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Multinational patterns of second line antihyperglycaemic drug initiation across cardiovascular risk groups: federated pharmacoepidemiological evaluation in LEGEND-T2DM

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ABSTRACT

OBJECTIVE To assess the uptake of second line antihyperglycaemic drugs among patients with type 2 diabetes mellitus who are receiving metformin.

DESIGN Federated pharmacoepidemiological evaluation in LEGEND-T2DM.

SETTING 10 US and seven non-US electronic health record and administrative claims databases in the Observational Health Data Sciences and Informatics network in eight countries from 2011 to the end of 2021.

PARTICIPANTS 4.8 million patients (≥18 years) across US and non-US based databases with type 2 diabetes mellitus who had received metformin monotherapy and had initiated second line treatments.

EXPOSURE The exposure used to evaluate each database was calendar year trends, with the years in the study that were specific to each cohort.

MAIN OUTCOMES MEASURES The outcome was the incidence of second line antihyperglycaemic drug use (ie, glucagon-like peptide-1 receptor agonists, sodium-glucose cotransporter-2 inhibitors, dipeptidyl peptidase-4 inhibitors, and sulfonylureas) among individuals who were already receiving treatment with metformin. The relative drug class level uptake across cardiovascular risk groups was also evaluated.

RESULTS 4.6 million patients were identified in US databases, 61 382 from Spain, 32 442 from Germany, 25 173 from the UK, 13 270 from France, 5580 from Scotland, 4614 from Hong Kong, and 2322 from Australia. During 2011-21, the combined proportional initiation of the cardioprotective antihyperglycaemic drugs (glucagon-like peptide-1 receptor agonists and sodium-glucose cotransporter-2 inhibitors) increased across all data sources, with the combined initiation of these drugs as second line drugs in 2021 ranging from 35.2% to 68.2% in the US databases, 15.4% in France, 34.7% in Spain, 50.1% in Germany, and 54.8% in Scotland. From 2016 to 2021, in some US and non-US databases, uptake of glucagon-like peptide-1 receptor agonists and sodium-glucose cotransporter-2 inhibitors increased more significantly among populations with no cardiovascular disease compared with patients with established cardiovascular disease. No data source provided evidence of a greater increase in the uptake of these two drug classes in populations with cardiovascular disease compared with no cardiovascular disease.

CONCLUSIONS Despite the increase in overall uptake of cardioprotective antihyperglycaemic

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Glucagon-like peptide-1 receptor agonists and sodium-glucose cotransporter two inhibitors are cardioprotective second line antihyperglycaemic drugs
⇒ These drugs treat hyperglycaemia and improve risk for diabetes mellitus at high risk of cardiovascular disorders, but uptake of these drugs lags
⇒ Studies have focused on prevalent use, and US studies have focused on single payers or small populations included in national surveys

WHAT THIS STUDY ADDS

⇒ Uptake was large of cardioprotective antihyperglycaemic drugs among patients with type 2 diabetes mellitus initiating a second line agent, representing nearly half of all patients across US and non-US cohorts
⇒ Patterns suggest non-selective use of cardioprotective drugs, with an increasing uptake among people who do not have cardiovascular disease compared with people who have established cardiovascular disease
⇒ This finding is despite people with established cardiovascular disease representing the only group with a strong recommendation for use in clinical practice guidelines

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE, OR POLICY

⇒ This federated framework can guide future research to fill in the remaining knowledge gaps in the field
⇒ This approach acts as a benchmark for monitoring the uptake of antihyperglycaemic drugs in response to regional guidelines, insurance, and evidence

drugs as second line treatments for type 2 diabetes mellitus, their uptake was lower in patients with cardiovascular disease than in people with no cardiovascular disease over the past decade. A strategy is needed to ensure that medication use is concordant with guideline recommendations to improve outcomes of patients with type 2 diabetes mellitus.

Introduction

The management of type 2 diabetes mellitus has advanced over the past decade with the introduction of novel drug and an emphasis on lowering cardiovascular and renal risks. Strong evidence from large, randomized controlled trials with patients who have type 2 diabetes show that glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and sodium-glucose cotransporter two inhibitors (SGLT2is) not only affect hyperglycaemia but also improve cardiovascular risk in populations at high risk.[1–5] Evidence also suggests SGLT2is additionally reduce the progression of renal disease.[1–3] Consequently, international clinical practice guidelines increasingly recognize the evolution of second line drugs as a treatment option for diabetes,[6] favoring the use of GLP-1 RAs in over a third and SGLT2is in over half of all patients with type 2 diabetes mellitus.[7]

Despite clinical trial and real-world evidence supporting the benefits of GLP-1 RAs (since 2017) and of SGLT2is (since 2016), the actual uptake of these drugs continues to lag.[7–12] Furthermore, studies characterizing patterns of use have exclusively focused on prevalent use, and US based studies have focused on single payers or small populations included in national surveys. These assessments likely do not accurately capture the uptake patterns for novel treatments, for which both the uptake and the use are likely to grow over time. Moreover, the cost of these drugs and their coverage through health insurance programs varies across healthcare systems and countries.[13–16]

An appraisal of the uptake of GLP-1 RAs and SGLT2is as second line treatments among those patients who were escalated from metformin monotherapy is important. This appraisal is particularly relevant as an assessment of their initiation relative to other second line drugs, namely, dipeptidyl peptidase-4 inhibitors (DPP-4is) and sulfonylureas that have been available for longer, but do not provide cardioprotective or renoprotective effects in the short term.[17–20] In a large, multinational study, we describe patterns of initiation of four key second line drugs—ie, GLP-1 RAs, SGLT2is, DPP-4is, and sulfonylureas—during escalation from metformin monotherapy, overall, and across clinical and demographic subgroups.

For the visual abstract of this paper, see figure 1.

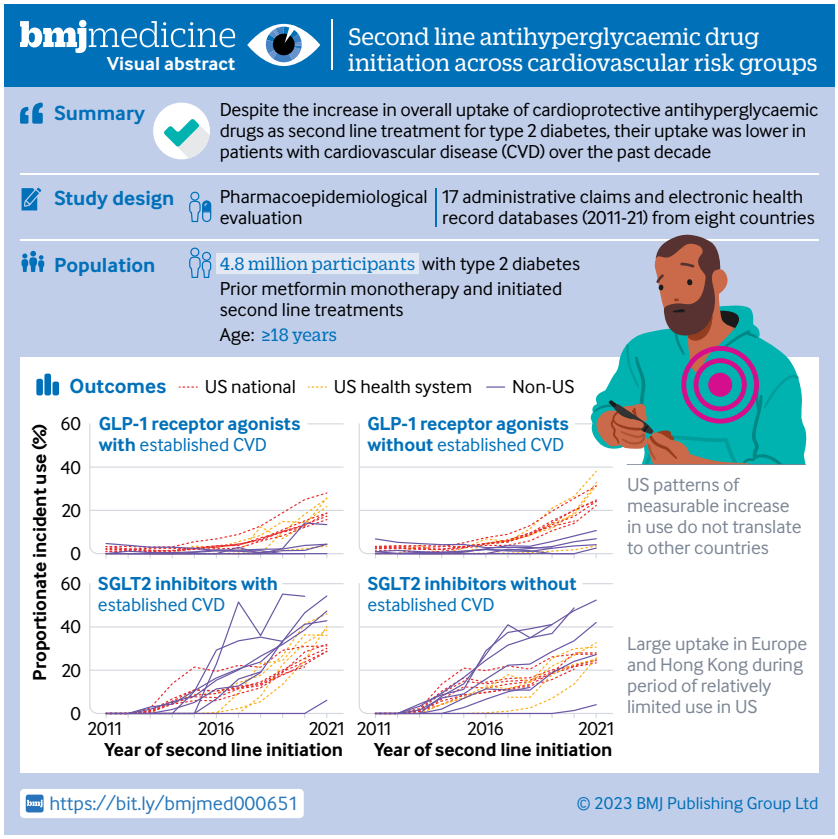

Figure 1 | Visual abstract

Materials and methods

Study overview

This study represents a federated pharmacoepidemiological analysis among type 2 diabetes mellitus patient records from a multinational consortium of data sources all mapped to the Observational Medical Outcomes Partnership Common Data Model.[21] We defined a cohort of type 2 diabetes mellitus patients receiving metformin therapy who were initiated on second line antihyperglycaemic drugs and evaluated patterns of uptake of traditionally second line antihyperglycaemic drugs with and without known cardioprotective effects, across patients spanning the cardiovascular risk spectrum.

Data sources

We identified participating data sources in the Large-scale Evidence Generation and Evaluation across a Network of Databases for Type 2 Diabetes Mellitus (LEGEND-T2DM) initiative. LEGEND-T2DM has been previously described.[22] Briefly, LEGEND-T2DM is a series of systematic, large scale observational studies of real-world characterization of second line antihyperglycaemic drugs. Of these, this study is based on 17 real-world data sources, spanning administrative claims and electronic health record databases, including six national level and four health system datasets from the US, and data sources from Spain, Germany, UK, France, Scotland, Hong Kong, and Australia. Further details about the data sources are included in table 1 and online supplemental table

Table 1 | Description of databases from the Observational Health Data Sciences and Informatics network included in the study.

Name of database	Abbreviation	Country of origin	Years of exposure included	No of participants
US national databases (claims data)				
IBM MarketScan Commercial Claims and Encounters Data	CCAE	USA	2011-21	265 874
IBM Health MarketScan Multi-State Medicaid Database	MDCD	USA	2011-20	40 064
IBM Health MarketScan Medicare Supplemental and Coordination of Benefits Database	MDCR	USA	2011-21	43 857
Optum Clinformatics Extended Data Mart - Date of Death	OCEDM	USA	2011-21	211 877
Optum de-identified Electronic Health Record Dataset	OEHR	USA	2011-21	299 008
US Open Claims	USOC	USA	2000-21	3 521 191
US health system databases (electronic health record data)				
Columbia University Irving Medical Centre	CUIMC	USA	2011-21	4561
Johns Hopkins Medicine	JHM	USA	2016-21	3759
Stanford Medicine	STARR	USA	2011-21	2993
Department of Veterans Affairs Healthcare System	VA	USA	2011-21	230 019
Non-US databases (electronic health record data)				
Australia Longitudinal Patient Database Practice Profile	ALPD	Australia	2012-21	2322
France Longitudinal Patient Database	FLPD	France	2012-21	13 270
Germany Disease Analyser	GDA	Germany	1992-21	32 442
Health Informatics Centre at the University of Dundee	HIC	Scotland	2011-21	5580
HKHA - Hong Kong Hospital Authority	HKHA	Hong Kong	2011-18	4614
UK-IQVIA Medical Research Data	IMRD	United Kingdom	2011-19	25 173
Information System for Research in Primary Care	SIDIAP	Spain	2011-21	61 382

S1. Patient records were from the past decade (2011-21) during which several second line antihyperglycaemic drugs have been introduced. The most recent data available across data sources varied from 2019 through 2021 (table 1). All patient records were standardized to the Observational Medical Outcomes Partnership, Common Data Model (Observational Health Data Sciences and Informatics, version 5), mapping international coding systems into standard vocabulary concepts.[23] These data sources have previously been leveraged in Observational Health Data Sciences and Informatics studies.[24–26]

The US populations included those commercially and publicly insured, enriched for older individuals (Medicare (MDCR), Veterans Health Administration (VA)), lower socioeconomic status (Managed Medicaid (MDCD)), and racially diverse populations (>20% black or African American in the VA, and 8% in Columbia University Irving Medical Center (CUIMC)). The study was designed at a data source level and followed federated analytical principles, so the same patients may be represented in more than one data source, particularly in the US. Some non-US databases, including Health Informatics Centre at the University of Dundee (HIC), Information System for Research in Primary Care (SIDIAP),[27] and UK-IQVIA Medical Research Data (IMRD), recorded primarily incident health conditions, as opposed to other data sources that often return multiple records of prevalent conditions. All data sources received institutional review board approval or exemption for their participation in LEGEND-T2DM. The study is reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.[28]

Study population

We included all adults (age ≥18 years) traditionally included in second line drug exposure cohorts in people with type 2 diabetes mellitus, as described in the LEGEND-T2DM study protocol.[22] Broadly, these cohorts consisted of type 2 diabetes mellitus patients who had prior metformin monotherapy and initiated second line treatment with one of the 22 drug ingredients that comprise the GLP-1 RAs, SGLT2is, DPP-4is, and sulfonylureas drug classes (online supplemental table S2). We did not consider thiazolidinediones given their known association with a risk of heart failure, weight gain, and bladder cancer.[29 30] The study population included patients with and without established cardiovascular disease based on the previously developed and validated definition for risk stratification among new users of second line type 2 diabetes mellitus drugs.[31] How cohorts were defined is detailed in the online supplemental methods.

