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Original research

Evaluation of clinical and antidiabetic treatment characteristics of different sub-groups of patients with type 2 diabetes: Data from a Mediterranean population database

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ABSTRACT

Aims: To describe the characteristics and antidiabetic treatment among type 2 diabetes patients according to the clinical conditions prioritized in the Spanish 2020 RedGDPS (Primary Care Diabetes Study Groups Network) therapeutic algorithm: obesity, older than 75 years, chronic kidney disease, cardiovascular disease, and heart failure.
Methods: Retrospective, cross-sectional study. Clinical characteristics, the use of antidiabetic drugs and the KDIGO renal risk categories at 31.12.2016 were retrieved from the SIDIAP (Information System for Research in Primary Care) database (Catalonia, Spain).
Results: From a total of 373,185 type 2 diabetes patients, 37% were older than 75 years, 45% obese, 33% had chronic kidney disease, 23.2% cardiovascular disease and 6.9% heart failure. Insulin was more frequently prescribed in chronic kidney disease, cardiovascular disease and heart failure whereas Sodium-Glucose cotransporter 2 inhibitors and Glucagon Like Peptide 1 receptor agonists were scarcely prescribed (2.6% and 1.4%, respectively). Among patients with severe renal failure, contraindicated drugs like metformin (16%) and sulfonylureas (6.1%) were still in use. The 2012 KDIGO renal risk categories distribution was: Low: 60.9%, Moderate: 21.6%, High: 9.8% and Very high: 7.7%.
Conclusions: Almost 80% of our T2DM patients meet one of the five clinical conditions that should be considered for treatment individualization. Importantly, a relevant number of patients with severe renal failure were found to use contraindicated drugs.

1. Introduction

The prevalence of type 2 diabetes mellitus (T2DM) is increasing rapidly in most parts of the world, which is likely to increase the incidence of complications associated with the disease [1]. This situation calls for improved treatment of hyperglycaemia and other risk factors associated with T2DM in order to lower the risk of both micro- and macrovascular complications and their related economic costs, as proposed by all international and national consensus documents and guidelines [2–6].

Despite scientific evidence from a number of cardiovascular outcome trials (CVOTs) [7–9] and the guideline recommendations [2–6], adequate management of these patients remains beset with challenges. Several observational studies performed around the world report a gap between guideline recommendations and daily clinical practice [10–19].

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The majority of guidelines and algorithms for treatment of T2DM, including the recent PCDE (Primary Care Diabetes Europe) 2020 position statement [4] and the 2020 Spanish RedGDPS (Primary Care Diabetes Study Groups Network) algorithm [5] call for the individualization of treatment. Individualized therapy is an effort to achieve optimal health outcomes for a patient by selecting drugs known to be beneficial in persons with specific attributes or disease characteristics. According to the Spanish RedGDPS algorithm, five main clinical conditions could affect the choice of therapy: age older than 75 years/frailty, obesity, established CVD, chronic kidney disease (CKD) and heart failure (HF) [5]. There is a need to know how many, and what the characteristics of these patients are, in order to better understand the prescription patterns in primary care and to find opportunities for improvement.

The implementation of universal electronic medical records systems in Catalonia (Spain) completed in 2006 allowed us to access the anonymized data of the entire diabetic population registered in the public healthcare system for our study [20]. Since 2012, our group has published several reports on the general aspects of the management and treatment of patients with T2DM in Catalonia (Spain) [19,21–24]. We undertook this study to specifically describe the differences in the clinical characteristics and antidiabetic treatment patterns among T2DM patients with five clinical conditions: obesity, older than 75 years, established cardiovascular disease (CVD), Chronic Kidney Disease (CKD) and heart failure (HF) proposed by the 2020 Spanish RedGDPS algorithm [5]. Secondary aims were to know the use of antidiabetic drugs according to renal function and to assess the CKD prognosis using the risk categories of the 2012 KDIGO guidelines [25].

2. Methods

This was a cross-sectional study using the SIDIAP database (Information system for the development of research in Primary Care) (www.sidiap.org) [20]. SIDIAP contains anonymized longitudinal patient information obtained from the electronic clinical records of the patients attended by 286 primary care teams of the Catalan Health Institute, which covered 74% of the total population in Catalonia in 2016 [21]. The database includes sociodemographic characteristics, morbidity (International Classification of Diseases; ICD-10), clinical variables, specialist referrals, laboratory tests and treatments (prescriptions and pharmacy invoicing) [20,21].

