Supplementary Material

Clinical Profile and Treatment Adherence in Patients With Type 2 Diabetes and Chronic Kidney Disease Who Initiate an SGLT2 Inhibitor: A Multi-Cohort Study

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Appendix A. Description of Data Sources

Danish National Health Registers (DNHR), Denmark

Access to DNHR data for this study was through a collaboration model. Administrative data were used from the Danish Health Care System. Denmark has 5.8 million inhabitants and is divided into 5 administrative regions. The tax-supported Danish National Health Service provides free of charge primary and secondary healthcare services to all Danish residents in all regions. Data on primary and secondary healthcare utilization is recorded in several Danish databases.

The Danish National Patient Registry records information on hospital-related diagnosis codes, surgical procedures, and discharge dates from inpatient hospitals in Denmark since 1977 and on outpatient clinics, emergency department, and psychiatric wards since 1995. Diagnoses are classified according to the *International Statistical Classification of Diseases, Tenth Revision* (ICD-10) since 1994, whereas surgical procedures have been coded according to the Danish version of the Nordic Medico-Statistical Committee Classification of Surgical Procedures since 1996. For this study, we used all primary and secondary diagnosis codes related to an inpatient, outpatient, and emergency department encounter.

The Danish National Prescription Registry records information on all reimbursed drug prescriptions from local pharmacies since 1995. The database contains information on dispensing details, such as name, date, ATC code, volume according to defined daily dosage, size of package, strength, and form.

The Danish Civil Registration System records daily updated individual-level data on civil status, vital status, and migration since 1968, allowing complete follow-up.

The Nationwide Register of Laboratory Results for Research contains information on biochemistry data from routinely collected blood tests covering hospitals and GPs for the entire Danish population. The database started recording laboratory data in 2013 for most Danish administrative regions and is considered complete nationwide from October 2015 onwards. Thus, related to the current study, there will be missing laboratory data in the study period before 2015 for some Danish regions.

The Danish National Health Service Register contains statistical information about the activities of health professionals contracted with the tax-funded public healthcare system (GPs, medical specialists, physiotherapists, etc.). These activities include a broad spectrum of healthcare services provided in the primary care setting, allowing the study of healthcare utilization patterns.

PHARMO Data Network

Access to PHARMO data for this study was through a collaboration model. The PHARMO Data Network is a population-based data source with combined anonymous electronic healthcare data from different primary and secondary healthcare settings in the Netherlands [22]. The different data sources, including data from GPs, in- and outpatient pharmacies, clinical laboratories, hospitals, the cancer registry, pathology registry, and perinatal registry, are linked on a patient level through validated algorithms. The data are collected, processed, linked, and anonymized by STIZON, an ISO/IEC 27001 and NEN 7510 certified foundation, compliant to the General Data Protection Regulation (GDPR). STIZON acts as a trusted third party between the data sources

and users of the anonymized data, which can request proportional study-specific datasets, in accordance with the GDPR.

The longitudinal nature of the PHARMO Data Network system enables to follow-up more than 10 million persons of a well-defined population in the Netherlands for an average of 12 years. Currently, the PHARMO Data Network covers over 7 million active persons out of 17 million inhabitants of the Netherlands. Data collection period, catchment area, and overlap between data sources differ. All electronic patient records in the PHARMO Data Network include information on age, sex, socioeconomic status, and mortality. Other information available is dependent on the data source. The PHARMO Data Network is updated yearly in Q4 with a lag of 1 to 1.5 years. To address the objectives of the present study, the PHARMO data described in the following paragraphs were used.

Outpatient pharmacy data

The outpatient pharmacy data comprise GP or specialist prescribed healthcare products dispensed by outpatient pharmacies, including community pharmacies as well as hospital-based outpatient pharmacies. The dispensing records include information on type of product, date, strength, dosage regimen, quantity, route of administration, prescriber specialty, and costs. Drug dispensings are coded according to the World Health Organization (WHO) ATC Classification System [41]. Outpatient pharmacy data cover a catchment area representing 4.2 million residents.

General practitioner data

The GP data comprise electronic patient records registered by GPs. The records include information on diagnoses and symptoms, laboratory test results, referrals to specialists, and

healthcare product/drug prescriptions. The prescription records include information on type of product, prescription date, strength, dosage regimen, quantity, and route of administration. Drug prescriptions are coded according to the WHO ATC Classification System [41]. Diagnoses and symptoms are coded according to the International Classification of Primary Care (ICPC) [42], which can be mapped to ICD codes, but also can be entered as free text. General practitioner data cover a catchment area representing 3.2 million residents.

Hospital data

The hospital data comprise datasets containing data on hospital admissions, ambulatory consultations, and high-cost medicines. For the present study, hospital admissions were used. Hospital data are collected and maintained by the Dutch Hospital Data Foundation [43] and comprise records from nearly all hospitals in the Netherlands. With permission from each hospital, the data are linked for research purposes with the PHARMO Data Network by the trusted third party.

This dataset comprises hospital admissions for more than 24 hours and admissions for less than 24 hours for which a bed is required (i.e., inpatient records). The records include information on hospital admission and discharge dates, discharge diagnoses, and procedures. Diagnoses are coded according to the WHO International Classification of Diseases, [44] and procedures are coded according to the Dutch Hospital Data Foundation registration system for procedures, [45] which links to the Dutch Healthcare Authority (NZa) declaration codes [46] and the Dutch Classification of Procedures [47]. Currently, the PHARMO Institute has access to data from 1998 onwards and for over 80% of the hospitals.

Valencia Health System Integrated Database

Access to the Valencia Health System Integrated Database (**VID**) data for this study was through a collaboration model. The **VID** is a set of multiple, public, population-wide electronic databases for the Valencia region, the fourth most populated Spanish region, with ∼5 million inhabitants, representing 10.7% of the Spanish population and approximately 1% of the European population. **VID** provides exhaustive longitudinal information, including sociodemographic and administrative data (sex, age, nationality, etc.), clinical (diagnoses, procedures, diagnostic tests, imaging, etc.), pharmaceutical (prescription, dispensation), and healthcare utilization data from hospital care, emergency departments, specialized care (including mental and obstetrics care), primary care, and other public health services. All the information in **VID** databases can be linked at the individual level through a single personal identification code.

Coding and registry in the relevant databases in VID for FINEGUST

The Population Information System (SIP) (Sistema de información Poblacional) is a region-wide database that provides basic information on VHS coverage (dates and causes of VHS entitlement or disentitlement, insurance modality, pharmaceutical copayment status, assigned Healthcare Department, Primary Healthcare District and primary care doctor, etc.) and also some sociodemographic data, such as sex, date of birth, nationality, country of origin, previous year income strata, employment status, risk of social exclusion, geographic location, address, and other administrative data. Importantly, SIP includes the date of death captured from the Mortality Registry. SIP is paramount to **VID** as it is the source of the individual, exclusive, and permanent identification number associated with each individual (the SIP number), which is then used throughout the rest of the databases, allowing data linkage across the multiple databases in the network.

The Ambulatory Medical Record (ABUCASIS) was implemented in 2006 as the electronic medical record for primary and specialized outpatient activity, reaching 96% population coverage in 2009. ABUCASIS is integrated by 2 main modules: the Ambulatory Information System (SIA) (Sistema de Información Ambulatoria) and the pharmaceutical module (GAIA) (Gestor Integral de la Prestación Farmacéutica), including pediatric and adult primary care, mental healthcare, prenatal care and specialist outpatient services, as well as providing information about dates, visits, procedures, lab test results, diagnoses, clinical and lifestyle information. It also includes information on several health programs (healthy children, vaccines, pregnancy, notifiable diseases, etc.), the primary care nurse clinical record, and the health-related social assistance record. The SIA module uses the *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) and the ICD-10-ES (a Spanish translation of the *International Classification of Diseases, Tenth Revision, Clinical Modification* [ICD-10-CM]) systems for coding. The SIA also uses the Clinical Risk Groups system (3M) to stratify the morbidity of the entire population.

The GAIA pharmaceutical module stores data on all outpatient pharmaceutical prescriptions and dispensations, including both primary care and outpatient hospital departments, using the ATC classification system and the National Pharmaceutical Catalogue, which allow the identification of the exact content of each dispensation. In-hospital medication is not included. GAIA provides detailed information on prescriptions issued by physicians, such as the duration of treatment and dosage. GAIA includes a comprehensive e-prescription paper-free system connected to all community pharmacies in the region that permits the linkage of individual prescriptions and dispensations through a specific prescription identification number. This results in a competitive advantage with regard to other pharmaceutical databases that usually have dispensation

information only from pharmacy claims and enables a refined estimation of common and relevant research features, such as medication adherence.

The Hospital Medical Record (ORION) has been in implementation since 2008 and provides comprehensive information covering all areas of specialized care from admission, outpatient consultations, hospitalization, emergencies, diagnostic services (laboratory tests, imaging, microbiology, pathology, etc.), pharmacy, surgical block (including day surgery), critical care, prevention and safety, social work, at-home hospitalization, and day hospitalization. ORION is currently in the process of being integrated for the whole region, with several databases already fully integrated and available for all hospitals, including the Minimum Basic Data Set at Hospital Discharge (MBDS) and the Accident & Emergency Department (AED) clinical record.

The MBDS is a synopsis of clinical and administrative information on all hospital admissions and major ambulatory surgery in the VHS hospitals, including public–private partnership hospitals (approximately 450,000 admissions per year in the region). The MBDS includes admission and discharge dates, age, sex, geographical area and zone of residence, main diagnosis at discharge, up to 30 secondary diagnoses (comorbidities or complications), clinical procedures performed during the hospital episode and the Diagnosis Related Groups assigned at discharge. The MBDS uses the ICD-9-CM system for coding until December 2015 and the ICD-10-ES thereafter. The MBDS was extended in 2015 to include the “present on admission” diagnosis marker and information on tumor morphology, as well as information on admissions from private hospitals.

The AED clinical record was launched in 2008 and collects triage data, diagnoses, tests, and procedures performed in public emergency departments. As with the MBDS, the coding system

used was ICD-9-CM until December 2015 and ICD-10-ES thereafter. Diagnosis codification has been increasing from about 45% of all emergency department visits between 2008 and 2014 up to approximately 75% in 2017, basically due to the progressive incorporation of hospital coding.