Study exposures and outcomes

This study evaluated changes in patterns of second line antihyperglycaemic initiation over time. We used calendar years as the exposure, with the years in the study that were specific to each cohort (outlined in table 1). The outcome was the incidence of second line antihyperglycaemic drugs use among all individuals who were already receiving treatment with metformin.

Study covariates

Study covariates were drawn from the broad set of characteristics outlined in the cohort characterization tool stack in Observational Health Data Sciences and Informatics.[32] We defined cohort demographics including age, sex, and race. The clinical characteristics were defined by standard Observational Medical Outcomes Partnership concepts for diseases and procedures, including all body systems, representing 33 covariates. A team of clinicians verified the covariates included for presentation in the study to focus on those relevant to the management of diabetes, spanning domains of cardiovascular risk factors, established cardiovascular disease, and kidney disease.

Statistical analysis

We evaluated the trend of yearly incident use of all four second line antihyperglycaemic drug classes across 17 databases. For each year, we excluded a database for analyses if the number of people in the database was less than 100. The number of people in the databases for each year is provided in online supplemental table S3. Given the protective effects of GLP-1 RAs and SGLT2is on cardiovascular outcomes, we further performed a stratified analysis among individuals who had or did not have established cardiovascular disease (online supplemental methods). To calculate the annual changes of the incidence rates for second line antihyperglycaemic drugs initiation from 2016 to 2021, we fitted linear regression models to the data using incidence rate as the dependent variable and the year (coded as 1 to 6) as the independent variable. The annual change was reported as the point estimate of the slope (95% confidence interval). We compared the annual changes between patients who had cardiovascular disease with people who did not for each second line agent using the interaction term of cardiovascular disease status and year in analysis of covariance (ANCOVA) models. Additionally, to account for the differences in the age and sex distribution between patients with and without cardiovascular disease, we calculated the age and sex standardized incident use of GLP-1 RAs, SGLT2is, DPP-4is, and sulfonylureas across data sources from 2016 to 2021 using direct standardization to the world standard population.[33] Subsequently, we compared the age and sex standardized slope for GLP-1 RAs, SGLT2is, DPP-4is, and sulfonylureas between patients with and without cardiovascular disease across data sources similarly. We developed an interactive webpage to allow exploration of the cohorts included in LEGEND-T2DM.[34]

Patient and public involvement

Patients and the public were not specifically involved in the development of research hypothesis or the outcome measures, or in the design and implementation of the study due to the federated approach of the study. We will disseminate the results of the study through press release and social media postings to explain the result to news media and public.

Results

Cohort characteristics

LEGEND-T2DM included over 4.8 million patients with type 2 diabetes mellitus across all cohorts, representing individuals initiating one of the four second line antihyperglycaemic drugs between 2011 and 2021 (figure 1, table 1). This included 4.6 million type 2 diabetes mellitus patients initiating second line therapy across US based databases and 145 000 from non-US databases. Among the US databases, the US Open Claims contributed the maximum of 3.5 million patient records. The non-US data includes 61 382 patient records from Spain, 32 442 from Germany, 25 173 from the UK, 13 270 from France, 5580 from Scotland, 4614 from Hong Kong, and 2322 from Australia.

Patient characteristics

Patients with type 2 diabetes mellitus who had initiated GLP-1 RA second line were more frequently female, while patients who had initiated treatment with SGLT2is were more frequently male. Overall, patients who were prescribed GLP-1 RA as the second line treatment for type 2 diabetes mellitus had a lower prevalence of cardiovascular disease, including ischemic heart disease, cerebrovascular disease, and heart failure, compared with patients who were prescribed other second-line drugs. For instance, according to the US Open Claims database, ischemic heart disease was reported in 2.7% of people who used GLP-1 RAs compared with in 4.1% of those using SGLT2is, DPP-4is, or sulfonylureas (online supplemental table S4–S7).

Similarly, for the IBM Health MarketScan Commercial Claims and Encounters Database (CCAE), 3.6% of the people using GLP-1 RA had ischemic heart disease, compared with 4.3% of people using SGLT2is, 3.9% of of people using DDP-4is, and 4.3% of people using sulfonylureas. Both in the US and non-US databases, fewer patients initiating GLP-1 RAs and SGLT2is had renal impairment at baseline. For instance, in US Open Claims, 4.1% of people using GLP-1 RA and SGLT2is had renal impairment compared with 6.5% of people using DPP-4is, and 6.7% of people using sulfonylureas. In the Information System for Research in Primary Care (SIDIAP) dataset from Spain, 1.5% of patients prescribed GLP-1 RAs or SGLT2is had renal impairment compared with 3.9% of people using DPP-4i, and 1.7% of people using sulfonylureas (online supplemental tables S8–S11).

Incident use across cohorts

In 2021, the choice of the prescribed second line antihyperglycaemic drugs varied among different US

databases. The combined incident use of cardioprotective drugs, GLP-1 RAs, and SGLT2is, ranged from 35.2% in Veterans Affairs Health System to 68.2% in Columbia University Irving Medical Center. The incident use of DDP-4is ranged from 14.5% in Stanford (STARR) to 23.5% in the Veterans Affairs Health System. By contrast, sulfonylureas incident use ranged from 11.1% in Columbia University Irving Medical Center to 41.3% in the Veterans Affairs Health System (figure 2).

Among the non-US databases, in 2021, the combined incident use of cardioprotective drugs differed widely, ranging from 15.4% in France up to 54.8% in Scotland (figure 2). Incident use of DPP-4is was greater in other countries than in the US, ranging from 44.2% in Scotland to 77.0% in France. By contrast, the incident use of sulfonylureas was less across the non-US databases as compared with the US databases, ranging from 1% in Scotland to 7.5% in France. The incident use of various antihyperglycaemic drugs in 2020 is shown in online supplemental figures S1–S3.

Uptake of drug use across study cohorts

The proportion of second line antihyperglycaemic drug uptake varied across cohorts. Between 2011 and 2021, the initiation of GLP-1 RAs as second line antihyperglycaemic drugs increased across all US national data sources, from no measured initiation in 2011 to 18.5% in 2021 in the IBM Health MarketScan Medicare (MDCR) population, and to 30.5% in CCAE (online supplemental figure S4).

Similarly, the uptake of SGLT2is in the US national databases increased from no uptake in 2011 across data sources to 25.2% in 2021 in the Optum de-identified Electronic Health Record Dataset (OEHR) and 30.2% in the Medicare population. The Department of Veterans Affairs Healthcare System had the lowest proportionate incident use of the cardioprotective antihyperglycaemic drugs in the US, driven predominantly by the low use of GLP-1 RAs (online supplemental figure S5). The uptake of SGLT2is in the non-US databases increased from no uptake in 2011 to 4.4% in France and up to 52.6% in Scotland by 2021. Throughout the study period, use of GLP-1 RAs in Australia was low. However, among the non-US databases available, the use of GLP-1 RAs increased most in France to 11.1% in 2021 (online supplemental figure S6).

From 2016 to 2021, the annual increase in the combined incident use of GLP-1 RAs and SGLT2is was 10.6% per year in CUIMC, and 6.2% per year in US Open Claims database. The annualised increase per year from 2016 to 2021 was 2.7% per year in France, 4.3% in Spain per year, and 5.2% per year in Scotland.

Drug use across cardiovascular risk groups

The uptake of GLP-1 RAs in patients with established cardiovascular disease in US national databases

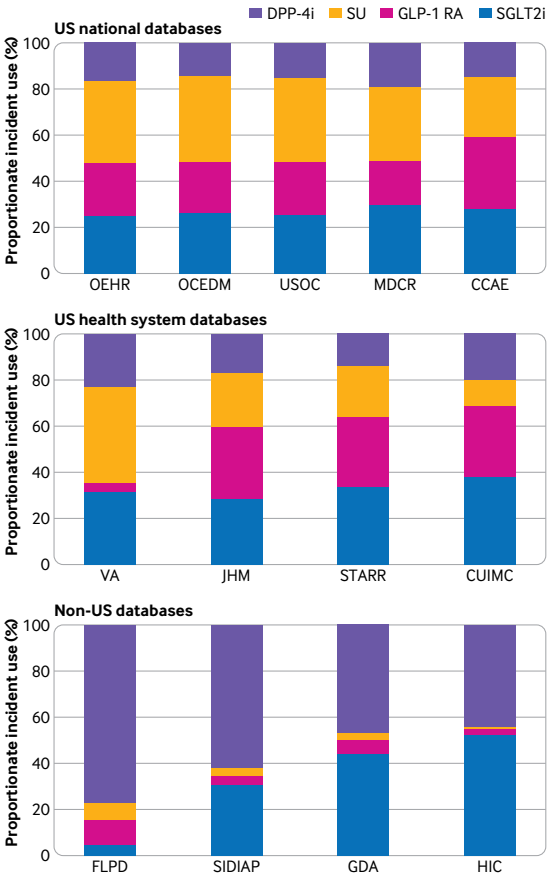

Figure 2 | Proportional incident use of second line antihyperglycaemic drugs in United States national databases, United States health system. CCAE=IBM MarketScan Commercial Claims and Encounters Data; CUIMC=Columbia University Irving Medical Centre; DPP-4i=dipeptidyl peptidase-4 inhibitors; FLPD=France Longitudinal Patient Database; GDA=Germany Disease Analyser; GLP-1 RA=glucagon-like peptide-1 receptor agonist; HIC=Health Informatics Centre at the University of Dundee; JHM=Johns Hopkins Medicine; MDCR=IBM Health MarketScan Medicare Supplemental and Coordination of Benefits Database; OCEDM=Optum Clinformatics Extended Data Mart-Date of Death; OEHR=Optum de-identified Electronic Health Record Dataset; SGLT2i=sodium-glucose cotransporter 2 inhibitor; SIDIAP=Information System for Research in Primary Care; STARR=Stanford Medicine; SU=sulfonylurea; USOC=United States Open Claims; VA=Department of Veterans Affairs Healthcare System

increased consistently from no incident use across databases in 2011 to 15.7% in patients in the Medicare (MDCR) system and up to 28.0% in the CCAE population in 2021 (figure 3). By contrast, the incident use of GLP-1 RA in patients without established cardiovascular disease increased from no uptake in 2011 to 22.3% in MDCR patients and up to 38.0% in CUIMC patients in 2021 (figure 3). Meanwhile, the incident use of SGLT2is in the patients with established cardiovascular disease, in the same period, reached 28.7% in Optum Clinformatics Extended DataMart (OCEDM) and 46.0% in CUIMC (figure 4). In patients without cardiovascular disease, the increase in

