Chronic Kidney Disease Eligible for SGLT2 Inhibitors Through the Integration of Italian Administrative and Primary Care Data

Articoli originali

Carlo Piccinni[1], Letizia Dondi[1], Silvia Calabria[1], Giulia Ronconi[1], Antonella Pedrini[1], Francesco Lapi[2], Ettore Marconi[2], Damiano Parretti[2], Gerardo Medea[2], Gaetano Piccinocchi[2], Claudio Cricelli[2], Roberto Pontremoli[3,4], Nello Martini[1], Aldo Pietro Maggioni[1,5]


Calabria Silvia

1 Fondazione ReS (Ricerca e Salute) – Research and Health Foundation, Roma, Italy
2 Health Search - Istituto di Ricerca della S.I.M.G., Firenze, Italy
3 Dipartimento di Medicina Interna e Specialità mediche, Università di Genova, Italy
4 IRCCS Ospedale Policlinico San Martino, Genova, Italy
5 ANMCO Research Center Heart Care Foundation, Firenze, Italy

Corresponding author:
Silvia Calabria, Pharm D
Fondazione ReS (Ricerca e Salute) – Research and Health Foundation
Via dei Due Macelli, 48 - 00187 Roma, Italy.
Tel.: +39 327 523 7055
Email: calabria@fondazioneres.it
ORCID: 0000-0001-9345-2855

ABSTRACT

Background. Patients with chronic kidney disease (CKD) can be successfully treated with sodium-glucose cotransporter-2 inhibitors (SGLT2-Is), regardless of diabetes. Fondazione Ricerca e Salute's (ReSD) administrative and Health Search's (HSD) primary care databases were combined in the Database Consortium ReS-HS to quantify and describe patients with CKD potentially eligible for SGLT2-Is and assess costs charged to the Italian National Health Service (SSN).

Methods. Patients aged ≥18 with CKD and estimated glomerular filtration rate (eGFR) <60 ml/min in 2018, without dialysis and/or renal transplantation, were included. HSD was used to develop and validate algorithms for estimating eGFR, based on covariates, within the ReSD. Comorbidities, dispensed drugs, and direct healthcare costs were assessed.

Results. In 2018, 66,297 (5.0% of HSD population) and 211,494 (4.4% of ReSD population) patients with CKD potentially eligible for SGLT2-Is were identified (females ≥58%). Prevalence increased with age with a peak at 75-84 years. Within HSD and ReSD cohorts, respectively: 31.0% and 41.5% had diabetes; in the observation periods, >82% and >96% received ≥1 pharmacological treatment, of which ≥50% and ≥25% received cardiovascular/blood agents and antidiabetics, respectively. From ReSD, mean per capita direct SSN cost was € 3,825 (CI 95%, € 3,655-€ 4,000): 50.1% due to hospitalizations, and 40.2% to pharmaceuticals (31.6% to cardiovascular drugs and 10.1% to antidiabetics).

Conclusion. The Database Consortium ReS-HS methodology found 5% of adult SSN beneficiaries with CKD potentially eligible for SGLT2-Is bringing with them a high cardio-metabolic burden which increases the risk of CKD progression.

KEYWORDS: Sodium-Glucose Transporter 2 Inhibitors, Chronic Kidney Diseases, Primary Care, Health Care Costs, National Healthcare System

Introduction

Sodium-glucose cotransporter-2 inhibitors (SGLT2-Is) have shown positive outcomes on the reduction of glycated hemoglobin (Hb1cA) levels, the protection from cardiovascular events in high-risk patients with type 2 diabetes mellitus (T2DM), the prevention of cardiovascular death and heart failure regardless of T2DM, and of the progression of chronic kidney disease (CKD) [1, 3]. The latter is likely to be independent from the glucose-lowering effects and favored by the glucose-related natriuresis and osmotic diuresis that reduce intraglomerular pressure; the DAPA-CKD (Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease) trial was based on this hypothesis and aimed at assessing the long-term efficacy and safety of dapagliflozin in patients with CKD, regardless of T2DM [4]. This trial has shown that patients with CKD assessed by an estimated glomerular filtration rate (eGFR) ranging from 25 to 75 ml/min, regardless of T2DM, have benefited from dapagliflozin through a significant reduction of the risk of sustained decline in eGFR of at least 50%, end-stage kidney disease (ESKD) and renal- or cardiovascular-related death [4].

CKD is characterized by a long-term decrease in kidney function and reduces life quality and expectance [5]. CKD is an independent cardiovascular risk factor that is often associated with other cardiovascular risk factors, which are also frequent cause of kidney damage, like hypertension, dyslipidemia and T2DM [6]. About 10% of the global population is affected by CKD; this rate increases in high-income countries and among older patients [5]. In Italy, 6-7% of adults are estimated to be affected by CKD [6].

Before SGLT2-Is, the sole pharmacological therapies able to reduce the renal function decline were angiotensin-converting enzyme inhibitors (ACE-Is) and angiotensin II receptor blockers (ARBs), even though most of the evidence was generated in patients with T2DM [8]. SGLT2-Is have shown new promising outcomes regardless of T2DM, breaking new grounds in the CKD therapeutic panorama. SGLT2-Is are recommended to treat patients with CKD when eGFR is between 25 and 75 ml/min. CKD is classified into five stages of increasing severity, based on cause (C), GFR (G) and albuminuria (A) categories, as in the most recently published KDIGO (Kidney international disease improving global outcomes) guidelines [7]. According to only eGFR values, SGLT2-Is can be prescribed to patients with CKD at stages from late G2 to initial G4.

Interestingly, G3-stage CKD can be difficult to diagnose, given lacking or very few symptoms, increasing the risk of progression until the need for kidney transplantation or long-term dialysis, and cardiovascular events [9]. Therefore, it is essential to quantify and characterize patients with G3-stage CKD eligible for SGLT2-Is in real-world settings. It is known that different real-world data (RWD) sources have limitations due to some lacking information, like clinical variables in administrative databases, and hospitalizations and healthcare costs in primary care databases. A direct linkage between these databases is unfeasible. To overcome this limitation, we developed and tested a methodology using algorithms to estimate some clinical parameters in the administrative data source (Fondazione Ricerca e Salute database – ReSD) by means of those registered in the primary care (Health Search database – HSD) database [10]. This approach has successfully identified target populations of SGLT2-Is affected by T2DM [10], and heart failure with reduced ejection fraction (HFrEF) [11].

This study aimed to identify, quantify, and describe patients with G3-stage CKD potentially eligible for SGLT2-Is, by using the “Database Consortium ReS-HS” methodology. The direct healthcare costs charged to the Italian National Health Service (SSN) were also assessed.

Methods

Data sources

All analyses were performed in 2022 in the framework of the "Database Consortium ReS-HS", the combination between HSD and ReSD. HSD is an Italian primary care database containing patients' records registered by a selected group of general practitioners (GPs), uniformly distributed across Italy [12]. The ReSD is an administrative healthcare database collecting and integrating the administrative healthcare data that Italian Local and Regional Healthcare Authorities annually convey to the Italian Ministry of Health, upon specific agreements [13]. More details about the two data sources are available in the supplementary box. Two recent publications [11, 10] describe the general methodological principles on which this study is based. The ethics approval and informed consent were not sought for the present study, because it was based on the reuse of anonymous administrative and primary care data and is conducted for institutional purposes, in agreement with the Italian health facilities (regions and local health units).

Study population

The choice of analysing, by using the Database Consortium ReS-HS, patients with G3-stage CKD potentially eligible for the SGLT2-Is is justified by some main reasons: (a) CKD can be identified in clinical and administrative [14] databases, by collecting each clinical process (drug prescription/dispensation, clinical examination, hospital admission, disease waiver claim of co-payment) related to this condition; (b) patients with different CKD stages are barely described through real-world observational studies; (c) eGFR values are registered in clinical data source for most of CKD patients, thus allowing the use of imputation strategies from different kinds of databases; (d) this patient's category is featured by the presence or absence of diabetes and other comorbidities commonly identified in clinical and administrative databases and used as covariates vector for the model imputing the eGFR threshold.

Identification of patients with CKD

Patients aged ≥18, alive by the end of 2018 (i.e., with at least one SSN record within the ReSD or being recorded as SSN beneficiaries of respective GPs within the HSD), and with an available 5-year look-back period, were identified from 1st January to 31st December 2018 (accrual period). Identification criteria of CKD are listed in Supplementary Table 1. For all patients, the index date was 01/01/2018.