Data lags in VID database

In all databases in **VID**, individual data are collected daily as part of the routine clinical care provided to patients. Accordingly, data sets are updated daily and hence data may be available for research up to the same day data are extracted. Only in some cases, such as the MBDS and the AED records, are data subject to a consolidation and quality-check process before data are available for research; in these situations, data from the last quarter before the data extraction may be missing or not consolidated.

Japan Chronic Kidney Disease Database Extension (J-CKD-DB-Ex)

Access to J-CKD-DB-Ex data for this study was through a collaboration model. The J-CKD-DB-Ex is a large-scale, nationwide comprehensive clinical database of patients with CKD based on EHR data from 5 participating university hospitals. The data were automatically extracted from records of all patients treated at participating university hospitals aged 18 years or older with CKD (proteinuria $\geq$ 1+ [dipstick test] and/or eGFR < 60 mL/min/1.73 m^2). Initiated in January 2014, the database contains information on all inpatient and outpatient encounters, prescriptions, diagnosis codes, and laboratory measurements. In principle, both diagnosis codes and diagnosis name are available in the database. J-CKD-DB-Ex contains longitudinal data with approximately 250,000 patients. The data are updated once per year, at the end of each calendar year.

Optum's de-identified Clinformatics® Data Mart Database (CDM)

Access to CDM data for this study was through a license. CDM is a database comprising administrative health claims for members of large commercial and Medicare Advantage health plans with service dates beginning January 2007 to the present. The population is geographically diverse, spanning all 50 states plus the District of Columbia and covering approximately 3% to 4% of the US population. The database includes approximately 15 to 20 million annual covered lives, for a total of approximately 68 million unique lives over the available period.

Pharmacy claims include drug name, dosage form, drug strength, fill date, days' supply, financial information, and de-identified patient and prescriber information, allowing longitudinal tracking of medication refill patterns and changes in medications. Medical claims or encounter data are collected from all available healthcare sites (e.g., inpatient hospital, outpatient hospital, emergency department, physician's office, surgery center) for virtually all types of provided services, including specialty, preventive, and office-based treatments. These administrative claims are submitted for payment by providers and pharmacies and are verified, adjudicated, adjusted, and de-identified prior to inclusion in CDM. Data are included for only those covered lives with both medical and prescription drug coverage to enable users to evaluate claims related to the complete healthcare experience. The data are ICD-10-CM compliant.

Additionally, the CDM includes results for outpatient laboratory tests processed by large national vendors under contract with the managed care organization. In addition to medical claims, pharmacy claims, and laboratory test results, CDM includes data tables related to member inpatient confinements, member enrollment, and provider data.

The data are updated quarterly, with a lag time of approximately 9 months.

Appendix Table A1. Summary of Characteristics of Participating Data Sources

Feature	Denmark, Danish National Health Registers (DNHR)	The Netherlands, PHARMO	Spain, VID	Japan Chronic Kidney Disease Database (J-CKD-DB-Ex)	US, Optum's de-identified Clinformatics® Data Mart Database (CDM)
General information					
Country population	5,964,059 [a]	17,407,585[b]	Valencia, 5,218,840[c]	125,710,000[d]	336 million[e]
Database population	5.8 million	4 million	5 million	--	68 million (15-20 million annual covered lives)
Database type	National health record databases capable of linkage with other databases through a unique personal identification number	Primary healthcare electronic medical record database plus partial linkage to other data	Regional health record databases capable of linkage with other databases through a unique personal identification number	Hospital-based, longitudinal electronic medical record database	Administrative health claims from commercial health plan and Medicare Advantage members
Drug dictionary codes/ therapeutic classification	ATC	ATC	ATC	National drug codes in Japan, HOT codes	NDC codes
Capture of medication information	Outpatient pharmacy prescriptions in Danish National Prescription Registry	Dispensing records in outpatient pharmacy data	Prescription and dispensation information linked at the individual level. Prescription data were used to define the index date and dispensing data to estimate days covered with the medication.	Prescriptions from hospital and outpatient encounters. Under Japanese regulation, any new medication should be renewed every 2 weeks during the first year that the medication is in the market, and for longer periods (e.g., 30 days) after that.	Outpatient pharmacy dispensing records

Feature	Denmark, Danish National Health Registers (DNHR)	The Netherlands, PHARMO	Spain, VID	Japan Chronic Kidney Disease Database (J-CKD-DB-Ex)	US, Optum's de-identified Clinformatics® Data Mart Database (CDM)
Disease and procedure coding system(s)	ICD-10 Procedure codes: NCSP	ICD-9-CM/ICD-10 WHO, ICPC	ICD-9-CM, ICD-10-ES	ICD-10 Disease name code	ICD-9-CM/ICD-10-CM CPT, HCPCS
Data privacy standards	Cell frequencies (categorical variables) of less than 5 are not reported, and related cells have additional masking, if needed, to prevent back calculation; for continuous variables, first and 99th percentiles are reported instead of minimum and maximum values	If the number of observations or patients is < 5 per stratum, results are not further specified.	Categorical variables with low counts, or low frequencies for a specific level of a categorical variable, are not reported. Masking may occur to prevent back calculation of low counts. For continuous variables, the first and 99th percentiles are reported instead of minimum and maximum values.	Categorical variables with low counts are not reported. For continuous variables, the first and 99th percentiles are reported instead of minimum and maximum values. Masking may occur to prevent back calculation of low count events.	CDM was designed to fully comply with HIPAA Privacy Rules. Techniques used to de-identify data include: • Removing all direct identifiers for an individual, including name, street address, social security number, phone numbers, and date of birth • Reducing the number of data elements that might be matched with an external data source or censoring their content In addition, access and use of the data are restricted by data use agreement with clients.
Study-specific information					
Definition of T1D	< 30 years old at first diabetes record (hospital diagnosis or	At least 1 diagnosis code for T1D in the general practitioner	ICD codes (recorded diagnosis in the index date in the electronic	ICD-10 codes	Recorded diagnoses from medical claims for encounter data from all

Feature	Denmark, Danish National Health Registers (DNHR)	The Netherlands, PHARMO	Spain, VID	Japan Chronic Kidney Disease Database (J-CKD-DB-Ex)	US, Optum's de-identified Clinformatics® Data Mart Database (CDM)
	medication prescription); if first diabetes record is on or after 1995, mandatory use of insulin around first record is required	data or single insulin dispensing, or aged < 30 years at first insulin dispensing recorded on or before the index date	medical record in VID covering primary and secondary care)		available healthcare sites (e.g., inpatient hospital, outpatient hospital, emergency department, physician's office, surgery center) for all types of provided services. At least 2 diagnosis codes for T1D during the baseline period [-all available, 0 days) were required.
Definition of T2D	Redemption of prescription for a glucose-lowering medication from community pharmacy or a hospital contact with a T2D diagnosis	Recorded diagnosis of T2D in the general practitioner data or ≥ 2 consecutive dispensings of non-insulin drugs used in diabetes (ATC code A10B) within 6 months	ICD codes (recorded diagnosis in the index date in the electronic medical record in VID covering primary and secondary care)	ICD-10 codes	Recorded diagnoses from medical claims for encounter data from all available healthcare sites (e.g., inpatient hospital, outpatient hospital, emergency department, physician's office, surgery center) for all types of provided services. One diagnosis code for T2D during the baseline period [-all available, 0 days) was required
Medical conditions	Diagnosis coded on or before the index date	Recorded diagnoses in primary care or	ICD codes (recorded diagnosis in the index	Recorded diagnoses in inpatient and	Recorded diagnoses from medical claims for

Feature	Denmark, Danish National Health Registers (DNHR)	The Netherlands, PHARMO	Spain, VID	Japan Chronic Kidney Disease Database (J-CKD-DB-Ex)	US, Optum's de-identified Clinformatics® Data Mart Database (CDM)
	during an inpatient, outpatient, or emergency department visit using both primary and secondary diagnosis as recorded in the Danish National Patient Registry	inpatient hospital setting	date in the electronic medical record in VID covering primary and secondary care)	outpatient settings in hospital care	encounter data from all available healthcare sites (e.g., inpatient hospital, outpatient hospital, emergency department, physician's office, surgery center) for all types of provided services
Estimation of day's supply of index medication	Actual days of supply not available. Estimated from the upper quartile of the times between prescriptions	Calculated by dividing the amount supplied by the prescribed dose	Days covered with a medication is estimated from prescription information (presentation, dosing schedule)	Days covered with a medication is obtained from dispensing data	Estimated day count the drug supply should last is reported in the data set
Obesity	BMI not available, obesity defined by diagnosis codes	BMI available, and obesity also defined by diagnosis codes	BMI available, but may be affected by registration bias or selective reporting	BMI not available, obesity defined by diagnosis codes	BMI not available, obesity defined by diagnosis codes

ATC = Anatomical Therapeutic Chemical Classification System; BMI = body mass index; CPT = Current Procedural Terminology; DNHR = Danish National Health Registers; HCPCS = Healthcare Common Procedure Coding System; HIPAA = Health Insurance Portability and Accountability Act; HOT = standard master codes for pharmaceutical products (http://www2.medis.or.jp/master/hcode/); ICD-10 = *International Classification of Diseases, Tenth Revision*; ICD-10-CM = *International Classification of Diseases, Tenth Revision, Clinical Modification*; ICD-10-ES = *International Classification of Diseases, Tenth Revision, Spanish Version*; ICD-9-CM = *International Classification of Diseases, Ninth Revision, Clinical Modification*; ICPC = International Classification of Primary Care; J-CKD-DB-Ex = Japan Chronic Kidney Disease Database Extension; NCSP = NOMESCO Classification of Surgical Procedures; NDC = National Drug Code; CDM = Optum's de-identified Clinformatics® Data Mart Database; PHARMO = PHARMO Data Network; T1D = type 1 diabetes; T2D = type 2 diabetes; US = United States; VID = Valencia Health System Integrated Database; WHO = World Health Organization.

[a] Population of Denmark from Statistics Denmark December 2023. Available at: Population figures - Statistics Denmark (dst.dk).