Catalonia, a Mediterranean region in north-eastern Spain, has a public health system in which every citizen is registered with a general practitioner and a nurse in a publicly funded primary care centre. The vast majority of T2DM patients are controlled in primary care and only a few, those on multiple insulin doses, are additionally visited in specialized centres. Antidiabetic medications are free for retired, severely ill or disabled people and at a very small cost for the rest of the patients. However, several administrative restrictions (for instance, the need of approval of the indication of a Glucagon Like Peptide-1 receptor agonist (GLP-1ra) by a pharmaceutical inspector and negative economic incentives for limiting the use of agents different from metformin, sulfonylureas or insulin) were in force during the study period.

The study population consisted of patients aged 18 years or older with a diagnosis of T2DM (ICD10 codes E11, E11.0-E11.9, E14, and E14.0-E14.9) on December 31st, 2016. We excluded patients with a diagnosis of type 1 diabetes, gestational diabetes mellitus, and any other type of diabetes.

The following data were collected from each patient: age, sex, time since diagnosis, Body Mass Index (BMI), blood pressure, lipid profile, estimated glomerular filtration rate (eGFR) using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) Equation, the Urine Albumin to Creatinine Ratio (UACR) and the last HbA1c value of the preceding 24 months (between January 1, 2015, and December 31, 2016).

ICD-10 codes and data on other cardiovascular risk factors and chronic complications and comorbidities were also available and have been extensively described elsewhere [21]. Data on glucose-lowering medication were obtained from the CatSalut drug pharmacy invoices database using the ATC codes (Anatomical Therapeutic Chemical classification system) [26].

Clinical characteristics and the use of antidiabetic drugs for each of five sub-groups of patients in the 2020 Spanish RedGDPS algorithm [5] were evaluated: obesity (BMI$\geq$30 kg/m^2), age older than 75, established CVD (defined as myocardial infarction, ischemic heart disease, cerebrovascular disease, or peripheral arterial disease), CKD (defined as eGFR < 60 ml/min/1.73 m^2 and/or UACR $\geq$ 30 mg/g) and HF. We additionaly collected data on the proportion of patients with eGFR 30–59 ml/min/1.73 m^2 and/or UACR > 30 mg/g, as well as the proportion of patients with eGFR < 30 ml/min/1.73 m^2 were calculated. Glycemic control for each clinical condition was stratified in four categories by HbA1c intervals (<6.5%, 6.5–6.9%, 7–8.9% and $\geq$9%). Antidiabetic treatment according to renal function categories was specifically analyzed to identify the use of contraindicated drugs in patients with chronic renal failure (CRF), defined as eGFR < 60 ml/min/1.73 m^2. Additionally, patients with available registers of both UACR and eGFR were classified according to the KDIGO 2012 CKD prognosis risk categories (low, mild, high and very high) for 5 renal events (all-cause mortality, cardiovascular mortality, renal failure treated with dialysis or transplantation, acute renal failure and progression of kidney disease) [25].

The study was approved by the Ethics Committee of the Primary Health Care University Research Institute (IDIAP) Jordi Gol (approval number: P17/015).

2.1. Statistical methods

The descriptive analysis consisted of summary statistics, the mean and standard deviation for continuous variables, and percentages for categorical variables. The statistical analyses were performed using R3.6.1 (https://www.r-project.org/).

3. Results

By December 31st, 2016, the SIDIAP database contained records from 7,251,277 people; of them, 373,185 (5.1%) met the inclusion criteria and were included in the analyses. T2DM patients had a mean age of 70 years, and men were slightly predominant (55%) (Table 1). 296,309 (79.4%) had at least one of these five baseline conditions: 37.1% were older than 75 years, 44.9% were obese, 33% had CKD (29.4% had eGFR 30–59 ml/min/1.73m^2 or UACR > 30 mg/g and 3.6% had eGFR < 30 ml/min/1.73 m^2), 23.2% established CVD and 6.9% HF (Table 1 and Fig. 1). With regards to conditions with demonstrated outcomes benefit in cardiovascular safety trials (CKD, CVD and HF), 45% of patients had CVD or CKD, 34.9% had CKD or HF and 55% had at least one of them. The prevalences of the five conditions in the RedGDPS algorithm are shown in Fig. 1.

The degree of glycemic control for each clinical condition, stratified by HbA1c intervals is shown in Table 1. Mean HbA1c was 7.1%, being 7.0% in older than 75 years and 7.3% in obese patients (Table 1).

Clinical characteristics of the five groups of patients (Table 1) differed significantly between groups: obese patients were younger, with a shorter diabetes duration, and had the highest mean HbA_{1c},

Table 1
Clinical characteristics and antidiabetic treatment for the five studied conditions.

