Post Authorization Safety Study (PASS) Report – Study Information

Acronym/Title	FINEGUST/**FINE**renone dru**G** **U**tilization **S**tudy and assessment of **T**emporal changes following availability of different treatment options in patients with chronic kidney disease and type 2 diabetes
Report version and date	v 1.0, 06 MAR 2025
GEMSTONE/IMPACT study number	21956
Study type / Study phase	PASS: ☒ YES ☐ NO Joint PASS: ☐ YES ☒ NO
EU PAS register number	EUPAS48148
Active substance	Finerenone
Medicinal product / Medical Device / Combination Product	Kerendia (ATC: C03DA05)
Product reference	BAY 94-8862
Procedure number	Not applicable
Comparator / Reference therapy	Not applicable
Study Initiator and Funder	Bayer, AG
Research question and objectives	The overall aim of this study was to describe patient profiles and treatment patterns in medication initiator cohorts of patients with chronic kidney disease (CKD) and type 2 diabetes (T2D). The primary objective was to describe baseline characteristics, comorbidities, and comedications in adult patients with CKD and T2D who initiate a sodium-glucose cotransporter 2 inhibitor (SGLT2i), a glucagon-like peptide-1 receptor agonist (GLP-1 RA), a steroidal mineral corticoid receptor antagonist (sMRA), finerenone, or other non-steroidal mineral corticosteroid receptor antagonist (nsMRA) (only in Japan) in each of two time periods corresponding to

	finerenone pre-launch and post-launch dates. The secondary objectives were to describe 1) changes over time in treatments in the initiator cohorts, including treatment discontinuation, treatment switches, add-on treatments, and titration (finerenone only) in each of two time periods corresponding to finerenone pre-launch and post-launch dates, and 2) temporal changes in the baseline characteristics of the medication-specific cohorts before and after finerenone launch.
Countries of study	US, Denmark, Japan, The Netherlands, Spain
Authors	PPD PPD* PPD PPD *Employed at RTI-HS at the time of Draft 1 of the Final Report

Marketing authorization holder

Marketing authorization holder(s)	Bayer AG
MAH contact person	PPD

Confidentiality statement:

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1. Abstract

Acronym/Title	FINEGUST/**FINE**renone dru**G** **U**tilization **S**tudy and assessment of **T**emporal changes following availability of different treatment options in patients with chronic kidney disease and type 2 diabetes
Report version and date **Author**	v 1.0, 06 MAR 2025 PPD, RTI-HS PPD, RTI-HS PPD, RTI-HS PPD, Bayer AG
GEMSTONE/IMPACT study number	21956
Keywords	Chronic kidney disease; type 2 diabetes; cohort study; drug utilization patterns; pre-finerenone; post-finerenone
Rationale and background	Patients with chronic kidney disease (CKD) are at high risk of kidney failure, cardiovascular disease, and death. Patients with type 2 diabetes mellitus (T2D) have a high prevalence and incidence of CKD. Prevention, early detection, and treatment of CKD may result in improved patient outcomes, especially among patients with diabetes. Approved therapies to prevent and treat CKD among patients with T2D include angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB), sodium-glucose cotransporter 2 inhibitors (SGLT2i), and glucagon-like peptide-1 receptor agonists (GLP-1 RA). Steroidal mineralocorticoid receptor antagonists (sMRA) are also used for the treatment and prevention of CKD in patients with T2D but are not approved for this indication. Finerenone is an oral, selective, non-steroidal mineralocorticoid receptor antagonist (nsMRA) developed by Bayer for the treatment of CKD in patients with T2D. Finerenone has been approved by the United States (US) Food and Drug Administration, the European Medicines Agency (EMA), and the Japanese Pharmaceutical and Medical Devices Agency (PMDA). The clinical landscape for the treatment of patients with CKD and T2D is rapidly evolving with the introduction of new treatments, and it is of interest to study how treatment patterns

	may have evolved with the approval of new drugs for this indication.
Research question and objectives	The overall aim of this study was to describe patient profiles and treatment patterns in medication initiator cohorts of patients with CKD and T2D. The primary objective was to describe baseline patient characteristics, comorbidities, and comedications in adult patients with CKD and T2D who initiate an SGLT2i, a GLP-1 RA, an sMRA, finerenone, or other nsMRA (only in Japan) in each of two time periods corresponding to finerenone pre-launch and post-launch dates. The secondary objectives were to describe: 1) treatment changes over time in the initiator cohorts, including treatment discontinuation, treatment switches, add-on treatments, and titration (finerenone only) in each of two time periods corresponding to finerenone pre-launch and post-launch dates, and 2) temporal changes in the baseline characteristics of the medication-specific cohorts before and after finerenone launch.
Study design	A multidatabase, multinational, observational (non-interventional) cohort study was conducted to describe drug utilization and temporal changes of different treatment options in adults with CKD and T2D using secondary data from data sources in the EU, Japan, and the US. The study identified separate medication-specific cohorts in two separate time periods corresponding to the pre-approval and post-approval dates of finerenone; dates of the time periods varied in each of the study countries. In the pre-finerenone period (study period I), four new-user cohorts were identified, based on the first use of any drug in these classes: SGLT2i, GLP-1 RA, sMRA, or nsMRA. The nsMRA cohort was only identified in Japan, where esaxerenone is available. In study period II (post-finerenone), new-user cohorts for SGLT2i, GLP-1 RA, and finerenone were created in a single data source (CDM) with an adequate number of finerenone users.
Setting	US, Denmark, Japan, The Netherlands, Spain
Subjects and study size, including dropouts	<u>Pre-finerenone:</u> • SGLT2i = 21,739 (DNHR); 381 (PHARMO); 31,785 (VID); 1,157 (J-CKD-DB-Ex); 56,219 (CDM) • GLP-1 RA = 18,929 (DNHR); 476 (PHARMO);

	11,798 (VID); 329 (J-CKD-DB-Ex); 70,158 (CDM) • sMRA = 12,689 (DNHR); 2,691 (PHARMO); 14,906 (VID); 1,769 (J-CKD-DB-Ex); 71,716 (CDM) • nsMRA = 63 (J-CKD-DB-Ex) <u>Post-finerenone (CDM):</u> • SGLT2i = 94,080 • GLP-1 RA = 72,816 • Finerenone = 3,591 • Wide Finerenone = 5,201 Across all cohorts, the greatest proportion of individuals were excluded from the cohort due to either having another prescription in the same medication class in the prior 12 months or not having a diagnosis of CKD.
Variables and data sources	The study was conducted in five data sources: DNHR (Denmark), PHARMO (The Netherlands), VID (Spain), J-CKD-DB-Ex (Japan), and CDM (US). Information on patient characteristics (e.g., age, sex), laboratory values (e.g., eGFR, HbA_{1c}), medication use, and diagnosis of comorbid conditions was obtained from each of the data sources for analysis.
Results	In study period I (pre-finerenone), common findings across all data sources were that ACEi or ARB medications were by far the most frequent medication types used before initiation of the index GLP-1 RA or SGLT2i, and hypertension was the most frequently recorded medical comorbidity. Most patients had used glucose-lowering drugs (GLD) in the 180 days before or on the index date, but the type of GLD used varied by data source, with metformin being the most frequently used GLD before SGLT2i or GLP-1 RA initiation in the data sources in Denmark, The Netherlands, and the US and dipeptidyl peptidase-4 inhibitors (DPP-4i) in the data sources in Japan and Spain (for SGLT2i only). For the SGLT2i cohort, treatment patterns during follow-up and the proportion of patients observed to be receiving treatment at each timepoint were similar among the DNHR, VID, and J-CKD-DB-Ex data sources. The largest proportional increase in the "no exposure" treatment state occurred between the 90-day and 180-day timepoints in each data source except for PHARMO, in which the proportion of patients not treated increased the most between two and three years. Within the GLP-1 cohort, the largest proportional increase in the "no exposure" treatment state occurred within the first six months of initiation (between

	the index date and the 90-day timepoint or between the 90-day timepoint and the 180-day timepoint). Patients within the sMRA cohort were notably different than the other medication cohorts. Initiators were older, with less severe T2D but with more complications, more advanced CKD, and a higher prevalence of heart failure as a comorbid condition. In study period II (post-finerenone), treatment intensity for T2D was more pronounced in the finerenone cohorts than in the other two cohorts (GLP-1 RA and SGLT2i) as reflected by more use of T2D medications (including insulin). Conversely, metabolic control as measured by HbA1c levels was better in the finerenone cohorts. A higher percentage of patients were in CKD stages 3 and 4 in the finerenone cohorts than in the other two cohorts of interest (GLP-1 RA and SGLT2i). In CDM (the only data source used to assess trends in the post-finerenone period), 18.0% of patients received the 20-mg dose of finerenone at baseline, and the rest received the 10-mg dose. Among patients receiving the 10-mg dose of finerenone at baseline, approximately 17% of patients had been titrated up to 20 mg at 12 months after cohort entry. Regarding concomitant medications, use of ARB, statins, and calcium channel blockers was more common in the finerenone cohorts than in the other two cohorts (GLP-1 RA and SGLT2i in the post-finerenone period). For both the GLP-1 RA and SGLT2i medication cohorts, patients in the post-finerenone period had lower severity of T2D but greater severity of CKD compared with the pre-finerenone period. In the SGLT2i cohort, the comorbidity burden was greater in the post-finerenone period (compared with the pre-finerenone period), but this trend was not observed in the GLP-1 RA cohort.
Discussion	In this study population with CKD and T2D in 2012-2021, largely before the approval of new CKD indications for existing treatments (SGLT2i and GLP-1 RA) and new CKD treatments (e.g., finerenone), treatment options and therapeutic approaches were heterogeneous and dynamic both within and among data sources. At one year of follow-up, half or more of patients who initiated an SGLT2i were currently receiving SGLT2i treatment across the data sources. We observed a steady increase in GLP-1 RA use across data sources during the study period, and persistence with treatment was high. Findings suggest that GLP-1 RA use is related to

	both severity of T2D and the presence of obesity. The sMRA cohort had a different clinical profile than the other two cohorts, which may be related to the fact that sMRAs are not indicated to treat T2D but may be used to treat resistant hypertension and heart failure, which are common among patients with T2D. In CDM, the differences observed between the pre- and post-finerenone periods in the SGLT2i and GLP-1 RA cohorts are likely related to changes in clinical guidelines that mainly involved SGLT2i medications. The percentage of patients receiving a 20-mg finerenone dose at cohort entry was consistent with the percentage of patients with eGFR levels at baseline that are recommended for this dosage. However, up-titration to the 20-mg daily dose among patients initially taking the 10-mg dose occurred in a lower percentage of patients than expected. The treatment landscape for the prevention of CKD progression in patients with T2D is evolving rapidly. Understanding the characteristics and patterns of use of existing treatments and characterizing the differences in populations and treatment patterns across data sources is a first step in designing future studies to evaluate kidney and cardiovascular outcomes with treatment to prevent CKD progression.
Marketing Authorization Holder(s)	Bayer AG
Names and affiliations of principal investigators	PPD; Bayer AG PPD; RTI-HS PPD; RTI-HS* PPD; RTI-HS PPD; FISABIO PPD; PHARMO Institute for Drug Outcomes Research PPD; Bayer Yakuhin, Ltd. PPD; University of Connecticut PPD; Aarhus University *Affiliation at time of Draft 1 of Final Report.

2. List of abbreviations

ACE	Angiotensin-Converting Enzyme
ACEi	Angiotensin-Converting Enzyme Inhibitor
ACR	Albumin-to-Creatinine Ratio
AD	Associated Document
AE	Adverse Event
AED	Accident & Emergency Department
AG	Aktiengesellschaft
ARB	Angiotensin Receptor Blocker
ATC	Anatomical Therapeutic Chemical (Classification System)
BMI	Body Mass Index
CDM	Optum's de-identified Clinformatics® DataMart
CFR	Code of Federal Regulations
CHD	Coronary Heart Disease
CI	Confidence Interval
CKD	Chronic Kidney Disease
COPD	Chronic Obstructive Pulmonary Disease
CPT	Current Procedural Terminology
CRF	Case Report Form
CVD	Cardiovascular Disease
DNHR	Danish National Health Registers
DPP-4i	Dipeptidyl Peptidase-4 Inhibitors
eGFR	Estimated Glomerular Filtration Rate
ED	Emergency Department
EHR	Electronic Health Record
EMA	European Medicine Agency
EU	European Union
FDA	Food and Drug Administration
GAIA	Gestor Integral de la Prestación Farmacéutica
GDPR	General Data Protection Regulation
GFR	Glomerular Filtration Rate
GLD	Glucose-Lowering Drug
GLP-1	Glucagon-Like Peptide-1
GP	General Practitioner

HbA1c	Hemoglobin A1c
HCPCS	Healthcare Common Procedure Coding System
HCRU	Healthcare Resource Use
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
ICD	*International Classification of Diseases*
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*
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISO	International Standards Organization
J-CKD-DB-Ex	Japan Chronic Kidney Disease Database Extension
KDIGO	Kidney Disease Improving Clinical Outcomes
MAH	Marketing Authorization Holder
MBDS	Minimum Basic Data Set at Hospital Discharge
MRA	Mineralocorticoid Receptor Antagonist
N	Number
N/A	Not Available
NA	Not Applicable
NDC	National Drug Code
NE	Not Estimable
NR	Not Reported
NSAID	Non-Steroidal Anti-inflammatory Drug
nsMRA	Non-Steroidal Mineralocorticoid Receptor Antagonists
NZa	Dutch Healthcare Authority
OR	Odds Ratio
OS	Observational Study
PAS	Post-Authorization Study
PASS	Post-Authorization Safety Study

PHARMO	PHARMO Data Network
RA	Receptor Agonist
RTI-HS	RTI Health Solutions
SAP	Statistical Analysis Plan
SD	Standard Deviation
SGLT2	Sodium-Glucose Cotransporter
SGLT2i	Sodium-Glucose Cotransporter Inhibitors
SIA	Ambulatory Information System
SIP	Population Information System
sMRA	Steroidal Mineralocorticoid Receptor Antagonist
SOP	Standard Operating Procedure
T1D	Type 1 Diabetes
T2D	Type 2 Diabetes
US	United States
VHAS	Veterans' Health Administration System
VHS	Valencia Health System
VID	Valencia Health System Integrated Database
WHO	World Health Organization

3. Investigators

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Role: PPD, CDM
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Company: University of Connecticut

4. Other responsible parties

Contact details on the principal investigators and research partners participating in the study are listed in a stand-alone document, which is available upon request.

Information on the Executive Advisory and Publication Committee Members is kept as stand-alone documents, which are available upon request.

5. Milestones

Table 1: Milestones

Milestone	Planned date	Actual date	Comments
Start of data collection / observation	01 SEP 2022	12 JUL 2022	
End of data collection / observation	30 SEP 2024	05 SEP 2024	
Registration in the EU PAS register	01 JUN 2022	22 AUG 2022	
Analysis plan completed	30 JUN 2022	16 AUG 2022	
Data analysis I completed	31 OCT 2022	09 JUL 2024	

Milestone	Planned date	Actual date	Comments
Data analysis II completed	31 OCT 2024	17 OCT 2024	
Temporal changes analysis completed	31 OCT 2024	17 OCT 2024	
Final report of study results	31 DEC 2024	06 MAR 2025	

*A complete list of IEC or IRB approvals is provided as a stand-alone document (see Annex 1).

6. Rationale and background

Chronic kidney disease (CKD) is defined as abnormalities of kidney structure or function, present for more than three months, with implications for health. Markers of kidney damage include the presence of increased urinary albumin excretion rate (AER) ≥ 30 mg/24 hours and/or urinary albumin-to-creatinine ratio (ACR) ≥ 30 mg/g [≥ 3 mg/mmol]). As kidney damage progresses, it can lead to a decline in kidney function with glomerular filtration rate (GFR) < 60 mL/min/1.73 m^2 as the threshold for diagnosed CKD.[1,2] Patients with CKD have an increased risk of kidney failure, cardiovascular disease (CVD), and death. Thus, the treatment goal in CKD is not only to prevent dialysis or transplant but also to reduce the CVD burden; this is especially relevant among patients with diabetes.[3,4]

Patients with type 2 diabetes mellitus (T2D) have a high prevalence and incidence of CKD.[5] The prevalence of CKD among patients with diabetes is 17% to 24% in Denmark[6,7]; 28% in Spain[8] and The Netherlands[9]; 38% in the United States (US)[10]; and 46% in Japan, which is the highest prevalence.[11]

Available therapies indicated for the prevention and treatment of CKD among patients with T2D include renin-angiotensin system inhibitor drugs (e.g., angiotensin-converting enzyme inhibitors [ACEi], angiotensin receptor blockers [ARB]), sodium-glucose cotransporter 2 inhibitors (SGLT2i), and finerenone (in the US); additional prevention strategies include treatment of risk factors for CKD (e.g., high blood pressure) with drugs or lifestyle modification.[12]

Clinical trials have shown improvement of kidney outcomes in patients with T2D treated with a SGLT2i. The CREDENCE trial demonstrated a lower risk of kidney failure and cardiovascular events among adult patients with T2D treated with canagliflozin than among patients receiving a placebo.[13] The DAPA-CKD trial showed that patients treated with dapagliflozin compared with a placebo had a lower risk of a composite outcome (sustained decline in eGFR of at least 50%, kidney failure, or death from kidney or cardiovascular events), and the effect was consistent whether or not the participants had T2D.[14] Canagliflozin received approval by the US Food and Drug Administration (FDA) in August 2020; for adults with T2D and diabetic nephropathy with albuminuria[15]; dapagliflozin received FDA approval in April 2020 for adults with CKD at risk of progression.[16] Dapagliflozin also received a positive opinion for market authorization for the same indication from the European Medicines Agency (EMA) in October 2021.[17] Current guidelines recommend both renin-angiotensin system (RAS) inhibition (e.g., ACEi, ARB) and SGLT2i as first-line drug therapy for people with T2D and CKD as part of a comprehensive disease management approach, and strongly recommend SGLT2i as first-line therapy for the prevention of CKD progression and cardiovascular events, regardless of other glucose-lowering treatment.[18]

The glucagon-like peptide-1 receptor agonists (GLP-1 RA) liraglutide and dulaglutide may also have beneficial effects on kidney outcomes. In a secondary analysis of the LEADER trial,[19] among patients with T2D at high risk for CVD, a lower risk of a composite kidney outcome was observed with liraglutide compared with placebo. There have been several cardiovascular outcome trials (CVOTs) of GLP-1 RA, although none have focused on renal events as primary outcomes. Such events have often been considered secondary outcomes in these trials. However, many of these CVOTs have tended to be heavily composed of patients at elevated risk of kidney disease, owing to the strong relationship between CKD and CVD.[20] In an exploratory analysis of the REWIND trial[21] that examined the effect of dulaglutide on CVD in adults with T2D, the exploratory results suggested a reduction in the progression of kidney disease with about five years of exposure to dulaglutide. A systematic review and network meta-analysis comparing GLP-1 RA and SGLT2i concluded that both drug classes have cardiovascular and kidney benefits but with notable differences in benefits and harms.[22] Lower risk of composite kidney outcomes has also been observed in observational studies of GLP-1 RA in Europe and the US.[23-25] Furthermore, the first dedicated kidney outcomes clinical trial for GLP-1 RA, FLOW, reported results in May 2024 after the trial was stopped early at a prespecified interim analysis.[26,27] The trial found that among 3,533 patients, those who were randomized to the GLP-1 RA (semaglutide) group had a 24% (HR, 0.76; 95% CI, 0.66-0.88) lower risk of major kidney disease events (a composite of kidney failure onset, at least a 50% reduction in eGFR from baseline or death from kidney-related or cardiovascular causes) than those in the placebo group.[27] Subsequently, in 2025 the FDA approved the first GLP-1 RA, semaglutide, for CKD treatment in adults with T2D and CKD.[28] The KDIGO guidelines recommend GLP-1 RA as a second-line therapy for patients with T2D and CKD who have not met their glycemic targets despite use of metformin and a SGLT2i or for those who are unable to tolerate these medications (KDIGO, 2022).

The steroidal mineralocorticoid receptor antagonists (sMRA) spironolactone (non-selective) and eplerenone (selective) have limited evidence of potential kidney benefit among patients with CKD and T2D.[29,30] These drugs are not approved for the treatment and prevention of CKD in patients with T2D, but they are used among patients with T2D for other indications such as hypertension and heart failure.[29]

Finerenone is a novel, oral, selective non-steroidal mineralocorticoid receptor antagonist (nsMRA) developed by Bayer for the treatment of CKD in patients with T2D. Because of its mechanism of action, finerenone is expected to have a lower risk of inducing hyperkalaemia, which has been shown in clinical studies.[31] In the phase 3, event-driven, placebo-controlled FIDELIO trial,[32] results showed that, among patients with stage 3 or 4 CKD with severely elevated albuminuria and type 2 diabetes, finerenone, when added to standard of care, reduced the incidence of CKD progression[33] and a composite cardiovascular outcome that included time to cardiovascular death, myocardial infarction, stroke, or hospitalization for heart failure.[34] In the FIGARO trial,[35] patients on finerenone had less severe kidney impairment, either stage 2 to 4 CKD and moderately elevated albuminuria or stage 1 or 2 CKD and severely increased albuminuria, but the cardiovascular benefit seen in the FIDELIO trial extended to those patients with less kidney impairment but who were still at high cardiovascular risk.[36] In the prespecified pooled analysis of the FIDELIO and FIGARO trials, the positive effects were demonstrated for both CKD and cardiovascular outcomes across a broad spectrum of CKD.[37]

Finerenone received approval from the FDA on 09 JUL 2021 and is indicated in adult patients with CKD associated with T2D to reduce the risk of sustained eGFR decline, kidney failure, cardiovascular death, non-fatal myocardial infarction, and hospitalization for heart failure.[38,39]

Finerenone received approval from the EMA on 16 FEB 2022 and is indicated for the treatment of CKD (stage 3 and 4 with albuminuria) associated with T2D in adults.[40] Finerenone received approval from the Pharmaceutical and Medical Devices Agency (PMDA) in Japan on 22 MAR 2022.[41] Marketing authorization applications have been submitted to the Medicines and Healthcare Products Regulatory Agency in the UK, and other countries globally.

The clinical landscape for the treatment of patients with CKD and T2D is rapidly evolving with the introduction of new treatments, and it is of interest to study how treatment patterns may evolve with the approval of new drugs for this indication.

The study was performed as part of the FOUNTAIN (**F**inerenone m**U**lti-database **N**e**T**work for evidence gener**A**t**I**o**N**) programme, an integrated approach to real-world evidence generation that supports multiple studies, one of which aims to describe drug utilization and treatment patterns in patients with CKD and T2D to understand the dynamic treatment landscape for the target indication of a new drug.[42]

7. Research question and objectives

The overall aim of this study was to describe patient profiles and treatment patterns in medication initiator cohorts of patients with CKD and T2D.

The primary objective of this study was:

- To describe baseline patient characteristics, comorbidities, and comedication of adult patients with CKD and T2D who initiate an SGLT2i, a GLP-1 RA, an sMRA, finerenone, or another non-steroidal MRA (only in Japan) in each of two time periods corresponding to the finerenone pre-launch ("pre-finerenone period") and post-launch dates ("post-finerenone period").

The secondary objective(s) of this study were:

- To describe treatment changes over time in the new-user cohorts, including treatment discontinuation, treatment switches, and add-on treatments in each of two time periods corresponding to finerenone pre-launch and post-launch dates; for finerenone, treatment titration (e.g., the percentages of finerenone patients uptitrating the dose from 10 mg to 20 mg within 12 months) was also described.
- To describe temporal changes in the baseline characteristics of the medication-specific cohorts before and after finerenone launch.

8. Amendments and updates

Table 2: Amendments

No.	Date	Section of study protocol	Amendment / update	Reason
1	22 MAY 2024	Research Methods	Decision was taken on 11 APR 2023 to not include CPRD in the FINEGUST study.	The decision to not include CPRD in the study was due to delays in obtaining data. No data were received, and therefore no analyses were

No.	Date	Section of study protocol	Amendment / update	Reason
			The data source used in the post-finerenone analyses was limited to US only (CDM); the sMRA and other (non-finerenone) nsMRA cohorts were removed from the post-finerenone period analysis. A "wide finerenone cohort" was added.	conducted, and no results obtained. The decision to restrict the post-finerenone analysis to CDM was due to a low number of finerenone users in Europe and Japan, precluding the conduct of the intended post-finerenone period analysis in those regions. The decision to remove sMRA and other nsMRA from the post-finerenone period analysis were due to limited or no use of these products in the US (with the only data source used for the post-finerenone period analysis being from the US) and the completely different clinical profile of those cohorts observed in the pre-finerenone period. The "wide finerenone cohort" was added to allow for the inclusion of more finerenone users due to the use of less restrictive inclusion/exclusion criteria.

CPRD = Clinical Practice Research Datalink; No. = number; US = United States.

9. Research methods

9.1 Study design

This was a multidatabase, multinational observational (non-interventional) cohort study identifying separate medication-specific cohorts of new users of SGLT2i, GLP-1 RA, sMRA, and nsMRA. Analyses were conducted in two separate time periods that correspond to the pre-approval (pre-finerenone period; study period I) and post-approval dates of finerenone (post-finerenone period; study period II). In the pre-finerenone study period, four new-user cohorts were identified, based on the first use of a drug in one of these classes: SGLT2i, GLP-1 RA, sMRA, or nsMRA (Japan only). In the post-finerenone study period, three new-user cohorts were identified: SGLT2i, GLP-1 RA, and finerenone. As described in Section 8 (Amendments and updates), the post-finerenone analysis was conducted in just one of the participating data sources (CDM, US), owing to delays in uptake of finerenone in Europe and Japan. Also, the post-finerenone period included an additional "wide finerenone cohort" in which patients with a prescription or dispensing for finerenone were included with a less

restrictive inclusion and exclusion criteria than was used for the other medication cohorts, along with differing censoring criteria.

Patients in all cohorts were followed prospectively until one of the censoring criteria was met.

The medication-specific cohorts were not mutually exclusive, and an individual patient could have been included in multiple cohorts. Patients included in a medication-specific cohort who switched to a different study medication continued to be followed in the first cohort but were also included as new users of the other medication(s) if they met the inclusion and exclusion criteria. This design increased the efficiency of the study, but importantly, as the different medication-specific cohorts are not intended for comparison, this approach enabled the assessment of the different medication-specific cohorts as if they were generated as stand-alone new-user cohorts. The medication-specific patient cohorts in each country were described, including baseline demographic characteristics, clinical characteristics, and treatment patterns.

9.2 Setting

9.2.1 Data sources

The study used secondary data from five participating data sources in Europe, Japan, and the US. These data sources were as follows:

- Danish National Health Registers (DNHR), Denmark: a large network of population-based health registers covering the entire population of Denmark, with administrative data from the Danish Health Care System.
- PHARMO Data Network (PHARMO) of the PHARMO Institute for Drug Outcomes Research, The Netherlands: a population-based network of electronic healthcare databases combining data from different primary and secondary healthcare settings in The Netherlands.
- Valencia Health System Integrated Database (VID), Spain: a set of multiple, public, population-wide electronic databases for Valencia, the fourth most-populated region of Spain.
- Japan Chronic Kidney Disease Database Extension (J-CKD-DB-Ex), Japan: a nationwide comprehensive clinical database of patients aged 18 years or older with CKD (proteinuria ≥ 1+ [dipstick test] and/or eGFR < 60 mL/min/1.73 m^2) that is based on electronic health record (EHR) data from five participating university hospitals.
- Optum's de-identified Clinformatics® DataMart (CDM), US: a database of administrative health claims with laboratory data for members of a large US managed care company affiliated with Optum, comprising commercial health plan data and Medicare Advantage members.

All data sources were used for the pre-finerenone analysis, but only CDM was used for the post-finerenone analysis.

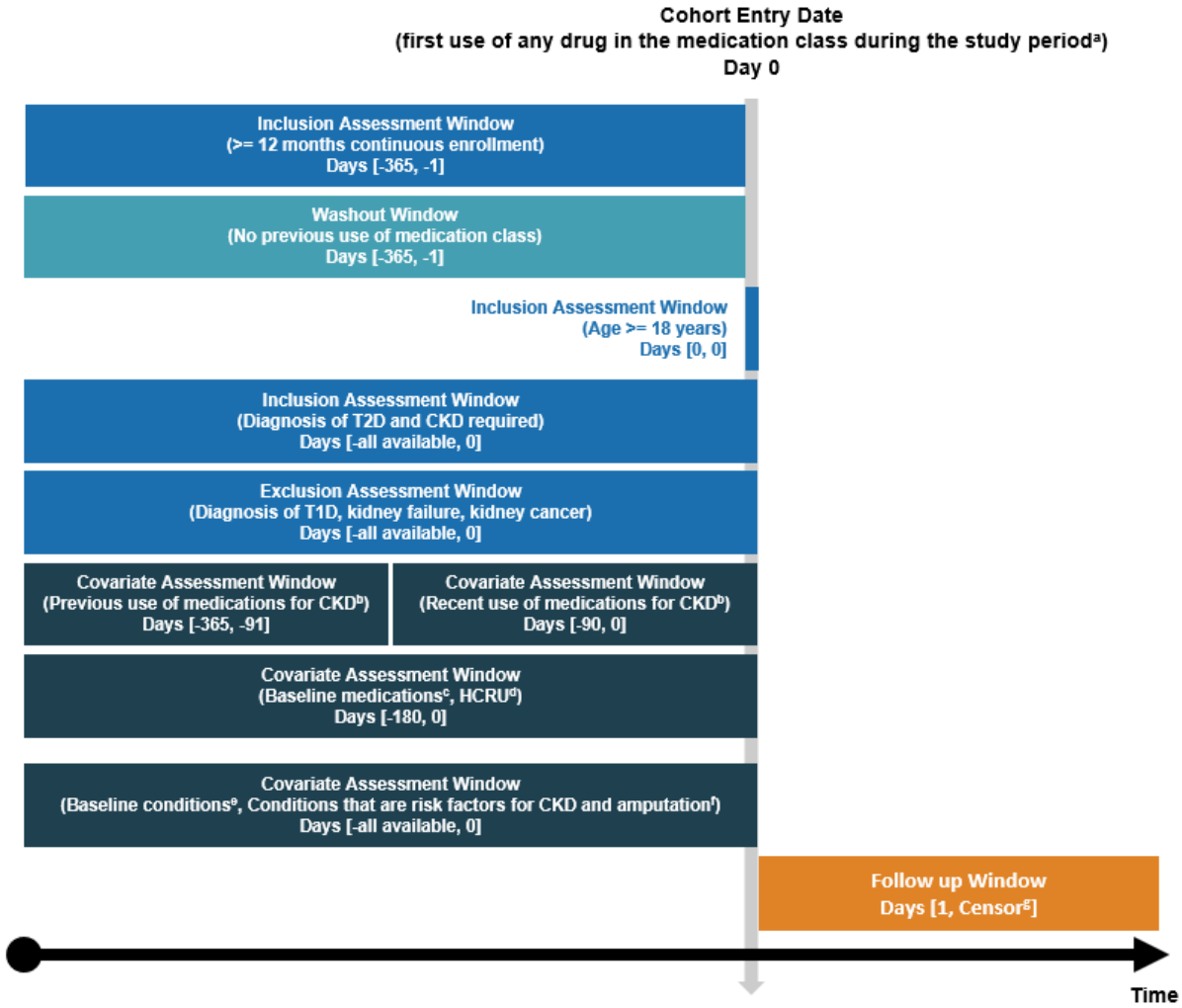
A detailed description of each data source is provided in Annex 2.

9.2.2 Study timeframe

For the pre-finerenone period analysis, within the European and US data sources, the study period was 01 JAN 2012 through 30 JUN 2021. The end of this period was just before finerenone approval in the US. Due to lag time in data availability at the time of analysis in PHARMO, the end of the study period was December 2020 for The Netherlands. In Japan, the start of the study period was 01 JAN 2014, the date on which J-CKD-DB-Ex had the first recorded information available, and the end of the study period was 30 JUN 2021. The post-finerenone period started after the approval of finerenone in the US (09 JUL 2021) and continued until the end of available data which was 30 SEP 2023.

Figure 1 depicts the study design features regarding cohort eligibility, cohort entry, baseline assessment periods, and follow-up described in the following sections and following the methods described by Schneeweiss et al.[43]

Figure 1: Variable assessment windows relative to the study index date for medication-specific cohorts



ACEi = angiotensin-converting enzyme inhibitors; ARB = angiotensin receptor blockers; CKD = chronic kidney disease; ED = emergency department; GLP-1 RA = glucagon-like peptide-1 receptor agonists; GP = general practitioner; HCRU = healthcare resource utilization; 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 I: 01 JAN 2012 until 30 JUN 2021; study period II: after finerenone launch in the US (09 JUL 2021) through 30 SEP 2023 (end of available data).

[b] SGLT2i, GLP-1 RA, sMRA, finerenone, other non-steroidal 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] HCRU measures: GP visits, hospital visits, hospitalizations, specialist visits, ED visits.
Baseline conditions: Chronic cardiovascular disease, hypertension, diabetes mellitus severity and complications, hyperlipidemia, lifestyle cardiovascular disease risk factors (smoking, obesity), stage of CKD, other kidney disorders, liver disease, chronic obstructive pulmonary disease, Charlson Comorbidity Index score.

[e] Censored at the earliest of death, disenrollment, exclusion criteria during follow-up (not applicable to the wide finerenone cohort), or end of the study period. Note that patients can be in more than one cohort at any given time based on index medication start date. Treatment change is not a censoring event. It is anticipated that many patients will have tried medications in more than one of the four cohort medication classes.

9.2.2.1 Baseline and lookback period

To characterize the new-user cohorts at the time of study drug initiation, information available in the 365 days before and including the date of cohort entry were collected (unless otherwise specified). All cohort members were required per the inclusion criteria (Section 9.3.2) to have at least 12 months of data before the cohort entry date (baseline period). All available lookback time was used to define kidney transplant, CKD, diabetes, selected conditions that predispose individuals to CKD, and lower extremity amputations. Baseline medications and healthcare resource utilization were assessed in the 180 days before and including the index date.

9.2.2.2 Follow-up

In both the pre-finerenone and post-finerenone periods, follow-up started the day *after* the date of inclusion in the cohort and continued until the first occurrence of one of the following censoring criteria:

- End of the study period, defined as 30 JUN 2021 for the pre-finerenone period (except for The Netherlands where the study end was 31 DEC 2020 because of the data lag time in PHARMO) and 30 SEP 2023 for the post-finerenone period
- Disenrollment from the database or emigration from the database catchment area
- Development of kidney failure
- Development of kidney cancer
- Death

Development of kidney failure and kidney cancer were not considered censoring criteria for the wide finerenone cohort (Section 9.3.2).

Information regarding death was identified from health system enrolment data or national death registries, as appropriate in each data source. Mortality data were not available in J-CKD-DB-Ex.

9.3 Subjects

9.3.1 Study population

For each data source, the source population included all patients initiating one of the study medication classes with at least 12 months of continuous enrolment during each study period whose records also fulfilled electronic algorithms for CKD and T2D. Four new-user cohorts were created in the pre-finerenone period (SGLT2i, GLP-1 RA, sMRA, non-steroidal MRA). New-user cohorts for SGLT2i, GLP-1 RA, and finerenone were created in the post-finerenone period. Eligibility for each new-user cohort within each study period was considered independently, meaning that a given patient could be eligible for inclusion in each of the medication cohorts in the pre-finerenone and post-finerenone periods. The nsMRA cohort was only identified in Japan where esaxerenone was available.

9.3.1.1 Determining new users and study index dates

For each study period (pre-finerenone and post-finerenone), new users for a given medication cohort were patients with an outpatient prescription or dispensing for a drug in that medication class during the study period with no other record of any other medication in that class during the previous 12 months. Depending on the data source, medications were

recorded as prescriptions (i.e., medication prescription) or a medication dispensing at a pharmacy. Hereafter, the term "prescription" will be used in the report to refer to prescribed or dispensed medications. Patients may have initiated multiple study classes during the study period, and patients were eligible for multiple medication-specific cohorts. Patients who switched to a different class of study medication remained in the first new-user cohort and were also entered into the second new-user cohort at the time of the switch if they met all inclusion and exclusion criteria. Patients who switched to a different medication within the same class remained in the initial cohort. The index prescription for a given medication cohort was the first eligible prescription that fulfilled the definition of new use during the study period; the date of this prescription or dispensing served as the index date.

At the time of each potential index date, an individual was assessed for the inclusion and exclusion criteria (Section 9.3.2). All potential index dates for which the individual met the inclusion criteria, and did not meet any of the exclusion criteria, were considered for inclusion in the study cohort. For each individual, these potential index dates were ordered in ascending order (with the earliest prescription record listed first). The first prescription for each individual that met the inclusion criteria was selected as the index prescription for that individual and the corresponding date served as the date of entry into that medication class cohort.

The index prescription did not need to be the first one ever written for that medication class. For example, a patient may have had an earlier prescription that did not qualify as the index prescription if other cohort entry requirements had not been met. This situation could occur, for example, if on the date of the candidate index prescription, the patient was not yet 18 years of age, had no history of CKD, or had evidence of the same medication (or a prescription from the same study drug class) during the previous 12 months. In such situations, a subsequent prescription for the same medication meeting all inclusion criteria could still qualify.

9.3.2 Inclusion and exclusion criteria

For each medication cohort, patients who met all inclusion criteria and did not meet any of the exclusion criteria before the index prescription initiation date (index date) were selected.

Patients were included in the study if they met all the following requirements on or before the index date:

- Had an active registration or continuous enrolment in each respective data source for at least 12 months before the index date (active registration was defined separately for each respective data source)
- Were aged 18 years or older on the index date
- Had no recorded prescription for any medication in that class during the 12 months before the index date
- Had a diagnosis of T2D ever recorded before or on the index date
- Had a diagnosis of CKD ever recorded before or on the index date

Patients were excluded from the study if they had any of the following medical conditions on or before the index date:

- Type 1 diabetes (T1D)
- Kidney cancer

- Kidney failure

For the "wide finerenone" cohort, which used less restrictive inclusion and exclusion criteria for patients with a prescription of finerenone, the index prescription was the first one in which the following inclusion criteria were met:

- Had an active registration or continuous enrolment in each respective data source for at least 12 months before the index date (active registration was defined separately for each respective data source)
- Were aged 18 years or older on the index date

No other inclusion or exclusion criteria were required for this cohort.

Operational definitions for these variables are found in Section 9.4.

9.4 Variables

9.4.1 Exposure

9.4.1.1 Medication exposures

Exposures to the index medication and concomitant medications were identified from outpatient prescription records in EHRs or administrative data for dispensing of medications at a pharmacy, depending on the data source. Relevant medications were defined by Anatomical Therapeutic Chemical (ATC) or standard master codes for pharmaceutical products (HOT) codes (Annex 3).

9.4.1.2 Current use of index medication

Current-use periods for a medication were defined from the day after the index date to the end of presumed supply for consecutive prescriptions plus a grace period of 30 days in all data sources, except in DNHR, which did not have data on dispensed days' supply. In DNHR, days' supply was estimated using a data-driven approach using the upper quartile of the times between prescriptions with a 30-day grace period. All data sources used a common approach to account for gaps off drug and for potential stockpiling of drug supply. Operational details are described in Annex 4.

9.4.1.3 Classifying index medication

For each medication cohort, the index medication was classified in relation to other drugs of interest (i.e., other medications examined in this study with known CKD-protective effects [SGLT2i, ACEi or ARB, and GLP-1 RA] and sMRA) in three distinct time periods: in the 90 days before the index date, on the index date, and in the 90 days after the index date. It is important to note, however, that information on indication was not available, so it could not be determined whether these classes of drugs were used for reno-protection or other indications. The study-defined categories were as follows: medication of interest initiated as the only drug of interest ("monotherapy"); simultaneous initiation of medication of interest together with another drug of interest ("combination therapy"); "add-on therapy," in which medication of interest was initiated and added to an existing drug of interest; "switched-to therapy," in which an existing drug of interest was replaced by the initiated medication of interest; both add-on and switched-to therapy at the same time; and non-evaluable index therapy. Detailed definitions of these exposure categories are provided in Annex 4.

9.4.1.4 Treatment utilization outcomes

The secondary objectives of the study included the following treatment utilization outcomes: treatment discontinuation, treatment switches, and add-on treatments during each study period. In addition, titration of the initial finerenone dose was measured.

Treatment discontinuation refers to the end of current use. The date following the last day of current use defined the date of treatment discontinuation. Note that in the FINEGUST study, treatment discontinuation may be temporary; following discontinuation of a study drug, if a patient received another prescription for the same drug (or member of that class), a new current-use period began (one day after that prescription).

9.5 Bias

Not applicable

9.6 Study size

Not applicable

9.7 Data transformation

9.7.1 Data rules

9.7.1.1 Assignment of dates for conditions that are established only after repeated measures

In this study, some variables required more than one data point to meet the case definition (e.g., maintenance dialysis and kidney failure as determined by eGFR). The onset date for such conditions was assigned as the date on which the final component of the case definition was satisfied.

9.7.1.2 Rules to identify and classify CKD using eGFR and other variables

In this study, one of the ways to identify CKD was through eGFR values. If eGFR was not recorded in the data source, it was calculated using the creatinine-based 2021 Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) equation (without including cystatin-C),[44] which removes a coefficient for Black race which is included in other equations:

$$\text{eGFR} = 142 \times \min(\text{Scr}/\kappa, 1)^{a_1} \times \max(\text{Scr}/\kappa, 1)^{a_2} \times c^{\text{Age}} \times d \text{ [if female]}$$

Where:

$a_1 = -0.241$ for females and -0.302 for males

$a_2 = -1.200$

$c = 0.9938$

$d = 1.012$

- κ is 0.7 for female participants, and 0.9 is for male participants; min indicates the minimum of Scr/κ and 1, and max indicates the maximum of Scr/κ and 1
- The coefficient a_1 is used for creatinine levels less than or equal to 0.9 mg per deciliter for male participants and 0.7 mg per deciliter for female participants. The coefficient a_2 is used for creatinine levels greater than 0.9 mg per deciliter for male participants and 0.7 mg per deciliter for female participants

- The Jm-EPI-CKD formula was used in Japan[45,46]

CKD stage based on eGFR categories (mL/min/1.73 m^2) was defined as follows:

- Stage 1: ≥ 90, normal or high
- Stage 2: 60-89, mildly decreased
- Stage 3a: 45-59, mildly to moderately decreased
- Stage 3b: 30-44, moderately to severely decreased
- Stage 4: 15-29, severely decreased
- Stage 5: < 15 OR treated by dialysis, kidney failure (this stage will be an exclusion criterion)

In this study, the diagnosis of CKD by eGFR required evidence of chronicity. Operationally, this required at least two measurements that were less than 60 mL/min/1.73 m^2 separated by at least 90 days and no more than 540 days.

For patients without eGFR values available, if recorded CKD diagnosis codes indicated CKD stage, the stage was recorded.

CKD was also considered if it was based on albuminuria measured with ACR.[1] For patients with ACR values available, the following albuminuria categories were assigned (ACR mg/g is approximately equivalent to AER mg/d):

- A1: < 30, normal to mildly increased
- A2: 30-300, moderately increased (formerly “microalbuminuria”)
- A3: > 300, severely increased (includes nephrotic syndrome, > ~ 2000).

The ACR categories were used if available, as they provided additional information regarding CVD risk and kidney prognosis.[12] However, for CKD staging, only eGFR values were used.

If eGFR, ACR, and stage-specific diagnosis codes were not present, the patient was classified as CKD stage unspecified.

9.7.1.3 Definition of derived variables and subgroups

Because this study relied on secondary data that were not collected for research purposes, nearly all variables that were used in the analysis are derived. A detailed enumeration of the variables that were used to generate study results, in addition to their assessment windows and some general operational definitions are listed in the SAP (version 1.2, dated 07 JUN 2024). Lists of relevant ICD-10-CM and ATC codes to identify study variables appear as stand-alone documents accompanying the SAP. Given the differences in data specifications across study data sources, more specific operational details appear in each research partners specific (RPS)-SAP. The code lists to identify study variables in each data source appear as stand-alone documents that supplement these RPS-SAPs.

9.8 Statistical methods

9.8.1 Main summary measures

Not applicable

9.8.2 Main statistical methods

Statistical analyses were performed on-site by each research partner according to a common statistical analysis plan with data source–specific adaptations. Analyses were programmed in SAS version 9.4 or higher (SAS Institute, Inc.; Cary, North Carolina), except for VID, which used R (version 4.1.0). Aggregated results were provided by the respective research partners to the coordinating center in a common data set format to allow for similar formatting of all results tables across research partners. All analyses were descriptive in nature.

Descriptive statistics were compiled using frequency distributions (counts, proportions) for categorical variables and mean, standard deviations, medians, first and third quartiles, and 1st and 99th percentiles for continuous variables, as appropriate. According to country-specific data privacy standards, categorical variables with low frequencies for a specific level were masked. The percentage of missing data for individual variables was described. Details on data privacy standards for each data source are provided in Annex 2.

9.8.2.1 Describe treatment changes over time

Analyses for treatment changes over time were restricted to three years post-index date. The following treatment states were assessed:

- Treated with index medication (i.e., patient was in any continuous current-use period on the date of the checkpoint)
- Untreated with index medication
- Lost to follow-up, end of study, or censored
- Death (information on death was not available in J-CKD-DB-Ex)

These treatment states were assessed in the pre-finerenone period at the following discrete times (“checkpoints”) post-index date: 90 days, 180 days, 270 days, one year, two years, and three years. In the post-finerenone period the following discrete times post-index were assessed: 90 days, 180 days, 270 days, and one year.

Exposure to other medications of interest in patients with T2D during follow-up was also recorded.

To capture movement of medication initiators between different treatment states at each checkpoint, shift tables were prepared. These tables described how patients moved between the categories of interest over consecutive pairs of checkpoints and were used to construct Sankey diagrams to illustrate the movement of patients across all checkpoints.[47,48] The checkpoints on the horizontal axis were 90 days, 180 days, 270 days, one year (last check point available in the post-finerenone period), two years, and three years after the index date. In the Sankey diagrams, treatment status (treated or untreated with the index medication class) was determined by whether a patient was in any continuous current-use period on the date of the checkpoint. If death occurred, the patient was placed in a separate category and remained in that state for each subsequent checkpoint. From one checkpoint to the next, patients could move between different treatment states (e.g., starting as treated, then discontinuing treatment and becoming untreated or changing the index medication, then dying). The denominator of each checkpoint included all patients still enrolled in the follow-up period and those who died. Patients who were lost to follow-up or censored were subtracted from the denominator of checkpoints after the censoring date for the calculations. Patients who died were retained in the denominator, as they continued to be displayed as a treatment state at each checkpoint.

9.8.2.2 Temporal analysis

To address the secondary objectives evaluating temporal changes in baseline characteristics of the medication-specific cohorts between the pre-finerenone and post-finerenone periods, descriptive statistics for baseline characteristics of the medication class cohorts (i.e., SGLT2i, GLP-1 RA) that were present in both study periods (before and after finerenone launch) were examined. To assess any change over time, the differences between the descriptive statistics in each study period were calculated. The analyses of temporal changes were only used to evaluate patient characteristics and treatment information available at the baseline evaluation. Any data characterizing follow-up or post-index information were not used.

For continuous variables, the difference estimate reported was the mean in the "post-finerenone" period minus the reported mean from the "pre-finerenone" period. To provide additional context for interpreting these differences, the standardized mean difference (SMD) for each baseline characteristic was calculated. The SMD estimate assesses the balance between the baseline covariates in the "pre-finerenone" study period compared with that in the "post-finerenone" study period, and it has the advantage of being able to display the results for both categorical and continuous variables on the same scale. According to Austin[49], the SMDs of 0.2, 0.5, and 0.8 roughly correspond to small, medium, and large differences, respectively, in the level of the covariate between the two treatment periods.

9.8.3 Missing values

Approaches to missing data varied across the different data sources examined.

Claims data comprised coded health claims; therefore, the absence of a code for a particular characteristic was interpreted as the patient not having that characteristic (as opposed to missing). Categorical demographic variables derived from enrolment information (e.g., sex, race, ethnicity) that may be categorized as unknown in the data were reported as such in descriptive tables.

For lifestyle variables, vital statistics, and laboratory values missing in EHR data, the percentage of missing data was described.

As this was a descriptive analysis and no multivariable analysis was conducted, methods to account for missing data (such as single or multiple imputation) were not deemed necessary; thus, the missing data were represented as they are, as a separate category.

9.8.4 Sensitivity analyses

Not applicable

9.8.5 Amendments to the statistical analysis plan

- SAP v1.1 dated 09 NOV 2022: The lookback periods for ascertaining information such as comorbid conditions and comedications were updated, as were lookback windows for ascertaining CKD diagnoses and characteristics in the US data source to align with most appropriate capture of relevant data in each data source.
- SAP v2.0 dated 07 JUN 2024: The follow-up times were updated to more accurately reflect data availability at the time the analyses were actually conducted. The SAP was updated to reflect the removal of CPRD as a data source and to note that the post-finerenone analyses would only be conducted in the CDM (US) owing to the slow uptake of finerenone in the other countries.

9.9 Quality control

Standard operating procedures or internal process guidance for study conduct were followed at each research center. These procedures included internal quality audits, rules for secure and confidential data storage, methods to maintain and archive project documents, quality-control procedures for programming, standards for writing analysis plans, and requirements for senior scientific review.

- DNHR: Programming written by a main analyst was partially reviewed by a second analyst. All key study documents underwent quality review and senior scientific review.
- J-CKD-DB-Ex: The database was compiled from electronic medical records from multiple medical institutions with a standardized data structure. Data analysis was performed by J-CKD-DB-Ex investigators. All key documents underwent quality-control review and scientific review by investigators of J-CKD-DB-Ex.
- PHARMO: All programming written by the executing researcher was reviewed independently by a senior researcher, and all key study documents underwent quality-control and senior scientific review.
- VID: Double-independent programming was performed by senior data analysts. Senior scientific review was performed in all key stages of the project and for all key study documents.
- CDM: Programming written by the main analyst was partially reviewed by a second analyst. All key study documents underwent quality review and senior scientific review.

10. Results

10.1 Participants

10.1.1 Pre-finerenone period

10.1.1.1 SGLT2i

There were 92,508 patients with use of an SGLT2i in DNHR, 3,234 in PHARMO, 163,844 in VID, 6,934 in J-CKD-DB-Ex, and 849,898 in CDM (Table 3). The number of potential index dates during the study period was 919,037 in DNHR, 39,186 in PHARMO, 3,876,105 in VID, 11,506 in J-CKD-DB-Ex, and 7,511,502 in CDM. After applying all inclusion and exclusion criteria, the final patient sample used for analyses was 21,739 in DNHR, 381 in PHARMO, 31,785 in VID, 1,157 in J-CKD-DB-Ex, and 56,219 in CDM (Table 3).

Table 3: 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%)
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%)

	DNHR	PHARMO	VID	J-CKD-DB-Ex	CDM
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

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

Note: Cohort selection involved evaluating multiple potential index dates per patient.

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

10.1.1.2 GLP-1 RA

There were 103,787; 3,983; 46,382; 2,991; and 1,094,916 patients who had at least one prescription or dispensing of a GLP-1 RA in the DNHR, PHARMO, VID, J-CKD-DB-Ex, and CDM databases, respectively (Table 4). During the study period, these patients had 2,127,523 potential index dates in DNHR; 57,993 in PHARMO; 1,628,298 in VID; 6,134 in J-CKD-DB-Ex; and 6,201,479 in CDM. After application of all inclusion and exclusion criteria, the final sample size was 18,929 for DNHR, 476 for PHARMO, 11,798 for VID, 329 for J-CKD-DB-Ex, and 70,158 for CDM (Table 4).

Table 4: Attrition of cohorts of GLP-1 RA users, by data source

	DNHR, N (%)	PHARMO, N (%)	VID, N (%)	J-CKD-DB-Ex, N (%)	CDM, N (%)
All patients in the current database build	NE	1,695,731	309,477	251,659	NE
All patients with recorded study drug use	103,787	3,983	46,382	2,991	1,094,916
Total number of potential index dates	2,536,406	62,110	1,628,298	6,134	10,858,407
Potential index dates reported outside the study period	408,883 (16.1)	4,117 (6.6)	0 (0)	0 (0)	4,656,928 (42.9)
Total number of potential index dates during the study period	2,127,523	57,993	1,628,298	6,134	6,201,479
Patients with < 12 months of lookback time at the potential index date	43,488 (2.0)	2,778 (4.8)	2,871 (0.2)	1,990 (32.4)	325,306 (5.2)
Had a recorded prescription/dispensing of any GLP-1 RA during the 12 months before the potential index date	2,040,032 (95.9)	54,408 (93.8)	1,579,971 (97.0)	2,944 (48.0)	5,554,474 (89.6)
Patients aged < 18 years at the potential index date	435 (< 0.1)	0 (0)	244 (< 0.1)	4 (0.1)	518 (< 0.1)
No diagnosis of T2D recorded on or before the potential index date	0 (0)	145 (0.3)	68,115 (4.2)	1,736 (28.3)	359,660 (5.8)
No diagnosis of CKD recorded on or before the potential index date	1,453,664 (68.3)	48,920 (84.4)	1,133,100 (69.6)	3,072 (50.1)	4,673,351 (75.4)
Patients with potential index dates meeting the inclusion criteria	20,673	536	13,005	708	84,553
Patients with T1D identified on or before the potential index date	240 (1.2)	14 (2.6)	0 (0)	236 (33.3)	5,015 (5.9)
Kidney cancer recorded on or before the potential index date	232 (1.1)	8 (1.5)	121 (0.9)	42 (5.9)	1,298 (1.5)
Kidney failure recorded on or before the potential index date[a]	193 (0.9)	5 (0.9)	373 (2.9)	137 (19.4)	4,522 (5.3)

	DNHR, N (%)	PHARMO, N (%)	VID, N (%)	J-CKD-DB-Ex, N (%)	CDM, N (%)
Number of patients with potential index dates eligible for study inclusion	20,023	510	12,518	339	74,368
Subsequent index dates removed due to inclusion of an earlier eligible index date	1,094 (5.5)	34 (6.7)	720 (5.8)	9 (2.7)	4,210 (5.7)
Final patient sample used for analyses	18,929	476	11,798	329	70,158

CDM = Optum's de-identified Clinformatics® DataMart; CKD = chronic kidney disease; DNHR = Danish National Health Registers; GLP-1 RA = glucagon-like peptide-1 receptor agonist; J-CKD-DB-Ex = Japan Chronic Kidney Disease Database Extension; NE = not estimable; T1D = type 1 diabetes; T2D = type 2 diabetes; VID = Valencia Health System Integrated Database.

Note: Cohort selection involved evaluating multiple potential index dates per patient.

[a] Patients may have had more than one indicator for kidney failure.

10.1.1.3 sMRA

There were 190,937 patients (representing 2,093,111 potential index dates during the study period) with a prescription or dispensing for an sMRA in the DNHR, 33,914 (1,002,304 index dates) in PHARMO, 119,099 (2,865,468 index dates) in VID, 18,974 (32,523 index dates) in J-CKD-DB-Ex and 1,491,798 (8,627,784 index dates) in CDM (Table 5). After implementation of all inclusion and exclusion criteria, the final sample size was 12,689 for DNHR, 2,691 for PHARMO, 14,906 for VID, 1,769 for J-CKD-DB-Ex, and 71,716 for CDM.

Table 5: Attrition of cohorts of sMRA users, by data source

	DNHR, N (%)	PHARMO, N (%)	VID, N (%)	J-CKD-DB-Ex, N (%)	CDM, N (%)
All patients in the current database build	NE	1,695,731	309,477	251,659	NE
All patients with recorded study drug use	190,937	33,914	119,099	18,974	1,491,798
Total number of potential index dates	CCI [redacted]				
Potential index dates reported outside the study period					
Total number of potential index dates during the study period					
Patients with < 12 months of lookback time at the potential index date					
Had a recorded prescription/dispensing of any sMRA during the 12 months before the potential index date					
Patients aged < 18 years at the potential index date					
No diagnosis of T2D recorded on or before the potential index date					
No diagnosis of CKD recorded on or before the potential index date					

	DNHR, N (%)	PHARMO, N (%)	VID, N (%)	J-CKD-DB-Ex, N (%)	CDM, N (%)
Patients with potential index dates meeting the inclusion criteria	CCI [redacted]				
Patients with T1D identified on or before the potential index date					
Kidney cancer recorded on or before the potential index date					
Kidney failure recorded on or before the potential index date[a]					
Number of patients with potential index dates eligible for study inclusion					
Subsequent index dates removed due to inclusion of an earlier eligible index date					
Final patient sample used for analyses	12,689	2,691	14,906	1,769	71,716

CDM = Optum's de-identified Clinformatics® DataMart; CKD = chronic kidney disease; DNHR = Danish National Health Registers; J-CKD-DB-Ex = Japan Chronic Kidney Disease Database Extension; NE = not estimable; sMRA = steroidal mineralocorticoid receptor antagonists; T1D = type 1 diabetes; T2D = type 2 diabetes; VID = Valencia Health System Integrated Database.

Note: Cohort selection involved evaluating multiple potential index dates per patient.

[a] Patients may have had more than one indicator for kidney failure.

10.1.1.4 nsMRA

Data on patients prescribed or dispensed an nsMRA were only available in J-CKD-DB-Ex. There were 301 patients with at least one prescription or dispensing for an nsMRA, representing 405 potential index dates. Although reasons for exclusion were not mutually exclusive, most patients (54.6%) were excluded due to not having a CKD diagnosis recorded on or before the potential index date. The final sample size for inclusion in the study was 63 patients after application of all the inclusion and exclusion criteria. The attrition figure for patients in the J-CKD-DB-Ex can be found in Annex 5, Figure 25.

10.1.2 Post-finerenone period (CDM only)

10.1.2.1 SGLT2i

There were 973,520 patients who had at least one prescription or dispensing of a SGLT2i in CDM (Table 6). These patients had 3,982,218 potential index dates during the study period. After application of all the inclusion and exclusion criteria, there were 95,104 index dates eligible for study inclusion and the final cohort size was 94,080 patients.

Table 6: Attrition of post-finerenone study cohorts, by medication

	Finerenone	SGLT2i	GLP-1 RA	Wide Finerenone
All patients in the current database build	NE	NE	NE	NE
All patients with recorded study drug use	7,572	973,520	1,278,878	7,572
Total number of potential index dates	30,693	8,678,551	12,832,428	NE
Potential index dates reported outside the study period	0 (0%)	4,696,333 (54.1%)	6,986,978 (54.4%)	NE
Total number of potential index dates during the study period	30,693	3,982,218	5,845,450	7,572
Patients with < 12 months of lookback time at the potential index date	2,418 (7.9%)	278,436 (7.0%)	360,201 (6.2%)	2,418 (31.9%)
Had a recorded prescription/dispensing of any medication in the drug class during the 12 months before the potential index date	23,091 (75.2%)	3,470,037 (87.1%)	5,185,807 (88.7%)	NE
Patients aged < 18 years at the potential index date	0 (0%)	197 (< 0.1%)	588 (< 0.1%)	0 (0%)
No diagnosis of T2D recorded on or before the potential index date	1,465 (4.8%)	295,355 (7.4%)	610,785 (10.4%)	NE
No diagnosis of CKD recorded on or before the potential index date	6,718 (21.9%)	2,724,885 (68.4%)	4,390,758 (75.1%)	NE
Potential index dates meeting the inclusion criteria	4,181	105,052	82,731	NE
Patients with T1D identified on or before the potential index date	220 (5.3%)	3,043 (2.9%)	2,674 (3.2%)	NE
Kidney cancer recorded on or before the potential index date	84 (2.0%)	1,944 (1.9%)	1,425 (1.7%)	NE
Kidney failure recorded on or before the potential index date[a]	301 (7.2%)	5,464 (5.2%)	5,390 (6.5%)	NE
Diagnosis code	292 (97.0%)	5,383 (98.5%)	5,335 (99.0%)	NE
Two eGFR[b]	24 (8.0%)	279 (5.1%)	711 (13.2%)	NE
Maintenance dialysis	5 (1.7%)	90 (1.6%)	249 (4.6%)	NE
Kidney transplantation	21 (7.0%)	762 (13.9%)	1,099 (20.4%)	NE
Number of potential index dates eligible for study inclusion	3,604	95,104	73,835	NE
Subsequent index dates removed due to inclusion of an earlier eligible index date	13 (0.4%)	1,024 (1.1%)	1,019 (1.4%)	NE

	Finerenone	**SGLT2i**	**GLP-1 RA**	**Wide Finerenone**
Final patient sample used for analyses	3,591	94,080	72,816	5,201

CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; GLP-1 RA = glucagon-like peptide-1 receptor agonists; SGLT2i = sodium-glucose cotransporter 2 inhibitors; sMRA = steroidal mineralocorticoid receptor antagonists; T1D = type 1 diabetes; T2D = type 2 diabetes.

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

[b] Two different eGFR test results < 15 mL/min/1.73 m^2 separated by at least 90 days and no more than 540 days.

10.1.2.2 GLP-1 RA

There were 1,278,878 patients who had at least one prescription or dispensing of a GLP-1 RA (Table 6). These patients had 5,845,450 potential index dates during the study period. After application of all the inclusion and exclusion criteria, there were 73,835 index dates eligible for study inclusion and the final cohort size was 72,816 patients.

10.1.2.3 Finerenone and wide finerenone

There were 7,572 patients who had at least one prescription or dispensing of finerenone (Table 6). These patients had 30,693 potential index dates during the study period. After application of all the inclusion and exclusion criteria, there were 3,604 index dates eligible for study inclusion and the final cohort size was 3,591 patients.

For the wide finerenone cohort, the only criteria were that patients are at least 18 years of age and have at least 12 months of active registration and continuous enrolment. After application of these criteria, the final study cohort size was 5,201 patients.

10.2 Descriptive data

10.2.1 Pre-finerenone

In all medication initiator cohorts, data for 2021 should be interpreted with the caveat that by design, only six months of observation were included, whereas data in PHARMO were only available until the end of 2020. Information on smoking was only available in PHARMO, VID, and CDM. Most patients in PHARMO were former smokers, whereas most patients in VID and CDM were nonsmokers. Recorded alcohol use was uncommon in all cohorts (observed in < 10% of patients).

10.2.1.1 SGLT2i

The mean age of SGLT2i initiators in the data sources was similar, ranging from 66.5 years to 70.7 years (Table 7). There was a higher percentage of males than females in all data sources. A higher percentage of patients with obesity was recorded in the three data sources with body mass index information available for some patients combined with diagnosis information (PHARMO, 57.5%; VID, 66.6%; CDM, 47.0%) than in the two data sources with only diagnosis information (DNHR, 26.7%; J-CKD-DB-Ex, 8.4%). Annual counts of new SGLT2i initiators were generally skewed towards the later years of the study.

