart (2013 –2019). CVKD: cardiovascular or kidney disease (heart failure, kidney disease, myocardial infarction, stroke, peripheral artery disease). *Database, ** excludes angina and transient ischemic accident. DM: type 2 diabetes mellitus CVD: cardiovascular disease CI: confidence interval

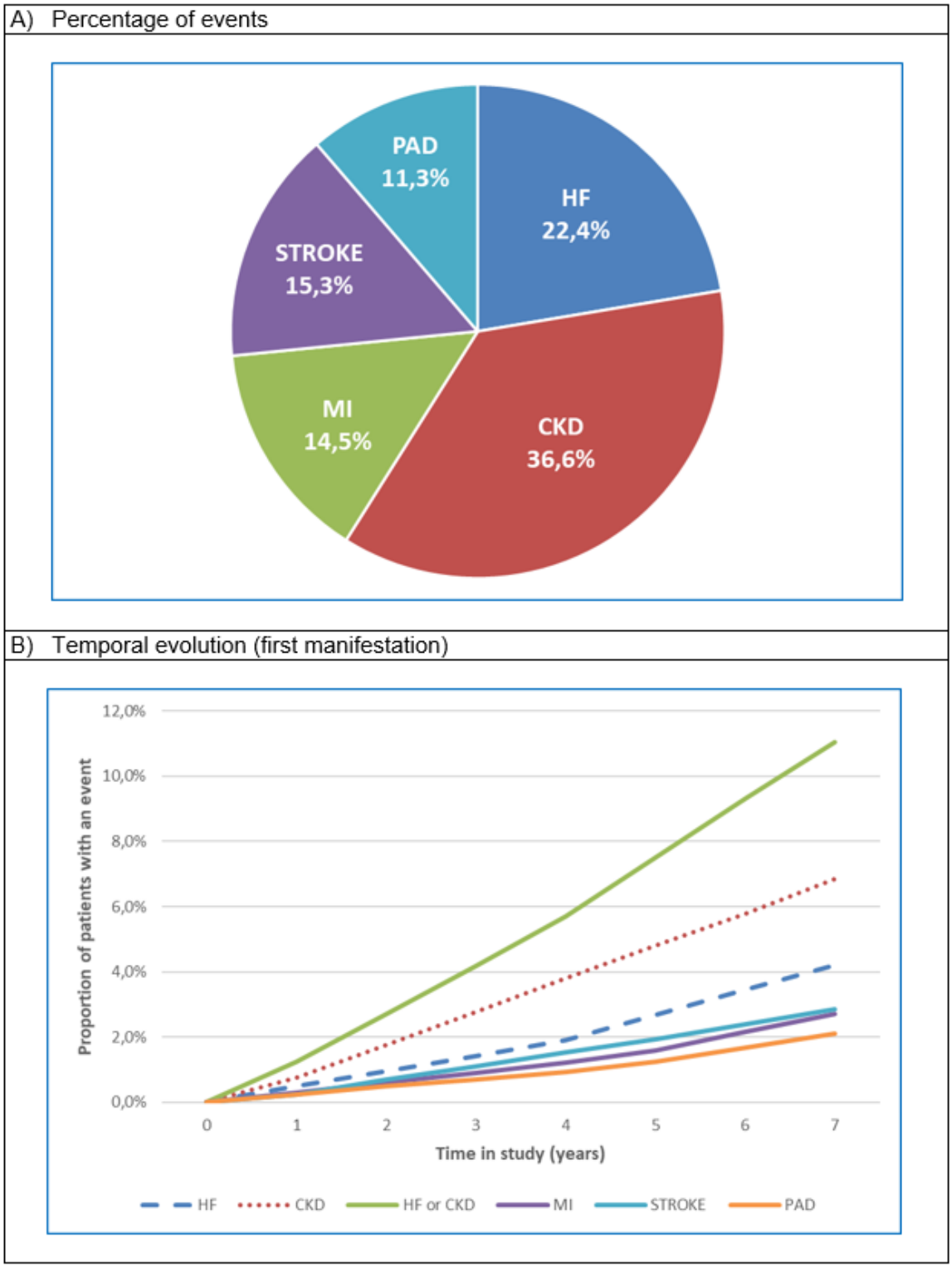

Figure 2

First cardiovascular/renal manifestation during follow-up in type 2 diabetes patients (2013 –2019). A) Percentage of events B) Temporal evolution (first manifestation) N=4,974 HF: heart failure CKD: chronic kidney disease MI: myocardial infarction PAD: peripheral artery disease