[b] Population data from Eurostat. Population data for European countries. 2021. Available at: https://ec.europa.eu/eurostat/statistics-explained/images/8/83/Population_and_population_change_statistics_YB2020.xlsx, except for the Valencia region of Spain.

[c] Population of Spain in 2023 by autonomous community (https://www.statista.com/statistics/445549/population-of-spain-by-autonomous-community/).

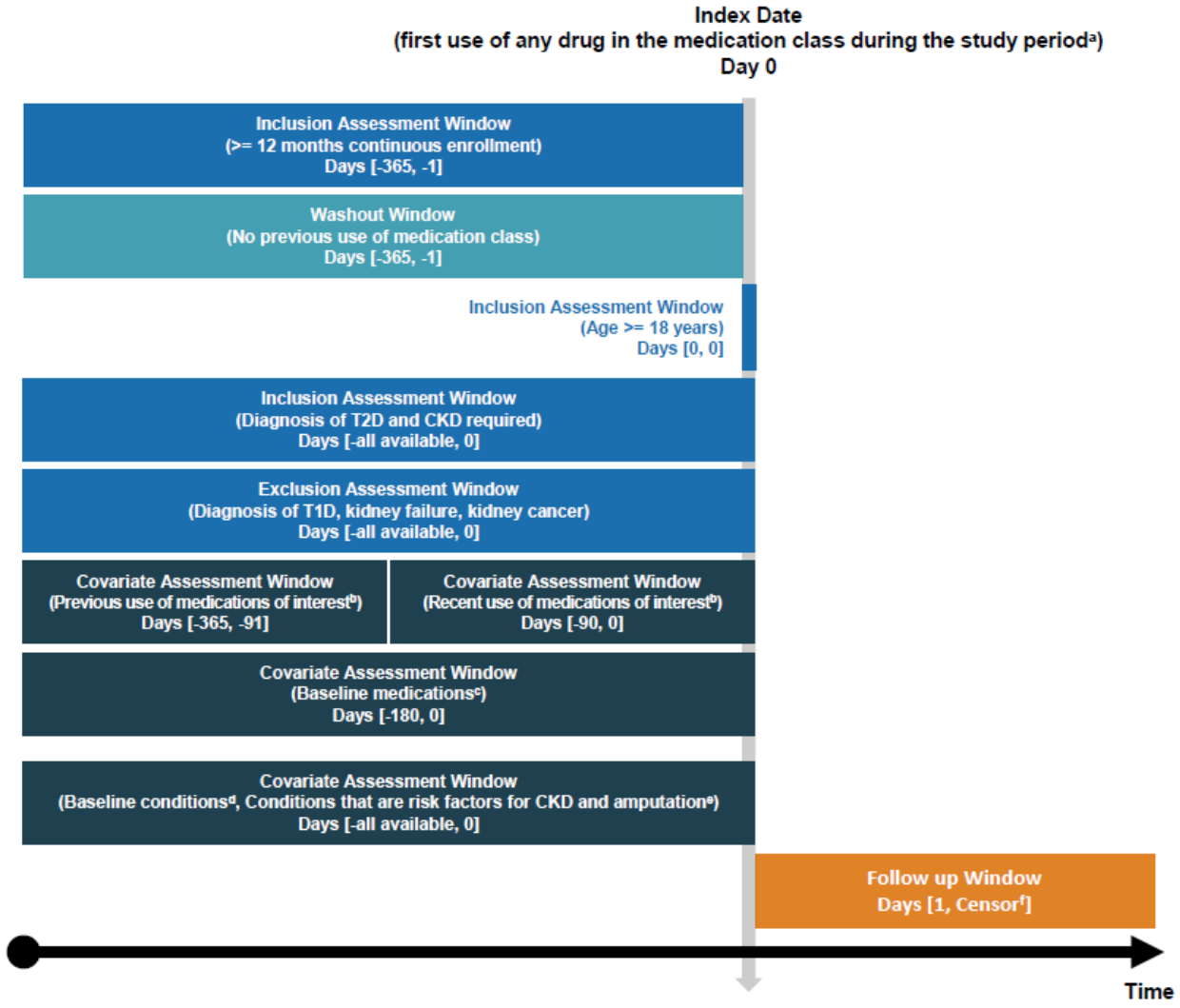
[d] Population data from Statistics Bureau of Japan (https://www.stat.go.jp/english/index.html)

[e] Population data from the US census in 2023 (https://www.census.gov/popclock/).

Appendix B. Variable Assessment and Classification of Index Medications

Variable Assessment Windows

Appendix Figure B1. Variable Assessment Windows Relative to the Study Index Date for the SGLT2i Cohorts



ACEi = angiotensin-converting enzyme inhibitors; ARB = angiotensin receptor blockers; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; GLP-1 RA = glucagon-like peptide-1 receptor agonists; HIV = human immunodeficiency virus; MRA = mineralocorticoid receptor antagonists; SGLT2i = sodium-glucose cotransporter 2 inhibitors; sMRA = steroidal mineralocorticoid receptor antagonists; T1D = type 1 diabetes; T2D = type 2 diabetes.

[a] Study period: 1 January 2012 through 30 June 2021.

[b] SGLT2i, GLP-1 RA, sMRA, other nonsteroidal MRA, ACEi, ARB.

[c] Cardiovascular medications (antihypertensives, beta blockers, direct renin inhibitors, angiotensin receptor-neprilysin inhibitor, lipid-lowering medications, anticoagulants, aspirin and other antiplatelets [e.g., clopidogrel, ticlopidine, prasugrel], digoxin, nitrates), anti-inflammatory drugs, antibiotics, other (acetaminophen, anticonvulsants, antifungals, antituberculars, chemotherapeutic agents).

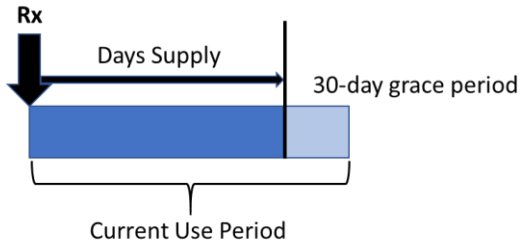
[d] Baseline conditions: chronic cardiovascular disease, hypertension, diabetes severity and complications, hyperlipidemia, lifestyle cardiovascular disease risk factors (smoking, obesity), stage of CKD, other kidney disorders, liver disease, HIV infection, dementia, COPD, and malignancies (other than kidney).

[e] Conditions predisposing individuals to CKD include hypertension, glomerulonephritis, renovascular disease, polycystic kidney disease, and autoimmune disease; amputations refer to amputations of the lower extremities.

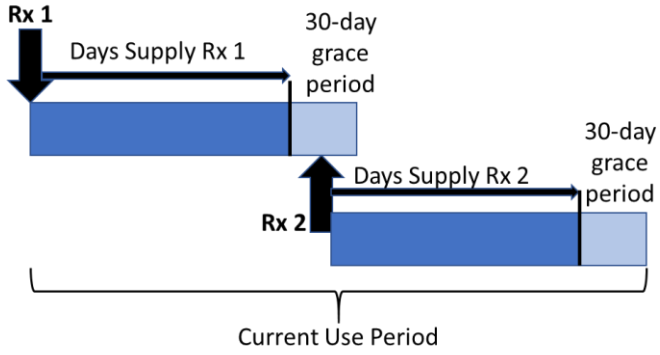
[f] Censored at the earliest of date of death, disenrollment, developing kidney cancer, kidney failure, or end of the study period.

Definition of current use

- New use of study drug. The date of the first observed prescription record or prescription dispensing for an SGLT2i during the study period was the *index date*, and follow-up started the day after. Any medication within the SGLT2i class was eligible. Patients without use of the study drug or any drug in that class in the 365 days before the index date (e.g., a washout period) were considered new users of the study drug.
- *Current-use* periods of the study drug were defined as starting on the day after the index date to the end of presumed supply for consecutive prescriptions plus a grace period of 30 days.

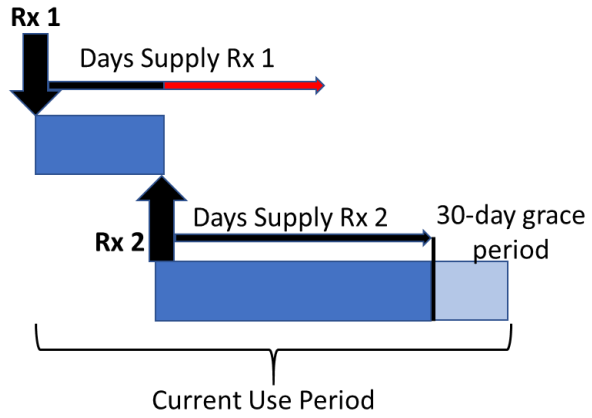


- For consecutive prescriptions of the study medication separated by gaps of 30 days or less, the time from current use included the gaps between prescriptions.

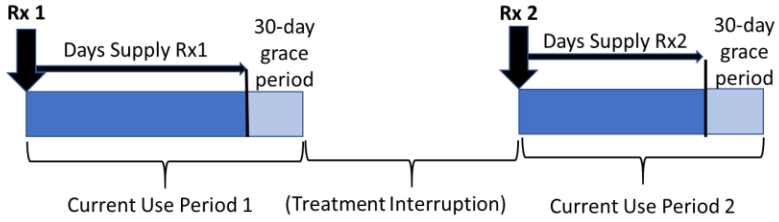


- Regarding stockpiling" or "banking" of unused drugs: In some situations, patients may be issued a renewed prescription or new dispensing of the index drug before the days' supply of the previous prescription has been exhausted. In this situation, we assume that

any drug supply on hand automatically resets to zero and that the current days' supply takes on the value of the new prescription. For example, the portion of days' supply from prescription 1 (red arrow below) will not be counted.



- Patients could have multiple current-use periods during follow-up if their treatment was interrupted and then restarted after a gap of more than 30 days. Treatment interruption was defined by the date corresponding to the end of current use.



Note: When handling fixed-dose combinations, each individual study drug used in the combination was considered as a separate prescription/dispensing with the associated days' supply. For example, a combined preparation of dapagliflozin and saxagliptin (Qtern) with a 30-day supply given on 1 January 2022 was treated as follows:

- A prescription/dispensing for SGLT2i (dapagliflozin) on 1 January 2022 with a 30-day supply

- A prescription/dispensing for dipeptidyl peptidase-4 inhibitor (saxagliptin) on 1 January 2022 with a 30-day supply

Therefore, a single prescription/dispensing was treated using the individual parts (2 separate prescriptions/dispensings), as shown in our example when identifying periods of current use as shown above and in the classification of the index medications.