Identification of patients with mild-to-moderate CKD and eligible for SGLT2-Is

Once the harmonization procedures were completed (i.e., data from the HSD and ReSD refer to similar populations of SSN beneficiaries) [10], patients potentially eligible for SGLT2-Is were identified among HSD and ReSD populations.

Within the HSD, patients with CKD potentially eligible to SGLT2-Is were identified by a specific diagnosis or disease waiver exemption code or an eGFR <60 ml/min (i.e., identifying G3a- to G5 stage CKD) and excluding patients undergoing dialysis or kidney transplantation (i.e., excluding G4- to G5-stage CKD), which are hereinafter called ESKD-related criteria (Supplementary Table 1). Within the ReSD, a two-step procedure was performed. In the first step, the CKD patients meeting the criteria based on only administrative healthcare data were selected, while those meeting the ESKD-related criteria (Supplementary Table 1) were excluded. A second step was planned given the possible identification of patients with more severe conditions. In the second step, patients with ≥2 creatinine tests, of which ≥1 during one year preceding and ≥1 during one year following index date, were identified. Among them, patients with eGFR values <60 ml/min were estimated through the models used for imputing other clinical variables in ReSD and previously published [11, 10].

The second step has developed and validated the estimation model through the following variables (codes and procedures in Supplementary Table 2): sex, age, previous creatinine tests, eGFR<60 ml/min, pharmacological therapies preceding and following index date (i.e., diuretics, ACE-Is, agents acting on renin-angiotensin system, antidiabetics, lipid lowering agents, antiplatelets and oral anticoagulants), and comorbidities (i.e., T2DM, arterial hypertension, heart failure, atrial fibrillation, ischemic heart disease, ischemic stroke and peripheral artery disease – PAD). This step has probably identified patients with less severe conditions.

The estimation model was validated on patients identified only through administrative healthcare data (Supplementary Table 1). Finally, the two resulting groups of patients with potentially G3-stage CKD were merged. Given the innate characteristics of the Database Consortium ReS-HS (see "Strengths and limitations" paragraph), the information useful to accurately recognize the specific CKD stages is not available; therefore, for the purpose of this study, we must refer only to a broad definition of CKD stages.

Description of patients with CKD and eligible for SGLT2-Is

Patients with CKD potentially eligible for SGLT2-Is were characterized by sex and age at index date, pharmacological therapy, clinical features (Supplementary Table 2), and direct costs charged to the SSN during different observation periods.

- *Clinical features*

During the overall observation period (i.e., 5-year look-back and 1-year follow-up), the following comorbidities were identified (Supplementary Table 2): T2DM, arterial hypertension, heart failure, atrial fibrillation, ischemic heart disease, ischemic stroke, and PAD. Specifically, the target population identified in the ReSD was categorized by the presence and absence of T2DM at baseline (index date and until 2013). Patients with and without T2DM were described as above (Supplementary Table 2); their direct healthcare costs charged to the SSN were also assessed.

- *Pharmacological therapy*

During one year preceding and following index date, proportions (with 95% confidence intervals – CI) of patients with at least one dispensation of the following cardiovascular and blood drugs were analyzed (ATC code): diuretics (C03), agents acting on the renin-angiotensin system (C09 codes), lipid lowering agents (C10AA and C10BX), antiplatelets (B01AC), oral anticoagulants (B01AA03, B01AA07, B01AE07, B01AF01, B01AF02 and B01AF03).

- *Healthcare costs charged to the SSN within the ReSD*

Direct costs due to the healthcare reimbursed by the SSN during one year following index date were assessed through the ReSD, as mean annual costs per patient by healthcare administrative database (pharmaceuticals, hospitalizations, and outpatient specialist care). Costs for antidiabetics (A10), cardiovascular and blood drugs (C and B01 codes) within the pharmaceutical flow, and hospitalizations with main diagnosis (ICD-9-CM code) related to cardiovascular causes (from 390.x to 459.x) and kidney disease (from 580.x to 589.x) were clearly displayed. Since Italian administrative healthcare databases have been created for reimbursement purposes, pharmaceutical costs are extrapolated from prices of community and hospital pharmacies (inclusive of value-added tax); in-hospital expenses are extrapolated from the Diagnosis-Related Group classification; costs for outpatient specialist care are based on current national tariffs.

- *Statistical analyses*

The statistical model which creates an operational crosstalk between clinical and administrative data sources, previously developed on T2DM [10] and HFrEF [11], following its application to patients

identified by creatinine tests within the ReSD, was validated on patients meeting only identification criteria within the ReSD. Among the different cut-offs of estimation probability, the one with the best specificity/sensitivity ratio was chosen and applied to patients with CKD within the ReSD, to identify subjects potentially eligible for SGLT2-Is according to eGFR <60ml/min (Supplementary Tables 3 and 4).

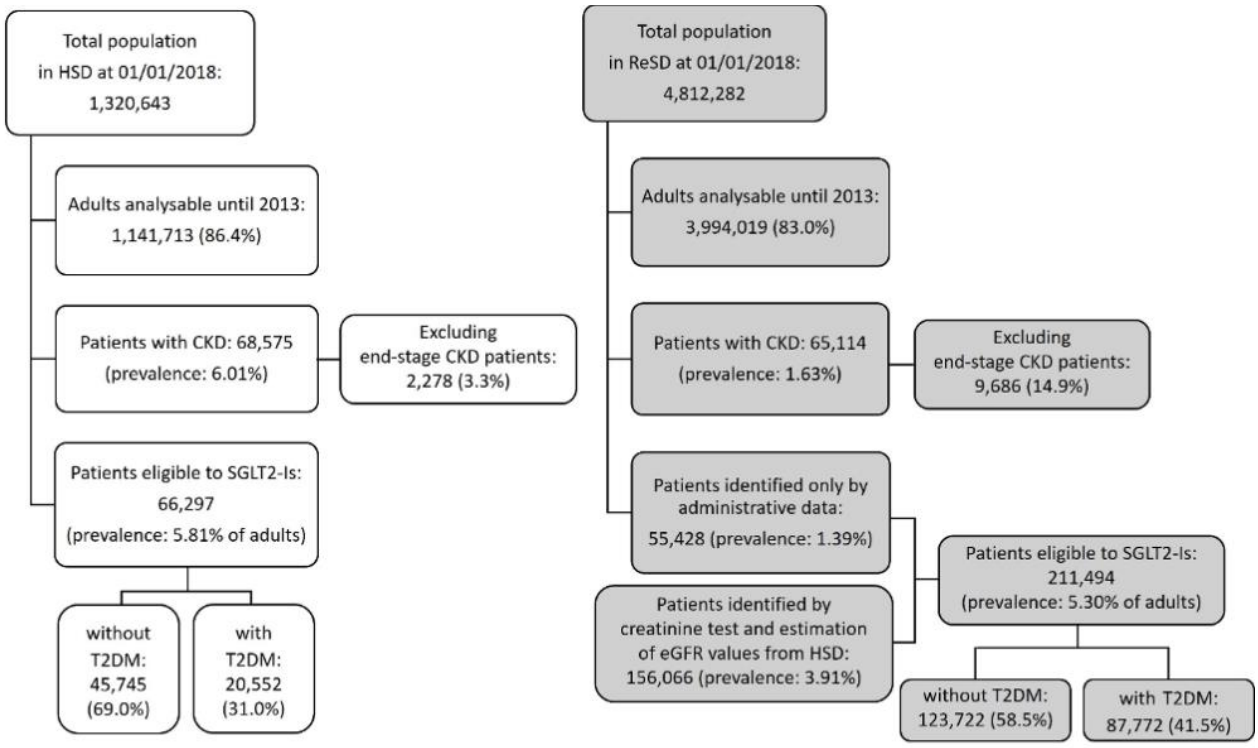
Following the demographic and clinical description, the prevalence rates and related 95% CI were compared to verify the consistency of CKD eligible for SGLT2-Is definitions. Every query identifying the studied variables and related 95% CI used in ReSD and in HSD were tested by means of repeated harmonization procedures [11, 15].