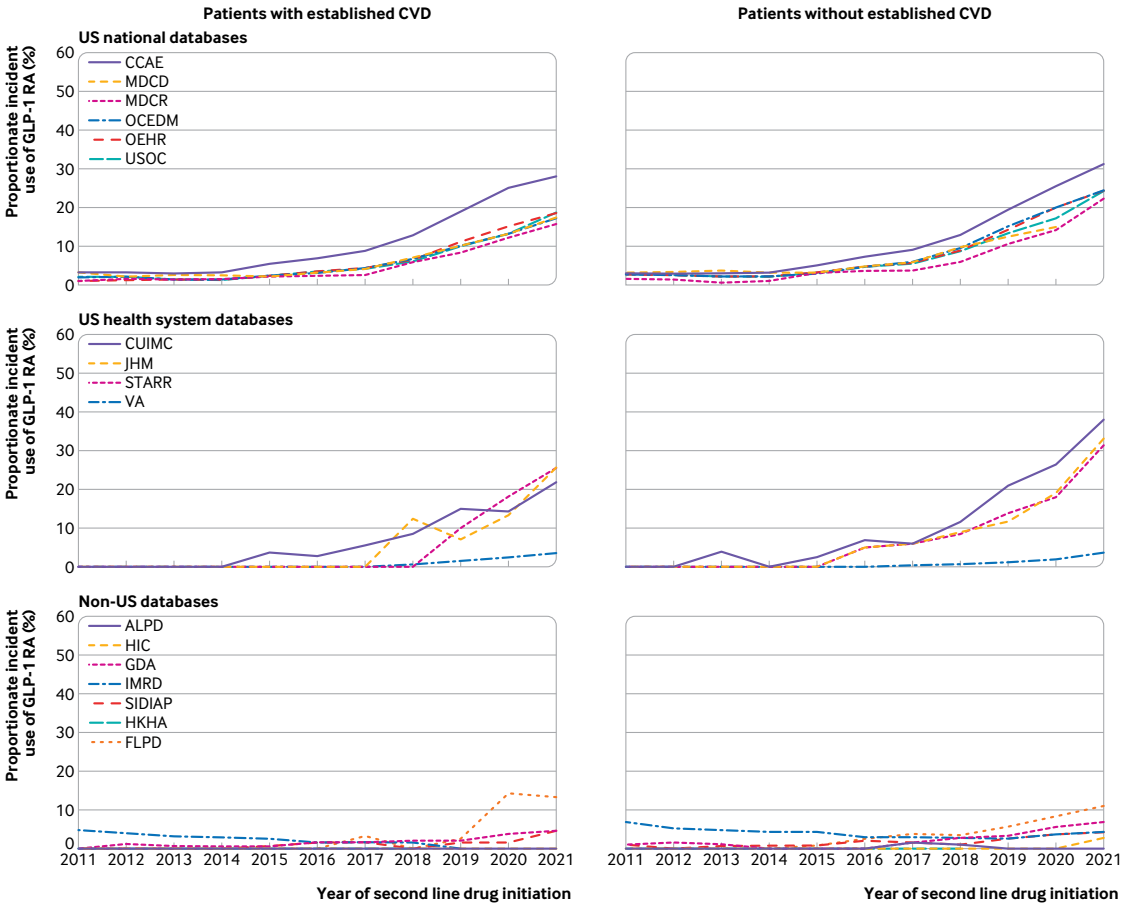

Figure 3 | Proportional first incident use of glucagon-like peptide-1 receptor agonists as second line therapy after metformin in patients with established cardiovascular disease, and patients without established cardiovascular disease. ALPD=Australia Longitudinal Patient Database Practice Profile; CCAE=IBM MarketScan Commercial Claims and Encounters Data; CUIMC=Columbia University Irving Medical Center; FLPD=France Longitudinal Patient Database; GDA=Germany Disease Analyser; GLP-1 RA=glucagon-like peptide-1 receptor agonist; HIC=Health Informatics Centre at the University of Dundee; HKHA=Hong Kong Hospital Authority; IMRD=UK-IQVIA Medical Research Data; JHM=Johns Hopkins Medicine; MDCD=IBM Health MarketScan Multi-State Medicaid Database; MDCR=IBM Health MarketScan Medicare Supplemental and Coordination of Benefits Database; OCEDM=Optum Clinformatics Extended Data Mart - Date of Death; OEHR=Optum de-identified Electronic Health Record Dataset; SIDIAP=Information System for Research in Primary Care; STARR=Stanford Medicine; USOC=United States Open Claims; VA=Department of Veterans Affairs Healthcare System

SGLT2is uptake was up to 23.3% in Optum de-identified Electronic Health Record Dataset (OEHR) and up to 32.7% at Stanford Medicine (STARR) (figure 4).

Among the non-US health systems, the uptake of GLP-1 RAs increased from no uptake in 2011 to 13.4% in 2021 in patients with cardiovascular disease in France, and to 10.7% in patients who did not have cardiovascular disease (figure 3). Although SGLT2is were not in use as second line antihyperglycaemic drugs in 2011 in any of the non-US databases, their uptake grew to include 6.1% of the patients with cardiovascular disease in France, and 54.2% in Scotland (figure 4). In the patients with no established cardiovascular disease, the uptake of SGLT2is increased from no uptake in 2011 to 4.1% in France, and up to 52.3% in Australia in 2021 (figure 4).

From 2016 to 2021, the uptake of GLP-1 RAs increased more significantly among patients without cardiovascular disease compared with patients with cardiovascular disease in France, UK, and some US databases; however, no database had a higher annual change of GLP-1 RA uptake in patients with cardiovascular disease compared with patients with no cardiovascular disease (table 2). A similar scenario was noted for SGLT2is. Although Australia, UK, Scotland, and some US databases showed greater increases in the uptake of SGLT2is among patients with no cardiovascular disease compared with patients with cardiovascular disease from 2016 to 2021, uptake of SGLT2is was not different between these populations in other databases (table 2). These patterns were consistent even after age and sex standardisation of the data across sources (online supplemental tables S12 and S13). The uptake trends of DPP-4is and sulfonylureas were inconsistent (online supplemental tables S14–S17).

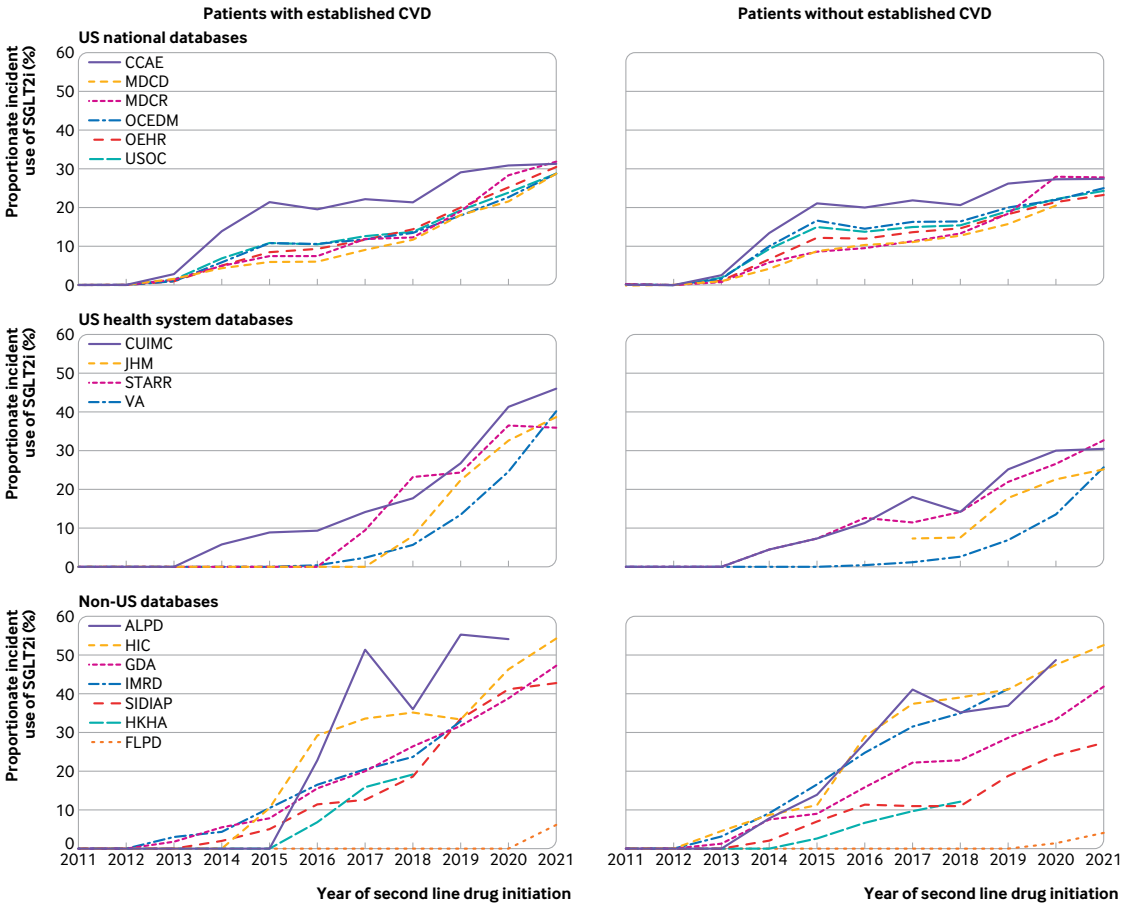

Figure 4 | Proportional first incident use of sodium-glucose Cctransporter 2 inhibitors as second line therapy after metformin in (A) patients with established cardiovascular disease, and (B) patients without established cardiovascular disease. ALPD=Australia Longitudinal Patient Database Practice Profile; CCAE=IBM MarketScan Commercial Claims and Encounters Data; CUIMC=Columbia University Irving Medical Centre; FLPD=France Longitudinal Patient Database; GDA=Germany Disease Analyser; HIC=Health Informatics Centre at the University of Dundee; HKHA=Hong Kong Hospital Authority; IMRD=UK-IQVIA Medical Research Data; JHM=Johns Hopkins Medicine; MDCD=IBM Health MarketScan Multi-State Medicaid Database; MDCR=IBM Health MarketScan Medicare Supplemental and Coordination of Benefits Database; OCEDM=Optum Clinformatics Extended Data Mart–Date of Death; OEHR=Optum de-identified Electronic Health Record Dataset; SGLT2i=sodium-glucose cotransporter 2 inhibitor; SIDIAP=Information System for Research in Primary Care; STARR=Stanford Medicine; USOC=United States Open Claims; VA=Department of Veterans Affairs Healthcare System

Discussion

Main findings

In this first investigation from the LEGEND-T2DM study, we report a large and comprehensive pharmacoepidemiological evaluation of the uptake of second line type 2 diabetes mellitus drugs across 17 international databases with over 4.8 million type 2 diabetes mellitus patient records. The study uses a federated approach to the study of patterns of medication use across multiple disparate data sources simultaneously, thereby allowing an informed assessment of individual trends in second line type 2 diabetes mellitus medication uptake. We observed a large uptake of cardioprotective antihyperglycaemic drugs among patients who had received a second line drug, representing nearly half of all included patients. Although both cardioprotective drug classes in the US increased, the initiation of SGLT2is increased at a higher rate than GLP-1 RAs, representing nearly a third of patients. By contrast, the initiation of SGLT2is increased to 40% to 50% of the population in a cohort mostly from Europe and Hong Kong, with lower initiation of GLP-1 RAs. Finally, patterns suggest non-selective uptake of cardioprotective drugs with an increasing uptake among people who do not have cardiovascular disease compared with those with established cardiovascular disease.

Implications

The study builds on previous assessments of GLP-1 RAs and SGLT2is use in both national US surveys and insurance datasets. These prior studies focused on the overall prevalent use of cardioprotective therapy in select years and found that, at most, 10%–15% of individuals with compelling indications use cardioprotective medications.[7 11 12 35–37] Our study adds to the literature by focusing on people who initiated second line therapy who are currently

Table 2 | Annual change in the incident use of glucagon-like peptide-1 receptor agonists and sodium-glucose cotransporter 2 inhibitors for patients with established cardiovascular disease and patients with no established cardiovascular disease.