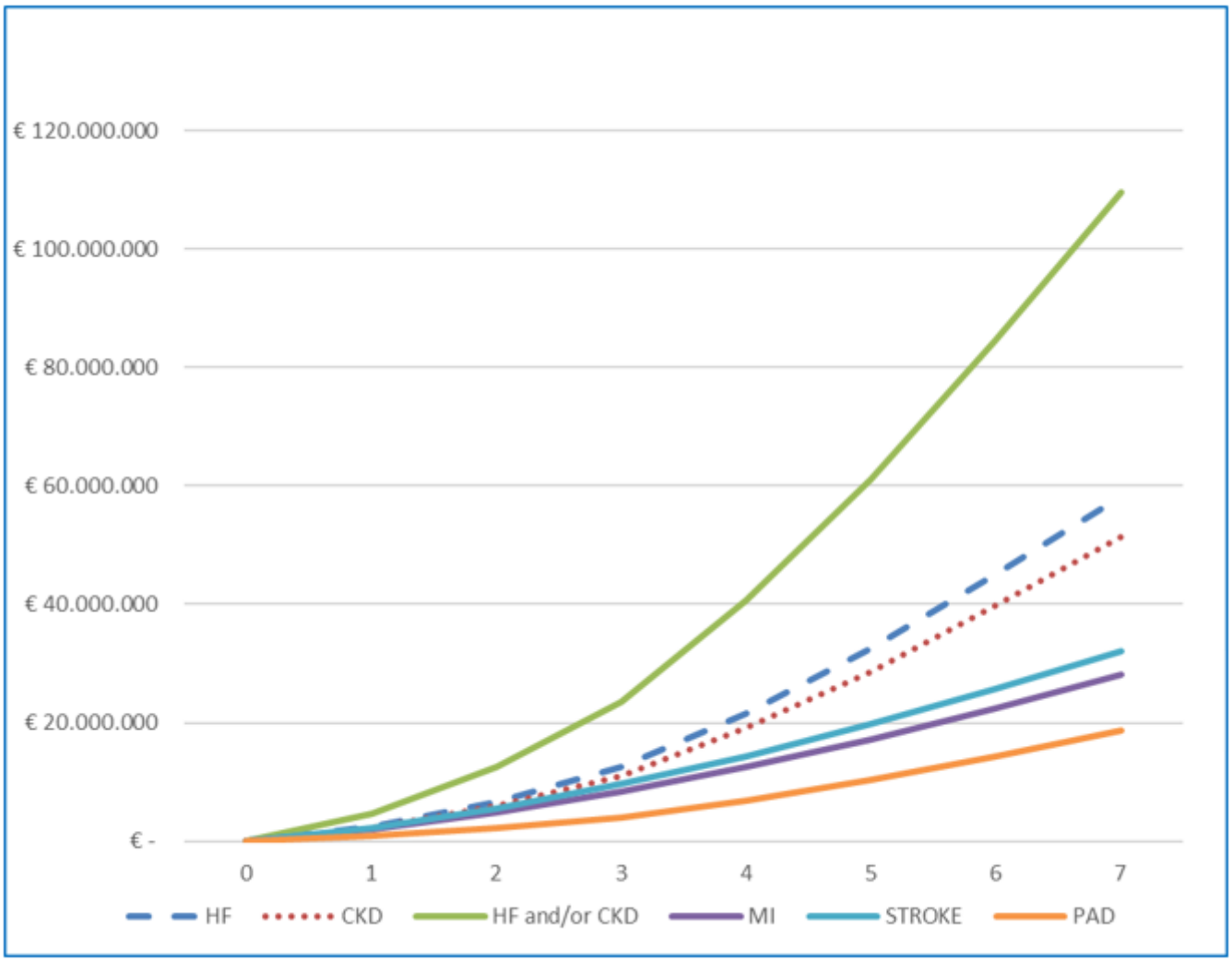

Figure 3

Cumulative total absolute hospital cost of cardiovascular/renal disease per follow-up year (2013 – 2019). N=4,974 HF: heart failure CKD: chronic kidney disease MI: myocardial infarction PAD: peripheral artery disease

Supplementary Files

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