Variables*	All Patients**	Obesity (IMC > 30 kg/m^2)	Age ≥ 75 years	Chronic kidney disease	Cardiovascular disease	Heart failure
N (%)	*N* = 373,185 (100%)	*N* = 144,592 (44.9%)	*N* = 138,374 (37.1%)	*N* = 122,996 (33.0%)	*N* = 86,534 (23.2%)	*N* = 25,925 (6.9%)
Mean age, years (SD)	70.3 (12.1)	68.1 (11.7)	82.6 (11.2)	74.4 (10.9)	74.8 (10.5)	78.9 (9.8)
Gender (female) %	45.1	49.1	55.6	45.5	34.3	48.1
Mean T2DM duration, years (SD)	8.7 (6.0)	8.8 (6.0)	11.2 (6.8)	10.9 (6.6)	10.9 (6.7)	11.2 (6.9)
Non-smoker, %	54.8	55.0	69.2	55.0	46.3	60.4
Current smoker, %	14.3	12.8	4.8	12.4	12.8	6.8
Former smoker, %	30.9	32.2	26.0	32.6	40.3	32.9
Mean Systolic blood pressure, mmHg (SD) (*N* = 353,331)	133.0 (13.6)	133.8 (13.3)	133.7 (14.4)	134.3 (14.4)	132.6 (14.6)	130.8 (15.8)
Mean Diastolic blood pressure, mmHg (SD) (*N* = 353,331)	75.0 (9.7)	76.5 (9.5)	71.4 (9.6)	73.5 (10.1)	72.1 (9.9)	70.4 (10.5)
Mean BMI, kg/m^2 (SD) (*N* = 321,739)	30.1 (5.2)	34.5 (4.2)	28.9 (4.7)	30.3 (5.3)	29.4 (4.9)	30.8 (5.8)
Comorbidities						
Obesity (BMI > 30 kg/m^2), % (*N* = 321,739)	44.9	100	36.1	45.0	40.3	51.1
Hypertension, %	71.9	77.7	84.4	85.9	80.9	86.6
Hyperlipidaemia, %	61.1	61.8	60.4	63.4	64.9	61.4
Cardiovascular disease, %	23.2	21	32.3	32.5	100	49.9
Heart Failure, %	6.9	8.2	13.0	13.7	14.9	100
Retinopathy, %	13.0	13.2	15.8	18.8	18.6	20.6
Neuropathy, %	10.4	12.5	10.0	12.1	12.5	12.8
Chronic Renal Failure (eGFR < 60 ml/min/1.73 m^2), % (*N* = 336,198)	28.0	26.5	50.3	68.1	42.4	63.3
Albuminuria (UACR > 30 mg/dl), %	14.2	15.5	16.1	57.1	19.8	22.3
Laboratory results						
Mean HbA1c, % (SD) (*N* = 330,014)	7.1 (1.3)	7.3 (1.3)	7.0 (1.1)	7.3 (1.3)	7.2 (1.2)	7.2 (1.3)
HbA1c < 6.5%, %	34.7	31.0	37.7	30.1	28.7	33.8
HbA1c 6.5–6.9%, %	20.7	20.2	21.5	19.1	17.8	19.2
HbA1c 7–8.9%, %	35.5	39.4	35.5	40.3	35.2	38.8
HbA1c ≥ 9%, %	9.0	9.3	5.3	9.7	7.5	8.5
Mean total cholesterol, mg/dL (SD) (*N* = 335,522)	182.0 (39.9)	186.0 (36.1)	178.7 (35.4)	179.5 (36.9)	166.5 (35.6)	169.5 (36.5)
Mean LDL-c, mg/dL (SD) (*N* = 315,578)	103.0 (32.5)	104.9 (30.2)	100.6 (29.5)	99.3 (30.0)	90.3 (28.6)	93.1 (29.3)
Mean HDL-c, mg/dL (SD) (*N* = 315,578)	48.8 (12.9)	47.6 (11.7)	50.4 (12.7)	47.7 (12.5)	45.9 (11.9)	46.2 (12.1)
Mean Triglycerides, mg/dL (SD) (*N* = 328,291))	159.0 (107.0)	174.6 (104.3)	142.7 (69.3)	169.5 (106.6)	156.8 (92.1)	157.3 (86.5)
Mean eGFR, ml/min/1.73 m^2 (SD) (*N* = 336,198)	76.8 (21.7)	78.2 (21.0)	63.7 (18.2)	62.5 (21.1)	68.9 (21.2)	58.7 (21.4)
Antidiabetic treatment						
Only lifestyle modification, *N* (%)	18.4	15.3	19.4	12.9	14.1	16.7
Non-Insulin antidiabetic drug Monotherapy, %	37.1	37.0	37.9	32.6	33.0	30.2
Non-Insulin antidiabetic drug Combination, %	23.2	24.1	19.7	23.6	21.4	15.4
Insulin monotherapy, %	6.0	5.1	8.5	9.1	10.4	16.7
Insulin + Non-Insulin antidiabetic drug, %	15.3	18.6	14.5	21.8	21.1	21.0
Metformin, %	66.3	70.1	58.4	64.2	63.9	48.6
Sulfonylureas, %	19.0	19.8	17.8	19.9	18.0	14.3
Repaglinide, %	4.9	4.9	6.7	7.7	6.5	8.1
DPP4i, %	17.0	17.8	16.1	20.7	18.5	17.1
SGLT2i, %	2.6	4.0	0.8	2.5	2.6	1.8
GLP1ra, %	1.4	2.9	0.3	1.6	1.4	1.3
Pioglitazone, %	0.8	1.1	0.6	0.9	0.7	1.8
Insulin, %	21.3	23.7	23.0	30.9	31.5	37.7