Continuous values are expressed as mean ± standard deviation (SD), median age and interquartile range (Q1; Q3), and proportions as percentages. All statistical analyses of ReSD were performed by means of Oracle SQL Developer, Italian version 18.1.0.095 (California, United States) and Excel (Microsoft Office 365).

Results

Patients with CKD eligible for SGLT2-Is

At 01/01/2018, out of 1,141,713 adults in the HSD analyzable until 2013 and alive during 2018, 68,575 patients with CKD (6.0%) were identified (Figure 1); after having excluded ESKD cases, 66,297 patients were potentially eligible for SGLT2-Is (5.81%; 95% CI 5.76-5.85), 68.9% of whom had a manually recorded eGFR <60 ml/min value by GPs. Within the ReSD, starting from 3,994,019 adults analyzable until 2013 and alive during 2018, 55,428 (step 1) and 156,066 (step 2) patients were potentially eligible for SGLT2-Is, totaling 211,494 (5.30%; 95% CI 5.27-5.32) (Figure 1).



HSD: Health Search's database; ReSD: Fondazione Ricerca e Salute's database; CKD: chronic kidney disease; SGLT2-Is: sodium-glucose transporter inhibitors; T2DM: type 2 diabetes mellitus

Figure 1. Identification of patients with chronic kidney disease and eligible for sodium-glucose cotransporter 2 inhibitors in the Health Search and Fondazione Ricerca e Salute databases.

In both cohorts of patients potentially eligible for SGLT2-Is, women were more than men, prevalence increased with age, with a peak at 75-84 years, and patients with cardiovascular comorbidities were in similar proportions. Patients with T2DM were 20,552 (31.0%) and 87,772 (41.5%) of HSD and ReSD target population, respectively (Table 1).

During one year preceding and following index date, respectively, slightly higher proportions of patients eligible for SGLT2-Is in the ReSD received at least one pharmacological therapy (97.2% and 96.4% vs 82.8% and 84.3% in the HSD). Also, by therapeutic class (Table 1), the ReSD cohort showed higher percentages of treated patients, both preceding and following index date (e.g., 52.7% vs 34.9% and 50.5% vs 34.2% patients treated with ARBs, respectively), except for patients treated with ACE-Is (33.1% vs 33.5% and 31.2% vs 33.0%, respectively). Overall, during one previous and subsequent year, respectively, the most prescribed drugs were diuretics (56.9% and 58.7%) to the ReSD cohort and antiplatelets (41.0% and 40.6%) to the HSD cohort. During the follow-up year, the number of patients treated with antiplatelets was reduced, while that of patients treated with oral anticoagulants increased.

	Health Search database		Fondazione Ricerca e Salute database	
	Patients with CKD eligible for SGLT2-Is (*n*=66,297)	95% CI	Patients with CKD eligible for SGLT2-Is (*n*=211,494)	95% CI
Demographics at baseline				
Mean age ± SD	76 ± 12	–	80 ± 9	–
Median age (Q1;Q3)	78 (69;85)	–	81 (75;86)	–
Females	58.0%	(57.58 – 58.34)	61.5%	(61.26-61.68)
Distributions by age group (N; %)				
18 – 39	698; 1.1	–	10,104; 0.5	–
40 – 54	2877; 4.3	–	2966; 1.4	–
55 – 64	7135; 10.8	–	6851; 3.2	–
65 – 74	15,080; 22.7	–	38,812; 18.4	–
75 – 84	23,707; 35.8		95,761; 45.3	
≥ 85	16,800; 25.3	–	66,000; 31.2	–
Clinical characteristics				
Creatinine test (% patients with ≥1)	–	–	97.4	(97.34-97.48)
Glomerular filtration rate (GFR) < 60ml/min	68.9	(68.52 – 69.22)	92.3	(92.22-92.45)
Comorbidities in the whole observational period (% patients)				
No comorbidity of interest	13.4	(13.11 – 13.63)	1.9	(1.89-2.01)
At least one comorbidity	86.6	(86.37 – 86.89)	98.1	(97.99-98.11)
Diabetes mellitus	31.0	(30.69 – 31.4)	41.5	(41.29-41.71)
Arterial hypertension	78.9	(78.56 – 79.19)	97.2	(97.13-97.27)
Ischemic heart disease	18.6	(18.27 – 18.86)	15.2	(15.06-15.37)
Atrial fibrillation	13.7	(13.46 – 13.98)	12.6	(12.43-12.71)
Heart failure	9.8	(9.61 – 10.06)	11.3	(11.15-11.42)
Peripheral artery disease	6.6	(6.36 – 6.74)	8.4	(8.27-8.51)
Ischemic stroke	7.0	(6.81 – 7.2)	4.1	(3.99-4.15)
Pharmacological treatments Patients treated with oral CV and blood drugs within one year before the index date (% on the cohort)				
HMG CoA reductase inhibitors	38.7	(38.28 – 39.03)	46.1	(45.84-46.27)
Angiotensin II receptor blockers	34.9	(34.51 – 35.24)	52.7	(52.52-52.94)

Angiotensin-converting enzyme inhibitors	33.5	(33.19 – 33.91)	33.1	(32.93-33.33)
Diuretics	32.2	(31.82 – 32.53)	56.9	(56.72-57.15)
Drugs used in diabetes	24.9	(24.57 – 25.23)	36.9	(36.67-37.08)
SGLT2-Is	0.1	(0.08-0.13)	0.9	(0.82-0.89)
Lipid lowering agents (excl. HMG CoA reductase inhibitors)	8.5	(8.24 – 8.67)	14.7	(14.57-14.87)
Renin inhibitors	0.1	(0.10 – 0.16)	0.2	(0.17-0.21)
Antiplatelets	41.0	(40.67 – 41.42)	56.3	(56.11-56.53)
Oral anticoagulants	12.0	(11.75 – 12.25)	19.6	(19.44-19.78)
Patients treated with oral CV and blood drugs within one year after the index date (% on the cohort)				
HMG CoA reductase inhibitors	39.1	(38.71 – 39.46)	44.9	(44.70-45.12)
Angiotensin II receptor blockers	34.2	(33.79 – 34.52)	50.5	(50.27-50.69)
Diuretics	34.0	(33.6 – 34.32)	58.7	(58.52-58.94)
Angiotensin-converting enzyme inhibitors	33.0	(32.67 – 33.39)	31.2	(31.01-31.40)
Drugs used in diabetes	25.1	(24.74 – 25.4)	36.8	(36.55-36.96)
SGLT2-Is	0.5	(0.48-0.59)	1.1	(1.10-1.19)
Lipid lowering agents (excl. HMG CoA reductase inhibitors)	8.9	(8.72 – 9.16)	14.5	(14.36-14.66)
Renin inhibitors	0.1	(0.07 – 0.12)	0.1	(0.13-0.16)
Antiplatelets	40.6	(40.22 – 40.97)	54.7	(54.48-54.91)
Oral anticoagulants	13.4	(13.17 – 13.69)	21.3	(21.08-21.43)

Table 1. Demographics, clinical characteristics and pharmacological treatments of patients with chronic kidney disease eligible for sodium-glucose cotransporter 2 inhibitors in the Health Search and Fondazione Ricerca e Salute databases. CI: confidence interval; SD: standard deviation; CV: cardiovascular; HMG CoA: 3-hydroxy-3-methylglutaryl coenzyme A; SGLT2-Is: sodium-glucose cotransporter-2 inhibitors.

Healthcare costs charged to the SSN within the ReSD

The mean per capita expenditure paid by the SSN was € 3,825 (95% CI: € 3,655 – € 4,000) (Table 2). Hospitalizations accounted for half of the total expenditure, followed by pharmaceuticals (40.2%) and local outpatient specialist care (9.8%). Of pharmaceutical expenditure, antidiabetics accounted for the 4.1%, cardiovascular drugs for the 12.7% and other concomitant therapies for the 23.4%.

Administrative healthcare database	**Patients with CKD eligible for SGLT2-Is (n = 211,494)** Mean annual cost per patient (€); % on the total expenditure; *% on total expenditure for the specific healthcare administrative database*
Pharmaceuticals	1536; 40.2
antidiabetic drugs	*156; 10.1*
CV drugs	*485; 31.6*
other drugs	*895; 58.3*
Hospitalizations	1915; 50.1
CV causes	*645; 33.7*
CKD-related causes	*98; 5.1*
other causes	*1172; 61.2*
Outpatient specialist care	374; 9.8
Total expenditure	3825; 100.0

Table 2. Annual direct costs due to the healthcare resource consumption reimbursed by the SSN of patients with chronic kidney disease eligible for SLGT2-Is in the Fondazione Ricerca e Salute's database.