Table 7: Selected baseline characteristics of SGLT2i new users, by data source

Characteristic **n (%), unless otherwise specified**	**DNHR** **(N = 21,739)**	**PHARMO** **(N = 381)**	**VID** **(N = 31,785)**	**J-CKD-DB-Ex** **(N = 1,157)**	**CDM** **(N = 56,219)**
Age group (years) at the index date, n (%)					
< 40	404 (1.9%)	0	189 (0.6%)	21 (1.8%)	415 (0.7%)
40-49	1,312 (6.0%)	8 (2.1%)	1,059 (3.3%)	87 (7.5%)	2,254 (4.0%)
50-59	3,871 (17.8%)	54 (14.2%)	4,171 (13.1%)	188 (16.2%)	7,556 (13.4%)
60-69	6,406 (29.5%)	111 (29.1%)	8,545 (26.9%)	341 (29.5%)	17,099 (30.4%)
70-79	7,323 (33.7%)	149 (39.1%)	11,175 (35.2%)	385 (33.3%)	21,872 (38.9%)
≥ 80	2,423 (11.1%)	59 (15.5%)	6,646 (20.9%)	135 (11.7%)	7,023 (12.5%)
Age at the index date (years)					
Mean (SD)	66.5 (11.4)	69.4 (9.5)	70.7 (10.9)	67.1 (11.7)	68.6 (10.1)
Median	68	70	71.8	68.7	70
1st, 99th percentiles	36, 88	47, 89	42, 91	36, 89	41, 88
Sex, n (%)					
Male	14,029 (64.5%)	212 (55.6%)	18,875 (59.4%)	726 (62.7%)	30,583 (54.4%)
Female	7,710 (35.5%)	169 (44.4%)	12,910 (40.6%)	431 (37.3%)	25,633 (45.6%)
Calendar year of index date, n (%)[a]					
2012	N/A	0 (0%)	0 (0.0%)	N/A	0 (%)
2013	123 (0.6%)	4 (1.0%)	5 (0.02%)	N/A	730 (1.3%)
2014	231 (1.1%)	21 (5.5%)	377 (1.2%)	N/A	2,142 (3.8%)
2015	666 (3.1%)	15 (3.9%)	2,343 (7.4%)	83 (7.2%)	3,503 (6.2%)
2016	1,651 (7.6%)	32 (8.4%)	3,941 (12.4%)	186 (16.1%)	3,633 (6.5%)
2017	2,663 (12.2%)	78 (20.5%)	4,175 (13.1%)	172 (14.9%)	5,355 (9.5%)

Characteristic **n (%), unless otherwise specified**	**DNHR** **(N = 21,739)**	**PHARMO** **(N = 381)**	**VID** **(N = 31,785)**	**J-CKD-DB-Ex** **(N = 1,157)**	**CDM** **(N = 56,219)**
2018	3,276 (15.1%)	78 (20.5%)	4,754 (15.0%)	186 (16.1%)	6,219 (11.1%)
2019	3,891 (17.9%)	72 (18.9%)	6,346 (20.0%)	184 (15.9%)	9,818 (17.5%)
2020	5,044 (23.2%)	81 (21.3%)	5,552 (17.5%)	208 (18.0%)	13,704 (24.4%)
2021	4,194 (19.3%)	NA	4,292 (13.5%)	138 (11.9%)	11,115 (19.8%)
Body mass index (calculated as kg/m^2), n (%)					
< 20 (underweight)	NA	0	108 (0.3%)	NA	156 (0.3%)
20-24.9 (normal)	NA	23 (6.0%)	2,380 (7.5%)	NA	1,373 (2.4%)
25-29.9 (overweight)	NA	124 (32.5%)	9,018 (28.4%)	NA	4,850 (8.6%)
30-39.9 (obese)	NA	174 (45.7%)	13,751 (43.3%)	NA	11,902 (21.2%)
≥ 40 (severely obese)	NA	37 (9.7%)	2,254 (7.1%)	NA	5,705 (10.1%)
Unknown	NA	23 (6.0%)	4,274 (13.5%)	NA	32,233 (57.3%)
Obesity, n (%)[b]					
Yes	5,811 (26.7%)	219 (57.5%)	21,156 (66.6%)	97 (8.4%)	26,443 (47.0%)
Smoking status					
Current smoker	NA	56 (14.7%)	4,778 (15.0%)	NA	11,583 (20.6%)
Former smoker	NA	179 (47.0%)	467 (1.5%)	NA	NE
Non-smoker	NA	123 (32.3%)	26,540 (83.5%)	NA	44,636 (79.4%)
Unknown	NA	23 (6.0%)	NA	NA	
Alcohol abuse, n (%)					
Yes	1,054 (4.8%)	6 (1.6%)	1,094 (3.4%)	35 (3.0%)	954 (1.7%)

BMI = body mass index; CDM = Optum's de-identified Clinformatics® DataMart; DNHR = Danish National Health Registers; J-CKD-DB-Ex = Japan Chronic Kidney Disease Database Extension; SGLT2i = sodium-glucose cotransporter 2 inhibitors; NA = not available; SD = standard deviation; VID = Valencia Health System Integrated Database.

[a] By design, only six months of observation were included in 2021, with the exception of PHARMO, where the end of the study period was December 2020.

[b] Obesity was defined based on BMI value or a diagnosis code.

10.2.1.2 GLP-1 RA

Select baseline characteristics of GLP-1 RA initiators by data source are presented in Table 8. There was a steady increase in GLP-1 RA new users from 2012 to 2019, which was evident across data sources in each of the countries. Age was similar across data sources, ranging from a mean age of 66.1 years in J-CKD-DB-Ex to 67.9 years in CDM. Males represented a lower percentage of new users of GLP-1 RA in CDM (48.0%) and PHARMO (46.6%) compared with J-CKD-DB-Ex (59.6%) and the other European data sources (DNHR, 59.4%; VID, 55.5%). The prevalence of obesity was quite variable, ranging from 15.5% (J-CKD-DB-Ex) to 90.1% (VID).

Table 8: Selected baseline characteristics of GLP-1 RA new users, by data source

Characteristic **n (%), unless otherwise specified**	**DNHR** **(N = 18,929)**	**PHARMO** **(N = 476)**	**VID** **(N = 11,798)**	**J-CKD-DB-Ex** **(N = 329)**	**CDM** **(N = 70,158)**
Age group (years) at the index date					
< 40	435 (2.3%)	1 (0.2%)	117 (1.0%)	15 (4.6%)	643 (0.9%)
40-49	1,266 (6.7%)	16 (3.4%)	622 (5.3%)	26 (7.9%)	2,977 (4.2%)
50-59	3,351 (17.7%)	80 (16.8%)	2,135 (18.1%)	65 (19.8%)	10,119 (14.4%)
60-69	5,513 (29.1%)	188 (39.5%)	3,795 (32.2%)	76 (23.1%)	22,577 (32.2%)
70-79	6,378 (33.7%)	169 (35.5%)	3,889 (33.0%)	96 (29.2%)	26,480 (37.7%)
≥ 80	1,986 (10.5%)	22 (4.6%)	1,240 (10.5%)	51 (15.5%)	7,362 (10.5%)
Age at the index date (years)					
Mean (SD)	66.2 (11.7)	66.6 (8.8)	67.3 (10.6)	66.1 (13.6)	67.9 (10.1)
Median (1st, 99th percentiles)	68 (35-88)	67 (45-86)	68 (40-88)	68 (29-89)	69 (40-87)
Sex					
Male	11,250 (59.4%)	222 (46.6%)	6,549 (55.5%)	196 (59.6%)	33,652 (48.0%)
Female	7,679 (40.6%)	254 (53.4%)	5,249 (44.5%)	133 (40.4%)	36,502 (52.0%)
Unknown	NA	NA	NA	NA	4 (< 0.1%)
Calendar year of index date[a]					
2012	436 (2.3%)	23 (4.8%)	188 (1.6%)	NA	1,879 (2.7%)
2013	290 (1.5%)	26 (5.5%)	350 (3.0%)	NA	1,956 (2.8%)
2014	270 (1.4%)	19 (4.0%)	587 (5.0%)	NA	2,030 (2.9%)
2015	590 (3.1%)	15 (3.2%)	682 (5.8%)	24 (7.3%)	2,885 (4.1%)
2016	1,024 (5.4%)	14 (2.9%)	909 (7.7%)	41 (12.5%)	4,308 (6.1%)
2017	1,585 (8.4%)	39 (8.2%)	1,098 (9.3%)	44 (13.4%)	7,424 (10.6%)
2018	2,526 (13.3%)	75 (15.8%)	1,768 (15.0%)	45 (13.7%)	10,249 (14.6%)

Characteristic **n (%), unless otherwise specified**	**DNHR** **(N = 18,929)**	**PHARMO** **(N = 476)**	**VID** **(N = 11,798)**	**J-CKD-DB-Ex** **(N = 329)**	**CDM** **(N = 70,158)**
2019	3,976 (21.0%)	150 (31.5%)	2,504 (21.2%)	65 (19.8%)	13,876 (19.8%)
2020	4,981 (26.3%)	115 (24.2%)	2,070 (17.6%)	75 (22.8%)	14,866 (21.2%)
2021	3,252 (17.2%)	NA	1,642 (13.9%)	35 (10.6%)	10,685 (15.2%)
BMI (calculated as kg/m^2)					
< 20 (underweight)	NA	0 (0%)	2 (0.2%)	NA	136 (0.2%)
20-24.9 (normal)	NA	6 (1.3%)	114 (1.0%)	NA	1,043 (1.5%)
25-29.9 (overweight)	NA	68 (14.3%)	1,263 (10.7%)	NA	4,589 (6.5%)
30-39.9 (obese)	NA	283 (59.5%)	7,167 (60.8%)	NA	15,039 (21.4%)
≥ 40 (severely obese)	NA	93 (19.5%)	2,026 (17.2%)	NA	9,711 (13.8%)
Unknown	NA	26 (5.5%)	1,226 (10.4%)	NA	39,640 (56.5%)
Obesity[b]					
Yes	6,063 (32.0%)	397 (83.4%)	10,635 (90.1%)	51 (15.5%)	37,234 (53.1%)
Smoking status					
Current smoker	NA	60 (12.6%)	1,844 (15.6%)	NA	14,612 (20.8%)
Former smoker	NA	275 (57.8%)	180 (1.5%)	NA	NE
Non-smoker	NA	119 (25.0%)	9,774 (82.8%)	NA	55,546 (79.2%)
Unknown	NA	22 (4.6%)	NA	NA	NA
Alcohol abuse					
Yes	829 (4.4%)	16 (3.4%)	370 (3.1%)	10 (3.0%)	1,061 (1.5%)

BMI = body mass index; CDM = Optum's de-identified Clinformatics® DataMart; DNHR = Danish National Health Registers; J-CKD-DB-Ex = Japan Chronic Kidney Disease Database Extension; NA = not available; NE = not estimable; SD = standard deviation; VID = Valencia Health System Integrated Database.

[a] By design, only six months of observation were included in 2021, with the exception of PHARMO, where the end of the study period was December 2020.

[b] Obesity was defined based on BMI value or a diagnosis code.

10.2.1.3 sMRA

Across all data sources, there was a steady increase in sMRA initiators between 2012 and 2017, after which there appeared to be a plateau (Table 9). The mean age of sMRA initiators ranged from 72.5 (DNHR) to 77.8 (VID) years. Males comprised a greater percentage of new users in DNHR (59.4%) and J-CKD-DB-Ex (57.0%) and a lower percentage in PHARMO (47.4%) and CDM (48.0%). The percentages of male and female initiators in VID were comparable (50.8% male and 49.2% female) (Table 9). The prevalence of obesity was variable, ranging from 2.8% in J-CKD-DB-Ex to 68.6% in VID. In the only US data source, CDM, obesity prevalence was 43.8% (Table 9).

Table 9: Selected baseline characteristics of sMRA new users, by data source

Characteristic **n (%), unless otherwise specified**	**DNHR** **(N = 12,689)**	**PHARMO** **(N = 2,691)**	**VID** **(N = 14,906)**	**J-CKD-DB-Ex** **(N = 1,769)**	**CDM** **(N = 71,716)**
Age group (years) at the index date					
< 40	CCI				
40-49					
50-59					
60-69					
70-79					
≥ 80					
Age at the index date (years)					
Mean (SD)					
Median (1st, 99th percentiles)					
Sex					
Male					
Female					
Unknown					
Calendar year of index date[a]					
2012					
2013					
2014					
2015					
2016					
2017					
2018					

Characteristic **n (%), unless otherwise specified**	**DNHR** **(N = 12,689)**	**PHARMO** **(N = 2,691)**	**VID** **(N = 14,906)**	**J-CKD-DB-Ex** **(N = 1,769)**	**CDM** **(N = 71,716)**
2019	CCI				
2020					
2021					
BMI (calculated as kg/m^2)					
< 20 (underweight)					
20-24.9 (normal)					
25-29.9 (overweight)					
30-39.9 (obese)					
≥ 40 (severely obese)					
Unknown					
Obesity[b]					
Yes					
Smoking status					
Current smoker					
Former smoker					
Non-smoker					
Unknown					
Alcohol abuse					
Yes					

BMI = body mass index; CDM = Optum's de-identified Clinformatics® DataMart; DNHR = Danish National Health Registers; J-CKD-DB-Ex = Japan Chronic Kidney Disease Database Extension; NA = not available; N/A = not applicable; NE = not estimable; SD = standard deviation; VID = Valencia Health System Integrated Database.

[a] By design, only six months of observation were included in 2021, with the exception of PHARMO, where the end of the study period was December 2020.

[b] Obesity was defined based on BMI value or a diagnosis code.

10.2.1.4 nsMRA

The first new users of nsMRA in J-CKD-DB-Ex were in 2019. The first nsMRA, esaxerenone, was approved in Japan that year. Most new users of the drug were in 2020 (58.7%) and 2021 (36.5%), with the last year restricted, by design, to only six months of data. The mean age of new users was 69.4 years, and the majority were male (61.9%) (Annex 6, Table 39). The prevalence of obesity and alcohol abuse was very low, at 4.8% and 1.6%, respectively, and all patients were nonsmokers.

10.2.2 Post-finerenone period (CDM only)

10.2.2.1 SGLT2i

Select baseline characteristics are presented in Table 10. Given the approval of finerenone in July 2021, by design, only six months of observation were included for all cohorts in 2021, which may partly explain why there were more users in 2022 and 2023 (approximately the same number in both years) than in 2021; in 2023, only nine months of data were included. Median age was 74 years, and patients were older than in the pre-finerenone period (median age, 70 years). Males represented 53% of the cohort. Information regarding BMI was missing for 54.5% of patients, but 46% of patients were considered obese by diagnosis or a BMI ≥ 30. The percentage of current smokers was 26%. The prevalence of alcohol abuse was low at 2.2%.

Table 10: Selected baseline characteristics of new users of study medications in the post-finerenone period, by medication

Characteristic **n (%), unless otherwise specified**	**Finerenone** **(N = 3,591)**	**SGLT2i** **(N = 94,080)**	**GLP-1 RA** **(N = 72,816)**	**Wide Finerenone** **(N = 5,201)**
Age group (years) at index date, n (%)				
< 40	6 (0.2%)	193 (0.2%)	334 (0.5%)	29 (0.6%)
40-49	59 (1.6%)	1,270 (1.3%)	1,970 (2.7%)	134 (2.6%)
50-59	256 (7.1%)	5,478 (5.8%)	7,403 (10.2%)	440 (8.5%)
60-69	837 (23.3%)	21,172 (22.5%)	21,129 (29.0%)	1,280 (24.6%)
70-79	1,759 (49.0%)	43,637 (46.4%)	32,262 (44.3%)	2,412 (46.4%)
≥ 80	674 (18.8%)	22,330 (23.7%)	9,718 (13.3%)	906 (17.4%)
Age at index date (years)				
Mean (SD)	72.2 (8.7)	73.1 (8.9)	70.0 (9.3)	71.2 (9.5)
Median	73	74	71	72
1st, 99th percentile	46, 89	47, 89	43, 88	43, 89
Sex, n (%)				
Male	1,885 (52.5%)	49,832 (53.0%)	32,007 (44.0%)	2,755 (53.0%)
Female	1,706 (47.5%)	44,244 (47.0%)	40,807 (56.0%)	2,446 (47.0%)
Unknown	0 (0%)	4 (< 0.1%)	2 (< 0.1 %)	0 (0%)
Calendar year of index date, n (%)				
2021[a]	101 (2.8%)	13,594 (14.4%)	10,354 (14.2%)	148 (2.8%)
2022	1,489 (41.5%)	40,803 (43.4%)	28,048 (38.5%)	2,102 (40.4%)
2023[b]	2,001 (55.7%)	39,683 (42.2%)	34,414 (47.3%)	2,951 (56.7%)

Characteristic **n (%), unless otherwise specified**	**Finerenone** **(N = 3,591)**	**SGLT2i** **(N = 94,080)**	**GLP-1 RA** **(N = 72,816)**	**Wide Finerenone** **(N = 5,201)**
Race, n (%)				
Asian	258 (7.2%)	4,058 (4.3%)	1,891 (2.6%)	359 (6.9%)
Black	784 (21.8%)	16,533 (17.6%)	12,181 (16.7%)	1,100 (21.1%)
Hispanic	597 (16.6%)	14,008 (14.9%)	10,311 (14.2%)	830 (16.0%)
White	1,667 (46.4%)	52,749 (56.1%)	43,255 (59.4%)	2,495 (48.0%)
Other/Unknown	285 (7.9%)	6,732 (7.2%)	5,178 (7.1%)	417 (8.0%)
BMI, n (%)				
< 20 (underweight)	16 (0.4%)	547 (0.6%)	148 (0.2%)	32 (0.6%)
20-24.9 (normal)	148 (4.1%)	3,037 (3.2%)	1,063 (1.5%)	215 (4.1%)
25-29.9 (overweight)	380 (10.6%)	9,256 (9.8%)	5,026 (6.9%)	561 (10.8%)
30-39.9 (obese)	833 (23.2%)	20,663 (22.0%)	18,212 (25.0%)	1,144 (22.0%)
≥ 40 (severely obese)	339 (9.4%)	9,271 (9.9%)	11,985 (16.5%)	512 (9.8%)
Unknown	1,875 (52.2%)	51,306 (54.5%)	36,382 (50.0%)	2,737 (52.6%)
Obesity, n (%)				
Yes (by diagnosis or BMI ≥ 30)	1,759 (49.0%)	43,308 (46.0%)	42,147 (57.9%)	2,468 (47.5%)
No	1,832 (51.0%)	50,772 (54.0%)	30,669 (42.1%)	2,733 (52.5%)
Smoking status, n (%)				
Current smoker	700 (19.5%)	24,436 (26.0%)	16,157 (22.2%)	1,025 (19.7%)
Former smoker	NE	NE	NE	NE
Non-smoker	NE	NE	NE	NE

Characteristic **n (%), unless otherwise specified**	**Finerenone** **(N = 3,591)**	**SGLT2i** **(N = 94,080)**	**GLP-1 RA** **(N = 72,816)**	**Wide Finerenone** **(N = 5,201)**
Alcohol abuse, n (%)				
Yes	53 (1.5%)	2,043 (2.2%)	1,274 (1.7%)	77 (1.5%)
No	3,538 (98.5%)	92,037 (97.8%)	71,542 (98.3%)	5,124 (98.5%)

GLP-1 RA = glucagon-like peptide-1 receptor agonists; NE = not estimable; SD = standard deviation; SGLT2i = sodium-glucose cotransporter 2 inhibitors; sMRA = steroidal mineralocorticoid receptor antagonists.

Note: Lifestyle variables are defined using the most recent evaluation, recorded on or before the index date.

[a] Only six months of data were available.

[b] Only nine months of data were available.

10.2.2.2 GLP-1 RA

There were more GLP-1 RA users in 2023 than in 2022 and 2021, despite only nine months of data being available in 2023. The median age was 71 years, and patients were slightly older than in the pre-finerenone period (median age: 69 years). Males represented 44.0% of the cohort. Information regarding BMI was missing for 50.0% of patients, but 57.9% of patients were considered obese either by diagnosis or a BMI ≥ 30. The percentage of current smokers was 22.2%. The prevalence of alcohol abuse was 1.7% (Table 10).

10.2.2.3 Finerenone and wide finerenone

The median age was 73 years and 72 years in the finerenone and wide finerenone cohorts, respectively. There were slightly more males than females in both cohorts (approximately 53%). Information regarding BMI was missing to a similar degree in both cohorts (approximately 52%), and 49.0% and 47.5% of patients were considered obese either by diagnosis or a BMI ≥ 30 in the finerenone and wide finerenone cohorts, respectively. The percentage of current smokers was approximately 20% in both cohorts. The prevalence of alcohol abuse was also similar in both cohorts (approximately 2%) (Table 10).

10.3 Outcome data

Not applicable

10.4 Main results

10.4.1 Pre-finerenone

10.4.1.1 SGLT2i

10.4.1.1.1 Markers of severity of T2D at index date

The median duration of T2D in the data sources ranged from 4.2 years in CDM to 12.4 years in PHARMO (Table 11). The most commonly prescribed glucose-lowering drug (GLD) in the 180 days before and including the date of initiating an SGLT2 inhibitor was metformin in DNHR (81.4%), PHARMO (85.8%), and CDM (60.2%), but dipeptidyl peptidase-4 inhibitors (DPP-4i) were the most frequent in VID (62.4%) and J-CKD-DB-Ex (74.3%). GLP-1 RA medications were prescribed to 24.4% of patients in DNHR, 17.8% in CDM, 17.5% in J-CKD-DB-Ex, 10.9% in VID, and 4.7% in PHARMO. Use of alpha-glucosidase inhibitors was less than 1% in all data sources except for J-CKD-DB-Ex (25.8%). Use of thiazolidinediones was highest in J-CKD-DB-Ex (17.0%) and CDM (9.4%) but was less than 3% in the other data sources. Meglitinide use was less than 1.5% in DNHR, PHARMO, and CDM but was 18.1% in VID and 19.3% in J-CKD-DB-Ex. The percentage of patients with no use of any GLD classes other than insulin in the 180 days before or on the index date was less than 10% in the European data sources, 12.5% in J-CKD-DB-Ex, and 16.0% in CDM. Most patients in the European data sources (just over 81%) and the US data source (67.8%) had used one or two GLD classes in this time period, but in J-CKD-DB-Ex, 42.3% had used one or two drug classes and 45.1% had used three or four GLD classes.

Insulin use was recorded in 48.6% of SGLT2i initiators in J-CKD-DB-Ex and in just over 31% of patients in DNHR, VID, and CDM, but in only 5.6% in PHARMO (Table 11). HbA1c recorded in the 365 days before or on the index date (the most recent diagnosis code or laboratory value) was ≤ 53 mmol/mol or ≤ 7% in 17.2% of patients in DNHR, 35.6% in J-CKD-DB-Ex, 24.2% in VID, 9.2% in PHARMO, and 12.5% in CDM. The proportion with the highest HbA1c values (> 74.9 mmol/mol or > 9%) was 27.5% in DNHR, 11.3% in J-

CKD-DB-Ex, 17.4% in VID, 26.0% in PHARMO, and 16.5% in CDM. Note that in CDM, HbA1c values were missing for 43.3% of patients.

The median Diabetes Severity Complications Index score, calculated as the sum of the scores for seven conditions and metabolic complications recorded in the 365 days before or on the index date, was higher in J-CKD-DB-Ex and VID (both with a median score of four) than in CDM (median score of three) and DNHR and PHARMO (both with a median score of two) (Table 11). The frequency of hyperkalaemia at baseline was low in DNHR (1.1%) and PHARMO (2.1%) and higher in J-CKD-DB-Ex (6.3%), CDM (6.5%), and VID (9.2%).

Table 11: Markers of T2D severity at the index date for new users of SGLT2i, by data source

Characteristic **n (%), unless otherwise specified**	**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%)
DPP-4i 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%)
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%)

Characteristic **n (%), unless otherwise specified**	**DNHR** **(N = 21,739)**	**PHARMO** **(N = 381)**	**VID** **(N = 31,785)**	**J-CKD-DB-Ex** **(N = 1,157)**	**CDM** **(N = 56,219)**
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%)
Metabolic complications, n (%)	941 (4.3%)	0 (0%)	4,081 (12.8%)	20 (1.7%)	3,343 (5.9%)

Characteristic **n (%), unless otherwise specified**	**DNHR** **(N = 21,739)**	**PHARMO** **(N = 381)**	**VID** **(N = 31,785)**	**J-CKD-DB-Ex** **(N = 1,157)**	**CDM** **(N = 56,219)**
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

CDM = Optum's de-identified Clinformatics® DataMart; 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; SD = standard deviation; SGLT2i = sodium-glucose cotransporter 2 inhibitors; T2D = type 2 diabetes; VID = Valencia Health System Integrated Database.

10.4.1.1.2 Markers of kidney dysfunction severity at index date

The median duration of CKD at the index date based on all available data was approximately two years in VID and J-CKD-DB-Ex, approximately three years in DNHR and CDM, and six years in PHARMO (Table 12). CKD stage was captured mainly from eGFR laboratory values in the data sources; diagnosis codes for CKD stage were not recorded in the year before the index date for over 93% of patients in DNHR, J-CKD-DB-Ex, and PHARMO, for 71.9% of patients in VID, and for 59.8% of patients in CDM.

Table 12: Baseline markers of kidney dysfunction severity 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 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[a] 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[b], 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%)
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%)

	DNHR (N = 21,739)	**PHARMO (N = 381)**	**VID (N = 31,785)**	**J-CKD-DB-Ex (N = 1,157)**	**CDM (N = 56,219)**
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[b] or diagnosis code[a], 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%)
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[b], 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%)

	DNHR (N = 21,739)	**PHARMO (N = 381)**	**VID (N = 31,785)**	**J-CKD-DB-Ex (N = 1,157)**	**CDM (N = 56,219)**
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%)
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%)

	DNHR (N = 21,739)	**PHARMO (N = 381)**	**VID (N = 31,785)**	**J-CKD-DB-Ex (N = 1,157)**	**CDM (N = 56,219)**
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%)
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%)

	DNHR (N = 21,739)	**PHARMO (N = 381)**	**VID (N = 31,785)**	**J-CKD-DB-Ex (N = 1,157)**	**CDM (N = 56,219)**
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; CDM = Optum's de-identified Clinformatics® DataMart; 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 available; NR = not reported; SD = standard deviation; SGLT2i = sodium-glucose cotransporter 2 inhibitors; sMRA = steroidal mineralocorticoid receptor antagonists; VID = Valencia Health System Integrated Database.

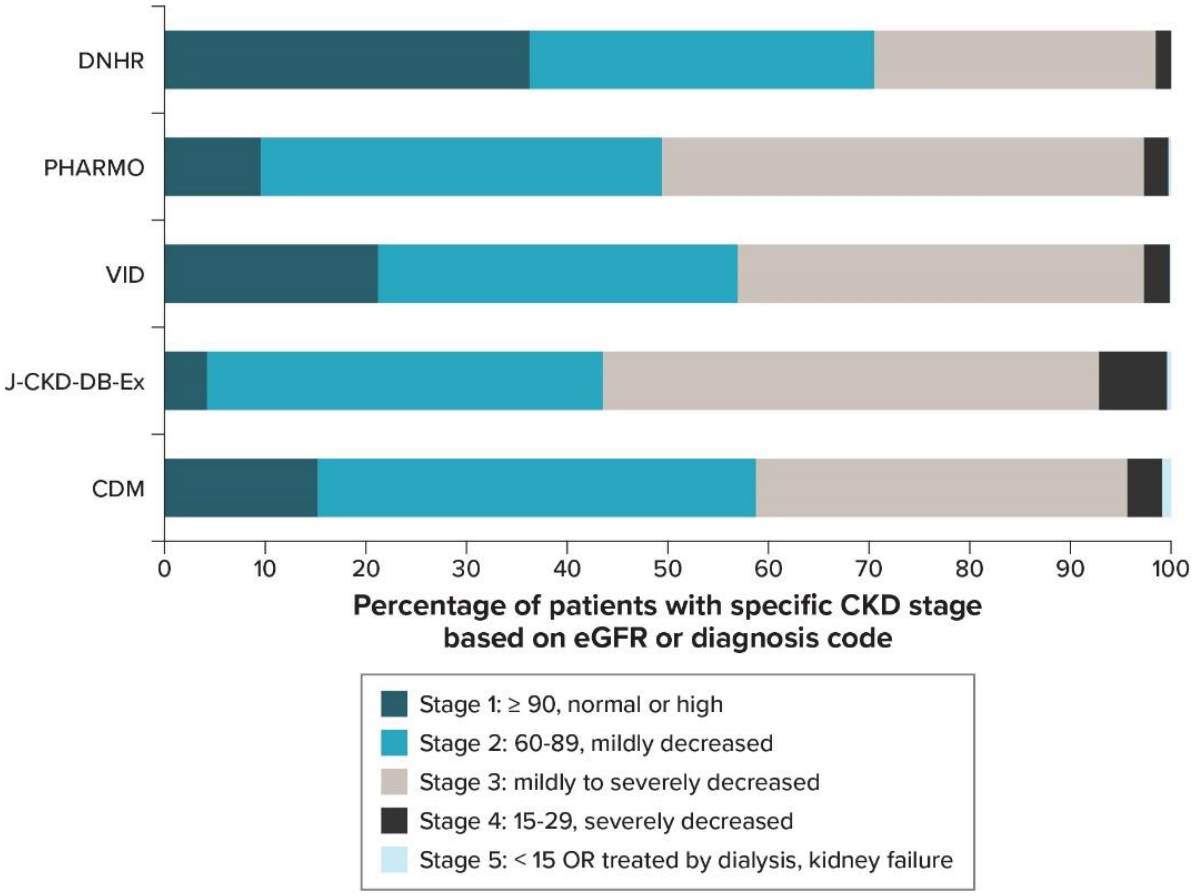
Notes: Recent use: defined as use in the 90 days before the index date (study days [−90, −1]); Previous use: defined using the remaining time of the previous year (study days [−365, −91]); Any historical use: defined as before the year before the index date (study days (−∞, −366]).

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

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

Based on CKD stage defined by eGFR or diagnosis code (Figure 2) amongst patients who had staging information, the proportion of patients in stage 1 CKD at baseline was highest in DNHR (36.3%) and lowest in J-CKD-DB-Ex (4.2%), which has a requirement of CKD (proteinuria and/or eGFR of < 60) to enter the database. Approximately 34% to 44% of patients across the data sources were in stage 2 CKD at baseline. Approximately half of patients in J-CKD-DB-Ex (49.3%) and PHARMO (48.0%) had stage 3 CKD at baseline. The percentage of patients in stage 3 CKD was 40.4% in VID, 37.0% in CDM, and 28.0% in DNHR. Severe CKD (stage 4) was uncommon, ranging from 1.6% to 6.8%, with the highest percentage in J-CKD-DB-Ex.

Figure 2: CKD stage at the index date for new users of SGLT2i defined based on eGFR value or diagnosis code, by data source



ACR = albumin-to-creatinine ratio; CDM = Optum's de-identified Clinformatics® DataMart; CKD = chronic kidney disease; DNHR = Danish National Health Registers; eGFR = estimated glomerular filtration rate; J-CKD-DB-Ex = Japan Chronic Kidney Disease Database Extension; PHARMO = PHARMO Data Network; SGLT2i = sodium-glucose cotransporter inhibitors; VID = Valencia Health System Integrated Database.

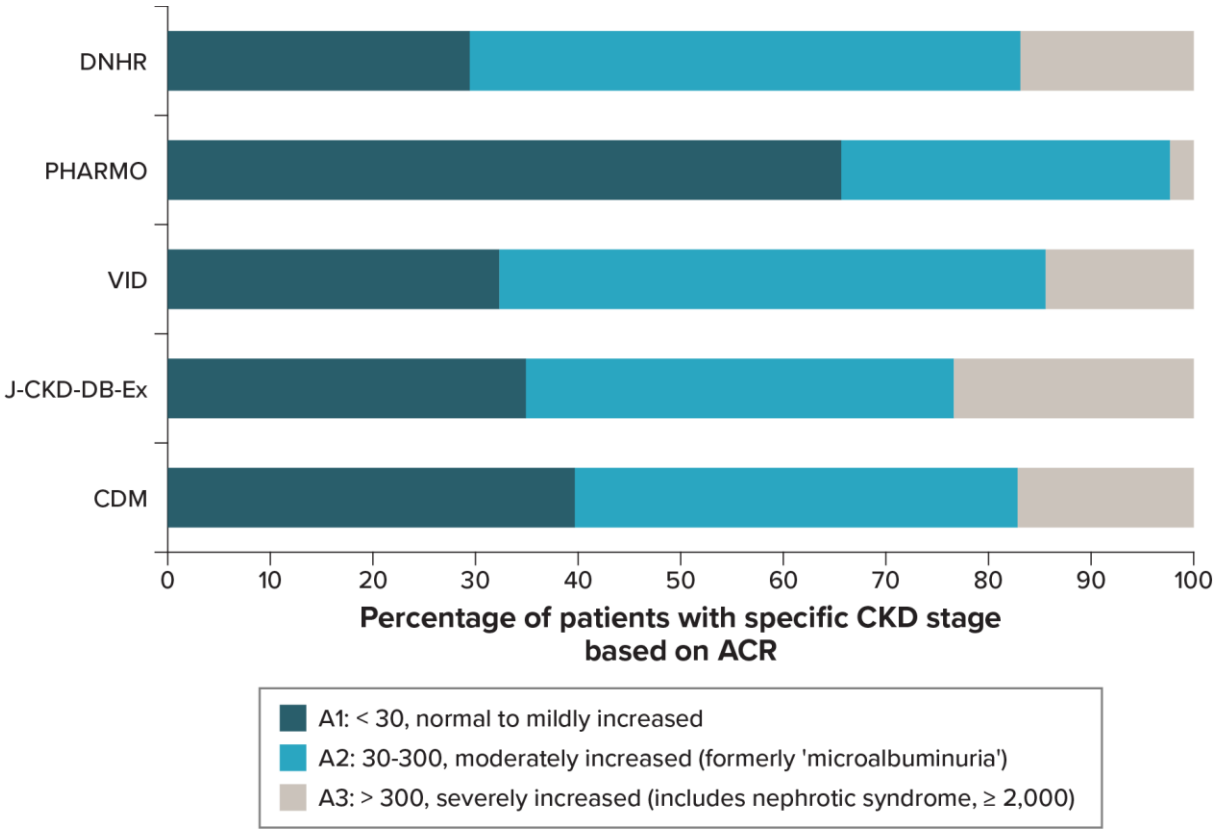
Notes: All patients met the inclusion eligibility criteria for CKD, which was assessed through diagnosis codes, eGFR test results, or urine ACR test results.

Percentages were calculated amongst patients with available staging information.

Across the data sources, 1.2% of patients in DNHR, 1.0% in PHARMO, 3.3% in VID, 0.3% in J-CKD-DB-Ex, and 20.2% in CDM were missing eGFR values or diagnosis codes needed to assess CKD stage. In VID and CDM, 1.4% and 8.6% of patients, respectively, had a diagnosis code or eGFR result but with an unspecified stage.

A large percentage of patients in all data sources (except DNHR) had no ACR assessment recorded in the year before the index date (71.7%, CDM; 66.4%, PHARMO; 55.4%, J-CKD-DB-Ex; 34.0%, VID), so categorization based on ACR level may not be reliable (Figure 3, Table 12). In DNHR, with missing ACR values for only 18.9% of patients, 23.929.4% were categorized as A1, 53.6% as A2, and 17.0% as A3 at baseline (Figure 3). The high availability of ACR results in DNHR may well account for the large proportion of patients observed with stage 1 CKD (Figure 2 and Figure 3).

Figure 3: ACR categories at the index date, by data source among new users of SGLT2i



ACR = albumin-to-creatinine ratio; CDM = Optum's de-identified Clinformatics® DataMart; CKD = chronic kidney disease; DNHR = Danish National Health Registers; J-CKD-DB-Ex = Japan Chronic Kidney Disease Database Extension; PHARMO = PHARMO Data Network; VID = Valencia Health System Integrated Database.

Notes: For CDM, 58.2% of patients in the category of no assessment of ACR recorded before the index date had a recorded claim for an ACR test, but no result was available.

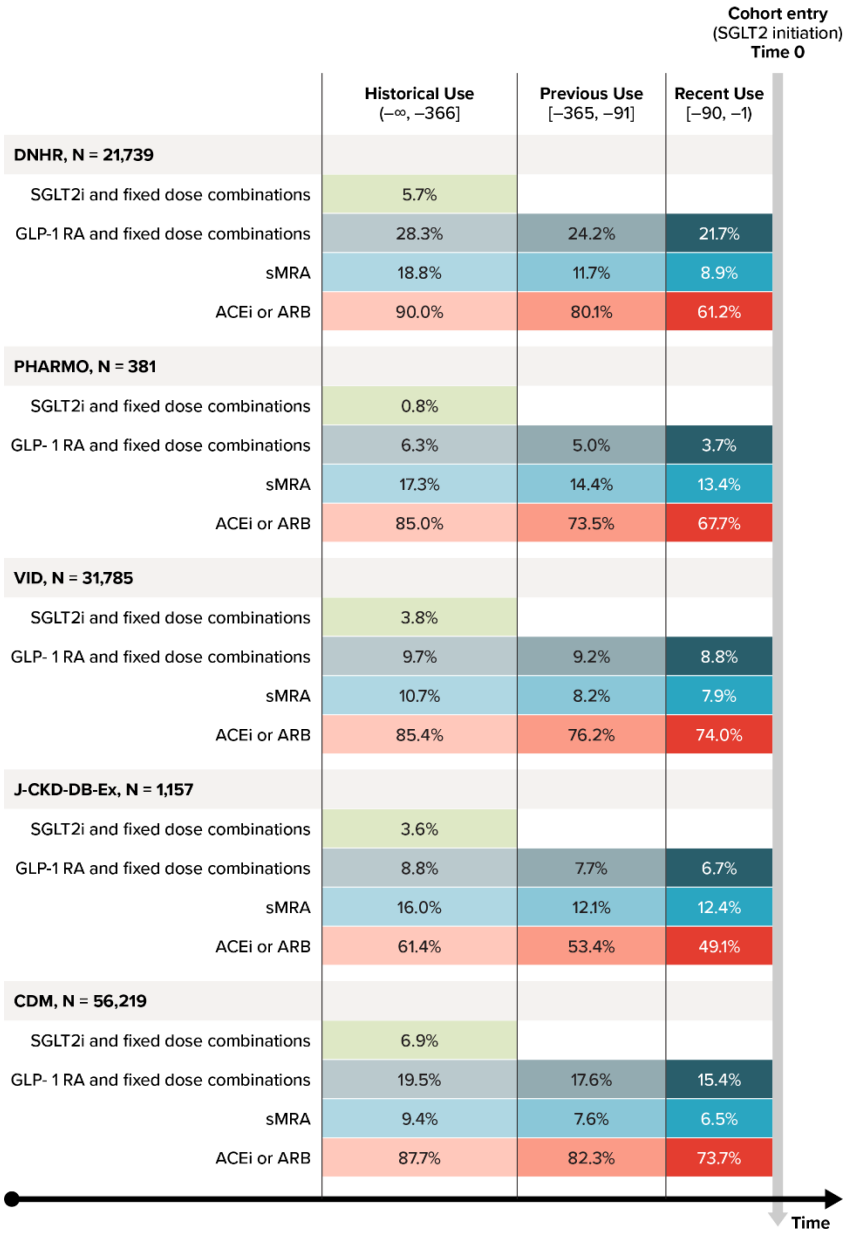
Percentages were calculated amongst patients who had an ACR value in the year before the index date.

No ACR assessment in the year before the index date was observed for 18.9% of patients in DNHR, 66.4% in PHARMO, 33.9% in VID, 55.4% in J-CKD-DB-Ex, and 71.7% in CDM.

A high proportion of SGLT2i initiators had used other medications of interest (i.e., ACEi or ARB, sMRA, GLP-1 RA) before initiating an SGLT2i (Figure 4). Historical or previous use (> 365 days or 365 to 91 days before the index date) of ACEi or ARB drugs was recorded for most patients in the data sources. Recent ACEi/ARB use (≤ 90 days before the index date) was recorded in 61.2% to 74.0% of patients in the European and US data sources and in 49.1% of patients in J-CKD-DB-Ex (Table 12). Historical or previous use of sMRA was observed in less than 20% of patients across all data sources, with recent use at 13.4% in PHARMO, 12.4% in J-CKD-DB-Ex, 8.9% in DNHR, 7.9% in VID, and 6.5% in CDM.

Recent use of GLP-1 RA was higher in DNHR (21.7%) than in CDM (15.4%), J-CKD-DB-Ex (6.7%), VID (8.8%), or PHARMO (3.7%). In all data sources and all time periods, it was most common for patients to have used only one of these drug classes.

Figure 4: Historical, previous, and recent use of medications of interest in relation to the index SGLT2i medication



ACEi = angiotensin-converting enzyme inhibitors; ARB = angiotensin receptor blockers; CDM = Optum's de-identified Clinformatics® DataMart; CKD = chronic kidney disease; GLP-1 RA = glucagon-like peptide-1 receptor agonists; SGLT2i = sodium-glucose cotransporter 2 inhibitors; sMRA = steroidal mineralocorticoid receptor antagonists.
Note: By design, SGLT2i use could not occur from −365 days to the day before the index date.

Of the clinical conditions known to be associated with an increased risk of CKD and assessed at any time before or on the index date, hypertension was the most common in all data sources (over 90% in CDM and VID, over 80% in DNHR and J-CKD-DB-Ex, and 71.1% in PHARMO) (Table 12). Glomerulonephritis, renovascular disease, and autoimmune disease

were recorded more frequently in J-CKD-DB-Ex than in the European or US data sources. Gout or hyperuricemia in the year before or on the index date was recorded in approximately a third of patients in J-CKD-DB-Ex and VID, approximately 11% of patients in CDM, and approximately 4% of patients in DNHR and PHARMO.

10.4.1.1.3 Baseline comorbidities and comedications

Other than hypertension, hypercholesterolemia was the most common baseline comorbidity in all data sources, recorded in approximately 90% of patients in CDM and in 77% to 79% in J-CKD-DB-Ex and VID (Table 13). Coronary heart disease was also frequent. Patients in J-CKD-DB-Ex, a hospital-based CKD registry, had a higher prevalence of coronary heart disease, cerebrovascular disease, congestive heart failure, HIV, COPD, and malignancy than did patients in the three European data sources and the US data source.

Table 13: 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%)

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

Medications other than GLD recorded in the 180 days before or on the index date are shown in Table 14. Regarding use of diuretics, thiazide-like diuretics (31.9%) were more frequently recorded than loop diuretics (22.4%) in CDM; however, in the other four data sources, loop diuretics were more commonly used (25.6%, DNHR; 13.7%, J-CKD-DB-Ex; 26.3%, VID; 20.2%, PHARMO) than thiazide-like diuretics (14.3%, DNHR; 6.4%, J-CKD-DB-Ex; 5.1%, VID; 19.9%, PHARMO). The use of potassium-sparing diuretics was uncommon, and the highest use occurred in PHARMO (2.4%). The use of renin inhibitors was < 1% in all five data sources. Angiotensin-converting enzyme inhibitors were used less frequently in J-CKD-DB-Ex (11.7%) than in the other data sources, with use ranging from 21.2% in VID to 40.5% in CDM. Angiotensin receptor blocker medications were used commonly, with use ranging from 35.4% in PHARMO to 59.7% in VID. Of the other cardiovascular medications, beta blockers were used in approximately a third or more of SGLT2i initiators (57.7%, PHARMO; 26.7%, J-CKD-DB-Ex; 36.3%, VID; 42.3%, DNHR). Calcium channel blockers use ranged from 25.4% in VID to 40.7% in J-CKD-DB-Ex. Statins were used in 75% or higher of patients in the European and US data sources, but use was lower in J-CKD-DB-Ex (43.6%). Anticoagulants were used in approximately 20% of SGLT2i new users in all data sources except CDM, where use was recorded in 11.5% of SGLT2i new users. Aspirin and other antiplatelet drugs were used in approximately 40% of SGLT2i new users in the European data sources; use was lower in J-CKD-DB-Ex (27.5%) and CDM (14.2%).

Table 14: Medication use other than GLD 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%)
ARB	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%)
Lipid-lowering drugs other than statins	1,234 (5.7%)	36 (9.4%)	6,061 (19.1%)	187 (16.2%)	9,573 (17.0%)

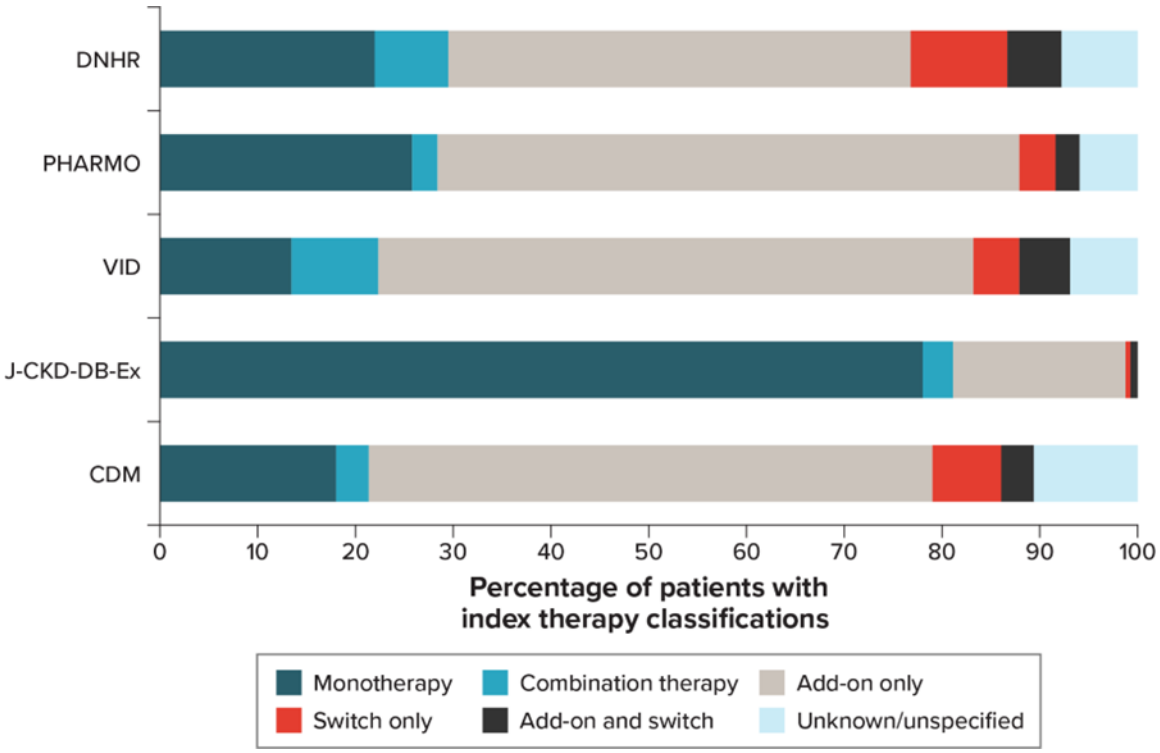
	DNHR (N = 21,739) n (%)	**PHARMO (N = 381) n (%)**	**VID (N = 31,785) n (%)**	**J-CKD-DB-Ex (N = 1,157) n (%)**	**CDM (N = 56,219) n (%)**
Other medications of interest					
Anti-inflammatory drugs (NSAIDs)	2,576 (11.8%)	45 (11.8%)	6,721 (21.2%)	78 (6.7%)	9,668 (17.2%)
Acetaminophen	8,665 (39.9%)	34 (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%)

ARB = angiotensin receptor blockers; CDM = Optum's de-identified Clinformatics® DataMart; DNHR = Danish National Health Registers; GLD = glucose-lowering drugs; NR = not reported; NSAID = non-steroidal anti-inflammatory drug; SGLT2i = sodium-glucose cotransporter 2 inhibitors; VID = Valencia Health System Integrated Database.

10.4.1.1.4 Characteristics of the index medication at baseline and during follow-up

The index SGLT2i was most commonly prescribed as "monotherapy" (i.e., with no other medications of interest—ACEi or ARB, sMRA, or GLP-1 RA) according to the study definition (Annex 4) for patients in J-CKD-DB-Ex (78.0%) and as an "add-on therapy" to another existing medication of interest in the other data sources (60.8%, VID; 59.6%, PHARMO; 57.6%, CDM; 47.2%, DNHR) (Figure 5, Table 15). Note that because the indication for drugs was not available in study data, we could not determine the intent for prescribing these medications, and during much of the study period, SGLT2i was indicated only for treatment of T2D. When the index SGLT2i was used an "add-on" therapy, it was most often added to an ACEi or ARB across all five data sources (46.5%, DNHR; 58.5%, PHARMO 62.5%, VID; 13.5%, J-CKD-DB-Ex; 64.9% CDM). Addition to a GLP-1 RA medication occurred in 18.0% of patients in DNHR but was lower in CDM (12.1%), J-CKD-DB-Ex and VID (6.5% in each), and PHARMO (3.7%). When the index SGLT2i met the study definition of a "switch" from a prior medication of interest, the prior therapy most often reported was an ACEi or ARB in DNHR (14.7%), VID (7.7%), CDM (8.8%), and PHARMO (5.8%). In J-CKD-DB-Ex, no patients "switched" to an SGLT2i from an ACEi or ARB.

Figure 5: Classification of index SGLT2i prescription or dispensing, by data source



CDM = Optum's de-identified Clinformatics® DataMart; CKD = chronic kidney disease; DNHR = Danish National Health Registers; J-CKD-DB-Ex = Japan Chronic Kidney Disease Database Extension; PHARMO = PHARMO Data Network; SGLT2i = sodium-glucose cotransporter 2 inhibitors; VID = Valencia Health System Integrated Database.

Notes: Monotherapy = SGLT2i initiated as the only medication of interest; Combination therapy = simultaneous initiation of SGLT2i together with another medication of interest; Add-on therapy = addition of SGLT2i to an existing medication of interest; Switch only = an existing medication of interest is replaced by SGLT2i; Add-on and switch = both add-on and switched-to SGLT2i at the same time.

Empagliflozin was the most common type of SGLT2i medication prescribed at the index date in DNHR (60.8%), J-CKD-DB-Ex (30.8%), VID (47.5%), and CDM (61.6%), whereas dapagliflozin was the most common index SGLT2i in PHARMO (57.5%) (data not shown).

The median duration of the initial SGLT2i exposure episode was only 2.8 months in PHARMO but almost a year in VID (11.6 months) (Table 15). In the other data sources, the median duration ranged from 5.4 months in CDM to 9.7 in DNHR. The median days' supply of the index SGLT2i was approximately 3.5 months in DNHR and approximately one month in the other four data sources. Note that days' supply was estimated in DNHR from the upper quartile of the times between prescriptions.

The median duration of total follow-up was 15.8 months in CDM, the only commercial claims-based data source, and ranged from 20.7 months to 26.5 months across the other four data sources. During follow-up, the median number of SGLT2i prescriptions filled was lower in DNHR (6) and PHARMO (6) than in VID (17), J-CKD-DB-Ex (10), or CDM (8). Half of the patients in CDM had only one distinct current-use period during follow-up; this percentage was higher in the other four data sources (range, 74% to 83%). A smaller proportion of patients in DNHR (9.2%), VID (11.9%), and PHARMO (6.6%) reported interruption of current use lasting 90 days or more—a proxy for discontinuation—than in CDM (32.2%) or J-CKD-DB-Ex (42.7%) (Table 15). The median total duration of SGLT2i therapy ranged from 7.5 months (PHARMO) to 17 months (VID). Of the other drug classes started during follow-up, ACEi or ARB were the most common across data sources (80.4%, DNHR; 61.3%, J-CKD-DB-Ex; 78.8%, VID; 73.8%, PHARMO) except CDM (3.5%), with GLP-1 RA medications started in 42.5% of patients in DNHR, 21.3% in VID, approximately 14% in J-CKD-DB-Ex and PHARMO, and 12.6% in CDM.

Table 15: Characteristics of the index SGLT2i at baseline and during follow-up, 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)**
Classification of the index SGLT2i at the index date, n (%)					
Monotherapy	4,769 (21.9%)	98 (25.7%)	4,247 (13.4%)	902 (78.0%)	10,117 (18.0%)
Combination therapy	1,645 (7.6%)	10 (2.6%)	2,828 (8.9%)	35 (3.0%)	1,846 (3.3%)
Add-on	10,268 (47.2%)	227 (59.6%)	19,339 (60.8%)	205 (17.7%)	32,392 (57.6%)
Switch	2,162 (9.9%)	14 (3.7%)	1,499 (4.7%)	6 (0.5%)	3,972 (7.1%)
Add-on and switch	1,194 (5.5%)	9 (2.4%)	1,643 (5.2%)	9 (0.8%)	1,873 (3.3%)
Indeterminate	1,701 (7.8%)	23 (6.0%)	2,229 (7.0%)	0 (0%)	6,019 (10.7%)
Index SGLT2i was an “Add-On” to…, n (%)					
GLP-1 RA	3,918 (18.0%)	14 (3.7%)	2,058 (6.5%)	75 (6.5%)	6,801 (12.1%)
sMRA	1,209 (5.6%)	46 (12.1%)	1,990 (6.3%)	136 (11.8%)	2,873 (5.1%)
ACEi/ARB	10,102 (46.5%)	223 (58.5%)	19,858 (62.5%)	156 (13.5%)	36,511 (64.9%)
Index SGLT2i was a “Switch” from…, n (%)					
GLP-1 RA	795 (3.7%)	2 (0.5%)	571 (1.8%)	4 (0.3%)	1,854 (3.3%)
sMRA	716 (3.3%)	8 (2.1%)	243 (0.8%)	11 (1.0%)	796 (1.4%)
ACEi/ARB	3,206 (14.7%)	22 (5.8%)	2,442 (7.7%)	0 (0%)	4,941 (8.8%)
Duration of initial exposure episode after cohort entry (months)					
Mean (SD)	15.6 (15.4)	2.6 (2.2)	17.9 (17.5)	14.9 (16.5)	10.2 (12.1)
Median	9.7	2.8	11.6	7.7	5.4
1st, 99th percentiles	0, 66	0, 12	0.3, 71	0, 67	1, 55
Days’ supply of index SGLT2i (days)					

	DNHR (N = 21,739)	**PHARMO (N = 381)**	**VID (N = 31,785)**	**J-CKD-DB-Ex (N = 1,157)**	**CDM (N = 56,219)**
Mean (SD)	121.8 (96.7)	28.9 (17.8)	29.5 (5.8)	36.0 (24.5)	47.2 (27.8)
Median	105	28	30	34	30
1st, 99th percentiles	33, 470	7, 90	9, 60	2, 92	14, 90
Number of prescriptions or dispensings during follow-up for the SGLT2i drug class					
Mean (SD)	8.1 (10.5)	8.4 (14.9)	18.3 (18.7)	13.2 (18.1)	6.6 (8.7)
Median	5	3	11	7	3
1st, 99th percentiles	1, 50	0, 78	1, 76	1, 82	1, 42
Number of distinct “current-use” periods (treatment episodes) during follow-up for the index SGLT2i drug class, n (%)					
1	17,801 (81.9%)	316 (82.9%)	23,381 (73.6%)	879 (76.0%)	28,202 (50.2%)
2	2,949 (13.6%)	42 (11.0%)	5,482 (17.3%)	199 (17.2%)	13,912 (24.7%)
3	700 (3.2%)	16 (4.2%)	1,732 (5.5%)	51 (4.4%)	6,748 (12.0%)
4	197 (0.9%)	6 (1.6%)	699 (2.2%)	13 (1.1%)	3,421 (6.1%)
5+	92 (0.4%)	1 (0.3%)	491 (1.5%)	15 (1.3%)	3,936 (7.0%)
Number of distinct prescriptions or dispensings during follow-up for the index SGLT2i drug class					
Mean (SD)	9.4 (11.1)	12.9 (19.9)	22.5 (20.4)	16.5 (20.1)	11.1 (12.0)
Median	6	6	17	10	8
1st, 99th percentiles	1, 54	1, 100	1, 79	1, 102	1, 57
Number of discontinuations (interruptions) of current use during follow-up, n (%)					
0	13,123 (60.4%)	316 (82.9%)	23,381 (73.6%)	535 (46.2%)	28,202 (50.2%)

	DNHR (N = 21,739)	**PHARMO (N = 381)**	**VID (N = 31,785)**	**J-CKD-DB-Ex (N = 1,157)**	**CDM (N = 56,219)**
1	6,942 (31.9%)	42 (64.6%)	5,482 (17.3%)	469 (40.5%)	13,912 (24.7%)
2	1,244 (5.7%)	16 (24.6%)	1,732 (5.5%)	109 (9.4%)	6,748 (12.0%)
3	295 (1.4%)	6 (9.2%)	699 (2.2%)	26 (2.2%)	3,421 (6.1%)
4	81 (0.4%)	0 (0%)	294 (0.9%)	6 (0.5%)	1,689 (3.0%)
5+	54 (0.2%)	1 (1.5%)	197 (0.6%)	12 (1.0%)	2,247 (4.0%)
Number of patients with an interruption of current use lasting 90 days or more, n (%)	2,001 (9.2%)	25 (6.6%)	3,769 (11.9%)	494 (42.7%)	18,100 (32.2%)
Duration of total exposure to index therapy (months)					
Mean (SD)	18.7 (17.3)	11.7 (11.9)	22.2 (19.4)	18.7 (18.7)	19.7 (17.6)
Median	12.8	7.5	17.0	11.9	14.5
1st, 99th percentile	0, 69	1, 43	0.3, 73	0, 70	2, 79
Other drug classes started during follow-up, n (%)					
GLP-1 RA	9,233 (42.5%)	53 (13.9%)	6,761 (21.3%)	164 (14.2%)	7,102 (12.6%)
sMRA	3,110 (14.3%)	65 (17.1%)	3,939 (12.4%)	206 (17.8%)	1,519 (2.7%)
ACEi/ARB	17,477 (80.4%)	281 (73.8%)	25,060 (78.8%)	709 (61.3%)	1,943 (3.5%)
Duration of total follow-up (months)					
Mean (SD)	25.3 (20.4)	24.8 (19.2)	30.0 (21.6)	28.1 (21.2)	21.9 (20.4)
Median	20.7	21.6	26.5	24.4	15.8
1st, 99th percentiles	0, 80	0, 82	0.3, 77	0, 72	0, 83

ACEi = angiotensin-converting enzyme inhibitors; ARB = angiotensin receptor blockers; CDM = Optum's de-identified Clinformatics® DataMart; DNHR = Danish National Health Registers; GLP-1 RA = glucagon-like peptide-1 receptor agonists; J-CKD-DB-Ex = Japan Chronic Kidney Disease Database Extension; SD = standard deviation; SGLT2i = sodium-glucose cotransporter 2 inhibitors; sMRA = steroidal mineralocorticoid receptor antagonists; VID = Valencia Health System Integrated Database.

10.4.1.1.5 Baseline characteristics stratified by ACR test recorded in the year before or on the index date

All baseline characteristics were stratified by the presence or absence of a recorded ACR test in the year before or on the index date. Results of selected baseline characteristics by data source are presented in Annex 6, Table 40. No notable trends were observed across all data sources.

10.4.1.1.6 Treatment changes over time during follow-up

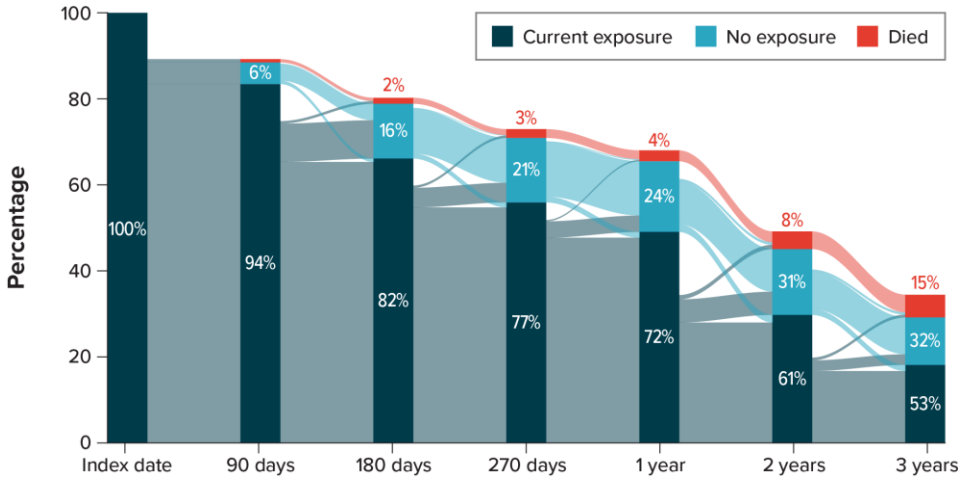
SGLT2i treatment patterns during follow-up were analyzed for each data source, beginning with a cohort of patients with new use of an SGLT2i who initiated treatment on their individual index dates. At six prespecified subsequent timepoints (90 days, 180 days, 270 days, one year, two years, three years), the proportion of the cohort in each treatment state (current use or non-use) was reported. Results are displayed in Sankey diagrams for each data source (Figure 6). Because SGLT2i treatment discontinuation and subsequent re-initiation have been shown to be common,[50] it is important to note that estimates presented are cross-sectional estimates of the entire cohort at each timepoint rather than an analysis of individual patient trajectories. Percentages reported in Sankey diagrams are of the number of patients remaining under observation in the study at that time. Individual patients could move between treatment states throughout study follow-up. Note that losses to follow-up and censoring are represented in the white space at the top of each diagram.

During the study period, the proportions of patients observed to be receiving treatment at each timepoint was similar among DNHR, VID, and J-CKD-DB-Ex. Of those under observation at yearly timepoints, the lowest proportion of patients currently receiving SGLT2i treatment during the study period was observed in CDM (one year, 50%; two years, 38%; three years, 29%) and PHARMO (one year, 59%; two years, 44%; three years, 30%). Among the other data sources (J-CKD-DB-Ex, VID, and DNHR), yearly proportions of patients observed to be receiving current treatment were similar at each timepoint; 69% to 72% of patients were observed to be receiving treatment at year one, 61% to 62% at year two, and 53% to 56% at year three. These percentages represent a combination of both patients who remained continuously on treatment up to the timepoint and other patients who had discontinued and restarted the medications.

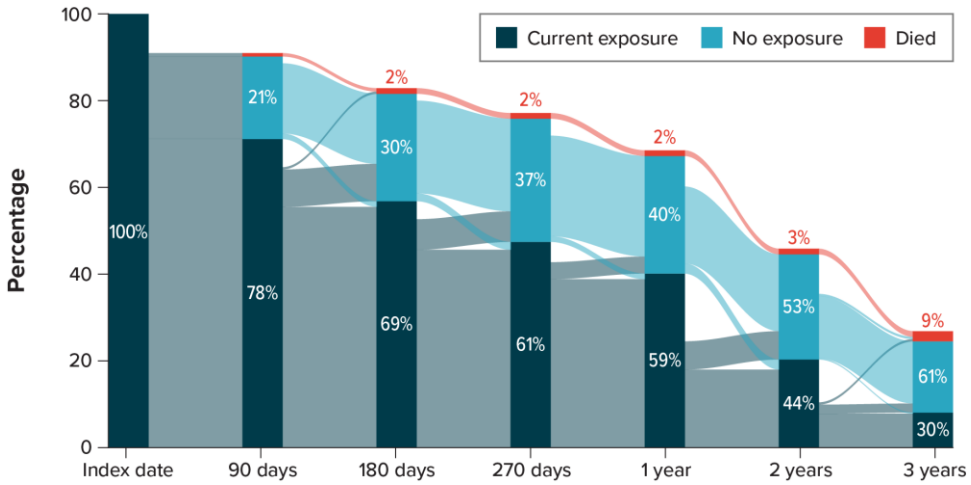
A common pattern in all data sources was that the largest proportional increase in the “no exposure” treatment state occurred between the 90-day and 180-day timepoints. Thereafter, the proportion of patients with no treatment remained fairly stable in each data source except for CDM and PHARMO, in which the proportion not treated increased at two and three years. At each timepoint, a small proportion of nonusers who remained under observation were found to change and become current users.