HbA1c: Glycated haemoglobin; LDL-c Low-density lipoprotein:; BMI: body mass index; SD: standard deviation; eGFR: estimated Glomerular Filtration Rate; UACR: Urinary albumin to creatinine ratio; DPP4i: Dipeptidyl Peptidase 4 inhibitors; SGLT2i: Sodium-Glucose cotransporter 2 inhibitors; GLP1ra Glucagon Like Peptide 1 receptor agonists.

* All percentages have been calculated on the total population (*N* = 373,185), except for Blood Pressure, BMI, eGFR, HbA1c, and lipids, where only patients with available data were considered. The N for each of them is included in the first box of the row of the variable.

** 76,884 patients (20.6%; 49,922 men and 26,962 women) from the entire population did not have any of the five conditions studied.

but fewer complications. Conversely, people older than 75 had better glycemic control, but a longer diabetes duration and more frequent comorbidities. Patients aged > 75 years and those with CVD or HF shared more clinical characteristics. For instance, CRF was present in 50.3%, 42.4% and 63.3%, respectively. CKD prevalence and eGFR categories for the five studied conditions are shown in (Table 2).

3.1. Glucose-lowering treatment

Data regarding the proportions of different glucose-lowering treatments in each of the five clinical conditions are shown in Table 1. Globally, metformin was the most frequently used agent (66.3%), followed by insulin (21.3%), sulfonylureas (19%) and dipeptidyl peptidase-inhibitors (DPP4-i) (17%). Patterns of pre-

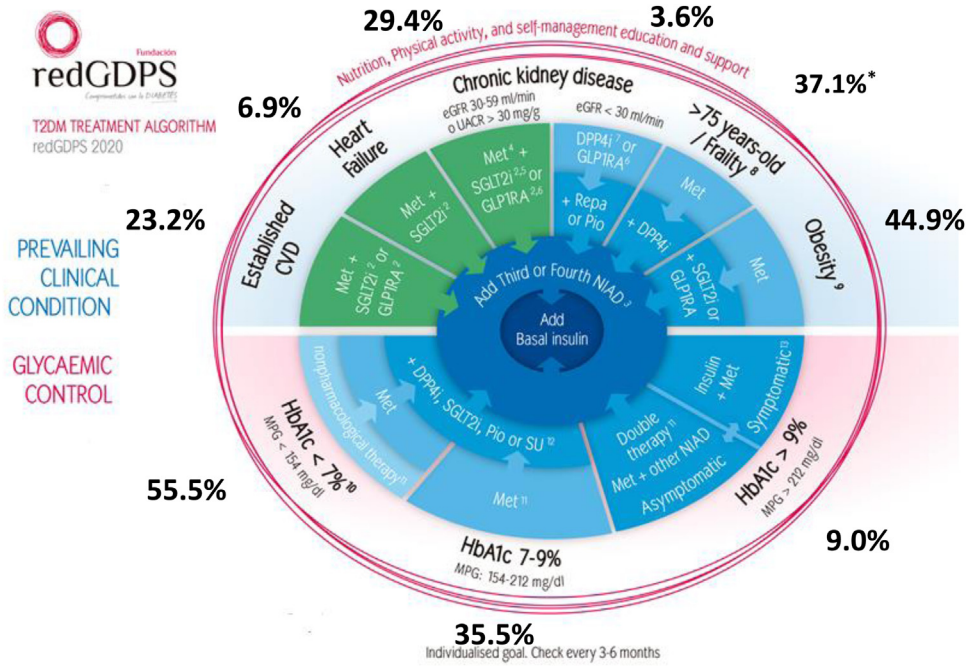

Fig. 1. Prevalence of the clinical conditions in the 2020 RedGDPS (Primary Care Diabetes Study Groups Network) T2D treatment algorithm (percentage of patients). *Data shown does not include frail patients.

Table 2
Chronic Kidney Disease prevalence and Estimated Glomerular Filtration Rate (eGFR) categories for the five studied conditions.