Discussion

This observational retrospective study of a contemporary population of SSN beneficiaries from different RWD sources, respectively the HSD and ReSD, found that, in 2018, 5.8% and 5.3% of adults with CKD were potentially eligible for SGLT2-Is. In literature, CKD prevalence rates are heterogeneous, especially in the early stages (i.e., from late G2- to G3b-stage CKD) when most of patients are asymptomatic [16]. Moreover, CKD prevalence rates based on eGFR<60 ml/min ranged from 2.5% to 11.2% when assessed in European, North American, Asian and Australian populations, making it difficult to compare prevalence rates worldwide; indeed, the use of eGFR thresholds to define the CKD stages, especially in older patients, raises some concerns on the accuracy of prevalence definitions in large-scale epidemiological studies, which are affected by ethnical, socioeconomic and environmental factors [16]. In Italy, the prevalence of CKD largely differs from those reported in US and other European countries and between the Italian Regions themselves; moreover, while large-scale ESKD registries are available (e.g., the Italian Registry of Dialysis and Transplantation), a specific national early-stage CKD registry is absent [17]. Whatever, in high socio-demographic index countries, higher rates of early-stage CKD are expected to be common given the ageing population and the increasing burden of obesity, smoking-related comorbidities, cardiovascular diseases, T2DM and hypertensive nephropathy [17].

Starting from recent analyses on CKD using ReSD [18] and HSD [19] and on the previous publications about the Database Consortium ReS-HS statistical model [11, 10], rates of CKD from the two databases were overlapping, also in their increase with age and higher female proportions, as already reported [16]. It is interesting that despite a generally higher prevalence of renal disease in men, in studies that adjusted for gender differences, the eGFR equations tend to identify more frequently CKD in stage-3 women [16].

SGLT2-Is have been firstly authorized to treat patients with T2DM, then patients with HFrEF (European Medicines Agency's approvals of dapagliflozin in 2020 [20] and of empagliflozin in 2021 [21]). More recently, they have shown significant improved renal outcomes, by reducing the albuminuria progression and slowing down the time-dependent decline of GFR, based on the DAPA-CKD [4] and the EMPA-KIDNEY [22] trials. Since the conclusion of the EMPA-KIDNEY trial ended following this study was performed, for our study the DAPA-CKD trial's eligibility criteria [4] were partly modified according to the clinical and epidemiological reasons (i.e., eGFR threshold) or information availability in at least one of the used databases (i.e., absence of albuminuria values). Moreover, although we are aware that clinical evidence and guidelines are constantly updated, for this study we referred to those potentially used for the clinical practice until the end of 2019. However, despite the promising benefits of SGLT2-Is on cardiovascular and renal functions [3], regardless of T2DM, real-world studies exploring the utilization rate of SGLT2-Is in non-diabetic patients are still limited [3, 23].

At least one comorbidity was found in 98.1% of ReSD patients, and in 86.6% of HSD patients. In ReSD hypertension was more frequent (97.2% vs 78.9%), followed by T2DM (41.5% vs 31.0%). The slight differences between the two databases could be probably due to the fact that in the HSD the diagnosis is recorded by GPs at the time a drug or a specialist care is prescribed, while, in the ReSD diagnoses are taken from the patient's access to whatever SSN healthcare collected in administrative flows.

The comorbidities analyzed in this study have also been previously found as frequent cause of cardiovascular hospitalizations [24]. Within non-dialyzed and early-stage CKD patients, the ageing population, the higher rates of T2DM and hypertension, low diagnosis rates and therapeutic inertia facilitate the progression to the ESKD [25]. Moreover, regardless of biological age, rates of heart

failure and arrhythmia (especially atrial fibrillation and ventricular tachyarrhythmia) raise with reduction of eGFR <60 ml/min [25, 26]. This suggests that the ageing population and higher comorbidity rates correspond to a substantial healthcare burden, especially in terms of hospitalizations. As also stated in the "Strengths and limitations" section, given that through the Database Consortium ReS-HS the precise CKD stages cannot be identified, comorbidities cannot be analyzed by CKD stage. However, since the study cohort was potentially affected by G3-stage CKD, these comorbidities could clinically describe patients with G3-stage CKD, although without being able to distinguish between G3a and G3b. Moreover, following the previous study analyzing the target population of SGLT2-Is among patients with HFrEF and eGFR<60ml/min [11], it is worth noting that diabetes was found in 44% and in 33% of patients with heart failure in HSD and ReSD, respectively, which was almost inverted in this study (31% in HSD and 41% in ReSD).

Proportions of patients treated with analyzed pharmacological therapies overlapped between the two databases, although somewhat higher in the ReSD (excluding ACE-Is), in both observation years. The therapeutic classes analyzed are recommended as first or subsequent lines of treatment [7]. The blood pressure control is a priority to reduce proteinuria, which is an independent cardiovascular risk factor and a biomarker of the kidney damage [17]. Renin-angiotensin-aldosterone inhibitors are first-line agents in CKD [25]. ACE-Is and ARBs in people with diabetic or non-diabetic CKD have been shown to reduce the risk of renal failure and major cardiovascular events; ACE-Is also reduced the risk of all-cause mortality in these populations [16]. In the ReSD, the use of diuretics appeared much higher than in the HSD (56.9% vs 32.2%). Diuretics are frequently prescribed in CKD at stages 3 and 4 to treat edema, reduce extracellular fluid, blood pressure, and strengthen the effect of other therapies; meanwhile, they have been significantly associated with a decline in eGFR, also in non-dialysis CKD patients [27]. This may suggest that patients selected in ReSD could be in later pre-dialysis stages. G3-stage CKD patients appear to benefit from anti-hypertensive agents, lipid lowering and aspirin-based antiplatelet therapies, likewise or more than the general population [16]. Whereas a large registry study suggests that CKD patients still receive fewer evidence-based therapies (e.g., statins and antiplatelet agents), contributing to higher cardiovascular mortality rates [25]. Also, this description of pharmacological dispensations can be potentially referred to patients with G3-stage CKD, although without being able to distinguish between G3a and G3b.

As per the analysis of the healthcare costs, hospitalizations accounted for half of the overall mean per capita annual expenditure (€ 1,915/€ 3,825). Hospitalizations and drugs are cost drivers of non-cardiovascular-related healthcare, suggesting that patients are highly complex and need multidisciplinary assessment.

Primary and secondary prevention strategies of complications from the late G2- to G3-stage CKD, especially for diabetic patients, benefit from SGLT2-Is [3]. Also, cost-effectiveness analyses of SGLT2-Is have shown high value from both clinical and economic perspectives [28, 29], although the health economic impact of SGLT2-Is regardless of diabetes remains unclear [28]. In general, through the best long-term preventing approach (i.e., improved management of obesity, diabetes, and hypertension), the delayed progression of CKD would reduce direct costs due to dialysis and renal transplantation, and indirect ones caused by a worst quality of life [16, 30, 31]. Findings from this type of studies can contribute to establish the cost-benefit ratio of incoming new therapies.

Strengths and limitations

The most important strength of real-world studies is the high level of representativeness, through the inclusion of very old people, women, racial/ethnic minority groups and patients with multimorbidity, generally excluded from clinical trials. Therefore, as regards patients with CKD

eligible for SGLT2-Is, in the interest of the healthcare planning, findings from our analysis complement those coming from screening studies or trials. Also, given the heterogeneity of prevalence rates in literature, our data can contribute to the epidemiological knowledge of G3-stage CKD patients in unspecific clinical settings, like ours.

Administrative data alone would give incomplete information on this clinical condition [14, 32, 33]. Indeed, the ReSD can reliably estimate the prevalence of late CKD stages and provide the direct healthcare costs charged to the SSN, while the HSD well identifies patients with G3-stage CKD [19]. Therefore, the Database Consortium ReS-HS strategy can comprehensively answer to the epidemiological needs of patients with CKD eligible for SGLT2-Is and assess the economic burden on the SSN, despite without explicitly referring to the specific CKD stages. Furthermore, given the ReSD representativeness of the Italian population, the crosstalk between clinical and administrative data sources allowed us to obtain more precise estimates of the population eligible for SGLT2i, useful to allocate the healthcare and economic resources.