Figure 6: Treatment states at specific timepoints for SGLT2 initiators for each data source

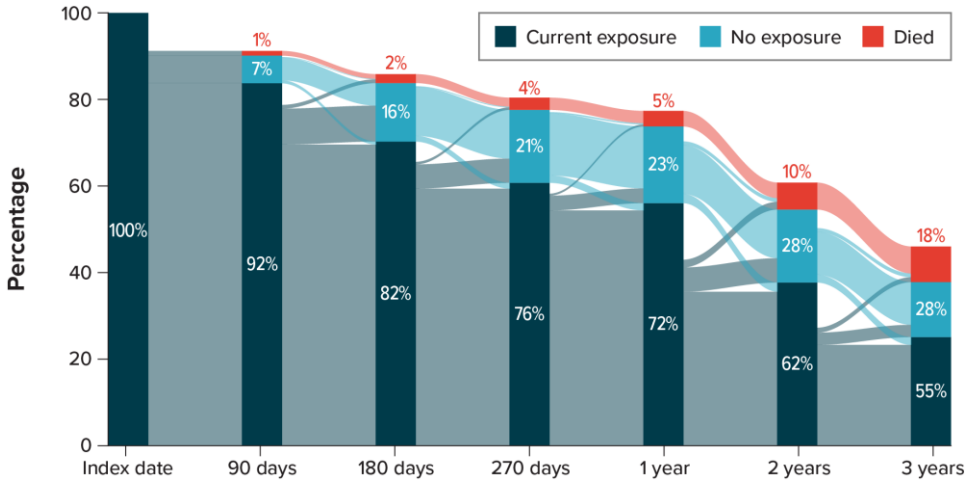
DNHR



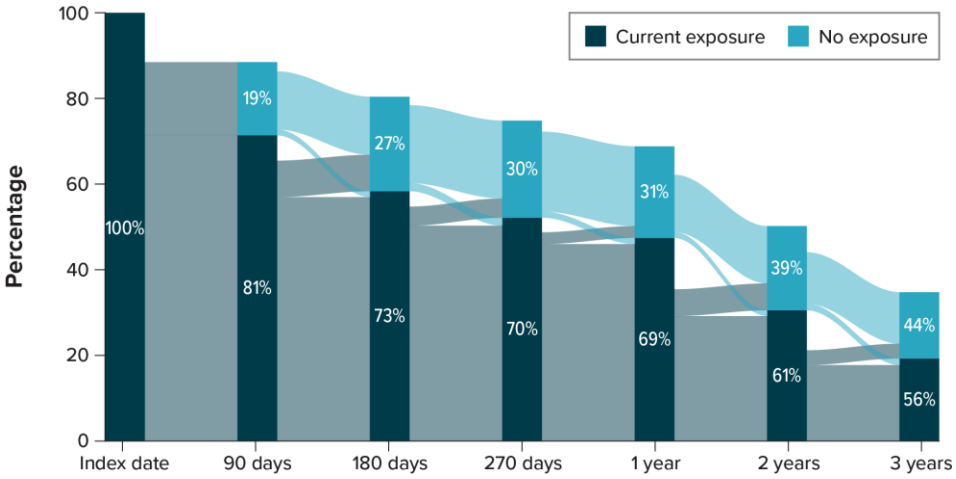
PHARMO



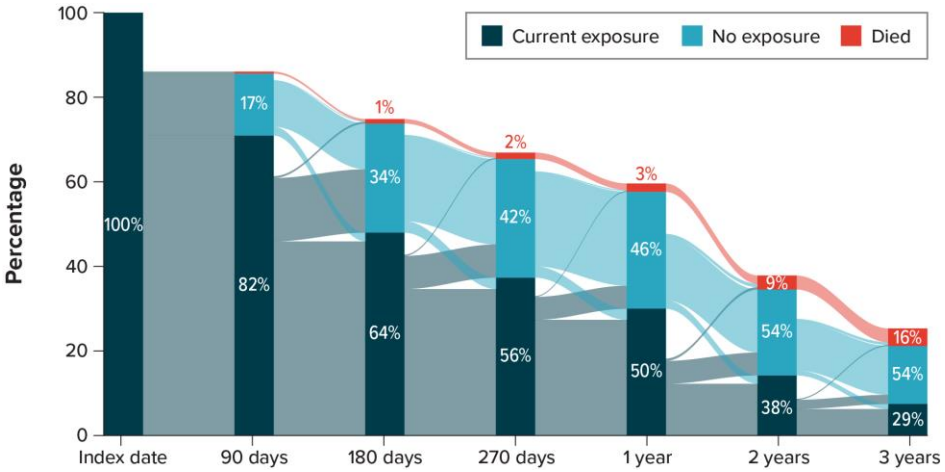
VID



J-CKD-DB-Ex



CDM



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

Notes: Sankey diagrams display the proportion of the population at each timepoint in each of the treatment states for each data source. The connecting bars between timepoints show the proportion of the population that moved from 1 state to a different state at the next timepoint. These figures display proportions of the population over time, and a patient may move between treatment states over time (e.g., begin as "treated," move to "untreated" at the next timepoint, then move back to "treated" at the next). If a death occurred, the patient was placed in a separate category and remained in that state for each subsequent checkpoint. Note that death information was not available in J-CKD-DB-Ex.

The height of the bar at each timepoint displays the relative size of the cohort remaining under observation at each timepoint. Patients who were lost to follow-up are not included in the percentage calculations at each timepoint; thus, the percentages sum to 100% for each timepoint. The percentages describe the amount of patients still under observation at that timepoint.

The sum of the bars for each timepoint may not equal 100% due to rounding.

10.4.1.2 GLP-1 RA

10.4.1.2.1 Markers of severity of T2D at index date

The percentage of patients with the highest HbA_{1c} levels (> 74.9 mmol/mol or > 9%) ranged from 17.8% in CDM to 31.3% in DNHR, although findings for CDM should be interpreted in the context of the fact that 47.5% of patients were missing HbA_{1c} values (Table 16). The percentage of patients with HbA_{1c} values > 53 mmol/mol (or > 7%) was 42.2% in CDM, 63.5% in J-CKD-DB-Ex, 68.7% in VID, 77.8% in PHARMO, and 84.2% in DNHR (the highest reported). The median duration of a T2D diagnosis was longest in PHARMO (13.2 years) and shortest in CDM (four years).

Insulin use in the 180 days before and including GLP-1 RA initiation date was recorded for between 13.2% (PHARMO) and 85.4% (J-CKD-DB-Ex) of patients (Table 16). The percentage of individuals with no use of GLD therapy other than insulin during this time was less than 10% in PHARMO, VID, and J-CKD-DB-Ex; 12.6% in DNHR; and 23.1% in CDM. The majority (> 60%) of patients in DNHR, PHARMO, VID, and CDM had used either one or two medications in a GLD class other than GLP-1 RA. In J-CKD-DB-Ex, 41.0% of patients had been prescribed or dispensed therapies in four or more drug classes during this time.

The most common medications for T2D prescribed or dispensed in the 180 days before and including the date of GLP-1 RA initiation varied by data source (Table 16). Metformin and fixed-dose combinations were the most common GLDs in DNHR (76.4%), PHARMO (80.9%), and CDM (52.6%), whereas dipeptidyl peptidase-4 inhibitor (DPP-4) was most common in J-CKD-DB-Ex (77.5%). In VID, similar proportions of patients had recorded use of metformin (64.2%) or DPP-4 (62.9%). A prescription for SGLT2i was more common among patients in J-CKD-DB-Ex (52.9%) and VID (41.5%) than in those from other data sources (ranging from 6.5% in PHARMO to 27.9% in DNHR). Similar findings were observed for sulfonylureas. Use of alpha-glucosidase inhibitors was less than 1% in all data sources, except for J-CKD-DB-Ex (39.2%). Use of thiazolidinediones was highest in J-CKD-DB-Ex (17.0%), followed by CDM (9.0%) and the other data sources, in which use was approximately 5% or less. Meglitinides were prescribed or dispensed more commonly in J-CKD-DB-Ex (35.9%) and VID (21.7%) than in the other data sources, in which use was less than 1.5% (Table 16).

The median score for the Diabetes Severity Complications Index, computed as the sum of seven conditions or complications, was higher in J-CKD-DB-Ex and VID (both with median scores of four) than in CDM (median = 3) and DNHR and PHARMO (both with scores of two) (Table 16). Of the conditions or complications that comprise the severity index, nephropathy was the most diagnosed condition in all databases, except for J-CKD-DB-Ex, where it was CVD. Additional key diagnoses assessed included hyperkalaemia (ranging from < 1.5% in DNHR to 13.4% in J-CKD-DB-Ex) and amputations (≤ 2.5% across all data sources).

Table 16: Markers of T2D severity at the index date for new users of GLP-1 RA, by data source

	DNHR (N = 18,929)	**PHARMO (N = 476)**	**VID (N = 11,798)**	**J-CKD-DB-Ex (N = 329)**	**CDM (N = 70,158)**
Duration of T2D (years) at the index date					
Mean (SD)	11.6 (6.7)	13.6 (10.1)	9.5 (4.1)	8.6 (5.5)	4.9 (3.4)
Median	11	13.2	10.1	7.9	4
1st, 99th percentiles	0, 27	2, 35	0, 17	0, 22	0, 14
Medications for T2D (hypoglycemic agents) ever prescribed from 180 days before and including the index date					
SGLT2i and fixed-dose combinations	5,282 (27.9%)	31 (6.5%)	4,890 (41.5%)	174 (52.9%)	9,359 (13.3%)
Metformin and fixed-dose combinations	14,454 (76.4%)	385 (80.9%)	7,570 (64.2%)	199 (60.5%)	36,888 (52.6%)
Sulfonylureas and fixed-dose combinations	2,532 (13.4%)	269 (56.5%)	1,040 (8.8%)	115 (35.0%)	26,089 (37.2%)
Alpha-glucosidase inhibitors	NR	1 (0.2%)	24 (0.2%)	129 (39.2%)	369 (0.5%)
Thiazolidinediones	10 (0.1%)	5 (1.1%)	609 (5.2%)	56 (17.0%)	6,334 (9.0%)
DPP-4i and fixed-dose combinations	6,662 (35.2%)	64 (13.4%)	7,418 (62.9%)	255 (77.5%)	17,042 (24.3%)
Meglitinides (including repaglinide, nateglinide, mitiglinide)	56 (0.3%)	2 (0.4%)	2,563 (21.7%)	118 (35.9%)	1,000 (1.4%)
Number of T2D drug classes other than insulin ever used in the 180 days before and including the index date					
0	2,390 (12.6%)	47 (9.9%)	723 (6.1%)	18 (5.5%)	16,185 (23.1%)
1	7,266 (38.4%)	160 (33.6%)	2,855 (24.2%)	32 (9.7%)	23,640 (33.7%)
2	6,402 (33.8%)	213 (44.7%)	4,345 (36.8%)	61 (18.5%)	19,721 (28.1%)
3	2,554 (13.5%)	54 (11.3%)	3,000 (25.4%)	83 (25.2%)	8,635 (12.3%)
4+	317 (1.7%)	2 (0.4%)	875 (7.4%)	135 (41.0%)	1,977 (2.8%)

	DNHR (N = 18,929)	**PHARMO (N = 476)**	**VID (N = 11,798)**	**J-CKD-DB-Ex (N = 329)**	**CDM (N = 70,158)**
Insulin use recorded in the 180 days before and including the index date	7,322 (38.7%)	299 (13.2%)	6,259 (53.1%)	281 (85.4%)	31,424 (44.8%)
HbA_{1c}					
$HbA_{1c} \leq 53$ mmol/mol or $\leq 7\%$	2,620 (13.8%)	22 (4.6%)	1,900 (16.1%)	67 (20.4%)	7,235 (10.3%)
$HbA_{1c} > 53$ mmol/mol and ≤ 63.9 mmol/mol or $> 7\%$ and $\leq 8\%$	4,897 (25.9%)	87 (18.3%)	2,716 (23.0%)	82 (24.9%)	8,846 (12.6%)
$HbA_{1c} > 63.9$ mmol/mol and ≤ 74.9 mmol/mol or $> 8\%$ and $\leq 9\%$	5,107 (27.0%)	89 (18.7%)	2,588 (21.9%)	76 (23.1%)	8,228 (11.7%)
$HbA_{1c} > 74.9$ mmol/mol or $> 9\%$	5,923 (31.3%)	126 (26.5%)	2,801 (23.7%)	98 (29.8%)	12,498 (17.8%)
HbA_{1c} missing	382 (2.0%)	152 (31.9%)	1,793 (15.2%)	6 (1.8%)	33,351 (47.5%)
Other key medical conditions					
Hyperkaliemia	205 (1.1%)	6 (1.3%)	1,326 (11.2%)	44 (13.4%)	5,368 (7.7%)
Amputation	476 (2.5%)	4 (0.8%)	195 (1.7%)	0 (0%)	1,676 (2.4%)
The Diabetes Severity Complications Index					
Key diagnoses for scoring of the index score					
Retinopathy	3,976 (21.0%)	13 (2.7%)	3,615 (30.6%)	82 (24.9%)	17,400 (24.8%)
Nephropathy	16,345 (86.3%)	452 (95.0%)	11,798 (100.0%)	130 (39.5%)	45,553 (64.9%)
Neuropathy	4,380 (23.1%)	22 (4.6%)	2,835 (24.0%)	113 (34.3%)	31,388 (44.7%)
Cerebrovascular	2,397 (12.7%)	28 (5.9%)	1,532 (13.0%)	171 (52.0%)	8,670 (12.4%)
Cardiovascular	7,917 (41.8%)	149 (31.3%)	5,536 (46.9%)	276 (83.9%)	35,373 (50.4%)
Peripheral vascular disease	3,171 (16.8%)	27 (5.7%)	3,628 (30.8%)	57 (17.3%)	20,546 (29.3%)
Metabolic complications	992 (5.2%)	0 (0%)	1,896 (16.1%)	7 (2.1%)	4,994 (7.1%)

	DNHR (N = 18,929)	**PHARMO (N = 476)**	**VID (N = 11,798)**	**J-CKD-DB-Ex (N = 329)**	**CDM (N = 70,158)**
Index score					
Mean (SD)	2.6 (1.7)	2.2 (1.6)	4.44 (2.1)	4.1 (2.2)	3.1 (2.2)
Median	2	2	4	4	3
1st, 99th percentiles	0, 7	0, 7	2, 10	0, 9	0, 9

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

10.4.1.2.2 Markers of kidney dysfunction severity at the index date

The median duration of CKD at GLP-1 RA initiation was approximately two years in VID; approximately three years in J-CKD-DB-Ex, CDM, and DNHR; and seven years in PHARMO (Table 17). CKD stage could be defined based on the presence of a diagnosis code, eGFR test results, or ACR values. Overall, the degree of completeness of eGFR and ACR measures varied by data source, and the prevalence of CKD based on eGFR or ACR values should be interpreted in the context of this. Across all data sources, most patients did not have a diagnostic code for CKD before GLP-1 RA initiation. However, most patients in all data sources had an eGFR test in the 365 days before initiation (in DNHR, no information was reported on the percentage of patients without eGFR assessment).

Table 17: Baseline markers of kidney dysfunction severity for new users of GLP-1 RA, by data source

	DNHR (N = 18,929)	**PHARMO (N = 476)**	**VID (N = 11,798)**	**J-CKD-DB-Ex (N = 329)**	**CDM (N = 70,158)**
Duration of CKD at the index date (based on all available data)					
Mean (SD)	4.0 (3.6)	7.1 (4.6)	2.7 (2.6)	3.0 (2.4)	3.6 (2.8)
Median	3.2	6.8	2.04	2.5	2.8
1st, 99th percentiles	0, 17	0, 18	0, 10	0, 9	0, 12
CKD stage based on diagnosis only[a], n (%)					
Stage 1: eGFR ≥ 90, normal or high	0 (0%)	2 (0.4%)	55 (0.5%)	0 (0%)	1,398 (2.0%)
Stage 2: eGFR 60-89, mildly decreased	72 (0.4%)	2 (0.4%)	288 (2.4%)	0 (0%)	8,997 (12.8%)
Stage 3: mildly to severely decreased	455 (2.4%)	15 (3.2%)	731 (6.2%)	15 (4.6%)	4,048 (5.8%)
Stage 3a: eGFR 45-59, mildly to moderately decreased	0 (0%)	8 (1.7%)	0 (0.0%)	0 (0%)	1,000 (1.4%)
Stage 3b: eGFR 30-44, moderately to severely decreased	0 (0%)	6 (1.3%)	0 (0.0%)	0 (0%)	787 (1.1%)
Stage 3 without specification of substage	455 (2.4%)	1 (0.2%)	731 (6.2%)	15 (4.6%)	2,261 (3.2%)
Stage 4: eGFR 15-29, severely decreased	207 (1.1%)	4 (0.8%)	220 (1.9%)	7 (2.1%)	3,491 (5.0%)
Stage 5: eGFR < 15 OR treated by dialysis; kidney failure	0 (0%)	0 (0%)	0 (0.0%)	0 (0%)	0 (0%)
Unspecified stage	1,055 (5.6%)	NA	NA	NA	11,543 (16.5%)
No diagnosis code in the year before the index date	17,140 (90.5%)	453 (95.2%)	7,678 (65.1%)	307 (93.3%)	40,681 (58.0%)
CKD stage based on eGFR only[b], n (%)					
Stage 1: eGFR ≥ 90, normal or high	6,077 (32.1%)	34 (7.1%)	2,494 (21.1%)	21 (6.4%)	5,965 (8.5%)
Stage 2: eGFR 60-89, mildly decreased	5,237 (27.7%)	148 (31.1%)	3,123 (26.5%)	111 (33.7%)	14,293 (20.4%)
Stage 3: mildly to severely decreased	6,720 (35.5%)	194 (40.8%)	4,776 (40.5%)	155 (47.1%)	19,729 (28.1%)
Stage 3a: eGFR 45-59, mildly to moderately decreased	4,109 (21.7%)	134 (28.2%)	2,698 (22.9%)	83 (25.2%)	12,229 (17.4%)

	DNHR (N = 18,929)	**PHARMO (N = 476)**	**VID (N = 11,798)**	**J-CKD-DB-Ex (N = 329)**	**CDM (N = 70,158)**
Stage 3b: eGFR 30-44, moderately to severely decreased	2,611 (13.8%)	60 (12.6%)	2,078 (17.6%)	72 (21.9%)	7,500 (10.7%)
Stage 3 without specification of substage	0 (0%)	NA	NA	NA	NA
Stage 4: eGFR 15-29, severely decreased	666 (3.5%)	16 (3.4%)	706 (6.0%)	37 (11.2%)	1,892 (2.7%)
Stage 5: eGFR < 15 OR treated by dialysis, kidney failure	NR	1 (0.2%)	26 (0.2%)	5 (1.5%)	416 (0.6%)
No assessment of eGFR in the year before the index date	NR	83 (17.4%)	673 (5.7%)	0 (0%)	27,863 (39.7%)
CKD stage based on eGFR[b] test result or diagnosis code[a], n (%)					
Stage 1: eGFR ≥ 90, normal or high	6,071 (32.1%)	49 (10.3%)	2,463 (20.9%)	21 (6.4%)	6,015 (8.6%)
Stage 2: eGFR 60-89, mildly decreased	5,202 (27.5%)	169 (35.5%)	3,059 (25.9%)	110 (33.4%)	17,872 (25.5%)
Stage 3: mildly to severely decreased	6,684 (35.3%)	229 (48.1%)	4,869 (41.3%)	155 (47.1%)	19,345 (27.6%)
Stage 3a: eGFR 45-59, mildly to moderately decreased	4,103 (21.7%)	149 (31.3%)	2,677 (22.7%)	83 (25.2%)	11,239 (16.0%)
Stage 3b: eGFR 30-44, moderately to severely decreased	2,541 (13.4%)	80 (16.8%)	2,018 (17.1%)	71 (21.6%)	6,376 (9.1%)
Stage 3 without specification of substage	40 (0.2%)	0 (0%)	174 (1.5%)	1 (0.3%)	1,730 (2.5%)
Stage 4: eGFR 15-29, severely decreased	743 (3.9%)	24 (5.0%)	818 (6.9%)	38 (11.6%)	3,590 (5.1%)
Stage 5: eGFR < 15 OR treated by dialysis, kidney failure	NR	2 (0.4%)	26 (0.2%)	5 (1.5%)	343 (0.5%)
Unspecified stage	NR	NA	229 (1.9%)	NA	7,763 (11.1%)
No assessment of GFR or diagnosis code any time before or on the index date	211 (1.1%)	3 (0.6%)	334 (2.8%)	0 (0%)	15,230 (21.7%)

	DNHR (N = 18,929)	**PHARMO (N = 476)**	**VID (N = 11,798)**	**J-CKD-DB-Ex (N = 329)**	**CDM (N = 70,158)**
CKD stage based on urine ACR[b], n (%)					
A1: urine ACR < 30, normal to mildly increased	4,847 (25.6%)	108 (22.7%)	2,433 (20.6%)	78 (23.7%)	7,159 (10.2%)
A2: urine ACR 30-300, moderately increased (formerly 'microalbuminuria')	8,035 (42.4%)	57 (12.0%)	3,946 (33.5%)	78 (23.7%)	7,967 (11.4%)
A3: urine ACR > 300, severely increased (includes nephrotic syndrome, >~2,000)	2,447 (12.9%)	2 (0.4%)	1,378 (11.7%)	48 (14.6%)	3,691 (5.3%)
No assessment of urine ACR recorded in year before the index date	3,600 (19.0%)	309 (64.9%)	4,041 (34.3%)	125 (38.0%)	51,341 (73.2%)
"Any historical use" of drug classes (> 365 days before the index date)					
Drug classes used, n (%)					
SGLT2i and fixed-dose combinations	4,530 (23.9%)	41 (8.6%)	3,641 (30.9%)	92 (28.0%)	9,769 (13.9%)
GLP-1 RA and fixed-dose combinations	3,092 (16.3%)	31 (6.5%)	947 (8.0%)	34 (10.3%)	9,249 (13.2%)
sMRA	3,448 (18.2%)	83 (17.4%)	1,595 (13.5%)	38 (11.6%)	6,454 (9.2%)
ACEi or ARB	17,065 (90.2%)	423 (88.9%)	10,436 (88.5%)	208 (63.2%)	61,102 (87.1%)
Number of drug classes used, n (%)					
0	1,230 (6.5%)	43 (9.0%)	829 (7.0%)	NA	7,307 (10.4%)
1	9,446 (49.9%)	304 (63.9%)	6,337 (53.7%)	131 (39.8%)	42,704 (60.9%)
2	6,293 (33.2%)	113 (23.7%)	3,690 (31.3%)	88 (26.7%)	16,766 (23.9%)
3	1,737 (9.2%)	16 (3.4%)	866 (7.3%)	19 (5.8%)	3,186 (4.5%)
4	223 (1.2%)	0 (0%)	76 (0.6%)	2 (0.6%)	195 (0.3%)
> 4	0 (0%)	0 (0%)	0 (0.0%)	0 (0%)	0 (0%)

	DNHR (N = 18,929)	**PHARMO (N = 476)**	**VID (N = 11,798)**	**J-CKD-DB-Ex (N = 329)**	**CDM (N = 70,158)**
"Any previous use" of drug classes (365-91 days before the index date)					
Drug classes used, n (%)					
SGLT2i and fixed-dose combinations	5,019 (26.5%)	36 (7.6%)	4,022 (34.1%)	89 (27.1%)	9,255 (13.2%)
sMRA	2,034 (10.7%)	68 (14.3%)	1,198 (10.2%)	27 (8.2%)	5,163 (7.4%)
ACEi or ARB	14,827 (78.3%)	378 (79.4%)	9,346 (79.2%)	176 (53.5%)	57,027 (81.3%)
Number of drug classes used, n (%)					
0	2,851 (15.1%)	84 (17.6%)	1,451 (12.3%)	NA	10,842 (15.5%)
1	10,708 (56.6%)	308 (64.7%)	6,478 (54.9%)	123 (37.4%)	47,715 (68.0%)
2	4,938 (26.1%)	78 (16.4%)	3,519 (29.8%)	71 (21.6%)	11,073 (15.8%)
3	432 (2.3%)	6 (1.3%)	350 (3.0%)	9 (2.7%)	528 (0.8%)
≥ 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 (%)					
SGLT2i RA and fixed-dose combinations	4,183 (22.1%)	23 (4.8%)	4,165 (35.3%)	93 (28.3%)	7,895 (11.3%)
sMRA	1,439 (7.6%)	60 (12.6%)	1,125 (9.5%)	28 (8.5%)	4,165 (5.9%)
ACEi or ARB	11,257 (59.5%)	358 (75.2%)	9,125 (77.3%)	177 (53.8%)	50,855 (72.5%)
Number of drug classes used, n (%)					
0	5,757 (30.4%)	103 (21.6%)	1,596 (13.5%)	NA	16,339 (23.3%)
1	9,701 (51.2%)	308 (64.7%)	6,339 (53.7%)	141 (42.9%)	45,059 (64.2%)
2	3,235 (17.1%)	62 (13.0%)	3,513 (29.8%)	65 (19.8%)	8,424 (12.0%)
3	236 (1.2%)	3 (0.6%)	350 (3.0%)	9 (2.7%)	336 (0.5%)
≥ 4	0 (0%)	0 (0%)	0 (0.0%)	0 (0%)	0 (0%)

	DNHR (N = 18,929)	**PHARMO (N = 476)**	**VID (N = 11,798)**	**J-CKD-DB-Ex (N = 329)**	**CDM (N = 70,158)**
Clinical conditions associated with risk of CKD[b]					
Hypertension, n (%)	15,204 (80.3%)	359 (75.4%)	11,000 (93.2%)	293 (89.1%)	65,828 (93.8%)
Glomerulonephritis (all causes), n (%)	430 (2.3%)	16 (3.4%)	582 (4.9%)	67 (20.4%)	1,515 (2.2%)
Renovascular disease, n (%)	76 (0.4%)	0 (0%)	157 (1.3%)	9 (2.7%)	661 (0.9%)
Autoimmune disease, n (%)	933 (4.9%)	6 (1.3%)	902 (7.7%)	99 (30.1%)	4,525 (6.4%)
Polycystic kidney disease, n (%)	97 (0.5%)	0 (0%)	45 (0.4%)	0 (0%)	329 (0.5%)
Gout or hyperuricemia[b], n (%)	1,023 (5.4%)	13 (2.7%)	3,858 (32.7%)	117 (35.6%)	8,193 (11.7%)
Hospitalizations for acute kidney injury in the previous year					
n (%)	128 (0.7%)	22 (4.6%)	331 (2.8%)	0 (0.0%)	941 (1.3%)
Mean (SD)	1.1 (0.3)	1.0 (0.0)	0.0 (0.2)	0.0 (0.1)	1.1 (0.3)
Median	1	1	0	0	1
1st, 99th percentiles	1, 3	1, 1	0, 1	0, 0	1, 2

ACEi = angiotensin-converting enzyme inhibitors; ACR = albumin-to-creatinine ratio; ARB = angiotensin receptor blockers; CDM = Optum's de-identified Clinformatics® DataMart; 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 agonist; J-CKD-DB-Ex = Japan Chronic Kidney Disease Database Extension; NA = not available; NR = not reported; SD = standard deviation; SGLT2i = sodium-glucose cotransporter 2 inhibitors; sMRA = steroidal mineralocorticoid receptor antagonists; VID = Valencia Health System Integrated Database.

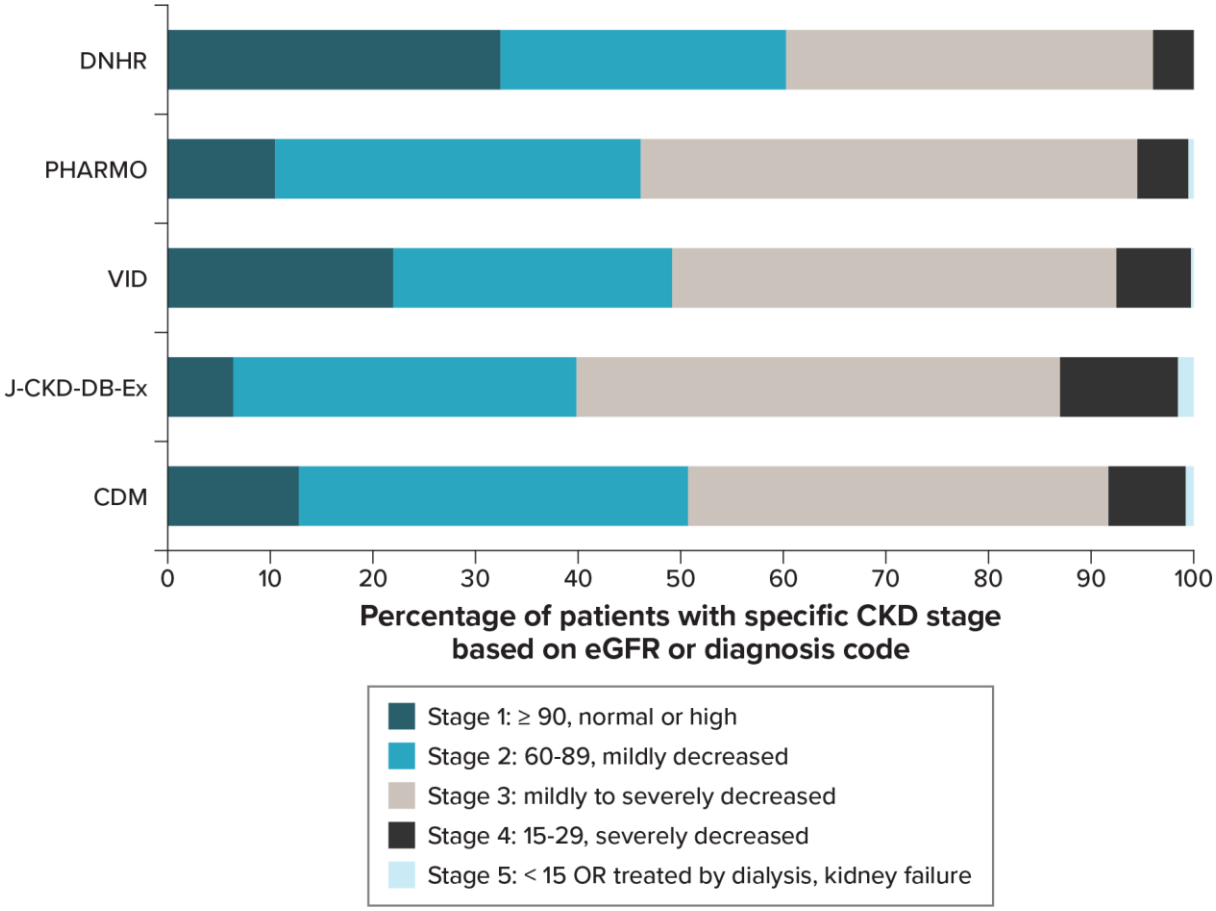
Notes: Recent use is defined as use in the 90 days before the index date (study days [−90, −1]); Previous use is defined as use within the remaining time of the previous year (study days [−365, −91]); Any historical use is defined as use before the year before the index date (study days (−∞, −366]).

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

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

Figure 7 displays the percentage of patients with a diagnosis of each CKD stage based on either a diagnostic code or eGFR test results amongst those with available CKD staging information across the different data sources. Approximately half of patients in J-CKD-DB-Ex (47.1%) and PHARMO (48.4%) had stage 3 CKD compared with 43.3% of patients in VID, 35.7% of patients in DNHR, and 41.0% of patients in CDM. The percentage of patients diagnosed with stage 1 CKD ranged from approximately 10% to 32% in the European data sources and was lowest in J-CKD-DB-Ex at 6.4%, which has a database entry requirement for CKD defined as proteinuria and/or an eGFR value < 60. Approximately 27% to 38% of patients were diagnosed with stage 2 CKD at baseline. Severe CKD (stage 4) ranged from 4.0% in DNHR to 11.6% in J-CKD-DB-Ex.

Figure 7: CKD stage at the index date for new users of GLP-1 RA defined based on eGFR value or diagnosis code, by data source



CDM = Optum's de-identified Clinformatics® DataMart; CKD = chronic kidney disease; DNHR = Danish National Health Registers; eGFR = estimated glomerular filtration rate; J-CKD-DB-Ex = Japan Chronic Kidney Disease Database Extension; PHARMO = PHARMO Data Network; VID = Valencia Health System Integrated Database.

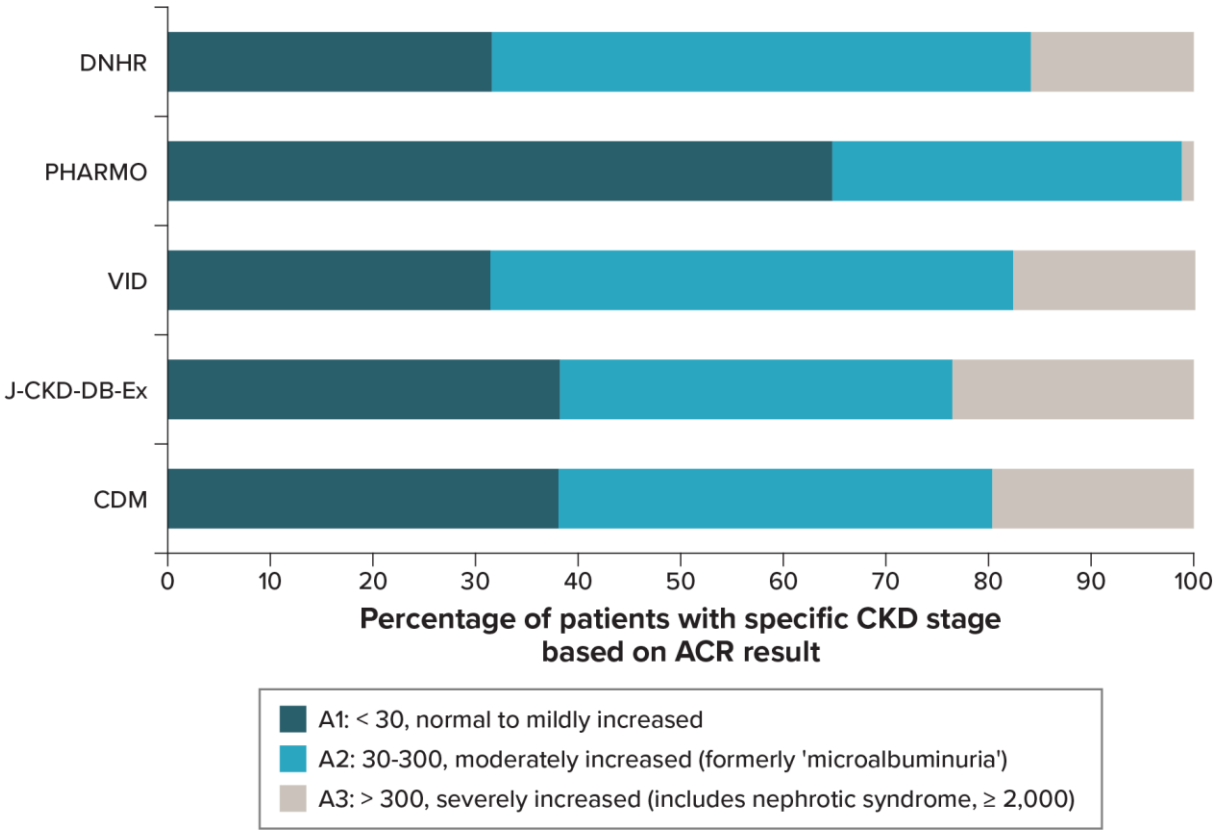
Note: All patients met the inclusion eligibility criteria for CKD, which was assessed through diagnosis codes, eGFR test results, or ACR test results.

Percentages were calculated amongst patients who have staging information available.

Across the data sources, 1.1% of patients in DNHR were missing eGFR values or diagnosis codes needed to assess CKD stage, 0.6% in PHARMO, 2.8% in VID, 0.0% in J-CKD-DB-Ex, and 21.7% in CDM. In VID, 1.9% of patients had a diagnostic code or eGFR result but it indicated an unspecified stage, and this occurred for 11.1% of patients in CDM.

Figure 8 displays the distribution of CKD diagnosis stage at baseline based on ACR test results among those with a urine ACR test in the year before the index date, across each data source. A similar proportion of patients in DNHR, VID, J-CKD-DB-Ex, and CDM were in ACR category A1 (31.4% in VID, 38.2% in J-CKD-DB-Ex, and 38.0% in CDM), although a large percentage of patients in VID, J-CKD-DB-Ex, and CDM did not have an assessment recorded in the year before the index date (34.3% in VID to 73.2% in CDM) (Table 17 and Figure 8). In the DNHR cohort, which was missing ACR values for only 19.0% of patients, 31.6% of patients were categorized as A1, 52.4% as A2, and 16.0% as A3 at baseline.

Figure 8: ACR categories at the index date, by data source among new users of GLP-1 RA



ACR = albumin-to-creatinine ratio; CDM = Optum's de-identified Clinformatics® DataMart; CKD = chronic kidney disease; DNHR = Danish National Health Registers; J-CKD-DB-Ex = Japan Chronic Kidney Disease Database Extension; PHARMO = PHARMO Data Network; VID = Valencia Health System Integrated Database.

Note: In CDM, ~42% of patients with no assessment of ACR recorded before the index date had a recorded claim for an ACR test, but no results were available.

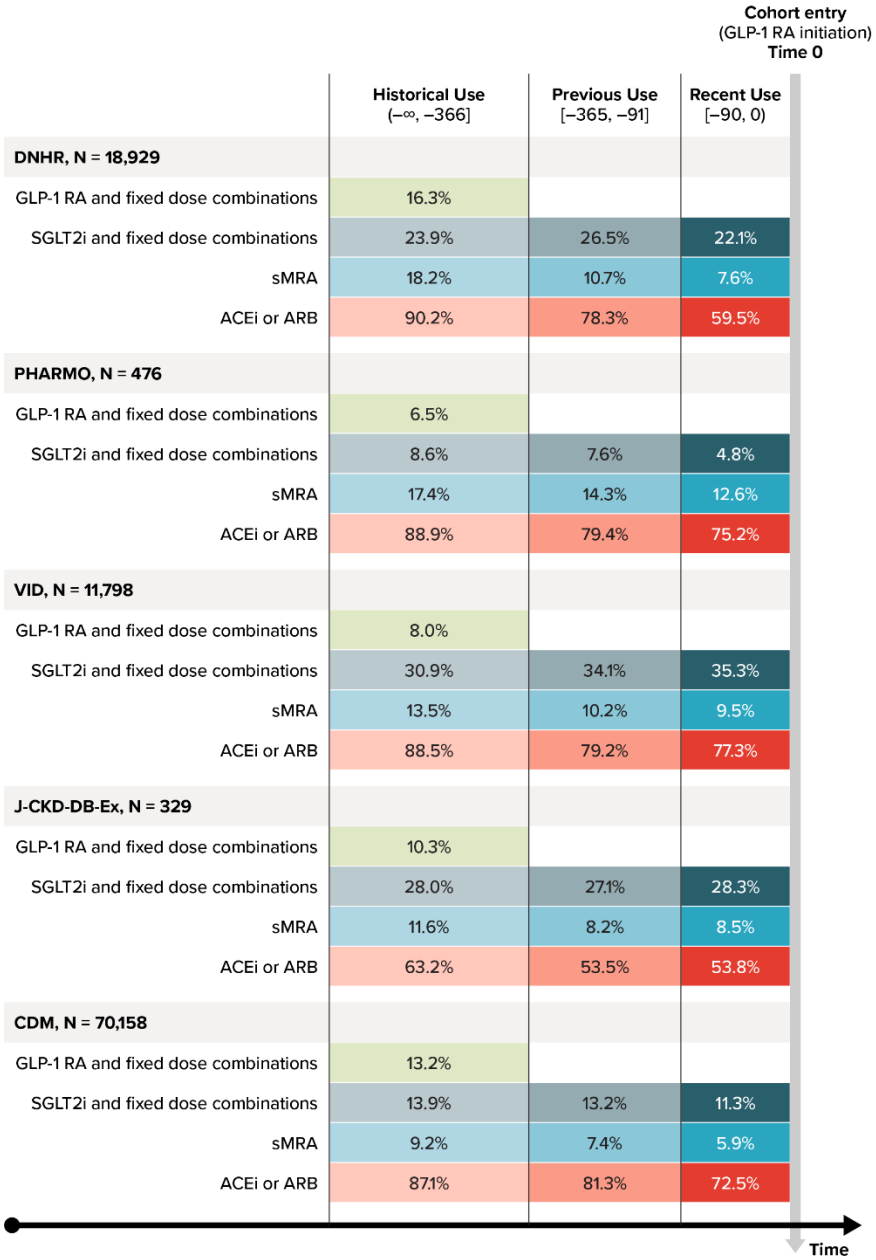
Percentages were calculated amongst patients who had an ACR value in the year before the index date.

No ACR assessment in the year before the index date was observed for 19.0% of patients in DNHR, 64.9% in PHARMO, 34.3% in VID, 38.0% in J-CKD-DB-Ex, and 73.2% in CDM.

Figure 9 displays the use of other medications of interest before initiation of GLP-1 RA in the > 365 days before the index date (historical use), 91 to 365 days before the index date (previous use), and within the 90 days before the index date (recent use). Across all time periods (historical, previous, or recent), patients were most likely to be on one other drug class, with ACEi or ARB being the most common (Figure 9 and Table 17). A high proportion

of GLP-1 RA initiators had used drug classes that belonged to the group of medications of interest (ACEi or ARB, sMRA, SGLT2i) before initiating a GLP-1 RA. Furthermore, within each data source, a consistent proportion of patients were taking each medication class regardless of whether the time window was within 90 days, 91 to 365 days, or > 365 days of the index date. Hypertension was the most common clinical condition associated with CKD risk, with more than 75% of patients diagnosed in PHARMO and up to almost 94% in CDM. Diagnosis of gout or hyperuricemia was variable across data sources, ranging from approximately 3% in PHARMO to 36% in J-CKD-DB-Ex (Table 17). Glomerulonephritis and autoimmune disease were also more common in J-CKD-DB-Ex than in the other data sources.

Figure 9: Historical, previous, and recent use of medications of interest in relation to the index GLP-1 RA medication



ACEi = angiotensin-converting enzyme inhibitors; ARB = angiotensin receptor blocker; CDM = Optum's de-identified Clinformatics® DataMart; CKD = chronic kidney disease; DNHR = Danish National Health Registers; GLP-1 RA = glucagon-like peptide-1 receptor agonist; J-CKD-DB-Ex = Japan Chronic Kidney

Disease Database Extension; PHARMO = PHARMO Data Network; SGLT2i = sodium-glucose cotransporter 2 inhibitors; sMRA = steroidal mineralocorticoid receptor antagonist; VID = Valencia Health System Integrated Database.

Note: By design, GLP-1 RA use could not occur from −365 days to the day before the index date; thus, no percentages were reported for these measures across any data source.

10.4.1.2.3 Baseline comorbidities and comedications

Table 18 displays the prevalence of select comorbidities among new users of GLP-1 RA. Hypertension was the most frequently diagnosed cardiovascular risk factor across all data sources, ranging from 75.4% in PHARMO to 93.8% in CDM. Hypercholesterolemia was the second most common diagnosis and was present in more than 80% of patients in J-CKD-DB-Ex, VID, and CDM. Diagnoses of macrovascular complications, specifically coronary heart disease (CHD), ranged from 26.9% (VID) to 33.0% (PHARMO and CDM) and 59.9% (J-CKD-DB-Ex). Cerebrovascular disease ranged from 10.7% (PHARMO) to 52.0% (J-CKD-DB-Ex). More than 20% of patients in J-CKD-DB-Ex, VID, and PHARMO had a malignancy diagnosis other than kidney cancer and non-melanoma skin cancers, whereas the percentage was approximately 12% in DNHR and CDM (Table 18).

Table 18: Baseline comorbidities in new users of GLP-1 RA medications, by data source

	DNHR (N = 18,929), N (%)	**PHARMO (N = 476), N (%)**	**VID (N = 11,798), N (%)**	**J-CKD-DB-Ex (N = 329), N (%)**	**CDM (N = 70,158), N (%)**
Macrovascular complications of diabetes					
CHD	5,557 (29.4%)	157 (33.0%)	3,171 (26.9%)	197 (59.9%)	23,175 (33.0%)
Cerebrovascular disease	2,397 (12.7%)	51 (10.7%)	1,488 (12.6%)	171 (52.0%)	8,670 (12.4%)
Peripheral vascular disease	3,088 (16.3%)	65 (13.7%)	3,041 (25.8%)	72 (21.9%)	20,167 (28.7%)
CVD risk factors					
Hypertension	15,204 (80.3%)	359 (75.4%)	10,974 (93.0%)	293 (89.1%)	65,828 (93.8%)
Hypercholesterolemia	6,337 (33.5%)	174 (36.6%)	9,611 (81.5%)	278 (84.5%)	62,519 (89.1%)
Congestive heart failure	2,448 (12.9%)	73 (15.3%)	634 (5.4%)	194 (59.0%)	14,543 (20.7%)
Severe liver disease	107 (0.6%)	23 (4.8%)	733 (6.2%)	16 (4.9%)	707 (1.0%)
HIV infection	32 (0.2%)	1 (0.2%)	41 (0.4%)	16 (4.9%)	346 (0.5%)
Dementia	260 (1.4%)	8 (1.7%)	279 (2.4%)	20 (6.1%)	2,808 (4.0%)
COPD	1,929 (10.2%)	79 (16.6%)	2,048 (17.4%)	105 (31.9%)	13,891 (19.8%)
Malignancy (other than kidney cancer and non-melanoma skin cancers)	2,344 (12.4%)	99 (20.8%)	2,814 (23.9%)	97 (29.5%)	8,347 (11.9%)

CDM = Optum's de-identified Clinformatics® DataMart; CHD = coronary heart disease; COPD = chronic obstructive pulmonary disease; CVD = cardiovascular disease; DNHR = Danish National Health Registers; HIV = human immunodeficiency virus; J-CKD-DB-Ex = Japan Chronic Kidney Disease Database Extension; PHARMO = PHARMO Data Network; VID = Valencia Health System Integrated Database.

Loop diuretics were the most common type of diuretic in DNHR (28.2%), J-CKD-DB-Ex (15.8%), and VID (32.0%), whereas thiazide-like diuretics were most common in PHARMO (25.4%) and CDM (32.8%) (Table 19). Potassium-sparing diuretics were prescribed to < 3% of patients in each of the data sources. A comparable number of patients were being prescribed or dispensed ACEi and ARB in DNHR, PHARMO, and CDM. In these data sources, ACEi were prescribed or dispensed to approximately 35% to 40% of patients, whereas approximately 44% to 51% of patients were prescribed or dispensed ARB. In J-CKD-DB-Ex, only 6% of patients had a prescription for an ACEi, whereas 55% had a prescription for an ARB; in VID, approximately 20% of patients had a prescription for an ACEi, whereas 64% had a prescription for an ARB. Statins were the most commonly prescribed cardiovascular medication in DNHR, PHARMO, VID, and CDM (> 76% of patients), whereas ARB (55.0%) and calcium channel blockers (53.5%) were more commonplace in J-CKD-DB-Ex. Use of other lipid-lowering medications was between 17.1% in CDM and 24.9% in VID and was < 10% in PHARMO and DNHR. Use of anticoagulants ranged from approximately 10% (J-CKD-DB-Ex) to 20% (VID) (Table 19).

Table 19: Medication use other than GLD recorded in the 180 days before or on the index date in new users of GLP-1 RA medications, by data source

	DNHR (N = 18,929), N (%)	**PHARMO (N = 476), N (%)**	**VID (N = 11,798), N (%)**	**J-CKD-DB-Ex (N = 329), N (%)**	**CDM (N = 70,158), N (%)**
Cardiovascular medications in the 180 days before or on the index date					
Thiazide-like diuretics	3,018 (15.9%)	121 (25.4%)	678 (5.8%)	28 (8.5%)	23,031 (32.8%)
Loop diuretics	5,332 (28.2%)	107 (22.5%)	3,771 (32.0%)	52 (15.8%)	17,894 (25.5%)
Potassium-sparing diuretics	163 (0.9%)	12 (2.5%)	160 (1.4%)	0 (0%)	1,703 (2.4%)
ACEi	6,755 (35.7%)	185 (38.9%)	2,314 (19.6%)	21 (6.4%)	28,644 (40.8%)
ARB	8,227 (43.5%)	221 (46.4%)	7,546 (64.0%)	181 (55.0%)	36,000 (51.3%)
Beta blockers	7,598 (40.1%)	268 (56.3%)	4,577 (38.8%)	83 (25.2%)	35,476 (50.6%)
Direct renin inhibitors	20 (0.1%)	4 (0.8%)	33 (0.3%)	1 (0.3%)	59 (0.1%)
Angiotensin receptor-neprilysin inhibitors	67 (0.4%)	1 (0.2%)	190 (1.6%)	0 (0%)	625 (0.9%)
Calcium channel blockers	7,537 (39.8%)	159 (33.4%)	3,484 (29.5%)	176 (53.5%)	23,752 (33.9%)
Other antihypertensives	0 (0%)	16 (3.4%)	1,906 (16.2%)	33 (10.0%)	4,939 (7.0%)
Statins	14,501 (76.6%)	371 (77.9%)	9,320 (79.0%)	160 (48.6%)	53,632 (76.4%)
Anticoagulants	3,134 (16.6%)	73 (15.3%)	2,296 (19.5%)	34 (10.3%)	7,786 (11.1%)
Digoxin	851 (4.5%)	12 (2.5%)	274 (2.3%)	1 (0.3%)	1,164 (1.7%)
Nitrates and other vasodilators	1,191 (6.3%)	40 (8.4%)	811 (6.9%)	28 (8.5%)	5,920 (8.4%)
Aspirin and other antiplatelet agents	7,713 (40.7%)	191 (40.1%)	5,135 (43.5%)	110 (33.4%)	9,339 (13.3%)
Lipid-lowering drugs other than statins	1,094 (5.8%)	47 (9.9%)	2,936 (24.9%)	67 (20.4%)	11,962 (17.1%)

	DNHR (N = 18,929), N (%)	**PHARMO (N = 476), N (%)**	**VID (N = 11,798), N (%)**	**J-CKD-DB-Ex (N = 329), N (%)**	**CDM (N = 70,158), N (%)**
Other medications of interest					
Anti-inflammatory drugs (NSAIDs)	2,485 (13.1%)	57 (12.0%)	2,511 (21.3%)	30 (9.1%)	12,271 (17.5%)
Acetaminophen	8,018 (42.4%)	52 (10.9%)	4,473 (37.9%)	70 (21.3%)	14,200 (20.2%)
Anticonvulsants	390 (2.1%)	2 (0.4%)	275 (2.3%)	6 (1.8%)	2,882 (4.1%)
Anti-infectives					
Antibacterial agents	4,921 (26.0%)	137 (28.8%)	4,554 (38.6%)	89 (27.1%)	20,959 (29.9%)
Antifungal agents	606 (3.2%)	4 (0.8%)	311 (2.6%)	13 (4.0%)	5,172 (7.4%)
Antitubercular agents	8 (< 0.1%)	1 (0.2%)	27 (0.2%)	1 (0.3%)	64 (0.1%)
Chemotherapeutic agents	16 (0.1%)	4 (0.8%)	61 (0.5%)	11 (3.3%)	2,031 (2.9%)
Bronchodilators	2,578 (13.6%)	105 (22.1%)	2,476 (21.0%)	18 (5.5%)	11,135 (15.9%)

ACEi = angiotensin-converting enzyme inhibitors; ARB = angiotensin receptor blockers; CDM = Optum's de-identified Clinformatics® DataMart; DNHR = Danish National Health Registers; GLD = glucose-lowering drugs; J-CKD-DB-Ex = Japan Chronic Kidney Disease Database Extension; NSAID = non-steroidal anti-inflammatory drug; PHARMO = PHARMO Data Network; VID = Valencia Health System Integrated Database.

10.4.1.2.4 Characteristics of the index medication at baseline and during follow-up

The median duration of the initial exposure episode was more than two months in all data sources (Table 20), ranging from 2.3 months (PHARMO) to 12.4 months (VID) in the European data sources. In CDM, the median duration was four months and 7.2 months in J-CKD-DB-Ex. The median number of prescriptions or dispensings within this initial exposure episode ranged from 3 (CDM) to 13 (VID). Between 7.6% (DNHR) and 41.3% (CDM) of GLP-1 RA initiators had an interruption of current use lasting 90 days or more during follow-up. Additionally, the total observed median duration of exposure to the index GLP-1 RA ranged from 5.2 months (PHARMO) to 18.1 months (VID) during study follow-up.

Table 20: Characteristics of the index GLP-1 RA at baseline and during follow-up, by data source

	DNHR (N = 18,929), N (%)[a]	**PHARMO (N = 476), N (%)[a]**	**VID (N = 11,798), N (%)[a]**	**J-CKD-DB-Ex (N = 329), N (%)[a]**	**CDM (N = 70,158), N (%)[a]**
Classification of the index GLP-1 RA at the index date					
Monotherapy	4,696 (24.8%)	90 (18.9%)	1,342 (11.4%)	212 (64.4%)	14,535 (20.7%)
Combination therapy	1,061 (5.6%)	13 (2.7%)	254 (2.2%)	4 (1.2%)	1,804 (2.6%)
Add-on	8,588 (45.4%)	298 (62.6%)	7,335 (62.2%)	104 (31.6%)	40,500 (57.7%)
Switch	2,272 (12.0%)	19 (4.0%)	497 (4.2%)	4 (1.2%)	5,244 (7.5%)
Add-on and switch	1,104 (5.8%)	21 (4.4%)	1,404 (11.9%)	5 (1.5%)	2,042 (2.9%)
Indeterminate	1,208 (6.4%)	35 (7.4%)	966 (8.2%)	0 (0%)	6,033 (8.6%)
Index GLP-1 RA was an “Add-On” to					
SGLT2i	2,667 (14.1%)	0 (0%)	2,744 (23.3%)	89 (27.1%)	5,577 (7.9%)
sMRA	940 (5.0%)	51 (10.7%)	902 (7.7%)	26 (7.9%)	3,318 (4.7%)
ACEi/ARB	8,667 (45.8%)	309 (64.9%)	7,879 (66.8%)	73 (22.2%)	44,708 (63.7%)
Index GLP-1 RA was a “Switch” from					
SGLT2i	1,516 (8.0%)	0 (0%)	1,082 (9.2%)	7 (2.1%)	2,318 (3.3%)
sMRA	499 (2.6%)	16 (3.4%)	107 (0.9%)	2 (0.6%)	847 (1.2%)
ACEi/ARB	2,590 (13.7%)	37 (7.8%)	840 (7.1%)	0 (0%)	6,147 (8.8%)
Duration of initial exposure episode after cohort entry (months)					
Mean (SD)	17.9 (18.1)	3.0 (3.1)	17.6 (17.3)	12.9 (14.4)	9.4 (12.3)
Median	11.5	2.3	12.4	7.2	4
1st, 99th percentiles	0, 87	0, 16	0, 79	0, 62	1, 57

	DNHR (N = 18,929), N (%)[a]	**PHARMO (N = 476), N (%)[a]**	**VID (N = 11,798), N (%)[a]**	**J-CKD-DB-Ex (N = 329), N (%)[a]**	**CDM (N = 70,158), N (%)[a]**
Days' supply of index GLP-1 RA (days)					
Mean (SD)	102.1 (66.1)	31.7 (30.4)	26.8 (4.2)	21.5 (27.9)	40.4 (23.4)
Median	86	28	28	21	30
1st, 99th percentiles	36, 320	7, 150	11, 30	1, 121	7, 90
Number of prescriptions or dispensings during follow-up for the GLP-1 RA drug class					
Mean (SD)	14.0 (15.3)	6.8 (9.4)	20.5 (21.8)	19.6 (26.8)	7.1 (10.0)
Median	9	4	13	12	3
1st, 99th percentiles	1, 71	0, 48	1, 101	1, 130	1, 49
Number of distinct "current-use" periods (treatment episodes) during follow-up for the index GLP-1 RA drug class					
1	16,266 (85.9%)	259 (54.4%)	8,193 (69.4%)	230 (69.9%)	28,047 (40.0%)
2	1,983 (10.5%)	75 (15.8%)	2,201 (18.7%)	55 (16.7%)	16,028 (22.8%)
3	444 (2.3%)	41 (8.6%)	822 (7.0%)	20 (6.1%)	9,629 (13.7%)
4	140 (0.7%)	35 (7.4%)	322 (2.7%)	9 (2.7%)	5,798 (8.3%)
5+	96 (0.5%)	66 (13.9%)	260 (2.2%)	15 (4.6%)	10,656 (15.2%)
Number of distinct prescriptions or dispensings during follow-up for the index GLP-1 RA drug class					
Mean (SD)	15.8 (16.2)	13.4 (12.9)	27.0 (26.4)	26.0 (33.9)	13.9 (14.7)
Median	11	10	20	17	9
1st, 99th percentiles	1, 75	1, 67	1, 118	1, 159	1, 68
Number of discontinuations (interruptions) of current use during follow-up					
0	13,140 (69.4%)	259 (54.4%)	8,193 (69.4%)	151 (45.9%)	28,047 (40.0%)
1	4,595 (24.3%)	75 (15.8%)	2,201 (18.7%)	114 (34.7%)	16,028 (22.8%)
2	849 (4.5%)	41 (8.6%)	822 (7.0%)	32 (9.7%)	9,629 (13.7%)

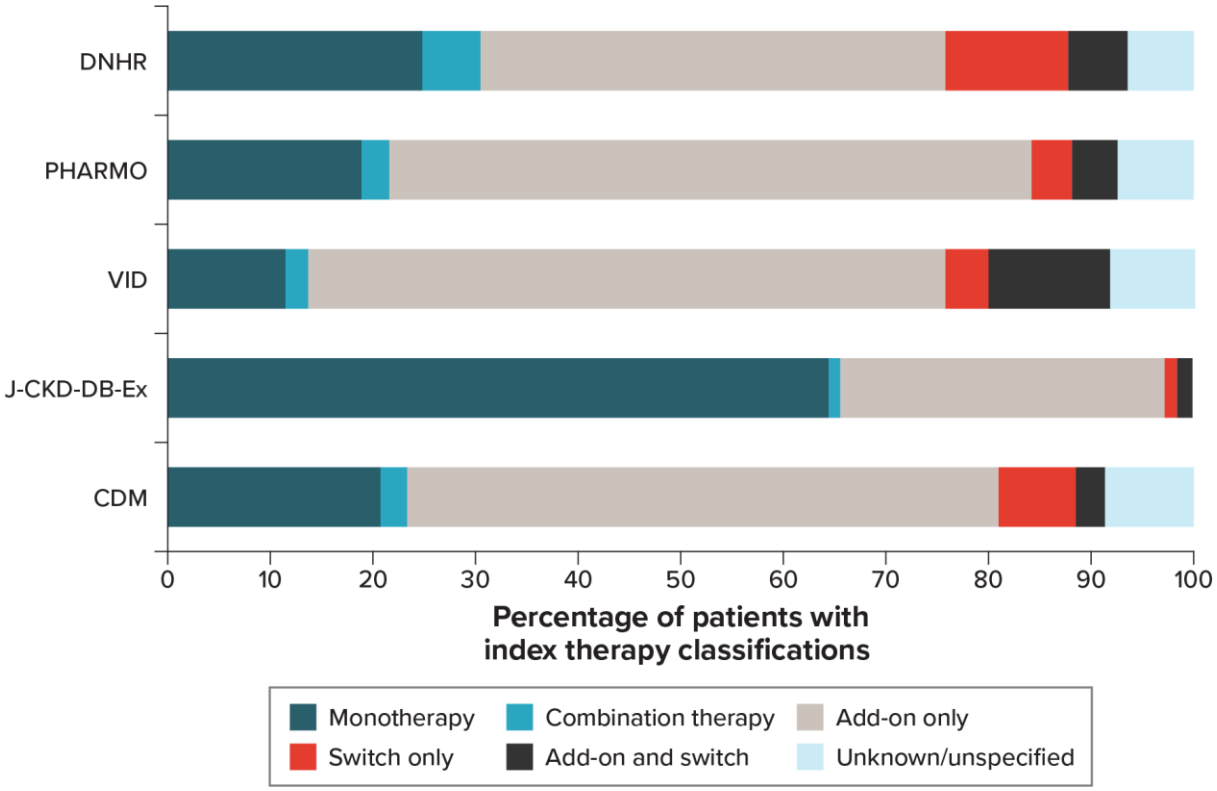
	DNHR (N = 18,929), N (%)[a]	**PHARMO (N = 476), N (%)[a]**	**VID (N = 11,798), N (%)[a]**	**J-CKD-DB-Ex (N = 329), N (%)[a]**	**CDM (N = 70,158), N (%)[a]**
3	206 (1.1%)	35 (7.4%)	322 (2.7%)	14 (4.3%)	5,798 (8.3%)
4	79 (0.4%)	22 (4.6%)	131 (1.1%)	6 (1.8%)	3,701 (5.3%)
5+	60 (0.3%)	44 (9.2%)	129 (1.1%)	12 (3.6%)	6,955 (9.9%)
Number of patients with an interruption of current use lasting 90 days or more	1,438 (7.6%)	74 (15.5%)	1,416 (12.0%)	127 (38.6%)	28,959 (41.3%)
Duration of total exposure to index therapy (months)					
Mean (SD)	20.7 (19.9)	12.1 (14.9)	23.2 (21.0)	17.6 (17.8)	21.9 (20.0)
Median	14.7	5.2	18.1	10.9	16.1
1st, 99th percentile	0, 96	1, 66	0, 89	0, 70	2, 89
Other drug classes started during follow-up					
SGLT2i	6,770 (35.8%)	29 (6.1%)	6,700 (56.8%)	131 (39.8%)	6,815 (9.7%)
sMRA	2,603 (13.8%)	82 (17.2%)	1,655 (14.0%)	39 (11.9%)	2,193 (3.1%)
ACEi/ARB	15,011 (79.3%)	368 (77.3%)	9,650 (81.8%)	200 (60.8%)	2,948 (4.2%)
Duration of total follow-up (months)					
Mean (SD)	26.0 (23.1)	24.8 (24.0)	31.8 (25.4)	25.4 (20.3)	23.8 (21.7)
Median	19.9	17.2	25.5	19.5	17.8
1st, 99th percentiles	0, 106	0, 103	0, 101	0, 75	0, 99

ACEi = angiotensin-converting enzyme inhibitors; ARB = angiotensin receptor blockers; CDM = Optum's de-identified Clinformatics® DataMart; DNHR = Danish National Health Registers; GLP-1 RA = glucagon-like peptide-1 receptor agonist; J-CKD-DB-Ex = Japan Chronic Kidney Disease Database Extension; SD = standard deviation; SGLT2i = sodium-glucose cotransporter 2 inhibitors; sMRA = steroidal mineralocorticoid receptor antagonists; VID = Valencia Health System Integrated Database.