Chronic Kidney Disease prevalence (total population is included)						
Chronic kidney disease categories	Total population *N* = 373,185 (100%)	Obesity *N* = 144,592 (44.9%)	Age ≥ 75 years N = 138,374 (37.1%)	CKD *N* = 122,996 (33.0%)	CVD *N* = 86,534 (23.2%)	HF *N* = 25,925 (6.9%)
Chronic Kidney Disease (eGFR < 60 ml/min/1.73 m^2 or UACR > 30 mg/dl)	122,996 (33.0%)	49,254 (34.1%)	71,848 (51.9%)	122,996 (100%)	41,310 (47.7%)	16,861 (65.0%)
UACR > 30 mg/dl with normal eGFR (>60 ml/min/1.73 m^2)	28,756 (7.7%)	14,231 (9.8%)	8,019 (5.8%)	39,236 (31.9%)	7,747 (8.9%)	10,759 (6.5%)
eGFR 30–59 ml/min/1.73 m^2	80,978 (21.7%)	31,013 (21.4%)	54,162 (39.1%)	72,567 (59.0%)	27,626 (31.9%)	11,165 (43.1%)
eGFR < 30 ml/min/1.73 m^2	13,262 (3.6%)	4,010 (2.8%)	9,667 (7.0%)	11,193 (9.1%)	5,937 (6.9%)	4,001 (15.4%)
eGFR stages (mL/min/1.73 m^2) (only patients with eGFR available are included)						
eGFR categories	Total population *N* = 336,198	Obesity *N* = 135,855	Age ≥ 75 years *N* = 127,010	CKD *N* = 122,996	CVD *N* = 79,158	HF *N* = 23,959
1–2 (≥60 mL/min/1.73 m^2)	241,958 (72.0%)	99,832 (73.5%)	63,181 (49.7%)	39,236 (31.9%)	45,595 (57.6%)	8,793 (36.7%)
3a (45–59 mL/min/1.73 m^2)	51,940 (15.4%)	20,049 (14.8%)	32,645 (25.7%)	46,984 (38.2%)	16,386 (20.7%)	5,535 (23.1%)
3b (30–44 mL/min/1.73 m^2)	29,038 (8.6%)	10,964 (8.1%)	21,517 (16.9%)	25,583 (20.8%)	11,240 (14.2%)	5,630 (23.5%)
4 (15–29 mL/min/1.73 m^2)	11,019 (3.3%)	4,261 (3.1%)	8,430 (6.6%)	9,594 (7.8%)	4,908 (6.2%)	3,354 (14.0%)
5 (<15 mL/min/1.73 m^2)	2,243 (0.7%)	749 (0.6%)	1,237 (1.0%)	1,599 (1.3%)	1,029 (1.3%)	647 (2.7%)

eGFR: estimated Glomerular Filtration Rate; CKD: chronic kidney disease; CVD: cardiovascular disease; HF: heart failure.

scription were quite similar among the five groups except in CKD, CVD and HF patients in which insulin was more frequently prescribed (30.9% and 31.5% and 37.7%, respectively). Sodium-Glucose cotransporter 2 inhibitors (SGLT2i) and GLP1ra were scarcely prescribed (2.6% and 1.4%, respectively), even in patients with obesity (4.0% and 2.9%, respectively), CVD (2.6% and 1.4%, respectively), CKD (2.5% and 1.6%, respectively) or HF (1.8% and 1.3%, respectively).

Data regarding pharmacological treatment according to baseline renal function are shown in Fig. 2. As eGFR decreased there was a progressive reduction in the use of metformin and sulfonylureas but an increase in insulin prescription. Among 13,262 patients (4%) with severe CRF (eGFR < 30 mL/min), insulin was the most commonly used drug (50%), followed by DPP-4i (23%), metformin (16%), repaglinide (16%) and sulfonylureas (6.1%). It should be noted that some patients were treated with drugs contraindicated in stages 4 (eGFR 15–29 ml/min) and 5 (eGFR < 15 ml/min). For instance metformin (18% in stage 4 and 7% in stage 5) and sulfonylureas (7% and 2%, respectively). On the other hand, 48.6% of patients in stage 4 were treated with insulin and a greater percentage (58.1%) in stage 5.

Finally, the distribution of patients according to the KDIGO 2012 CKD prognosis categories is shown in Table 3. The risk categories' distribution among the 236,830 patients with available values of both UACR and eGFR was: Low: 60.9%; Mild: 21.6%, High: 9.8% and Very high: 7.7%.