Different limitations are worthy of attention. The CKD staging based on proteinuria and albuminuria values, which are both important prognostic markers for cardiovascular and/or renal risk [7, 25] other than eGFR, was not possible for this analysis, because they were not analyzed in the two databases. Nevertheless, in a recent paper, we proposed a strategy to overcome this limitation [34]. Even though the DAPA-CKD trial included patients with eGFR between 25 and 75 ml/min [4], we only used an eGFR<60 ml/min. It is conceivable that by applying a broader definition of CKD, which included an eGFR<75 ml/min in the presence of moderately increased albuminuria (i.e., albumin-creatinine ratio >200 mg/g), according to the DAPA-CKD trial's criteria, the number of potential beneficiaries might have increased considerably. Nevertheless, patients with G3-stage CKD (i.e., with eGFR<60 ml/min) can be difficult to diagnose, given lacking or very few symptoms, leading to the increase of progression risk until the need for kidney transplantation or long-term dialysis, and cardiovascular complications [9]. This specific population needs special attention within clinical practice and epidemiological research. This study can help to fill this real-world evidence gap, although without being able to distinguish between G3a and G3b. Indeed, despite based on the tendency that, generally, patients with G3a-stage CKD refer to GPs while people with G3b-stage CKD are cared by nephrologists, the proportions based on the two different G3 stages cannot be estimated by means of the Database Consortium ReS-HS.

The differences between HSD and ReSD are due to the aforementioned intrinsic characteristics and limitations. Particularly, administrative databases tend to underestimate patients with CKD, as already discussed. Indeed, it is worth reminding that the GP's diagnosis is mandatory for drug, test, or examination prescriptions, and refers to the patients' entire medical history; whereas, administrative data, by recording punctual healthcare deliveries, refer to shorter lifetimes.

Some limitations affect the pharmacological therapy analysis through the ReSD, such as the absence of any out-of-pocket purchase, patient's self-administration, or diagnosis mandatory for prescriptions, and through the HSD, such as the absence of drug supplies or self-administrations. Nevertheless, it is exactly the combination of ReSD and HSD that allowed us to assess the therapeutic approach of both specialists and GPs in a more reliable and representative setting.

Conclusion

This analysis of the Database Consortium ReS-HS identified prevalence rates of patients with G3-stage CKD eligible for SGLT2-Is. About 5% of real-world adult SSN beneficiaries regardless of T2DM were identified through the crosstalk between clinical and administrative databases, which can be adjusted based on different clinical variables (missing from administrative data) and covariates. As

CKD brings with it a high cardio-metabolic disease-related burden, and the standards of care are not enough to face the still substantial risk of progression towards ESKD and mortality, findings from recent trials together with RWD can help foster healthcare and economic resources allocation, together with multidisciplinary patient reassessment.

Abbreviations

CKD: Chronic Kidney Disease; **ReSD:** Fondazione Ricerca e Salute Database; **HSD:** Health Search Database; **SGLT2-Is:** sodium-glucose cotransporter-2 inhibitors; **T2DM:** type 2 diabetes mellitus; **ESKD:** End-Stage Kidney Disease; **HFrEF:** Heart Failure with Reduced Ejection Fraction; **PAD:** Peripheral Artery Disease; **RWD:** real-world data; **SSN:** Italian National Healthcare Service; **GP:** general practitioner; **eGFR:** estimated glomerular filtration rate; **ACE-Is:** angiotensin converting enzyme inhibitors; **ARBs:** angiotensin II receptor blockers

Primary care clinical (Health Search) database	Administrative healthcare (Fondazione ReS) database
HSD is an Italian primary care database established in 1998. It contains patients' records registered by a selected group of general practitioners (GPs), uniformly distributed across Italy, performing their activity through solo or group practice in both rural and urban areas [1]. In HSD, patients' demographics are linked using an anonymized unique identifier with medical records and clinical values (diagnoses, performed tests, outcomes, hospital admissions, etc.), drug prescriptions (trade name, dosage form, Anatomical Therapeutic Chemical – ATC – code according to the World Health Organization's ATC classification [2], Italian marketing code, active substances, date of prescription, dosing schedule), risk factors and lifestyle variables (i.e., body mass index, smoking habits, alcohol use), date of death. Diagnoses are recorded according to the Italian version of the International Classification of Diseases – 9th Revision – Clinical Modification (ICD-9-CM) [3]. Ambulatory procedures are recorded in accordance with the current national classification system [4]. To be considered for participation in epidemiological studies, GPs must meet up-to standard quality criteria pertaining to the levels of coding, prevalence of well-known diseases, mortality rates, and years of recording. Thanks to its representativeness of Italian outpatient population, the HSD has been adopted for different clinical research questions [5, 7]. It has been documented as a reliable data source for assessing the epidemiology of chronic diseases, such as HF [8]. Neither informed consent nor ethical approval were applicable because this study relied on the re-use of anonymous data and on institutional purposes.	Fondazione ReS is a non-profit foundation working on Italian healthcare real-world data with the aim of planning and monitoring healthcare policy issues, for different stakeholders and in various clinical fields, since 2018 [9, 11]. Through the collaboration with Cineca (Interuniversity Consortium [12]), which guarantees quality and security of the data management (international standard certifications), the ReSD, after further quality and accuracy data checks, collects and integrates the administrative healthcare data that Italian Local and Regional Healthcare Authorities (HAs) annually convey to the Italian Ministry of Health. Data from some HAs, owners of these data, are made available to ReS under specific agreements, to be analyzed and supplied in an aggregated form. Demographics (age, sex, local HA of residency and disease waiver claim for co-payment) of each patient are completely anonymized at the source according to European privacy rules [13]. The pharmaceuticals' database contains drugs reimbursed by the SSN and supplied from local and hospital pharmacies (Italian marketing code, ATC code, dose, number of packages and dispensing date). The hospitalizations' database contains in-hospital diagnoses and procedures, according to the Italian version of ICD-9-CM, accessible through the hospital discharge forms of overnight and day in-hospital stay. The outpatient specialist care database (visits, diagnostic and invasive/non-invasive procedures charged to the SSN) is analyzed based on the current national classification system [4]. Administrative healthcare databases also provide direct costs incurred by the SSN, due to reimbursement purposes. The catchment community of over 5 million inhabitants in the ReSD shows age distributions comparable to those reported for the entire country by the Italian Institute of Statistics (ISTAT) [14]. Finally, neither informed consent nor ethical approval were applicable, because of anonymization, according to the current European and Italian rules on privacy and observational studies, in agreement with the HAs owners of these data.

Box. Description of the data sources.

Identification from Fondazione Ricerca e Salute database (at least one of the following criteria)	
Administrative healthcare database	Description
Hospitalizations	Hospitalization with one of the following main/secondary diagnoses (ICD-9-CM code): 585.x – Chronic kidney disease 585.6 – End stage renal disease* 586 – Renal failure unspecified 587 – Renal sclerosis unspecified 588 – Disorders resulting from impaired renal function 403.x – Hypertensive chronic kidney disease 404.x – Hypertensive heart and chronic kidney disease 250.4 – Diabetes with renal manifestations V56.x – Encounter for dialysis and dialysis catheter care* V42.0 – Kidney replaced by transplant* Hospitalization with one of the following DRG codes: 316 – Renal failure 317 – Hospitalization for renal dialysis* One of the following procedures (ICD-9-CM code): 39.95 – Hemodialysis * 54.98 – Peritoneal dialysis* 54.93 – Creation of cutaneoperitoneal fistula* 97.82 – Removal of peritoneal drainage device* 38.95 – Venous catheterization for renal dialysis* 55.6x – Transplant of kidney*
Outpatient specialist care	Outpatient specialist service among the following: 39.95 – Hemodialysis* 55.6x – Transplant of kidney* 54.98 – Peritoneal dialysis* 54.93 – Creation of cutaneoperitoneal fistula* 97.82 – Removal of peritoneal drainage device* 38.95 – Venous catheterization for renal dialysis*
Disease waiver claim	One of the following disease waiver claim codes: 023 – Renal failure 061 – Chronic kidney diseases 052.v42.0 – Kidney replaced by transplant*
Identification from Health Search database (at least one of the following criteria)	
Electronic medical record	Description
Diagnosis	One of the following diagnoses (ICD-9-CM code): 585.x – Chronic kidney disease 585.6 – End stage renal disease * 586 – Renal failure unspecified 587 – Renal sclerosis unspecified 588 – Disorders resulting from impaired renal function 403.x – Hypertensive chronic kidney disease 404.x – Hypertensive heart and chronic kidney disease 250.4 – Diabetes with renal manifestations
Procedure	V56.x – Encounter for dialysis and dialysis catheter care* V42.0 – Kidney replaced by transplant* Transplant of kidney* (free-text field) Hemodialysis*(free-text field) Peritoneal dialysis* (free-text field) Last outcome of glomerular filtration rate (GFR) ≤60 ml/min
Disease waiver claim	One of the following disease waiver claim codes: 023 – Renal failure 061 – Chronic kidney diseases 052.v42.0 – Kidney replaced by transplant *

Supplementary table 1. Identification criteria of patients with chronic kidney disease from Fondazione Ricerca e Salute administrative healthcare database and Health Search clinical database. Patients identified by at least one of the criteria with (*) were considered to be affected by the end-stage kidney disease and were excluded.