	Glucagon-like peptide-1 receptor agonists			Sodium-glucose cotransporter 2 inhibitors		
Data source	Slope for patients with CVD, % (95% CI)	Slope for patients with no CVD, % (95% CI)	P value for slope difference	Slope for patients with CVD, % (95% CI)	Slope for patients with no CVD, % (95% CI)	P value for slope difference
US national databases						
CCAE	1.87 (1.11 to 2.64)	6.81 (3.69 to 9.92)	0.003	1.43 (0.58 to 2.28)	3.48 (1.12 to 5.85)	0.053
MDCD	0.58 (0.36 to 0.81)	0.92 (0.73 to 1.1)	0.01	0.99 (0.71 to 1.26)	0.83 (0.24 to 1.42)	0.457
MDCR	5.05 (0.9 to 9.21)	5.1 (−0.03 to 10.22)	0.986	9.18 (1.1 to 17.25)	5.62 (0.81 to 10.44)	0.325
OCEDM	3.21 (1.72 to 4.7)	5.51 (3.32 to 7.71)	0.042	4.75 (2.27 to 7.24)	3.94 (2.19 to 5.68)	0.477
OEHR	2.36 (1.03 to 3.7)	7.82 (3.77 to 11.88)	0.007	3.6 (1.64 to 5.56)	6.46 (3.42 to 9.5)	0.06
USOC	2 (0.61 to 3.4)	5.32 (1.74 to 8.9)	0.044	2.87 (1.00 to 4.74)	4.22 (1.28 to 7.17)	0.313
US health system databases						
CUIMC	1.68 (1.08 to 2.27)	3.13 (1.59 to 4.66)	0.04	3.71 (2.23 to 5.2)	2.37 (1.34 to 3.41)	0.074
JHM	0.75 (−0.08 to 1.58)	2.59 (0.58 to 4.61)	0.036	1.36 (0.95 to 1.77)	2.09 (1.38 to 2.8)	0.03
STARR	0.65 (0.17 to 1.14)	2.07 (0.38 to 3.76)	0.056	0.91 (0.56 to 1.27)	2.01 (0.74 to 3.28)	0.049
VA	1.4 (0.4 to 2.39)	1.84 (0.3 to 3.39)	0.517	15.94 (3.9 to 27.99)	13.85 (2.48 to 25.22)	0.734
Non-US databases						
ALPD	0	−0.1 (−0.77 to 0.56)	0.633	0.63 (0.39 to 0.88)	9.6 (4.99 to 14.2)	0.001
FLPD	0.34 (0.07 to 0.62)	1.35 (0.38 to 2.32)	0.024	0.12 (−0.07 to 0.3)	0.5 (−0.11 to 1.1)	0.132
GDA	0.47 (0.11 to 0.83)	0.92 (0.21 to 1.62)	0.155	5.11 (1.75 to 8.48)	5.22 (1.47 to 8.97)	0.955
HIC	0	0.25 (−0.15 to 0.64)	0.122	0.81 (−0.16 to 1.78)	3.75 (2.49 to 5)	0.001
HKHA	NA	NA	NA	4.98 (−3.07 to 13.04)	4.13 (−8.35 to 16.61)	0.542
IMRD	−0.08 (−0.26 to 0.11)	0.16 (−0.13 to 0.44)	0.042	1.15 (0.11 to 2.2)	7.24 (2.28 to 12.19)	0.007
SIDIAP	0.27 (−0.09 to 0.62)	0.99 (0.13 to 1.86)	0.062	3.26 (1.63 to 4.89)	6.47 (1.71 to 11.23)	0.115

ALPD=Australia Longitudinal Patient Database Practice Profile; CCAE=IBM MarketScan Commercial Claims and Encounters Data; CUIMC=Columbia University Irving Medical Centre; FLPD=France Longitudinal Patient Database; GDA=Germany Disease Analyser; HIC=Health Informatics Centre at the University of Dundee, HKHA=Hong Kong Hospital Authority; IMRD=UK-IQVIA Medical Research Data, JHM=Johns Hopkins Medicine; MDCD=IBM Health MarketScan Multi-State Medicaid Database, MDCR=IBM Health MarketScan Medicare Supplemental and Coordination of Benefits Database; NA=not available; OCEDM=Optum Clinformatics Extended Data Mart-Date of Death; OEHR=Optum de-identified Electronic Health Record Dataset; SIDIAP=Information System for Research in Primary Care; STARR=Stanford Medicine; USOC=United States Open Claims, VA=Department of Veterans Affairs Healthcare System

using metformin alone, therefore, assessing initiation of these drugs exclusively in individuals who likely required clinical escalation of antihyperglycaemic treatment as recommended by the American Diabetes Association.[38] The study further covers 11 years of data, which results in additional qualitative information on the trajectory of the uptake of antihyperglycaemic drugs. Moreover, this study assessed the trends observed in the US with those in other countries and showed the large uptake of SGLT2is that has occurred in many countries in Europe and in Hong Kong, during a period when the drug's use has been relatively limited in the US. We also find that the increase in GLP-1 RA initiation has been differential, with US patterns of measurable increase in GLP-1 RAs not reported in other countries.

The findings also suggest potential mechanisms for the patterns noted in the US. Initial studies finding low uptake for cardioprotective drugs in the US had posited that this use may represent clinician inertia,[8] despite strong support in guidelines,[6 38] given the novel nature of these drugs. This suggestion was supported by the low use even among patients with medical insurance. However, the rapid uptake in most countries with a nationally funded healthcare program with preventive medical coverage highlights that the underuse in the US may be financially motivated. Although not evaluated in this study, these motivations may include barriers associated with high out-of-pocket costs or other insurer driven strategies to restrict drug use.[39 40] This scenario is particularly concerning in the US given the absence of requirement for commercial insurance to cover preventive therapy, for which a return on investment for insurers is often delayed.

A key exception to this pattern was France, where despite a national health insurance with prescription coverage,[41] the relative uptake of cardioprotective therapies was low. A review of clinical directives and guidelines in France suggests that national policies that urged caution against possible adverse events with novel drugs may underlie these patterns.[42 43] The limited uptake of GLP-1 RAs in non-US countries despite their cardioprotective effects, may, however, indicate a barrier with the injectable method of administration, and the alternative of SGLT2is, which has broader tolerability.[13 35 44] Therefore, financial rather than informational strategies are essential to promote the uptake of cardioprotective treatments in the US, particularly among people with cardiovascular disease.

We noted a greater increase in the uptake of GLP-1 RAs and SGLT2is among patients who do not have cardiovascular disease compared with patients with

established cardiovascular disease between 2016 and 2021. Nevertheless, patients with established disease represent the only group with robust recommendations for the use of these medications in clinical practice guidelines.[45 46] The non-selective uptake of cardioprotective drugs may potentially be attributed to the fact that cardiologists contribute to less than 2% of prescribed GLP-1 RAs and SGLT2is. By contrast, more than two thirds of these drugs are prescribed by primary care physicians, internists, and endocrinologists.[47] As a result, patients with type 2 diabetes mellitus and cardiovascular disease who are often treated by cardiologists may be less likely to receive cardioprotective antihyperglycaemic drugs compared with people with type 2 diabetes mellitus but no cardiovascular disease who are probably managed by people who are not cardiologists.

Strengths and limitations

A key strength of our study is the novel strategy for monitoring medication use patterns on an international scale without the need for sharing of individual level data, which can be easily adapted for monitoring the effect of local and international interventions. The study builds on evidence to illustrate the uptake patterns of cardioprotective antihyperglycaemic drugs across multiple US and non-US databases in a context where all populations are consistently described. This breadth of information enabled us to not only assess the effect of international differences in guideline recommendations and insurance coverage but also to identify practice variations at health systems in the US.

Our study has some limitations. Our findings represent available observational datasets, including administrative claims and electronic health record databases, and may not be representative of respective national or subnational populations. The study included all individuals who met inclusion criteria, but the representativeness of the overall population of diabetes was not explicitly confirmed. We believe the current approach may be adopted as a benchmark for monitoring the uptake of antihyperglycaemic drugs in response to changes in regional guidelines, insurance coverage, and contemporary evidence rather than inferring generalizable estimates of the use of antihyperglycaemic drugs. Modest data differences might be present for some of the clinical features across data sources. However, these differences are unlikely to be the reason for observed patterns because the study used broadly defined exposure and outcome groups, which are less likely to be affected by variations in coding practices. Additionally, we included data sources that have been consistently used in rigorous federated studies previously.[48] Medical records could have overlap in some US databases, such that the same patients could have been captured across multiple sources. Having different record views of the same patient can be an advantage in capturing the real-life health events experienced by the patient. But, because licensing agreements prohibit attempts to link patients between most databases, the extent of this overlap cannot be precisely assessed. Given the heterogeneity in the included databases, standardising the patients on the basis of outcomes and assessing the incident drug use might be essential. Although the drugs included are commonly used as second line escalation treatments for type 2 diabetes mellitus, the precise reasons for initiation cannot be determined. Other potential reasons for prescription may include indications for weight loss, selection based on low cost of one drug over the other, or safer side effect profile. The study cannot identify the barriers to optimal uptake of cardioprotective antihyperglycaemic drugs. However, our approach highlights a potential strategy for benchmarking the use of these drugs in various patient populations with cardiovascular disease. Our findings illustrate the uptake patterns of antihyperglycaemic drugs as second line treatments instead of providing a comprehensive overview of overall uptake patterns. Nevertheless, the study establishes a federated framework that can guide future research in addressing the remaining knowledge gaps in the field.

Conclusions

Despite the increase in overall uptake of cardioprotective antihyperglycaemic drugs as second line treatment for type 2 diabetes mellitus, these drugs have been underused in the US relative to other countries, particularly among people with established cardiovascular disease. A strategy to ensure medication uptake concordant with guideline recommendations is essential to improve outcomes of patients with type 2 diabetes mellitus.

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Contributors All authors acquired, analyzed, and interpreted the data and critically revised the manuscript for important intellectual content. RK and MAS conceived and designed the study. RK, LSD, KL, JJZ, AA, and MAS conducted the statistical analysis and drafted the manuscript. RK and MAS provided supervision. MAS is the study guarantor. RK and MAS had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. RK and MAS are responsible for the overall content as guarantors. Transparency: The lead author (the guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained

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Ethics approval Institutional ethics committees/institutional review boards approved the use of data at individual sites. This included Columbia University Irving Medical Center (AAAO7805), Johns Hopkins Medicine (IRB00296724), Leland Stanford Junior University (RB-53248), Hong Kong Hospital Authority (UW 22-640), and UK-IQVIA (22SRC004). The use of the VA-Observational Medical Outcomes Partnership data source was reviewed by the Department of Veterans Affairs Central IRB and was determined to meet the criteria for exemption under Exemption Category 4(3) and approved the request for Waiver of HIPAA Authorization. Other sites with approvals and without associated identifying numbers are ALPD, FLPD, GDA, IBM, Optum, SIDIAP, and University of Dundee.

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Data availability statement Data are available in a public, open access repository. The summary data can be accessed online at https://data.ohdsi.org/LegendT2dmClassCohortExplorer/ to allow exploration of the cohorts included in LEGEND-T2DM. Some of the datasets used within this study are available via license. The data that support the findings of this study are available to license from IBM (CCAE, MDCD, MDCR), Optum (OCEDM, OEHR), and IQVIA (IMRD). Data are available from IBM at https://www.ibm.com/products/marketscan-research-databases, from Optum at https://www.optum.com/business/solutions/life-sciences/real-world-data.html, and from IQVIA at https://www.iqvia.com/solutions/real-world-evidence/real-world-data-and-insights. Outside the license data previously described, this study was performed as a federated network study, meaning the data remained with the data partner. Individual organizations would need to be contacted in order to gain access to those data assets.