Classification of index medications

The new use of an SGLT2i may relate in time to other drugs given to modify CKD (i.e., SGLT2i plus ACEi/ARB) in several ways. For example, the index SGLT2i medication may be started as monotherapy (with no prior CKD-protective treatment), added to an existing CKD-protective treatment, "switched" from an existing CKD-protective to an SGLT2i medication, or initiated as combined therapy (simultaneous initiation of SGLT2i together with another CKD-protective treatment with no prior treatment). Each index medication was classified into 1 of the following categories:

- Monotherapy
- Combination therapy
- Add-on therapy
- Switched-to index therapy
- Both add-on and switched-to index therapy
- Non-evaluable index therapy

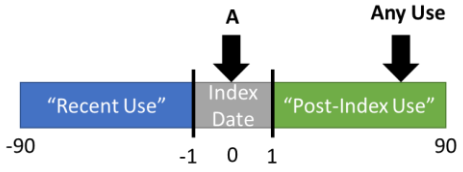
To make these classifications, we evaluated whether other CKD-protective drugs were prescribed at any point during 3 distinct periods. These medications included study drugs plus

ACEi/ARB. (Because the indication for drugs was not available in study data, we could not tell whether the intent of prescribing these medications was to modify CKD).

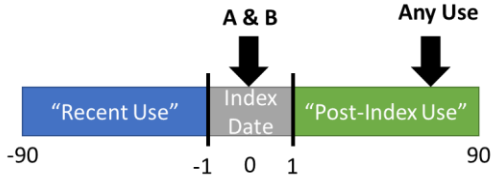
- "Recent use": the 90 days before the index date [−90, −1]
- "Index date": on the index date [0]
- "Post-index use": the 90-day period after the index date [1, 90]

Using the patient's treatment record, if there was no prescription or dispensing of 1 or more of our study drug class(es) in the period of "recent use," the index medication was classified as follows:

- Monotherapy: If only 1 drug of interest (A) was prescribed on the index date. Any use of other drugs in the post-index period was ignored.

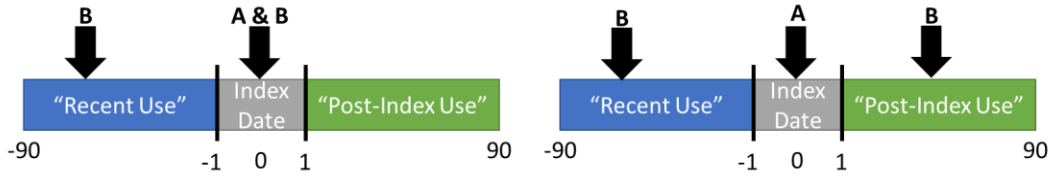


- Combination therapy: (1) the index medication was a fixed combination product or (2) 2 or more study drugs (A & B) were prescribed on the index date.

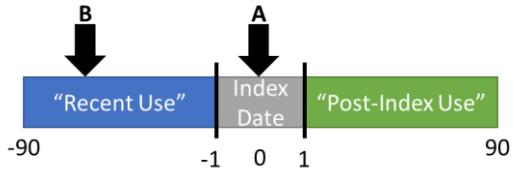


However, if another study drug (B or C in the examples below) was prescribed during the period of "recent use," to classify the index medication (A in the examples below), both the "index date" and "post-index" periods were evaluated. Based on the pattern of prescribing, the index medication was classified as follows:

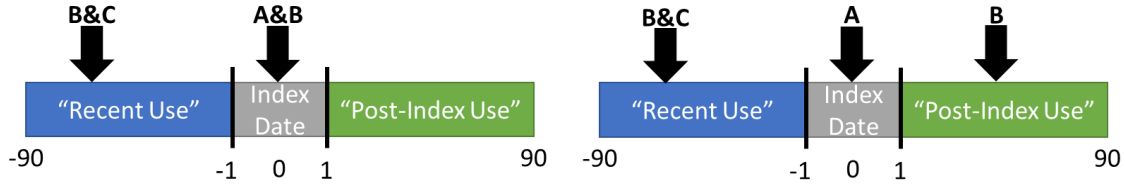
- Add-on therapy: If the drug class(es) used during the period of "recent use" had a subsequent prescription of the same drug class(es) either on the "index date" or in the "post-index" period"



- Switched-to index therapy: If another drug class(es) was prescribed during the period of "recent use" *and* that drug class(es) had no recorded prescription both on the "index date" and during the "post-index" period



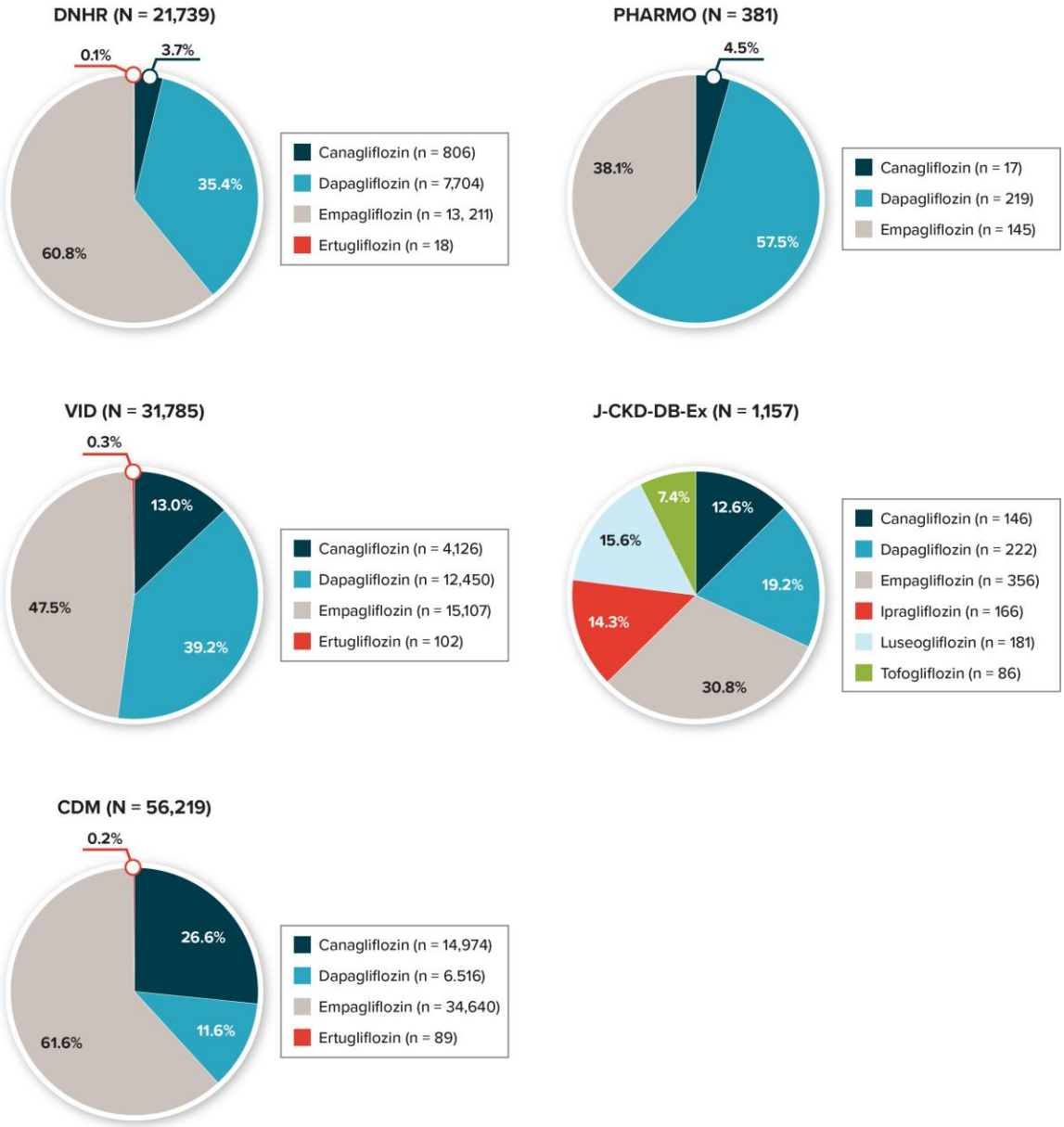
- Both add-on and switched-to index therapy: When more than 1 other drug class was identified in the period of "recent use" and only a subset of those classes had a prescription either at the "index date" or in the "post-index" period, as illustrated below



Non-evaluable index therapy: When another drug class was prescribed during the period of "recent use" and the "post-index" period was shorter than 90 days, (regardless of study discontinuation criteria), the initiation of drug A was deemed non-evaluable.

Appendix C. Additional Results

Appendix Figure C1. Type of SGLT2i at Initiation



CDM = Optum's de-identified Clinformatics® Data Mart Database; DNHR = Danish National Health Registers; J-CKD-DB-Ex = Japan Chronic Kidney Disease Database Extension; VID = Valencia Health System Integrated Database.

Appendix Table C1. List of SGLT2i drugs by drug substance and ATC code

Drug substance	ATC code
dapagliflozin	A10BK01, A10BX09 (historical code)
canagliflozin	A10BK02
empagliflozin	A10BK03
ertugliflozin	A10BK04
ipragliflozin	A10BK05
sotagliflozin	A10BK06
luseogliflozin	A10BK07
dapagliflozin and metformin	A10BD15
dapagliflozin, metformin, and saxagliptin	A10BD25
dapagliflozin and saxagliptin	A10BD21
empagliflozin and linagliptin	A10BD19
empagliflozin and metformin	A10BD20
canagliflozin and metformin	A10BD16
ertugliflozin and metformin	A10BD23
ertugliflozin and sitagliptin	A10BD24

ATC = Anatomical Therapeutic Chemical; SGLT2i = sodium-glucose cotransporter 2 inhibitors.