	Health search database	Fondazione Ricerca e Salute database
Variable	Codes and Descriptions	Codes and Descriptions
Clinical characteristics related to mild to severe (excluded end-stage) chronic kidney disease		
Creatinine test	–	At least one outpatient creatinine test within the period before the index date (national classification system): 90.16.3 creatinine [[s/u/du/la]] 90.16.4 creatinine clearance
Glomerular filtration rate (GFR)	GFR <60ml/min: last available measurement during the accrual year (i.e., 2018), starting from the index date (i.e., 01/01/2018)	Estimation of absent data
Comorbidities (within the overall observation period)		
Diabetes mellitus	Diagnosis (ICD9CM code) of: 250.x – Diabetes mellitus	– Hospitalization with one of the following primary/secondary diagnoses (ICD9CM code): 250.x – Diabetes mellitus – Disease waiver claim code: 013 – Diabetes mellitus – Prescription of a specific drug (ATC code): A10 – Drugs used in diabetes – Filled prescription with the disease waiver claim code: 013 – Diabetes mellitus
Arterial hypertension	Diagnosis (ICD9CM code) of: 401.x – Essential hypertension 402.x – Hypertensive heart disease 403.x – Hypertensive chronic kidney disease 404.x – Hypertensive heart and chronic kidney disease 405.x – Secondary hypertension	– Hospitalization with one of the following primary/secondary diagnoses (ICD9CM code): 401.x – Essential hypertension 402.x – Hypertensive heart disease 403.x – Hypertensive chronic kidney disease 404.x – Hypertensive heart and chronic kidney disease 405.x – Secondary hypertension – Disease waiver claim code: 31 – Arterial hypertension A31 – Arterial hypertension without organ damage – Prescription of ≥4 packs of ≥1specific drugs (ATC code): C02 – Antihypertensive C03 – Diuretics C07 – Beta blocking agents C08 – Calcium channel blockers C09 – Agents acting on the renin-angiotensin system – Filled prescription with the disease waiver claim code 031 or A31
Heart failure	Diagnosis (ICD9CM code) of: 402.01 – Malignant hypertensive heart disease with heart failure 402.11 – Benign hypertensive heart disease with heart failure 402.91 – Unspecified hypertensive heart disease with heart failure 404.01 – Hypertensive heart and chronic kidney disease, malignant, with heart failure and with chronic kidney disease stage I through stage IV, or unspecified 404.03 – Hypertensive heart and chronic kidney disease, malignant, with heart failure and with chronic kidney disease stage V or end stage renal disease 404.11 – Hypertensive heart and chronic kidney disease, benign, with heart failure and with chronic kidney disease stage I through stage IV, or unspecified	– Hospitalization with one of the following primary/secondary diagnoses (ICD-9-CM code): 402.01 – Malignant hypertensive heart disease with heart failure 402.11 – Benign hypertensive heart disease with heart failure 402.91 – Unspecified hypertensive heart disease with heart failure 404.01 – Hypertensive heart and chronic kidney disease, malignant, with heart failure and with chronic kidney disease stage I through stage IV, or unspecified 404.03 – Hypertensive heart and chronic kidney disease, malignant, with heart failure and with chronic kidney disease stage V or end stage renal disease

	404.13 – Hypertensive heart and chronic kidney disease, benign, with heart failure and chronic kidney disease stage V or end stage renal disease 404.91 – Hypertensive heart and chronic kidney disease, unspecified, with heart failure and with chronic kidney disease stage I through stage IV, or unspecified 404.93 – Hypertensive heart and chronic kidney disease, unspecified, with heart failure and chronic kidney disease stage V or end stage renal disease 428.x – Heart failure	404.11 – Hypertensive heart and chronic kidney disease, benign, with heart failure and with chronic kidney disease stage I through stage IV, or unspecified 404.13 – Hypertensive heart and chronic kidney disease, benign, with heart failure and chronic kidney disease stage V or end stage renal disease 404.91 – Hypertensive heart and chronic kidney disease, unspecified, with heart failure and with chronic kidney disease stage I through stage IV, or unspecified 404.93 – Hypertensive heart and chronic kidney disease, unspecified, with heart failure and chronic kidney disease stage V or end stage renal disease 428.x – Heart failure – Disease waiver claim code: 021.428 – Heart failure – Filled prescription with the disease waiver claim code 021
Atrial fibrillation	Diagnosis (ICD9CM code) of: 427.3x – Atrial fibrillation and flutter	Hospitalization with one of the following primary/secondary diagnoses (ICD9CM code): 427.3x – Atrial fibrillation and flutter
Ischemic heart disease	Diagnosis (ICD9CM code) of: 410.0x Acute myocardial infarction of anterolateral wall 410.1x Acute myocardial infarction of other anterior wall 410.2x Acute myocardial infarction of inferolateral wall 410.3x Acute myocardial infarction of inferoposterior wall 410.4x Acute myocardial infarction of other inferior wall 410.5x Acute myocardial infarction of other lateral wall 410.6x True posterior wall infarction 410.7x Subendocardial infarction 410.8x Acute myocardial infarction of other specified sites 410.9x Acute myocardial infarction of unspecified site 411.0x Postmyocardial infarction syndrome 411.1x Intermediate coronary syndrome 411.8x Other acute and subacute forms of ischemic heart disease 412.x Old myocardial infarction 413.x Angina pectoris 414.x Other forms of chronic ischemic heart disease 429.7 Sequelae of myocardial infarction not elsewhere classified V45.81 Postsurgical aortocoronary bypass status V45.82 Percutaneous transluminal coronary angioplasty status (PTCA)	– Hospitalization with one of the following primary/secondary diagnoses (ICD9CM code): 410.x – Acute myocardial infarction 411.x – Other acute and subacute forms of ischemic heart disease 412 – Old myocardial infarction 413.x – Angina pectoris 414.x – Other forms of chronic ischemic heart disease – Hospitalization with one of the following procedures (ICD9CM code): 36.x – Operations on vessels of heart 00.66 – Percutaneous transluminal coronary angioplasty (PTCA)
Ischemic stroke	Diagnosis (ICD9CM code) of: 433.01 Occlusion and stenosis of basilar artery with cerebral infarction 433.11 Occlusion and stenosis of carotid artery with cerebral infarction 433.21 Occlusion and stenosis of vertebral	Hospitalization with one of the following primary/secondary diagnoses (ICD9CM code): 433.01 Occlusion and stenosis of basilar artery with cerebral infarction 433.11 Occlusion and stenosis of