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Multinational Patterns of Second-line Anti-hyperglycemic Drug Initiation Across Cardiovascular Risk Groups: A Federated Pharmacoepidemiologic Evaluation in LEGEND-T2DM

ONLINE SUPPLEMENT

Supplemental Methods – Exposure Cohort Definitions

I. Class-vs-Class Exposure (DPP4 New-User) Cohort / OT1

i. Cohort Entry Events

People with continuous observation of 365 days before the event may enter the cohort when observing any of the following:

1. drug exposure of 'DPP4 inhibitors' for the first time in the person's history.

Limit cohort entry events to the earliest event per person.

Restrict entry events to with all of the following criteria:

1. with the following event criteria: who are >= 18 years old.
2. having at least 1 condition occurrence of 'Type 2 diabetes mellitus,' starting anytime on or before cohort entry start date; allow events outside observation period.
3. having no condition occurrences of 'Type 1 diabetes mellitus,' starting anytime on or before cohort entry start date; allow events outside observation period.
4. having no condition occurrences of 'Secondary diabetes mellitus,' starting anytime on or before cohort entry start date; allow events outside observation period.

ii. Additional Inclusion Criteria

1. No prior GLP-1 receptor agonist exposure

Entry events having no drug exposures of 'GLP-1 receptor agonists,' starting anytime on or before cohort entry start date; allow events outside observation period.

2. No prior SGLT-2 inhibitor exposure

Entry events having no drug exposures of 'SGLT2 inhibitors,' starting anytime on or before cohort entry start date; allow events outside observation period.

3. No prior SU exposure

Entry events having no drug exposures of 'Sulfonylureas,' starting anytime on or before cohort entry start date; allow events outside observation period.

4. No prior other anti-diabetic exposure

Entry events having no drug exposures of 'Other anti-diabetics,' starting anytime on or before cohort entry start date; allow events outside observation period.

5. Prior metformin use

Entry events with any of the following criteria:

1. having at least 1 drug era of 'Metformin,' starting anytime up to 90 days before cohort entry start date; allow events outside observation period; with era length >= 90 days.
2. having at least 3 drug exposures of 'Metformin,' starting anytime on or before cohort entry start date; allow events outside observation period.

- No prior insulin use or combo initiation: Proxy for < 30 days drug era anytime before index and no combination use on index

Entry events with all of the following criteria:

1. having no drug eras of 'Insulin,' starting anytime up to 30 days before cohort entry start date; allow events outside observation period; with era length > 30 days.
2. having no drug eras of 'Insulin,' starting between 30 days before and 0 days after cohort entry start date; allow events outside observation period.

iii. Cohort Exit

The cohort end date will be based on a continuous exposure to 'DPP4 inhibitors': allowing 30 days between exposures, adding 0 days after exposure ends, and using days supply and exposure end date for exposure duration.

iv. Cohort Eras

Entry events will be combined into cohort eras if they are within 0 days of each other.

v. Concept: DPP4 inhibitors

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
43013884	alogliptin	1368001	RxNorm	NO	YES	NO
40239216	linagliptin	1100699	RxNorm	NO	YES	NO
40166035	saxagliptin	857974	RxNorm	NO	YES	NO
1580747	sitagliptin	593411	RxNorm	NO	YES	NO
19122137	vildagliptin	596554	RxNorm	NO	YES	NO

vi. Concept: GLP-1 receptor agonists

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
44816332	albiglutide	1534763	RxNorm	NO	YES	NO
45774435	dulaglutide	1551291	RxNorm	NO	YES	NO
1583722	exenatide	60548	RxNorm	NO	YES	NO
4017041	liraglutide	475968	RxNorm	NO	YES	NO
44506754	lixisenatide	1440051	RxNorm	NO	YES	NO
793143	semaglutide	1991302	RxNorm	NO	YES	NO

vii. Concept: SGLT2 inhibitors

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
43526465	canagliflozin	1373458	RxNorm	NO	YES	NO
44785829	dapagliflozin	1488564	RxNorm	NO	YES	NO
45774751	empagliflozin	1545653	RxNorm	NO	YES	NO
793293	ertugliflozin	1992672	RxNorm	NO	YES	NO

viii. Concept: Sulfonylureas

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
1594973	chlorpropamide	2404	RxNorm	NO	YES	NO
1597756	glimepiride	25789	RxNorm	NO	YES	NO
1560171	glipizide	4821	RxNorm	NO	YES	NO
1509821	gliquidone	25793	RxNorm	NO	YES	NO
1559684	glyburide	4815	RxNorm	NO	YES	NO
1502809	tolazamide	10633	RxNorm	NO	YES	NO
1502855	tolbutamide	10635	RxNorm	NO	YES	NO

ix. Concept: Other anti-diabetics

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
1529331	acarbose	16681	RxNorm	NO	YES	NO
1530014	acetohexamide	173	RxNorm	NO	YES	NO
730548	bromocriptine	1760	RxNorm	NO	YES	NO
19033498	carbutamide	2068	RxNorm	NO	YES	NO
19001409	glibornuride	102846	RxNorm	NO	YES	NO
19059796	gliclazide	4816	RxNorm	NO	YES	NO
19001441	glymidine	102848	RxNorm	NO	YES	NO
1510202	miglitol	30009	RxNorm	NO	YES	NO
1502826	nateglinide	274332	RxNorm	NO	YES	NO
1525215	pioglitazone	33738	RxNorm	NO	YES	NO
1516766	repaglinide	73044	RxNorm	NO	YES	NO
1547504	rosiglitazone	84108	RxNorm	NO	YES	NO
1515249	troglitazone	72610	RxNorm	NO	YES	NO

x. Concept: Insulin

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
1596977	insulin, regular, human	253182	RxNorm	NO	YES	NO
1550023	insulin lispro	86009	RxNorm	NO	YES	NO
1567198	insulin aspart, human	51428	RxNorm	NO	YES	NO
1502905	insulin glargine	274783	RxNorm	NO	YES	NO
1513876	insulin lispro protamine, human	314684	RxNorm	NO	YES	NO
1531601	insulin aspart protamine, human	352385	RxNorm	NO	YES	NO
1586346	insulin, regular, pork	221109	RxNorm	NO	YES	NO
1544838	insulin glulisine, human	400008	RxNorm	NO	YES	NO
1516976	insulin detemir	139825	RxNorm	NO	YES	NO
1590165	insulin, regular, beef-pork	235275	RxNorm	NO	YES	NO
1513849	lente insulin, human	314683	RxNorm	NO	YES	NO
1562586	lente insulin, pork	93108	RxNorm	NO	YES	NO
1588986	insulin human, rDNA origin	631657	RxNorm	NO	YES	NO
1513843	lente insulin, beef-pork	314682	RxNorm	NO	YES	NO
1586369	ultralente insulin, human	221110	RxNorm	NO	YES	NO
35605670	insulin argine	1740938	RxNorm	NO	YES	NO
35602717	insulin degludec	1670007	RxNorm	NO	YES	NO
21600713	INSULINS AND ANALOGUES	A10A	ATC	NO	YES	NO
19078608	insulin, protamine zinc, beef-pork 100 UNT/ML Injectable Suspension	311053	RxNorm	NO	YES	NO

xi. Concept: Metformin

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
1503297	metformin	6809	RxNorm	NO	YES	NO

xii. Concept: Secondary diabetes mellitus

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
195771	Secondary diabetes mellitus	8801005	SNOMED	NO	YES	NO

xiii. Concept: Type 1 diabetes mellitus

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
201254	Type 1 diabetes mellitus	46635009	SNOMED	NO	YES	NO
435216	Disorder due to type 1 diabetes mellitus	420868002	SNOMED	NO	YES	NO
200687	Renal disorder due to type 1 diabetes mellitus	421893009	SNOMED	NO	YES	NO
377821	Disorder of nervous system due to type 1 diabetes mellitus	421468001	SNOMED	NO	YES	NO
318712	Peripheral circulatory disorder due to type 1 diabetes mellitus	421365002	SNOMED	NO	YES	NO

xiv. Concept: Type 2 diabetes mellitus

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
201826	Type 2 diabetes mellitus	44054006	SNOMED	NO	YES	NO
443734	Ketoacidosis due to type 2 diabetes mellitus	421750000	SNOMED	NO	YES	NO
443767	Disorder of eye due to diabetes mellitus	25093002	SNOMED	NO	YES	NO
192279	Disorder of kidney due to diabetes mellitus	127013003	SNOMED	NO	YES	NO
443735	Coma due to diabetes mellitus	420662003	SNOMED	NO	YES	NO
376065	Disorder of nervous system due to type 2 diabetes mellitus	421326000	SNOMED	NO	YES	NO
443729	Peripheral circulatory disorder due to type 2 diabetes mellitus	422166005	SNOMED	NO	YES	NO
443732	Disorder due to type 2 diabetes mellitus	422014003	SNOMED	NO	YES	NO

II. Metformin Use Modifier

i. No prior metformin use

Entry events having no drug eras of 'Metformin,' starting anytime on or before cohort entry start date; allow events outside observation period.

III. Drug-vs-Drug Exposure (Alogliptin New-User) Cohort / OT1

i. Cohort Entry Events

People with continuous observation of 365 days before event may enter the cohort when observing any of the following:

1. drug exposure of 'alogliptin' for the first time in the person's

history. Limit cohort entry events to the earliest event per person.

Restrict entry events to with all of the following criteria:

1. with the following event criteria: who are >= 18 years old.
2. having at least 1 condition occurrence of 'Type 2 diabetes mellitus,' starting anytime on or before cohort entry start date; allow events outside observation period.
3. having no condition occurrences of 'Type 1 diabetes mellitus,' starting anytime on or before cohort entry start date; allow events outside observation period.
4. having no condition occurrences of 'Secondary diabetes mellitus,' starting anytime on or before cohort entry start date; allow events outside observation period.

ii. Additional Inclusion Criteria

- No prior with-in class exposure

Entry events having no drug exposures of 'DPP4 inhibitors excluding alogliptin,' starting anytime on or before cohort entry start date; allow events outside observation period.

- No prior GLP-1 receptor agonist exposure

Entry events having no drug exposures of 'GLP-1 receptor agonists,' starting anytime on or before cohort entry start date; allow events outside observation period.

- No prior SGLT-2 inhibitor exposure

Entry events having no drug exposures of 'SGLT2 inhibitors,' starting anytime on or before cohort entry start date; allow events outside observation period.

- No prior SU exposure

Entry events having no drug exposures of 'Sulfonylureas,' starting anytime on or before cohort entry start date; allow events outside observation period.

- No prior other anti-diabetic exposure

Entry events having no drug exposures of 'Other anti-diabetics,' starting anytime on or before cohort entry start date; allow events outside observation period.

- Prior metformin use

Entry events with any of the following criteria:

1. having at least 1 drug era of 'Metformin,' starting anytime up to 90 days before cohort entry start date; allow events outside observation period; with era length >= 90 days.
2. having at least 3 drug exposures of 'Metformin,' starting anytime on or before cohort entry start date; allow events outside observation period.