[a] Unless otherwise specified.

Within DNHR, PHARMO, VID, and CDM, the index GLP-1 RA prescription was most commonly an add-on therapy to another medication of interest, with prescriptions ranging from 45.4% for patients in DNHR to 62.6% for patients in VID and PHARMO (Figure 10). In J-CKD-DB-Ex, 31.6% of GLP-1 RA initiations were add-on therapies, with the vast majority (64.4%) being a monotherapy. Where the index GLP-1 RA was an add-on therapy, the most common drugs to which it was added were ACEi/ARB in the European data sources and CDM and SGLT2i in J-CKD-DB-Ex (Table 20). Information was not available regarding the reason for prescribing these drugs; therefore, no definitive conclusions can be reached as to what indication they were being used for. Some of these therapies (ACEi/ARB) can also be used to treat high blood pressure (hypertension), which was found to be the most prevalent comorbid condition (Table 20), as well as diabetes. Few patients had their index GLP-1 RA prescription resulting from a switch from a different therapy (ranging from 1.2% of patients in J-CKD-DB-Ex to 12% of patients in DNHR). Where the index drug was a switch, the most frequent switch was from ACEi/ARB in DNHR, PHARMO, and CDM and from SGLT2i in J-CKD-DB-Ex and VID (Table 20).

Figure 10: Classification of the index GLP-1 RA at the index date



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

Across all data sources, the median duration of follow-up from date of GLP-1 RA initiation was > 17 months (Table 20). Where other therapy was started during follow-up, it was most commonly an ACEi/ARB in DNHR, PHARMO, VID, and J-CKD-DB-Ex (ranging from 60.8% in J-CKD-DB-Ex to 81.8% in VID). In CDM, SGLT2i was the most common drug class started during follow-up, though this was the case for only < 10% of patients (Table 20).

10.4.1.2.5 Baseline characteristics stratified by ACR test

All baseline characteristics were stratified by the presence or absence of an ACR test recorded in the year before and including the date of index GLP-1 RA therapy. The results of select characteristics are presented in Annex 6, Table 41, stratified by ACR test status. No notable differences were observed among patients with and without an ACR test; however, those without an ACR test were slightly older and more likely to be female, had more advanced disease (CKD stage 3, except in J-CKD-DB-Ex and CDM), and were more likely to be prescribed loop diuretics compared with those who had an ACR test.

10.4.1.2.6 Treatment changes over time for GLP-1 RA during follow-up

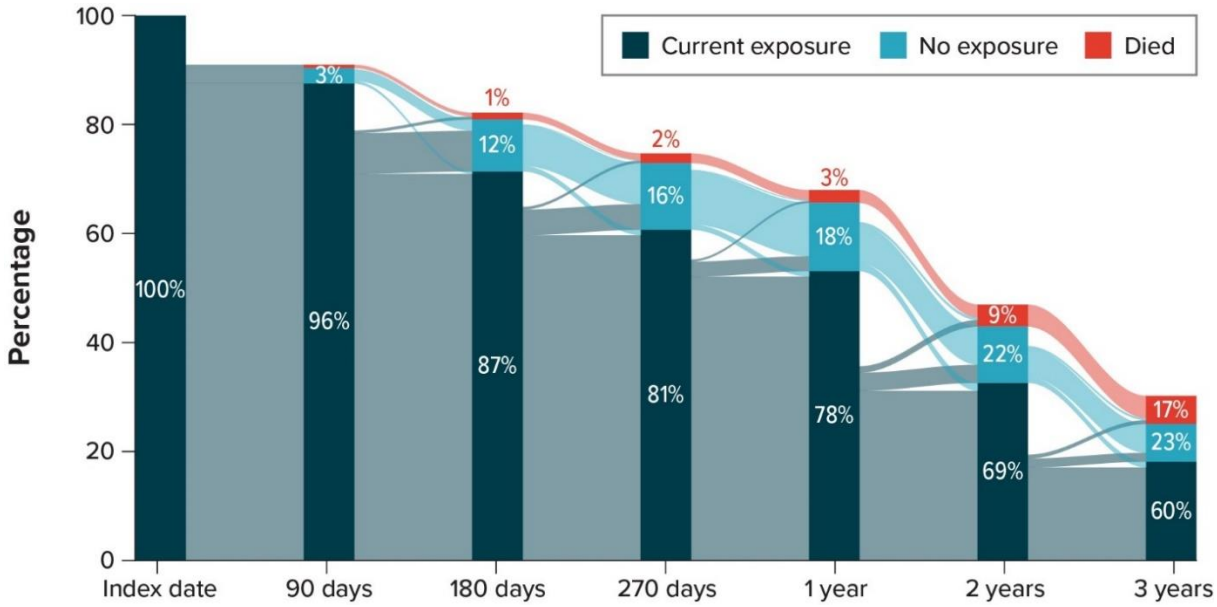
Figure 11 displays a series of Sankey diagrams that visually depict the treatment patterns of patients who initiated a GLP-1 RA over the course of follow-up starting with the index date (at which point, all patients were currently exposed by design). The proportion of the cohort in each treatment state (current use or non-use) was reported by cohort at six prespecified subsequent timepoints (90 days, 180 days, 270 days, one year, two years, and three years).

The percentage of patients observed to be receiving treatment at each timepoint was similar across the European data sources (Figure 11). Of those under observation at yearly timepoints during the study period, the lowest proportion of patients currently receiving GLP-1 RA treatment was observed in CDM (one year, 52%; two years, 42%; three years, 33%). Among the other data sources (DNHR, PHARMO, VID, and J-CKD-DB-Ex), yearly proportions of patients observed to be receiving current GLP-1 RA treatment were similar at each timepoint; 71% to 78% of patients were observed to be receiving treatment at year one, 64% to 69% at year two, and 54% to 60% at year three. These percentages represent a combination of patients who remained continuously on treatment up to the given timepoint and other patients who had discontinued and restarted the medications.

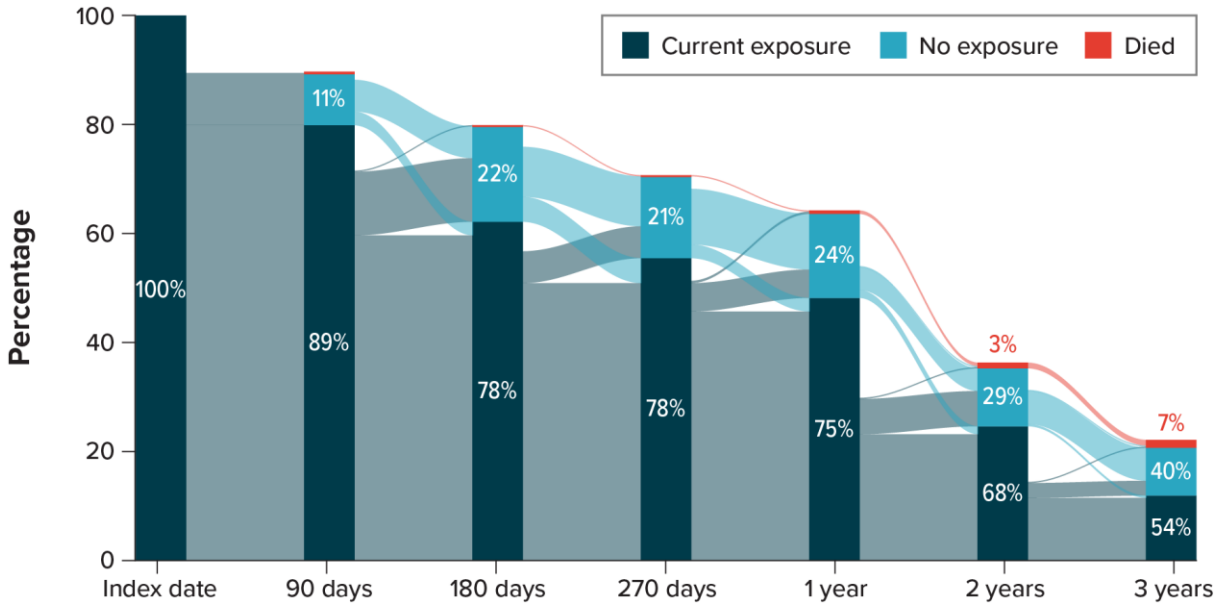
A common pattern in all data sources was that the largest proportional increase in the “no exposure” treatment state occurred between either the index and 90-day timepoints (VID and J-CKD-DB-Ex) or between the 90- and 180-day timepoints (DNHR and CDM). In PHARMO, the increase in the “no exposure” treatment state was similar at these timepoints. At each timepoint, a small proportion of nonusers who remained under observation were found to change and become current users.

Figure 11: Treatment states at specific timepoints for GLP-1 RA initiators for each data source

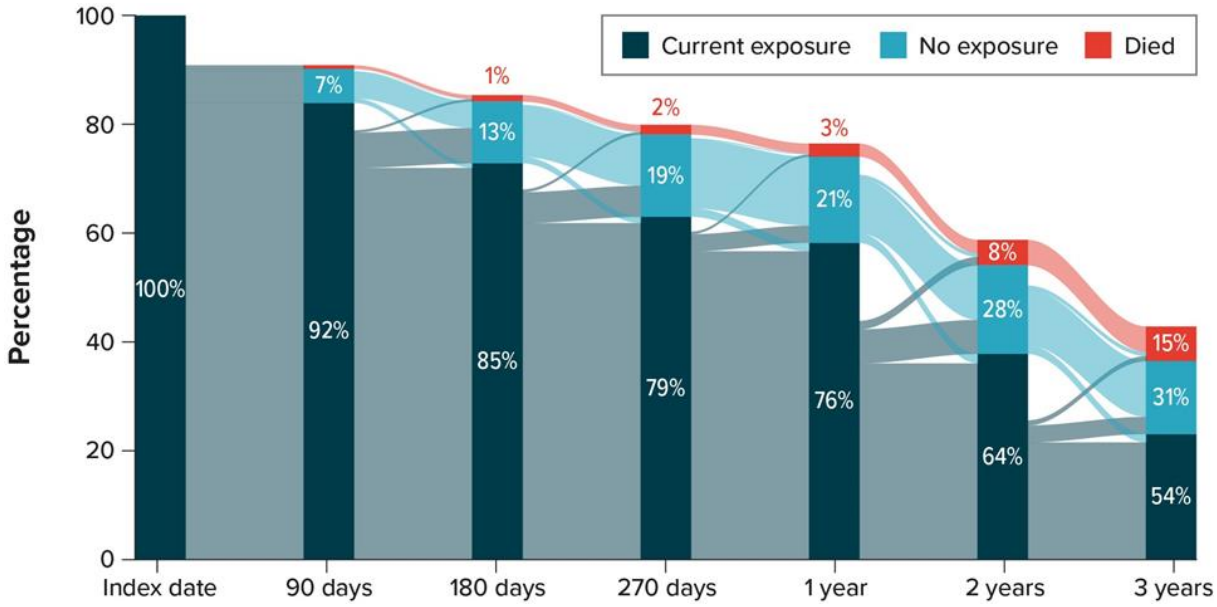
DNHR



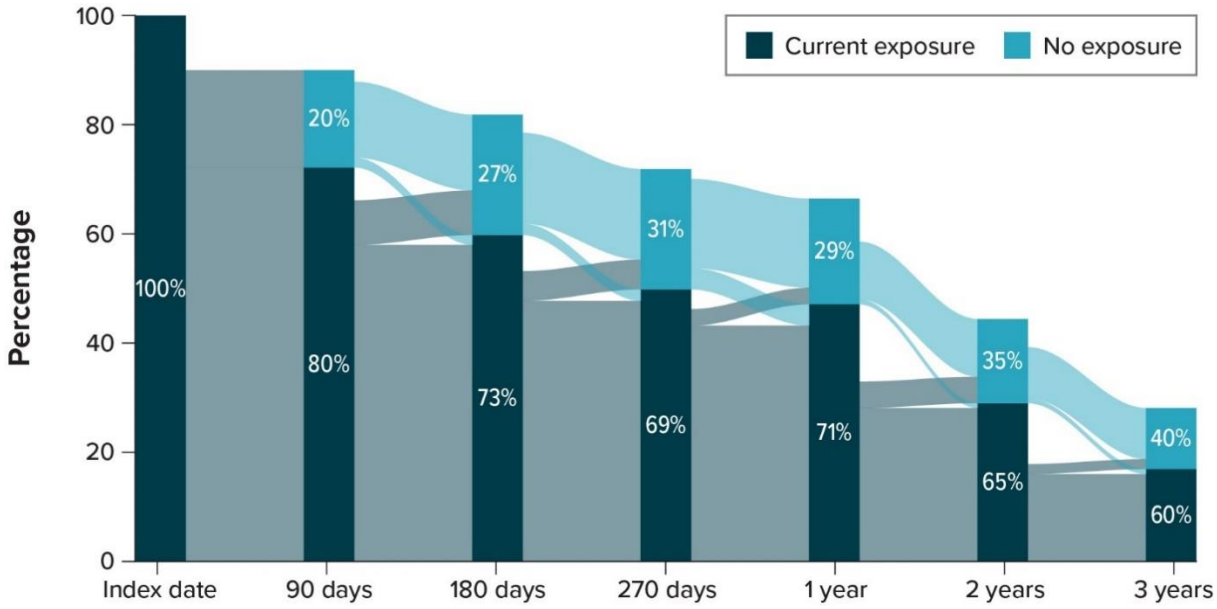
PHARMO



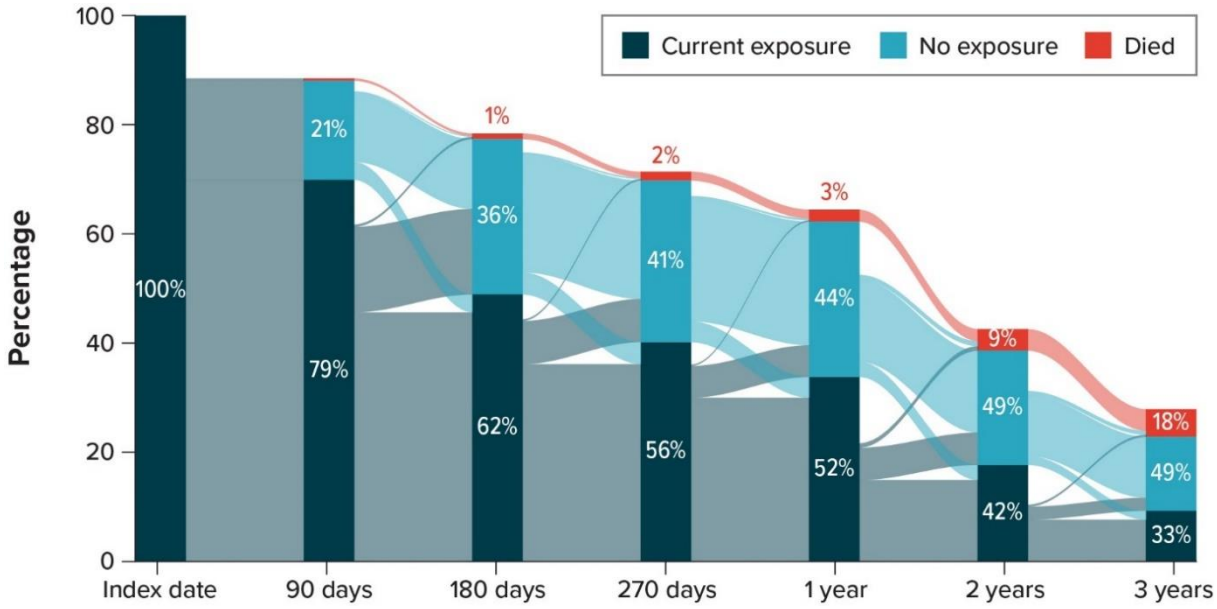
VID



J-CKD-DB-Ex



CDM



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

Notes: Sankey diagrams display the proportion of the population at each timepoint in each of the treatment states for each data source. The connecting bars between timepoints show the proportion of the population that moved from 1 state to a different state at the next timepoint. These figures display proportions of the population over time, and a patient may move between treatment states over time (e.g., begin as "treated," move to "untreated" at the next timepoint, then move back to "treated" at the next). If death occurred, the patient was placed in a separate category and remained in that state for each subsequent checkpoint. Note that death information was not available in J-CKD-DB-Ex.

The height of the bar at each timepoint displays the relative size of the cohort remaining under observation at each timepoint. Patients who were lost to follow-up are not included in the percentage calculations at each timepoint; thus, the percentages sum to 100% for each timepoint. The percentages describe the amount of patients still under observation at that timepoint.

The sum of the bars for each timepoint may not equal 100% due to rounding.

10.4.1.3 sMRA

10.4.1.3.1 Markers of severity of T2D at index date

The median duration of a T2D diagnosis ranged from approximately four years (CDM) to 11 years (PHARMO) (Table 21). The percentage of patients with the highest HbA_{1c} (> 74.9 mmol/mol or > 9%) ranged from 1.9% in J-CKD-DB-Ex to 8.4% in DNHR. Notably, 61% of individuals in CDM were missing an HbA_{1c} value. Insulin use in the 180 days before and including the index date was comparable across most data sources, ranging from 24.6% (CDM) to 38.5% (VID). However, the percentage of patients with a recorded use of insulin during this time was markedly lower in PHARMO (1.2%). The percentage of patients who were not taking any other T2D drugs (aside from insulin) was lowest in the European data sources (ranging from 25.5% in VID to 32.4% in PHARMO) and highest in CDM (52.6%) and J-CKD-DB-Ex (65.0%). Across the European data sources, patients were most commonly taking one class of T2D drugs (other than insulin) before and including the index date (41.2% in PHARMO to 44.4% in VID). The most common T2D medication, including their fixed-dose combinations, was metformin in DNHR (57.5%) and PHARMO (58.6%) and was DPP-4 in VID (44.2%) and J-CKD-DB-Ex (28.8%). Within CDM, metformin (30.3%) and sulfonylureas (20.9%) were the most common T2D medications prescribed. Alpha-

glucosidase inhibitors, meglitinides, and thiazolidinediones were amongst the least prescribed medications in the European data sources and CDM. The median Diabetes Severity Complications Index score ranged from three (in both DNHR and PHARMO) to five (in VID). Median scores in both J-CKD-DB-Ex and CDM were four (Table 21).

When comparing the diabetes severity of the sMRA medication cohort with the other medication cohorts (i.e., GLP-1 RA, SGLT2i), no medication therapy for T2D was markedly more common than in the other medication cohorts across data sources. The same was true for metabolic control (HbA_{1c} levels) being much better in this cohort than in the other medication cohorts. Conversely, the median diabetes severity score was the same or worse than in the other medication cohorts across data sources, likely because of the older ages in this sMRA cohort.

Table 21: Markers of T2D severity at the index date for new users of sMRA, by data source

	DNHR (N = 12,689)	PHARMO (N = 2,691)	VID (N = 14,906)	J-CKD-DB-Ex (N = 1,769)	CDM (N = 71,716)
Duration of T2D (years) at the index date					
Mean (SD)	CCI				
Median					
1st, 99th percentiles					
Medications for T2D (hypoglycemic agents) ever prescribed from 180 days before and including the index date					
GLP-1 RA and fixed-dose combinations	CCI				
SGLT2i and fixed-dose combinations					
Metformin and fixed-dose combinations					
Sulfonylureas and fixed-dose combinations					
Alpha-glucosidase inhibitors					
Thiazolidinediones					
DPP-4i and fixed-dose combinations					
Meglitinides (including repaglinide, nateglinide, mitiglinide)					
Number of T2D drug classes other than insulin ever used in the 180 days before and including the index date					
0	CCI				
1					
2					
3					
4+					
Insulin use recorded in the 180 days before and including the index date					

	DNHR (N = 12,689)	**PHARMO (N = 2,691)**	**VID (N = 14,906)**	**J-CKD-DB-Ex (N = 1,769)**	**CDM (N = 71,716)**
HbA_{1c}					
$HbA_{1c} \leq 53$ mmol/mol or $\leq 7\%$	CCI				
$HbA_{1c} > 53$ mmol/mol and ≤ 63.9 mmol/mol or $> 7\%$ and $\leq 8\%$					
$HbA_{1c} > 63.9$ mmol/mol and ≤ 74.9 mmol/mol or $> 8\%$ and $\leq 9\%$					
$HbA_{1c} > 74.9$ mmol/mol or $> 9\%$					
HbA_{1c} missing					
Other key medical conditions					
Hyperkalaemia	CCI				
Amputation					
The Diabetes Severity Complications Index					
Key diagnoses for scoring of the index score					
Retinopathy	CCI				
Nephropathy					
Neuropathy					
Cerebrovascular					
Cardiovascular					
Peripheral vascular disease					
Metabolic complications					

	DNHR (N = 12,689)	PHARMO (N = 2,691)	VID (N = 14,906)	J-CKD-DB-Ex (N = 1,769)	CDM (N = 71,716)
Index score					
Mean (SD)	CCI				
Median					
1st, 99th percentiles					

CDM = Optum's de-identified Clinformatics® DataMart; DNHR = Danish National Health Registers; GLP-1 RA = glucagon-like peptide-1 receptor agonist; HbA1c = hemoglobin A1c (glycated hemoglobin); J-CKD-DB-Ex = Japan Chronic Kidney Disease Database Extension; N = number; NR = not reported; SD = standard deviation; SGLT2i = sodium-glucose cotransporter 2 inhibitors; sMRA = steroidal mineralocorticoid receptor antagonists; T2D = type 2 diabetes; VID = Valencia Health System Integrated Database.

Note: N (%), unless otherwise specified.

10.4.1.3.2 Markers of kidney dysfunction severity at the index date

The median duration since a CKD diagnosis at the time of the index prescription was lowest in VID (1.8 years) and highest in PHARMO (5.8 years) (Table 22). When assessing CKD stage based on either eGFR results or a diagnosis code, a diagnosis of stage 1 CKD was lowest in J-CKD-DB-Ex (2.0%), followed by PHARMO (3.1%) and CDM (8.1%) (Table 22; Figure 12). The percentage was highest in VID (8.0%) and DNHR (18.3%). Most patients in each data source had stage 3 CKD, ranging from 39.7% in CDM to 61.6% in PHARMO. Stage 5 CKD was not commonplace in any of the data sources.

Among clinical conditions associated with risk of CKD, hypertension was the most commonly diagnosed condition, ranging from 77.3% in PHARMO to 98.1% in DNHR (Table 22). Renovascular disease (ranging from 0.1% in PHARMO to 2.8% in J-CKD-DB-Ex) and polycystic kidney disease (ranging from < 0.1% in PHARMO to 0.8% in CDM) were not commonplace within this cohort. Conditions such as glomerulonephritis (20.1%) and autoimmune disease (31.2%) were more common in J-CKD-DB-Ex than in the other data sources.

Table 22: Baseline markers of kidney dysfunction severity for new users of sMRA, by data source

	DNHR (N = 12,689)	PHARMO (N = 2,691)	VID (N = 14,906)	J-CKD-DB-Ex (N = 1,769)	CDM (N = 71,716)
Duration of CKD at the index date (based on all available data)					
Mean (SD)	CCI				
Median					
1st, 99th percentiles					
CKD stage based on diagnosis only,[a] n (%)					
Stage 1: eGFR ≥ 90, normal or high	CCI				
Stage 2: eGFR 60-89, mildly decreased					
Stage 3: mildly to severely decreased					
Stage 3a: eGFR 45-59, mildly to moderately decreased					
Stage 3b: eGFR 30-44, moderately to severely decreased					
Stage 3 without specification of substage					
Stage 4: eGFR 15-29, severely decreased					
Stage 5: eGFR < 15 OR treated by dialysis; kidney failure					
Unspecified stage					
No diagnosis code in the year before the index date					
CKD stage based on eGFR only,[b] n (%)					
Stage 1: eGFR ≥ 90, normal or high	CCI				
Stage 2: eGFR 60-89, mildly decreased					

	DNHR (N = 12,689)	**PHARMO (N = 2,691)**	**VID (N = 14,906)**	**J-CKD-DB-Ex (N = 1,769)**	**CDM (N = 71,716)**
Stage 3: mildly to severely decreased	CCI [redacted]				
Stage 3a: eGFR 45-59, mildly to moderately decreased					
Stage 3b: eGFR 30-44, moderately to severely decreased					
Stage 3 without specification of substage					
Stage 4: eGFR 15-29, severely decreased					
Stage 5: eGFR < 15 OR treated by dialysis, kidney failure					
No assessment of eGFR in the year before the index date					
CKD stage based on eGFR[b] test result or diagnosis code,[a] n (%)					
Stage 1: eGFR ≥ 90, normal or high	CCI [redacted]				
Stage 2: eGFR 60-89, mildly decreased					
Stage 3: mildly to severely decreased					
Stage 3a: eGFR 45-59, mildly to moderately decreased					
Stage 3b: eGFR 30-44, moderately to severely decreased					
Stage 3 without specification of substage					
Stage 4: eGFR 15-29, severely decreased					
Stage 5: eGFR < 15 OR treated by dialysis, kidney failure					
Unspecified stage					
No assessment of GFR or diagnosis code any time before or on the index date					

	DNHR (N = 12,689)	**PHARMO (N = 2,691)**	**VID (N = 14,906)**	**J-CKD-DB-Ex (N = 1,769)**	**CDM (N = 71,716)**
CKD stage based on urine ACR,[b] n (%)					
A1: urine ACR < 30, normal to mildly increased	CCI				
A2: urine ACR 30-300, moderately increased (formerly 'microalbuminuria')					
A3: urine ACR > 300, severely increased (includes nephrotic syndrome, >~2,000)					
No assessment of urine ACR recorded in year before the index date					
"Any historical use" of drug classes (> 365 days before the index date)					
Drug classes used, n (%)					
SGLT2i and fixed-dose combinations	CCI				
GLP-1 RA and fixed-dose combinations					
sMRA					
ACEi or ARB					
Number of drug classes used, n (%)					
0	CCI				
1					
2					
3					
≥ 4					

	DNHR (N = 12,689)	**PHARMO (N = 2,691)**	**VID (N = 14,906)**	**J-CKD-DB-Ex (N = 1,769)**	**CDM (N = 71,716)**
"Any previous use" of drug classes (365-91 days before the index date)					
Drug classes used, n (%)					
SGLT2i and fixed-dose combinations	CCI				
GLP-1 RA and fixed-dose combinations					
ACEi or ARB					
Number of drug classes used, n (%)					
0	CCI				
1					
2					
3					
≥ 4					
"Any recent use" of drug classes (in the 90 days before the index date)					
Drug classes used, n (%)					
SGLT2i RA and fixed-dose combinations	CCI				
GLP-1 RA and fixed-dose combinations					
ACEi or ARB					
Number of drug classes used, n (%)					
0	CCI				
1					
2					
3					
≥ 4					

	DNHR (N = 12,689)	**PHARMO (N = 2,691)**	**VID (N = 14,906)**	**J-CKD-DB-Ex (N = 1,769)**	**CDM (N = 71,716)**
Clinical conditions associated with risk of CKD[b]					
Hypertension, n (%)	CCI				
Glomerulonephritis (all causes), n (%)					
Renovascular disease, n (%)					
Autoimmune disease, n (%)					
Polycystic kidney disease, n (%)					
Gout or hyperuricemiab, n (%)					
Hospitalizations for acute kidney injury in the previous year					
n (%)	CCI				
Mean (SD)					
Median					
1st, 99th percentiles					

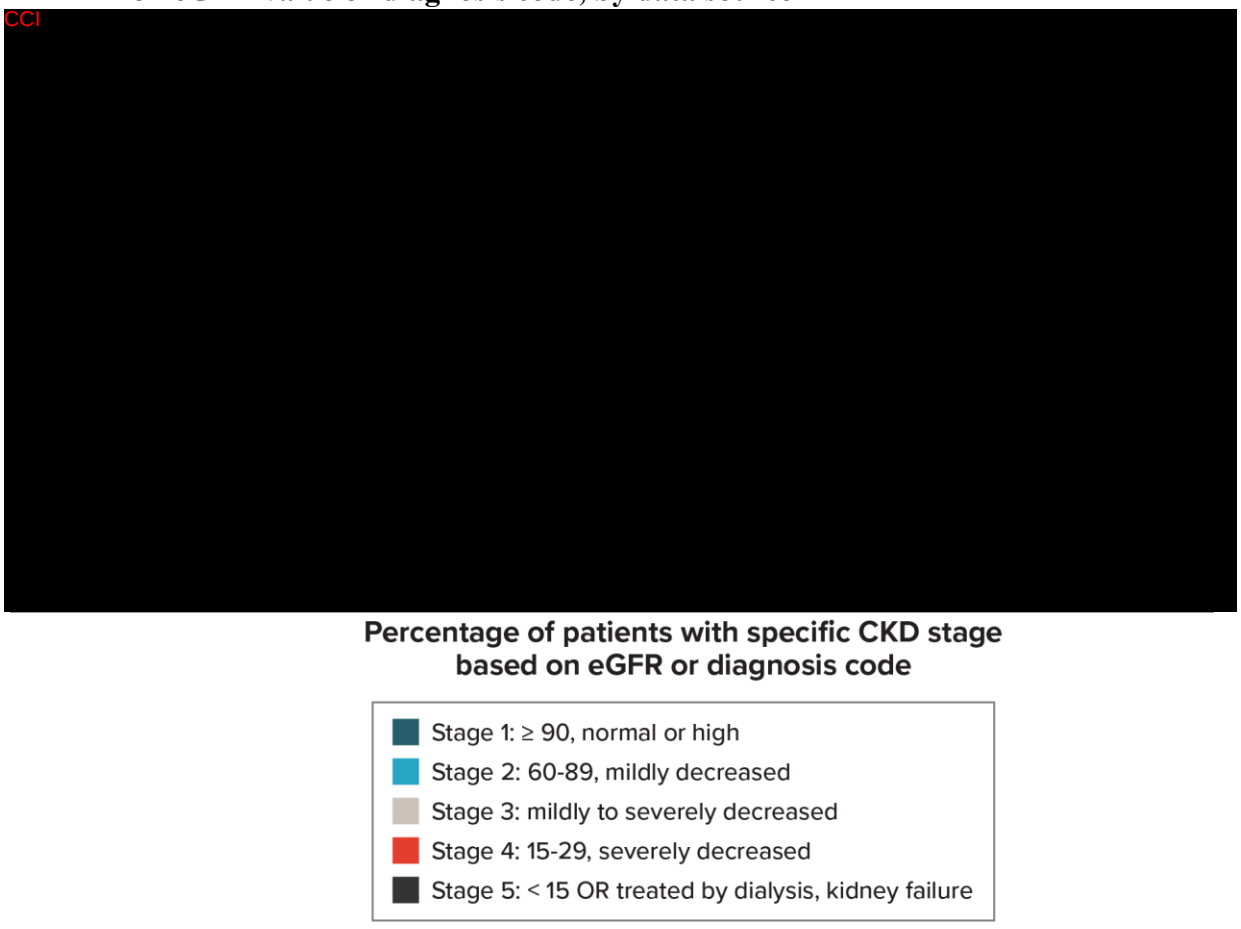
ACEi = angiotensin-converting enzyme inhibitors; ACR = albumin-to-creatinine ratio; ARB = angiotensin receptor blockers; CDM = Optum's de-identified Clinformatics® DataMart; CKD = chronic kidney disease; DNHR = Danish National Health Registers; eGFR = estimated glomerular filtration rate; GFR = glomerular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

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

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

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

Figure 12: CKD stage at the index date for new users of sMRA defined based on eGFR value or diagnosis code, by data source



CDM = Optum's de-identified Clinformatics® DataMart; CKD = chronic kidney disease; DNHR = Danish National Health Registers; eGFR = estimated glomerular filtration rate; J-CKD-DB-Ex = Japan Chronic Kidney Disease Database Extension; PHARMO = PHARMO Data Network; VID = Valencia Health System Integrated Database.

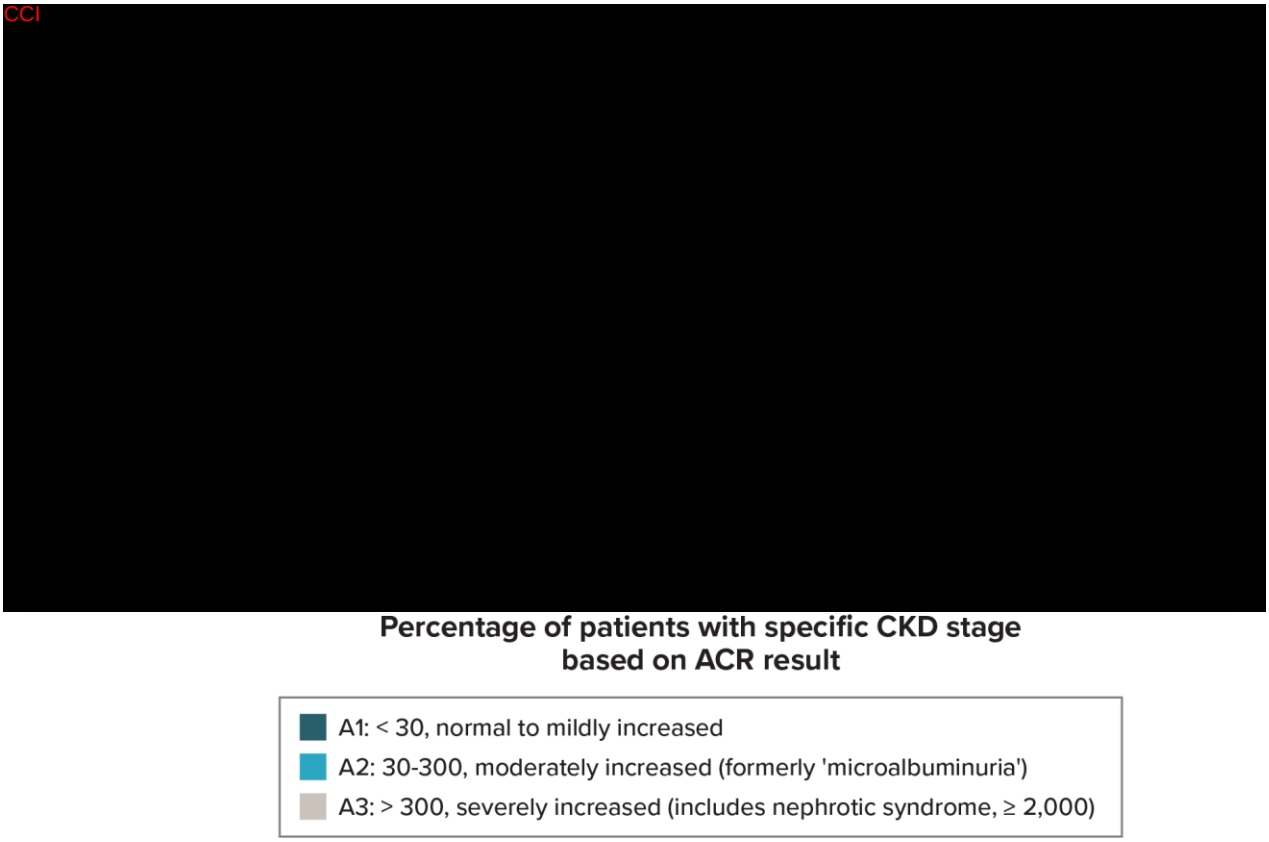
Note: All patients met the inclusion eligibility criteria for CKD, which was assessed through diagnosis codes, eGFR test results, or urine ACR test results.

Percentages were calculated amongst patients who have staging information available.

Across the data sources, 1.6% of patients in DNHR were missing eGFR values or diagnosis codes needed to assess CKD stage, 0.7% in PHARMO, 3.6% in VID, 0.3% in J-CKD-DB-Ex, and 22.3% in CDM. In VID, 6.2% of patients had a diagnostic code or eGFR result but it indicated an unspecified stage, and this occurred for 21.1% of patients in CDM.

Across all data sources, a large percentage of patients were missing ACR assessments in the year before the index date (Table 22). The percentage without an assessment was lowest in the European data sources, ranging from 33.3% in DNHR to 61.9% in PHARMO. Missing assessments were highest in CDM (83.3%) and J-CKD-DB-Ex (85.2%). In these data sources, the percentage of patients with each CKD stage was comparable. Amongst patients with ACR values in the year before the index date, in the DNHR, 46.0% of patients were classified as having CKD stage A2, followed by 28.4% with stage A1, and 25.5% with stage A3 (Figure 13). Similar results were observed in VID; however, in PHARMO, 63.8% of patients had stage A1, 32.7% had A2, and 3.5% had A3. However, the distribution of CKD staging based on ACR values should be interpreted with caution owing to the large number of patients without an assessment.

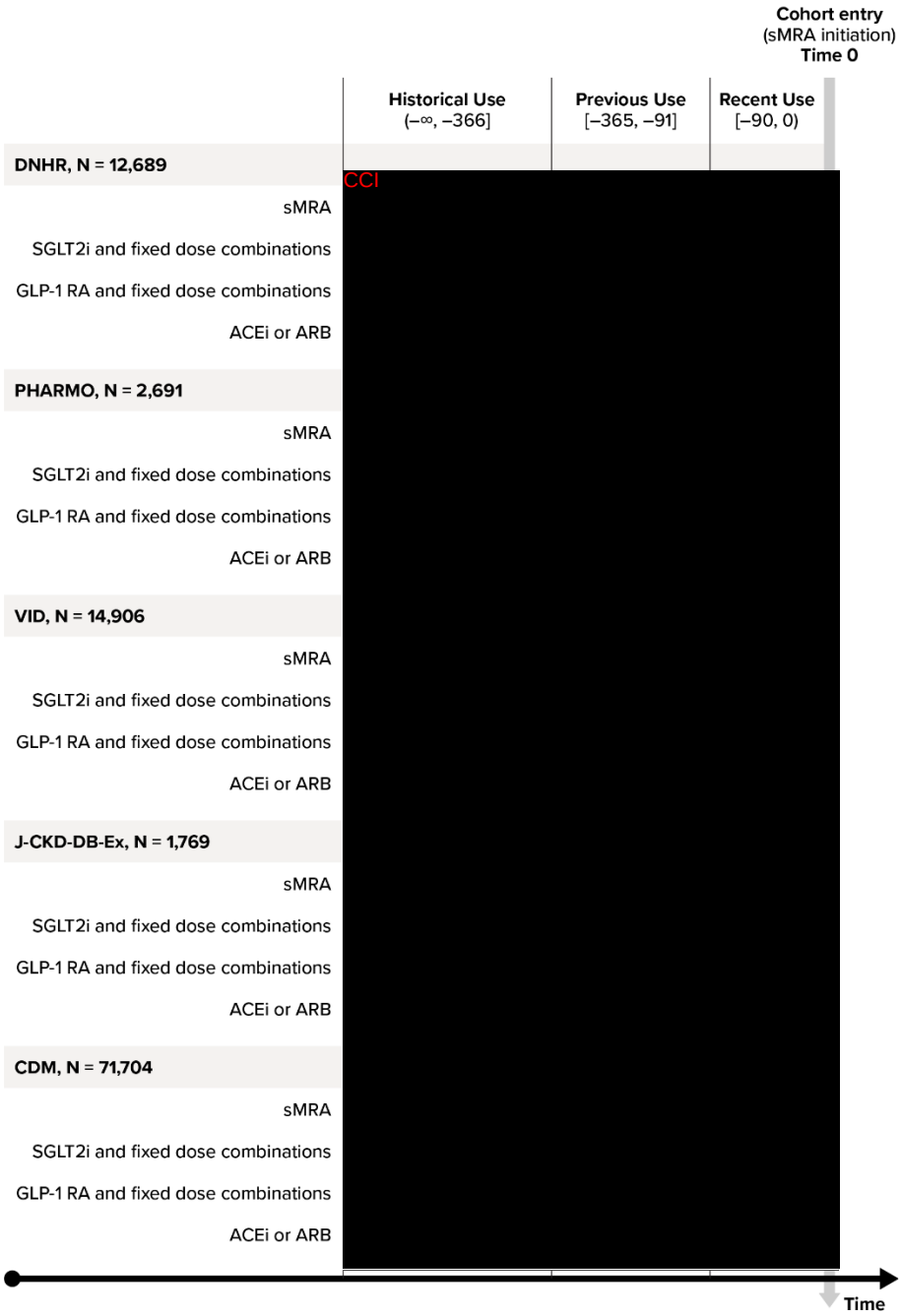
Figure 13: ACR categories at the index date, by data source among new users of sMRA



ACR = albumin-to-creatinine ratio; CDM = Optum's de-identified Clinformatics® DataMart; CKD = chronic kidney disease; DNHR = Danish National Health Registers; J-CKD-DB-Ex = Japan Chronic Kidney Disease Database Extension; PHARMO = PHARMO Data Network; VID = Valencia Health System Integrated Database.
Note: In CDM, ~60% of patients in the category of no assessment of ACR recorded before the index date had a recorded claim for an ACR test, but no results were available.
Percentages were calculated amongst patients who had an ACR value in the year before the index date.
No ACR assessment in the year before the index date was observed for 33.3% of patients in DNHR, 61.9% in PHARMO, 49.8% in VID, 85.2% in J-CKD-DB-Ex, and 83.3% in CDM.

Figure 14 displays the use of other medications of interest before sMRA initiation in the > 365 days before the index date (historical use), within the 91 to 365 days before the index date (previous use), and within the 90 days before the index date (recent use). Across all time periods and data sources, patients were taking at least one other drug class, with the most common being an ACEi or ARB.

Figure 14: Historical, previous, and recent use of medications of interest in relation to the index sMRA medication



ACEi = angiotensin-converting enzyme inhibitors; ARB = angiotensin receptor blocker; CDM = Optum's de-identified Clinformatics® DataMart; CKD = chronic kidney disease; DNHR = Danish National Health Registers; GLP-1 RA = glucagon-like peptide-1 receptor agonist; J-CKD-DB-Ex = Japan Chronic Kidney Disease Database Extension; PHARMO = PHARMO Data Network; SGLT2i = sodium-glucose cotransporter 2 inhibitors; sMRA = steroidal mineralocorticoid receptor antagonist; VID = Valencia Health System Integrated Database.

Note: By design, sMRA use could not occur from −365 days to the day before the index date; thus, no percentages were reported for these measures across any data source.

10.4.1.3.3 Baseline comorbidities and comedications

Table 23 displays the prevalence of select comorbidities in new users of sMRAs. Hypertension was the most commonly diagnosed cardiovascular risk factor (77.3% in PHARMO, 80.7% in J-CKD-DB-Ex, 95.9% in VID, 96.8% in CDM, and 98.1% in DNHR). Hypercholesterolemia was the second most commonly diagnosed risk factor in VID (70.2%) and CDM (85.4%), whereas congestive heart failure was the second most common risk factor in DNHR (38.0%), PHARMO (57.6%), and J-CKD-DB-Ex (76.8%). Coronary heart disease was the most commonly diagnosed macrovascular complication of diabetes, ranging from 42.8% of patients in VID to 62.5% of patients in J-CKD-DB-Ex. The percentage of patients with a cerebrovascular disease diagnosis was ~20% or less across all data sources, except for J-CKD-DB-Ex, where 45.6% of individuals had a diagnosis. Conversely, approximately 22% to 37% of patients had a diagnosis of peripheral vascular disease across all data sources, except for J-CKD-DB-Ex, where only 15% of individuals had a diagnosis.

Table 23: Baseline comorbidities in new users of sMRA, by data source

	DNHR (N = 12,689), N (%)	PHARMO (N = 2,691), N (%)	VID (N = 14,906), N (%)	J-CKD-DB-Ex (N = 1,769), N (%)	CDM (N = 71,716), N (%)
Macrovascular complications of diabetes					
CHD	CCI				
Cerebrovascular disease					
Peripheral vascular disease					
CVD risk factors					
Hypertension	CCI				
Hypercholesterolemia					
Congestive heart failure					
Severe liver disease					
HIV infection					
Dementia					
COPD					
Malignancy (other than kidney cancer and non-melanoma skin cancers)					

CDM = Optum's de-identified Clinformatics® DataMart; CHD = coronary heart disease; COPD = chronic obstructive pulmonary disease; CVD = cardiovascular disease; DNHR = Danish National Health Registers; HIV = human immunodeficiency virus; J-CKD-DB-Ex = Japan Chronic Kidney Disease Database Extension; PHARMO = PHARMO Data Network; VID = Valencia Health System Integrated Database.

Across all data sources, loop diuretics were the most commonly prescribed diuretic (Table 24). The percentage was similar in DNHR, J-CKD-DB-Ex, and CDM, at approximately 60%. Medication use was higher in PHARMO (73.8%) and VID (84.6%). Prescriptions for ACEi were comparable in DNHR (40.3%), PHARMO (46.2%), and CDM (35.5%) but lower in VID (29.7%) and J-CKD-DB-Ex (13.1%). Prescriptions for ARBs were similar in VID and CDM, at 58.1% and 51.5%, respectively, and similar but lower in DNHR, PHARMO, and J-CKD-DB-Ex (44.0%, 39.2%, and 32.1%, respectively). Statins were the most commonly prescribed cardiovascular medication across all data sources (> 64%), with the exception of J-CKD-DB-Ex, where calcium channel blockers were most commonly prescribed (41.7%) (Table 24). Use of other lipid-lowering medications ranged from 4.3% in DNHR to 12.4% in VID. Prescriptions for acetaminophen were common in DNHR (50.9%) and VID (50.4%), as were antibacterial agents in VID (57.9%).

Table 24: Medication use other than GLD recorded in the 180 days before or on the index date in new users of sMRA, by data source

	DNHR (N = 12,689), N (%)	PHARMO (N = 2,691), N (%)	VID (N = 14,906), N (%)	J-CKD-DB-Ex (N = 1,769), N (%)	CDM (N = 71,716), N (%)
Cardiovascular medications in the 180 days before or on the index date					
Thiazide-like diuretics	CCI [redacted]				
Loop diuretics					
Potassium-sparing diuretics					
ACEi					
ARB					
Beta blockers					
Direct renin inhibitors					
Angiotensin receptor-neprilysin inhibitors					
Calcium channel blockers					
Other antihypertensives					
Statins					
Anticoagulants					
Digoxin					
Nitrates and other vasodilators					
Aspirin and other antiplatelet agents					
Lipid-lowering drugs other than statins					

	DNHR (N = 12,689), N (%)	**PHARMO (N = 2,691), N (%)**	**VID (N = 14,906), N (%)**	**J-CKD-DB-Ex (N = 1,769), N (%)**	**CDM (N = 71,716), N (%)**
Other medications of interest					
Anti-inflammatory drugs (NSAIDs)	CCI [redacted]				
Acetaminophen					
Anticonvulsants					
Anti-infectives					
Antibacterial agents	CCI [redacted]				
Antifungal agents					
Antitubercular agents					
Chemotherapeutic agents					
Bronchodilators					

ACEi = angiotensin-converting enzyme inhibitors; ARB = angiotensin receptor blockers; CDM = Optum's de-identified Clinformatics® DataMart; DNHR = Danish National Health Registers; GLD = glucose-lowering drugs; J-CKD-DB-Ex = Japan Chronic Kidney Disease Database Extension; NSAID = non-steroidal anti-inflammatory drug; PHARMO = PHARMO Data Network; VID = Valencia Health System Integrated Database.

10.4.1.3.4 Characteristics of the index medication at baseline and during follow-up

The median duration of initial exposure episode after cohort entry was lowest in PHARMO (1.4 months) and J-CKD-DB-Ex (2.0 months) and highest in DNHR (9.7 months) (Table 25). Median duration of initial exposure episode in VID and CDM was 5.6 and 3.9 months, respectively. The median number of prescriptions or dispensings during the follow-up time ranged from three in DNHR and CDM to six in PHARMO. During follow-up, ACEi/ARB were the most common drug class started in all data sources (ranging from 40.0% in J-CKD-DB-Ex to 76.4% in DNHR), with the exception of CDM, where SGLT2i, GLP-1 RA, and ACEi/ARB were started by a similar percentage of patients (~4%). The percentage of patients with an interruption of current use lasting 90 days or more was similar in the European data sources (10.4% in DNHR, 14.5% in PHARMO, and 12.8% in VID) and higher in CDM (34.4%) and J-CKD-DB-Ex (51.3%). During follow-up, the median duration of total exposure to the index therapy was similar across data sources except J-CKD-DB-Ex, ranging from 7.2 to 11.9 months. In J-CKD-DB-Ex, the median duration was 2.5 months (Table 25).

Table 25: Characteristics of the index sMRA at baseline and during follow-up, by data source

	DNHR (N = 12,689), N (%)[a]	PHARMO (N = 2,691), N (%)[a]	VID (N = 14,906), N (%)[a]	J-CKD-DB-Ex (N = 1,769), N (%)[a]	CDM (N = 71,716), N (%)[a]
Classification of the index sMRA at the index date					
Monotherapy	CCI				
Combination therapy					
Add-on					
Switch					
Add-on and switch					
Indeterminate					
Index sMRA was an “add-on” to					
SGLT2i	CCI				
GLP-1 RA					
ACEi/ARB					
Index sMRA was a “switch” from					
SGLT2i	CCI				
GLP-1 RA					
ACEi/ARB					
Duration of initial exposure episode after cohort entry (months)					
Mean (SD)	CCI				
Median					
1st, 99th percentiles					

	DNHR (N = 12,689), N (%)[a]	**PHARMO (N = 2,691), N (%)[a]**	**VID (N = 14,906), N (%)[a]**	**J-CKD-DB-Ex (N = 1,769), N (%)[a]**	**CDM (N = 71,716), N (%)[a]**
Days' supply of index sMRA (days)					
Mean (SD)	CCI				
Median					
1st, 99th percentiles					
Number of prescriptions or dispensings during follow-up for the sMRA drug class					
Mean (SD)	CCI				
Median					
1st, 99th percentiles					
Number of distinct "current-use" periods (treatment episodes) during follow-up for the index sMRA drug class					
1	CCI				
2					
3					
4					
5+					
Number of distinct prescriptions or dispensings during follow-up for the index sMRA drug class					
Mean (SD)	CCI				
Median					
1st, 99th percentiles					
Number of discontinuations (interruptions) of current use during follow-up					
0	CCI				
1					

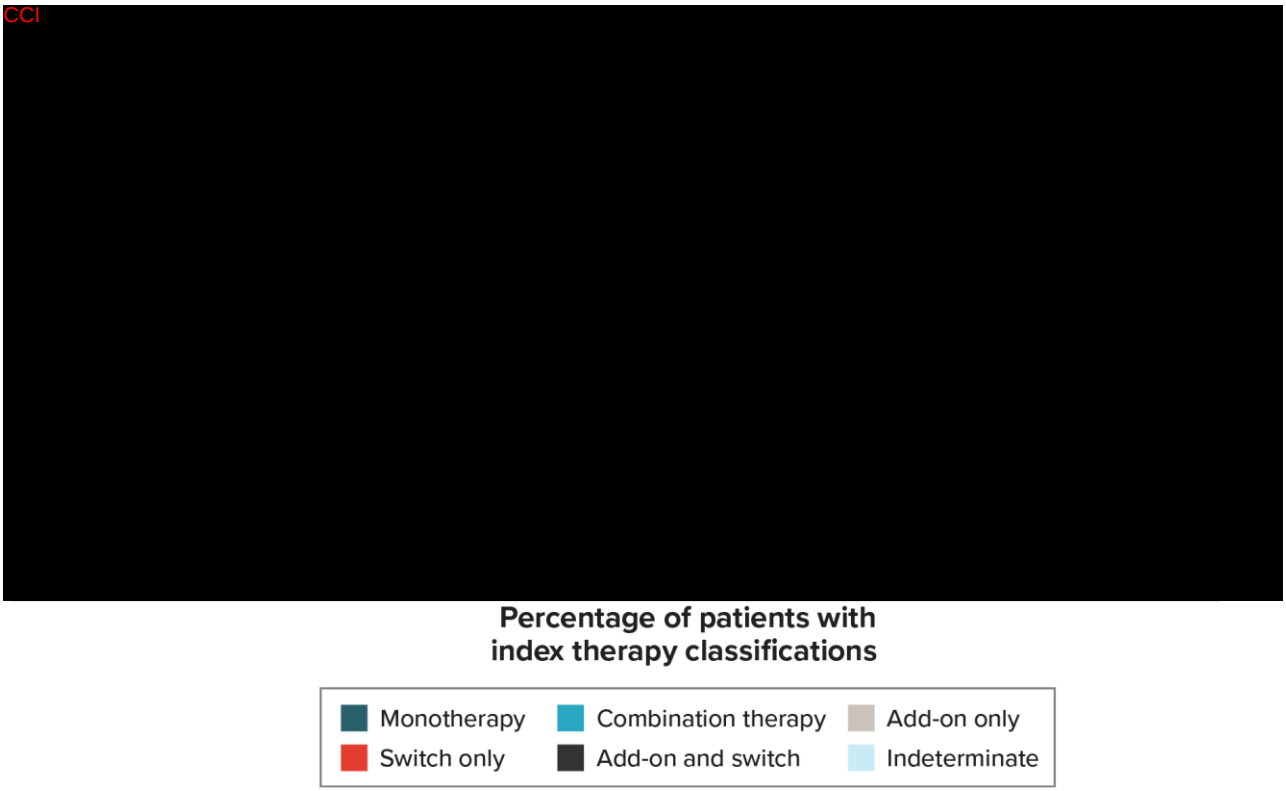
	DNHR (N = 12,689), N (%)[a]	PHARMO (N = 2,691), N (%)[a]	VID (N = 14,906), N (%)[a]	J-CKD-DB-Ex (N = 1,769), N (%)[a]	CDM (N = 71,716), N (%)[a]
2	CCI				
3					
4					
5+					
Number of patients with an interruption of current use lasting 90 days or more					
Duration of total exposure to index therapy (months)					
Mean (SD)	CCI				
Median					
1st, 99th percentile					
Other drug classes started during follow-up					
SGLT2i	CCI				
GLP-1 RA					
ACEi/ARB					
Duration of total follow-up (months)					
Mean (SD)	CCI				
Median					
1st, 99th percentiles					

ACEi = angiotensin-converting enzyme inhibitors; ARB = angiotensin receptor blockers; CDM = Optum's de-identified Clinformatics® DataMart; DNHR = Danish National Health Registers; GLP-1 RA = glucagon-like peptide-1 receptor agonist; J-CKD-DB-Ex = Japan Chronic Kidney Disease Database Extension; SD = standard deviation; SGLT2i = sodium-glucose cotransporter 2 inhibitors; sMRA = steroidal mineralocorticoid receptor antagonists; VID = Valencia Health System Integrated Database.

[a] Unless otherwise specified.

In DNHR, PHARMO, VID, and CDM, the index sMRA was most often prescribed as an add-on to other medications of interest, ranging from approximately 47% in CDM to 53% in PHARMO. In J-CKD-DB-Ex, only 2.9% of sMRA index prescriptions were add-ons to existing therapies, whereas the vast majority (95.4%) were monotherapies (Table 25; Figure 15). Where the index sMRA was an add-on to an existing therapy, it was most often added to an ACEi/ARB (e.g., DNHR, 48.8%; CDM, 52.5%). Information was not available regarding the reason for prescribing these drugs; therefore, no definitive conclusions can be reached regarding the indication that the medications were used for. Some of these therapies (ACEi/ARB) can also be used to treat hypertension, which was found to be the most prevalent comorbid condition (Table 23), as well as diabetes. It was uncommon for patients to have their index sMRA prescription be a switch from a different therapy (< 10% in all data sources, except for VID, where it was 13.4%). Where the index prescription was a switch from another therapy, it was most commonly an ACEi/ARB.

Figure 15: Classification of the index sMRA at the index date



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

10.4.1.3.5 Baseline characteristics stratified by ACR test

All baseline characteristics were stratified by the presence or absence of an ACR test recorded in the year before and including the date of index sMRA therapy. The results of select demographic variables, T2D and CKD severity, and comorbid conditions and medicines are presented in Annex 6, Table 42, stratified by ACR test status. No notable differences were observed among patients with and without an ACR test.

10.4.1.3.6 Treatment changes over time for sMRA during follow-up

The cross-sectional estimates of the cohort remaining under observation in each treatment state (current use or non-use) are reported by cohort at six prespecified subsequent timepoints (90 days, 180 days, 270 days, one year, two years, and three years) in Figure 16. Note that loss to follow-up and censoring are represented in the white space at the top of each diagram. The greatest increase in patients without current exposure occurred within the first 90 days of the index date in PHARMO, VID, J-CKD-DB-Ex, and CDM and was between 180 and 270 days in DNHR. These percentages represent a combination of patients who remained continuously on treatment up to the given timepoint and other patients who had discontinued and restarted the medications. The percentage of patients observed to be receiving treatment at the one-, two-, and three-year mark was similar in DNHR and PHARMO. In these data sources, the percentage of patients currently receiving sMRA therapy was 56% and 58%, respectively, at the one-year mark; 40% and 44%, respectively, at the two-year mark; and 30% and 36%, respectively, three years post-index date. The percentage was lower in VID and J-CKD-DB-Ex. Of those under observation at yearly timepoints during the study period, the lowest proportion of patients currently receiving GLP-1 RA treatment was observed in CDM (one year, 42%; two years, 26%; three years, 18%).

Figure 16: Treatment states at specific timepoints for sMRA initiators for each data source

DNHR

CCI

PHARMO

CCI

VID

CCI

J-CKD-DB-Ex

CCI

CDM

CCI

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

Notes: Sankey diagrams display the proportion of the population at each timepoint in each of the treatment states for each data source. The connecting bars between timepoints show the proportion of the population that moved from 1 state to a different state at the next timepoint. These figures display proportions of the population over time, and a patient may move between treatment states over time (e.g., begin as "treated," move to "untreated" at the next timepoint, then move back to "treated" at the next). If death occurred, the patient was placed in a separate category and remained in that state for each subsequent checkpoint. Note that death information was not available in J-CKD-DB-Ex.

The height of the bar at each timepoint displays the relative size of the cohort remaining under observation at each timepoint. Patients who were lost to follow-up are not included in the percentage calculations at each timepoint; thus, the percentages sum to 100% for each timepoint. The percentages describe the amount of patients still under observation at that timepoint.
The sum of the bars for each timepoint may not equal 100% due to rounding.

10.4.1.4 nsMRA (J-CKD-DB-Ex only)

10.4.1.4.1 Markers of severity of T2D at index date

The median duration of T2D diagnosis in J-CKD-DB-Ex was approximately seven years (Annex 6, Table 43). None of the 63 patients with a prescription for nsMRA had HbA_{1c} levels > 74.9 mmol/mol or > 9% (highest level). Most patients (76.2%) had HbA_{1c} levels ≤ 53 mmol/mol or ≤ 7%, followed by 7.9% of patients with HbA1c levels > 53 mmol/mol and ≤ 63.9 mmol/mol (> 7% and ≤ 9%). Approximately 21% of new initiators of nsMRA had insulin use in the six months before the initiation date, with most new users (58.7%) not using any other drug classes during this period. If nsMRA initiators were taking an additional drug class, it was mostly likely one other drug class (15.9%). The most common medications prescribed in the six months before and including the index date were DPP-4 and fixed-dose combinations (25.4%) and SGLT2i and fixed-dose combinations (23.8%). The median Diabetes Severity Complications Index score was 4.0, with the most prevalent diagnoses comprising the score consisting of cardiovascular (88.9%) and cerebrovascular diseases (47.6%) and nephropathy (39.7%).

10.4.1.4.2 Markers of kidney dysfunction severity at the index date

The median duration of CKD diagnosis was four years (Annex 6, Table 44). Data on eGFR and diagnosis codes were largely complete, with only one patient not having an eGFR assessment in the year before index date. When assessing CKD stage based on either eGFR result or diagnosis code, most individuals (66.1%) had stage 3 CKD and 27.4% had stage 2 CKD. Few individuals had stage 1, 4, or 5 CKD (< 5% for each of these stages).

Almost 90% of nsMRA initiators were missing ACR values. Amongst the eight individuals who did have an ACR values, 6.3% had stage A1 and a similar number had stage A2.

Annex 6, Table 44, notes the use of other medications of interest before nsMRA initiation in three distinct time periods (historical, previous, and recent). In the 91-365 days before the index date (previous use) and within the 90 days before the index date (recent use), patients were most commonly using only one drug class (54% and 52.4%, respectively). However, when medication use in the > 365 days before the index date (historical use) was considered, an equal percentage of patients were taking either one or two drug classes (34.9% each). Across each time period, ACEi and ARB were the most commonly prescribed drug classes, ranging from 58.7% (recent use) to 73.0% (historical use). Among clinical conditions associated with risk of CKD, the most common condition was hypertension (88.9%), followed by autoimmune disease (44.4%) and gout or hyperuricemia (34.9%).

10.4.1.4.3 Baseline comorbidities and comedications

Annex 6, Table 45, displays the prevalence of select comorbidities among nsMRA new users. In addition to hypertension, other common comorbidities were hypercholesterolemia (73.0%), congestive heart failure (CHF) (71.4%), and CHD (60.3%). Just under 30% of patients had a malignancy diagnosis (22.2%) and COPD (28.6%); other conditions examined occurred in less than 5% of new users.

The most common cardiovascular medications prescribed to new users in the 180 days before or on the index date were calcium channel blockers (61.9%) and ARBs (60.3%). Statins were prescribed for less than half (41.3%) of patients (Annex 6, Table 46). Amongst the diuretics examined, thiazide-like and loop diuretics were each prescribed to 14.3% of patients; no patients were prescribed potassium-sparing diuretics.

10.4.1.4.4 Characteristics of the index medication at baseline and during follow-up

The median duration of the initial nsMRA exposure episode and total exposure to nsMRA was approximately six months (Annex 6, Table 47), with a median of five distinct nsMRA prescriptions over the study period. Approximately 16% of new users had an interruption of current use lasting 90 days or more during follow-up. In relation to other medications of interest, the index nsMRA was most commonly prescribed as monotherapy (60.3%), and 31.7% started the nsMRA as an add-on to an existing therapy. When the nsMRA was started as an add-on to an existing therapy, it was most commonly an sMRA (25.4%) or an ACEi/ARB (20.6%). No new users switched from an existing therapy to an nsMRA. The total median duration of follow-up for patients in this study was 7.8 months; if patients started any additional drug classes over the course of follow-up, it was most commonly an ACEi/ARB (54.0%), followed by an SGLT2i (19.0%).

10.4.1.4.5 Baseline characteristics stratified by ACR test

Only eight of 63 new users of nsMRA (12.7%) had an ACR test before the index date. With this small number, stratification by baseline characteristics was not considered informative.

10.4.1.4.6 Treatment changes over time for nsMRA during follow-up

The cross-sectional estimates of the cohort remaining under observation at each treatment state (current use or non-use) at 90 days, 180 days, 270 days, one year, two years, and three years highlight that the greatest increase in patients no longer exposed to therapy (switch from exposed to unexposed) occurred within 90 days of initiating the therapy (100% at the index date to 86% at 90 days). The next greatest increase among new users not exposed to the drug occurred between 90 and 180 days (86% exposed vs. 79% exposed), after which the percentage stayed fairly consistent (data not shown).

10.4.2 Post-finerenone (CDM only)

10.4.2.1 SGLT2i

10.4.2.1.1 Markers of severity of T2D at index date

The percentage of patients with the highest HbA1c levels (> 74.9 mmol/mol or > 9%) was 8.6%, but approximately half of the patients in all cohorts in CDM did not have HbA1c results available (Table 26). The percentage of patients with HbA1c values > 53 mmol/mol (or > 7%) was 29.4%. The median duration of a T2D diagnosis was 5.1 years and was higher than in the pre-finerenone period (4.2).