Appendix Table C2. Attrition of cohorts of SGLT2i users, by data source

	DNHR	PHARMO	VID	J-CKD-DB-Ex	CDM
All patients in the current database build	NE	1,695,731	309,477	251,659	NE
All patients with recorded study drug use	92,508	3,234	163,844	6,934	849,898
Total number of potential index dates	1,090,250	39,189	3,876,105	11,506	7,511,502
Potential index dates reported outside the study period	171,213 (15.7%)	3 (< 0.1%)	0 (0%)	0 (0%)	2,844,271 (37.9%)
Total number of potential index dates during the study period	919,037	39,186	3,876,105	11,506	4,667,231
Patients with < 12 months of lookback time at the potential index date	5,068 (0.6%)	1,079 (2.8%)	9,514 (0.2%)	2,990 (26.0%)	257,222 (5.5%)
Had a recorded prescription/dispensing of any SGLT2i during the 12 months before the potential index date	831,396 (90.5%)	35,861 (91.5%)	3,720,227 (96.0%)	4,201 (36.5%)	4,133,575 (88.6%)
Patients aged < 18 years at the potential index date	14 (< 0.1%)	0 (0%)	307 (< 0.1%)	5 (< 0.1%)	219 (< 0.1%)
No diagnosis of T2D recorded on or before the potential index date	0 (0%)	150 (0.4%)	117,573 (3.0%)	3,002 (26.1%)	172,619 (3.7%)
No diagnosis of CKD recorded on or before the potential index date	639,367 (69.6%)	33,953 (86.6%)	2,871,279 (74.1%)	6,592 (57.3%)	3,826,344 (82.0%)
Patients with potential index dates meeting the inclusion criteria	23,630	414	34,224	1,895	64,031
T1D identified on or before the potential index date	159 (0.7%)	8 (1.9%)	0 (0%)	566 (29.9%)	2,804 (4.4%)
Kidney cancer recorded on or before the potential index date	194 (0.8%)	8 (1.9%)	193 (0.6%)	71 (3.7%)	792 (1.2%)

	DNHR	PHARMO	VID	J-CKD-DB-Ex	CDM
Kidney failure recorded on or before the potential index date[a]	88 (0.4%)	6 (1.4%)	397 (1.2%)	84 (4.4%)	1,923 (3.0%)
Number of patients with potential index dates eligible for study inclusion	23,195	392	33,636	1,218	58,735
Subsequent index dates removed due to inclusion of an earlier eligible index date	1,456 (6.3%)	11 (2.8%)	1,851 (5.5%)	59 (4.8%)	2,516 (4.3%)
Final patient sample used for analyses	21,739	381	31,785	1,157	56,219

CKD = chronic kidney disease; DNHR = Danish National Health Registers; J-CKD-DB-Ex = Japan Chronic Kidney Disease Database Extension; NE = not estimable; CDM = Optum's de-identified Clinformatics® Data Mart Database; SGLT2i = sodium-glucose cotransporter 2 inhibitors; T1D = type 1 diabetes; T2D = type 2 diabetes; VID = Valencia Health System Integrated Database.

Note: The selection of the cohort involved evaluating multiple potential index dates per patient.

[a] Patients may have had more than 1 indicator of kidney failure.

Appendix Table C3. Markers of severity of T2D at the index date for new users of SGLT2i, by data source

	DNHR (N = 21,739)	PHARMO (N = 381)	VID (N = 31,785)	J-CKD-DB-Ex (N = 1,157)	CDM (N = 56,219)
Duration of T2D (years) at the index date					
Mean (SD)	11.2 (6.8)	12.2 (5.4)	9.2 (4.3)	7.4 (4.9)	5.1 (3.4)
Median	10.7	12.4	9.9	6.8	4.2
1st, 99th percentiles	0, 27	1, 26	0, 18	0, 21	0, 14
Medications for T2D (hypoglycemic agents) ever prescribed from 180 days before and including the index date, n (%)					
GLP-1 RA and fixed-dose combinations	5,303 (24.4%)	18 (4.7%)	3,455 (10.9%)	203 (17.5%)	9,989 (17.8%)
Metformin and fixed-dose combinations	17,700 (81.4%)	327 (85.8%)	16,336 (51.4%)	604 (52.2%)	33,851 (60.2%)
Sulfonylureas and fixed-dose combinations	3,002 (13.8%)	247 (64.8%)	3,636 (11.4%)	341 (29.5%)	21,746 (38.7%)
Alpha-glucosidase inhibitors	NR	3 (0.8%)	102 (0.3%)	298 (25.8%)	343 (0.6%)
Thiazolidinediones	13 (0.1%)	9 (2.4%)	818 (2.6%)	197 (17.0%)	5,285 (9.4%)
Dipeptidyl peptidase-4 inhibitors and fixed-dose combinations	6,060 (27.9%)	71 (18.6%)	19,834 (62.4%)	860 (74.3%)	13,457 (23.9%)
Meglitinides (including repaglinide, nateglinide, mitiglinide)	59 (0.3%)	2 (0.5%)	5,747 (18.1%)	223 (19.3%)	760 (1.4%)
Number of T2D drug classes other than insulin ever used in the 180 days before and including the index date, n (%)					
0	2,113 (9.7%)	19 (5.0%)	1,878 (5.9%)	145 (12.5%)	9,013 (16.0%)
1	9,050 (41.6%)	109 (28.6%)	14,207 (44.7%)	218 (18.8%)	19,470 (34.6%)
2	8,720 (40.1%)	192 (50.4%)	11,896 (37.4%)	272 (23.5%)	18,676 (33.2%)

	DNHR (N = 21,739)	PHARMO (N = 381)	VID (N = 31,785)	J-CKD-DB-Ex (N = 1,157)	CDM (N = 56,219)
3	1,774 (8.2%)	60 (15.7%)	3,318 (10.4%)	251 (21.7%)	7,740 (13.8%)
4+	82 (0.4%)	1 (0.3%)	486 (1.5%)	271 (23.4%)	1,320 (2.3%)
Insulin use recorded in the 180 days before and including the index date, n (%)	6,657 (30.6%)	82 (5.6%)	10,088 (31.7%)	562 (48.6%)	18,447 (32.8%)
HbA1c, n (%)					
HbA1c ≤ 53 mmol/mol or ≤ 7%	3,735 (17.2%)	35 (9.2%)	7,697 (24.2%)	412 (35.6%)	7,006 (12.5%)
HbA1c > 53 mmol/mol and ≤ 63.9 mmol/mol or > 7% and ≤ 8%	6,186 (28.5%)	87 (22.8%)	8,190 (25.8%)	382 (33.0%)	8,662 (15.4%)
HbA1c > 63.9 mmol/mol and ≤ 74.9 mmol/mol or > 8% and ≤ 9%	5,434 (25.0%)	71 (18.6%)	6,188 (19.5%)	204 (17.6%)	6,930 (12.3%)
HbA1c > 74.9 mmol/mol or > 9%	5,989 (27.5%)	99 (26.0%)	5,527 (17.4%)	131 (11.3%)	9,261 (16.5%)
HbA1c missing	395 (1.8%)	89 (23.4%)	4,183 (13.2%)	28 (2.4%)	24,360 (43.3%)
Other key medical conditions					
Hyperkaliemia, n (%)	244 (1.1%)	8 (2.1%)	2,917 (9.2%)	73 (6.3%)	3,639 (6.5%)
Amputation, n (%)	457 (2.1%)	1 (0.3%)	323 (1.0%)	0 (0%)	991 (1.8%)
The Diabetes Severity Complications Index					
Key diagnoses for scoring of index score					
Retinopathy, n (%)	4,724 (21.7%)	5 (1.3%)	8,333 (26.2%)	231 (20.0%)	12,937 (23.0%)
Nephropathy, n (%)	18,424 (84.8%)	358 (94.0%)	31,785 (100.0%)	390 (33.7%)	33,245 (59.1%)
Neuropathy, n (%)	4,803 (22.1%)	24 (6.3%)	6,236 (19.6%)	295 (25.5%)	22,737 (40.4%)
Cerebrovascular, n (%)	2,863 (13.2%)	23 (6.0%)	4,271 (13.4%)	484 (41.8%)	6,854 (12.2%)
Cardiovascular, n (%)	9,676 (44.5%)	128 (33.6%)	14,793 (46.5%)	947 (81.8%)	28,862 (51.3%)
Peripheral vascular disease, n (%)	3,455 (15.9%)	22 (5.8%)	8,139 (25.6%)	170 (14.7%)	16,026 (28.5%)

	DNHR (N = 21,739)	PHARMO (N = 381)	VID (N = 31,785)	J-CKD-DB-Ex (N = 1,157)	CDM (N = 56,219)
Metabolic complications, n (%)	941 (4.3%)	0 (0%)	4,081 (12.8%)	20 (1.7%)	3,343 (5.9%)
Index score					
Mean (SD)	2.6 (1.7)	2.1 (1.6)	4.2 (2.0)	3.6 (2.1)	2.9 (2.1)
Median	2	2	4	4	3
1st, 99th percentiles	0, 7	0, 8	2, 10	0, 8	0, 8

DNHR = Danish National Health Registers; GLP-1 RA = glucagon-like peptide-1 receptor agonists; HbA1c = hemoglobin A1c (glycated hemoglobin); J-CKD-DB-Ex = Japan Chronic Kidney Disease Database Extension; CDM = Optum's de-identified Clinformatics® Data Mart Database; SD = standard deviation; SGLT2i = sodium-glucose cotransporter 2 inhibitors; T2D = type 2 diabetes; VID = Valencia Health System Integrated Database.