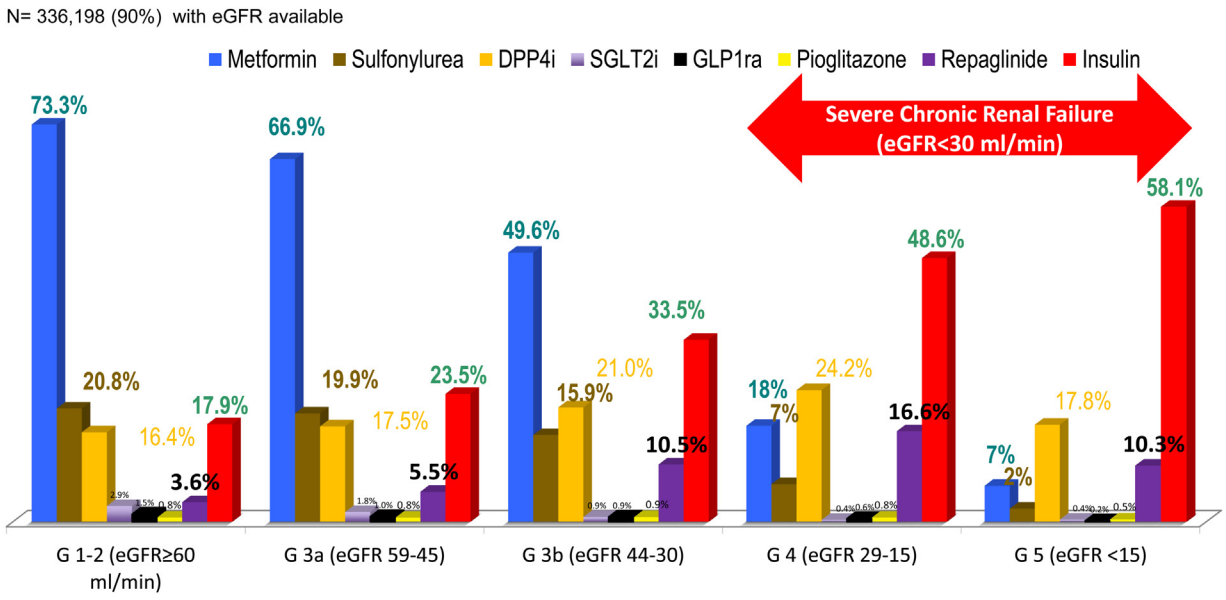

Fig. 2. Antidiabetic drugs prescription according to the estimated Glomerular Filtration Rate (eGFR) (percentage of patients). IDPP4, inhibitors dipeptidyl peptidase-4; SGLT-2i, inhibitors sodium/glucose cotransporter 2; GLP1-RA, Glucagon-like peptide-1 Receptor Agonist.

Table 3
Prognosis of Chronic Kidney Disease by Estimated Glomerular Filtration Rate and Albuminuria categories according to KDIGO 2012* (24). Green, low risk (if no other markers of kidney disease, no CKD) (60.9%); yellow, moderately increased risk (21.6%); orange, high risk (9.7%); red, very high risk (7.7%). *N* = 236,830 (63.5%) patients with information on eGFR and albuminuria; data are presented as absolute numbers (percent of 236,830).

	G1 - G2 eGFR ≥60 ml/min/1.73m²	G3a eGFR 45-59 ml/min/1.73m²	G3b eGFR 30-44 ml/min/1.73m²	G4 eGFR 15-29 ml/min/1.73m²	G5 eGFR <15 ml/min/1.73m²	
A1 Normoalbuminuria (UACR <30 mg/g)	144238 (60.9%)	25443 (10.7%)	11320 (4.78%)	2920 (1.23%)	254 (0.11%)	*77.8%*
A2 Microalbuminuria (UACR 30-300 mg/g)	25693 (10.9%)	8274 (3.49%)	6007 (2.54%)	2731 (1.15%)	350 (0.15%)	*18.2%*
A3 Macroalbuminuria (UACR >300 mg/g)	3556 (1.50%)	1793 (0.76%)	1988 (0.84%)	1649 (0.70%)	614 (0.26%)	*4.1%*
	73.2%	*15.0%*	*8.2%*	*3.1%*	*0.5%*	*100%*

CKD: Chronic Kidney Disease; eGFR: estimated Glomerular Filtration Rate; UACR: Urinary Albumin-to-Creatinine Rate
*Adjusted relative risk for 5 events (overall mortality, cardiovascular mortality, renal failure treated with dialysis or transplantation, acute renal failure and progression of kidney disease).

4. Discussion

In this real-world observational study, 80% of patients with T2DM meet criteria for some of the five conditions (obesity, older than 75 years, chronic kidney disease, cardiovascular diseases, or heart failure) of the 2020 Spanish RedGDPS algorithm [5]. Besides the differences in clinical characteristics of each group of patients, the results from our study show that the use of antidiabetic drugs with cardio-renal benefits was far from the current therapeutic recommendations and a relevant number of T2DM patients with CRF were treated with contraindicated antidiabetic drugs.