- No prior insulin use or combo initiation: Proxy for < 30 days drug era anytime before index and no combination use on index

Entry events having no drug eras of 'Insulin,' starting anytime on or before cohort entry start date; allow events outside observation period; with era length > 30 days.

iii. Cohort Exit

The cohort end date will be based on a continuous exposure to 'alogliptin': allowing 30 days between exposures, adding 0 days after exposure ends, and using days supply and exposure end date for exposure duration.

iv. Cohort Eras

Entry events will be combined into cohort eras if they are within 0 days of each other.

v. Concept: alogliptin

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
43013884	alogliptin	1368001	RxNorm	NO	YES	NO

vi. Concept: DPP4 inhibitors excluding alogliptin

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
40239216	linagliptin	1100699	RxNorm	NO	YES	NO
40166035	saxagliptin	857974	RxNorm	NO	YES	NO
1580747	sitagliptin	593411	RxNorm	NO	YES	NO
19122137	vildagliptin	596554	RxNorm	NO	YES	NO

IV. Heterogenity Study Inclusion Criteria

i. Lower age group

Entry events with the following event criteria: who are < 45 years old.

ii. Middle age group

Entry events with all of the following criteria:

1. with the following event criteria: who are >= 45 years old.
2. with the following event criteria: who are < 65 years old.

iii. Older age group

Entry events with the following event criteria: who are >= 65 years old.

iv. Female stratum

Entry events with the following event criteria: who are female.

v. Male stratum

Entry events with the following event criteria: who are male.

vi. Race stratum

Entry events with the following event criteria: race is: “black or african american,” “black,” “african american,” “african,” “bahamian,” “barbadian,” “dominican,” “dominica islander,” “haitian,” “jamaican,” “tobagoan,” “trinidadian” or “west indian.”

vii. Low cardiovascular risk

Entry events with all of the following criteria:

1. having no condition occurrences of ‘Conditions indicating established cardiovascular disease,’ starting anytime on or before cohort entry start date; allow events outside observation period.
2. having no procedure occurrences of ‘Procedures indicating established cardiovascular disease,’ starting anytime on or before cohort entry start date; allow events outside observation period.

viii. Higher cardiovascular risk

Entry events with any of the following criteria:

1. having at least 1 condition occurrence of ‘Conditions indicating established cardiovascular disease,’ starting anytime on or before cohort entry start date; allow events outside observation period.
2. having at least 1 procedure occurrence of ‘Procedures indicating established cardio- vascular disease,’ starting anytime on or before cohort entry start date; allow events outside observation period.

ix. Concept: Conditions indicating established cardiovascular disease

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
319844	Acute ischemic heart disease	413439005	SNOMED	NO	YES	NO
321318	Angina pectoris	194828000	SNOMED	NO	YES	NO
4124841	Aortic bifurcation syndrome	23397005	SNOMED	YES	YES	NO
312337	Arterial embolus and thrombosis	266262004	SNOMED	NO	YES	NO
4278217	Arterial thrombosis	65198009	SNOMED	NO	YES	NO
40484167	Arteriosclerosis of artery of extremity	44397004	SNOMED	NO	YES	NO
318443	Arteriosclerotic vascular disease	72092001	SNOMED	NO	YES	NO
314659	Arteritis	52089001	SNOMED	NO	NO	NO
40479625	Atherosclerosis of artery	441574008	SNOMED	NO	YES	NO
40484541	Atherosclerosis of autologous vein bypass graft of limb	442693003	SNOMED	YES	YES	NO
312902	Benign intracranial hypertension	68267002	SNOMED	YES	YES	NO
4288310	Carotid artery obstruction	69798007	SNOMED	YES	YES	NO
372924	Cerebral artery occlusion	20059004	SNOMED	NO	YES	NO
376713	Cerebral hemorrhage	274100004	SNOMED	NO	YES	NO
381591	Cerebrovascular disease	62914000	SNOMED	NO	YES	NO
316494	Cerebrovascular disorder in the puerperium	6594005	SNOMED	YES	YES	NO
315286	Chronic ischemic heart disease	413838009	SNOMED	NO	YES	NO
44782819	Chronic occlusion of artery of extremity	698816006	SNOMED	NO	YES	NO
4313767	Chronic peripheral venous hypertension	423674003	SNOMED	YES	YES	NO
372721	Congenital anomaly of cerebrovascular system	65587001	SNOMED	YES	YES	NO
316995	Coronary occlusion	63739005	SNOMED	NO	YES	NO
134057	Disorder of cardiovascular system	49601007	SNOMED	NO	NO	NO
40480453	Disorder of vein of lower extremity	441739009	SNOMED	YES	YES	NO
46272492	Dissection of artery	710864009	SNOMED	YES	YES	NO
4324690	Fracture of skull	71642004	SNOMED	YES	YES	NO
441246	Hemangioma of intracranial structure	93468003	SNOMED	YES	YES	NO
380113	Hemorrhage in optic nerve sheaths	14460007	SNOMED	YES	YES	NO
192763	Injury of blood vessel	57662003	SNOMED	YES	YES	NO
4275428	Injury of vein	64583005	SNOMED	YES	YES	NO
44277	Intermittent claudication	63491006	SNOMED	NO	YES	NO
439847	Intracranial hemorrhage	1386000	SNOMED	NO	YES	NO
434056	Late effects of cerebrovascular disease	195239002	SNOMED	NO	YES	NO
4146311	Leriche's syndrome	307816004	SNOMED	NO	YES	NO
4329847	Myocardial infarction	22298006	SNOMED	NO	YES	NO
4296029	Periarteritis	76805007	SNOMED	NO	YES	NO
260841	Perinatal subarachnoid hemorrhage	21202004	SNOMED	YES	YES	NO
317309	Peripheral arterial occlusive disease	399957001	SNOMED	NO	YES	NO
321822	Peripheral vascular disorder due to diabetes mellitus	421895002	SNOMED	NO	YES	NO
313928	Peripheral vascular complication	10596002	SNOMED	NO	YES	NO
321052	Peripheral vascular disease	400047006	SNOMED	NO	NO	NO
44782775	Peripheral vascular disease associated with another disorder	34881000119105	SNOMED	NO	YES	NO
318137	Phlebitis and thrombophlebitis of intracranial sinuses	192753009	SNOMED	YES	YES	NO
441039	Phlebitis of lower limb vein	312588002	SNOMED	NO	YES	NO
4067424	Polyarteritis	20258000	SNOMED	NO	YES	NO
320749	Polyarteritis nodosa	155441006	SNOMED	YES	YES	NO
443239	Precerebral arterial occlusion	266253001	SNOMED	NO	YES	NO
440417	Pulmonary embolism	59282003	SNOMED	YES	YES	NO
4318842	Renal vasculitis	95578000	SNOMED	NO	YES	NO
380943	Rupture of syphilitic cerebral aneurysm	186893003	SNOMED	YES	YES	NO
432923	Subarachnoid hemorrhage	21454007	SNOMED	NO	YES	NO
439040	Subdural hemorrhage	35486000	SNOMED	NO	YES	NO
320741	Thrombophlebitis	64156001	SNOMED	YES	YES	NO
4141106	Thrombosis of arteries of the extremities	33391000	SNOMED	NO	YES	NO
4132546	Traumatic brain injury	127295002	SNOMED	YES	YES	NO
4194610	Trunk arterial embolus	312593004	SNOMED	NO	YES	NO
318169	Varicose veins of lower extremity	72866009	SNOMED	YES	YES	NO
4189293	Vascular disorder of lower extremity	37340800	SNOMED	NO	YES	NO
443752	Ventricular hemorrhage	23276006	SNOMED	YES	YES	NO
432346	Dissection of vertebral artery	230730001	SNOMED	YES	YES	NO

x. Concept: Procedures indicating established cardiovascular disease

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
4150819	Operative procedure on coronary artery	31413008	SNOMED	NO	YES	NO
4331725	Operative procedure on artery of extremity	22701007	SNOMED	NO	YES	NO

xi. Without renal impairment

Entry events having no condition occurrences of 'Renal impairment,' starting anytime on or before cohort entry start date; allow events outside observation period.

xii. Renal impairment

Entry events having at least 1 condition occurrence of 'Renal impairment,' starting anytime on or before cohort entry start date; allow events outside observation period.

xiii. Concept: Renal impairment

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
4030518	Renal impairment	236423003	SNOMED	NO	YES	NO

V. Escalation Exit Criteria

The cohort end date will be based on a continuous exposure to 'DPP4 inhibitors': allowing 30 days between exposures, adding 0 days after exposure ends, and using days supply and exposure end date for exposure duration.

The person also exists the cohort when encountering any of the following events:

1. drug exposures of 'All alternative target exposures.'
2. drug exposures of 'Other anti-diabetics.'
3. drug eras of 'Insulin,' with era length > 30 days.

i. Concept: All alternative target exposures

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
44816332	albiglutide	1534763	RxNorm	NO	YES	NO
43526465	canagliflozin	1373458	RxNorm	NO	YES	NO
1594973	chlorpropamide	2404	RxNorm	NO	YES	NO
44785829	dapagliflozin	1488564	RxNorm	NO	YES	NO
45774435	dulaglutide	1551291	RxNorm	NO	YES	NO
45774751	empagliflozin	1545653	RxNorm	NO	YES	NO
793293	ertugliflozin	1992672	RxNorm	NO	YES	NO
1583722	exenatide	60548	RxNorm	NO	YES	NO
1597756	glimepiride	25789	RxNorm	NO	YES	NO
1560171	glipizide	4821	RxNorm	NO	YES	NO
19097821	gliquidone	25793	RxNorm	NO	YES	NO
1559684	glyburide	4815	RxNorm	NO	YES	NO
40170911	liraglutide	475968	RxNorm	NO	YES	NO
44506754	lixisenatide	1440051	RxNorm	NO	YES	NO
793143	semaglutide	1991302	RxNorm	NO	YES	NO
1502809	tolazamide	10633	RxNorm	NO	YES	NO
1502855	tolbutamide	10635	RxNorm	NO	YES	NO

Supplemental Table S1 | Brief Descriptions of Databases from the Observational Health Data Sciences and Informatics Network Included in the Study

Name of Database	Abbreviation	Brief Description
US National Databases		
IBM MarketScan® Commercial Claims an d Encounters Data	CCAE	IBM Health MarketScan® Commercial Claims and Encounters Database (CCAE) represent data from individuals enrolled in United States employer-sponsored insurance health plans. The data includes adjudicated health insurance claims (e.g. inpatient, outpatient, and outpatient pharmacy) as well as enrollment data from large employers and health plans who provide private healthcare coverage to employees, their spouses, and dependents. Additionally, it captures laboratory tests for a subset of the covered lives. This administrative claims database includes a variety of fee-for-service, preferred provider organizations, and capitated health plans.
IBM Health MarketScan® Multi-State Medicaid Database	MDCD	IBM MarketScan® Multi-State Medicaid Database (MDCD) adjudicated US health insurance claims for Medicaid enrollees from multiple states and includes hospital discharge diagnoses, outpatient diagnoses and procedures, and outpatient pharmacy claims as well as ethnicity and Medicare eligibility. Members maintain their same identifier even if they leave the system for a brief period however the dataset lacks lab data.
IBM Health MarketScan Medicare Supplemental and Coordination of Benefits Database	MDCR	IBM Health MarketScan® Medicare Supplemental and Coordination of Benefits Database (MDCR) represents health services of retirees in the United States with primary or Medicare supplemental coverage through privately insured fee-for-service, point-of-service, or capitated health plans. These data include adjudicated health insurance claims (e.g. inpatient, outpatient, and outpatient pharmacy). Additionally, it captures laboratory tests for a subset of the covered lives.
Optum Clinformatics Extended Data Mart - Date of Death (DOD)	OCEDM	Optum Clinformatics Extended DataMart is an adjudicated US administrative health claims database for members of private health insurance, who are fully insured in commercial plans or in administrative services only (ASOs), Legacy Medicare Choice Lives (prior to January 2006), and Medicare Advantage (Medicare Advantage Prescription Drug coverage starting January 2006). The population is primarily representative of commercial claims patients (0-65 years old) with some Medicare (65+ years old) however ages are capped at 90 years. It includes data captured from administrative claims processed from inpatient and outpatient medical services and prescriptions as dispensed, as well as results for outpatient lab tests processed by large national lab vendors who participate in data exchange with Optum. This dataset also provides date of death (month and year only) for members with both medical and pharmacy coverage from the Social Security Death Master File (however after 2011 reporting frequency changed due to changes in reporting requirements) and location information for patients is at the US state level.
Optum© de-identified Electronic Health Record Dataset	OEHR	Optum© de-identified Electronic Health Record Dataset represents Humedica's Electronic Health Record data a medical records database. The medical record data includes clinical information, inclusive of prescriptions as prescribed and administered, lab results, vital signs, body measurements, diagnoses, procedures, and information derived from clinical Notes using Natural Language Processing (NLP).
US Open Claims	USOC	US Open Claims is a United States database of open, pre-adjudicated claims from 2000 to present. Data are reported at anonymized patient