Insulin use in the 180 days before and including the SGLT2i initiation date was recorded for 29.1% of patients (Table 26). The percentage of individuals with no use of GLD therapy other than insulin during this time was 28.7%. Most patients (> 50%) had used either one or two medications in a GLD class other than SGLT2i.

The most common medications for T2D prescribed or dispensed in the 180 days before and including the date of SGLT2i initiation were metformin and fixed-dose combinations

(46.4%), followed by sulfonylureas and fixed-dose combinations (28.0%), GLP-1 RA and fixed-dose combinations (16.7%), and DPP-4i and fixed-dose combinations (13.0%). Use of the other drugs was always below 10% (Table 26).

The median Diabetes Severity Complications Index score, computed as the sum of seven conditions or complications, was three. Of the conditions or complications comprising the severity index, CVD was the most commonly diagnosed condition (63.3%). Hyperkalaemia and amputation occurred in 10.5% and 2.3% of patients, respectively (Table 26).

Table 26: Markers of T2D severity at the index date in the post-finerenone period, by medication

	Finerenone (N = 3,591)	**SGLT2i (N = 94,080)**	**GLP-1 RA (N = 72,816)**	**Wide Finerenone (N = 5,201)**
Duration of T2D (years) at index date				
Mean (SD)	6.1 (4.2)	5.9 (4.1)	5.7 (4.1)	5.9 (4.2)
Median	5.3	5.1	4.8	5
1st, 99th percentile	1, 16	0, 16	0, 16	0, 16
Medications for T2D (hypoglycemic agents) ever prescribed from 180 days before and including the index date, n (%)				
GLP-1 RA and fixed-dose combinations	1,207 (33.6%)	15,754 (16.7%)	N/A	1,747 (33.6%)
SGLT2i and fixed-dose combinations	1,660 (46.2%)	N/A	17,010 (23.4%)	2,317 (44.5%)
Metformin and fixed-dose combinations	1,338 (37.3%)	43,614 (46.4%)	36,704 (50.4%)	2,010 (38.6%)
Sulfonylureas and fixed-dose combinations	778 (21.7%)	26,363 (28.0%)	21,080 (28.9%)	1,059 (20.4%)
Sulfonamides	NA	NA	NA	NA
Alpha-glucosidase inhibitors	19 (0.5%)	320 (0.3%)	260 (0.4%)	28 (0.5%)
Thiazolidinediones	299 (8.3%)	6,811 (7.2%)	5,895 (8.1%)	377 (7.2%)
DPP-4i and fixed-dose combinations	507 (14.1%)	12,276 (13.0%)	10,655 (14.6%)	684 (13.2%)
Meglitinides (including repaglinide, nateglinide, mitiglinide)	48 (1.3%)	969 (1.0%)	718 (1.0%)	67 (1.3%)
Imeglimin (Japan only)	N/A	N/A	N/A	N/A
Number of T2D drug classes ever used 180 days before and including the index date, n (%)				
No therapy	583 (16.2%)	27,036 (28.7%)	18,646 (25.6%)	985 (18.9%)
Monotherapy	1,154 (32.1%)	36,605 (38.9%)	26,831 (36.8%)	1,600 (30.8%)
Dual therapy	1,075 (29.9%)	22,837 (24.3%)	18,395 (25.3%)	1,486 (28.6%)
Triple therapy	598 (16.7%)	6,641 (7.1%)	7,237 (9.9%)	851 (16.4%)
Quadruple therapy or more	181 (5.0%)	961 (1.0%)	1,707 (2.3%)	279 (5.4%)

	Finerenone (N = 3,591)	**SGLT2i (N = 94,080)**	**GLP-1 RA (N = 72,816)**	**Wide Finerenone (N = 5,201)**
Insulin use recorded 180 days before and including the index date, n (%)	1,472 (41.0%)	27,369 (29.1%)	25,213 (34.6%)	2,157 (41.5%)
HbA1c, n (%)				
HbA1c ≤ 53 mmol/mol or ≤ 7%	1,094 (30.5%)	18,486 (19.6%)	12,512 (17.2%)	1,449 (27.9%)
HbA1c > 53 mmol/mol and ≤ 63.9 mmol/mol or > 7% and ≤ 8%	494 (13.8%)	11,972 (12.7%)	8,921 (12.3%)	641 (12.3%)
HbA1c > 63.9 mmol/mol and ≤ 74.9 mmol/mol or > 8% and ≤ 9%	212 (5.9%)	7,582 (8.1%)	6,850 (9.4%)	292 (5.6%)
HbA1c > 74.9 mmol/mol or > 9%	180 (5.0%)	8,079 (8.6%)	8,894 (12.2%)	252 (4.8%)
HbA1c missing	1,611 (44.9%)	47,961 (51.0%)	35,639 (48.9%)	2,567 (49.4%)
Other key diagnoses				
Hyperkalaemia, n (%)	336 (9.4%)	9,896 (10.5%)	5,554 (7.6%)	468 (9.0%)
Amputation, n (%)	68 (1.9%)	2,185 (2.3%)	1,679 (2.3%)	120 (2.3%)
The Diabetes Severity Complications Index				
Key diagnoses for scoring of index score				
Retinopathy, n (%)	1,169 (32.6%)	24,691 (26.2%)	18,301 (25.1%)	1,634 (31.4%)
Nephropathy, n (%)	2,095 (58.3%)	44,587 (47.4%)	30,148 (41.4%)	2,648 (50.9%)
Neuropathy, n (%)	1,567 (43.6%)	38,614 (41.0%)	31,302 (43.0%)	2,192 (42.1%)
Cerebrovascular, n (%)	546 (15.2%)	14,880 (15.8%)	9,210 (12.6%)	781 (15.0%)
Cardiovascular, n (%)	2,026 (56.4%)	59,596 (63.3%)	38,497 (52.9%)	2,860 (55.0%)
Peripheral vascular disease, n (%)	1,244 (34.6%)	32,330 (34.4%)	22,678 (31.1%)	1,717 (33.0%)
Metabolic complications, n (%)	197 (5.5%)	5,725 (6.1%)	4,434 (6.1%)	288 (5.5%)
Index score				

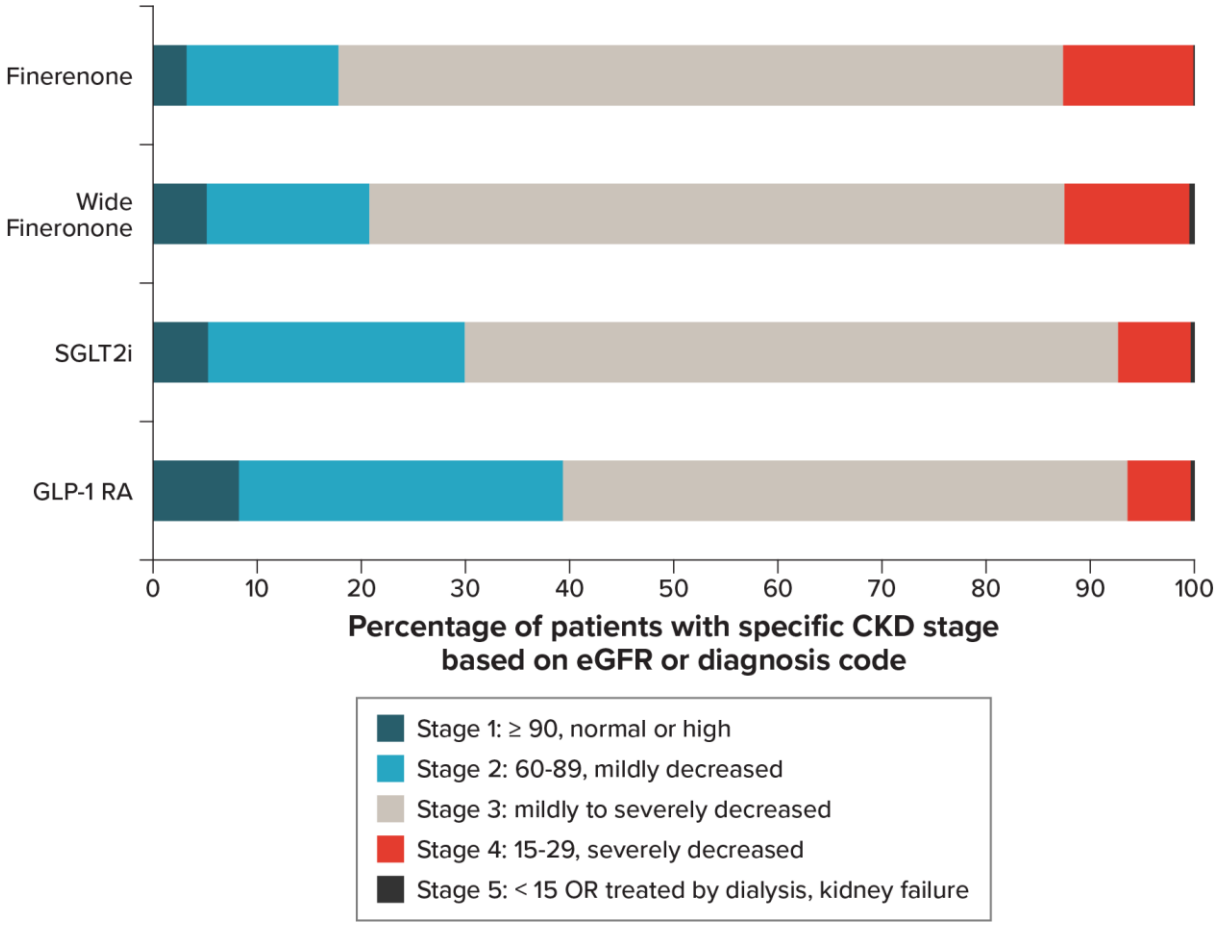
	Finerenone (N = 3,591)	**SGLT2i (N = 94,080)**	**GLP-1 RA (N = 72,816)**	**Wide Finerenone (N = 5,201)**
Mean (SD)	3.4 (2.2)	3.3 (2.2)	2.9 (2.2)	3.3 (2.3)
Median	3	3	3	3
1st, 99th percentile	0, 9	0, 9	0, 9	0, 9

ACR = urine albumin-creatinine ratio; DPP-4i = dipeptidyl peptidase-4 inhibitors; GLP-1 RA = glucagon-like peptide-1 receptor agonists; HbA1c = hemoglobin A1c (glycated hemoglobin); N/A = not applicable; NR = not reportable; SD = standard deviation; SGLT2i = sodium-glucose cotransporter 2 inhibitors; sMRA = steroidal mineralocorticoid receptor antagonists; T2D = type 2 diabetes

10.4.2.1.2 Markers of kidney dysfunction severity at index date

The median duration of CKD at the index date based on all available data on SGLT2i was four years (Table 27). The stage of CKD was captured mainly from eGFR laboratory values (36.6% of patients did not have an eGFR result in the year before the index date); diagnosis codes for CKD stage were not recorded in the year before the index date for 29.0% of patients. Based on CKD stage defined by eGFR result or diagnosis code, amongst patients with available staging information (Figure 17), the proportion of patients with stage 1 CKD at baseline was 5.3%; 24.6% for stage 2; 62.7% for stage 3; 6.9% for stage 4; and less than 0.5% for stage 5. For some patients, either the stage was unspecified or no diagnosis code or eGFR test was available during the year before the index date (17%).

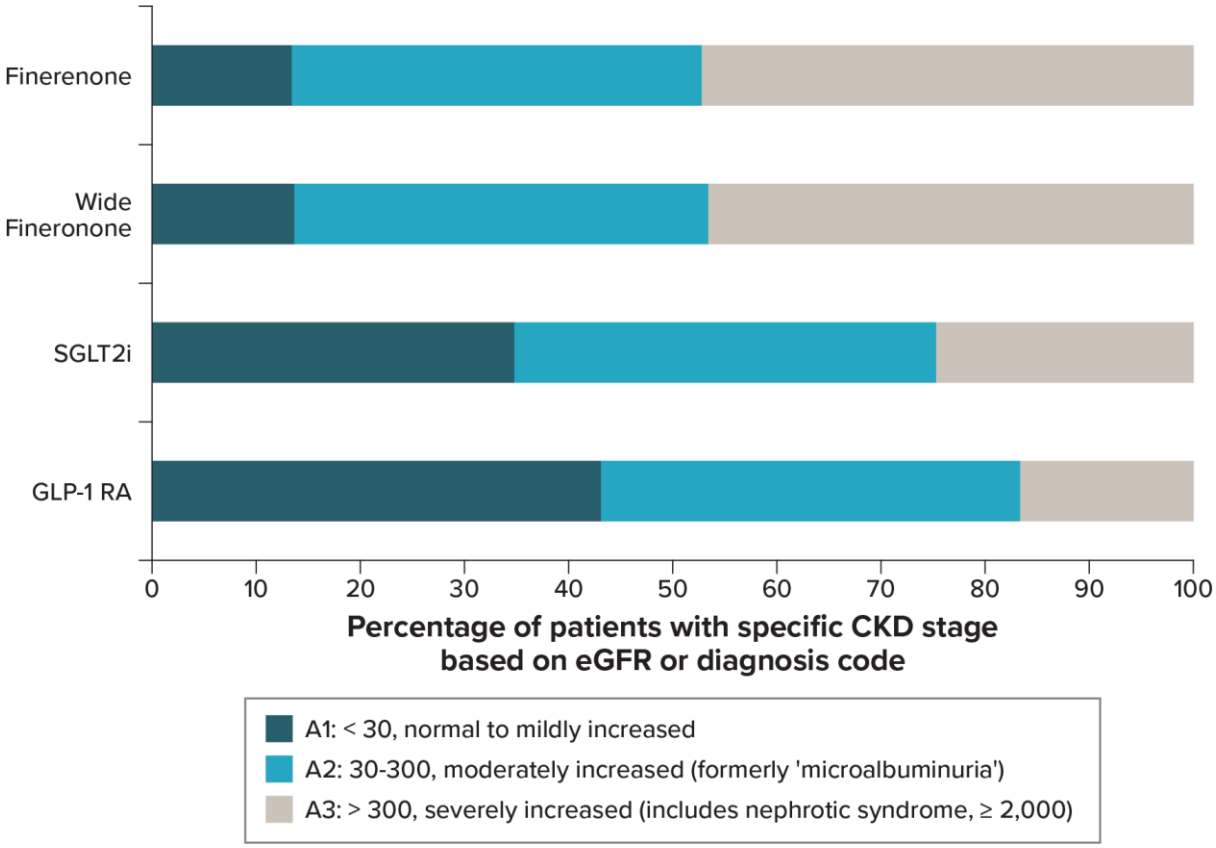
Figure 17: CKD stage at the index date defined based on eGFR value or diagnosis code, by medication



CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate.
Note: All patients met the inclusion eligibility criteria for CKD, which was assessed through diagnosis codes, eGFR test results, or urine ACR test results.
Percentages were calculated amongst patients who have staging information available.
Across the data sources, 3.3% of patients in the finerenone cohort were missing eGFR values or diagnosis codes needed to assess CKD stage, 9.0% in the wide finerenone cohort, 9.0% in the SGLT2i cohort, and 12.0% in the GLP-1 RA cohort. In the finerenone cohort, 6.8% of patients had a diagnostic code or eGFR value but it indicated an unspecified stage, whereas this occurred for 5.5%, 8.0%, and 6.9% of patients in the wide finerenone, SGLT2i, and GLP-1 RA cohorts, respectively.

A large percentage of patients in all medication cohorts had no ACR assessment recorded in the year before the index date (between 67.9% and 75.2%), so categorization based on ACR level may not be reliable (Figure 18).

Figure 18: ACR categories at the index date, by medication



ACR = albumin-to-creatinine ratio; CKD = chronic kidney disease.
Percentages were calculated amongst patients who had an ACR value in the year before the index date.
No ACR assessment in the year before the index was observed for 67.9% of patients in the finerenone cohort, 71.9% in the wide finerenone cohort, 75.1% in the SGLT2i cohort, and 75.2% in the GLP-1 RA cohort.

A high proportion of SGLT2i initiators had used other medication classes of interest (ACEi/ARB, sMRA, GLP-1 RA) before initiating an SGLT2i (Table 27). Historical or previous use (> 365 days or 365 to 91 days before the index date) of ACEi/ARB drugs was recorded for most patients (81.9% or more). Recent ACEi/ARB use (≤ 90 days before the index date) was recorded for 72.5% of patients. Historical or previous use of sMRA was observed in 24.9% of patients. Recent use was present in 9.5% of patients (Table 27).

Table 27: Baseline markers of severity for kidney dysfunction at the index date during the post-finerenone period, by medication

	Finerenone (N = 3,591)	**SGLT2i (N = 94,080)**	**GLP-1 RA (N = 72,816)**	**Wide Finerenone (N = 5,201)**
Duration of CKD at index date (based on all available data)				
Mean (SD)	5.0 (3.6)	4.8 (3.6)	4.6 (3.6)	4.8 (3.7)
Median	4.2	4	3.7	3.8
1st, 99th percentile	0, 15	0, 15	0, 15	0, 15
CKD stage based on diagnosis only,[a] n (%)				
Stage 1: ≥ 90, normal or high	47 (1.3%)	1,001 (1.1%)	887 (1.2%)	79 (1.5%)
Stage 2: 60-89, mildly decreased	352 (9.8%)	9,437 (10.0%)	8,371 (11.5%)	413 (7.9%)
Stage 3: mildly to severely decreased	2,033 (56.6%)	41,302 (43.9%)	25,894 (35.6%)	2,698 (51.9%)
Stage 3a: 45-59, mildly to moderately decreased	628 (17.5%)	13,744 (14.6%)	9,456 (13.0%)	840 (16.2%)
Stage 3b: 30-44, moderately to severely decreased	754 (21.0%)	11,207 (11.9%)	6,126 (8.4%)	978 (18.8%)
Stage 3 without specification of substage	651 (18.1%)	16,351 (17.4%)	10,312 (14.2%)	880 (16.9%)
Stage 4: 15-29, severely decreased	365 (10.2%)	4,810 (5.1%)	3,123 (4.3%)	474 (9.1%)
Stage 5: < 15 OR treated by dialysis, kidney failure	0 (0%)	0 (0%)	0 (0%)	20 (0.4%)
Unspecified stage	331 (9.2%)	10,282 (10.9%)	7,192 (9.9%)	392 (7.5%)
No diagnosis code in the year before index	463 (12.9%)	27,248 (29.0%)	27,349 (37.6%)	1,125 (21.6%)
CKD stage based on GFR only,[b] n (%)				
Stage 1: ≥ 90, normal or high	106 (3.0%)	4,259 (4.5%)	5,057 (6.9%)	223 (4.3%)
Stage 2: 60-89, mildly decreased	393 (10.9%)	16,985 (18.1%)	16,064 (22.1%)	618 (11.9%)

	Finerenone (N = 3,591)	**SGLT2i (N = 94,080)**	**GLP-1 RA (N = 72,816)**	**Wide Finerenone (N = 5,201)**
Stage 3: mildly to severely decreased	1,752 (48.8%)	34,138 (36.3%)	21,967 (30.2%)	2,144 (41.2%)
Stage 3a: 45-59, mildly to moderately decreased	813 (22.6%)	19,324 (20.5%)	13,801 (19.0%)	1,000 (19.2%)
Stage 3b: 30-44, moderately to severely decreased	939 (26.1%)	14,814 (15.7%)	8,166 (11.2%)	1,144 (22.0%)
Stage 3 without specification of substage	NA	NA	NA	NA
Stage 4: 15-29, severely decreased	332 (9.2%)	3,779 (4.0%)	2,377 (3.3%)	447 (8.6%)
Stage 5: < 15 OR treated by dialysis, kidney failure	14 (0.4%)	471 (0.5%)	370 (0.5%)	35 (0.7%)
No assessment of GFR in the year before index date	994 (27.7%)	34,448 (36.6%)	26,981 (37.1%)	1,734 (33.3%)
CKD stage based on GFR[a] or diagnosis code[b], n (%)				
Stage 1: ≥ 90, normal or high	105 (2.9%)	4,146 (4.4%)	4,919 (6.8%)	234 (4.5%)
Stage 2: 60-89, mildly decreased	472 (13.1%)	19,236 (20.4%)	18,324 (25.2%)	693 (13.3%)
Stage 3: mildly to severely decreased	2,242 (62.4%)	48,996 (52.1%)	32,005 (44.0%)	2,964 (57.0%)
Stage 3a: 45-59, mildly to moderately decreased	823 (22.9%)	21,545 (22.9%)	15,938 (21.9%)	1,086 (20.9%)
Stage 3b: 30-44, moderately to severely decreased	927 (25.8%)	15,999 (17.0%)	8,964 (12.3%)	1,201 (23.1%)
Stage 3 without specification of substage	492 (13.7%)	11,452 (12.2%)	7,103 (9.8%)	677 (13.0%)
Stage 4: 15-29, severely decreased	401 (11.2%)	5,391 (5.7%)	3,514 (4.8%)	533 (10.2%)
Stage 5: < 15 OR treated by dialysis, kidney failure	7 (0.2%)	346 (0.4%)	282 (0.4%)	26 (0.5%)
Unspecified stage	244 (6.8%)	7,487 (8.0%)	5,038 (6.9%)	284 (5.5%)
No assessment of GFR or diagnosis code in the year before index date	120 (3.3%)	8,478 (9.0%)	8,734 (12.0%)	467 (9.0%)

	Finerenone (N = 3,591)	**SGLT2i (N = 94,080)**	**GLP-1 RA (N = 72,816)**	**Wide Finerenone (N = 5,201)**
CKD stage based on ACR[a], n (%)				
A1: < 30, normal to mildly increased	155 (4.3%)	8,141 (8.7%)	7,790 (10.7%)	200 (3.8%)
A2: 30-300, moderately increased (formerly 'microalbuminuria')	455 (12.7%)	9,473 (10.1%)	7,250 (10.0%)	582 (11.2%)
A3: > 300, severely increased (includes nephrotic syndrome, > ~ 2,000)	544 (15.1%)	5,773 (6.1%)	3,003 (4.1%)	682 (13.1%)
No assessment of ACR recorded in year before index date	2,437 (67.9%)	70,693 (75.1%)	54,773 (75.2%)	3,737 (71.9%)
'Any historical use' of drug classes				
Drug classes used, n (%)				
Finerenone	3 (0.1%)	38 (< 0.1%)	30 (< 0.1%)	7 (0.1%)
SGLT2i and fixed-dose combinations	1,299 (36.2%)	10,532 (11.2%)	16,703 (22.9%)	1,800 (34.6%)
GLP-1 RA and fixed-dose combinations	1,253 (34.9%)	19,360 (20.6%)	14,186 (19.5%)	1,753 (33.7%)
sMRA	432 (12.0%)	13,139 (14.0%)	8,190 (11.2%)	586 (11.3%)
nsMRA	N/A	N/A	N/A	N/A
ACEi or ARB	3,311 (92.2%)	83,940 (89.2%)	63,418 (87.1%)	4,703 (90.4%)
Number of drug classes used, n (%)				
0	179 (5.0%)	7,740 (8.2%)	6,866 (9.4%)	342 (6.6%)
1	1,427 (39.7%)	53,513 (56.9%)	37,334 (51.3%)	2,093 (40.2%)
2	1,183 (32.9%)	25,646 (27.3%)	21,317 (29.3%)	1,671 (32.1%)
3	703 (19.6%)	6,521 (6.9%)	6,639 (9.1%)	966 (18.6%)
4	99 (2.8%)	659 (0.7%)	658 (0.9%)	129 (2.5%)
> 4	0 (0%)	1 (< 0.1%)	2 (< 0.1%)	0 (0%)

	Finerenone (N = 3,591)	**SGLT2i (N = 94,080)**	**GLP-1 RA (N = 72,816)**	**Wide Finerenone (N = 5,201)**
'Any previous use' of drug classes				
Drug classes used, n (%)				
Finerenone	N/A	209 (0.2%)	166 (0.2%)	N/A
SGLT2i and fixed-dose combinations	1,582 (44.1%)	N/A	16,391 (22.5%)	2,202 (42.3%)
GLP-1 RA and fixed-dose combinations	1,180 (32.9%)	16,204 (17.2%)	N/A	1,689 (32.5%)
sMRA	273 (7.6%)	10,233 (10.9%)	6,133 (8.4%)	361 (6.9%)
nsMRA	N/A	N/A	N/A	N/A
ACEi or ARB	3,151 (87.7%)	77,009 (81.9%)	58,037 (79.7%)	4,532 (87.1%)
Number of drug classes used, n (%)				
0	199 (5.5%)	13,029 (13.8%)	11,359 (15.6%)	342 (6.6%)
1	1,346 (37.5%)	59,893 (63.7%)	43,754 (60.1%)	1,994 (38.3%)
2	1,341 (37.3%)	19,715 (21.0%)	16,146 (22.2%)	1,867 (35.9%)
3	662 (18.4%)	1,440 (1.5%)	1,547 (2.1%)	936 (18.0%)
4	43 (1.2%)	3 (< 0.1%)	10 (< 0.1%)	62 (1.2%)
> 4	0 (0%)	0 (0%)	0 (0%)	0 (0%)

	Finerenone (N = 3,591)	**SGLT2i (N = 94,080)**	**GLP-1 RA (N = 72,816)**	**Wide Finerenone (N = 5,201)**
'Any recent use' of drug classes				
Drug classes used, n (%)				
Finerenone	N/A	224 (0.2%)	199 (0.3%)	N/A
SGLT2i and fixed-dose combinations	1,487 (41.4%)	N/A	14,492 (19.9%)	2,083 (40.0%)
GLP-1 RA and fixed-dose combinations	1,083 (30.2%)	13,228 (14.1%)	N/A	1,571 (30.2%)
sMRA	169 (4.7%)	8,966 (9.5%)	4,991 (6.9%)	235 (4.5%)
nsMRA	N/A	N/A	N/A	N/A
ACEi or ARB	2,873 (80.0%)	68,229 (72.5%)	51,831 (71.2%)	4,151 (79.8%)
Number of drug classes used, n (%)				
0	335 (9.3%)	20,387 (21.7%)	16,397 (22.5%)	521 (10.0%)
1	1,466 (40.8%)	57,618 (61.2%)	42,378 (58.2%)	2,140 (41.1%)
2	1,245 (34.7%)	15,198 (16.2%)	12,990 (17.8%)	1,754 (33.7%)
3	524 (14.6%)	875 (0.9%)	1,049 (1.4%)	752 (14.5%)
4	21 (0.6%)	2 (< 0.1%)	2 (< 0.1%)	34 (0.7%)
> 4	0 (0%)	0 (0%)	0 (0%)	0 (0%)

	Finerenone (N = 3,591)	**SGLT2i (N = 94,080)**	**GLP-1 RA (N = 72,816)**	**Wide Finerenone (N = 5,201)**
Clinical conditions associated with risk of CKD				
Hypertension, n (%)	3,473 (96.7%)	89,006 (94.6%)	67,617 (92.9%)	4,990 (95.9%)
Glomerulonephritis (all causes), n (%)	83 (2.3%)	878 (0.9%)	452 (0.6%)	138 (2.7%)
Renovascular disease, n (%)	55 (1.5%)	1,286 (1.4%)	712 (1.0%)	79 (1.5%)
Autoimmune disease, n (%)	233 (6.5%)	5,334 (5.7%)	4,687 (6.4%)	336 (6.5%)
Polycystic kidney disease, n (%)	10 (0.3%)	318 (0.3%)	223 (0.3%)	17 (0.3%)
Gout or hyperuricemia, n (%)	623 (17.3%)	12,465 (13.2%)	7,780 (10.7%)	869 (16.7%)
Hospitalizations for acute kidney injury in the previous year				
n (%)	42 (1.2%)	1,488 (1.6%)	861 (1.2%)	65 (1.2%)
Mean (SD)	1.0 (0.2)	1.1 (0.3)	1.1 (0.3)	1.1 (0.2)
Median	1	1	1	1
1st, 99th percentile	1, 2	1, 2	1, 2	1, 2

ACEi = angiotensin-converting enzyme inhibitors; ACR = urine albumin-to-creatinine ratio; ARB = angiotensin receptor blockers; CKD = chronic kidney disease; GFR = glomerular filtration rate; GLP-1 RA = glucagon-like peptide-1 receptor agonists; NA = not available; N/A = not applicable; SD = standard deviation; SGLT2i = sodium-glucose cotransporter 2 inhibitors; sMRA = steroidal mineralocorticoid receptor antagonists.

Note: Recent use: defined 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 the index date (study days [−∞,−366]).

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

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

Of the clinical conditions known to be associated with an increased risk of CKD and assessed at any time before or on the index date, hypertension was the most common (94.6%) among SGLT2i initiators. Glomerulonephritis, renovascular disease, and autoimmune disease were not common (less than 6% in all instances). Gout or hyperuricemia in the year before or on the index date was recorded for 13.2% of patients (Table 27).

10.4.2.1.3 Baseline comorbidities and comedications

Other than hypertension, hypercholesterolemia was the most common baseline comorbidity among SGLT2i initiators, recorded for approximately 88.9% of patients (Table 28). Coronary heart disease was the most frequent macrovascular complication (43.8%), followed by peripheral vascular disease (34.6%) and cerebrovascular disease (15.8%). Congestive heart failure (35.9%) and chronic obstructive pulmonary disease (21.5%) were also common. The prevalence of hyperkalaemia was 10.5%. Other comorbidities were less common.

Table 28: Baseline comorbidities in new users of medications in the pre-finerenone period, by medication

	Finerenone (N = 3,591)	**SGLT2i (N = 94,080)**	**GLP-1 RA (N = 72,816)**	**Wide Finerenone (N = 5,201)**
Macrovascular complications				
Coronary heart disease, n (%)	1,330 (37.0%)	41,248 (43.8%)	24,513 (33.7%)	1,896 (36.5%)
Cerebrovascular disease, n (%)	546 (15.2%)	14,880 (15.8%)	9,210 (12.6%)	781 (15.0%)
Peripheral vascular disease, n (%)	1,246 (34.7%)	32,551 (34.6%)	22,714 (31.2%)	1,723 (33.1%)
Cardiovascular risk factors				
Hypertension, n (%)	3,473 (96.7%)	89,006 (94.6%)	67,617 (92.9%)	4,990 (95.9%)
Hypercholesterolemia, n (%)	3,272 (91.1%)	83,606 (88.9%)	63,825 (87.7%)	4,688 (90.1%)
Congestive heart failure, n (%)	907 (25.3%)	33,790 (35.9%)	16,772 (23.0%)	1,255 (24.1%)
Severe liver disease, n (%)	19 (0.5%)	961 (1.0%)	665 (0.9%)	31 (0.6%)
HIV infection, n (%)	20 (0.6%)	486 (0.5%)	396 (0.5%)	27 (0.5%)
Dementia, n (%)	139 (3.9%)	4,889 (5.2%)	2,909 (4.0%)	191 (3.7%)
Chronic obstructive pulmonary disease, n (%)	666 (18.5%)	20,211 (21.5%)	14,037 (19.3%)	947 (18.2%)
Malignancy (other than kidney cancer and non-melanoma skin cancers), n (%)	521 (14.5%)	14,657 (15.6%)	9,563 (13.1%)	807 (15.5%)

ACR = urine albumin-creatinine ratio; GLP-1 RA = glucagon-like peptide-1 receptor agonists; HIV = human immunodeficiency virus; SGLT2i = sodium-glucose cotransporter 2 inhibitors; sMRA = steroidal mineralocorticoid receptor antagonists.

Medications other than GLDs recorded in the 180 days before or on the index date are shown in Table 29. Angiotensin receptor blocker medications (59%) and statins (80.1%) were the most commonly used medications in SGLT2i, followed by beta blockers (58.3%). Regarding use of diuretics, loop diuretics (32.7%) were more frequently recorded than thiazide-like diuretics (27.6%), which was in contrast to the pre-finerenone period where use of thiazide-like diuretics (32.8%) was more common than use of loop diuretics (25.5%). The use of potassium-sparing diuretics was uncommon (1.6%). Angiotensin-converting enzyme inhibitors and calcium channel blockers were used by 33.1% and 37.7% of patients, respectively. Anticoagulants were used in 18.7% of SGLT2i new users. Aspirin and other antiplatelet drugs were used in 15.3% of SGLT2i new users. Of other medications of interest, bronchodilators (17.7%) and antibacterial agents (24.7%) were the most used.

Table 29: Medication use other than GLD recorded in the 180 days before or on the index date in the pre-finerenone period, by medication

	Finerenone (N = 3,591)	**SGLT2i (N = 94,080)**	**GLP-1 RA (N = 72,816)**	**Wide Finerenone (N = 5,201)**
Cardiovascular medications				
Thiazide-like diuretics, n (%)	1,025 (28.5%)	26,012 (27.6%)	22,236 (30.5%)	1,498 (28.8%)
Loop diuretics, n (%)	991 (27.6%)	30,757 (32.7%)	18,163 (24.9%)	1,390 (26.7%)
Potassium-sparing diuretics, n (%)	51 (1.4%)	1,534 (1.6%)	1,514 (2.1%)	74 (1.4%)
ACE inhibitors, n (%)	1,039 (28.9%)	31,159 (33.1%)	24,253 (33.3%)	1,584 (30.5%)
ARB, n (%)	2,504 (69.7%)	55,551 (59.0%)	40,225 (55.2%)	3,533 (67.9%)
Beta blockers, n (%)	2,142 (59.6%)	54,843 (58.3%)	36,771 (50.5%)	2,977 (57.2%)
Direct renin inhibitors, n (%)	8 (0.2%)	23 (< 0.1%)	15 (< 0.1%)	10 (0.2%)
Angiotensin receptor-neprilysin inhibitors, n (%)	99 (2.8%)	5,039 (5.4%)	1,567 (2.2%)	142 (2.7%)
Calcium channel blockers, n (%)	1,721 (47.9%)	35,476 (37.7%)	24,937 (34.2%)	2,411 (46.4%)
Other antihypertensives, n (%)	399 (11.1%)	6,574 (7.0%)	4,500 (6.2%)	536 (10.3%)
Statins, n (%)	3,034 (84.5%)	75,405 (80.1%)	56,981 (78.3%)	4,308 (82.8%)
Anticoagulants, n (%)	530 (14.8%)	17,606 (18.7%)	9,594 (13.2%)	750 (14.4%)
Digoxin, n (%)	32 (0.9%)	1,679 (1.8%)	644 (0.9%)	44 (0.8%)
Nitrates and other vasodilators, n (%)	520 (14.5%)	11,103 (11.8%)	6,312 (8.7%)	708 (13.6%)
Aspirin and other antiplatelet agents, n (%)	552 (15.4%)	14,431 (15.3%)	8,949 (12.3%)	747 (14.4%)
Lipid-lowering drugs other than statins, n (%)	837 (23.3%)	14,374 (15.3%)	11,588 (15.9%)	1,176 (22.6%)

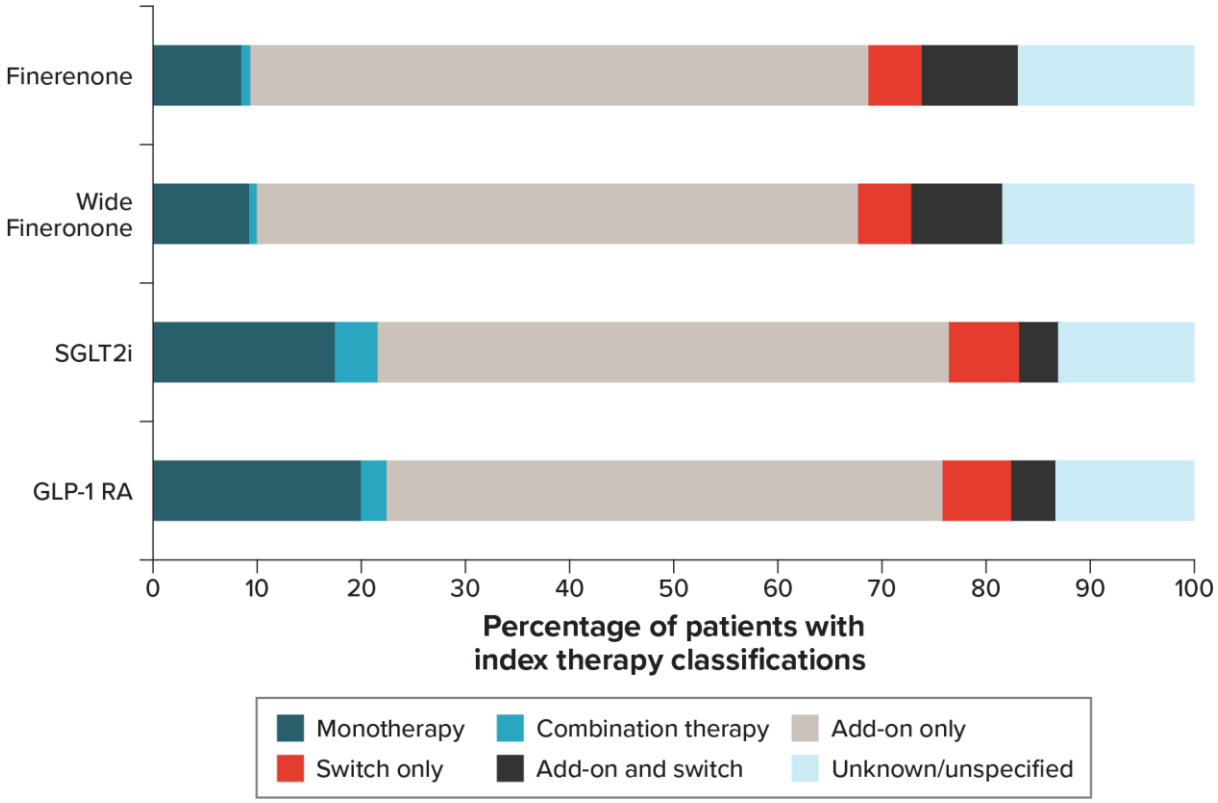
	Finerenone (N = 3,591)	**SGLT2i (N = 94,080)**	**GLP-1 RA (N = 72,816)**	**Wide Finerenone (N = 5,201)**
Other medications of interest				
Anti-inflammatory drugs (NSAIDs), n (%)	564 (15.7%)	14,077 (15.0%)	13,834 (19.0%)	849 (16.3%)
Acetaminophen, n (%)	532 (14.8%)	13,385 (14.2%)	12,244 (16.8%)	788 (15.2%)
Anticonvulsants, n (%)	118 (3.3%)	3,180 (3.4%)	3,228 (4.4%)	185 (3.6%)
Anti-infectives				
Antibacterial agents, n (%)	997 (27.8%)	23,244 (24.7%)	20,062 (27.6%)	1,464 (28.1%)
Antifungal agents, n (%)	268 (7.5%)	4,659 (5.0%)	5,684 (7.8%)	398 (7.7%)
Antitubercular agents, n (%)	2 (0.1%)	61 (0.1%)	44 (0.1%)	3 (0.1%)
Chemotherapeutic agents, n (%)	87 (2.4%)	2,689 (2.9%)	2,117 (2.9%)	139 (2.7%)
Bronchodilators, n (%)	604 (16.8%)	16,621 (17.7%)	13,476 (18.5%)	878 (16.9%)

ACE = angiotensin-converting enzymes; ARB = angiotensin receptor blockers; GLD = glucose-lowering drugs; GLP-1 RA = glucagon-like peptide-1 receptor agonists; NSAID = non-steroidal anti-inflammatory drug; SGLT2i = sodium-glucose cotransporter 2 inhibitors; sMRA = steroidal mineralocorticoid receptor antagonists.

10.4.2.1.4 Characteristics of the index medication at baseline and during follow-up

At the index date, SGLT2i was most commonly prescribed as an "add-on therapy" to another medication of interest (54.9%) (Table 30, Figure 19). Note that because medication indication was not available in the study data, we could not tell whether the intent of prescribing these medications was to modify CKD. However, during the post-finerenone period (after 2021), SGLT2i were indicated for CKD. When SGLT2i was used as "add-on" therapy, it was most often added to an ACEi or ARB (54.0%). Addition to a GLP-1 RA medication occurred in 9.0% of patients. When the SGLT2i met the study definition of a "switch" from a prior medication of interest, the prior therapy most often reported was an ACEi or ARB (6.7%).

Figure 19: Classification of index therapy in each medication cohort



Notes: Monotherapy = index medication initiated as the only CKD-protective drug; combination therapy = simultaneous initiation of index medication together with another CKD-protective drug; add-on therapy = addition of index medication to an existing CKD-protective drug; switch only = an existing CKD-protective drug is replaced by index medication; add-on and switch = both add-on and switched-to index medication at the same time.

The median duration of the initial SGLT2i exposure episode was 4.3 months (Table 30). The median days' supply of the index SGLT2i was 30 days. The median duration of total follow-up was 8.8 months. During follow-up, the median number of SGLT2i prescriptions filled was four. Most patients (70.7%) had only one distinct current-use period during follow-up. Interruption of current use lasting 90 days or more—a proxy for discontinuation—was reported in 18.3% of patients. The median total duration of SGLT2i therapy was 7.8 months. Of the other drug classes started during follow-up, GLP-1 RA were the most commonly started (8.7%).

Table 30: Classification of the index medication at the index date, by medication

	Finerenone (N = 3,591)	**SGLT2i (N = 94,080)**	**GLP-1 RA (N = 72,816)**	**Wide Finerenone (N = 5,201)**
Classification of index therapy at the index date, n (%)[a]				
Monotherapy	307 (8.5%)	16,483 (17.5%)	14,571 (20.0%)	479 (9.2%)
Combination therapy	28 (0.8%)	3,904 (4.1%)	1,826 (2.5%)	42 (0.8%)
Add-on	2,133 (59.4%)	51,623 (54.9%)	38,882 (53.4%)	3,003 (57.7%)
Switch	187 (5.2%)	6,321 (6.7%)	4,810 (6.6%)	264 (5.1%)
Add-on and switch	329 (9.2%)	3,585 (3.8%)	3,034 (4.2%)	456 (8.8%)
Indeterminate	607 (16.9%)	12,164 (12.9%)	9,693 (13.3%)	957 (18.4%)
Index drug was an ‘add-on’ to…, n (%)				
Finerenone	N/A	104 (0.1%)	105 (0.1%)	N/A
SGLT2i	1,007 (28.0%)	N/A	8,826 (12.1%)	1,357 (26.1%)
GLP-1 RA	757 (21.1%)	8,478 (9.0%)	N/A	1,061 (20.4%)
sMRA	66 (1.8%)	5,770 (6.1%)	3,276 (4.5%)	94 (1.8%)
nsMRA (Japan only)	N/A	N/A	N/A	N/A
ACEi/ARB	2,100 (58.5%)	50,777 (54.0%)	38,374 (52.7%)	2,971 (57.1%)
Index drug was a ‘switch’ to…, n (%)				
Finerenone	N/A	53 (0.1%)	39 (0.1%)	N/A
SGLT2i	174 (4.8%)	N/A	2,980 (4.1%)	251 (4.8%)
GLP-1 RA	103 (2.9%)	2,470 (2.6%)	N/A	153 (2.9%)
sMRA	76 (2.1%)	1,665 (1.8%)	783 (1.1%)	94 (1.8%)
nsMRA (Japan only)	N/A	N/A	N/A	N/A
ACEi/ARB	231 (6.4%)	6,309 (6.7%)	4,601 (6.3%)	326 (6.3%)

	Finerenone (N = 3,591)	**SGLT2i (N = 94,080)**	**GLP-1 RA (N = 72,816)**	**Wide Finerenone (N = 5,201)**
Duration of initial exposure episode after cohort entry (months)				
Mean (SD)	5.4 (4.7)	6.4 (5.8)	5.2 (5.1)	5.3 (4.6)
Median	3.5	4.3	3.2	3.5
1st, 99th percentile	1, 20	1, 25	1, 24	1, 20
Days' supply of index drug (days)				
Mean (SD)	45.2 (26.7)	50.5 (30.0)	40.0 (22.6)	44.9 (26.5)
Median	30	30	28	30
1st, 99th percentile	14, 100	7, 100	14, 90	14, 100
Number of prescriptions/dispensings for initial exposure episode after cohort entry				
Mean (SD)	3.7 (3.5)	4.0 (4.2)	4.0 (4.3)	3.6 (3.5)
Median	2	2	2	2
1st, 99th percentile	1, 17	1, 20	1, 21	1, 17
Number of distinct 'current use' periods for the index therapy, n (%)				
1	2,901 (80.8%)	66,520 (70.7%)	43,432 (59.6%)	4,212 (81.0%)
2	562 (15.7%)	18,264 (19.4%)	15,668 (21.5%)	814 (15.7%)
3	107 (3.0%)	5,662 (6.0%)	6,637 (9.1%)	144 (2.8%)
4	19 (0.5%)	1,949 (2.1%)	3,061 (4.2%)	28 (0.5%)
5+	2 (0.1%)	1,685 (1.8%)	4,018 (5.5%)	3 (0.1%)
Number of prescriptions/dispensings for the index therapy over the study period				
Mean (SD)	4.3 (3.7)	5.5 (5.8)	6.7 (7.4)	4.2 (3.7)
Median	3	4	4	3
1st, 99th percentile	1, 17	1, 27	1, 35	1, 17

	Finerenone (N = 3,591)	**SGLT2i (N = 94,080)**	**GLP-1 RA (N = 72,816)**	**Wide Finerenone (N = 5,201)**
Number of discontinuations (interruptions) of 'current use,' n (%)				
0	2,901 (80.8%)	66,520 (70.7%)	43,412 (59.6%)	4,212 (81.0%)
1	562 (15.7%)	18,264 (19.4%)	15,668 (21.5%)	814 (15.7%)
2	107 (3.0%)	5,662 (6.0%)	6,637 (9.1%)	144 (2.8%)
3	19 (0.5%)	1,949 (2.1%)	3,061 (4.2%)	28 (0.5%)
4	0 (0%)	830 (0.9%)	1,597 (2.2%)	1 (< 0.1%)
5+	2 (0.1%)	855 (0.9%)	2,421 (3.3%)	2 (< 0.1%)
Number of patients with an interruption of 'current use' lasting 90 days or more, n (%)	222 (6.2%)	17,228 (18.3%)	20,032 (27.5%)	322 (6.2%)
Duration of total exposure to index therapy (months)				
Mean (SD)	7.5 (5.1)	10.3 (8.7)	10.7 (10.6)	7.4 (5.0)
Median	6.4	7.8	7.5	6.3
1st, 99th percentile	NE, NE	NE, NE	2, 54	2, 22
Other drug classes started during follow-up, n (%)				
Finerenone	N/A	967 (1.0%)	409 (0.6%)	N/A
SGLT2i	256 (7.1%)	N/A	5,528 (7.6%)	363 (7.0%)
GLP-1 RA	204 (5.7%)	8,146 (8.7%)	N/A	277 (5.3%)
sMRA	66 (1.8%)	2,810 (3.0%)	1,282 (1.8%)	89 (1.7%)
nsMRA (Japan only)	N/A	N/A	N/A	N/A
ACEi/ARB	39 (1.1%)	2,244 (2.4%)	1,907 (2.6%)	60 (1.2%)

	Finerenone (N = 3,591)	**SGLT2i (N = 94,080)**	**GLP-1 RA (N = 72,816)**	**Wide Finerenone (N = 5,201)**
Duration of total follow-up (months)				
Mean (SD)	8.1 (5.4)	10.4 (7.1)	10.0 (7.2)	7.9 (5.4)
Median	7.1	8.8	8.1	6.8
1st, 99th percentile	0, 23	0, 26	0, 26	0, 23
Administrative reason for end of follow-up, n (%)				
End of study period	3,098 (86.3%)	78,244 (83.2%)	62,322 (85.6%)	4,413 (84.8%)
Disenrollment from the database or emigration from the database catchment area	304 (8.5%)	9,370 (10.0%)	7,268 (10.0%)	432 (8.3%)
Development of kidney failure during follow-up	104 (2.9%)	1,925 (2.0%)	1,198 (1.6%)	202 (3.9%)
Development of kidney cancer	4 (0.1%)	202 (0.2%)	135 (0.2%)	48 (0.9%)
Death	81 (2.3%)	4,336 (4.6%)	1,891 (2.6%)	106 (2.0%)

GLP-1 RA = glucagon-like peptide-1 receptor agonists; N/A = not applicable; NE = not estimated; SD = standard deviation; SGLT2i = sodium-glucose cotransporter 2 inhibitors; sMRA = steroidal mineralocorticoid receptor antagonists; ACEi/ARB = angiotensin-converting enzyme inhibitors/angiotensin receptor blockers.

[a] Index therapy was classified according to use of study-defined medications of interest.

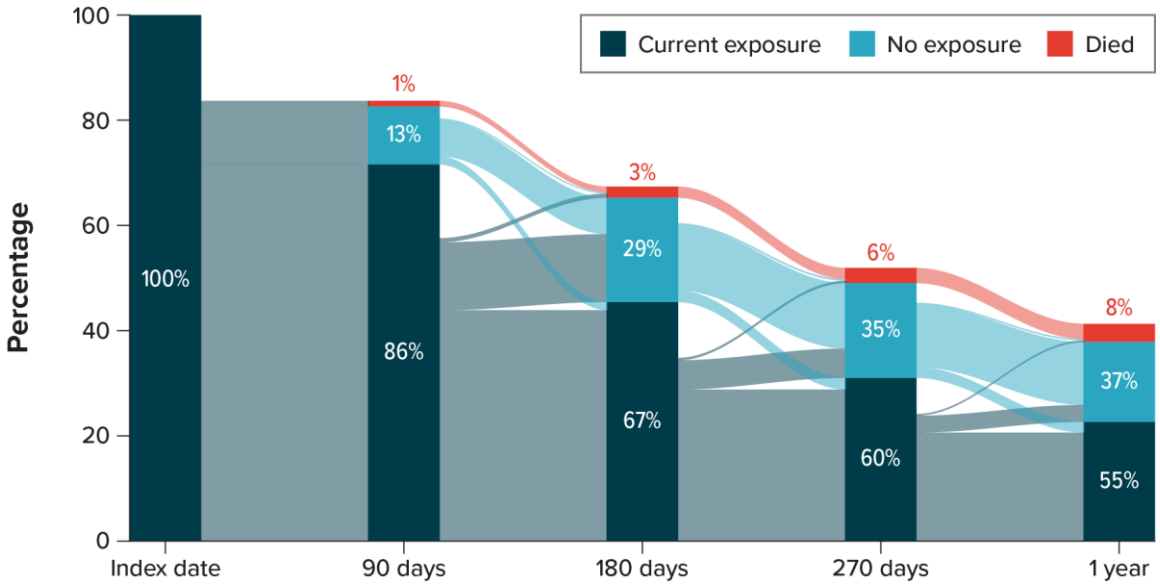
10.4.2.1.5 Treatment changes over time during follow-up

SGLT2i treatment patterns during follow-up were analyzed at four prespecified subsequent timepoints (90 days, 180 days, 270 days, and one year). Results are displayed in a Sankey diagram (Figure 20). Because SGLT2i treatment discontinuation and subsequent re-initiation have been shown to be common (Malik et al., 2023), it is important to note that estimates presented are cross-sectional estimates of the entire cohort at each timepoint rather than an analysis of individual patient trajectories. Note that losses to follow-up and censoring are represented in the white space at the top of each diagram.

At one year, 55% of patients were observed to be receiving treatment. This percentage represents a combination of patients who remained continuously on treatment up to the timepoint as well as other patients who had discontinued and restarted the medications.

The largest proportional increase in the "no exposure" treatment state occurred between the 90-day and 180-day timepoints. Thereafter, the proportion of patients with no treatment remained fairly stable. At each timepoint, a small proportion of nonusers who remained under observation were found to change and become current users.

Figure 20: Treatment states at specific timepoints for SGLT2i initiators during the post-finerenone period



Notes: Sankey diagrams display the proportion of the population at each timepoint in each of the treatment states for each data source. The connecting bars between timepoints show the proportion of the population that moved from 1 state to a different state at the next timepoint. These figures display proportions of the population over time, and a patient may move between treatment states over time (e.g., begin as "treated," move to "untreated" at the next timepoint, then move back to "treated" at the next). If death occurred, the patient was placed in a separate category and remained in that state for each subsequent checkpoint.

The height of the bar at each timepoint displays the relative size of the cohort remaining under observation at each timepoint. Patients who were lost to follow-up are not included in the percentage calculations at each timepoint; thus, the percentages sum to 100% for each timepoint. The percentages describe the amount of patients still under observation at that timepoint.

The sum of the bars for each timepoint may not equal 100% due to rounding.

10.4.2.2 GLP-1 RA

10.4.2.2.1 Markers of severity of T2D at index date

The percentage of patients with the highest HbA1c levels (> 74.9 mmol/mol or > 9%) was 12.2% among GLP-1 RA initiators in the post-finerenone period (Table 26). The percentage of patients with HbA1c values that were > 53 mmol/mol (or > 7%) was 33.9%. The median duration of a T2D diagnosis was 4.8 years and was higher than in the pre-finerenone period (four years).

Insulin use in the 180 days before and including the GLP-1 RA initiation date was recorded for 34.6% of patients (Table 26). The percentage of individuals with no use of GLD therapy other than insulin during this time was 25.6%. Most patients (> 50%) had used either one or two medications in a GLD class other than GLP-1 RA.

The most common medications for T2D prescribed or dispensed in the 180 days before and including date of GLP-1 RA initiation were metformin and fixed-dose combinations (50.4%), followed by sulfonylureas and fixed-dose combinations (28.9%), SGLT2i and fixed-dose combinations (23.4%), and DPP-4i and fixed-dose combinations (14.6%). Use of the other medications was always below 10% (Table 26).

The median score for the Diabetes Severity Complications Index, computed as the sum of seven conditions or complications, was 3. Of the conditions or complications comprising the severity index, CVD was the most commonly diagnosed condition (52.9%). Hyperkalaemia and amputation occurred in 7.6% and 2.3% of patients, respectively (Table 26).

10.4.2.2.2 Markers of kidney dysfunction severity at index date

The median duration of CKD at the index date based on all available data was 3.7 years (Table 27). The CKD stage was captured mainly from eGFR laboratory values (37.1% of patients did not have an eGFR result in the year before index date); diagnosis codes for CKD stage were not recorded in the year before the index date for 37.6% of patients. Based on CKD stage defined by eGFR result or diagnosis code, amongst patients with available staging information (Figure 17), the proportion of patients with stage 1 CKD at baseline was 8.3%; 31.0% for stage 2; 54.2% for stage 3; 6.0% for stage 4; and 0.5% for stage 5. For some patients, an eGFR test or diagnosis code was not available during the year before the index date (12%).

A large percentage of patients in all cohorts had no ACR assessment recorded in the year before the index date (between 67.9% and 75.2%), so categorization based on ACR level may not be reliable (Figure 18).

A high proportion of GLP-1 RA initiators had used medication classes of interest (ACEi/ARB, sMRA, SGLT2i) before initiating a GLP-1 RA (Table 27). Historical or previous use (> 365 days or 365 to 91 days before the index date) of ACEi or ARB drugs was recorded for most patients (79.7% or more). Recent ACEi/ARB use (≤ 90 days before the index date) was recorded for 71.2% of patients. Historical or previous use of sMRA was observed in 19.6% of patients. Recent use was present in 6.9% of patients (Table 27).

Of the clinical conditions known to be associated with an increased risk of CKD and assessed at any time before or on the index date, hypertension was the most common (92.9%). Glomerulonephritis, renovascular disease, and autoimmune disease were not common (less than 7% in all instances). Gout or hyperuricemia in the year before or on the index date was recorded for 10.7% of patients (Table 27).

10.4.2.2.3 Baseline comorbidities and comedications

Other than hypertension, hypercholesterolemia was the most common baseline comorbidity, recorded for approximately 87.7% of GLP-1 RA initiators (Table 28). Coronary heart disease was the most frequent macrovascular complication (33.7%), followed by peripheral vascular disease (31.2%), and cerebrovascular disease (12.6%). Congestive heart failure (23.0%) and chronic obstructive pulmonary disease (19.3%) were also common. The prevalence of hyperkalaemia was 7.6%. Other comorbidities were less common.

Medications other than GLDs recorded in the 180 days before or on the index date are shown in Table 29. Angiotensin receptor blocker medications (55.2%) and statins (78.3%) were the most commonly used medications, followed by beta blockers (50.5%) in GLP-1 RA initiators. Regarding use of diuretics, thiazide-like diuretics (30.5%) were more frequently recorded than loop diuretics (24.9%), similar to the pre-finerenone period. Use of potassium-sparing diuretics was uncommon (2.1%). Angiotensin-converting enzyme inhibitors and calcium channel blockers were used by 33.3% and 34.2% of patients, respectively. Anticoagulants were used in 13.2% of GLP-1 RA initiators. Aspirin and other antiplatelet drugs were used in 12.3% of GLP-1 RA new users. Of other medications of interest, NSAIDs (19.0%) and antibacterial agents (27.6%) were the most commonly used.

10.4.2.2.4 Characteristics of the index medication at baseline and during follow-up

At the index date, the GLP-1 RA was most commonly prescribed as an “add-on therapy” (53.4%) (Table 30, Figure 19) to a medication of interest. When the GLP-1 RA was used as “add-on” therapy, it was most often added to an ACEi or ARB (52.7%). Addition to a SGTL2i medication occurred in 12.1% of patients. When the index GLP-1 RA met the study definition of a “switch” from a prior medication of interest, the prior therapy most often reported was an ACEi or ARB (6.3%).

The median duration of the initial GLP-1 RA exposure episode was 3.2 months (Table 30). The median days’ supply of the index GLP-1 RA was 28 days. The median duration of total follow-up was 8.1 months. During follow-up, the median number of GLP-1 RA prescriptions filled was four. Most patients (59.6%) had only one distinct current-use period during follow-up.

Interruption of current use lasting 90 days or more—a proxy for discontinuation—was reported for 27.5% of patients. The median total duration of GLP-1 RA therapy was 7.5 months. Of the other drug classes started during follow-up, SGLT2i were the most commonly started (7.6%).

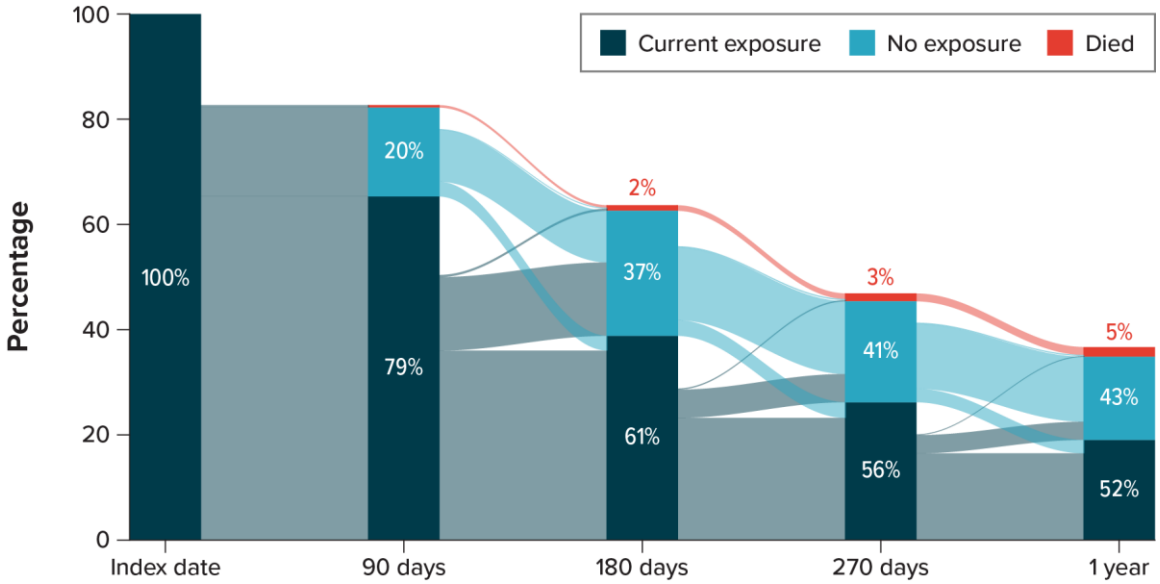
10.4.2.2.5 Treatment changes over time during follow-up

GLP-1 RA treatment patterns during follow-up were analyzed, beginning with a cohort of new users who initiated treatment on their individual index dates. At four prespecified subsequent timepoints (90 days, 180 days, 270 days, and one year), the proportion of the cohort in each treatment state (current use or non-use) was reported. Results are displayed in Sankey diagrams for each index medication (Figure 21). Because GLP-1 RA treatment discontinuation and subsequent re-initiation have been shown to be common (Malik et al., 2023), it is important to note that estimates presented are cross-sectional estimates of the entire cohort at each timepoint rather than an analysis of individual patient trajectories.

At one year, 52% of patients were observed to be receiving treatment. This percentage represents a combination of patients who remained continuously on treatment up to the timepoint as well as other patients who had discontinued and restarted the medications.

The largest proportional increase in the "no exposure" treatment state occurred between the index date and 90-day timepoints (21%), followed by the drop between the 90-day and 180-day timepoints (18%). Thereafter, the proportion of patients with no treatment remained fairly stable. At each timepoint, a small proportion of nonusers who remained under observation were found to change and become current users.

Figure 21: Treatment states at specific timepoints for GLP-1 RA initiators during the post-finerenone period



Notes: Sankey diagrams display the proportion of the population at each timepoint in each of the treatment states for each data source. The connecting bars between timepoints show the proportion of the population that moved from 1 state to a different state at the next timepoint. These figures display proportions of the population over time, and a patient may move between treatment states over time (e.g., begin as "treated," move to "untreated" at the next timepoint, then move back to "treated" at the next). If death occurred, the patient was placed in a separate category and remained in that state for each subsequent checkpoint.
The height of the bar at each timepoint displays the relative size of the cohort remaining under observation at each timepoint. Patients who were lost to follow-up are not included in the percentage calculations at each timepoint; thus, the percentages sum to 100% for each timepoint. The percentages describe the amount of patients still under observation at that timepoint.
The sum of the bars for each timepoint may not equal 100% due to rounding.

10.4.2.3 Finerenone cohorts

10.4.2.3.1 Markers of severity of T2D at index date

In this section, the results described refer to the finerenone cohorts. Results for the wide finerenone cohort are mentioned only if relevant differences were found to exist between the finerenone and wide finerenone cohorts.

The percentage of patients with the highest HbA1c levels (> 74.9 mmol/mol or > 9%) was 5% in the finerenone cohort (Table 26). The percentage of patients with HbA1c values > 53 mmol/mol (or > 7%) was 24.7%. The median duration since T2D diagnosis was 5.3 years.

Insulin use in the 180 days before and including the index date was recorded for 41.0% of patients in the finerenone cohort (Table 26). The percentage of individuals with no use of GLD therapy other than insulin during this time was 16.2%. Most patients (> 50%) had used either one or two medications in a GLD class.

The most common medications for T2D prescribed or dispensed in the 180 days before and including the date of the finerenone initiation were SGLT2i and fixed-dose combinations (46.2%), followed by metformin and fixed-dose combinations (37.3%), GLP-1 RA and fixed-dose combinations (33.6%), sulfonylureas and fixed-dose combinations (21.7%), and DPP-4i and fixed-dose combinations (14.1%). Use of the other GLDs was always below 10% (Table 26).