Looking at the treatment of each of the five analyzed conditions, starting with patients with obesity, nearly half of the patients in our study showed a large gap between guidelines and prescriptions. In these patients, SLGT2i and GLP1ra are preferable as a second-line drug after metformin failure due to the effect on weight loss [2–5]. Looking at our results, there was slightly greater use of SLGT2i and GLP1ra in comparison to the whole population, but far from its recommended use. The reason for this could be the lack of confidence in the use of these relatively new drugs by primary care professionals but also due to the health authorities recommendation against its use because of their high cost during the study period [6]. Moreover, there were some administrative restrictions for the prescription of GLP1ra and negative incentivisation for several groups of drugs: DPP4i, GLP1ra and SGLT2i. The prescription of sulfonylureas is considered the best option as a second line therapy in our institution guidelines [6].

About 37.1% of patients in our study were older than 75 years. We observed better glycemic control for this population, with nearly 38% of them having an HbA1c < 6.5%, which is in concordance with previously reported observational studies [21,27,28]. Half of them had CRF, which could explain the frequent use of insulin (23%) and repaglinide (6.7%), and some degree of overtreatment has to be suspected. The possibility of de-intensification or

simplification of the therapeutic plan needs to be considered. Furthermore, sulfonylureas were also frequently prescribed (17.8%), likely due to their initiation years before some other NIADs were available. Nowadays, the use of insulin and sulfonylureas should be used with caution in patients with frailty and/or older than 75 years due to the frequent and dangerous side effect of hypoglycemia [29,30], These patients would be good candidates for reducing overall medication levels deprescribing [2–5,31]. A recent meta-analysis confirms that deprescribing is safe [32], but is uncommon in clinical practice, even in individuals with limited life expectancy [33]. In recent years, there has been a progressive replacement of sulfonylureas with DPP4i [10–15,34], especially in older adults. Results from the recently published observational study from five European countries, including Spain (data provided by the SIDIAP database), showed that after initial therapy failure, most patients in the Netherlands, Spain, and the United Kingdom switched to a combination of metformin and sulfonylurea, while sulfonylureas were outnumbered by repaglinide in Italy and by DPP4i in France [11]. In our study, only 16.1% of older adults received a DPP4i. Increased use of DPP4i as second line agents is recommended in the RedGDPS Algorithm [5] and elsewhere [2–4]. In a multinational study comparing antidiabetic treatment patterns in 37 countries, combinations of metformin with either a DPP-4i (25.1%) or a sulfonylurea (21.3%) were the most commonly prescribed second-line therapies [16]. Another study from Spain reported that add-ons to metformin were mainly DPP-4is (79.9%), followed by insulin (6.6%) and sulfonylureas (6.3%) [15].

CKD is a frequent complication of diabetes that occurs in 20% to 40% of all patients [35]. In our study, 33% of patients had CKD, 23% CRF and 14.2% albuminuria. These results were similar to another study in primary care (CKD: 34.6%; CRF: 25.2%; albuminuria: 16.1%) [36] but higher than observed in the PERCEDIME study (CKD: 27.9%; CRF: 18%; albuminuria: 15.4%) in which a prospective stratified sample of the Spanish T2DM population was thoroughly studied [37]. According to the KDIGO categories, in our study, the renal risk was moderate to very high in 40% of patients.

The most frequently prescribed antidiabetic drugs in patients with CKD were quite similar to those prescribed to patients with CVD or HF, with 30.9% of them on insulin and SGLT2i and GLP1ra (2.5 and 1.6%, respectively) being less frequently used. A recent meta-analysis shows that SGLT2i reduce the combination of kidney events: dialysis, kidney transplant and/or death from kidney causes [8]. Furthermore, GLP1ra drugs also demonstrated renal benefits in another recent meta-analysis, especially due to the significant reduction in the appearance of macroalbuminuria [9]. The low prescription rates of these two classes of medications could be explained due to the restrictions in force during the study period: SGLT2i drugs should not be started with eGFR < 60 ml/min and should be discontinued if the eGFR falls below 45 ml/min, while GLP1ra drugs were not recommended for patients with eGFR < 30 ml/min [6].

The prevalence of CRF in patients with available eGFR data was 28%, higher than that observed in two other Spanish studies: 18% [37] and 25.2% [36]. It was also greater than that observed in one study from the US (16.3%) [10], but lower than in another from the US (35.2%) [38] and one from Germany (50%) [39]. When severe CRF is established (eGFR < 30 ml/min, categories G4 and G5), sulfonylureas and metformin should not be prescribed [2–5]. We observed a concerning percentage of these patients taking metformin or sulfonylureas in G4 (eGFR 29–15 ml/min): 18% and 7%, respectively; and in G5 (eGFR < 15 ml/min): 7% and 2%, respectively. This may have been from not noticing the appearance of a reduction in the glomerular filtration rather than a real ignorance of the contraindications. Since 2010 a special aid for prescription was integrated with our electronic medical records system that automatically alerts physicians of this contraindication. Compared with a previously published study using the SIDIAP database, we could observe a lower prescription of both metformin and sulfonylureas: in 2013, 35.3% of patients with CKD stages 4–5 were receiving metformin and 22.5% sulfonylureas [40].