Appendix Table C4. Baseline markers of severity of kidney dysfunction for new users of SGLT2i, by data source

	DNHR (N = 21,739)	PHARMO (N = 381)	VID (N = 31,785)	J-CKD-DB-Ex (N = 1,157)	CDM (N = 56,219)
Duration of CKD (years) at the index date (based on all available data)					
Mean (SD)	3.9 (3.6)	6.4 (4.1)	2.5 (2.4)	2.8 (2.5)	3.8 (2.9)
Median	3	6	1.9	2.2	3.1
1st, 99th percentiles	0, 17	0, 17	0.01, 10.1	0, 12	0, 12
CKD stage based on diagnosis only[b], n (%)					
Stage 1: eGFR ≥ 90, normal or high	NR	0 (0%)	158 (0.5%)	1 (0.1%)	1,291 (2.3%)
Stage 2: eGFR 60-89, mildly decreased	NR	3 (0.8%)	828 (2.6%)	2 (0.2%)	8,220 (14.6%)
Stage 3: mildly to severely decreased	330 (1.5%)	7 (1.8%)	1,208 (3.8%)	15 (1.3%)	4,510 (8.0%)
Stage 3a: eGFR 45-59, mildly to moderately decreased	0 (0%)	3 (0.8%)	0 (0.0%)	0 (0%)	1,202 (2.1%)
Stage 3b: eGFR 30-44, moderately to severely decreased	0 (0%)	4 (1.0%)	0 (0.0%)	0 (0%)	806 (1.4%)
Stage 3 without specification of substage	330 (1.5%)	0 (0%)	1,208 (3.8%)	15 (1.3%)	2,502 (4.5%)
Stage 4: eGFR 15-29, severely decreased	104 (0.5%)	1 (0.3%)	224 (0.7%)	5 (0.4%)	1,316 (2.3%)
Stage 5: eGFR < 15 OR treated by dialysis; kidney failure	0 (0%)	0 (0%)	0 (0.0%)	0 (0%)	0 (0%)
Unspecified stage	978 (4.5%)	NA	NA	NA	7,289 (13.0%)
No diagnosis code in the year before index	20,277 (93.3%)	370 (97.1%)	22,839 (71.9%)	1,134 (98.0%)	33,593 (59.8%)
CKD stage based on eGFR only[a], n (%)					
Stage 1: eGFR ≥ 90, normal or high	7,795 (35.9%)	28 (7.3%)	6,480 (20.4%)	48 (4.1%)	6,119 (10.9%)
Stage 2: eGFR 60-89, mildly decreased	7,360 (33.9%)	133 (34.9%)	11,009 (34.6%)	457 (39.5%)	14,536 (25.9%)

	DNHR (N = 21,739)	PHARMO (N = 381)	VID (N = 31,785)	J-CKD-DB-Ex (N = 1,157)	CDM (N = 56,219)
Stage 3: mildly to severely decreased	6,032 (27.7%)	158 (41.5%)	11,953 (37.6)	568 (49.1%)	14,069 (25.0%)
Stage 3a: eGFR 45-59, mildly to moderately decreased	4,214 (19.4%)	117 (30.7%)	8,069 (25.4%)	374 (32.3%)	10,093 (18.0%)
Stage 3b: eGFR 30-44, moderately to severely decreased	1,818 (8.4%)	41 (10.8%)	3,884 (12.2%)	194 (16.8%)	3,976 (7.1%)
Stage 3 without specification of substage	0 (0%)	NA	NA	NA	NA
Stage 4: eGFR 15-29, severely decreased	276 (1.3%)	6 (1.6%)	634 (2.0%)	76 (6.6%)	810 (1.4%)
Stage 5: eGFR < 15 OR treated by dialysis, kidney failure	NR	1 (0.3%)	22 (0.1%)	5 (0.4%)	392 (0.7%)
No assessment of eGFR in the year before the index date	NR	55 (14.4%)	0 (0.0%)	3 (0.3%)	20,293 (36.1%)
CKD stage based on eGFR[a] or diagnosis code[b], n (%)					
Stage 1: eGFR ≥ 90, normal or high	7,790 (35.8%)	36 (9.4%)	6,404 (20.2%)	48 (4.1%)	6,063 (10.8%)
Stage 2: eGFR 60-89, mildly decreased	7,329 (33.7%)	150 (39.4%)	10,814 (34.0%)	454 (39.2%)	17,470 (31.1%)
Stage 3: mildly to severely decreased	6,006 (27.6%)	181 (47.5%)	12,233 (38.5%)	569 (49.2%)	14,800 (26.3%)
Stage 3a: eGFR 45-59, mildly to moderately decreased	4,205 (19.3%)	130 (34.1%)	8,027 (25.3%)	374 (32.3%)	9,414 (16.7%)
Stage 3b: eGFR 30-44, moderately to severely decreased	1,767 (8.1%)	51 (13.4%)	3,809 (12.0%)	192 (16.6%)	3,521 (6.3%)
Stage 3 without specification of substage	34 (0.2%)	0 (0%)	397 (1.3%)	3 (0.3%)	1,865 (3.3%)
Stage 4: eGFR 15-29, severely decreased	339 (1.6%)	9 (2.4%)	797 (2.5%)	78 (6.7%)	1,380 (2.5%)
Stage 5: eGFR < 15 OR treated by dialysis, kidney failure	NR	1 (0.3%)	22 (0.1%)	5 (0.4%)	345 (0.6%)

	DNHR (N = 21,739)	PHARMO (N = 381)	VID (N = 31,785)	J-CKD-DB-Ex (N = 1,157)	CDM (N = 56,219)
Unspecified stage	NR	NA	459 (1.44%)	NA	4,818 (8.6%)
No assessment of GFR or diagnosis code any time before or on the index date	264 (1.2%)	4 (1.0%)	1,056 (3.3%)	3 (0.3%)	11,343 (20.2%)
CKD stage based on urine ACR[a], n (%)					
A1: urine ACR < 30, normal to mildly increased	5,185 (23.9%)	84 (22.0%)	6,778 (21.3%)	180 (15.6%)	6,301 (11.2%)
A2: urine ACR 30-300, moderately increased (formerly 'microalbuminuria')	9,451 (43.5%)	41 (10.8%)	11,164 (35.1%)	215 (18.6%)	6,857 (12.2%)
A3: urine ACR > 300, severely increased (includes nephrotic syndrome, > ~2,000)	2,997 (13.8%)	3 (0.8%)	3,038 (9.6%)	121 (10.5%)	2,736 (4.9%)
No assessment of urine ACR recorded in year before the index date	4,106 (18.9%)	253 (66.4%)	10,805 (34.0%)	641 (55.4%)	40,325 (71.7%)
"Any historical use" of drug classes (> 365 days before the index date)					
Drug classes used, n (%)					
SGLT2i and fixed-dose combinations	1,240 (5.7%)	3 (0.8%)	1,210 (3.8%)	42 (3.6%)	3,864 (6.9%)
GLP-1 RA and fixed-dose combinations	6,153 (28.3%)	24 (6.3%)	3,081 (9.7%)	102 (8.8%)	10,968 (19.5%)
sMRA	4,081 (18.8%)	66 (17.3%)	3,399 (10.7%)	185 (16.0%)	5,297 (9.4%)
ACEi or ARB	19,564 (90.0%)	324 (85.0%)	27,140 (85.4%)	710 (61.4%)	49,332 (87.7%)
Number of drug classes used, n (%)					
0	1,641 (7.5%)	53 (13.9%)	4,010 (12.6%)	NA	5,534 (9.8%)
1	11,073 (50.9%)	243 (63.8%)	21,513 (67.7%)	546 (47.2%)	34,588 (61.5%)
2	7,249 (33.3%)	81 (21.3%)	5,515 (17.4%)	217 (18.8%)	13,545 (24.1%)
3	1,637 (7.5%)	4 (1.0%)	701 (2.2%)	17 (1.5%)	2,425 (4.3%)

	DNHR (N = 21,739)	PHARMO (N = 381)	VID (N = 31,785)	J-CKD-DB-Ex (N = 1,157)	CDM (N = 56,219)
4	139 (0.6%)	0 (0%)	46 (0.1%)	2 (0.2%)	127 (0.2%)
> 4	0 (0%)	0 (0%)	0 (0.0%)	0 (0%)	0 (0%)
“Any previous use” of drug classes (365-91 days before the index date)					
Drug classes used, n (%)					
GLP-1 RA and fixed-dose combinations	5,266 (24.2%)	19 (5.0%)	2,909 (9.2%)	89 (7.7%)	9,885 (17.6%)
sMRA	2,545 (11.7%)	55 (14.4%)	2,597 (8.2%)	140 (12.1%)	4,273 (7.6%)
ACEi or ARB	17,413 (80.1%)	280 (73.5%)	24,228 (76.2%)	618 (53.4%)	46,279 (82.3%)
Number of drug classes used, n (%)					
0	3,265 (15.0%)	91 (23.9%)	6,478 (20.4%)	NA	7,958 (14.2%)
1	12,276 (56.5%)	230 (60.4%)	21,117 (66.4%)	529 (45.7%)	36,758 (65.4%)
2	5,646 (26.0%)	56 (14.7%)	3,953 (12.4%)	150 (13.0%)	10,830 (19.3%)
3	552 (2.5%)	4 (1.0%)	237 (0.8%)	7 (0.6%)	673 (1.2%)
≥ 4	0 (0%)	0 (0%)	0 (0.0%)	0 (0%)	0 (0%)
“Any recent use” of drug classes (in the 90 days before the index date)					
Drug classes used, n (%)					
GLP-1 RA and fixed-dose combinations	4,713 (21.7%)	14 (3.7%)	2,804 (8.8%)	78 (6.7%)	8,655 (15.4%)
sMRA	1,925 (8.9%)	51 (13.4%)	2,513 (7.9%)	144 (12.4%)	3,669 (6.5%)
ACEi or ARB	13,308 (61.2%)	258 (67.7%)	23,517 (74.0%)	568 (49.1%)	41,452 (73.7%)
Number of drug classes used, n (%)					
0	6,414 (29.5%)	108 (28.3%)	7,075 (22.3%)	NA	11,963 (21.3%)
1	11,015 (50.7%)	223 (58.5%)	20,791 (65.4%)	473 (40.9%)	35,173 (62.6%)
2	3,999 (18.4%)	50 (13.1%)	3,714 (11.7%)	151 (13.1%)	8,646 (15.4%)