The median score for the Diabetes Severity Complications Index in finerenone initiators was three. Of the conditions or complications comprising the severity index, nephropathy was the most commonly diagnosed condition (58.3%) in the finerenone cohort, whereas CVD was the most commonly diagnosed condition in the wide finerenone cohort (55%). Regarding the second most common conditions, the findings were flipped across the two cohorts, with the second-most diagnosed condition being CVD (56.4%) in the finerenone cohort and nephropathy (50.9%) in the wide finerenone cohort. Hyperkalaemia and amputation occurred in 9.4% and 1.9% of patients, respectively, in the finerenone cohort (Table 26).

10.4.2.3.2 Markers of kidney dysfunction severity at index date

The median duration of CKD at the index date based on all available data was approximately four years (Table 27). Approximately 30% of patients did not have an eGFR result in the year before the index date; diagnosis codes for CKD stage were not recorded in the year before the index date for 12.9% of patients in the finerenone cohort and 21.6% of patients in the wide finerenone cohort. Based on CKD stage defined by eGFR result or diagnosis code amongst patients with available staging information (Figure 17), the proportion of patients with stage 1 CKD at baseline was 3.3% in the finerenone cohort and 5.3% in the wide finerenone cohort. In both cohorts, the proportion of patients in stage 2 was approximately 15%, with approximately 70% in stage 3, approximately 12% in stage 4, and 0.6% or less in stage 5. For some patients, either the stage was unspecified (6.8% in the finerenone cohort and 5.5% in the wide finerenone cohort) or there was no diagnosis code or eGFR test during the year before the index date (3.3% in the finerenone cohort and 9.0% in the wide finerenone cohort).

A large percentage of patients in all cohorts had no ACR assessment recorded in the year before the index date (between 67.9% and 75.2%), so categorization based on ACR level may not be reliable (Figure 18).

A high proportion of finerenone initiators had used medication classes of interest (ACEi/ARB, sMRA, GLP-1 RA) before initiating finerenone. Historical or previous use (> 365 days or 365 to 91 days before the index date) of ACEi or ARB drugs was recorded for most patients (90% or more in both the finerenone and wide finerenone cohorts). Recent ACEi/ARB use (≤ 90 days before the index date) was recorded for approximately 80% of patients in both cohorts. Historical or previous use of sMRA was observed in approximately 10% of patients in both cohorts, whereas recent use was present for approximately 5% of patients in the finerenone and wide finerenone cohorts (Table 27).

Of the clinical conditions known to be associated with an increased risk of CKD and assessed at any time before or on the index date, hypertension was the most common (96.7% in the finerenone cohort). Glomerulonephritis, renovascular disease, and autoimmune disease were not common (less than 7% in both the finerenone and wide finerenone cohorts). Gout or

hyperuricemia in the year before or on the index date was recorded for 17.3% of patients in the finerenone cohort (Table 27).

10.4.2.3.3 Baseline comorbidities and comedications

Other than hypertension, hypercholesterolemia was the most common baseline comorbidity, recorded for approximately 91.1% of patients in the finerenone cohort (Table 28). Coronary heart disease was the most frequent macrovascular complication (37.0%), followed by peripheral vascular disease (34.7%) and cerebrovascular disease (15.2%). Congestive heart failure (25.3%) and chronic obstructive pulmonary disease (18.5%) were also common. The prevalence of hyperkalaemia was approximately 9% in both finerenone cohorts (Table 26). Other comorbidities were less common.

Medications other than GLDs recorded in the 180 days before or on the index date for the finerenone and wide finerenone cohorts are shown in Table 29. Statins (84.5%) and angiotensin receptor blocker medications (69.7%) were the most commonly used medications, followed by beta blockers (59.6%) in the finerenone cohort. Regarding use of diuretics, thiazide-like diuretics and loop diuretics were used to a similar degree in the finerenone cohort (approximately 30% of patients). The use of potassium-sparing diuretics was uncommon (1.4%). Angiotensin-converting enzyme inhibitors and calcium channel blockers were used by 28.9% and 47.9% of patients, respectively. Anticoagulants were used by 14.8% of finerenone new users. Aspirin and other antiplatelet drugs were used by 15.4% of finerenone new users. Among other medications of interest, antibacterial agents (27.8%) and bronchodilators (16.8%) were the most commonly used.

10.4.2.3.4 Characteristics of the index medication at baseline and during follow-up

At the index date, finerenone was most commonly prescribed as an “add-on therapy” (59.4%) (Table 30, Figure 19) to other medications of interest. When finerenone was used as “add-on” therapy, it was most often added to an ACEi or ARB (58.5%). Addition to a SGTL2i medication and a GLP-1 RA occurred for 28.0% and 21.1% of patients, respectively. When finerenone met the study definition of a “switch” from a prior medication of interest, the prior therapy most often reported was an ACEi or ARB (6.4%).

The median duration of the initial finerenone exposure episode was 3.5 months (Table 30). The median days’ supply of the initial finerenone prescription was 30 days. The median duration of total follow-up was 7.1 months. During follow-up, the median number of finerenone prescriptions filled was three. Most patients (80.8%) had only one distinct current-use period during follow-up. Interruption of current use lasting 90 days or more—a proxy for discontinuation—was reported for 6.2% of patients, and this percentage was smaller than for the SGLT2i and GLP-1 RA cohorts (18.3% and 27.5%, respectively). The median total duration of finerenone therapy was 6.4 months. Of the other drug classes started during follow-up, SGLT2i were the most commonly started (7.1%).

Regarding finerenone dosing (Table 31), 18.0% of patients received the 20-mg daily dose at the index date. Of those who received a daily dose of 10 mg at the index date, few patients titrated up to 20 mg. For example, among patients receiving a 10-mg daily dose, approximately 11% titrated up to 20 mg by 12 months after entering the cohort. When stratifying by whether patients had SGLT2i use at baseline, patients without SGLT2i use were more likely to have their index finerenone prescription classified as “monotherapy” (15.1% vs. 1.3%, respectively). Conversely, those with SGLT2i use were more likely to have their

index finerenone prescription as "add-on and switch" than those without SGLT2i use (15.0% vs. 3.9%, respectively). The prevalence of GLP-1 RA use was higher among those with SGLT2i use at baseline than among those without (26.0% vs. 16.7%, respectively) (Annex 6, Table 62). Similar findings were observed in the wide finerenone cohort.

Table 31: Description of finerenone dosing at cohort entry and during follow-up (CDM, 09 JUL 2021-30 SEP 2023)

	Finerenone (N = 3,591)	**Wide Finerenone (N = 5,201)**
Strength of index finerenone (mg), n (%)		
10 mg	2,948 (82.1%)	4,190 (80.6%)
20 mg	643 (17.9%)	1,011 (19.4%)
Dose frequency of index finerenone, n (%)		
Once daily	3,572 (99.5%)	5,169 (99.4%)
Other	19 (0.5%)	32 (0.6%)
Daily dose (mg) (strength*frequency) at the index date, n (%)		
10 mg	2,933 (81.7%)	4,166 (80.1%)
20 mg	647 (18.0%)	1,017 (19.6%)
Other	11 (0.3%)	18 (0.3%)
Proportion of patients who had a 10-mg daily dose at the index date and titrated up to 20 mg (n/N)…		
by 1 month[a]	50/2,993 (1.7%)	65/4,166 (1.6%)
by 6 months[a]	267/2,993 (8.9%)	371/4,166 (8.9%)
by 12 months[a]	342/2,993 (11.4%)	488/4,166 (11.7%)
at 1 month[b]	49/2,808 (1.7%)	64/3,917 (1.6%)
at 6 months[c]	195/1,797 (10.9%)	260/2,468 (10.5%)
at 12 months[d]	117/701 (16.7%)	162/937 (17.3%)
Proportion of patients who had a 20-mg daily dose at the index date and titrated down to 10 mg (n/N)…		
by 1 month[e]	4/647 (0.6%)	9/1,017 (0.9%)
by 6 months[e]	17/647 (2.6%)	36/1,017 (3.5%)
by 12 months[e]	28/647 (4.3%)	50/1,017 (4.9%)
at 1 month[f]	4/607 (0.7%)	9/940 (1.0%)
at 6 months[g]	10/367 (2.7%)	23/578 (4.0%)
at 12 months[h]	13/151 (8.6%)	20/229 (8.7%)

n = numerator count; N = denominator count.

[a] Denominator includes all patients with an initial dose of 10 mg.

[b] Denominator includes only those patients with an initial dose of 10 mg who were still being followed 1 month after the index date.

[c] Denominator includes only those patients with an initial dose of 10 mg who were still being followed 6 months after the index date.

[d] Denominator includes only those patients with an initial dose of 10 mg who were still being followed 12 months after the index date.
[e] Denominator includes all patients with an initial dose of 20 mg.
[f] Denominator includes only those patients with an initial dose of 20 mg who were still being followed 1 month after the index date.
[g] Denominator includes only those patients with an initial dose of 20 mg who were still being followed 6 months after the index date.
[h] Denominator includes only those patients with an initial dose of 20 mg who were still being followed 12 months after the index date.

10.4.2.3.5 Treatment changes over time during follow-up

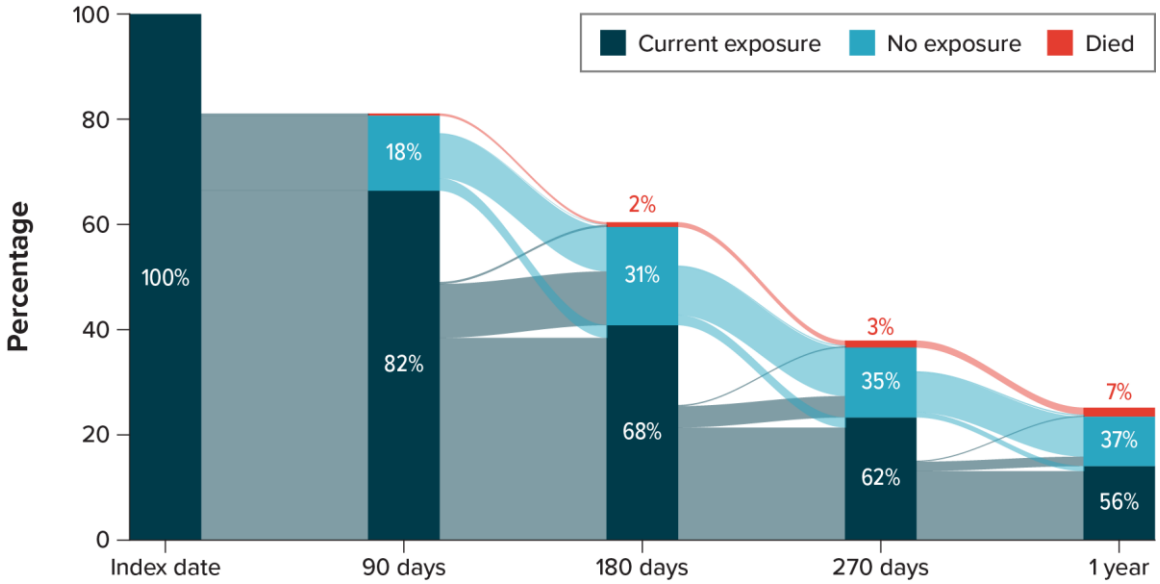
Finerenone treatment patterns during follow-up were analyzed, beginning with a cohort of new users who initiated treatment on their individual index dates. At four prespecified subsequent timepoints (90 days, 180 days, 270 days, and one year), the proportion of the cohort in each treatment state (current use or non-use) was reported. Results are displayed in Sankey diagrams for the finerenone and wide finerenone cohorts (Figure 22).

At one year, 56% of patients in both the finerenone and wide finerenone cohorts were observed to be receiving treatment.

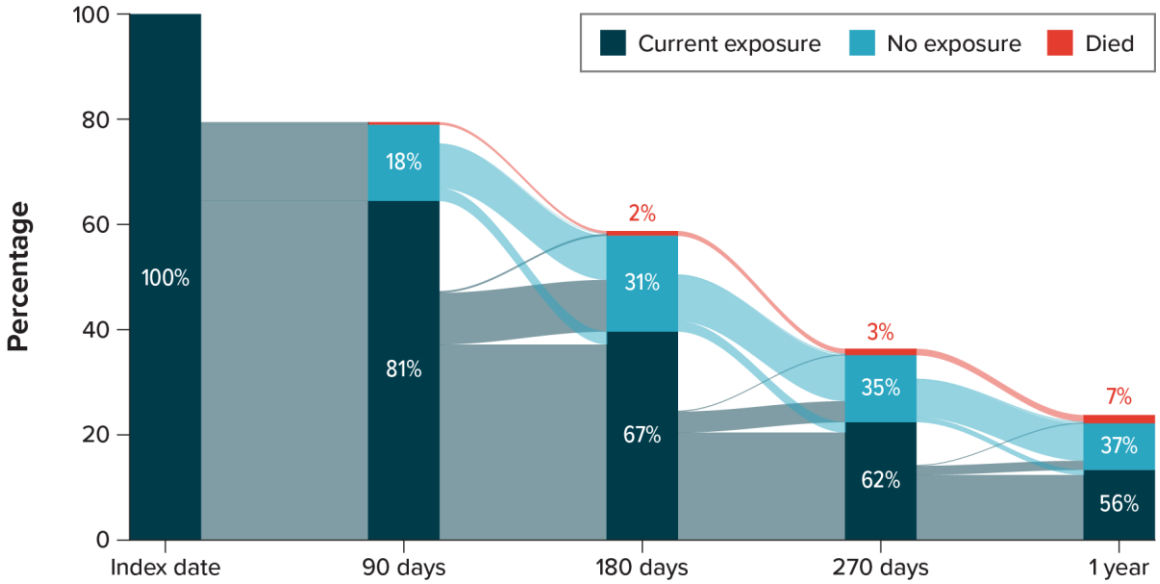
For both cohorts, the largest proportional increase in the “no exposure” treatment state occurred between the index date and 90-day timepoints (18% difference) followed by the 90-day and 180-day timepoints (14% difference). Thereafter, the proportion of patients with no treatment remained fairly stable. At each timepoint, a small proportion of nonusers who remained under observation were found to change and become current users.

Figure 22: Treatment states at specific timepoints for initiators in the finerenone and wide finerenone cohorts during the post-finerenone period

Finerenone



Wide Finerenone



Notes: Sankey diagrams display the proportion of the population at each timepoint in each of the treatment states for each data source. The connecting bars between timepoints show the proportion of the population that moved from one state to a different state at the next timepoint. These figures display proportions of the population over time, and a patient may move between treatment states over time (e.g., begin as "treated," move to "untreated" at the next timepoint, then move back to "treated" at the next). If death occurred, the patient was placed in a separate category and remained in that state for each subsequent checkpoint.

The height of the bar at each timepoint displays the relative size of the cohort remaining under observation at each timepoint. Patients who were lost to follow-up are not included in the percentage calculations at each timepoint; thus, the percentages sum to 100% for each timepoint. The percentages describe the amount of patients still under observation at that timepoint.

The sum of the bars for each timepoint may not equal 100% due to rounding.

10.4.3 Trend analysis

10.4.3.1 SGLT2i

Annex 6, Table 48 to Table 54, show the differences in baseline characteristics between the pre- and post-finerenone periods for the SGLT2i cohorts. Standardized mean differences between the two periods are displayed in Figure 23 and in the text of this section. The figure is focused on variables with SMDs equal to or greater than ± 0.20.

Baseline demographics

The largest SMD was for age (0.48). Comparing the post- and pre-finerenone periods, new users of SGLT2i were older (mean [SD] age of 73.1 [8.9] years vs. 68.6 [10.1] years) in the post-finerenone period than in the pre-finerenone period.

Markers of severity of T2D

Duration of T2D was greater in the post-finerenone period than in the pre-finerenone period (mean [SD] in years of 5.9 [4.1] vs. 5.1 [3.4], respectively). Both users of metformin and users of sulfonylureas were less common in the post-finerenone period than in the pre-finerenone period (46.4% vs. 60.2% and 28.0% vs. 38.7%, respectively). Users of DPP-4i were also less common in the post-finerenone period than in the pre-finerenone period (13.0% vs. 23.9%, respectively).

The percentage of patients with no GLD therapy was larger in the post-finerenone period than in the pre-finerenone period (28.7% vs. 16.0%, respectively). Conversely, dual and triple therapy were more common in the pre-finerenone period than in the post-finerenone period (33.2% vs. 24.3% and 13.8% vs. 7.1%, respectively).

Regarding metabolic control, a higher percentage of patients had HbA1c levels < 7% in the post-finerenone period than in the pre-finerenone period (19.6% vs. 12.5%, respectively). However, a higher percentage of patients had HbA1c levels indicating lack of metabolic control (> 9%) in the pre-finerenone period than in the post-finerenone periods (16.5% vs. 8.6%, respectively).

In the pre-finerenone period, a higher percentage of patients had nephropathy complications than in the post-finerenone period (59.1% vs. 47.4%, respectively) and a lower percentage had cardiovascular complications (51.3% vs. 63.3%, respectively).

Markers of severity of kidney dysfunction

Patients in the post-finerenone period had more severe kidney dysfunction than in the pre-finerenone period. A higher percentage of patients had stage 3 in the post-finerenone period than in the pre-finerenone period (52.1% vs. 26.3%, respectively). Additionally, a lower percentage of patients had stages 1 and 2 in the post-finerenone than in the pre-finerenone period (4.4% vs. 10.8% and 20.4% vs. 31.1%, respectively).

However, there were more patients without assessment of renal function in the pre-finerenone than in the post-finerenone period (20.2% vs. 9.0%, respectively).

Medication use

The pattern of diuretics use was different in the two periods. Although thiazide-like diuretics were used more commonly than loop diuretics in the pre-finerenone period (31.9% vs. 22.4%), loop diuretics were used more commonly than thiazide-like diuretics in the post-finerenone period (32.7% vs. 27.6%). Use of anticoagulants was more common in the post-finerenone than in the pre-finerenone period (18.7% vs. 11.5%).

Other comorbidities

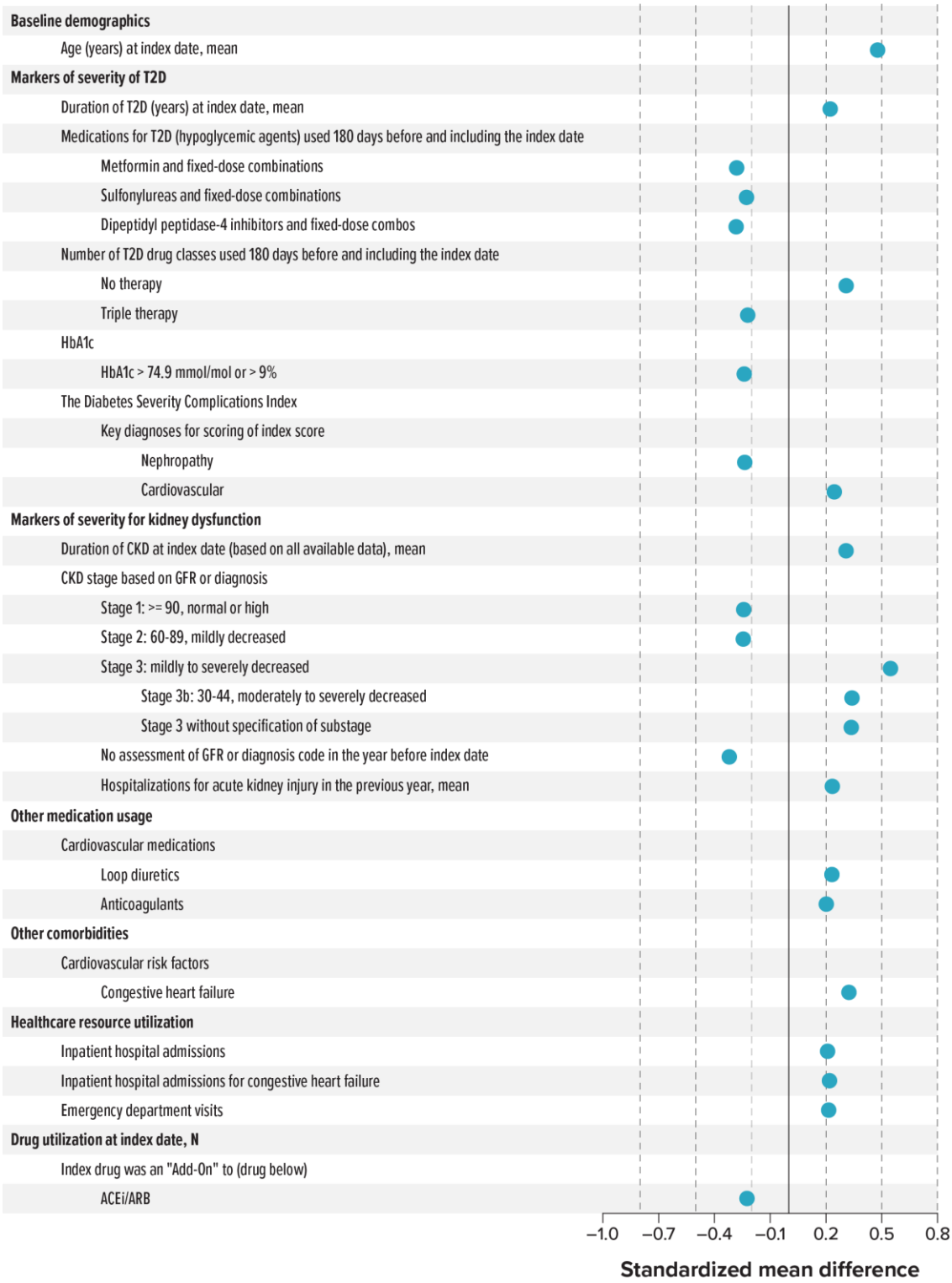
The highest difference between periods was for CHF, which was higher in the post-finerenone period than in the pre-finerenone period (35.9% vs. 21.5%). In general, comorbidities were higher in the post-finerenone than in the pre-finerenone period.

Healthcare resource utilization

As expected, given the older age of patients and higher prevalence of comorbidities in the post-finerenone period, healthcare utilization was higher in the post-finerenone period than in the pre-finerenone period. Patient hospital admissions, hospital admissions for CHF, and emergency department (ED) visits were all higher in the post-finerenone period than in the pre-finerenone period.

In summary, diabetes severity among new users of SGLT2i seemed lower in the post-finerenone period than in the pre-finerenone period, though CKD was more severe in the post-finerenone period and the comorbidity burden was higher.

Figure 23: Standardized mean differences by variable between the pre-finerenone and post-finerenone periods for SGLT2i initiators



ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blockers; CKD = chronic kidney disease; GFR = glomerular filtration rate; HbA_{1c} = hemoglobin A_{1C}; N = number; SMD = standardized mean difference; T2D = type 2 diabetes.

Notes: Baseline covariates with an absolute SMD of 0.2 or greater are shown, with the exception of CKD stage covariates that met the 0.2 threshold and were classified by "diagnosis only" or "GFR only." Those covariates were omitted due to their observed rates of missingness.

10.4.3.2 GLP-1 RA

Annex 6, Table 55 to Table 61, presents the differences in baseline characteristics between the pre- and post-finerenone periods for the GLP-1 RA cohorts. Standardized mean differences between the two periods are displayed in Figure 24, and the text of this section is focused on variables with SMDs equal to or greater than ± 0.20.

Baseline demographics

The largest SMD was for age (0.21). Comparing the post- and pre-finerenone periods, new users of SGLT2i were older (mean [SD] age, 70.0 [9.3] years vs. 67.9 [10.1] years) in the post-finerenone period than in the pre-finerenone period.

Markers of severity of T2D

Duration of T2D was greater in the post-finerenone period than in the pre-finerenone period (mean [SD] in years of 5.7 [4.1] vs. 4.9 [3.4], respectively). Users of SGLT2i were more common in the post-finerenone than in the pre-finerenone period (23.4% vs. 13.3%). Users of DPP-4i were less common in the post-finerenone period than in the pre-finerenone period (14.6% vs. 24.3%).

Insulin use recorded 180 days before and including the index date was lower in the post-finerenone period than in the pre-finerenone period (34.6% vs. 44.8%).

Regarding metabolic control, a higher percentage of patients had HbA1c levels < 7% in the post-finerenone period than in the pre-finerenone period (17.2% vs. 10.3%, respectively). However, a higher percentage of patients had HbA1c levels indicating lack of metabolic control (greater than 9%) in the pre-finerenone period than in the post-finerenone period (17.8% vs. 12.2%).

There was a higher percentage of patients with nephropathy complications in the pre-finerenone period than in the post-finerenone period (64.9% vs. 41.4%).

Markers of severity of kidney dysfunction

The prevalence of kidney dysfunction was higher in the post-finerenone period than in the pre-finerenone period. There were more patients in stage 3 in the post-finerenone period than in the pre-finerenone period (44.0% vs. 27.6%).

However, there were more patients without assessment of renal function in the pre-finerenone period than in the post-finerenone period (21.7% vs. 12.0%).

Any use (historical, previous, or recent) of SGLT2i increased in the post-finerenone compared with the pre-finerenone period (e.g., 19.9% vs. 11.3% for recent use).

Medication use

No differences with SMDs equal to or greater than 0.20 were observed in medication use.

Other comorbidities

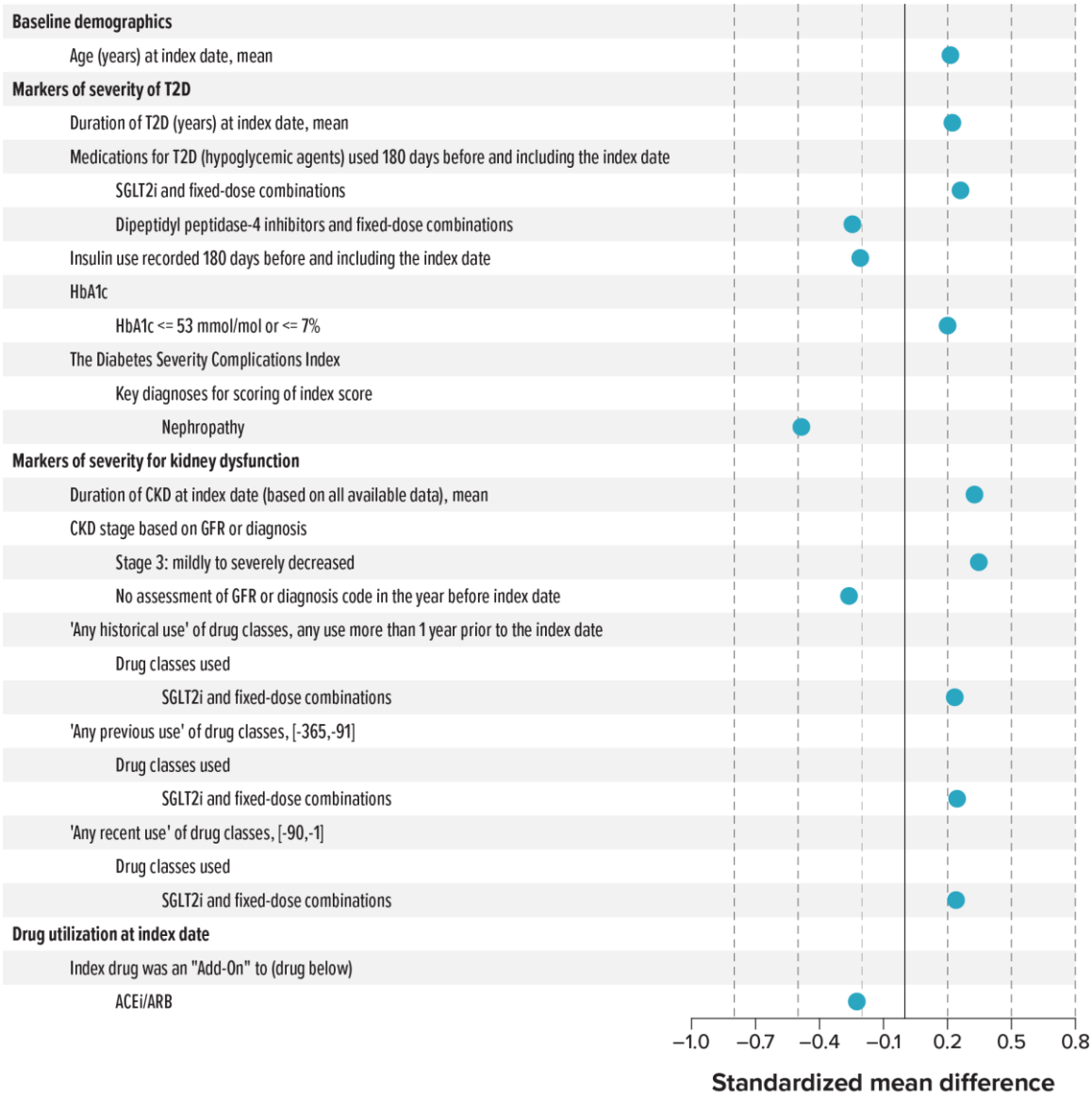
No differences with SMDs equal to or greater than 0.10 were observed in other comorbidities.

Healthcare resource utilization

No differences with SMDs equal to or greater than 0.05 were observed in HCRU.

In summary, similar to new users of SGLT2i, new users of GLP-1 RA seemed to have less severe diabetes in the post-finerenone period than in the pre-finerenone period and more severe kidney dysfunction. However, no difference in comorbidity burden was noted in the pre-finerenone period compared with the post-finerenone period.

Figure 24: Standardized mean differences by variable between the pre-finerenone and post-finerenone periods for GLP-1 RA initiators



ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blockers; CKD = chronic kidney disease; GFR = glomerular filtration rate; HbA_{1c} = hemoglobin A_{1C}; N = number; SMD = standardized mean difference; T2D = type 2 diabetes.

Notes: Baseline covariates with an absolute SMD of 0.2 or greater are shown, with the exception of CKD stage covariates that met the 0.2 threshold and were classified by "diagnosis only" or "GFR only." Those covariates were omitted due to their observed rates of missingness.

10.5 Other analyses

Not applicable

10.6 Adverse events/adverse reactions

Not applicable

11. Discussion

11.1 Key results

11.1.1 Pre-finerenone

11.1.1.1 SGLT2i

Patient characteristics at baseline reflected similarities and heterogeneity among the patient samples in the study. In all data sources, the median age was similar, ranging from 68 to 72 years, and a higher proportion of males than females was observed. Differences were observed in baseline characteristics, including markers of T2D severity and kidney dysfunction, baseline comorbidities and medication use, and patterns of SGLT2i utilization at baseline and over time.

Most patients had used GLDs in the 180 days before or on the index date, but the type of GLDs used varied by data source, with metformin being the most frequently used GLD before SGLT2i initiation in the data sources in Denmark, The Netherlands, and the US and DPP-4i in the data sources in Japan and Spain.

The Diabetes Severity Complications Index score was higher in J-CKD-DB-Ex and VID (both with a median score of four) than in CDM (median score of three) or the other two data sources, both with a median score of two.

A high proportion of patients had stage 1 or 2 CKD at baseline, reflecting the relatively mild CKD in all cohorts in the pre-finerenone period. The proportion of stage 3 or stage 4 disease was highest in J-CKD-DB-Ex and PHARMO.

Common findings across all data sources were that ACEi or ARB medications were by far the most frequent type of medication used before initiation of the index SGLT2i, and hypertension was the most frequently recorded medical comorbidity.

Patients in J-CKD-DB-Ex tended to have a higher prevalence of most other medical comorbidities than patients in the other data sources.

Regarding treatment patterns during follow-up, the proportions of patients observed to be receiving treatment at each timepoint were similar among DNHR, VID, and J-CKD-DB-Ex. The largest proportional increase in the “no exposure” treatment state occurred between the 90-day and 180-day timepoints in each data source.

11.1.1.2 GLP-1 RA

Median age was comparable across the data sources, ranging from 67 to 69 years. The proportion of males and females varied across data sources, with some having a higher proportion of females and others having a lower proportion. The prevalence of CHD and cerebrovascular disease was comparable across the European and US data sources, and the highest prevalence was found in J-CKD-DB-Ex. The prevalence of CVD risk factors was variable across data sources, with hypertension and hypercholesterolemia being notably lower in PHARMO. The second-lowest prevalence was observed in DNHR.

Most patients in each data source were taking another glucose-lowering medication in the six months before the index date, and metformin was the most commonly prescribed drug in

all data sources, with the exception of J-CKD-DB-Ex. In the present study, the diabetes severity score was higher in J-CKD-DB-Ex and VID (median score of four) than in the other data sources.

The greatest proportion of patients in each data source were classified as having stage 3 CKD based on eGFR values or a diagnostic code. Moderate or severe CKD was comparably higher in DNHR and J-CKD-DB-Ex than in the other data sources, with both DNHR and J-CKD-DB-Ex also having the lowest percentage of patients missing ACR values. Across all data sources, the most common drug class used before initiation of a GLP-1 RA was either ACEi or ARB.

Comorbidities, such as hypertension, hypercholesterolemia, and macrovascular complications of T2D, were common in all data sources.

A common pattern in the Sankey diagrams was that the largest proportional increase in the "no exposure" treatment state occurred within the first six months of initiation (between the index date and the 90-day timepoint or between the 90-day timepoint and the 180-day timepoint).

11.1.1.3 sMRA

Median age across the data sources (73 to 79 years) was older than that observed in the other medication cohorts. In most data sources, cardiovascular conditions such as CHD were higher in the sMRA cohort compared with other medication cohorts. Similar to other medication cohorts, hypertension was the most common comorbidity in the sMRA cohort, though the prevalence varied by data source. CHF was more prevalent in this cohort than in other medication cohorts.

Most patients in each data source were taking another glucose-lowering medication in the six months before the index date, and metformin was the most commonly prescribed drug in all data sources, with the exception of J-CKD-DB-Ex and VID, where it was DPP-4. The Diabetes Severity Complications Index score ranged from three to five. Additionally, the prevalence of nephropathy and CVD was high in this cohort and comprised the most common diagnoses within the score.

Most patients in the data sources had moderate CKD (stage 3), with the exception of CDM, where a comparable percentage of patients also had stage 2 CKD. Data on ACR values were sparse. As observed in other cohorts, patients were likely to be taking another drug class alongside, in the past, or historically with sMRA, with ACEi or ARB being most common.

The median duration of exposure to the index sMRA therapy was less than one year, ranging from approximately one month in PHARMO to 10 months in DNHR. The percentage of patients with interruptions of the index medication lasting more than three months ranged from 10% to 15% in the European data sources and were higher in J-CKD-DB-Ex and CDM.

A cross-sectional assessment of treatment states at prespecified time periods showed that the greatest increase in patients no longer exposed to the therapy occurred within the first 90 days in all data sources, except for DNHR. The percentage of patients exposed at the one, two, and three-year marks was comparable in PHARMO and DNHR and lower in J-CKD-DB-Ex, CDM, and VID.

11.1.1.4 nsMRA

Only one nsMRA, namely esaxerenone, was used in Japan. Data for new users of nsMRA were only available from J-CKD-DB-Ex and were based on a study size of 63 patients. In this

cohort of new users of nsMRA with T2D and CKD, the median duration of T2D was seven years, most patients had HbA1c levels ≤ 7%, and most did not have previous use of any GLD in the prior six months. The median diabetes severity index score was four.

Median duration of CKD was shorter in the nsMRA population at approximately four years, with stage 3 CKD being most common. ACEi/ARB were the most common medications prescribed before initiation of nsMRA, ranging from 59% (recent use) to 73% (historical use).

Hypertension was the most common comorbidity followed by hypercholesterolemia, consistent with other drug classes. This was followed closely by the prevalence of CHF. Distinct from other drug cohorts, calcium channel blockers and ARB were the most common cardiovascular drugs prescribed in the 180 days before initiation, with statins prescribed for less than half of patients.

The median duration of nsMRA use was approximately six months, with few patients (16%) having an interruption of use lasting more than 90 days. When assessing treatment patterns, most patients switched from current use to no current use within the first 180 days, after which medication exposure plateaued.

11.1.2 Post-finerenone

11.1.2.1 Differences in cohort characteristics

Although the cohorts were not mutually exclusive and no formal comparisons were planned, some patterns can be described. Median age was approximately 70 years in all medication cohorts. There were more males than females in all cohorts except the GLP-1 RA cohort. Obesity was more prevalent in the GLP-1 RA cohort than in the other cohorts (approximately 60% vs. the highest, 49%, in the other three cohorts).

Treatment intensity for T2D was more pronounced in the finerenone cohorts than in the other two cohorts as reflected by more use of T2D medications (including insulin). Conversely, metabolic control as measured by HbA1c levels was better in the finerenone cohorts than in the other two cohorts.

A higher percentage of patients had stage 3 and stage 4 CKD in the finerenone cohorts than in the other two cohorts.

Regarding concomitant medications, use of ARB, statins, and calcium channel blockers was more common in the finerenone cohorts than in the other two cohorts. Finerenone was less frequently used as monotherapy than in the other cohorts; conversely, the “add-on” and “add-on and switch” categories were more common in the finerenone cohorts than in the other two cohorts.

Patients in the finerenone cohorts had less frequent discontinuations of current use and fewer interruptions of current use lasting more than 90 days than those in the other two cohorts. Conversely, duration of total exposure was lower in the finerenone cohort than in the other two cohorts, but this was related to the shorter duration of follow-up in the finerenone cohort. At the index date, approximately 18% of patients were receiving a 20-mg daily dose. At the one-year mark, titration of finerenone up to 20 mg during follow-up occurred in approximately 17% of the patients who were taking 10 mg at baseline.

11.1.2.2 SGLT2i and GLP-1 RA trends in the pre- and post-finerenone periods

Comparing the pre- and post-finerenone periods, patients were older in the post-finerenone period for both cohorts. Use of medication for T2D was less intensive and metabolic control was better in the post-finerenone period than in the pre-finerenone period.

For both cohorts, patients had more severe CKD in the post-finerenone period than in the pre-finerenone period, but more patients had their renal function assessed in the post-finerenone period.

In the SGLT2i cohort, use of loop diuretics was more common than use of thiazide-like diuretics during the post-finerenone period, whereas the opposite was observed in the pre-finerenone period. Additionally, the prevalence of heart failure increased during the post-finerenone period. In the GLP-1 RA cohort, use of SGLT2i increased considerably during the post-finerenone period.

11.2 Limitations

The findings of this study should be interpreted in the context of some limitations. First, DNHR and PHARMO data may underestimate the prevalence of some clinical conditions diagnosed and managed primarily by general practitioners (GPs) or primary care doctors. In PHARMO, GPs do not necessarily code all diagnoses but can include them in free-text fields, which were not considered in this study. Additionally, some conditions may be indicated through recording of laboratory or clinical measurements, which were also not available for use in this study. However, for this study, all primary and secondary diagnosis codes in DNHR related to inpatient, outpatient, and ED encounters were used to define medical conditions. To capture T2D, all available historical data were used, and T2D was defined by an algorithm that included dispensing of a GLD prescription from a community pharmacy or an inpatient or outpatient hospital encounter with a T2D diagnosis.

Second, under-capture of medications in J-CKD-DB-Ex is possible if medications were dispensed before entry into the J-CKD-DB-Ex cohort or at a hospital outside the catchment area of this registry. Under-capture of medications in CDM is possible if patients paid out of pocket or sought care out of network where a prescription was written. In the case of countries without universal health coverage, including coverage for medications, there may also be the possibility of misclassifying new users of these medications. For example, in CDM, if an individual were to fill a prescription outside their network, then it would appear within CDM data that they have had no prior prescription for the medication of interest and, thus, they may be classified as a new user. Several study design considerations, such as a large window (12 months) in which patients could not have had a prescription for the drug of interest, as well as being on the health plan for at least one year, were aimed at mitigating this possibility.

Third, information on indication for therapy was lacking in all but one data source; therefore, we were not able to assess across data sources for what condition(s) the medications of interest were prescribed nor for what prior or subsequent therapy. For example, despite J-CKD-DB-Ex being a CKD registry, just over 50% of potential index dates were excluded due to missing CKD diagnosis through any means (i.e., eGFR test result, ACR value, or diagnosis code) before the GLP-1 RA prescription date. This may be partly due to an individual having prescription information for a GLP-1 RA before receiving a CKD diagnosis. In the present study, we did not assess the order in which individuals were diagnosed with T2D and CKD because some of the medications under study, namely GLP-1 RA and SGLT2i, are often prescribed for treatment of T2D and we had no way to know whether the GLP-1 RA or

SGLT2i was prescribed for CKD, T2D, or both. Additionally, we could not capture temporal trends within a given country with respect to timing of information on benefits of the studied medications for CKD, CVD and heart failure outcomes, or label expansions.

Fourth, as with all studies based in existing healthcare data sources, the data were generated primarily for healthcare delivery rather than for research purposes. Therefore, mechanisms such as healthcare use patterns can lead to missing data and misclassification of study variables is possible. Additionally, information within these data sources is captured passively rather than with specific study objectives in mind. Furthermore, despite the availability of data from disparate data sources, there is heterogeneity of data types (e.g., EHR data, population registries), coding systems, formularies, and data availability, which may result in key differences between data sources. There are also differences across data sources regarding underlying data generation processes (e.g., claims vs. EHRs) and health systems. Although direct comparisons across data sources were outside the scope of the current work, differences in the observed results could reflect this inherent heterogeneity among the data sources in the type and nature of data captured as well as differences in healthcare systems, treatment guidelines, country-specific clinical practices, formulary policies, and application of diagnostic coding systems in the participating countries. However, the use of healthcare data from multiple countries and data sources is a strength, as using multiple data sources allowed evaluation of study parameters in diverse settings, populations, and healthcare systems.

This was a descriptive drug utilization study and was not focused on making direct comparisons across data sources. Instead, the study aimed to describe patient and clinical characteristics and treatment patterns in the different data sources (and countries). Therefore, comparisons across data sources should be interpreted in this context. Similarly, comparisons in patient demographic and clinical characteristics among new users of SGLT2i or GLP-1 RA in the period before and after approval of finerenone in the US were made independently of other characteristics and could be due to a host of factors, including differences in patient characteristics, medication tolerability, or patient preferences. Therefore, we were unable to determine what was driving differences between the groups across these time periods. However, describing and understanding utilization of current treatments for patients with CKD and T2D and heterogeneity among data sources is an important first step to guiding future research on new treatments in this same therapeutic area. This is particularly poignant in the current study, in which use of other therapies in a population with T2D and CKD was assessed during the time in which a new therapy (finerenone) was available, despite the analysis being limited to one data set (CDM) with sufficient sample size.

Finally, in the present study, a prescription could refer to a written prescription for a medication or a dispensing of the drug. However, neither of these imply that an individual took the drug as intended or was exposed to the drug, including any refills.

11.3 Interpretation

11.3.1 Pre-finerenone period

Across all data sources in both the GLP-1 RA and SGLT2i drug cohorts, the largest number of potential SGLT2i index dates were lost due to (1) use of another medication in the same drug class in the year before the index date and (2) no diagnosis of CKD recorded before or on the potential index date. The CKD hospital-based database in Japan was the only data source with non-trivial exclusions of potential index dates or patients due to the absence of diagnoses of T2D, T1D, kidney cancer, and kidney failure. J-CKD-DB-Ex is a hospital-based CKD registry constructed from EHR data from five participating university hospitals in Japan.[51] Patients were included in J-CKD-DB-Ex if they had dipstick proteinuria ≥ 1+ or an eGFR value of < 60 mL/min/1.73 m^2. Despite J-CKD-DB-Ex being a CKD registry, just over 50% of potential index dates were excluded due to missing CKD diagnosis through any means (i.e., eGFR test result, ACR value, or diagnosis code) before the GLP-1 RA or SGLT2i initiation date. This may be partly due to an individual having prescription information for a GLP-1 RA or SGLT2i before receiving a CKD diagnosis. In the present study, we did not assess the order in which individuals were diagnosed with T2D and CKD because GLP-1 RA and SGLT2i are often prescribed for treatment of T2D.

Mean age was similar across data sources, with a median age of 67 to 69 years in the GLP-1 RA cohort and 68 to 72 years in the SGLT2i cohort. The proportion of males and females varied across data sources, with some having a higher proportion of females and others a lower proportion. Though not directly a comparable cohort, a previous study performed using CDM data noted female gender to be associated with higher odds of being prescribed a GLP-1 RA (OR, 1.22; 95% CI, 1.20-1.24).[52] The increase in the proportion of individuals with an index GLP-1 RA or SGLT2i prescription by year may be a general reflection of an increasing trend in use and the increasing number of studies highlighting their protective effects on cardiovascular and kidney outcomes.[53,54] Of note, the high prevalence of obesity in VID within the GLP-1 RA cohort may partly be driven by the fact that Spain has a mechanism of prior authorization for GLP-1 RA for diabetes wherein a prescription for a GLP-1 RA is only authorized in patients with a BMI > 30 as reported by the physician in the authorization formulary. The lag time for data incorporation was longer for PHARMO than for the other data sources; thus, fewer years of data were available in PHARMO, with no data captured in 2021.

The prevalence of CVD risk factors was variable across data sources, with hypertension and hypercholesterolemia being notably lower in PHARMO and DNHR. However, hypertension and hypercholesterolemia were the most prevalent comorbidities across all data sources. A limitation in defining medical conditions in DNHR is that diagnoses made by GPs are not captured in the National Patient Registry unless a patient has a hospital encounter with that condition or at which the condition is noted; thus, diseases managed mainly by GPs, such as hypercholesterolemia, may be under-recorded in the data source rather than a true reflection of lower prevalence of these conditions in these countries. The prevalence of chronic conditions being higher in J-CKD-DB-Ex than in the other data sources may be partly attributed to the nature of J-CKD-DB-Ex being a hospital-based data source. Individuals admitted to hospitals often tend to be less healthy and have more severe disease than those seen in primary care settings and those from the general population; thus, there may be selection factors that draw individuals with worse health to hospital settings.

In the present study, among patients with HbA_{1c} values, most patients across all data sources had HbA_{1c} levels > 8% in the GLP-1 RA and SGLT2i cohorts. Similar findings were observed in a cross-sectional analysis of SGLT2i and GLP-1 RA prescriptions from 01 JAN 2019 to 31 DEC 2020 in the Veterans Health Administration System (VHAS), where those with higher HbA_{1c} levels were more likely to be prescribed a GLP-1 RA.[55] This was not as pronounced within the SGLT2i cohort, where HbA_{1c} values were more evenly distributed, especially in the European data sources. In both the GLP-1 RA and SGLT2i cohorts, across data sources, the median duration of T2D among GLP-1 RA new users ranged from 4 to 12 years, with the lowest duration noted in CDM, which is composed of enrollees of a US commercial insurer, and the highest noted in the European databases, which are composed of EHRs from national or regional healthcare systems. Duration of chronic conditions such as T2D and CKD before initiating index treatment is dependent on the length and completeness of pre-index data. Enrollee turnover is high in US commercial health plans,[56] resulting in shorter pre-index time than in countries in which most residents have national insurance over their lifetime.

The finding that metformin was the most prescribed GLD before the index medication in all data sources, with the exception of J-CKD-DB-Ex in the GLP-1 RA drug cohort and J-CKD-DB-Ex and VID in the SGLT2i cohort sources, could be attributed to a host of factors, including differences in treatment guidelines, medical training, drug availability, pricing, effectiveness of treatment in populations with different characteristics, or patient preferences. A recent study using the National Health Insurance Database in Japan also reported a high prescription rate for DPP-4 inhibitors, noting that one of the reasons for this finding might be that this drug class is more effective at reducing HbA_{1c} levels among individuals of East Asian ethnicity, including Japanese ethnicity, than among other groups due to differences in genetics and adiposity.[57] Recommendations from the Japan Diabetes Society (JDS) have led to preferential use of DPP-4 inhibitors, including within non–JDS certified facilities.[58] In the present study, the diabetes severity score was higher in J-CKD-DB-Ex and VID than in the other data sources for both the GLP-1 RA and SGLT2i medication cohorts. Differences in health systems and access to care factors may contribute to the differences observed here.

Although the present study was descriptive in nature, the finding that the greatest proportion of patients in each data source in the GLP-1 RA cohort were classified as having stage 3 CKD based on eGFR values or a diagnostic code aligns with a previous study in VHAS, which found that having a CKD diagnosis was a risk factor for receiving a GLP-1 RA prescription (adjusted OR, 1.13; 95% CI, 1.12-1.15), with worse CKD stage associated with increased odds of receiving a GLP-1 RA prescription.[55] Although CKD was not an approved indication for GLP-1 RA at the time of the present study, these results may reflect clinical practice based on the protective renal effects observed in trials.[54]

In the GLP-1 RA cohort, the finding of median duration of CKD at baseline being lower in CDM and J-CKD-DB-Ex than in the other data sources may be attributed in CDM to the nature of commercial health insurance; if patients are switching insurance frequently and earlier diagnoses while on another health insurance plan are thus not captured, it would appear as though the diagnoses were more nascent than in actuality. The generally shorter duration of CKD diagnosis compared with the previously mentioned T2D diagnosis duration may also provide some insight into the temporal sequence of diagnosis, with more patients diagnosed with diabetes first, followed by CKD in both the GLP-1 RA and SGLT2i cohorts. However, the sequence of diagnoses was not specifically examined in the present study. CKD stage 3 (based on eGFR value or diagnosis code) was lowest in CDM, which may be partly attributed

to the higher percentage of patients missing either an eGFR measure or a diagnosis code in the data. In the present study, we only had access to claims data from CDM, which contained limited information on laboratory measures such as eGFR, potentially resulting in an under-capture of cases based on eGFR values alone. Similarly, the percentage of patients with severe CKD based on ACR measures was among the lowest in CDM in the GLP-1 RA cohort and CDM and PHARMO in the SGLT2i cohort, in which > 70% of patients were missing an ACR reading before or on the index date. This finding may once again be attributed to the use of CDM claims data alone, where information on ACR measures was limited.

The most common drug class used before the index medication was either ACEi or ARB across all data sources and within the GLP-1 RA and SGLT2i cohorts. This finding is consistent with other studies, which have noted antihypertensive agents to be most frequently prescribed for patients with CKD and T2D.[59] An additional study found an increased use of ACEi/ARB from 1999 to 2014.[60] In the present study, another consistent finding across all data sources was that hypertension was the most frequently recorded medical condition associated with increased risk of CKD. Patients in J-CKD-DB-Ex had a higher prevalence of other medical conditions associated with risk of CKD (i.e., glomerulonephritis, renovascular disease, autoimmune disease, and gout or hyperuricemia). This was seen with comorbidities in general and is likely attributed to J-CKD-DB-Ex being a hospital-based data source.

When compared with the other medication cohorts, and across data sources, sMRA initiators were more frequently noted to have stage 3 and 4 CKD than those in the other cohorts and hypertension tended to be even more common than in the other cohorts. sMRAs are commonly used for the treatment of hypertension, which might explain the higher prevalence in this group. Similarly, use of digoxin was consistently higher among sMRA initiators than in the other cohorts. Medication use was another difference consistent across data sources. Use of loop diuretics was much more common among sMRA initiators than among patients from other medication cohorts (in all data sources, use larger than 50% compared with the highest use of 32% in the other medication cohorts). Regarding comorbidities, the most striking and consistent difference was the prevalence of heart failure, which, across data sources, was much higher in the sMRA cohort than in the other medication cohorts. This difference was also reflected in the much higher hospital admission rate for heart failure in this cohort than in the other two medications cohorts, which was also consistent across all data sources. Similarly, CHD and cerebrovascular disease tended to be consistently higher in the sMRA cohort than in the other two cohorts. This may be attributed to the older age of the cohort. Overall, the clinical profile of the sMRA cohort was clearly different from that of the other two medication cohorts. sMRA initiators were older, with less severe T2D but with more complications, more advanced CKD, and higher coexistence of heart failure. Although the greatest proportion of patients switching from exposed to not exposed occurred within the first year of the index date for all medication cohorts, the percentage of patients who died at each timepoint was higher in the sMRA cohort than in the other medication cohorts. This outcome may be partly attributed to the more severe disease profile among these patients compared with patients not taking these medications.[61]

In the present study, the index GLP-1 RA and SGLT2i were most commonly an add-on to an existing study-defined medication of interest, except for those in J-CKD-DB-Ex. In the J-CKD-DB-Ex cohort, the index GLP-1 RA and SGLT2i were most commonly a monotherapy. This may be partly because prescriptions in J-CKD-DB-Ex may be under-captured before entry into the registry. The J-CKD-DB-Ex database does not include medical record information before the first encounter at a J-CKD-DB-Ex hospital. In addition, although

nearly all prescriptions issued in the inpatient or outpatient settings of J-CKD-DB-Ex hospitals are captured in the database, prescriptions issued at community clinics or non–J-CKD-DB-Ex hospitals are not; this means that patients might have received other classes of drugs in these other settings, which would not have been reflected in this data source. Whether the index GLP-1 RA or SGLT2i was an add-on or a switch to a study-defined medication of interest, ACEi/ARB were the most common drug class that patients' were receiving before or on the index date, except for patients in J-CKD-DB-Ex. The use of ACEi/ARB might be partially attributed to the high prevalence of hypertension in these cohorts, as these medication classes are considered first-line therapies for hypertension in patients with non-proteinuria CKD.[62,63] In the case of an SGLT2i index medication, the findings of this study are in alignment with practice guidelines.

In the SGLT2i cohort, the length of the initial treatment episode was shortest in PHARMO as was the total duration of exposure to the SGLT2i class of medications during follow-up. SGLT2i has been used in The Netherlands since 2013 for T2D, but uptake was initially limited. SGLT2i use was included in the GP guidelines from 2018 and gained more prominence in 2021 when the indication for renal protection was added to the prescribing information. The median days' supply of the index SGLT2i was notably higher in DNHR (over 100 days compared with approximately 30 days in the other data sources), but this variable was not directly available in DNHR and had to be calculated. This finding may also reflect differences in prescribing patterns in Denmark compared with the other countries. Interruptions in SGLT2i use lasting 90 days or more was more likely in J-CKD-DB-Ex than in the other data sources, but the mean duration of total exposure to the index therapy in J-CKD-DB-Ex was similar to that in DNHR and VID. Somewhat similarly, the percentage of patients with an interruption of current use of an index GLP-1 RA lasting 90 days or more was most common in J-CKD-DB-Ex and CDM and was notably higher than in the other data sources. Duration of the initial exposure episode after cohort entry was notably shorter in CDM and PHARMO. Differences observed in J-CKD-DB-Ex and CDM may be driven by under-capture of medicines outside J-CKD-DB-Ex hospitals and, in the case of CDM, a change in insurance provider or a prescription written by an out-of-network provider or dispensed at an out-of-network pharmacy. These factors may make it likely to appear that the episode was shorter than in actuality.

Although the GLP-1 RA and SGLT2i cohorts identified in these analyses are not mutually exclusive and comparisons should be interpreted in the context that this study was not designed to compare the medication cohorts directly, some interesting patterns did emerge. First, there were more male patients than female patients who were new users of SGLT2i than new users of GLP-1 RA in all data sources, except CDM and PHARMO. Obesity was more common in the GLP-1 RA cohorts than in the SGLT2i cohorts, which reflects the indication for GLP-1 RA during the study periods, as was baseline use of insulin. Duration of both T2D and CKD was generally longer in the GLP-1 RA cohorts than in the SGLT2i cohorts. The severity of T2D was also greater in the GLP-1 RA cohorts than in the SGLT2i cohorts. Additionally, across all data sources, the GLP-1 RA cohorts tended to have worse kidney function at baseline than the SGLT2i cohorts. Similar differences have been found in other studies.[53,55,64,65] These findings suggest later use of GLP-1 RA relative to SGLT2i in the T2D treatment pathway. Finally, at one year of follow-up, the GLP-1 RA cohorts generally had a higher proportion of patients with current use (more than 70%, except in CDM) than the SGLT2i cohorts (more than 50%). These results could suggest better patient adherence to GLP-1 RA medications, but many other factors could explain the results, such as differences

in patient profiles and characteristics, differences in side effects, and variations in patient preferences that were not measured in this study.

Despite the heterogeneity noted, some elements of data quality were consistently observed across the data sources and GLP-1 RA and SGLT2i cohorts. The completeness of data on CKD stage (based on eGFR test result or diagnosis code) was very high in all data sources, and HbA_{1c} values were missing for few patients (in DNHR and J-CKD-DB-Ex). Additionally, the characteristics of patients with T2D in this study resemble those expected in patient populations with T2D and CKD.[55,66] For example, metformin was the most commonly prescribed medication before or on the date of initiation in most data sources. In the data sources with information on BMI, a low amount of the population was not overweight. Additionally, comorbidities, such as hypertension, hypercholesterolemia, and macrovascular complications of T2D, were common in all data sources and across medication cohorts.

11.3.2 Post-finerenone period

In CDM, some of the differences between the SGLT2i and the GLP-1 RA cohorts described in the pre-finerenone period remained during the post-finerenone period. A higher percentage of patients in the GLP-1 RA cohort were obese and had more complex treatment for T2D than those in the SGLT2i cohort. However, renal function in the GLP-1 RA cohort was not worse than that in the SGLT2i cohort. The finerenone cohorts had worse renal function than the other two cohorts, which, together with the fact that use of finerenone as "add-on" and as "add-on and switch" to study-defined medications of interest was more common than in the other two cohorts, could indicate that finerenone (at least in CDM) is prescribed more as add-on therapy than as initial therapy for CKD in patients with T2D.

The differences between the pre- and post-finerenone periods for the SGLT2i and GLP-1 RA cohorts can be explained by changes in guidelines that may lead to better control of T2D and more use of SGLT2i. The increased prevalence of CHF among patients taking SGLT2i may be related to the new indication of that medication for heart failure in 2022.[67,68]

Regarding finerenone dosing, 18% of patients were started with the 20-mg daily dose, which is the initial dose recommended for patients with eGFR ≥ 60, and this percentage is comparable to the percentage of patients at CKD stages 1 or 2 (with eGFR ≥ 60) at baseline (Figure 17). However, approximately 17% of patients were up titrated to the 20-mg daily dose at the one-year mark following initiation, which seems lower than would be expected given the percentage of patients with hyperkalaemia at baseline (less than 10%). It should be noted that potassium levels during follow-up were not assessed in this study, and given the cross-sectional nature of the study, we were unable to assess titration patterns and corresponding hyperkalaemia diagnosis within the same patient.

11.4 Generalizability

This study used healthcare data from multiple countries and data sources. Using multiple data sources enabled the evaluation of patients and treatment patterns in diverse settings, populations, and healthcare systems, which may be more reflective of the general population with CKD and T2D. Additionally, the data sources represented EHR data, commercial insurance claims and population registries, coding systems, and formularies. Conducting the study in a variety of different healthcare contexts and settings likely improved how broadly the findings can be applied, while also enabling us to examine how differences in guidelines and treatment recommendations by country may impact findings. The exclusion criteria were minimized with the intent of including patients with CKD and T2D initiating these

medications in the real-world setting. Furthermore, for finerenone, the inclusion and exclusion criteria were broad and aligned with the clinical criteria for medication prescription; alongside testing a cohort definition for inclusion in the wide finerenone cohort, which was less restrictive. Finally, the healthcare databases used in the study capture information as part of routine healthcare interactions. This may limit generalizability because patients who seek care frequently enough to enter the study may differ from those with less HCRU. This may be especially true for the US data source, in which patients may be reflective of patients on a particular insurance plan for whom the drug is covered, as opposed to eligible patients more broadly or those who have long-term coverage with a single insurer (12 months was required for inclusion in the current study). Similarly, the characteristics of patients in the medication cohorts in J-CKD-DB-Ex, which is a longitudinal, tertiary, hospital-based registry, may reflect patients with more severe illness, with younger patients with advanced CKD being more likely to be referred to and managed in university hospitals.[69] In the US and Japan data sources, the inclusion criterion of a minimum of 12 months continuous enrolment in the database may exclude some patients without sufficient baseline histories.

12. Other information

Not applicable

13. Conclusions

In conclusion, in this study population with CKD and T2D in 2012-2021, largely before the approval of new CKD indications for existing treatments (SGLT2i and GLP-1 RA) and new CKD treatments (e.g., finerenone), treatment options and therapeutic approaches were heterogeneous and dynamic both within and among data sources. At one year of follow-up, half or more of patients who initiated an SGLT2i were currently receiving SGLT2i treatment across the data sources.

We observed a steady increase in GLP-1 RA use across data sources during the study period, and persistence with treatment was high. Findings suggest that GLP-1 RA use is related to both severity of T2D and the presence of obesity.

The sMRA cohort had a completely different clinical profile from that of the other two cohorts. This may be related to the fact that sMRAs are not indicated to treat T2D or CKD but may be used to treat resistant hypertension and heart failure, which are common among patients with T2D.

In CDM, the differences observed between the pre- and post-finerenone periods in the SGLT2i and GLP-1 RA cohorts are likely related to changes in clinical guidelines that mainly involved SGLT2i. Patients who initiated finerenone had worse renal function than patients in the other two cohorts, and finerenone seems to be prescribed more as second-line therapy for patients with worsening renal function than as initial therapy among patients with T2D and CKD. The percentage of patients with a finerenone dose of 20 mg at cohort entry was consistent with the baseline eGFR levels of the finerenone initiators; however, up-titration to the 20-mg daily dose occurred in a lower than expected percentage of patients initiating with a 10-mg dose.

The treatment landscape for the prevention of CKD progression in patients with T2D is evolving rapidly. Understanding the characteristics and patterns of use of existing treatments and characterizing the differences in populations and treatment patterns across data sources is

a first step in designing future studies to evaluate kidney and cardiovascular outcomes with treatment to prevent CKD progression.

14. References

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Appendices

Annex 1: List of stand-alone documents

Table 32: List of stand-alone documents

Document name	Final version and date (if available)
Investigator List	V2.0, 19 DEC 2024
Publication Committee Member List	V2.0, 17 JAN 2023
Executive Advisory Committee Member List	V3.0, 17 JAN 2023
Statistical Analysis Plan	V2.0, 07 JUN 2024
List of Institutional Review Board Approvals	V1.0, 12 DEC 2024

Annex 2: Description of data sources

Danish National Health Registers (DNHR), Denmark

Administrative data were used from the Danish Health Care System. Denmark has 5.8 million inhabitants and is divided into five 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 are recorded in several Danish databases.

DNHR contains data on hospital-related diagnosis codes, surgical procedures, and discharge dates from inpatient hospitals in Denmark since 1977 and data from outpatient clinics, EDs, 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 inpatient, outpatient, or ED encounters.

DNHR contains data on all reimbursed drug prescriptions from local pharmacies since 1995. The database also contains information on dispensing details, such as name, date, ATC code, volume according to defined daily dosage, package size, 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 began recording laboratory data in 2013 for most Danish administrative regions and is considered complete nationwide from July 2015 onwards (except for a data “hole” for the Central Denmark Region in 2019-2020). Thus, for the current study, there are missing laboratory data for the period before 2015 for some Danish regions.

DNHR contains information about the activities of health professionals contracted with the tax-funded public healthcare system (e.g., GPs, medical specialists, physiotherapists). 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 (PHARMO), The Netherlands

PHARMO is a population-based data source with combined anonymous electronic healthcare data from different primary and secondary healthcare settings in The Netherlands.[70] The different data sources, including data from GPs, inpatient and outpatient pharmacies, clinical laboratories, hospitals, the cancer registry, the pathology registry, and the 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 with the General Data Protection Regulation (GDPR). STIZON acts as a trusted third party between the data sources and users of the anonymized data and can request proportional study-specific data sets, in accordance with the GDPR.