	artery with cerebral infarction 433.31 Occlusion and stenosis of multiple and bilateral precerebral arteries with cerebral infarction 433.81 Occlusion and stenosis of other specified precerebral artery with cerebral infarction 433.91 Occlusion and stenosis of unspecified precerebral artery with cerebral infarction 434.01 Cerebral thrombosis with cerebral infarction 434.11 Cerebral embolism with cerebral infarction 434.91 Cerebral artery occlusion unspecified with cerebral infarction 435.x Transient cerebral ischemia 436.x Apoplexy, cerebral apoplexy, cerebrovascular accident	carotid artery with cerebral infarction 433.21 Occlusion and stenosis of vertebral artery with cerebral infarction 433.31 Occlusion and stenosis of multiple and bilateral precerebral arteries with cerebral infarction 433.81 Occlusion and stenosis of other specified precerebral artery with cerebral infarction 433.91 Occlusion and stenosis of unspecified precerebral artery with cerebral infarction 434.01 Cerebral thrombosis with cerebral infarction 434.11 Cerebral embolism with cerebral infarction 434.91 Cerebral artery occlusion unspecified with cerebral infarction 435.x Transient cerebral ischemia 436.x Apoplexy, cerebral apoplexy, cerebrovascular accident
Peripheral artery disease	Diagnosis (ICD9CM code) of: 440.2 – Atherosclerosis of native arteries of the extremities 443.0 – Raynaud's syndrome 443.1 – Thromboangiitis obliterans (Buerger's disease) 443.8 – Other specified peripheral vascular diseases 443.9 – Peripheral vascular disease unspecified V45.89 Angioplasty of lower extremities V49.7x Lower limb amputation status	– Hospitalization with one of the following primary/secondary diagnoses (ICD9CM code): 250.7- Diabetes with peripheral circulatory disorders 440.x – Atherosclerosis 441.x – Aortic aneurysm and dissection 442.x – Other aneurysm 443.x – Other peripheral vascular disease 444.x – Arterial embolism and thrombosis 447.1 – Stricture of artery 707.1- Ulcer of lower limb except decubitus 785.4 – Gangrene V49.6 – Upper limb amputation status V49.7 – Lower limb amputation status – Hospitalization with one of the following procedures (ICD9CM code): 00.45 – Insertion of one vascular stent 00.55 – Insertion of drug-eluting stent(s) of other peripheral vessel(s) 00.61 – Percutaneous angioplasty of extracranial vessel(s) 00.63 – Percutaneous insertion of carotid artery stent(s) 00.64 – Percutaneous insertion of other extracranial artery stent(s) 38.02 – Incision of vessel, other vessels of head and neck 38.12 – Endarterectomy, other vessels of head and neck 38.18 – Endarterectomy, lower limb arteries 38.32 – Resection of vessel with anastomosis, other vessels of head and neck 38.42 – Resection of vessel with replacement, other vessels of head and neck 38.62 – Other excision of vessels, other vessels of head and neck 38.82 – Other surgical occlusion of vessels, other vessels of head and neck 39.22 – Aorta-subclavian-carotid

		bypass 39.25 – Aorta-iliac-femoral bypass 39.29 – Other (peripheral) vascular shunt or bypass 39.50 – Angioplasty of other non-coronary vessel(s) 39.90 – Insertion of non-drug-eluting peripheral (non-coronary) vessel stent(s) 84.0x – Amputation of upper limb 84.1x – Amputation of lower limb
Cardiovascular and blood pharmacological treatment within one year before and after the index date		
	The following drugs (ATC code): – diuretics (C03); – angiotensin-converting enzyme inhibitors (C09A and C09B); – angiotensin II receptor blockers (C09C and C09D); – renin inhibitors (C09XA); – antidiabetics (A10) and SGLT2-Is (A10BK01, A10BK02, A10BK03, A10BK04, A10BD15, A10BD16, A10BD20, A10BD23); – HMG CoA reductase inhibitors (C10AA and C10BX); – lipid lowering agents (excl. HMG CoA reductase inhibitors) (C10, excl. C10AA and C10BX); – antiplatelets (B01AC); – oral anticoagulants (B01AA03, B01AA07, B01AE07, B01AF01, B01AF02, B01AF03).	The following drugs (ATC code): – diuretics (C03); – angiotensin-converting enzyme inhibitors (C09A and C09B); – angiotensin II receptor blockers (C09C and C09D); – renin inhibitors (C09XA); – antidiabetics (A10) and SGLT2-Is (A10BK01, A10BK02, A10BK03, A10BK04, A10BD15, A10BD16, A10BD20, A10BD23); – HMG CoA reductase inhibitors (C10AA and C10BX); – lipid lowering agents (excl. HMG CoA reductase inhibitors) (C10, excl. C10AA and C10BX); – antiplatelets (B01AC); – oral anticoagulants (B01AA03, B01AA07, B01AE07, B01AF01, B01AF02, B01AF03).

Supplementary table 2. Clinical variables and related identification criteria in Health Search and Fondazione Ricerca e Salute databases.

Cut-off	Sensitivity	Specificity	Positive predictive value (PPV)	Negative predictive value (NPV)
0.20	73.4 [[72.5], [74.2]]	68.6 [[68.1], [69.1]]	36.8 [[36.1], [37.5]]	91.2 [[90.8], [91.5]]
0.25	63.1 [[62.1], [64.0]]	77.1 [[76.7], [77.5]]	40.7 [[39.9], [41.5]]	89.3 [[89.0], [89.7]]
0.30	53.4 [[52.4], [54.4]]	83.7 [[83.3], [84.0]]	44.9 [[43.9], [45.8]]	87.8 [[87.5], [88.1]]

Supplementary table 3. Cut-off values of estimation probability of patients with chronic kidney disease and eligible to SGLT2-Is selected within the Fondazione Ricerca e Salute database through the methodology described for the step 1, with related specificity and sensitivity.

Cut-off	Sensitivity	Specificity	Positive predictive value (PPV)	Negative predictive value (NPV)
0.20	77.4	–	100.0	–
0.25	70.8	–	100.0	–
0.30	63.6	–	100.0	–

Supplementary table 4. Validation of the estimation model. Cut-off values of estimation probability of patients with chronic kidney disease and eligible to SGLT2-Is selected within the Fondazione Ricerca e Salute databasethrough the methodology described for the step 1, with related specificity and sensitivity.

This work was supported by an unconditional grant from Astra Zeneca Italy SpA. The financial support for this study was provided with a funding agreement ensuring maintenance of author independence in study design, data interpretation, writing, and decision to publish.

Competing interests: APM received personal fees for the participation in clinical studies supported by Bayer, Novartis, Sanofi and Astra Zeneca, outside the present work. FL and EM and provided consultancies in protocol preparation for epidemiological studies and data analyses for AstraZeneca and Mundipharma. DP, CC, GP and GM provided clinical consultancies for AstraZeneca. RP received honoraria for lectures from Lilly, Boehringer, AstraZeneca, Novo-Nordisk, Vifor, Alfa-Sigma, and Bayer, outside the present work. CP, LD, SC, GR and NM are employees of Fondazione Ricerca e Salute (ReS). AP is consultant for Fondazione Ricerca e Salute (ReS).