		level collected from office-based physicians and specialists via office management software and clearinghouse switch sources for the purpose of reimbursement. A subset of medical claims data has adjudicated claims.
US Health System Databases		
Columbia University Irving Medical Center	CUIMC	The Columbia University Irving Medical Center (CUIMC) database comprises electronic health records on 6,666,613 patients, with data collection starting in 1985. CUIMC is a northeast US quaternary care center with primary care practices in northern Manhattan and surrounding areas, and the database includes inpatient and outpatient care. The database currently holds information about the person (demographics), visits (inpatient and outpatient), conditions (billing diagnoses and problem lists), drugs (outpatient prescriptions and inpatient orders and administrations), devices, measurements (laboratory tests and vital signs), and other observations (symptoms). The data sources include current and previous electronic health record systems (homegrown Clinical Information System, homegrown WebCIS, Allscripts Sunrise Clinical Manager, Allscripts TouchWorks, Epic Systems), administrative systems (IBM PCS-ADS, Eagle Registration, IDX Systems, Epic Systems), and ancillary systems (homegrown LIS, Sunquest, Cerner Laboratory).
Johns Hopkins Medicine	JHM	The Johns Hopkins Medicine (JHM) database comprises electronic health records on 2.58 million patients, with data collection starting in 2016. JHM is a northeast US quaternary care center with inpatient hospitals and outpatient care centers in Baltimore, Maryland and the surrounding Chesapeake area.
Stanford Medicine	STARR	STAnford medicine Research data Repository, a clinical data warehouse containing live Epic data from Stanford Health Care, the Stanford Children's Hospital, the University Healthcare Alliance and Packard Children's Health Alliance clinics and other auxiliary data from Hospital applications such as radiology PACS. STARR platform is developed and operated by Stanford Medicine Research IT team and is made possible by Stanford School of Medicine Research Office.[44]
Department of Veterans Affairs health care system	VA	VA OMOP data reflects the national Department of Veterans Affairs health care system, which is the largest integrated provider of medical and mental health services in the United States. Care is provided at 170 VA Medical Centers and 1,063 outpatient sites serving more than 9 million enrolled Veterans each year.
Non-US Databases		
Australia Longitudinal Patient Database and Practice Profile	ALPD	Australia Electronic Medical Record is comprised of anonymized patient records collected from patient management software used by general practitioners to document patients' clinical records. Data are collected from 2 sources (LPD – Longitudinal Patient Data and PP – Practice Profiles). LPD and PP data comes through in different tables and is integrated into one common data source. This data coverages primary care and general practices mainly for office-based patients. Data coverage includes over 2.9 million patient records with at least one visit. Dates of service include from 2012 through present. Observation time is defined by the first and last consultation dates. Drugs are captured as prescription records with product, quantity, dosing directions, strength, indication and date of consultation.

France Longitudinal Patient Database	FLPD	France Longitudinal Patient Database is a computerized network of physicians including general practitioners who contribute to a centralized database of anonymized patient EMR. The database covers a time period from 2012 through the present. Observation time is defined by the first and last consultation dates. Drug information is derived from GP prescriptions. Drugs obtained over the counter by the patient outside the prescription system are not reported. No explicit registration or approval is necessary for drug utilization studies.
Germany Disease Analyser	GDA	Germany Disease Analyser is collected from extracts of patient management software used by general practitioners and specialists practicing in ambulatory care settings. Data coverage includes 40.2 million distinct person records, about 48.2% population in the country and collected from 2,800 providers. Patient visiting more than one provider are not cross identified for data protection reasons and therefore recorded as separate in the system. Dates of service include from 1992 through present. Observation time is defined by the first and last consultation dates. Germany has no mandatory general practitioner system and patient have free choice of specialist. Drugs are recorded as prescriptions of marketed products. No registration or approval is required for drug utilization studies.
Health Informatics Centre at the University of Dundee	HIC	Health datasets covering approximately 1.2 million people from the Tayside and Fife regions of Scotland, provided by the Health Informatics Centre (HIC) at the University of Dundee.
Hong Kong Hospital Authority	HKHA	Hong Kong Hospital Authority is the only regulatory body for all public hospitals in Hong Kong, which include 43 hospitals and institutions, 49 specialist Out-patient Clinics, and 73 general Out-patient Clinics. The electronic health record contains data on patient demographics, prescriptions, and diagnoses with real-time updates for routine clinical management used.
Information System for Research in Primary Care	SIDIAP	The Information System for Research in Primary Care (SIDIAP; www.sidiap.org) is a primary care records database that covers approximately 80% of the population of Catalonia, North-East Spain.[45] Healthcare is universal and tax-payer funded in the region, and primary care physicians are gatekeepers for all care and responsible for repeat prescriptions.
UK-IQVIA Medical Research Data	IMRD	The UK-IQVIA Medical Research Data (IMRD), previously known as The Health Improvement Network (THIN), contains anonymized electronic health records from over 744 general practices in the UK, covering approximately 6% of the UK population. It contains data on prescriptions, diagnoses, referrals, and patient demographics broadly representative of the UK.

Supplemental Table S2 | Pharmacological Agents Included in the Drug Classes

GLP-1 RA	SGLT2i	DPP-4i	SU
Albiglutide	Canagliflozin	Alogliptin	Chlorpropamide
Dulaglutide	Dapagliflozin	Linagliptin	Glimepiride
Exenatide	Empagliflozin	Saxagliptin	Glipizide
Liraglutide	Ertugliflozin	Sitagliptin	Gliquidone
Lixisenatide		Vildagliptin	Glyburide
Semaglutide			Tolazamide
			Tolbutamide

Abbreviations: DPP-4i - Dipeptidyl Peptidase-4 Inhibitors, GLP-1 RA - Glucagon-like Peptide-1 Receptor Agonist, SGLT2i - Sodium-Glucose Cotransporter 2 Inhibitor, SU - Sulfonylurea

Supplemental Table S3 | Number of Participants of Databases from the Observational Health Data Sciences and Informatics Network Included in the Study by Calendar Year

Database	Cohort Counts by Calendar Year										
	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021
US National Databases											
CCAE	23507	27701	21648	26728	26621	27894	25953	23826	26827	26400	8769
MDCD	1671	1682	2241	2607	5315	6254	6540	5500	5353	2901	NA
MDCR	5597	5193	5279	5570	4616	4874	3528	2117	2478	2098	2507
OCEDM	12326	13095	13677	13987	15868	18032	23039	24939	27873	30043	18998
OEHR	11404	15230	21046	26266	34297	37556	38057	35986	38817	32346	8003
USOC	158201	202498	257454	301627	349550	364960	375617	372409	390281	410644	337950
US Health System Databases											
CUIMC	181	200	216	219	396	506	537	532	613	638	523
JHM	NA	NA	NA	NA	NA	0	211	669	794	841	1244
STARR	65	84	152	148	260	287	362	397	423	427	537
VA	19816	18579	18546	19247	20076	19619	21181	22395	24202	24319	22039
Non-US Databases											
ALPD	0	85	125	230	239	216	323	499	381	309	54
FLPD	0	470	1459	1377	1325	1308	1420	1504	1705	1604	1098
GDA	1561	2009	2114	2365	2712	3076	3885	4102	4437	4772	1409
HIC	364	354	360	369	433	522	606	593	639	609	731
HKHA	436	460	651	562	538	588	584	795	NA	NA	NA
IMRD	2335	2684	2691	2840	3401	3508	3557	3267	890	NA	NA
SIDIAP	4131	4457	4117	4191	4911	5735	6039	6681	8328	6861	5931

Abbreviations: ALPD - Australia Longitudinal Patient Database Practice Profile, CCAE - IBM MarketScan® Commercial Claims and Encounters Data (CCAE), CUIMC - Columbia University Irving Medical Center, FLPD - France Longitudinal Patient Database, GDA - Germany Disease Analyser, HIC - Health Informatics Centre at the University of Dundee, HKHA - Hong Kong Hospital Authority, IMRD - UK-IQVIA Medical Research Data, JHM - Johns Hopkins Medicine, MDCD - IBM Health MarketScan® Multi-State Medicaid Database, MDCR - IBM Health MarketScan® Medicare Supplemental and Coordination of Benefits Database, OCEDM - Optum Clinformatics Extended Data Mart - Date of Death (DOD), OEHR - Optum© de-identified Electronic Health Record Dataset, SIDIAP - Information System for Research in Primary Care, STARR - Stanford Medicine, USOC - United States Open Claims, VA - Department of Veterans Affairs Healthcare System

Supplemental Table S4 | Baseline Characteristics and Clinical Covariates in Patients Using Glucagon-like Peptide-1 Receptor Agonists as Second-Line Antihyperglycemic Agents in Databases in the United States
*** The table reports clinical covariates within 365 days of treatment initiation.**

Characteristic	CCAE (%) (N = 33592)	CUIMC (%) (N = 535)	JHM (%) (N = 723)	MDCD (%) (N = 2761)	MDCR (%) (N = 2239)	OCEDM (%) (N = 20184)	OEHR (%) (N = 22745)	STARR (%) (N = 475)	USOC (%) (N = 287861)	VA (%) (N = 335920)
Gender										
Female	61.3	61.5	67.2	73.7	55.0	57.8	60.0	59.0	59.3	16.1
Male	38.7	38.5	32.8	26.3	45.0	42.2	40.0	41.0	40.7	83.9
Age group										
< 45	22.9	11.8	20.0	42.6	0	16.6	22.3	18.4	19.0	8.9
45 - 64	75.8	54.7	56.9	53.8	4.5	55.5	62.0	56.0	59.3	45.9
65 - 84	1.3	31.3	20.9	3.5	93.9	27.5	15.5	24.9	21.4	43.7
> 85	0	0	0	0	1.3	0.4	0.1	0	0.2	0.9
Race										
American Indian Or Alaska Native	0	< 0.1	< 0.1	0	0	0	0	< 0.1	0	0.5
Asian	0	1.9	5.5	0	0	0	1.6	18.7	0	1.4
Black Or African American	0	13.6	37.6	24.2	0	0	11.7	6.7	0	16.8
Native Hawaiian Or Other Pacific Islander	0	< 0.1	< 0.1	0	0	0	0	2.5	0	1.4
White	0	52.1	51.6	63.6	0	0	79.5	48	0	73.1
Other	0	0	0	0	0	0	0	20.4	0	0
Unknown/Missing	100.0	32.4	5.3	12.2	100.0	100.0	7.2	3.7	100.0	6.8
Cardiovascular disease										
Cerebrovascular disease	2.1	7.3	2.8	3.4	9.4	4.0	1.8	1.0	1.9	3.3
Coronary arteriosclerosis	6.2	11.8	8.4	9.1	21.6	11.0	6.9	8.4	5.6	19.9
Heart failure	1.9	4.9	4.3	7.3	7.1	5.2	2.4	4.0	2.5	6.0
Hypertensive disorder	65.3	55.1	62.9	72.3	76.1	75.4	62.8	62.7	46.9	73.2
Ischemic heart disease	3.6	2.8	5.0	5.9	9.0	6.0	3.5	4.0	2.7	7.8
Peripheral vascular disease	3.6	3.7	3.6	6.5	11.3	8.7	4.2	3.2	3.4	4.8
Pulmonary embolism	0.5	< 0.1	0.8	1.1	0.8	0.8	0.6	< 0.1	0.5	0.9
Venous thrombosis	1.0	< 0.1	2.2	1.9	1.7	1.3	0.9	< 0.1	0.7	1.1
Diabetes-related complications										
Ketoacidosis	0.1	0	< 0.1	0.5	< 0.1	0.1	0.1	< 0.1	0.1	0
Peripheral neuropathy	2.9	1.5	4.3	9.2	7.6	7.6	4.5	4.8	3.0	3.3
Retinopathy	1.5	< 0.1	1.7	2.1	3.6	2.7	0.9	2.7	1.0	2.6
Endocrine disorders										
Goiter	5.1	8.8	3.5	5.1	5.4	5.1	3.9	5.5	2.7	1.9
Hyperthyroidism	1.2	1.3	< 0.1	1.9	1.1	1.2	1.1	< 0.1	0.6	0.5
Hypothyroidism	17.8	15.5	13.0	19.1	19.3	21.0	15.2	20.4	11.0	11.1
Gastrointestinal disorders										
Acute pancreatitis	0.2	0	< 0.1	0.8	< 0.1	0.2	0.2	0	0.2	< 0.1
Chronic liver disease	2.0	1.3	< 0.1	3.6	2.0	2.1	2.3	< 0.1	0.9	2.3
Crohn's disease	0.3	0	< 0.1	0.5	0.3	0.3	0.2	< 0.1	0.2	0.4
Ulcerative colitis	0.3	0	< 0.1	< 0.1	< 0.1	0.3	0.2	0	0.2	< 0.1
Metabolic	0	0	0	0	0	0	0	0	0	0
Hyperlipidemia	65.4	58.5	55.9	59.9	67.1	76.6	62.2	71.6	40.5	69.0
Hypoglycemia	0.9	1.7	0	1.1	< 0.1	0.7	0.5	< 0.1	0.3	< 0.1
Obesity	34.6	52.1	48.5	57.0	28.6	44.6	44.8	43.0	19.6	51.6
Musculoskeletal disorders										
Bone fracture	2.6	3.2	2.2	5.0	4.1	3.1	1.9	2.9	2.0	1.5
Osteoarthritis	20.8	17.4	16.0	38.2	37.5	29.0	17.3	14.5	15.4	26.5
Neoplasms										
Malignant neoplastic disease	5.4	9.2	4.6	4.4	16.9	8.0	5.1	9.5	4.4	7.0
Malignant breast tumor	1.2	1.3	1.1	1.0	3.6	1.7	1.2	2.1	1.0	< 0.1
Malignant urinary bladder tumor	0.1	0	< 0.1	< 0.1	1.3	0.2	0.1	< 0.1	0.1	0.4
Other										
Chronic obstructive lung disease	2.5	4.3	4.3	18.5	11.2	7.4	4.2	2.1	4.1	10.5
Dementia	0.1	< 0.1	< 0.1	1.0	1.3	0.8	0.4	< 0.1	0.3	1.6
Depressive disorder	14.4	13.1	16.9	40.1	13.7	20.4	19.7	17.0	10.0	30.1
Renal impairment	3.2	5.2	6.8	6.0	10.9	9.4	4.7	5.9	4.1	9.5
Urinary tract infectious disease	7.8	3.4	1.4	12.4	9.7	9.2	4.5	3.6	4.8	3.5
Visual system disorder	24.3	18.1	26.6	43.4	52.5	34.6	11.7	25.5	15.7	42.2