	DNHR (N = 21,739)	PHARMO (N = 381)	VID (N = 31,785)	J-CKD-DB-Ex (N = 1,157)	CDM (N = 56,219)
3	311 (1.4%)	0 (0%)	205 (0.6%)	6 (0.5%)	437 (0.8%)
≥ 4	0 (0%)	0 (0%)	0 (0.0%)	0 (0%)	0 (0%)
Clinical conditions associated with risk of CKD[b]					
Hypertension, n (%)	17,575 (80.8%)	271 (71.1%)	28,846 (90.8%)	957 (82.7%)	52,558 (93.5%)
Glomerulonephritis (all causes), n (%)	484 (2.2%)	12 (3.1%)	989 (3.1%)	233 (20.1%)	965 (1.7%)
Renovascular disease, n (%)	74 (0.3%)	0 (0%)	371 (1.2%)	36 (3.1%)	532 (0.9%)
Autoimmune disease, n (%)	1,077 (5.0%)	7 (1.8%)	2,229 (7.0%)	327 (28.3%)	3,387 (6.0%)
Polycystic kidney disease, n (%)	104 (0.5%)	0 (0%)	132 (0.4%)	1 (0.1%)	170 (0.3%)
Gout or hyperuricemia[b], n (%)	1,051 (4.8%)	15 (3.9%)	9,397 (29.6%)	381 (32.9%)	6,046 (10.8%)
Hospitalizations for acute kidney injury in the previous year					
n (%)	122 (0.6%)	16 (4.2%)	666 (2.1%)	0	557 (1.0%)
Mean (SD)	1.1 (0.2)	1.0 (0.0)	0.02 (0.2)	0.0 (0.1)	1.0 (0.3)
Median	1	1	0	0	1
1st, 99th percentiles	1, 2	1, 1	0, 1	0, 0	1, 2

ACEi = angiotensin-converting enzyme inhibitors; ACR = albumin-to-creatinine ratio; ARB = angiotensin receptor blockers; CKD = chronic kidney disease; DNHR = Danish National Health Registers; eGFR = estimated glomerular filtration rate; GFR = glomerular filtration rate; GLP-1 RA = glucagon-like peptide-1 receptor agonists; J-CKD-DB-Ex = Japan Chronic Kidney Disease Database Extension; NA = not applicable; NR = not reported; CDM = Optum's de-identified Clinformatics® Data Mart Database; SD = standard deviation; SGLT2i = sodium-glucose cotransporter 2 inhibitors; sMRA = steroidal mineralocorticoid receptor antagonists; VID = Valencia Health System Integrated Database.

Note: Recent use: Defined as use in the 90 days before the index date (study days [−90, −1]); Previous use: defined using the remaining time of the previous year (study days [−365, −91]); Any historical use: defined as before the year before index (study days (−∞, −366]).

[a] Lookback period for these variables is the year before or on the index date (study days [−365, 0]).

[b] Lookback period for these variables is any time before or on the index date (study days (−∞, 0]).

Appendix Table C5. Selected Characteristics of new users of SGLT2i, stratified by whether an albumin-to-creatinine ratio test was recorded in the year before or on the index date, by data source

	DNHR		PHARMO		VID		J-CKD-DB-Ex		CDM	
	ACR	No ACR	ACR	No ACR	ACR	No ACR	ACR	No ACR	ACR	No ACR
Variable	N, 17,633	N, 4,106	N, 128	N, 253	N, 20,980	N, 10,805	N, 516	N, 641	N, 39,382	N, 16,837
Age group (years) at index date, %										
< 40	2.0	1.4	0	0	0.7	0.3	2.3	1.4	0.8	0.6
40-49	6.5	4.1	3.1	1.6	3.8	2.4	9.1	6.2	4.2	3.6
50-59	18.9	12.9	19.5	11.5	14.9	9.6	20.0	13.3	14.0	12.2
60-69	30.3	25.7	25.8	30.8	28.5	23.7	33.7	26.1	30.7	29.8
70-79	32.8	37.5	35.2	41.1	33.7	38.0	27.1	38.2	39.0	38.7
≥ 80	9.5	18.3	16.4	15.0	18.3	26.0	7.8	14.8	11.4	15.1
Median age (years) at index date	67	71	70	71	70.6	73.8	66.1	70.7	70	70
Sex, %										
Male	65.9	58.6	63.3	51.8	61.6	55.0	62.4	63.0	54.9	53.2
Female	34.1	41.4	36.7	48.2	38.4	45.0	37.6	37.0	45.1	46.8
Obesity, %	26.8	26.4	55.5	58.5	66.5	66.7	11.0	6.2	48.5	43.5
Medications for T2D ever prescribed in the 180 days before or on the index date [a], %										
GLP-1 RA	26.0	17.4	0.8	6.7	11.0	10.6	25.8	10.9	19.2	14.4

	DNHR		PHARMO		VID		J-CKD-DB-Ex		CDM	
	ACR	No ACR	ACR	No ACR	ACR	No ACR	ACR	No ACR	ACR	No ACR
Variable	N, 17,633	N, 4,106	N, 128	N, 253	N, 20,980	N, 10,805	N, 516	N, 641	N, 39,382	N, 16,837
Metformin	83.6	71.8	88.3	84.6	52.2	51.7	71.5	36.7	61.8	56.5
Sulfonylureas	14.2	12.2	68.0	63.2	12.1	10.1	37.0	23.4	39.9	35.8
Dipeptidyl peptidase-4 inhibitors	27.8	28.1	24.2	15.8	64.5	58.3	79.5	70.2	24.6	22.4
Insulin use 180 days before or on the index date, %	31.7	26.2	14.0	9.2	32.2	30.8	52.7	45.2	34.1	29.8
Diabetes Severity Complications Index Score[b]										
Mean (SD)	2.5 (1.7)	2.6 (1.8)	2.1 (1.5)	2.1 (1.6)	4.1 (2.0)	4.5 (2.0)	3.6 (2.2)	3.6 (2.0)	2.9 (2.1)	2.9 (2.1)
Median	2	3	1	2	4	4	3	4	3	3
1st, 99th percentile	0, 7	0, 7	1, 8	1, 8	2, 10	2, 10	0, 9	0, 8	0, 8	0, 8
CKD stage based on GFR[c] or diagnosis code[d], %										
Stage 1: ≥ 90, normal or high	39.4	20.6	15.6	6.3	26.0	8.7	7.4	1.6	12.8	6.1
Stage 2: 60-89, mildly decreased	34.1	32.2	36.7	40.7	37.4	27.5	51.7	29.2	33.3	25.8
Stage 3: mildly to severely decreased	24.4	41.6	43.8	49.4	34.1	47.1	36.8	59.1	27.0	24.8
Stage 4: 15-29, severely decreased	1.5	1.6	3.9	1.6	2.2	3.0	3.5	9.4	2.5	2.2

	DNHR		PHARMO		VID		J-CKD-DB-Ex		CDM	
	ACR	No ACR	ACR	No ACR	ACR	No ACR	ACR	No ACR	ACR	No ACR
Variable	N, 17,633	N, 4,106	N, 128	N, 253	N, 20,980	N, 10,805	N, 516	N, 641	N, 39,382	N, 16,837
Stage 5: < 15 OR treated by dialysis, kidney failure	NR	NR	0	0.4	0.1	0.1	0.4	0.5	0.6	0.6
Medical conditions associated with risk of CKD[d], %										
Hypertension	80.3	83.2	72.7	70.4	89.9	92.4	84.9	81.0	94.2	91.9
Glomerulonephritis (all causes)	2.3	1.7	3.1	3.2	2.9	3.5	23.6	17.3	2.1	0.9
Renovascular disease	0.3	0.3	0	0	1.2	1.2	2.9	3.3	0.9	1.0
Autoimmune disease	4.8	5.7	1.6	2.0	6.5	8.1	24.6	31.2	6.1	5.8
Polycystic kidney disease	0.4	0.6	0	0	0.4	0.4	0.0	0.2	0.3	0.3
Gout or hyperuricemia[d]	4.6	5.8	3.1	4.3	27.9	32.7	29.1	36.0	11.0	10.2
Other medical conditions[d], %										
Coronary heart disease	29.7	37.5	29.7	36.0	24.0	32.6	55.4	61.0	33.8	37.7
Cerebrovascular disease	12.4	16.5	8.6	11.5	12.1	14.8	45.5	38.8	11.6	13.6
Peripheral vascular disease	15.2	16.4	16.4	12.3	20.3	22.4	17.2	17.2	28.8	26.2
Hypercholesterolemia	33.4	35.9	38.3	33.6	79.0	79.7	82.4	72.1	91.0	85.8
Congestive heart failure	13.7	29.3	14.1	15.8	4.4	8.0	55.8	66.9	19.7	25.7
Severe liver disease	0.4	0.8	3.9	5.1	5.2	7.0	3.1	3.9	0.9	1.2
HIV infection	0.1	0.2	0	0	0.3	0.7	2.5	4.1	0.5	0.5
Dementia	0.9	2.2	3.1	2.4	2.8	4.8	3.7	2.8	2.6	4.6
Chronic obstructive pulmonary disease	9.2	13.1	7.8	11.1	14.3	17.9	35.3	27.1	17.5	20.3

	DNHR		PHARMO		VID		J-CKD-DB-Ex		CDM	
	ACR	No ACR	ACR	No ACR	ACR	No ACR	ACR	No ACR	ACR	No ACR
Variable	N, 17,633	N, 4,106	N, 128	N, 253	N, 20,980	N, 10,805	N, 516	N, 641	N, 39,382	N, 16,837
Malignancy (other than kidney cancer and non-melanoma skin cancers)	11.7	15.4	20.3	19.8	21.7	28.1	27.3	27.6	12.3	12.8
Medications other than glucose-lowering drugs in the 180 days before or on the index date, %										
Thiazide-like diuretics	14.8	12.1	26.6	16.6	4.7	5.8	6.6	6.2	32.1	31.3
Loop diuretics	22.8	37.5	11.7	24.5	22.5	33.7	7.9	18.4	20.9	25.9
Potassium-sparing diuretics	0.7	1.0	1.6	2.8	1.2	1.7	0.0	0.0	2.2	2.3
ACEi	38.6	35.1	44.5	37.5	21.5	20.4	6.4	15.9	41.4	38.5
ARB	45.1	42.5	39.8	33.2	59.2	60.8	60.3	47.4	53.7	50.4
Beta blockers	40.5	50.0	55.5	58.9	32.8	43.2	17.4	34.2	49.7	52.6
Angiotensin receptor-neprilysin inhibitors	1.0	5.9	1.6	1.2	1.8	4.3	0.0	1.2	2.0	3.4
Calcium channel blockers	41.7	30.4	43.8	28.5	25.2	25.5	40.9	40.6	34.0	31.5
Other antihypertensives	0	0	5.5	2.0	9.7	10.8	6.0	3.1	6.4	5.9
Statins	78.9	72.2	80.5	74.7	75.1	74.5	47.3	40.6	79.1	74.0
Anticoagulants	16.5	26.4	19.5	18.6	17.3	25.5	8.7	25.3	10.7	13.6
Digoxin	4.6	8.1	3.1	3.6	2.8	3.9	0.2	2.0	1.7	2.5