BIBLIOGRAPHY

1. Wanner C, Inzucchi SE, Lachin JM, Fitchett D, von Eynatten M, Mattheus M et al. Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes. N Engl J Med. 2016;375(4):323-34. https://doi.org/10.1056/NEJMoa1515920.
2. Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJL, Charytan DM et al. Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. N Engl J Med. 2019;380(24):2295-306. https://doi.org/10.1056/NEJMoa1811744.
3. Fadini GP, Del Prato S, Avogaro A, Solini A. Challenges and opportunities in real-world evidence on the renal effects of sodium-glucose cotransporter-2 inhibitors. Diabetes Obes Metab. 2022;24(2):177-86. https://doi.org/10.1111/dom.14599.
4. Heerspink HJL, Stefánsson BV, Correa-Rotter R, Chertow GM, Greene T, Hou FF et al. Dapagliflozin in Patients with Chronic Kidney Disease. N Engl J Med. 2020;383(15):1436-46. https://doi.org/10.1056/NEJMoa2024816.
5. GBD Chronic Kidney Disease Collaboration. Global, regional, and national burden of chronic kidney disease, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet. 2020;395(10225):709-33. https://doi.org/10.1016/s0140-6736(20)30045-3.
6. De Nicola L, Donfrancesco C, Minutolo R, Lo Noce C, Palmieri L, De Curtis A et al. Prevalence and cardiovascular risk profile of chronic kidney disease in Italy: results of the 2008-12 National Health Examination Survey. Nephrol Dial Transplant. 2015;30(5):806-14. https://doi.org/10.1093/ndt/gfu383.
7. Stevens PE, Levin A. Evaluation and management of chronic kidney disease: synopsis of the kidney disease: improving global outcomes 2012 clinical practice guideline. Ann Intern Med. 2013;158(11):825-30. https://doi.org/10.7326/0003-4819-158-11-201306040-00007.
8. Chatzimanouil MKT, Wilkens L, Anders HJ. Quantity and Reporting Quality of Kidney Research. J Am Soc Nephrol. 2019;30(1):13-22. https://doi.org/10.1681/asn.2018050515.
9. Tangri N, Peach EJ, Franzén S, Barone S, Kushner PR. Patient Management and Clinical Outcomes Associated with a Recorded Diagnosis of Stage 3 Chronic Kidney Disease: The REVEAL-CKD Study. Adv Ther. 2023;40(6):2869-85. https://doi.org/10.1007/s12325-023-02482-5.
10. Lapi F, Bianchini E, Marconi E, Medea G, Piccinni C, Maggioni AP et al. A methodology to assess the population size and estimate the needed resources for new licensed medications by combining clinical and administrative databases: The example of glycated haemoglobin in type 2 diabetes. Pharmacoepidemiol Drug Saf. 2023;32(10):1083-92. https://doi.org/10.1002/pds.5641.
11. Piccinni C, Dondi L, Calabria S, Ronconi G, Pedrini A, Lapi F et al. How many and who are patients with heart failure eligible to SGLT2 inhibitors? Responses from the combination of administrative healthcare and primary care databases. Int J Cardiol. 2022. https://doi.org/https://doi.org/10.1016/j.ijcard.2022.09.053.
12. HealthSearch. XI Report Health Search2018.
13. Calabria S, Andreotti F, Ronconi G, Dondi L, Campeggi A, Piccinni C et al. Antiplatelet Therapy during the First Year after Acute Coronary Syndrome in a Contemporary Italian Community of over 5 Million Subjects. Journal of clinical medicine. 2022;11(16). https://doi.org/10.3390/jcm11164888.
14. van Oosten MJM, Logtenberg SJJ, Edens MA, Hemmelder MH, Jager KJ, Bilo HJG et al. Health claims databases used for kidney research around the world. Clinical Kidney Journal. 2020;14(1):84-97. https://doi.org/10.1093/ckj/sfaa076.
15. Avillach P, Coloma PM, Gini R, Schuemie M, Mougin F, Dufour JC et al. Harmonization process for the identification of medical events in eight European healthcare databases: the experience from the EU-ADR project. J Am Med Inform Assoc. 2013;20(1):184-92. https://doi.org/10.1136/amiajnl-2012-000933.
16. Lv JC, Zhang LX. Prevalence and Disease Burden of Chronic Kidney Disease. Adv Exp Med Biol. 2019;1165:3-15. https://doi.org/10.1007/978-981-13-8871-2_1.
17. Provenzano M, Mancuso C., Garofalo C, De Nicola L, Andreucci M. Temporal variation of Chronic Kidney Disease's epidemiology. Giornale Italiano di Nefrologia. 2019; marzo-aprile 2019.
18. Maggioni AP, Dondi L, Andreotti F, Ronconi G, Calabria S, Piccinni C et al. Prevalence, prescriptions, outcomes and costs of type 2 diabetes patients with or without prior coronary artery disease or stroke: a longitudinal 5-year claims-data analysis of over 7 million inhabitants. Ther Adv Chronic Dis. 2021;12:20406223211026390. https://doi.org/10.1177/20406223211026390.
19. Minutolo R, Lapi F, Chiodini P, Simonetti M, Bianchini E, Pecchioli S et al. Risk of ESRD and death in patients with CKD not referred to a nephrologist: a 7-year prospective study. Clin J Am Soc Nephrol. 2014;9(9):1586-93. https://doi.org/10.2215/cjn.10481013.

20. European Medicines Agency. CHMP post-authorisation summary of positive opinion for Forxiga (WS-1737), First published: 16/10/2020 – EMA/CHMP/535224/2020. 2020. https://www.ema.europa.eu/en/documents/smop/chmp-post-authorisation-summary-positive-opinion-forxiga-ws-1737_en.pdf.
21. European Medicines Agency. CHMP post-authorisation summary of positive opinion for Jardiance (II-55). First published: 21/05/2021. EMA/CHMP/275069/2021. 2021.
22. Herrington WG, Staplin N, Wanner C, Green JB, Hauske SJ, Emberson JR et al. Empagliflozin in Patients with Chronic Kidney Disease. N Engl J Med. 2023;388(2):117-27. https://doi.org/10.1056/NEJMoa2204233.
23. Raschi E, Fadini GP, Diemberger I, Poluzzi E, De Ponti F. SGLT2 inhibitors for heart failure with reduced ejection fraction: a real EMPEROR? Expert Opin Pharmacother. 2021;22(5):647-50. https://doi.org/10.1080/14656566.2020.1846719.
24. Maggioni AP, Orso F, Calabria S, Rossi E, Cinconze E, Baldasseroni S et al. The real-world evidence of heart failure: findings from 41 413 patients of the ARNO database. Eur J Heart Fail. 2016;18(4):402-10. https://doi.org/10.1002/ejhf.471.
25. Jankowski J, Floege J, Fliser D, Böhm M, Marx N. Cardiovascular Disease in Chronic Kidney Disease: Pathophysiological Insights and Therapeutic Options. Circulation. 2021;143(11):1157-72. https://doi.org/10.1161/circulationaha.120.050686.
26. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) With the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2021. https://doi.org/10.1093/eurheartj/ehab368.
27. Khan YH, Sarriff A, Mallhi TH, Adnan AS, Khan AH. Is diuretic use beneficial or harmful for patients with chronic kidney disease? European journal of hospital pharmacy : science and practice. 2017;24(4):253-4. https://doi.org/10.1136/ejhpharm-2017-001285.
28. Igarashi A, Maruyama-Sakurai K, Kubota A, Akiyama H, Yajima T, Kohsaka S et al. Cost-Effectiveness Analysis of Initiating Type 2 Diabetes Therapy with a Sodium-Glucose Cotransporter 2 Inhibitor Versus Conventional Therapy in Japan. Diabetes Ther. 2022;13(7):1367-81. https://doi.org/10.1007/s13300-022-01270-8.
29. Vareesangthip K, Deerochanawong C, Thongsuk D, Pojchaijongdee N, Permsuwan U. Cost-Utility Analysis of Dapagliflozin as an Add-on to Standard of Care for Patients with Chronic Kidney Disease in Thailand. Adv Ther. 2022;39(3):1279-92. https://doi.org/10.1007/s12325-021-02037-6.
30. Tisdale RL, Cusick MM, Aluri KZ, Handley TJ, Joyner AKC, Salomon JA et al. Cost-Effectiveness of Dapagliflozin for Non-diabetic Chronic Kidney Disease. J Gen Intern Med. 2022;37(13):3380-7. https://doi.org/10.1007/s11606-021-07311-5.
31. Jha V, Al-Ghamdi SMG, Li G, Wu MS, Stafylas P, Retat L et al. Global Economic Burden Associated with Chronic Kidney Disease: A Pragmatic Review of Medical Costs for the Inside CKD Research Programme. Adv Ther. 2023;40(10):4405-20. https://doi.org/10.1007/s12325-023-02608-9.
32. Di Domenicantonio R, Cappai G, Agabiti N, Marino C, Simonato L, Canova C et al. A Systematic Review of Case-Identification Algorithms Based on Italian Healthcare Administrative Databases for Three Relevant Diseases of the Digestive and Genitourinary System: Inflammatory Bowel Diseases, Celiac Disease, and Chronic Kidney Disease. Epidemiol Prev. 2019;43(4 Suppl 2):88-98. https://doi.org/10.19191/ep19.4.S2.P088.095.
33. Marino C, Ferraro PM, Bargagli M, Cascini S, Agabiti N, Gambaro G et al. Prevalence of chronic kidney disease in the Lazio region, Italy: a classification algorithm based on health information systems. BMC Nephrol. 2020;21(1):23. https://doi.org/10.1186/s12882-020-1689-z.
34. Lapi F, Marconi E, Piccinocchi G, Medea G, Piccinni C, Maggioni AP et al. To retrieve values of albuminuria to define the size of CKD patients eligible to SGLT-2Is: An explorative analysis using a primary care database. Pharmacoepidemiol Drug Saf. 2023. https://doi.org/10.1002/pds.5742.