The longitudinal nature of PHARMO enables follow-up of more than 10 million individuals from a well-defined population in The Netherlands for an average of 12 years. Currently, PHARMO covers over 7 million active individuals out of 17 million inhabitants of The Netherlands. Data collection period, catchment area, and overlap between data sources differ. All electronic patient records in PHARMO include information on age, sex, socioeconomic status, and mortality. Other available information is dependent on the data source. PHARMO is updated yearly in Q4, with a lag of 1 to 1.5 years (i.e., in Q4 2022, the data from 2021 became available). 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 and 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.[71] 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 and 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.[71] Diagnoses and symptoms are coded according to the *International Classification of Primary Care* (ICPC),[72] which can be mapped to ICD codes, but can also be entered as free text. General practitioner data cover a catchment area representing 3.2 million residents.

Hospital data

The hospital data comprise data sets containing information 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[73] and comprise records from nearly all hospitals in The Netherlands. With permission from each hospital, the data are linked with PHARMO for research purposes by the trusted third party.

This data set 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,[74] and procedures are coded according to the Dutch Hospital Data Foundation registration system for procedures,[75] which links to the Dutch Healthcare Authority (NZa) declaration codes[76] and the Dutch Classification of Procedures.[77] Currently, PHARMO has access to data from 1998 onwards and for over 80% of hospitals in The Netherlands.

Valencia Health System Integrated Database (VID), Spain

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 (e.g., sex, age, nationality), clinical data (e.g., diagnoses, procedures, diagnostic tests, imaging), pharmaceutical data (e.g., prescription, dispensation), and healthcare utilization data from hospital care, EDs, specialized care (including mental health and obstetrics care), primary care, and other public health services. All information in VID 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 (e.g., dates and causes of VHS entitlement or disentitlement, insurance modality, pharmaceutical copayment status, assigned Healthcare Department, Primary Healthcare District, primary care doctor) as well as some sociodemographic data (e.g., sex, date of birth, nationality, country of origin, previous year income strata, employment status, risk of social exclusion, geographic location, address, other administrative data). Importantly, SIP includes patients' dates 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 other 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 through two 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 and provides information on dates, visits, procedures, laboratory test results, diagnoses, and clinical and lifestyle information. It also includes information on several health programmes (e.g., those for healthy children, vaccines, pregnancy, notifiable diseases), 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 those from both primary care and outpatient hospital departments, using the ATC classification system and the National Pharmaceutical Catalogue, which allow 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 and permits linkage of individual prescriptions and dispensations through a specific prescription identification number. This results in a competitive advantage compared with other pharmaceutical databases that generally 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 use since 2008 and provides comprehensive information covering all areas of specialized care from admission, outpatient consultations, hospitalization, emergencies, diagnostic services (e.g., laboratory tests, imaging, microbiology, pathology), 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 surgeries in the VHS hospitals, including public–private partnership hospitals (approximately 450,000 admissions per year in the region). The MBDS includes information on 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 used 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 tumour 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 EDs. 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 approximately 45% of all ED visits between 2008 and 2014 up to approximately 75% in 2017, primarily due to the progressive incorporation of hospital coding.

Data lags in VID

In all databases within VID, individual data are collected daily as part of the routine clinical care provided to patients. Accordingly, because data sets are updated daily, data may be available for research up to the same day that 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 becoming 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)

J-CKD-DB-Ex is a large-scale, nationwide comprehensive clinical database of patients with CKD based on EHR data from five participating university hospitals. J-CKD-DB-Ex data are automatically extracted from the records of all patients treated at participating university hospitals who are aged 18 years or older and have CKD (proteinuria ≥ 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 for approximately 250,000 patients. The data are updated once per year, at the end of each calendar year.

Optum's de-identified Clinformatics® DataMart (CDM), United States

CDM is a database comprising administrative health claims for members of a large national managed care company affiliated with Optum. It comprises commercial health plan data and Medicare Advantage members with service dates beginning January 2007 to the present. The population in CDM is geographically diverse, spanning all 50 US states plus the District of Columbia and covering approximately 3% to 4% of the US population. CDM 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 medication changes. Medical claims or encounter data are collected from all available healthcare sites (e.g., inpatient hospital, outpatient hospital, ED, 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 before 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, 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 also includes data tables related to member inpatient confinements, member enrolment, and provider data.

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

Table 33: Summary of characteristics of participating data sources

Feature	Denmark, DNHR	The Netherlands, PHARMO	Spain, VID	Japan, J-CKD-DB-Ex	US, 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	NDCs
Capture of medication information	Outpatient pharmacy prescriptions in Danish National Prescription Registry	Dispensing records in Outpatient Pharmacy Database	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 two weeks during the first year that the medication is on the market, and for longer periods (e.g., 30 days) thereafter.	Outpatient pharmacy dispensing records
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

Feature	Denmark, DNHR	The Netherlands, PHARMO	Spain, VID	Japan, J-CKD-DB-Ex	US, CDM
Data privacy standards	Cell frequencies (categorical variables) of less than five are not reported, and related cells have additional masking, if needed, to prevent back calculation; for continuous variables, 1st and 99th percentiles are reported instead of minimum and maximum values.	If the number of observations or patients is less than five per stratum, these are not specified further.	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 1st and 99th percentiles are reported instead of minimum and maximum values.	Categorical variables with low counts are not reported. For continuous variables, the 1st 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 Restrictions from data-use agreements with clients
Study-specific information					
Definition of T1D	< 30 years old at first diabetes record (hospital diagnosis or medication prescription); if first diabetes record is on or after 1995, mandatory use of insulin around first record is required.	At least one diagnosis code for T1D in the GP data or single insulin dispensing, or aged < 30 years at first insulin dispensing recorded on or before the index date.	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, ED, physician's office, surgery center) for all types of provided services. At least two diagnosis codes for T1D during the baseline period [− all available, 0 days) were required.

Feature	Denmark, DNHR	The Netherlands, PHARMO	Spain, VID	Japan, J-CKD-DB-Ex	US, CDM
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 GP data or at least two consecutive dispensings of non-insulin drugs used in diabetes (ATC code A10B) within six 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, ED, 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 during an inpatient, outpatient, or ED visit using both primary and secondary diagnosis as recorded in the Danish National Patient Registry.	Recorded diagnoses in primary care or inpatient hospital setting.	ICD codes (recorded diagnosis in the index date in the electronic medical record in VID covering primary and secondary care).	Recorded diagnoses in inpatient and outpatient settings in hospital care.	Recorded diagnoses from medical claims for encounter data from all available healthcare sites (e.g., inpatient hospital, outpatient hospital, ED, physician's office, surgery center) for all types of provided services.
Estimation of days' 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 (e.g., 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; obesity 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; CDM = Optum's de-identified Clinformatics® DataMart; CPT = Current Procedural Terminology; DNHR = Danish National Health Registers; ED = emergency department; GP = general practitioner; 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; 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 2023 US census (https://www.census.gov/popclock/).

Annex 3: Medication codes

Table 34: 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.

Table 35: List of GLP-1 RA drugs by drug substance and ATC code

Drug substance	ATC code
Exenatide	A10BJ01
Liraglutide	A10BJ02
Lixisenatide	A10BJ03
Albiglutide	A10BJ04
Dulaglutide	A10BJ05
Semaglutide	A10BJ06
Lixisenatide and insulin glargine	A10AE54
Liraglutide and insulin degludec	A10AE56

ATC = Anatomical Therapeutic Chemical; GLP-1 RA = glucagon-like peptide-1 receptor agonist.

Table 36: List of sMRA drugs by drug substance and ATC code

Drug substance	ATC code
Spironolactone	C03DA01
Potassium Canrenoate	C03DA02
Canrenone	C03DA03
Eplerenone	C03DA04

ATC = Anatomical Therapeutic Chemical; sMRA = steroidal mineralocorticoid antagonists.

Table 37: List of nsMRA drugs by drug substance and HOT code

Drug substance	HOT code
Esaxerenone	1.25 mg: 1267013010101, 1291018010101, 1291018010102 2.5 mg: 1267020010101, 1291025010101, 1291025010102, 1291025010201 5 mg: 1267037010101, 1291032010101, 1291032010102
Apararenone	Not Available

HOT = standard master codes for pharmaceutical products; nsMRA = non-steroidal mineralocorticoid receptor antagonists.

Table 38: List of finerenone ATC code

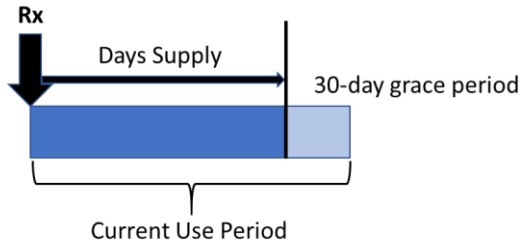
Drug substance	ATC code
Finerenone	C03DA05

ATC = Anatomical Therapeutic Chemical.

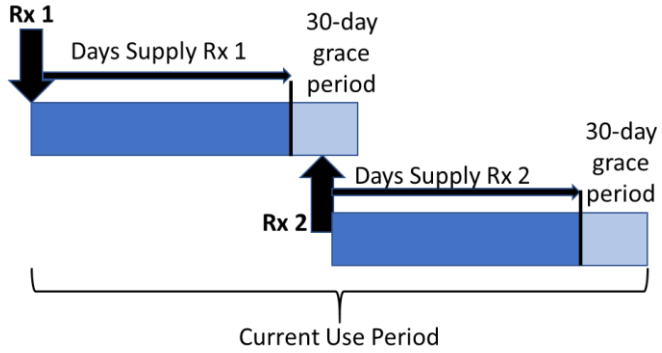
Annex 4: Classification of index medications

Definition of current use

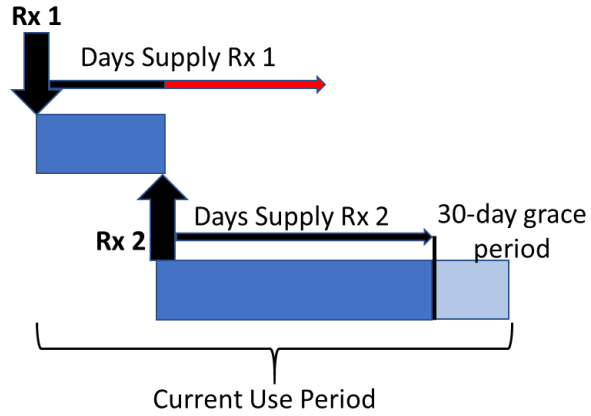
- New use of study drug: The date of the first observed prescription record or prescription dispensing for a study drug during the study period was the *index date,* and follow-up started the day after. Any medication within the same class as the study drug class was eligible. Patients without use of 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.



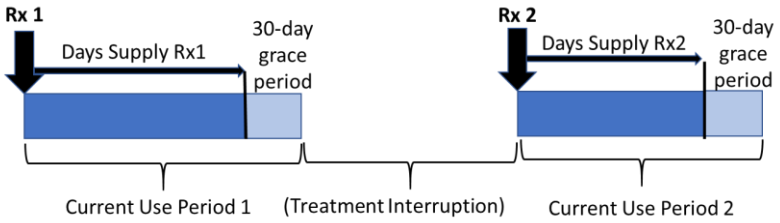
- For consecutive prescriptions of the study medication separated by gaps of 30 days or less, the time from current use included the gaps between prescriptions.



- 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) was not 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 exenatide and liraglutide (both GLP-1 RA) with a 30-day supply given on 01 JAN 2022 was treated as follows:

- A prescription/dispensing for GLP-1 RA (exenatide) on 01 JAN 2022 with a 30-day supply
- A prescription/dispensing for liraglutide RA on 01 JAN 2022 with a 30-day supply

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

Classification of index medications

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

- Monotherapy
- Combination therapy
- Add-on therapy
- Switched-to index therapy

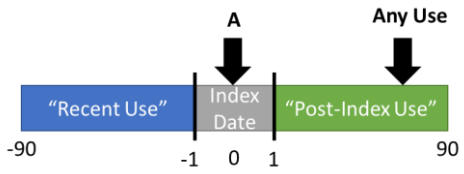
- Both add-on and switched-to index therapy
- Non-evaluable index therapy

To make these classifications, we evaluated whether other drugs of interest were prescribed at any point during three distinct periods. These medications included study drugs plus ACEi/ARB. Because treatment indication was not available in the study data, we could not determine whether the intent of prescribing these medications was to modify CKD.

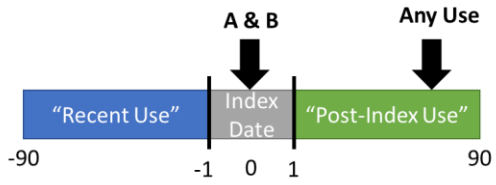
- "Recent use": the 90 days before the index date [−90, −1]
- "Index date": on the index date [0]
- "Post-index use": the 90-day period after the index date [1, 90]

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

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

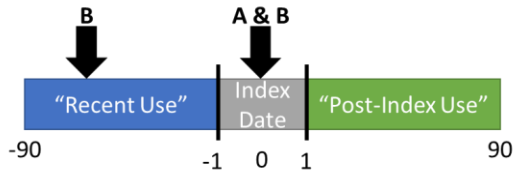


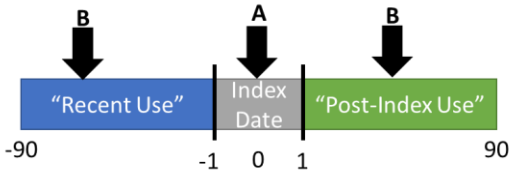
- Combination therapy: (1) The index medication was a fixed-combination product or (2) two or more study drugs (A & B) were prescribed on the index date.



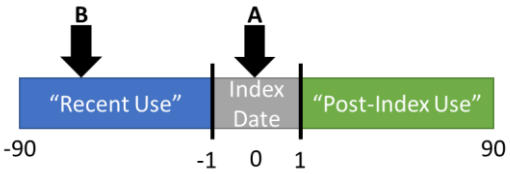
However, if another study drug (B or C in the examples below) was prescribed during the period of "recent use" to classify the index medication (A in the examples below), both the "index date" and "post-index" periods were evaluated. Based on the pattern of prescribing, the index medication was classified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

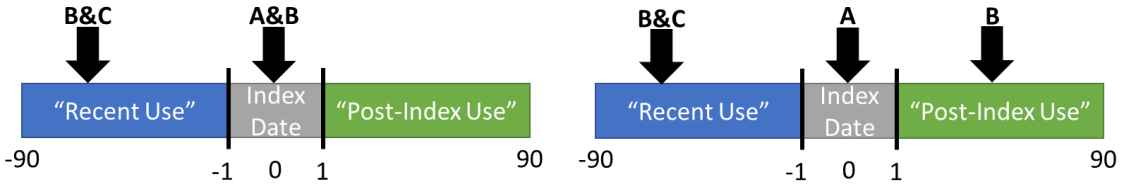




- Switched-to index therapy: If another drug class(es) was prescribed during the period of "recent use" *and* that drug class(es) had no recorded prescription both on the "index date" and during the "post-index" period



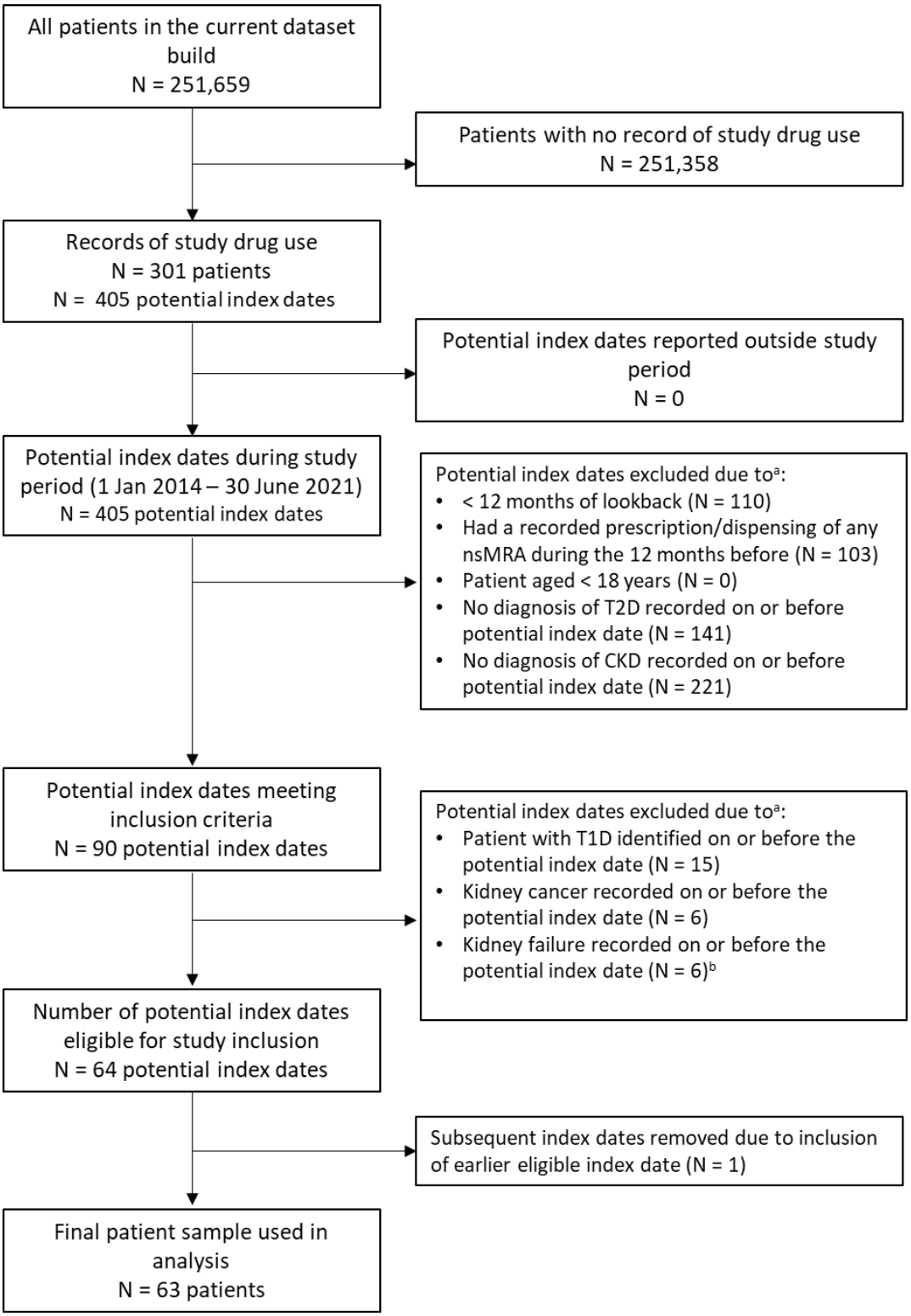
- Both add-on and switched-to index therapy: When more than one other drug class was identified in the period of "recent use" and only a subset of those classes had a prescription either at the "index date" or in the "post-index" period, as illustrated below



- 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

Annex 5: Figures

Figure 25: Attrition of cohort of nsMRA users in J-CKD-DB-Ex



CKD = chronic kidney disease; GLP-1 RA = glucagon-like peptide-1 receptor agonist; J-CKD-DB-Ex = Japan Chronic Kidney Disease Database Extension; nsMRA = non-steroidal mineralocorticoid receptor antagonists; T1D = type 1 diabetes; T2D = type 2 diabetes.

Note: Cohort selection involved evaluating multiple potential index dates per patient.

a Not mutually exclusive. Assessed at the time of potential index date for the medication.

b Patients may have had more than 1 indicator for kidney failure.

Annex 6: Tables

Table 39: Selected baseline characteristics of nsMRA new users

Characteristic	**J-CKD-DB-Ex (N = 63), N (%) (unless otherwise noted)**
Age group (years) at the index date	
< 40	1 (1.6%)
40-49	5 (7.9%)
50-59	4 (6.3%)
60-69	19 (30.2%)
70-79	25 (39.7%)
≥ 80	9 (14.3%)
Age at the index date (years)	
Mean (SD)	69.4 (10.9)
Median (1st, 99th percentiles)	71 (40, 94)
Sex	
Male	39 (61.9%)
Female	24 (38.1%)
Unknown	NA
Calendar year of index date[a]	
2012	NA
2013	NA
2014	NA
2015	NA
2016	NA
2017	NA
2018	NA
2019	3 (4.8%)
2020	37 (58.7%)
2021	23 (36.5%)
BMI (calculated as kg/m^2)	
< 20 (underweight)	(0.0%)
20-24.9 (normal)	(0.0%)
25-29.9 (overweight)	(0.0%)
30-39.9 (obese)	(0.0%)
≥ 40 (severely obese)	(0.0%)
Unknown	63 (100.0%)

Characteristic	**J-CKD-DB-Ex (N = 63), N (%) (unless otherwise noted)**
Obesity[b]	
Yes	3 (4.8%)
Smoking status	
Current smoker	(0.0%)
Former smoker	(0.0%)
Non-smoker	63 (100.0%)
Alcohol abuse	
Yes	1 (1.6%)

BMI = body mass index; J-CKD-DB-Ex = Japan Chronic Kidney Disease Database Extension; NA = not available; NE = not estimable; SD = standard deviation.

Note: The nsMRA used in Japan was esaxerenone.

[a] By design, only 6 months of observation were included in 2021.

[b] Obesity was defined based on the presence of a diagnostic code or BMI.

Table 40: Selected characteristics of new users of SGLT2i, stratified by whether an ACR test was recorded in the year before or on the index date, by data source

Variable	DNHR		PHARMO		VID		J-CKD-DB-Ex		CDM	
	ACR	No ACR	ACR	No ACR	ACR	No ACR	ACR	No ACR	ACR	No ACR
	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
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
DPP-4i	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

Variable	**DNHR**		**PHARMO**		**VID**		**J-CKD-DB-Ex**		**CDM**	
	ACR	**No ACR**	**ACR**	**No ACR**	**ACR**	**No ACR**	**ACR**	**No ACR**	**ACR**	**No ACR**
	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**
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
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

Variable	DNHR		PHARMO		VID		J-CKD-DB-Ex		CDM	
	ACR	No ACR	ACR	No ACR	ACR	No ACR	ACR	No ACR	ACR	No ACR
	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
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
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 GLD 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

Variable	DNHR		PHARMO		VID		J-CKD-DB-Ex		CDM	
	ACR	No ACR	ACR	No ACR	ACR	No ACR	ACR	No ACR	ACR	No ACR
	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
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
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; CDM = Optum's de-identified Clinformatics® DataMart; CKD = chronic kidney disease; DNHR = Danish National Health Registers; DPP-4i = dipeptidyl peptidase-4 inhibitors; GFR = glomerular filtration rate; GLD = glucose-lowering drugs; 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 = non-steroidal anti-inflammatory drug; 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 key diagnoses: retinopathy, nephropathy, neuropathy, cerebrovascular disease, cardiovascular disease, peripheral vascular disease, and metabolic complications.

[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]).

Table 41: Selected characteristics of new users of GLP-1 RA, stratified by whether an ACR test was recorded in the year before or on the index date, by data source

Variable	DNHR		PHARMO		VID		J-CKD-DB-Ex		CDM	
	ACR (N = 15,329)	No ACR (N = 3,600)	ACR (N = 167)	No ACR (N = 309)	ACR (N = 7,757)	No ACR (N = 4,041)	ACR (N = 204)	No ACR (N = 125)	ACR (N = 48,612)	No ACR (N = 21,546)
Age group (years) at index date										
< 40	2.4	1.7	0.0	0.3	1.2	0.7	5.9	2.4	1.0	0.7
40-49	7.0	5.5	6.6	1.6	5.9	4.0	7.4	8.8	4.3	4.1
50-59	18.3	15.3	17.4	16.5	20.3	13.9	20.1	19.2	14.5	14.3
60-69	29.8	26.1	40.7	38.8	33.0	30.6	23.0	23.2	32.7	31.0
70-79	33.2	35.7	30.5	38.2	30.6	37.6	29.9	28.0	38.0	37.1
≥ 80	9.3	15.6	4.8	4.5	9.2	13.2	13.7	18.4	9.5	12.8
Median age (years) at index date	67.0	70.0	66.0	67.0	67.2	70.2	67.1	69.0	69.0	69.0
Sex										
Male	61.4	51.2	59.9	39.5	57.0	52.6	59.3	60.0	48.8	46.0
Female	38.6	48.8	40.1	60.5	43.0	47.4	40.7	40.0	51.2	54.0
Unknown	NA	NA	NA	NA	NA	NA	NA	NA	< 0.1	0.0
Obesity	31.4	34.6	84.4	82.8	90.3	89.8	17.6	12.0	54.6	49.6
Medications for T2D ever prescribed in the 180 days before or on the index date[a]										
SGLT2i	28.8	24.1	6.6	6.5	43.6	37.3	56.4	47.2	14.2	11.5
Metformin	78.0	69.4	88.0	77.0	66.6	59.6	72.5	40.8	53.8	49.9
Sulfonylureas	13.5	12.7	57.5	56.0	9.6	7.4	39.7	27.2	38.7	33.8

Variable	DNHR		PHARMO		VID		J-CKD-DB-Ex		CDM	
	ACR (N = 15,329)	**No ACR (N = 3,600)**	**ACR (N = 167)**	**No ACR (N = 309)**	**ACR (N = 7,757)**	**No ACR (N = 4,041)**	**ACR (N = 204)**	**No ACR (N = 125)**	**ACR (N = 48,612)**	**No ACR (N = 21,546)**
DPP-4i	35.9	32.1	15.0	12.6	64.4	60.0	83.3	68.0	25.1	22.4
Insulin use 180 days before or on the index date	39.0	37.2	38.0	20.2	52.6	53.9	82.4	90.4	45.7	42.7
Diabetes Severity Complications Index Score[b]										
Mean (SD)	2.5 (1.7)	2.6 (1.9)	2.3 (1.6)	2.1 (1.6)	4.3 (2.1)	4.7 (2.1)	4.1 (2.2)	4.1 (2.2)	3.1 (2.2)	3.0 (2.2)
Median	2	2	2	2	4	4	4	4	3	3
1st, 99th percentile	0, 7	0, 8	1, 8	1, 8	2, 10	2, 11	0, 9	0, 9	0, 9	0, 9
CKD stage based on GFR[c] or diagnosis code[d]										
Stage 1: ≥ 90, normal or high	35.0	19.8	15.0	7.8	26.5	10.2	9.3	1.6	10.2	5.0
Stage 2: 60-89, mildly decreased	27.8	26.1	35.3	35.6	28.9	20.3	35.8	29.6	27.0	21.9
Stage 3: mildly to severely decreased	33.0	45.3	46.1	49.2	38.3	47.1	47.1	47.2	29.0	24.3
Stage 4: 15-29, severely decreased	3.8	4.4	3.0	6.1	6.1	8.6	7.4	18.4	5.5	4.4
Stage 5: < 15 OR treated by dialysis, kidney failure	NR	NR	0.6	0.3	0.2	0.3	0.5	3.2	0.5	0.5
Unspecified stage	NR	NR	NA	NA	0.1	5.6	NA	NA	10.0	13.5
Medical conditions associated with risk of CKD[d]										
Hypertension	80.1	81.1	72.5	77.0	92.1	95.4	91.2	85.6	94.6	92.0
Glomerulonephritis (all causes)	2.4	1.6	5.4	2.3	4.4	5.9	18.1	24.0	2.5	1.4

Variable	DNHR		PHARMO		VID		J-CKD-DB-Ex		CDM	
	ACR (N = 15,329)	No ACR (N = 3,600)	ACR (N = 167)	No ACR (N = 309)	ACR (N = 7,757)	No ACR (N = 4,041)	ACR (N = 204)	No ACR (N = 125)	ACR (N = 48,612)	No ACR (N = 21,546)
Renovascular disease	0.4	0.4	0.0	0.0	1.2	1.5	3.4	1.6	1.0	0.8
Autoimmune disease	4.8	5.6	0.6	1.6	7.3	8.3	28.4	32.8	6.6	6.0
Polycystic kidney disease	0.5	0.5	0.0	0.0	0.3	0.5	0.0	0.0	0.5	0.4
Gout or hyperuricemia[d]	5.2	6.4	4.2	1.9	30.3	37.3	35.8	35.2	12.1	10.8
Other medical conditions[d]										
Coronary heart disease	28.7	32.2	35.3	31.7	24.5	31.4	59.8	60.0	32.6	34.1
Cerebrovascular disease	11.9	15.9	10.8	10.7	11.6	14.6	54.9	47.2	12.1	13.1
Peripheral vascular disease	15.7	18.8	13.8	13.6	24.7	27.8	21.6	22.4	29.1	27.9
Hypercholesterolemia	33.2	34.8	33.5	38.2	81.3	81.9	88.2	78.4	91.1	84.6
CHD	11.7	18.2	15.0	15.5	4.3	7.5	58.3	60.0	19.3	24.0
Severe liver disease	0.4	1.1	6.6	3.9	5.8	7.0	3.4	7.2	1.0	1.0
HIV infection	0.2	0.2	0.0	0.3	0.2	0.6	4.9	4.8	0.5	0.4
Dementia	1.0	2.9	2.4	1.3	1.9	3.3	6.4	5.6	2.9	6.5
COPD	9.5	13.3	16.8	16.5	16.3	19.4	28.9	36.8	19.0	21.7
Malignancy (other than kidney cancer and non-melanoma skin cancers)	12.1	13.8	19.2	21.7	21.8	27.8	31.4	26.4	11.9	11.9
Medications other than GLD in the 180 days before or on the index date										
Thiazide-like diuretics	16.4	13.8	29.3	23.3	5.6	6.0	10.3	5.6	33.3	31.7
Loop diuretics	26.2	36.7	16.8	25.6	27.8	39.9	12.7	20.8	24.7	27.4
Potassium-sparing diuretics	0.8	1.1	3.0	2.3	1.2	1.8	0.0	0.0	2.4	2.5

Variable	DNHR		PHARMO		VID		J-CKD-DB-Ex		CDM	
	ACR (N = 15,329)	No ACR (N = 3,600)	ACR (N = 167)	No ACR (N = 309)	ACR (N = 7,757)	No ACR (N = 4,041)	ACR (N = 204)	No ACR (N = 125)	ACR (N = 48,612)	No ACR (N = 21,546)
ACEi	36.4	32.4	47.3	34.3	19.7	19.4	3.9	10.4	41.6	39.0
ARB	44.3	39.9	43.7	47.9	64.4	63.2	61.8	44.0	52.6	48.5
Beta blockers	39.4	43.1	54.5	57.3	35.7	44.7	23.0	28.8	50.6	50.4
Direct renin inhibitors	NR	NR	0.6	1.0	0.3	0.2	0.5	0.0	0.1	0.1
Angiotensin receptor-neprilysin inhibitors	0.3	0.7	0.6	0.0	1.1	2.6	0.0	0.0	0.8	1.1
Calcium channel blockers	41.3	33.7	38.9	30.4	29.2	30.2	50.5	58.4	34.5	32.3
Other antihypertensives	0.0	0.0	4.2	2.9	15.5	17.5	10.8	8.8	7.1	6.8
Statins	77.9	71.2	79.6	77.0	79.0	79.0	50.0	46.4	78.6	71.7
Anticoagulants	15.8	19.8	16.2	14.9	17.4	23.3	6.9	16.0	10.2	13.0
Digoxin	4.2	5.9	4.2	1.6	2.1	2.8	0.0	0.8	1.6	1.9
Nitrates and other vasodilators	6.0	7.6	7.8	8.7	5.8	8.9	9.3	7.2	8.3	8.6
Aspirin and other antiplatelet agents	41.0	39.8	34.1	43.4	42.5	45.6	35.8	29.6	13.2	13.6
Lipid-lowering drugs other than statins	6.1	4.3	9.6	10.0	25.9	23.0	24.5	13.6	17.7	15.6
Anti-inflammatory drugs (NSAIDs)	13.1	13.3	11.4	12.3	22.0	19.9	9.8	8.0	17.0	18.6
Acetaminophen	41.0	48.2	7.2	12.9	36.5	40.6	15.7	30.4	19.8	21.2
Anticonvulsants	1.9	2.8	0.0	0.6	2.3	2.5	2.0	1.6	3.7	5.1
Antibacterial agents	24.7	31.4	24.6	31.1	37.3	41.1	24.0	32.0	29.4	30.8

Variable	DNHR		PHARMO		VID		J-CKD-DB-Ex		CDM	
	ACR (N = 15,329)	No ACR (N = 3,600)	ACR (N = 167)	No ACR (N = 309)	ACR (N = 7,757)	No ACR (N = 4,041)	ACR (N = 204)	No ACR (N = 125)	ACR (N = 48,612)	No ACR (N = 21,546)
Antifungal agents	3.0	3.9	1.2	0.6	2.8	2.4	2.0	7.2	7.2	7.8
Chemotherapeutic agents	0.1	0.2	1.2	0.6	0.5	0.6	3.9	2.4	2.9	3.0
Bronchodilators	12.8	17.0	24.6	20.7	19.8	23.3	5.9	4.8	15.2	17.4

ACEi = angiotensin-converting enzyme inhibitors; ACR = albumin-creatinine ratio; ARB = angiotensin receptor blockers; CDM = Optum's de-identified Clinformatics® DataMart; CHD = coronary heart disease; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; CVD = cardiovascular disease; DNHR = Danish National Health Registers; DPP-4i = dipeptidyl peptidase-4 inhibitors; GFR = glomerular filtration rate; GLD = glucose-lowering drugs; GLP-1 RA = glucagon-like peptide-1 receptor agonist; HIV = human immunodeficiency virus; J-CKD-DB-Ex = Japan Chronic Kidney Disease Database Extension; NA = not available; NR = not reported; NSAID = non-steroidal anti-inflammatory drug; OR = odds ratio; PHARMO = PHARMO Data Network; SD = standard deviation; SGLT2i = sodium-glucose cotransporter 2 inhibitors; T2D = type 2 diabetes; VID = Valencia Health System Integrated Database.

Note: Values are %, unless otherwise specified.

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

[b] Score is based on key diagnoses: retinopathy, nephropathy, neuropathy, cerebrovascular disease, CVD, peripheral vascular disease, and metabolic complications.

[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]).

Table 42: Selected characteristics of new users of sMRA, stratified by whether an ACR test was recorded in the year before or on the index date, by data source

Variable	DNHR		PHARMO		VID		J-CKD-DB-Ex		CDM	
	ACR (N = 8,465)	No ACR (N = 4,224)	ACR (N = 1,025)	No ACR (N = 1,666)	ACR (N = 7,480)	No ACR (N = 7,426)	ACR (N = 261)	No ACR (N = 1,508)	ACR (N = 35,551)	No ACR (N = 36,165)
Age group (years) at index date										
< 40	CCI									
40-49										
50-59										
60-69										
70-79										
≥ 80										
Median age (years) at index date										
Sex										
Male	CCI									
Female										
Unknown										
Obesity										
Medications for T2D ever prescribed in the 180 days before or on the index date[a]										
SGLT2i	CCI									
GLP-1 RA										
Metformin										

Variable	DNHR		PHARMO		VID		J-CKD-DB-Ex		CDM	
	ACR (N = 8,465)	No ACR (N = 4,224)	ACR (N = 1,025)	No ACR (N = 1,666)	ACR (N = 7,480)	No ACR (N = 7,426)	ACR (N = 261)	No ACR (N = 1,508)	ACR (N = 35,551)	No ACR (N = 36,165)
Sulfonylureas	CCI									
DPP-4i										
Insulin use 180 days before or on the index date										
Diabetes Severity Complications Index Score[b]										
Mean (SD)	CCI									
Median										
1st, 99th percentile										
CKD stage based on GFR[c] or diagnosis code[d]										
Stage 1: ≥ 90, normal or high	CCI									
Stage 2: 60-89, mildly decreased										
Stage 3: mildly to severely decreased										
Stage 4: 15-29, severely decreased										
Stage 5: < 15 OR treated by dialysis, kidney failure										
Unspecified stage										

Variable	DNHR		PHARMO		VID		J-CKD-DB-Ex		CDM	
	ACR (N = 8,465)	No ACR (N = 4,224)	ACR (N = 1,025)	No ACR (N = 1,666)	ACR (N = 7,480)	No ACR (N = 7,426)	ACR (N = 261)	No ACR (N = 1,508)	ACR (N = 35,551)	No ACR (N = 36,165)
Medical conditions associated with risk of CKD[d]										
Hypertension	CCI									
Glomerulonephritis (all causes)										
Renovascular disease										
Autoimmune disease										
Polycystic kidney disease										
Gout or hyperuricemiad										
Other medical conditions[d]										
Coronary heart disease	CCI									
Cerebrovascular disease										
Peripheral vascular disease										
Hypercholesterolemia										
CHF										
Severe liver disease										
HIV infection										

Variable	DNHR		PHARMO		VID		J-CKD-DB-Ex		CDM	
	ACR (N = 8,465)	No ACR (N = 4,224)	ACR (N = 1,025)	No ACR (N = 1,666)	ACR (N = 7,480)	No ACR (N = 7,426)	ACR (N = 261)	No ACR (N = 1,508)	ACR (N = 35,551)	No ACR (N = 36,165)
Dementia	CCI									
COPD										
Malignancy (other than kidney cancer and non-melanoma skin cancers)										
Medications other than GLD in the 180 days before or on the index date										
Thiazide-like diuretics										
Loop diuretics										
Potassium-sparing diuretics										
ACEi										
ARB										
Beta blockers										
Direct renin inhibitors										
Angiotensin receptor-neprilysin inhibitors										
Calcium channel blockers										
Other antihypertensives										

Variable	DNHR		PHARMO		VID		J-CKD-DB-Ex		CDM	
	ACR (N = 8,465)	No ACR (N = 4,224)	ACR (N = 1,025)	No ACR (N = 1,666)	ACR (N = 7,480)	No ACR (N = 7,426)	ACR (N = 261)	No ACR (N = 1,508)	ACR (N = 35,551)	No ACR (N = 36,165)
Statins	CCI									
Anticoagulants										
Digoxin										
Nitrates and other vasodilators										
Aspirin and other antiplatelet agents										
Lipid-lowering drugs other than statins										
Anti-inflammatory drugs (NSAIDs)										
Acetaminophen										
Anticonvulsants										
Antibacterial agents										
Antifungal agents										
Chemotherapeutic agents										
Bronchodilators										

ACEi = angiotensin-converting enzyme inhibitors; ACR = albumin-creatinine ratio; ARB = angiotensin receptor blockers; CDM = Optum's de-identified Clinformatics® DataMart; CHF = congestive heart failure; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; CVD = cardiovascular disease; DNHR = Danish National Health Registers; DPP-4i = dipeptidyl peptidase-4 inhibitors; GFR = glomerular filtration rate; GLP-1 RA = glucagon-like peptide-1 receptor agonist; HIV = human immunodeficiency virus; J-CKD-DB-Ex = Japan Chronic Kidney Disease Database Extension; NA = not available; NR = not reported; NSAID = non-steroidal anti-inflammatory drug; OR = odds ratio; PHARMO = PHARMO Data Network; SD = standard deviation; SGLT2i = sodium-glucose cotransporter 2 inhibitors; T2D = type 2 diabetes; VID = Valencia Health System Integrated Database.

Note: Values are %, unless otherwise specified.

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

[b] Score is based on key diagnoses: retinopathy, nephropathy, neuropathy, cerebrovascular disease, CVD, peripheral vascular disease, and metabolic complications.

[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]).

Table 43: Markers of T2D severity at the index date for new users of nsMRA, in J-CKD-DB-Ex

	J-CKD-DB-Ex (N = 63), N (%) (unless otherwise specified)
Duration of T2D (years) at the index date	
Mean (SD)	7.1 (4.4)
Median	7.3
1st, 99th percentiles	0.3, 20.7
Medications for T2D (hypoglycemic agents) ever prescribed from 180 days before and including the index date	
GLP-1 RA and fixed-dose combinations	1 (1.6%)
SGLT2i and fixed-dose combinations	15 (23.8%)
Metformin and fixed-dose combinations	7 (11.1%)
Sulfonylureas and fixed-dose combinations	5 (7.9%)
Alpha-glucosidase inhibitors	6 (9.5%)
Thiazolidinediones	4 (6.3%)
DPP-4i and fixed-dose combinations	16 (25.4%)
Meglitinides (including repaglinide, nateglinide, mitiglinide)	4 (6.3%)
Number of T2D drug classes other than insulin ever used in the 180 days before and including the index date	
0	37 (58.7%)
1	10 (15.9%)
2	7 (11.1%)
3	6 (9.5%)
4+	3 (4.8%)
Insulin use recorded in the 180 days before and including the index date	13 (20.6%)
HbA_{1c}	
HbA1c ≤ 53 mmol/mol or ≤ 7%	48 (76.2%)
HbA1c > 53 mmol/mol and ≤ 63.9 mmol/mol or > 7% and ≤ 8%	5 (7.9%)
HbA1c > 63.9 mmol/mol and ≤ 74.9 mmol/mol or > 8% and ≤ 9%	2 (3.2%)
HbA1c > 74.9 mmol/mol or > 9%	0 (0.0%)
HbA1c missing	8 (12.7%)
Other key diagnoses	
Hyperkaliemia	5 (7.9%)
Amputation	0 (0.0%)

	J-CKD-DB-Ex (N = 63), N (%) (unless otherwise specified)
The Diabetes Severity Complications Index	
Key diagnoses for scoring of the index score	
Retinopathy	9 (14.3%)
Nephropathy	25 (39.7%)
Neuropathy	12 (19.0%)
Cerebrovascular	30 (47.6%)
Cardiovascular	56 (88.9%)
Peripheral vascular disease	9 (14.3%)
Metabolic complications	1 (1.6%)
Index score	
Mean (SD)	3.8 (1.9)
Median	4.0
1st, 99th percentiles	(0.0, 9.0)

DPP-4i = dipeptidyl peptidase-4 inhibitors; GLP-1 RA = glucagon-like peptide-1 receptor agonist; HbA1c = hemoglobin A1c (glycated hemoglobin); J-CKD-DB-Ex = Japan Chronic Kidney Disease Database Extension; N = number; SD = standard deviation; SGLT2i = sodium-glucose cotransporter 2 inhibitors; T2D = type 2 diabetes.

Note: The nsMRA used in Japan was esaxerenone.

Table 44: Baseline markers of severity of kidney dysfunction for new users of nsMRA, by data source

	J-CKD-DB-Ex (N = 63), N (%) (unless otherwise specified)
Duration of CKD at the index date (based on all available data)	
Mean (SD)	4.0 (3.3)
Median	4.0
1st, 99th percentiles	(0.0, 20.6)
CKD stage based on diagnosis only[a], n (%)	
Stage 1: eGFR ≥ 90, normal or high	0 (0.0%)
Stage 2: eGFR 60-89, mildly decreased	0 (0.0%)
Stage 3: mildly to severely decreased	6 (9.5%)
Stage 3a: eGFR 45-59, mildly to moderately decreased	0 (0.0%)
Stage 3b: eGFR 30-44, moderately to severely decreased	0 (0.0%)
Stage 3 without specification of substage	6 (9.5%)
Stage 4: eGFR 15-29, severely decreased	0 (0.0%)
Stage 5: eGFR < 15 OR treated by dialysis; kidney failure	0 (0.0%)
Unspecified stage	NA
No diagnosis code in the year before the index date	57 (90.5%)
CKD stage based on eGFR only[b], n (%)	
Stage 1: eGFR ≥ 90, normal or high	1 (1.6%)
Stage 2: eGFR 60-89, mildly decreased	17 (27.0%)
Stage 3: mildly to severely decreased	41 (65.1%)
Stage 3a: eGFR 45-59, mildly to moderately decreased	29 (46.0%)
Stage 3b: eGFR 30-44, moderately to severely decreased	12 (19.0%)
Stage 3 without specification of substage	NA
Stage 4: eGFR 15-29, severely decreased	3 (4.8%)
Stage 5: eGFR < 15 OR treated by dialysis, kidney failure	0 (0.0%)
No assessment of eGFR in the year before the index date	1 (1.6%)
CKD stage based on eGFR[b] test result or diagnosis code[a], n (%)	
Stage 1: eGFR ≥ 90, normal or high	1 (1.6%)
Stage 2: eGFR 60-89, mildly decreased	17 (27.0%)
Stage 3: mildly to severely decreased	41 (65.1%)
Stage 3a: eGFR 45-59, mildly to moderately decreased	29 (46.0%)
Stage 3b: eGFR 30-44, moderately to severely decreased	12 (19.0%)
Stage 3 without specification of substage	0 (0.0%)
Stage 4: eGFR 15-29, severely decreased	3 (4.8%)

	J-CKD-DB-Ex (N = 63), N (%) (unless otherwise specified)
Stage 5: eGFR < 15 OR treated by dialysis, kidney failure	0 (0.0%)
Unspecified stage	NA
No assessment of GFR or diagnosis code any time before or on the index date	1 (1.6%)
CKD stage based on urine ACR[b], n (%)	
A1: urine ACR < 30, normal to mildly increased	4 (6.3%)
A2: urine ACR 30-300, moderately increased (formerly 'microalbuminuria')	4 (6.3%)
A3: urine ACR > 300, severely increased (includes nephrotic syndrome, >~2,000)	0 (0.0%)
No assessment of urine ACR recorded in year before the index date	55 (87.3%)
"Any historical use" of drug classes (> 365 days before the index date)	
Drug classes used, n (%)	
SGLT2i and fixed-dose combinations	7 (11.1%)
GLP-1 RA and fixed-dose combinations	1 (1.6%)
sMRA	25 (39.7%)
ACEi or ARB	46 (73.0%)
Number of drug classes used, n (%)	
0	NA
1	22 (34.9%)
2	22 (34.9%)
3	3 (4.8%)
≥ 4	1 (1.6%)
"Any previous use" of drug classes (365-91 days before the index date)	
Drug classes used, n (%)	
SGLT2i and fixed-dose combinations	9 (14.3%)
GLP-1 RA and fixed-dose combinations	0 (0.0%)
sMRA	18 (28.6%)
ACEi or ARB	39 (61.9%)
Number of drug classes used, n (%)	
0	NA
1	34 (54.0%)
2	7 (11.1%)
3	6 (9.5%)
≥ 4	0 (0.0%)
"Any recent use" of drug classes (in the 90 days before the index date)	

	J-CKD-DB-Ex (N = 63), N (%) (unless otherwise specified)
Drug classes used, n (%)	
SGLT2i RA and fixed-dose combinations	9 (14.3%)
GLP-1 RA and fixed-dose combinations	0 (0.0%)
sMRA	19 (30.2%)
ACEi or ARB	37 (58.7%)
Number of drug classes used, n (%)	
0	NA
1	33 (52.4%)
2	7 (11.1%)
3	6 (9.5%)
≥ 4	0 (0.0%)
Clinical conditions associated with risk of CKD[b]	
Hypertension, n (%)	56 (88.9%)
Glomerulonephritis (all causes), n (%)	13 (20.6%)
Renovascular disease, n (%)	4 (6.3%)
Autoimmune disease, n (%)	28 (44.4%)
Polycystic kidney disease, n (%)	0 (0.0%)
Gout or hyperuricemia[b], n (%)	22 (34.9%)
Hospitalizations for acute kidney injury in the previous year	
n (%)	0 (0.0)
Mean (SD)	0.0 (0.0)
Median	0.0
1st, 99th percentiles	(0.0, 0.0)

ACEi = angiotensin-converting enzyme inhibitors; ACR = albumin-to-creatinine ratio; ARB = angiotensin receptor blockers; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; GFR = glomerular filtration rate; GLP-1 RA = glucagon-like peptide-1 receptor agonist; J-CKD-DB-Ex = Japan Chronic Kidney Disease Database Extension; NA = not applicable; NR = not reported; SD = standard deviation; SGLT2i = sodium-glucose cotransporter 2 inhibitors; sMRA = steroidal mineralocorticoid receptor antagonists.

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

The nsMRA used in Japan was esaxerenone.

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

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

Table 45: Baseline comorbidities in new users of nsMRA, in J-CKD-DB-Ex

	J-CKD-DB-Ex (N = 63), N (%)
Macrovascular complications of diabetes	
CHD	38 (60. %3)
Cerebrovascular disease	30 (47.6%)
Peripheral vascular disease	8 (12.7%)
CVD risk factors	
Hypertension	56 (88.9%)
Hypercholesterolemia	46 (73.0%)
Congestive heart failure	45 (71.4%)
Severe liver disease	3 (4.8%)
HIV infection	1 (1.6%)
Dementia	2 (3.2%)
COPD	18 (28.6%)
Malignancy (other than kidney cancer and non-melanoma skin cancers)	14 (22.2%)

CHD = coronary heart disease; COPD = chronic obstructive pulmonary disease; CVD = cardiovascular disease; HIV = human immunodeficiency virus; J-CKD-DB-Ex = Japan Chronic Kidney Disease Database Extension.

Table 46: Medication use other than GLD recorded in the 180 days before or on the index date in new users of sMRA, in J-CKD-DB-Ex

	J-CKD-DB-Ex (N = 63), N (%)
Cardiovascular medications in the 180 days before or on the index date	
Thiazide-like diuretics	9 (14.3%)
Loop diuretics	9 (14.3%)
Potassium-sparing diuretics	0 (0.0%)
ACEi	10 (15.9%)
ARB	38 (60.3%)
Beta blockers	25 (39.7%)
Direct renin inhibitors	4 (6.3%)
Angiotensin receptor-neprilysin inhibitors	0 (0.0%)
Calcium channel blockers	39 (61.9%)
Other antihypertensives	7 (11.1%)
Statins	26 (41.3%)
Anticoagulants	13 (20.6%)
Digoxin	0 (0.0%)
Nitrates and other vasodilators	3 (4.8%)
Aspirin and other antiplatelet agents	15 (23.8%)
Lipid-lowering drugs other than statins	8 (12.7%)
Other medications of interest	
Anti-inflammatory drugs (NSAIDs)	2 (3.2%)
Acetaminophen	11 (17.5%)
Anticonvulsants	1 (1.6%)
Anti-infectives	
Antibacterial agents	10 (15.9%)
Antifungal agents	0 (0.0%)
Antitubercular agents	0 (0.0%)
Chemotherapeutic agents	0 (0.0%)
Bronchodilators	3 (4.8%)

ACEi = angiotensin-converting enzyme inhibitors; ARB = angiotensin receptor blockers; GLD = glucose-lowering drugs; J-CKD-DB-Ex = Japan Chronic Kidney Disease Database Extension; NSAID = non-steroidal anti-inflammatory drug.

Table 47: Characteristics of the index nsMRA at baseline and during follow-up, by data source

	J-CKD-DB-Ex (N = 63), N (%)[a]
Classification of the index nsMRA at the index date	
Monotherapy	38 (60.3%)
Combination therapy	3 (4.8%)
Add-on	20 (31.7%)
Switch	0 (0.0%)
Add-on and switch	0 (0.0%)
Indeterminate	2 (3.2%)
Index nsMRA was an “Add-On” to	
SGLT2i	9 (14.3%)
GLP-1 RA	0 (0.0%)
sMRA	16 (25.4%)
ACEi/ARB	13 (20.6%)
Index nsMRA was a “Switch” from	
SGLT2i	0 (0.0%)
GLP-1 RA	0 (0.0%)
sMRA	0 (0.0%)
ACEi/ARB	0 (0.0%)
Duration of initial exposure episode after cohort entry (months)	
Mean (SD)	6.7 (5.2)
Median	5.7
1st, 99th percentiles	0.4, 22.0
Days’ supply of index nsMRA (days)	
Mean (SD)	43.9 (25.0)
Median	43.0
1st, 99th percentiles	2.0, 94.0
Number of prescriptions or dispensings during follow-up for the nsMRA drug class	
Mean (SD)	6.1 (5.3)
Median	5.0
1st, 99th percentiles	1.0, 29.0
Number of distinct “current-use” periods (treatment episodes) during follow-up for the index nsMRA drug class	
1	60 (95.2%)
2	3 (4.8%)
3	0 (0.0%)

	J-CKD-DB-Ex (N = 63), N (%)[a]
4	0 (0.0%)
5+	0 (0.0%)
Number of distinct prescriptions or dispensings during follow-up for the index nsMRA drug class	
Mean (SD)	6.5 (5.8)
Median	5.0
1st, 99th percentiles	1.0, 29.0
Number of discontinuations (interruptions) of current use during follow-up	
0	14 (22.2%)
1	1 (1.6%)
2	0 (0.0%)
3	0 (0.0%)
4	0 (0.0%)
5+	0 (0.0%)
Number of patients with an interruption of current use lasting 90 days or more	10 (15.9)
Duration of total exposure to index therapy (months)	
Mean (SD)	7.0 (5.2)
Median	5.9
1st, 99th percentile	0.4, 22.0
Other drug classes started during follow-up	
SGLT2i	12 (19.0%)
GLP-1 RA	0 (0.0%)
sMRA	3 (4.8%)
ACEi/ARB	34 (54.0%)
Duration of total follow-up (months)	
Mean (SD)	8.3 (5.5)
Median	7.8
1st, 99th percentiles	0.4, 22.7

ACEi = angiotensin-converting enzyme inhibitors; ARB = angiotensin receptor blockers; GLP-1 RA = glucagon-like peptide-1 receptor agonist; J-CKD-DB-Ex = Japan Chronic Kidney Disease Database Extension; SD = standard deviation; SGLT2i = sodium-glucose cotransporter 2 inhibitors; sMRA = steroidal mineralocorticoid receptor antagonists.

Note: The nsMRA used in Japan was esaxerenone.

[a] Unless otherwise specified.

Table 48: Changes in baseline demographics between study periods among new users of SGLT2i

	Study period I: pre-finerenone era (01 JAN 2014-30 JUN 2021)	Study period II: post-finerenone era (09 JUL 2021-30 SEP 2023)	Difference estimates (period II - period I)			
			Estimate (period II - period I)	95% confidence interval		SMD
				Lower bound	Upper bound	
New users of the drug class	56,219	94,080				
Baseline demographics						
Age (years) at index date, mean (SD)	68.6 (10.1)	73.1 (8.9)	4.54 (0.05)	4.44	4.64	0.478
Male, n (%)	30,583 (54.4%)	49,832 (53.0%)	−1.43 (0.27)	−1.95	−0.91	−0.029
Race, n (%)						
White	31,362 (55.8%)	52,749 (56.1%)	0.28 (0.26)	−0.24	0.8	0.006
Black	9,167 (16.3%)	16,533 (17.6%)	1.27 (0.20)	0.88	1.66	0.034
Hispanic	10,582 (18.8%)	14,008 (14.9%)	−3.93 (0.20)	−4.33	−3.54	−0.105
Asian	2,752 (4.9%)	4,058 (4.3%)	−0.58 (0.11)	−0.8	−0.36	−0.028
Other/Unknown	2,356 (4.2%)	6,732 (7.2%)	2.96 (0.12)	2.73	3.2	0.128
Body mass index (kg/m^2), n(%)						
< 20 (underweight)	156 (0.3%)	547 (0.6%)	0.30 (0.03)	0.24	0.37	0.046
20-24.9 (normal)	1,373 (2.4%)	3,037 (3.2%)	0.79 (0.09)	0.62	0.96	0.047
25-29.9 (overweight)	4,850 (8.6%)	9,256 (9.8%)	1.21 (0.15)	0.91	1.51	0.042
30-39.9 (obese)	11,902 (21.2%)	20,663 (22.0%)	0.79 (0.22)	0.36	1.22	0.019
≥ 40 (severely obese)	5,705 (10.1%)	9,271 (9.9%)	−0.29 (0.16)	−0.61	0.02	−0.01
Unknown	32,233 (57.3%)	51,306 (54.5%)	−2.80 (0.26)	−3.32	−2.28	−0.056
Obesity, n (%)	26,443 (47.0%)	43,308 (46.0%)	−1.00 (0.27)	−1.52	−0.48	−0.02

	Study period I: pre-finerenone era (01 JAN 2014-30 JUN 2021)	**Study period II: post-finerenone era (09 JUL 2021-30 SEP 2023)**	**Difference estimates (period II - period I)**			
				95% confidence interval		
			Estimate (period II - period I)	**Lower bound**	**Upper bound**	**SMD**
Current smoker, n (%)	11,583 (20.6%)	24,436 (26.0%)	5.37 (0.22)	4.93	5.81	0.127
Alcohol abuse, n (%)	954 (1.7%)	2,043 (2.2%)	0.47 (0.07)	0.33	0.62	0.034

Table 49: Changes in markers of T2D severity between study periods among new users of SGLT2i

	Study period I: pre-finerenone era (01 JAN 2014-30 JUN 2021)	Study period II: post-finerenone era (09 JUL 2021-30 SEP 2023)	Difference estimates (period II - period I)			
				95% confidence interval		
			Estimate (period II - period I)	Lower bound	Upper bound	SMD
New users of the drug class	56,219	94,080				
Duration of T2D (years) at index date, mean (SD)	5.1 (3.4)	5.9 (4.1)	0.84 (0.02)	0.81	0.88	0.223
Medications for T2D (hypoglycemic agents) used 180 days before and including the index date, n (%)						
GLP-1 RA and fixed-dose combinations	9,989 (17.8%)	15,754 (16.7%)	−1.02 (0.20)	−1.42	−0.63	−0.027
SGLT2i and fixed-dose combinations	N/A	N/A				
Metformin and fixed-dose combinations	33,851 (60.2%)	43,614 (46.4%)	−13.85 (0.26)	−14.37	−13.34	−0.28
Sulfonylureas and fixed-dose combinations	21,746 (38.7%)	26,363 (28.0%)	−10.66 (0.25)	−11.15	−10.16	−0.228
Sulfonamides	NA	NA				
Alpha-glucosidase inhibitors	343 (0.6%)	320 (0.3%)	−0.27 (0.04)	−0.34	−0.2	−0.039
Thiazolidinediones	5,285 (9.4%)	6,811 (7.2%)	−2.16 (0.15)	−2.45	−1.87	−0.078
DPP-4i and fixed-dose combos	13,457 (23.9%)	12,276 (13.0%)	−10.89 (0.21)	−11.3	−10.48	−0.283
Meglitinides (including repaglinide, nateglinide)	760 (1.4%)	969 (1.0%)	−0.32 (0.06)	−0.44	−0.21	−0.03
Imeglimin (Japan only)	N/A	N/A				
Number of T2D drug classes used 180 days before and including the index date, n (%)						
No therapy	9,013 (16.0%)	27,036 (28.7%)	12.71 (0.21)	12.29	13.12	0.308
Monotherapy	19,470 (34.6%)	36,605 (38.9%)	4.28 (0.26)	3.77	4.78	0.089
Dual therapy	18,676 (33.2%)	22,837 (24.3%)	−8.95 (0.24)	−9.42	−8.47	−0.199

	Study period I: pre-finerenone era (01 JAN 2014-30 JUN 2021)	**Study period II: post-finerenone era (09 JUL 2021-30 SEP 2023)**	**Difference estimates (period II - period I)**			
				95% confidence interval		
			Estimate (period II - period I)	**Lower bound**	**Upper bound**	**SMD**
Triple therapy	7,740 (13.8%)	6,641 (7.1%)	−6.71 (0.17)	−7.04	−6.38	−0.221
Quadruple therapy or more	1,320 (2.3%)	961 (1.0%)	−1.33 (0.07)	−1.47	−1.19	−0.103
Insulin use recorded 180 days before and including the index date, n (%)	18,447 (32.8%)	27,369 (29.1%)	−3.72 (0.25)	−4.21	−3.24	−0.081
HbA1c, n (%)						
HbA1c ≤ 53 mmol/mol or ≤ 7%	7,006 (12.5%)	18,486 (19.6%)	7.19 (0.19)	6.81	7.56	0.197
HbA1c > 53 mmol/mol and ≤ 63.9 mmol/mol or > 7% and ≤ 8%	8,662 (15.4%)	11,972 (12.7%)	−2.68 (0.19)	−3.05	−2.32	−0.077
HbA1c > 63.9 mmol/mol and ≤ 74.9 mmol/mol or > 8% and ≤ 9%	6,930 (12.3%)	7,582 (8.1%)	−4.27 (0.16)	−4.59	−3.95	−0.141
HbA1c > 74.9 mmol/mol or > 9%	9,261 (16.5%)	8,079 (8.6%)	−7.89 (0.18)	−8.24	−7.53	−0.24
HbA1c missing	24,360 (43.3%)	47,961 (51.0%)	7.65 (0.27)	7.13	8.17	0.154
Other key diagnoses						
Hyperkalaemia, n (%)	3,639 (6.5%)	9,896 (10.5%)	4.05 (0.14)	3.76	4.33	0.145
Amputation, n (%)	991 (1.8%)	2,185 (2.3%)	0.56 (0.07)	0.41	0.7	0.04
The Diabetes Severity Complications Index						
Key diagnoses for scoring of index score						
Retinopathy, n (%)	12,937 (23.0%)	24,691 (26.2%)	3.23 (0.23)	2.79	3.68	0.075
Nephropathy, n (%)	33,245 (59.1%)	44,587 (47.4%)	−11.74 (0.26)	−12.26	−11.23	−0.237
Neuropathy, n (%)	22,737 (40.4%)	38,614 (41.0%)	0.60 (0.26)	0.09	1.11	0.012

	Study period I: pre-finerenone era (01 JAN 2014-30 JUN 2021)	**Study period II: post-finerenone era (09 JUL 2021-30 SEP 2023)**	**Difference estimates (period II - period I)**			
				95% confidence interval		
			Estimate (period II - period I)	**Lower bound**	**Upper bound**	**SMD**
Cerebrovascular, n (%)	6,854 (12.2%)	14,880 (15.8%)	3.62 (0.18)	3.27	3.98	0.105
Cardiovascular, n (%)	28,862 (51.3%)	59,596 (63.3%)	12.01 (0.26)	11.49	12.52	0.245
Peripheral vascular disease, n (%)	16,026 (28.5%)	32,330 (34.4%)	5.86 (0.25)	5.38	6.34	0.126
Metabolic complications, n (%)	3,343 (5.9%)	5,725 (6.1%)	0.14 (0.13)	-0.11	0.39	0.006
Index score, mean (SD)	2.9 (2.1)	3.3 (2.2)	0.40 (0.01)	0.38	0.43	0.189

Table 50: Changes in markers of severity of kidney dysfunction between study periods among new users of SGLT2i

	Study period I: pre-finerenone era (01 JAN 2014-30 JUN 2021)	Study period II: post-finerenone era (09 JUL 2021-30 SEP 2023)	Difference estimates (period II - period I)			
			Estimate (period II - period I)	95% confidence interval		SMD
				Lower bound	Upper bound	
New users of the drug class	56,219	94,080				
Duration of CKD at index date (based on all available data), mean (SD)	3.8 (2.9)	4.8 (3.6)	1.01 (0.02)	0.97	1.04	0.308
CKD stage based on diagnosis only (%)						
Stage 1: ≥ 90, normal or high	1,291 (2.3%)	1,001 (1.1%)	−1.23 (0.07)	−1.37	−1.09	−0.096
Stage 2: 60-89, mildly decreased	8,220 (14.6%)	9,437 (10.0%)	−4.59 (0.18)	−4.94	−4.24	−0.14
Stage 3: mildly to severely decreased	4,510 (8.0%)	41,302 (43.9%)	35.88 (0.20)	35.49	36.27	0.897
Stage 3a: 45-59, mildly to moderately decreased	1,202 (2.1%)	13,744 (14.6%)	12.47 (0.13)	12.22	12.73	0.462
Stage 3b: 30-44, moderately to severely decreased	806 (1.4%)	11,207 (11.9%)	10.48 (0.12)	10.25	10.71	0.429
Stage 3 without specification of substage	2,502 (4.5%)	16,351 (17.4%)	12.93 (0.15)	12.63	13.23	0.424
Stage 4: 15-29, severely decreased	1,316 (2.3%)	4,810 (5.1%)	2.77 (0.10)	2.58	2.96	0.147
Stage 5: < 15 OR treated by dialysis, kidney failure	0 (0%)	0 (0%)	0 (NE)			NE
Unspecified stage	7,289 (13.0%)	10,282 (10.9%)	−2.04 (0.17)	−2.38	−1.69	−0.063
No diagnosis code in the year before index	33,593 (59.8%)	27,248 (29.0%)	−30.79 (0.25)	−31.29	−30.29	−0.652