The leading cause of death in people with T2DM is CVD, therefore prevention of cardiovascular events is a key focus in the management of T2DM patients [1]. Several observational studies have shown that the use of antidiabetic drugs with demonstrated cardiovascular benefits in these patients is far from optimal, even in patients controlled by specialists [17,18]. This was also the case in our study: SGLT2i and GLP1ra were infrequently prescribed in patients with CVD (2.6% and 1.4%, respectively). The patients with established CVD in our study were older and had a higher comorbidity burden (especially CRF), which could limit the use of the newer antidiabetic therapies. This likely explains the high use of insulin (alone or in combination with NIADs) observed (30.9%).

Regarding patients with HF (6.9% of our T2DM population), SGLT2i were barely prescribed (1.8%) while 37.7% of them were treated with insulin, likely due to the fact that 63.3% of them have some degree of CRF.

5. Limitations and strengths

Our study has several limitations. Since most of the selected clinical conditions were based on those diagnoses recorded in the database, a misclassification cannot be ruled out; however, the validity and consistency of the SIDIAP database for studying the prevalence of comorbidities and cardiovascular risk factors has been shown in previous studies [10,18,20]. However, it should be noted that in the RedGDPS algorithm the subgroup of patients older than 75 years includes also frail people below this age. Unfortunately, we were not able to accurately identify frailty in our database. Adding younger patients with HF or severe CRF would increase the prevalence of this group from 37.7% to 40.2%, but the results presented in tables and figures refer only to patients older than 75 years. Additionally, the definition of elderly in the RedGDPS algorithm includes patients older than 75 years, while our study includes those ≥75 years, which is the cut-off point used in previous studies of our group [21,28] as well as in the vital statistics. There is a certain underreporting of some chronic complications such as diabetic neuropathy in our database. However, the low percentages of diabetic retinopathy were previously validated and published, and similar results in our study were obtained (12.2%) [24].

Finally, we have to remark that evidence-based recommendations for CVD, CKD and HF were not in force during the study period, so our results should be considered as an area for improvement in patient's care.

The strengths of our study include a population-based design, the use of a primary care registry with a large number of subjects managed under real-world conditions, and, unlike other population-based studies the HbA1c and eGFR values were available in almost 90% of cases (88.4% for HbA1c and 90.1% for eGFR). Conversely, the proportion of missing data for albuminuria, needed for the estimation of the 2012 KDIGO categories of renal risk, was very high (36.5%), but the observed prevalence of albuminuria was similar to another Spanish study in which all participants were screened prospectively [31].

6. Conclusions

Almost 80% of our T2DM patients had at least one of the five studied conditions. The clinical profile of each population can help to choose antidiabetic drugs. Use of antidiabetic drugs with cardio-

renal benefits was far lower than the recommended in the most recent guidelines but the study period was prior to these recommendations. A relevant number of T2DM patients were treated with contraindicated antidiabetic drugs regarding their renal function. Finally, according to the KDIGO categories, the renal risk was moderate to very high in 40% of patients.

Authors' contribution

M.M-C., J.F-N., A.G-G., B.V., and D.M. contributed to study design and discussion. J.R. was involved in data management and statistical analyses. M.M-C. wrote the first draft of the manuscript. All authors contributed to the analysis and interpretation of the data, provided critical input during the development of the manuscript and approved the final version for submission. M.M-C. had full access to all data in the study and takes responsibility for the integrity of data and the accuracy of the data analysis.

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Competing interests

Manel Mata-Cases has received advisory and or speaking fees from Astra-Zeneca, Bayer, Boehringer Ingelheim, GSK, Lilly, MSD, NOVARTIS, NovoNordisk, and Sanofi; he has received research grants to institution from Astra-Zeneca, GSK, Lilly, MSD, Novartis, NovoNordisk, and Sanofi; he has received research grants from Institut Universitari d'Investigació en Atenció Primària Jordi Gol (IDIAP Jordi Gol)(Barcelona, Spain), Instituto de Salud Carlos III (Madrid, Spain), Generalitat de Catalunya. Peris 2016-2020. The Strategic Plan for Health Research and Innovation (Barcelona, Spain).

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Data sharing

The data that support the findings of this study are available from the SIDIAP database (System for the Development of Research in Primary Care). Restrictions apply to the availability of these data, which were used under license for this study.

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