	DNHR		PHARMO		VID		J-CKD-DB-Ex		CDM	
	ACR	No ACR	ACR	No ACR	ACR	No ACR	ACR	No ACR	ACR	No ACR
Variable	N, 17,633	N, 4,106	N, 128	N, 253	N, 20,980	N, 10,805	N, 516	N, 641	N, 39,382	N, 16,837
Nitrates and other vasodilators	6.6	8.0	10.2	9.9	5.6	8.9	6.2	7.0	7.9	9.1
Aspirin and other antiplatelet agents	42.3	40.9	35.9	37.9	38.9	42.4	23.4	30.7	13.6	15.5
Lipid-lowering drugs other than statins	5.9	4.6	8.6	9.9	19.7	18.0	19.2	13.7	17.5	16.0
Anti-inflammatory drugs (NSAIDs)	12.0	11.2	10.9	12.3	21.7	20.1	6.8	6.7	16.9	17.8
Acetaminophen	38.6	45.4	12.5	7.1	35.9	40.3	12.6	19.3	16.6	18.5
Anticonvulsants	1.7	2.2	0.8	0.8	1.9	2.4	1.4	2.2	3.2	3.5
Antibacterial agents	21.4	27.2	21.9	22.9	33.5	37.2	14.9	19.8	26.3	27.3
Antifungal agents	1.7	2.4	0.8	1.2	1.4	1.3	1.9	3.1	5.7	5.9
Chemotherapeutic agents	0.1	0.1	0.8	2.0	0.5	0.6	2.5	4.4	2.9	3.0
Bronchodilators	12.5	16.1	15.6	13.4	17.2	20.5	4.8	5.0	13.7	15.4

ACEi = angiotensin-converting enzyme inhibitors; ACR = albumin-creatinine ratio; ARB = angiotensin receptor blockers; CKD = chronic kidney disease; DNHR = Danish National Health Registers; GFR = glomerular filtration rate; GLP-1 RA = glucagon-like peptide-1 receptor agonists; HIV = human immunodeficiency virus; J-CKD-DB-Ex = Japan Chronic Kidney Disease Database Extension; NR = not reported; NSAID = nonsteroidal anti-inflammatory drug; CDM = Optum's de-identified Clinformatics® Data Mart Database; SGLT2i = sodium-glucose cotransporter 2 inhibitors; T2D = type 2 diabetes; SD = standard deviation; VID = Valencia Health System Integrated Database.

[a] The medications listed include the drug alone and in fixed-dose combinations.

[b] Score is based on based on the sum of scores of 0 (no diagnoses found), 1, or 2 for individual cerebrovascular, cardiovascular, peripheral vascular disease, and metabolic complications [31].

[c] Lookback period for these variables is the year before or on the index date (study days [−365,0]).

[d] Lookback period for these variables is any time before or on the index date (study days (−∞,0]).

Appendix Table C6. Baseline comorbidities in new users of SGLT2i, by data source

	DNHR (N = 21,739) n (%)	PHARMO (N = 381) n (%)	VID (N = 31,785) n (%)	J-CKD-DB-Ex (N = 1,157) n (%)	CDM (N = 56,219) n (%)
Macrovascular complications of diabetes					
Coronary heart disease	6,774 (31.2%)	129 (33.9%)	8,550 (26.9%)	677 (58.5%)	19,663 (35.0%)
Cerebrovascular disease	2,863 (13.2%)	40 (10.5%)	4,140 (13.0%)	484 (41.8%)	6,854 (12.2%)
Peripheral vascular disease	3,352 (15.4%)	52 (13.6%)	6,674 (21.0%)	199 (17.2%)	15,737 (28.0%)
Cardiovascular disease risk factors					
Hypertension	17,575 (80.8%)	271 (71.1%)	28,783 (90.6%)	957 (82.7%)	52,558 (93.5%)
Hypercholesterolemia	7,369 (33.9%)	134 (35.2%)	25,186 (79.2%)	887 (76.7%)	50,291 (89.5%)
Congestive heart failure	3,611 (16.6%)	58 (15.2%)	1,776 (5.6%)	717 (62.0%)	12,073 (21.5%)
Severe liver disease	108 (0.5%)	18 (4.7%)	1,846 (5.8%)	41 (3.5%)	556 (1.0%)
HIV infection	31 (0.1%)	0 (0%)	127 (0.4%)	39 (3.4%)	297 (0.5%)
Dementia	258 (1.2%)	10 (2.6%)	1,098 (3.5%)	37 (3.2%)	1,808 (3.2%)
Chronic obstructive pulmonary disease	2,163 (9.9%)	38 (10.0%)	4,929 (15.5%)	356 (30.8%)	10,300 (18.3%)
Malignancy (other than kidney cancer and non-melanoma skin cancers)	2,703 (12.4%)	76 (19.9%)	7,581 (23.9%)	318 (27.5%)	7,017 (12.5%)

DNHR = Danish National Health Registers; HIV = human immunodeficiency virus; J-CKD-DB-Ex = Japan Chronic Kidney Disease Database Extension; CDM = Optum's de-identified Clinformatics® Data Mart Database; SGLT2i = sodium-glucose cotransporter 2 inhibitors; VID = Valencia Health System Integrated Database.

Appendix Table C7. Medication use other than glucose-lowering drugs recorded in the 180 days before or on the index date in new users of SGLT2i, by data source

	DNHR (N = 21,739) n (%)	PHARMO (N = 381) n (%)	VID (N = 31,785) n (%)	J-CKD-DB-Ex (N = 1,157) n (%)	CDM (N = 56,219) n (%)
Cardiovascular medications in the 180 days before or on the index date					
Thiazide-like diuretics	3,099 (14.3%)	76 (19.9%)	1,617 (5.1%)	74 (6.4%)	17,919 (31.9%)
Loop diuretics	5,557 (25.6%)	77 (20.2%)	8,360 (26.3%)	159 (13.7%)	12,595 (22.4%)
Potassium-sparing diuretics	162 (0.7%)	9 (2.4%)	426 (1.3%)	0 (0%)	1,255 (2.2%)
Angiotensin-converting enzyme inhibitors	8,252 (38.0%)	152 (39.9%)	6,728 (21.2%)	135 (11.7%)	22,793 (40.5%)
Angiotensin receptor blockers	9,702 (44.6%)	135 (35.4%)	18,984 (59.7%)	615 (53.2%)	29,637 (52.7%)
Beta blockers	9,195 (42.3%)	220 (57.7%)	11,552 (36.3%)	309 (26.7%)	28,416 (50.5%)
Direct renin inhibitors	13 (0.1%)	1 (0.3%)	54 (0.2%)	2 (0.2%)	40 (0.1%)
Angiotensin receptor-neprilysin inhibitors	411 (1.9%)	5 (1.3%)	837 (2.6%)	8 (0.7%)	1,354 (2.4%)
Calcium channel blockers	8,607 (39.6%)	128 (33.6%)	8,056 (25.4%)	471 (40.7%)	18,711 (33.3%)
Other antihypertensives	0 (0%)	12 (3.1%)	3,212 (10.1%)	51 (4.4%)	3,519 (6.3%)
Statins	16,870 (77.6%)	292 (76.6%)	23,797 (74.9%)	504 (43.6%)	43,609 (77.6%)
Anticoagulants	3,985 (18.3%)	72 (18.9%)	6,395 (20.1%)	207 (17.9%)	6,480 (11.5%)
Digoxin	1,137 (5.2%)	13 (3.4%)	1,008 (3.2%)	14 (1.2%)	1,106 (2.0%)
Nitrates and other vasodilators	1,493 (6.9%)	38 (10.0%)	2,150 (6.8%)	77 (6.7%)	4,645 (8.3%)
Aspirin and other antiplatelet agents	9,136 (42.0%)	142 (37.3%)	12,747 (40.1%)	318 (27.5%)	7,970 (14.2%)

	DNHR (N = 21,739) n (%)	PHARMO (N = 381) n (%)	VID (N = 31,785) n (%)	J-CKD-DB-Ex (N = 1,157) n (%)	CDM (N = 56,219) n (%)
Lipid-lowering drugs other than statins	1,234 (5.7%)	36 (9.4%)	6,061 (19.1%)	187 (16.2%)	9,573 (17.0%)
Other medications of interest					
Anti-inflammatory drugs (NSAIDs)	2,576 (11.8%)	45 (11.8%)	6,721 (21.2%)	78 (6.7%)	9,668 (17.2%)
Acetaminophen	8,665 (39.9%)	34 (8.9%)	11,881 (37.4%)	189 (16.3%)	9,675 (17.2%)
Anticonvulsants	396 (1.8%)	3 (0.8%)	653 (2.1%)	21 (1.8%)	1,862 (3.3%)
Anti-infectives					
Antibacterial agents	4,896 (22.5%)	86 (22.6%)	11,049 (34.8%)	204 (17.6%)	14,964 (26.6%)
Antifungal agents	391 (1.8%)	4 (1.0%)	427 (1.3%)	30 (2.6%)	3,254 (5.8%)
Antitubercular agents	NR	--	33 (0.1%)	3 (0.3%)	45 (0.1%)
Chemotherapeutic agents	26 (0.1%)	6 (1.6%)	165 (0.5%)	41 (3.5%)	1,653 (2.9%)
Bronchodilators	2,858 (13.1%)	54 (14.2%)	5,812 (18.3%)	57 (4.9%)	7,987 (14.2%)

DNHR = Danish National Health Registers; NR = not reported; NSAID = nonsteroidal anti-inflammatory drug; CDM = Optum's de-identified Clinformatics® Data Mart Database; SGLT2i = sodium-glucose cotransporter 2 inhibitors; VID = Valencia Health System Integrated Database.