	Study period I: pre-finerenone era (01 JAN 2014-30 JUN 2021)	**Study period II: post-finerenone era (09 JUL 2021-30 SEP 2023)**	**Difference estimates (period II - period I)**			
				95% confidence interval		
			Estimate (period II - period I)	**Lower bound**	**Upper bound**	**SMD**
CKD stage based on GFR only (%)						
Stage 1: ≥ 90, normal or high	6,119 (10.9%)	4,259 (4.5%)	−6.36 (0.15)	−6.65	−6.07	−0.24
Stage 2: 60-89, mildly decreased	14,536 (25.9%)	16,985 (18.1%)	−7.80 (0.22)	−8.24	−7.36	−0.189
Stage 3: mildly to severely decreased	14,069 (25.0%)	34,138 (36.3%)	11.26 (0.24)	10.79	11.73	0.246
Stage 3a: 45-59, mildly to moderately decreased	10,093 (18.0%)	19,324 (20.5%)	2.59 (0.21)	2.18	3	0.066
Stage 3b: 30-44, moderately to severely decreased	3,976 (7.1%)	14,814 (15.7%)	8.67 (0.16)	8.36	8.99	0.275
Stage 3 without specification of substage	NA	NA				
Stage 4: 15-29, severely decreased	810 (1.4%)	3,799 (4.0%)	2.58 (0.08)	2.42	2.74	0.159
Stage 5: < 15 OR treated by dialysis, kidney failure	392 (0.7%)	471 (0.5%)	−0.20 (0.04)	−0.28	−0.11	−0.025
No assessment of GFR in the year before index date	20,293 (36.1%)	34,448 (36.6%)	0.52 (0.26)	0.02	1.02	0.011
CKD stage based on GFR or diagnosis, n(%)						
Stage 1: ≥ 90, normal or high	6,063 (10.8%)	4,146 (4.4%)	−6.38 (0.15)	−6.67	−6.09	−0.242
Stage 2: 60-89, mildly decreased	17,470 (31.1%)	19,236 (20.4%)	−10.63 (0.24)	−11.09	−10.17	−0.245
Stage 3: mildly to severely decreased	14,800 (26.3%)	48,996 (52.1%)	25.75 (0.25)	25.27	26.24	0.547
Stage 3a: 45-59, mildly to moderately decreased	9,414 (16.7%)	21,545 (22.9%)	6.16 (0.21)	5.75	6.56	0.155

	Study period I: pre-finerenone era (01 JAN 2014-30 JUN 2021)	**Study period II: post-finerenone era (09 JUL 2021-30 SEP 2023)**	**Difference estimates (period II - period I)**			
				95% confidence interval		
			Estimate (period II - period I)	**Lower bound**	**Upper bound**	**SMD**
Stage 3b: 30-44, moderately to severely decreased	3,521 (6.3%)	15,999 (17.0%)	10.74 (0.16)	10.43	11.06	0.34
Stage 3 without specification of substage	1,865 (3.3%)	11,452 (12.2%)	8.86 (0.13)	8.6	9.11	0.336
Stage 4: 15-29, severely decreased	1,380 (2.5%)	5,391 (5.7%)	3.28 (0.10)	3.08	3.47	0.166
Stage 5: < 15 OR treated by dialysis, kidney failure	345 (0.6%)	346 (0.4%)	−0.25 (0.04)	−0.32	−0.17	−0.035
Unspecified stage	4,818 (8.6%)	7,487 (8.0%)	−0.61 (0.15)	−0.9	−0.32	−0.022
No assessment of GFR or diagnosis code in the year before index date	11,343 (20.2%)	8,478 (9.0%)	−11.16 (0.19)	−11.54	−10.79	−0.32
CKD stage based on ACR (%)						
A1: < 30, normal to mildly increased	6,301 (11.2%)	8,141 (8.7%)	−2.55 (0.16)	−2.87	−2.24	−0.085
A2: 30-300, moderately increased (formerly 'microalbuminuria')	6,857 (12.2%)	9,473 (10.1%)	−2.13 (0.17)	−2.46	−1.8	−0.068
A3: > 300, severely increased (includes nephrotic syndrome, > ~ 2,000)	2,736 (4.9%)	5,773 (6.1%)	1.27 (0.12)	1.03	1.5	0.056
No assessment of ACR recorded in year before index date	40,325 (71.7%)	70,693 (75.1%)	3.41 (0.24)	2.95	3.88	0.077
'Any historical use' of drug classes, any use more than 1 year before the index date						
Drug classes used (%)						
Finerenone	N/A	38 (< 0.1%)				

	Study period I: pre-finerenone era (01 JAN 2014-30 JUN 2021)	**Study period II: post-finerenone era (09 JUL 2021-30 SEP 2023)**	**Difference estimates (period II - period I)**			
				95% confidence interval		
			Estimate (period II - period I)	**Lower bound**	**Upper bound**	**SMD**
SGLT2i and fixed-dose combinations	3,864 (6.9%)	10,532 (11.2%)	4.32 (0.15)	4.03	4.61	0.151
GLP-1 RA and fixed-dose combinations	10,968 (19.5%)	19,360 (20.6%)	1.07 (0.21)	0.65	1.49	0.027
sMRA	5,297 (9.4%)	13,139 (14.0%)	4.54 (0.17)	4.22	4.87	0.142
nsMRA	NA	NA				
ACEi or ARB	49,332 (87.7%)	83,940 (89.2%)	1.47 (0.17)	1.14	1.81	0.046
Number of drug classes used (%)						
0	5,534 (9.8%)	7,740 (8.2%)	−1.62 (0.15)	−1.92	−1.31	−0.056
1	34,588 (61.5%)	53,513 (56.9%)	−4.64 (0.26)	−5.16	−4.13	−0.095
2	13,545 (24.1%)	25,646 (27.3%)	3.17 (0.23)	2.71	3.62	0.073
3	2,425 (4.3%)	6,521 (6.9%)	2.62 (0.12)	2.38	2.85	0.114
4	127 (0.2%)	659 (0.7%)	0.47 (0.03)	0.41	0.54	0.07
> 4	0 (0%)	1 (< 0.1%)	(0,0.01) (0.00)	0	0	0.005
'Any previous use' of drug classes, [−365,−91]						
Drug classes used, n (%)						
Finerenone	N/A	209 (0.2%)				
SGLT2i and fixed-dose combinations	N/A	N/A				
GLP-1 RA and fixed-dose combinations	9,885 (17.6%)	16,204 (17.2%)	−0.36 (0.20)	−0.76	0.04	−0.009
sMRA	4,273 (7.6%)	10,233 (10.9%)	3.28 (0.15)	2.98	3.57	0.113
nsMRA	N/A	N/A				

	Study period I: pre-finerenone era (01 JAN 2014-30 JUN 2021)	**Study period II: post-finerenone era (09 JUL 2021-30 SEP 2023)**	**Difference estimates (period II - period I)**			
				95% confidence interval		
			Estimate (period II - period I)	**Lower bound**	**Upper bound**	**SMD**
ACEi or ARB	46,279 (82.3%)	77,009 (81.9%)	−0.46 (0.20)	−0.86	−0.06	−0.012
Number of drug classes used, n (%)						
0	7,958 (14.2%)	13,029 (13.8%)	−0.31 (0.19)	−0.67	0.06	−0.009
1	36,758 (65.4%)	59,893 (63.7%)	−1.72 (0.25)	−2.22	−1.22	−0.036
2	10,830 (19.3%)	19,715 (21.0%)	1.69 (0.21)	1.27	2.11	0.042
3	673 (1.2%)	1,440 (1.5%)	0.33 (0.06)	0.21	0.45	0.029
4	0 (0%)	3 (< 0.1%)	(0,0.01) (0.00)	0	0.01	0.008
> 4	0 (0%)	0 (0%)	0 (NE)			NE
'Any recent use' of drug classes, [−90,−1]						
Drug classes used, n (%)						
Finerenone	N/A	224 (0.2%)				
SGLT2i and fixed-dose combinations	N/A	N/A				
GLP-1 RA and fixed-dose combinations	8,655 (15.4%)	13,228 (14.1%)	−1.33 (0.19)	−1.71	−0.96	−0.038
sMRA	3,669 (6.5%)	8,966 (9.5%)	3.00 (0.14)	2.73	3.28	0.111
nsMRA	N/A	N/A				
ACEi or ARB	41,452 (73.7%)	68,229 (72.5%)	−1.21 (0.24)	−1.67	−0.75	−0.027
Number of drug classes used, n (%)						
0	11,963 (21.3%)	20,387 (21.7%)	0.39 (0.22)	−0.04	0.82	0.01
1	35,173 (62.6%)	57,618 (61.2%)	−1.32 (0.26)	−1.83	−0.81	−0.027

	Study period I: pre-finerenone era (01 JAN 2014-30 JUN 2021)	**Study period II: post-finerenone era (09 JUL 2021-30 SEP 2023)**	**Difference estimates (period II - period I)**			
				95% confidence interval		
			Estimate (period II - period I)	**Lower bound**	**Upper bound**	**SMD**
2	8,646 (15.4%)	15,198 (16.2%)	0.78 (0.19)	0.4	1.15	0.021
3	437 (0.8%)	875 (0.9%)	0.15 (0.05)	0.06	0.25	0.017
4	0 (0%)	2 (< 0.1%)	(0,0.01) (0.00)	0	0.01	0.007
> 4	0 (0%)	0 (0%)	0 (NE)			NE
Clinical conditions associated with risk of CKD						
Hypertension, n (%)	52,558 (93.5%)	89,006 (94.6%)	1.12 (0.13)	0.87	1.37	0.047
Glomerulonephritis (all causes), n (%)	965 (1.7%)	878 (0.9%)	−0.78 (0.06)	−0.91	−0.66	−0.069
Renovascular disease, n (%)	532 (0.9%)	1,286 (1.4%)	0.42 (0.06)	0.31	0.53	0.039
Autoimmune disease	3,387 (6.0%)	5,334 (5.7%)	−0.36 (0.13)	−0.6	−0.11	−0.015
Polycystic kidney disease, n (%)	170 (0.3%)	318 (0.3%)	(0.03)	-0.02	0.09	0.006
Gout or hyperuricemia	6,046 (10.8%)	12,465 (13.2%)	2.49 (0.17)	2.16	2.83	0.077
Hospitalizations for acute kidney injury in the previous year, mean (SD)	1.0 (0.3)	1.1 (0.3)	0.07 (0.00)	0.06	0.07	0.234

Table 51: Changes in use of other medications between study periods among new users of SGLT2i

	Study period I: pre-finerenone era (01 JAN 2014-30 JUN 2021)	Study period II: post-finerenone era (09 JUL 2021-30 SEP 2023)	Difference estimates (period II - period I)			
			Estimate (period II - period I)	95% confidence interval		SMD
				Lower bound	Upper bound	
New users of the drug class	56,219	94,080				
Cardiovascular medications						
Thiazide-like diuretics, n (%)	17,919 (31.9%)	26,012 (27.6%)	−4.22 (0.24)	−4.7	−3.75	−0.093
Loop diuretics, n (%)	12,595 (22.4%)	30,757 (32.7%)	10.29 (0.23)	9.83	10.75	0.232
Potassium-sparing diuretics, n (%)	1,255 (2.2%)	1,534 (1.6%)	−0.60 (0.07)	−0.75	−0.46	−0.044
ACE inhibitors, n (%)	22,793 (40.5%)	31,159 (33.1%)	−7.42 (0.26)	−7.93	−6.92	−0.154
ARB, n (%)	29,637 (52.7%)	55,551 (59.0%)	6.33 (0.26)	5.81	6.85	0.128
Beta blockers, n (%)	28,416 (50.5%)	54,843 (58.3%)	7.75 (0.27)	7.23	8.27	0.156
Direct renin inhibitors, n (%)	40 (0.1%)	23 (< 0.1%)	−0.05 (0.01)	−0.07	−0.02	−0.021
Angiotensin receptor-neprilysin inhibitors, n (%)	1,354 (2.4%)	5,039 (5.4%)	2.95 (0.10)	2.76	3.14	0.153
Calcium channel blockers, n (%)	18,711 (33.3%)	35,476 (37.7%)	4.43 (0.25)	3.93	4.92	0.093
Other antihypertensives, n (%)	3,519 (6.3%)	6,574 (7.0%)	0.73 (0.13)	0.47	0.99	0.029
Statins, n (%)	43,609 (77.6%)	75,405 (80.1%)	2.58 (0.22)	2.15	3.01	0.063
Anticoagulants, n (%)	6,480 (11.5%)	17,606 (18.7%)	7.19 (0.19)	6.82	7.55	0.202
Digoxin, n (%)	1,106 (2.0%)	1,679 (1.8%)	−0.18 (0.07)	−0.33	−0.04	−0.013
Nitrates and other vasodilators, n (%)	4,645 (8.3%)	11,103 (11.8%)	3.54 (0.16)	3.23	3.85	0.118
Aspirin and other antiplatelet agents, n (%)	7,970 (14.2%)	14,431 (15.3%)	1.16 (0.19)	0.79	1.53	0.033

	Study period I: pre-finerenone era (01 JAN 2014-30 JUN 2021)	**Study period II: post-finerenone era (09 JUL 2021-30 SEP 2023)**	**Difference estimates (period II - period I)**			
				95% confidence interval		
			Estimate (period II - period I)	**Lower bound**	**Upper bound**	**SMD**
Lipid-lowering drugs other than statins, n (%)	9,573 (17.0%)	14,374 (15.3%)	−1.75 (0.20)	−2.14	−1.36	−0.048
Other medications of interest						
Anti-inflammatory drugs (NSAIDs), n (%)	9,668 (17.2%)	14,077 (15.0%)	−2.23 (0.20)	−2.62	−1.85	−0.061
Acetaminophen, n (%)	9,675 (17.2%)	13,385 (14.2%)	−2.98 (0.20)	−3.37	−2.6	−0.082
Anticonvulsants, n (%)	1,862 (3.3%)	3,180 (3.4%)	0.07 (0.10)	-0.12	0.26	0.004
Anti-infectives						
Antibacterial agents, n (%)	14,964 (26.6%)	23,244 (24.7%)	−1.91 (0.23)	−2.37	−1.45	−0.044
Antifungal agents, n (%)	3,254 (5.8%)	4,659 (5.0%)	−0.84 (0.12)	−1.07	−0.6	−0.037
Antitubercular agents, n (%)	45 (0.1%)	61 (0.1%)	−0.02 (0.01)	−0.04	0.01	−0.006
Chemotherapeutic agents, n (%)	1,653 (2.9%)	2,689 (2.9%)	−0.08 (0.09)	−0.26	0.09	−0.005
Bronchodilators, n (%)	7,987 (14.2%)	16,621 (17.7%)	3.46 (0.19)	3.08	3.84	0.095

Table 52: Changes in other comorbidities between study periods among new users of SGLT2i

	Study period I: pre-finerenone era (01 JAN 2014-30 JUN 2021)	Study period II: post-finerenone era (09 JUL 2021-30 SEP 2023)	Difference estimates (period II - period I)			
				95% confidence interval		
			Estimate (period II - period I)	Lower bound	Upper bound	SMD
New users of the drug class	56,219	94,080				
Macrovascular complications						
Coronary heart disease, n (%)	19,663 (35.0%)	41,248 (43.8%)	8.87 (0.26)	8.36	9.37	0.182
Cerebrovascular disease, n (%)	6,854 (12.2%)	14,880 (15.8%)	3.62 (0.18)	3.27	3.98	0.105
Peripheral vascular disease, n (%)	15,737 (28.0%)	32,551 (34.6%)	6.61 (0.24)	6.13	7.09	0.143
Cardiovascular risk factors						
Hypertension, n (%)	52,558 (93.5%)	89,006 (94.6%)	1.12 (0.13)	0.87	1.37	0.047
Hypercholesterolemia, n (%)	50,291 (89.5%)	83,606 (88.9%)	−0.59 (0.17)	−0.91	−0.26	−0.019
CHF, n (%)	12,073 (21.5%)	33,790 (35.9%)	14.44 (0.23)	13.98	14.9	0.323
Severe liver disease, n (%)	556 (1.0%)	961 (1.0%)	(0.05)	−0.07	0.14	0.003
HIV infection, n (%)	297 (0.5%)	486 (0.5%)	−0.01 (0.04)	−0.09	0.06	−0.002
Dementia, n (%)	1,808 (3.2%)	4,889 (5.2%)	1.98 (0.10)	1.78	2.18	0.099
Chronic obstructive pulmonary disease, n (%)	10,300 (18.3%)	20,211 (21.5%)	3.16 (0.21)	2.75	3.58	0.079
Malignancy (other than kidney cancer and non-melanoma skin cancers), n (%)	7,017 (12.5%)	14,657 (15.6%)	3.10 (0.18)	2.74	3.46	0.089

CHF = congestive heart failure.

Table 53: Changes in healthcare resource utilization between study periods among new users of SGLT2i

	Study period I: pre-finerenone era (01 JAN 2014-30 JUN 2021)	**Study period II: post-finerenone era (09 JUL 2021-30 SEP 2023)**	**Difference estimates (period II - period I)**			
				95% confidence interval		
			Estimate (period II - period I)	**Lower bound**	**Upper bound**	**SMD**
New users of the drug class	56,219	94,080				
GP (or primary care) visits, n (%)	N/A	N/A				
Hospital visits (as ambulatory patient), n (%)	N/A	N/A				
Inpatient hospital admissions, n (%)	6,497 (11.6%)	17,895 (19.0%)	7.46 (0.19)	7.1	7.83	0.209
Inpatient hospital admissions for CHF, n (%)	1,091 (1.9%)	5,880 (6.3%)	4.31 (0.10)	4.12	4.5	0.219
Specialist visits, n (%)	N/A	N/A				
ED visits, n (%)	12,091 (21.5%)	29,048 (30.9%)	9.37 (0.23)	8.92	9.82	0.214

CHF = congestive heart failure; ED = emergency department; GP = general practitioner; SGLT2i = sodium-glucose cotransporter 2 inhibitors.

Table 54: Changes in drug utilization between study periods among new users of SGLT2i

	Study period I: pre-finerenone era (01 JAN 2014-30 JUN 2021)	Study period II: post-finerenone era (09 JUL 2021-30 SEP 2023)	Difference estimates (period II - period I)			
				95% confidence interval		
			Estimate (period II - period I)	Lower bound	Upper bound	SMD
New users of the drug class	56,219	94,080				
Classification of index therapy at cohort entry, n (%)						
Monotherapy	10,117 (18.0%)	16,483 (17.5%)	−0.48 (0.20)	−0.88	−0.08	−0.012
Combination therapy	1,846 (3.3%)	3,904 (4.1%)	0.87 (0.10)	0.67	1.06	0.046
Add-on	32,392 (57.6%)	51,623 (54.9%)	−2.75 (0.26)	−3.26	−2.23	−0.055
Switch	3,972 (7.1%)	6,321 (6.7%)	−0.35 (0.14)	−0.61	−0.08	−0.014
Add-on and switch	1,873 (3.3%)	3,585 (3.8%)	0.48 (0.10)	0.29	0.67	0.026
Indeterminate	6,019 (10.7%)	12,164 (12.9%)	2.22 (0.17)	1.89	2.56	0.069
Index drug was an ‘Add-On’ to…, n(%)						
SGLT2i	NA	NA				
GLP-1 RA	6,801 (12.1%)	8,474 (9.0%)	−3.09 (0.17)	−3.41	−2.76	−0.101
sMRA	2,873 (5.1%)	5,770 (6.1%)	1.02 (0.12)	0.78	1.26	0.044
nsMRA (Japan only)	NA	NA				
ACEi/ARB	36,511 (64.9%)	50,777 (54.0%)	−10.97 (0.26)	−11.48	−10.47	−0.225
Index drug was a ‘Switch’ from…, n(%)						
SGLT2i	N/A	N/A				
GLP-1 RA	1,854 (3.3%)	2,470 (2.6%)	-0.67 (0.09)	-0.85	−0.49	-0.04
sMRA	796 (1.4%)	1,665 (1.8%)	0.35 (0.07)	0.22	0.48	0.028

	Study period I: pre-finerenone era (01 JAN 2014-30 JUN 2021)	**Study period II: post-finerenone era (09 JUL 2021-30 SEP 2023)**	**Difference estimates (period II - period I)**			
				95% confidence interval		
			Estimate (period II - period I)	**Lower bound**	**Upper bound**	**SMD**
nsMRA (Japan only)	N/A	N/A				
ACEi/ARB	4,941 (8.8%)	6,309 (6.7%)	-2.08 (0.14)	-2.37	-1.8	-0.078
Day's supply of index drug (days), mean (SD)	47.2 (27.8)	50.5 (30.0)	3.29 (0.15)	2.99	3.59	0.114

Table 55: Changes in baseline demographics between study periods among new users of GLP-1 RA

	Study period I: pre-finerenone era (01 JAN 2014-30 JUN 2021)	Study period II: post-finerenone era (09 JUL 2021-30 SEP 2023)	Difference estimates (period II - period I)			
			Estimate (period II - period I)	95% confidence interval		SMD
				Lower bound	Upper bound	
New users of the drug class	70,158	72,816				
Baseline demographics						
Age (years) at index date, mean (SD)	67.9 (10.1)	70.0 (9.3)	2.08 (0.05)	1.98	2.18	0.214
Male, n (%)	33,652 (48.0%)	32,007 (44.0%)	−4.01 (0.26)	−4.53	−3.49	−0.081
Race, n (%)						
White	41,030 (58.5%)	43,255 (59.4%)	0.92 (0.26)	0.41	1.43	0.019
Black	11,900 (17.0%)	12,181 (16.7%)	−0.23 (0.20)	−0.62	0.15	−0.006
Hispanic	12,225 (17.4%)	10,311 (14.2%)	−3.26 (0.19)	−3.64	−2.89	−0.09
Asian	2,131 (3.0%)	1,891 (2.6%)	−0.44 (0.09)	−0.61	−0.27	−0.027
Other/Unknown	2,872 (4.1%)	5,178 (7.1%)	3.02 (0.12)	2.78	3.25	0.131
Body mass index (kg/m^2), n(%)						
< 20 (underweight)	136 (0.2%)	148 (0.2%)	(0.02)	−0.04	0.06	0.002
20-24.9 (normal)	1,043 (1.5%)	1,063 (1.5%)	−0.03 (0.06)	−0.15	0.1	−0.002
25-29.9 (overweight)	4,589 (6.5%)	5,026 (6.9%)	0.36 (0.13)	0.1	0.62	0.014
30-39.9 (obese)	15,039 (21.4%)	18,212 (25.0%)	3.58 (0.22)	3.14	4.01	0.085
≥ 40 (severely obese)	9,711 (13.8%)	11,985 (16.5%)	2.62 (0.19)	2.25	2.99	0.073
Unknown	39,640 (56.5%)	36,382 (50.0%)	−6.54 (0.26)	−7.05	−6.02	−0.131
Obesity, n (%)	37,234 (53.1%)	42,147 (57.9%)	4.81 (0.26)	4.3	5.32	0.097
Current smoker, n (%)	14,612 (20.8%)	16,157 (22.2%)	1.36 (0.22)	0.94	1.79	0.033
Alcohol abuse, n (%)	1,061 (1.5%)	1,274 (1.7%)	0.24 (0.07)	0.11	0.37	0.019

Table 56: Changes in markers of T2D severity between study periods among new users of GLP-1 RA

	Study period I: pre-finerenone era (01 JAN 2014-30 JUN 2021)	Study period II: post-finerenone era (09 JUL 2021-30 SEP 2023)	Difference estimates (period II - period I)			
			Estimate (period II - period I)	95% confidence interval		SMD
				Lower bound	Upper bound	
New users of the drug class	70,158	72,816				
Duration of T2D (years) at index date, mean (SD)	4.9 (3.4)	5.7 (4.1)	0.84 (0.02)	0.8	0.88	0.223
Medications for T2D (hypoglycemic agents) used 180 days before and including the index date, n (%)						
GLP-1 RA and fixed-dose combinations	NA	NA				
SGLT2i and fixed-dose combinations	9,359 (13.3%)	17,010 (23.4%)	10.02 (0.20)	9.62	10.42	0.261
Metformin and fixed-dose combinations	36,888 (52.6%)	36,704 (50.4%)	−2.17 (0.26)	−2.69	−1.65	−0.043
Sulfonylureas and fixed-dose combinations	26,089 (37.2%)	21,080 (28.9%)	−8.24 (0.25)	−8.72	−7.75	−0.176
Sulfonamides	NA	NA				
Alpha-glucosidase inhibitors	369 (0.5%)	260 (0.4%)	−0.17 (0.04)	−0.24	−0.1	−0.025
Thiazolidinediones	6,334 (9.0%)	5,895 (8.1%)	−0.93 (0.15)	−1.22	−0.64	−0.033
DPP-4i and fixed-dose combos	17,042 (24.3%)	10,655 (14.6%)	−9.66 (0.21)	−10.07	−9.25	−0.246
Meglitinides (including repaglinide, nateglinide)	1,000 (1.4%)	718 (1.0%)	−0.44 (0.06)	−0.55	−0.33	−0.04
Imeglimin (Japan only)	N/A	N/A				
Number of T2D drug classes used 180 days before and including the index date, n (%)						
No therapy	16,185 (23.1%)	18,646 (25.6%)	2.54 (0.23)	2.09	2.98	0.059
Monotherapy	23,640 (33.7%)	26,831 (36.8%)	3.15 (0.25)	2.66	3.65	0.066
Dual therapy	19,721 (28.1%)	18,395 (25.3%)	−2.85 (0.23)	−3.31	−2.39	−0.064

	Study period I: pre-finerenone era (01 JAN 2014-30 JUN 2021)	**Study period II: post-finerenone era (09 JUL 2021-30 SEP 2023)**	**Difference estimates (period II - period I)**			
			Estimate (period II - period I)	**95% confidence interval**		**SMD**
				Lower bound	**Upper bound**	
Triple therapy	8,635 (12.3%)	7,237 (9.9%)	−2.37 (0.17)	−2.7	−2.04	−0.075
Quadruple therapy or more	1,977 (2.8%)	1,707 (2.3%)	−0.47 (0.08)	−0.64	−0.31	−0.03
Insulin use recorded 180 days before and including the index date, n (%)	31,424 (44.8%)	25,213 (34.6%)	−10.16 (0.26)	−10.67	−9.66	−0.209
HbA1c, n (%)						
HbA1c ≤ 53 mmol/mol or ≤ 7%	7,235 (10.3%)	12,512 (17.2%)	6.87 (0.18)	6.52	7.23	0.201
HbA1c > 53 mmol/mol and ≤ 63.9 mmol/mol or > 7% and ≤ 8%	8,846 (12.6%)	8,921 (12.3%)	−0.36 (0.17)	−0.7	−0.02	−0.011
HbA1c > 63.9 mmol/mol and ≤ 74.9 mmol/mol or > 8% and ≤ 9%	8,228 (11.7%)	6,850 (9.4%)	−2.32 (0.16)	−2.64	−2	−0.076
HbA1c > 74.9 mmol/mol or > 9%	12,498 (17.8%)	8,894 (12.2%)	−5.60 (0.19)	−5.97	−5.23	−0.157
HbA1c missing	33,351 (47.5%)	35,639 (48.9%)	1.41 (0.26)	0.89	1.92	0.028
Other key diagnoses						
Hyperkalaemia, n (%)	5,368 (7.7%)	5,554 (7.6%)	−0.02 (0.14)	−0.3	0.25	−0.001
Amputation, n (%)	1,676 (2.4%)	1,679 (2.3%)	−0.08 (0.08)	−0.24	0.07	−0.005
The Diabetes Severity Complications Index						
Key diagnoses for scoring of index score						
Retinopathy, n (%)	17,400 (24.8%)	18,301 (25.1%)	0.33 (0.23)	−0.12	0.78	0.008
Nephropathy, n (%)	45,553 (64.9%)	30,148 (41.4%)	−23.53 (0.26)	−24.03	−23.02	−0.485
Neuropathy, n (%)	31,388 (44.7%)	31,302 (43.0%)	−1.75 (0.26)	−2.27	−1.24	−0.035
Cerebrovascular, n (%)	8,670 (12.4%)	9,210 (12.6%)	0.29 (0.17)	−0.05	0.63	0.009

	Study period I: pre-finerenone era (01 JAN 2014-30 JUN 2021)	**Study period II: post-finerenone era (09 JUL 2021-30 SEP 2023)**	**Difference estimates (period II - period I)**			
			Estimate (period II - period I)	**95% confidence interval**		**SMD**
				Lower bound	**Upper bound**	
Cardiovascular, n (%)	35,373 (50.4%)	38,497 (52.9%)	2.45 (0.26)	1.93	2.97	0.049
Peripheral vascular disease, n (%)	20,546 (29.3%)	22,678 (31.1%)	1.86 (0.24)	1.38	2.33	0.04
Metabolic complications, n (%)	4,994 (7.1%)	4,434 (6.1%)	−1.03 (0.13)	−1.29	−0.77	−0.041
Index score, mean (SD)	3.1 (2.2)	2.9 (2.2)	−0.21 (0.01)	−0.23	−0.19	−0.096

Table 57: Changes in markers of severity of kidney dysfunction between study periods among new users of GLP-1 RA

	Study period I: pre-finerenone era (01 JAN 2014-30 JUN 2021)	Study period II: post-finerenone era (09 JUL 2021-30 SEP 2023)	Difference estimates (period II - period I)			
			Estimate (period II - period I)	95% confidence interval		SMD
				Lower bound	Upper bound	
New users of the drug class	70,158	72,816				
Duration of CKD at index date (based on all available data), mean (SD)	3.6 (2.8)	4.6 (3.6)	1.05 (0.02)	1.01	1.08	0.327
CKD stage based on diagnosis only (%)						
Stage 1: ≥ 90, normal or high	1,398 (2.0%)	887 (1.2%)	−0.77 (0.07)	−0.91	−0.64	−0.062
Stage 2: 60-89, mildly decreased	8,997 (12.8%)	8,371 (11.5%)	−1.33 (0.17)	−1.67	−0.99	−0.041
Stage 3: mildly to severely decreased	4,048 (5.8%)	25,894 (35.6%)	29.79 (0.20)	29.4	30.18	0.791
Stage 3a: 45-59, mildly to moderately decreased	1,000 (1.4%)	9,456 (13.0%)	11.56 (0.13)	11.3	11.82	0.459
Stage 3b: 30-44, moderately to severely decreased	787 (1.1%)	6,126 (8.4%)	7.29 (0.11)	7.08	7.51	0.347
Stage 3 without specification of substage	2,261 (3.2%)	10,312 (14.2%)	10.94 (0.15)	10.65	11.22	0.396
Stage 4: 15-29, severely decreased	3,491 (5.0%)	3,123 (4.3%)	−0.69 (0.11)	−0.91	−0.47	−0.033
Stage 5: < 15 OR treated by dialysis, kidney failure	0 (0%)	0 (0%)	0 (NE)			NE
Unspecified stage	11,543 (16.5%)	7,192 (9.9%)	−6.58 (0.18)	−6.93	−6.23	−0.195
No diagnosis code in the year before index	40,681 (58.0%)	27,349 (37.6%)	−20.43 (0.26)	−20.93	−19.92	−0.418
CKD stage based on GFR only (%)						
Stage 1: ≥ 90, normal or high	5,965 (8.5%)	5,057 (6.9%)	−1.56 (0.14)	−1.83	−1.28	−0.058

	Study period I: pre-finerenone era (01 JAN 2014-30 JUN 2021)	**Study period II: post-finerenone era (09 JUL 2021-30 SEP 2023)**	**Difference estimates (period II - period I)**			
			Estimate (period II - period I)	**95% confidence interval**		**SMD**
				Lower bound	**Upper bound**	
Stage 2: 60-89, mildly decreased	14,293 (20.4%)	16,064 (22.1%)	1.69 (0.22)	1.26	2.11	0.041
Stage 3: mildly to severely decreased	19,729 (28.1%)	21,967 (30.2%)	2.05 (0.24)	1.58	2.52	0.045
Stage 3a: 45-59, mildly to moderately decreased	12,229 (17.4%)	13,801 (19.0%)	1.52 (0.20)	1.12	1.92	0.039
Stage 3b: 30-44, moderately to severely decreased	7,500 (10.7%)	8,166 (11.2%)	0.52 (0.17)	0.2	0.85	0.017
Stage 3 without specification of substage	NA	NA				
Stage 4: 15-29, severely decreased	1,892 (2.7%)	2,377 (3.3%)	0.57 (0.09)	0.39	0.74	0.033
Stage 5: < 15 OR treated by dialysis, kidney failure	416 (0.6%)	370 (0.5%)	−0.08 (0.04)	−0.16	−0.01	−0.011
No assessment of GFR in the year before index date	27,863 (39.7%)	26,981 (37.1%)	−2.66 (0.26)	−3.17	−2.16	−0.055
CKD stage based on GFR or diagnosis, n(%)						
Stage 1: ≥ 90, normal or high	6,015 (8.6%)	4,919 (6.8%)	−1.82 (0.14)	−2.09	−1.54	−0.068
Stage 2: 60-89, mildly decreased	17,872 (25.5%)	18,324 (25.2%)	−0.31 (0.23)	−0.76	0.14	−0.007
Stage 3: mildly to severely decreased	19,345 (27.6%)	32,005 (44.0%)	16.38 (0.25)	15.89	16.87	0.347
Stage 3a: 45-59, mildly to moderately decreased	11,239 (16.0%)	15,938 (21.9%)	5.87 (0.21)	5.46	6.27	0.15
Stage 3b: 30-44, moderately to severely decreased	6,376 (9.1%)	8,964 (12.3%)	3.22 (0.16)	2.9	3.54	0.104
Stage 3 without specification of substage	1,730 (2.5%)	7,103 (9.8%)	7.29 (0.12)	7.04	7.53	0.308

	Study period I: pre-finerenone era (01 JAN 2014-30 JUN 2021)	**Study period II: post-finerenone era (09 JUL 2021-30 SEP 2023)**	**Difference estimates (period II - period I)**			
			Estimate (period II - period I)	**95% confidence interval**		**SMD**
				Lower bound	**Upper bound**	
Stage 4: 15-29, severely decreased	3,590 (5.1%)	3,514 (4.8%)	−0.29 (0.12)	−0.52	−0.07	−0.013
Stage 5: < 15 OR treated by dialysis, kidney failure	343 (0.5%)	282 (0.4%)	−0.10 (0.03)	−0.17	−0.03	−0.015
Unspecified stage	7,763 (11.1%)	5,038 (6.9%)	−4.15 (0.15)	−4.44	−3.85	−0.145
No assessment of GFR or diagnosis code in the year before index date	15,230 (21.7%)	8,734 (12.0%)	−9.71 (0.20)	−10.1	−9.33	−0.262
CKD stage based on ACR (%)						
A1: < 30, normal to mildly increased	7,159 (10.2%)	7,790 (10.7%)	0.49 (0.16)	0.18	0.81	0.016
A2: 30-300, moderately increased (formerly 'microalbuminuria')	7,967 (11.4%)	7,250 (10.0%)	−1.40 (0.16)	−1.72	−1.08	−0.045
A3: > 300, severely increased (includes nephrotic syndrome, > ~ 2,000)	3,691 (5.3%)	3,003 (4.1%)	−1.14 (0.11)	−1.36	−0.92	−0.054
No assessment of ACR recorded in year before index date	51,341 (73.2%)	54,773 (75.2%)	2.04 (0.23)	1.59	2.5	0.047
'Any historical use' of drug classes, any use more than 1 year before the index date						
Drug classes used (%)						
Finerenone	N/A	30 (< 0.1%)				
SGLT2i and fixed-dose combinations	9,769 (13.9%)	16,703 (22.9%)	9.01 (0.20)	8.62	9.41	0.234
GLP-1 RA and fixed-dose combinations	9,249 (13.2%)	14,186 (19.5%)	6.30 (0.19)	5.92	6.68	0.171
sMRA	6,454 (9.2%)	8,190 (11.2%)	2.05 (0.16)	1.73	2.36	0.068

	Study period I: pre-finerenone era (01 JAN 2014-30 JUN 2021)	**Study period II: post-finerenone era (09 JUL 2021-30 SEP 2023)**	**Difference estimates (period II - period I)**			
			Estimate (period II - period I)	**95% confidence interval**		**SMD**
				Lower bound	**Upper bound**	
nsMRA	N/A	N/A				
ACEi or ARB	61,102 (87.1%)	63,418 (87.1%)	(0,0.01) (0.18)	−0.35	0.35	0
Number of drug classes used (%)						
0	7,307 (10.4%)	6,866 (9.4%)	−0.99 (0.16)	−1.3	−0.68	−0.033
1	42,704 (60.9%)	37,334 (51.3%)	−9.60 (0.26)	−10.11	−9.09	−0.194
2	16,766 (23.9%)	21,317 (29.3%)	5.38 (0.23)	4.92	5.83	0.122
3	3,186 (4.5%)	6,639 (9.1%)	4.58 (0.13)	4.32	4.84	0.182
4	195 (0.3%)	658 (0.9%)	0.63 (0.04)	0.55	0.7	0.082
> 4	0 (0%)	2 (< 0.1%)	(0,0.01) (0.00)	0	0.01	0.007
'Any previous use' of drug classes, [−365,−91]						
Drug classes used, n (%)						
Finerenone	N/A	166 (0.2%)				
SGLT2i and fixed-dose combinations	9,255 (13.2%)	16,391 (22.5%)	9.32 (0.20)	8.93	9.71	0.245
GLP-1 RA and fixed-dose combinations	N/A	N/A				
sMRA	5,163 (7.4%)	6,133 (8.4%)	1.06 (0.14)	0.78	1.34	0.039
nsMRA	NA	NA				
ACEi or ARB	57,027 (81.3%)	58,037 (79.7%)	−1.58 (0.21)	−1.99	−1.17	−0.04
Number of drug classes used, n (%)						
0	10,842 (15.5%)	11,359 (15.6%)	0.15 (0.19)	−0.23	0.52	0.004

	Study period I: pre-finerenone era (01 JAN 2014-30 JUN 2021)	**Study period II: post-finerenone era (09 JUL 2021-30 SEP 2023)**	**Difference estimates (period II - period I)**			
			Estimate (period II - period I)	**95% confidence interval**		**SMD**
				Lower bound	**Upper bound**	
1	47,715 (68.0%)	43,754 (60.1%)	−7.92 (0.25)	−8.42	−7.43	−0.166
2	11,073 (15.8%)	16,146 (22.2%)	6.39 (0.21)	5.99	6.8	0.164
3	528 (0.8%)	1,547 (2.1%)	1.37 (0.06)	1.25	1.49	0.115
4	0 (0%)	10 (< 0.1%)	(0.00)	0.01	0.02	0.017
> 4	0 (0%)	0 (0%)	0 (NE)			NE
'Any recent use' of drug classes, [−90,−1]						
Drug classes used, n (%)						
Finerenone	N/A	199 (0.3%)				
SGLT2i and fixed-dose combinations	7,895 (11.3%)	14,492 (19.9%)	8.65 (0.19)	8.28	9.02	0.24
GLP-1 RA and fixed-dose combinations	N/A	N/A				
sMRA	4,165 (5.9%)	4,991 (6.9%)	0.92 (0.13)	0.66	1.17	0.038
nsMRA	N/A	N/A				
ACEi or ARB	50,855 (72.5%)	51,831 (71.2%)	−1.31 (0.24)	−1.77	−0.84	−0.029
Number of drug classes used, n (%)						
0	16,339 (23.3%)	16,397 (22.5%)	−0.77 (0.22)	−1.21	−0.33	−0.018
1	45,059 (64.2%)	42,378 (58.2%)	−6.03 (0.26)	−6.53	−5.52	−0.124
2	8,424 (12.0%)	12,990 (17.8%)	5.83 (0.19)	5.46	6.2	0.164
3	336 (0.5%)	1,049 (1.4%)	0.96 (0.05)	0.86	1.06	0.099
4	0 (0%)	2 (< 0.1%)	(0,0.01) (0.00)	0	0.01	0.007

	Study period I: pre-finerenone era (01 JAN 2014-30 JUN 2021)	**Study period II: post-finerenone era (09 JUL 2021-30 SEP 2023)**	**Difference estimates (period II - period I)**			
			Estimate (period II - period I)	**95% confidence interval**		**SMD**
				Lower bound	**Upper bound**	
> 4	0 (0%)	0 (0%)	0 (NE)			NE
Clinical conditions associated with risk of CKD						
Hypertension, n (%)	65,828 (93.8%)	67,617 (92.9%)	−0.97 (0.13)	−1.23	−0.71	−0.039
Glomerulonephritis (all causes), n (%)	1,515 (2.2%)	452 (0.6%)	−1.54 (0.06)	−1.66	−1.42	−0.132
Renovascular disease, n (%)	661 (0.9%)	712 (1.0%)	(0.05)	-0.07	0.14	0.004
Autoimmune disease	4,525 (6.4%)	4,687 (6.4%)	−0.01 (0.13)	−0.27	0.24	−0.001
Polycystic kidney disease, n (%)	329 (0.5%)	223 (0.3%)	−0.16 (0.03)	−0.23	−0.1	−0.026
Gout or hyperuricemia	8,193 (11.7%)	7,780 (10.7%)	−0.99 (0.17)	−1.32	−0.67	−0.032
Hospitalizations for acute kidney injury in the previous year, mean (SD)	1.1 (0.3)	1.1 (0.3)	−0.04 (0.00)	−0.05	−0.04	−0.153

Table 58: Changes in use of other medications between study periods among new users of GLP-1 RA

	Study period I: pre-finerenone era (01 JAN 2014-30 JUN 2021)	Study period II: post-finerenone era (09 JUL 2021-30 SEP 2023)	Difference estimates (period II - period I)			
			Estimate (period II - period I)	95% confidence interval		SMD
				Lower bound	Upper bound	
New users of the drug class	70,158	72,816				
Cardiovascular medications						
Thiazide-like diuretics, n (%)	23,031 (32.8%)	22,236 (30.5%)	−2.29 (0.25)	−2.77	−1.81	−0.049
Loop diuretics, n (%)	17,894 (25.5%)	18,163 (24.9%)	−0.56 (0.23)	−1.01	−0.11	−0.013
Potassium-sparing diuretics, n (%)	1,703 (2.4%)	1,514 (2.1%)	−0.35 (0.08)	−0.5	−0.19	−0.023
ACE inhibitors, n (%)	28,644 (40.8%)	24,253 (33.3%)	−7.52 (0.25)	−8.02	−7.02	−0.156
ARB, n (%)	36,000 (51.3%)	40,225 (55.2%)	3.93 (0.26)	3.41	4.45	0.079
Beta blockers, n (%)	35,476 (50.6%)	36,771 (50.5%)	−0.07 (0.26)	−0.59	0.45	−0.001
Direct renin inhibitors, n (%)	59 (0.1%)	15 (< 0.1%)	−0.06 (0.01)	−0.09	−0.04	−0.028
Angiotensin receptor-neprilysin inhibitors, n (%)	625 (0.9%)	1,567 (2.2%)	1.26 (0.06)	1.13	1.39	0.103
Calcium channel blockers, n (%)	23,752 (33.9%)	24,937 (34.2%)	0.39 (0.25)	−0.1	0.88	0.008
Other antihypertensives, n (%)	4,939 (7.0%)	4,500 (6.2%)	−0.86 (0.13)	−1.12	−0.6	−0.035
Statins, n (%)	53,632 (76.4%)	56,981 (78.3%)	1.81 (0.22)	1.37	2.24	0.043
Anticoagulants, n (%)	7,786 (11.1%)	9,594 (13.2%)	2.08 (0.17)	1.74	2.42	0.064
Digoxin, n (%)	1,164 (1.7%)	644 (0.9%)	−0.77 (0.06)	−0.89	−0.66	−0.069
Nitrates and other vasodilators, n (%)	5,920 (8.4%)	6,312 (8.7%)	0.23 (0.15)	−0.06	0.52	0.008
Aspirin and other antiplatelet agents, n (%)	9,339 (13.3%)	8,949 (12.3%)	−1.02 (0.18)	−1.37	−0.68	−0.031

	Study period I: pre-finerenone era (01 JAN 2014-30 JUN 2021)	**Study period II: post-finerenone era (09 JUL 2021-30 SEP 2023)**	**Difference estimates (period II - period I)**			
			Estimate (period II - period I)	**95% confidence interval**		**SMD**
				Lower bound	**Upper bound**	
Lipid-lowering drugs other than statins, n (%)	11,962 (17.1%)	11,588 (15.9%)	−1.14 (0.20)	−1.52	−0.75	−0.031
Other medications of interest						
Anti-inflammatory drugs (NSAIDs), n (%)	12,271 (17.5%)	13,834 (19.0%)	1.51 (0.20)	1.11	1.91	0.039
Acetaminophen, n (%)	14,200 (20.2%)	12,244 (16.8%)	−3.43 (0.21)	−3.83	−3.02	−0.088
Anticonvulsants, n (%)	2,882 (4.1%)	3,228 (4.4%)	0.33 (0.11)	0.12	0.53	0.016
Anti-infectives						
Antibacterial agents, n (%)	20,959 (29.9%)	20,062 (27.6%)	−2.32 (0.24)	−2.79	−1.85	−0.051
Antifungal agents, n (%)	5,172 (7.4%)	5,684 (7.8%)	0.43 (0.14)	0.16	0.71	0.016
Antitubercular agents, n (%)	64 (0.1%)	44 (0.1%)	−0.03 (0.01)	−0.06	0	−0.011
Chemotherapeutic agents, n (%)	2,031 (2.9%)	2,117 (2.9%)	(0.09)	−0.16	0.19	0.001
Bronchodilators, n (%)	11,135 (15.9%)	13,476 (18.5%)	2.64 (0.20)	2.24	3.03	0.07

Table 59: Changes in other comorbidities between study periods among new users of GLP-1 RA

	Study period I: pre-finerenone era (01 JAN 2014-30 JUN 2021)	Study period II: post-finerenone era (09 JUL 2021-30 SEP 2023)	Difference estimates (period II - period I)			
			Estimate (period II - period I)	95% confidence interval		SMD
				Lower bound	Upper bound	
New users of the drug class	70,158	72,816				
Macrovascular complications						
Coronary heart disease, n (%)	23,175 (33.0%)	24,513 (33.7%)	0.63 (0.25)	0.14	1.12	0.013
Cerebrovascular disease, n (%)	8,670 (12.4%)	9,210 (12.6%)	0.29 (0.17)	−0.05	0.63	0.009
Peripheral vascular disease, n (%)	20,167 (28.7%)	22,714 (31.2%)	2.45 (0.24)	1.97	2.92	0.053
Cardiovascular risk factors						
Hypertension, n (%)	65,828 (93.8%)	67,617 (92.9%)	−0.97 (0.13)	−1.23	−0.71	−0.039
Hypercholesterolemia, n (%)	62,519 (89.1%)	63,825 (87.7%)	−1.46 (0.17)	−1.79	−1.13	−0.046
CHF, n (%)	14,543 (20.7%)	16,772 (23.0%)	2.30 (0.22)	1.88	2.73	0.056
Severe liver disease, n (%)	707 (1.0%)	665 (0.9%)	−0.09 (0.05)	−0.2	0.01	−0.01
HIV infection, n (%)	346 (0.5%)	396 (0.5%)	0.05 (0.04)	−0.02	0.13	0.007
Dementia, n (%)	2,808 (4.0%)	2,909 (4.0%)	−0.01 (0.10)	−0.21	0.2	0
Chronic obstructive pulmonary disease, n (%)	13,891 (19.8%)	14,037 (19.3%)	−0.52 (0.21)	−0.93	−0.11	−0.013
Malignancy (other than kidney cancer and non-melanoma skin cancers), n (%)	8,347 (11.9%)	9,563 (13.1%)	1.24 (0.17)	0.89	1.58	0.037

CHF = congestive heart failure.

Table 60: Changes in healthcare resource utilization between study periods among new users of GLP-1 RA

	Study period I: pre-finerenone era (01 JAN 2014-30 JUN 2021)	**Study period II: post-finerenone era (09 JUL 2021-30 SEP 2023)**	**Difference estimates (period II - period I)**			
			Estimate (period II - period I)	**95% confidence interval**		**SMD**
				Lower bound	**Upper bound**	
New users of the drug class	70,158	72,816				
GP (or primary care) visits, n (%)	N/A	N/A				
Hospital visits (as ambulatory patient), n (%)	N/A	N/A				
Inpatient hospital admissions, n (%)	7,872 (11.2%)	7,721 (10.6%)	−0.62 (0.16)	−0.94	−0.29	−0.02
Inpatient hospital admissions for CHF, n (%)	830 (1.2%)	995 (1.4%)	0.18 (0.06)	0.07	0.3	0.016
Specialist visits, n (%)	N/A	N/A				
ED visits, n (%)	15,572 (22.2%)	17,453 (24.0%)	1.77 (0.22)	1.34	2.21	0.042

CHF = congestive heart failure; ED = emergency department; GP = general practitioner.

Table 61: Changes in drug utilization between study periods among new users of GLP-1 RA

	Study period I: pre-finerenone era (01 JAN 2014-30 JUN 2021)	**Study period II: post-finerenone era (09 JUL 2021-30 SEP 2023)**	**Difference estimates (period II - period I)**			
			Estimate (period II - period I)	**95% confidence interval**		**SMD**
				Lower bound	**Upper bound**	
New users of the drug class	70,158	72,816				
Classification of index therapy at cohort entry, n (%)						
Monotherapy	14,535 (20.7%)	14,571 (20.0%)	−0.71 (0.21)	−1.12	−0.29	−0.018
Combination therapy	1,804 (2.6%)	1,826 (2.5%)	−0.06 (0.08)	−0.23	0.1	−0.004
Add-on	40,500 (57.7%)	38,882 (53.4%)	−4.33 (0.26)	−4.84	−3.82	−0.087
Switch	5,244 (7.5%)	4,810 (6.6%)	−0.87 (0.14)	−1.13	−0.6	−0.034
Add-on and switch	2,042 (2.9%)	3,034 (4.2%)	1.26 (0.10)	1.06	1.45	0.068
Indeterminate	6,033 (8.6%)	9,693 (13.3%)	4.71 (0.16)	4.39	5.03	0.151
Index drug was an ‘Add-On’ to…, n (%)						
SGLT2i	5,577 (7.9%)	8,862 (12.1%)	4.17 (0.16)	3.86	4.48	0.139
GLP-1 RA	N/A	N/A				
sMRA	3,318 (4.7%)	3,27 (4.5%)	−0.23 (0.11)	−0.45	−0.01	-0.011
nsMRA (Japan only)	N/A	N/A				
ACEi/ARB	44,708 (63.7%)	38,374 (52.7%)	−11.02 (0.26)	−11.53	−10.52	−0.225
Index drug was a ‘Switch’ from…, n(%)						
SGLT2i	2,318 (3.3%)	2,980 (4.1%)	0.79 (0.10)	0.59	0.98	0.042
GLP-1 RA	N/A	N/A				
sMRA	847 (1.2%)	783 (1.1%)	−0.13 (0.06)	−0.24	−0.02	−0.012
nsMRA (Japan only)	NA	NA				

	Study period I: pre-finerenone era (01 JAN 2014-30 JUN 2021)	**Study period II: post-finerenone era (09 JUL 2021-30 SEP 2023)**	**Difference estimates (period II - period I)**			
			Estimate (period II - period I)	**95% confidence interval**		**SMD**
				Lower bound	**Upper bound**	
ACEi/ARB	6,147 (8.8%)	4,601 (6.3%)	−2.44 (0.14)	−2.72	−2.17	−0.093
Day's supply of index drug (days), mean (SD)	40.4 (23.4)	40.0 (22.6)	−0.35 (0.12)	−0.59	−0.12	−0.015

N/A = not applicable.

Table 62: Description of new users of finerenone (and wide finerenone) and all current-use periods, stratified by SGLT2i baseline use

	Study period II: post-finerenone (09 JUL 2021-30 SEP 2023) finerenone		**Study period II: post-finerenone (09 JUL 2021-30 SEP 2023) wide finerenone**	
	No SGLT2i (N = 1,885)	**SGLT2i (N = 1,706)**	**No SGLT2i (N = 2,807)**	**SGLT2i (N = 2,394)**
Classification of finerenone at the index date, n (%)				
Monotherapy	284 (15.1%)	23 (1.3%)	443 (15.8%)	36 (1.5%)
Index combination therapy	20 (1.1%)	8 (0.5%)	27 (1.0%)	15 (0.6%)
Add-on	1,117 (59.3%)	1,016 (59.6%)	1,617 (57.6%)	1,386 (57.9%)
Switch	120 (6.4%)	67 (3.9%)	172 (6.1%)	92 (3.8%)
Add-on and switch	73 (3.9%)	256 (15.0%)	108 (3.8%)	348 (14.5%)
Indeterminate	271 (14.4%)	336 (19.7%)	440 (15.7%)	517 (21.6%)
Finerenone was an “Add-On” to…, n (%)				
SGLT2i	0 (0%)	1,007 (59.0%)	0 (0%)	1,357 (56.7%)
GLP-1 RA	314 (16.7%)	443 (26.0%)	448 (16.0%)	613 (25.6%)
sMRA	34 (1.8%)	32 (1.9%)	51 (1.8%)	43 (1.8%)
nsMRA	NA	NA	NA	NA
ACE/ARB	1,101 (58.4%)	999 (58.6%)	1,590 (56.6%)	1,381 (57.7%)
Finerenone was a “Switch” from…, n (%)				
SGLT2i	0 (0%)	174 (10.2%)	0 (0%)	251 (10.5%)
GLP-1 RA	49 (2.6%)	54 (3.2%)	76 (2.7%)	77 (3.2%)
sMRA	38 (2.0%)	38 (2.2%)	42 (1.5%)	52 (2.2%)

	Study period II: post-finerenone (09 JUL 2021-30 SEP 2023) finerenone		**Study period II: post-finerenone (09 JUL 2021-30 SEP 2023) wide finerenone**	
	No SGLT2i (N = 1,885)	**SGLT2i (N = 1,706)**	**No SGLT2i (N = 2,807)**	**SGLT2i (N = 2,394)**
nsMRA	NA	NA	NA	NA
ACE/ARB	115 (6.1%)	116 (6.8%)	177 (6.3%)	149 (6.2%)
Duration of initial exposure episode of finerenone after the index date (months)				
Mean (SD)	5.2 (4.6)	5.6 (4.7)	5.2 (4.6)	5.5 (4.7)
Median	3.3	3.9	3.3	3.8
1st, 99th percentile	1, 20	1, 21	1, 20	1, 21
Days' supply of index finerenone (days)				
Mean (SD)	43.8 (26.2)	46.6 (27.2)	43.8 (26.1)	46.0 (27.0)
Median	30	30	30	30
1st, 99th percentile	7, 100	28, 100	7, 100	15, 100
Strength of index finerenone (mg), n (%)				
10 mg	1,552 (82.3%)	1,396 (81.8%)	2,274 (81.0%)	1,916 (80.0%)
20 mg	333 (17.7%)	310 (18.2%)	533 (19.0%)	478 (20.0%)
Dose frequency of index finerenone, n (%)				
Once daily	1,872 (99.3%)	1,700 (99.6%)	2,785 (99.2%)	2,384 (99.6%)
Other	13 (0.7%)	6 (0.4%)	22 (0.8%)	10 (0.4%)

	Study period II: post-finerenone (09 JUL 2021-30 SEP 2023) finerenone		**Study period II: post-finerenone (09 JUL 2021-30 SEP 2023) wide finerenone**	
	No SGLT2i (N = 1,885)	**SGLT2i (N = 1,706)**	**No SGLT2i (N = 2,807)**	**SGLT2i (N = 2,394)**
Daily dose (mg) (strength*frequency) at the index date, n (%)				
10 mg	1,543 (81.9%)	1,390 (81.5%)	2,258 (80.4%)	1,908 (79.7%)
20 mg	334 (17.7%)	313 (18.3%)	537 (19.1%)	480 (20.1%)
Other	8 (0.4%)	3 (0.2%)	12 (0.4%)	6 (0.3%)
Number of prescriptions/dispensings for initial finerenone exposure episode after the index date, n (%)				
Mean (SD)	3.6 (3.6)	3.7 (3.4)	3.6 (3.6)	3.7 (3.5)
Median	2	3	2	2
1st, 99th percentile	1, 17	1, 17	1, 17	1, 17
Number of distinct “Current Use” periods for finerenone, n (%)				
1	1,488 (78.9%)	1,413 (82.8%)	2,222 (79.2%)	1,990 (83.1%)
2	309 (16.4%)	253 (14.8%)	466 (16.6%)	348 (14.5%)
3	74 (3.9%)	33 (1.9%)	99 (3.5%)	45 (1.9%)
4	13 (0.7%)	6 (0.4%)	18 (0.6%)	10 (0.4%)
5+	1 (0.1%)	1 (0.1%)	2 (0.1%)	1 (< 0.1%)
Number of prescriptions/dispensings for finerenone over study period				
Mean (SD)	4.3 (3.8)	4.2 (3.6)	4.3 (3.8)	4.2 (3.6)

	Study period II: post-finerenone (09 JUL 2021-30 SEP 2023) finerenone		**Study period II: post-finerenone (09 JUL 2021-30 SEP 2023) wide finerenone**	
	No SGLT2i (N = 1,885)	**SGLT2i (N = 1,706)**	**No SGLT2i (N = 2,807)**	**SGLT2i (N = 2,394)**
Median	3	3	3	3
1st, 99th percentile	1, 17	1, 17	1, 17	1, 17
Duration of total exposure of finerenone				
Mean (SD)	7.5 (5.0)	7.6 (5.1)	7.4 (5.0)	7.5 (5.0)
Median	6.4	6.5	6.2	6.3
1st, 99th percentile	2, 22	2, 23	2, 22	2, 23
Another drug class started during follow-up, n (%)				
SGLT2i	167 (8.9%)	89 (5.2%)	235 (8.4%)	128 (5.3%)
GLP-1 RA	102 (5.4%)	102 (6.0%)	138 (4.9%)	139 (5.8%)
sMRA	33 (1.8%)	33 (1.9%)	45 (1.6%)	44 (1.8%)
nsMRA	NA	NA	NA	NA
ACE/ARB	29 (1.5%)	10 (0.6%)	43 (1.5%)	17 (0.7%)
Duration of total follow-up				
Mean (SD)	8.5 (5.5)	7.6 (5.3)	8.3 (5.5)	7.4 (5.2)
Median	7.6	6.6	7.4	6.5
1st, 99th percentile	0, 23	0, 23	0, 23	0, 23
Administrative reason for end of follow-up, n (%)				
End of study period	1,609 (85.4%)	1,489 (87.3%)	2,358 (84.0%)	2,055 (85.8%)

	Study period II: post-finerenone (09 JUL 2021-30 SEP 2023) finerenone		**Study period II: post-finerenone (09 JUL 2021-30 SEP 2023) wide finerenone**	
	No SGLT2i (N = 1,885)	**SGLT2i (N = 1,706)**	**No SGLT2i (N = 2,807)**	**SGLT2i (N = 2,394)**
Disenrollment from the database or emigration from the database catchment area	172 (9.1%)	132 (7.7%)	242 (8.6%)	190 (7.9%)
First occurrence of any exclusion criteria during follow-up	63 (3.3%)	45 (2.6%)	151 (5.4%)	99 (4.1%)
Death	41 (2.2%)	40 (2.3%)	56 (2.0%)	50 (2.1%)
Proportion of patients who had a 10-mg daily dose at index and titrated up to 20 mg (n/N)…				
by 1 month[a]	19/1,543 (1.2%)	31/1,390 (2.2%)	27/2,258 (1.2%)	38/1,908 (2.0%)
by 6 months[a]	118/1,543 (7.6%)	149/1,390 (10.7%)	174/2,258 (7.7%)	197/1,908 (10.3%)
by 12 months[a]	156/1,543 (10.1%)	186/1,390 (13.4%)	238/2,258 (10.5%)	250/1,908 (13.1%)
at 1 month[b]	19/1,491 (1.3%)	30/1,317 (2.3%)	27/2,143 (1.3%)	37/1,774 (2.1%)
at 6 months[c]	94/998 (9.4%)	101/799 (12.6%)	132/1,414 (9.3%)	128/1,054 (12.1%)
at 12 months[d]	61/416 (14.7%)	56/285 (19.6%)	90/569 (15.8%)	72/368 (19.6%)
Proportion of patients who had a 20-mg daily dose at index and titrated down to 10 mg (n/N)…				
by 1 month[e]	4/334 (1.2%)	0/313 (0.0%)	7/537 (1.3%)	2/480 (0.4%)
by 6 months[e]	11/334 (3.3%)	6/313 (1.9%)	22/537 (4.1%)	14/480 (2.9%)
by 12 months[e]	18/334 (5.4%)	10/313 (3.2%)	30/537 (5.6%)	20/480 (4.2%)
at 1 month[f]	4/315 (1.3%)	0/292 (0.0%)	7/500 (1.4%)	2/440 (0.5%)

	Study period II: post-finerenone (09 JUL 2021-30 SEP 2023) finerenone		**Study period II: post-finerenone (09 JUL 2021-30 SEP 2023) wide finerenone**	
	No SGLT2i (N = 1,885)	**SGLT2i (N = 1,706)**	**No SGLT2i (N = 2,807)**	**SGLT2i (N = 2,394)**
at 6 months[f]	8/204 (3.9%)	2/163 (1.2%)	15/323 (4.6%)	8/255 (3.1%)
at 12 months[f]	8/86 (9.3%)	4/65 (6.2%)	12/131 (9.2%)	8/98 (8.2%)

ACEi/ARB = angiotensin-converting enzyme inhibitors/angiotensin receptor blockers; GLP-1 RA = glucagon-like peptide-1 receptor agonists; NA = not applicable; n = numerator value; N = denominator value; SD = standard deviation; SGLT2i = sodium-glucose cotransporter 2 inhibitors; sMRA = steroidal mineralocorticoid receptor antagonists.

a Denominator includes all patients with an initial dose of 10 mg.
b Denominator includes only those patients with an initial dose of 10 mg who were still being followed 1 month after the index date.
c Denominator includes only those patients with an initial dose of 10 mg who were still being followed 6 months after the index date.
d Denominator includes only those patients with an initial dose of 10 mg who were still being followed 12 months after the index date.
e Denominator includes all patients with an initial dose of 20 mg.
f Denominator includes only those patients with an initial dose of 20 mg who were still being followed 1 month after the index date.
g Denominator includes only those patients with an initial dose of 20 mg who were still being followed 6 months after the index date.
h Denominator includes only those patients with an initial dose of 20 mg who were still being followed 12 months after the index date.