Abbreviations: CCAE: IBM MarketScan® Commercial Claims and Encounters Data (CCAE), CUIMC: Columbia University Irving Medical Center, JHM: Johns Hopkins Medicine, MDCD: IBM Health MarketScan® Multi-State Medicaid Database, MDCR: IBM Health MarketScan® Medicare Supplemental and Coordination of Benefits Database, OCEDM: Optum Clinformatics Extended Data Mart - Date of Death (DOD), OEHR: Optum© de-identified Electronic Health Record Dataset, STARR: Stanford Medicine, USOC: US Open Claims

Supplemental Table S5 | Baseline Characteristics and Clinical Covariates in Patients Using Sodium-Glucose Cotransporter 2 Inhibitors as Second-Line Antihyperglycemic Agents in US Databases
*** The table reports clinical covariates within 365 days of treatment initiation.**

Characteristic	CCAE (%) (N = 43037)	CUIMC (%) (N = 854)	JHM (%) (N = 819)	MDCD (%) (N = 3942)	MDCR (%) (N = 3626)	OCEDM (%) (N = 30331)	OEHR (%) (N = 36897)	STARR (%) (N = 642)	USOC (%) (N = 488394)	VA (%) (N = 430370)
Gender										
Female	43.9	46.0	43.8	61.8	41.1	42.4	45.2	39.9	45.6	6.2
Male	56.1	53.9	56.2	38.2	58.9	57.6	54.8	60.1	54.4	93.8
Age group										
< 45	16.7	5.6	9.4	34.3	0	10.8	15.9	14.2	13.3	5.1
45 - 64	81.4	46.5	50.1	61.1	3.1	50.8	63.0	55.0	59.0	38.3
65 - 84	1.7	44.4	39.1	4.4	94.7	37.3	20.9	29.1	27.4	54.9
> 85	0	2.2	0.9	0	2.1	1.0	0.4	1.4	0.3	1.6
Race										
American Indian Or Alaska Native	0	< 0.1	< 0.1	0	0	0	0	< 0.1	0	0.9
Asian	0	4.4	6.6	0	0	0	2.4	27.4	0	1.3
Black Or African American	0	15.5	34.1	23.6	0	0	10.7	6.5	0	16.8
Native Hawaiian Or Other Pacific Islander	0	< 0.1	0	0	0	0	0	2.2	0	1.1
White	0	40.6	50.2	62.4	0	0	78.9	36.6	0	73.7
Other	0	0	0	0	0	0	0	20.7	0	0
Unknown/Missing	100.0	39.5	9.1	14.0	100.0	100.0	8.0	6.6	100.0	6.2
Cardiovascular disease										
Cerebrovascular disease	2.3	8.6	3.2	4.0	10.9	5.4	2.3	1.9	2.4	4.5
Coronary arteriosclerosis	8.2	26.2	18.9	11.2	28.8	17.1	11.6	12.3	8.5	30.9
Heart failure	2.3	13.8	12.2	7.7	9.8	7.5	3.3	7.3	3.7	13.5
Hypertensive disorder	70.8	64.6	70.4	74.7	83.8	78.3	66.4	65.3	49.0	77.0
Ischemic heart disease	4.3	13.0	8.4	7.5	12.1	9.3	5.4	6.5	4.1	13.7
Peripheral vascular disease	3.7	8.4	6.3	7.5	13.8	10.3	5.0	4.2	3.9	6.2
Pulmonary embolism	0.4	< 0.1	1.1	1.0	0.9	0.8	0.4	< 0.1	0.4	0.8
Venous thrombosis	0.9	0.7	0.9	1.5	2.0	1.4	0.9	1.4	0.7	1.0
Diabetes-related complications										
Ketoacidosis	0.2	0	< 0.1	0.3	0.2	0.1	0.1	< 0.1	< 0.1	< 0.1
Peripheral neuropathy	3.0	2.0	7.4	10.3	8.2	7.6	4.6	3.1	2.8	3.8
Retinopathy	1.7	1.4	1.6	2.5	3.7	3.1	0.7	3.7	1.2	2.7
Endocrine disorders										
Goiter	3.5	5.4	4.9	3.5	4.6	3.7	2.8	2.8	2.0	1.8
Hyperthyroidism	0.8	1.2	2.0	1.1	0.9	1.0	0.8	0.8	0.5	0.4
Hypothyroidism	14.1	10.1	11.1	16.5	17.4	16.3	12.5	10.8	8.8	8.4
Gastrointestinal disorders										
Acute pancreatitis	0.5	< 0.1	0	0.9	0.3	0.5	0.3	< 0.1	0.4	0.3
Chronic liver disease	1.9	1.9	2.0	3.4	2.1	1.9	2.0	1.4	1.1	2.1
Crohn's disease	0.2	< 0.1	< 0.1	0.4	0.3	0.3	0.2	0	0.1	0.2
Ulcerative colitis	0.3	< 0.1	< 0.1	0.2	0.4	0.4	0.2	< 0.1	0.2	0.4
Metabolic	0	0	0	0	0	0	0	0	0	0
Hyperlipidemia	73.0	58.4	61.5	65.4	81.3	80.3	66.8	75.6	44.7	73.7
Hypoglycemia	0.4	0	0	0.7	0.2	0.3	0.2	0	0.1	0.1
Obesity	27.8	28.6	35.5	43.0	24.2	31.5	33.2	22.3	13.0	33.1
Musculoskeletal disorders										
Bone fracture	2.2	1.9	1.7	4.4	3.5	2.8	1.8	2.2	1.8	1.1
Osteoarthritis	17.8	15.5	15.8	35.8	32.1	25.5	15.2	11.1	13.3	20.8
Neoplasms										
Malignant neoplastic disease	5.4	10.2	6.6	5.1	16.6	8.8	5.1	8.6	4.8	8.8
Malignant breast tumor	1.1	2.0	1.8	1.6	2.5	1.4	0.9	2.3	0.9	0.1
Malignant urinary bladder tumor	0.1	0.7	< 0.1	< 0.1	0.9	0.3	0.2	0	0.2	0.5
Other										
Chronic obstructive lung disease	2.5	3.8	5.2	18.1	10.0	7.7	4.5	2.2	4.1	13.1
Dementia	0.2	< 0.1	0.7	0.9	1.2	0.9	0.4	< 0.1	0.4	1.1
Depressive disorder	10.6	8.3	12.2	35.1	9.4	14.9	14.3	9.8	7.0	23.0
Renal impairment	3.2	7.1	13.4	6.2	11.8	10.3	4.4	9.8	4.1	10.1
Urinary tract infectious disease	5.7	2.7	1.7	9.2	7.2	7.1	3.4	2.0	3.9	1.6
Visual system disorder	24.1	16.0	30.6	44.2	54.4	36.7	11.0	20.9	16.4	43.1

Abbreviations: CCAE: IBM MarketScan® Commercial Claims and Encounters Data (CCAE), CUIMC: Columbia University Irving Medical Center, JHM: Johns Hopkins Medicine, MDCD: IBM Health MarketScan® Multi-State Medicaid Database, MDCR: IBM Health MarketScan® Medicare Supplemental and Coordination of Benefits Database, OCEDM: Optum Clinformatics Extended Data Mart - Date of Death (DOD), OEHR: Optum© de-identified Electronic Health Record Dataset, STARR: Stanford Medicine, USOC: US Open Claims

Supplemental Table S6 | Baseline Characteristics and Clinical Covariates in Patients Using Dipeptidyl Peptidase-4 Inhibitors as Second-Line Antihyperglycemic Agents in US Databases

*** The table reports clinical covariates within 365 days of treatment initiation.**

Characteristic	CCAE (%) (N = 98398)	CUIMC (%) (N = 1804)	JHM (%) (N = 931)	MDCD (%) (N = 11956)	MDCR (%) (N = 18381)	OCEDM (%) (N = 60386)	OEHR (%) (N = 77186)	STARR (%) (N = 748)	USOC (%) (N = 957634)	VA (%) (N = 983980)
Gender										
Female	46.2	50.7	51.7	65.0	47.9	48.9	50.4	50.4	50.9	8.1
Male	53.8	49.3	48.3	35.0	52.0	51.1	49.6	49.6	49.1	91.9
Age group										
< 45	16.0	4.6	11.6	29.3	0	9.8	14.0	9.7	11.3	5.8
45 - 64	81.9	42.7	49.5	60.7	2.2	45.1	55.9	47.5	51.3	39.2
65 - 84	2.1	47.0	34.8	9.6	90.6	42.4	29.3	39.4	37.2	51.5
> 85	0	5.2	2.9	0.5	7.2	2.7	0.9	2.8	0.2	3.2
Race										
American Indian Or Alaska Native	0	0.3	< 0.1	0	0	0	0	< 0.1	0	0.9
Asian	0	3.2	8.8	0	0	0	3	28.2	0	1.6
Black Or African American	0	14.4	30.7	24.1	0	0	12.4	6.3	0	17.9
Native Hawaiian Or Other Pacific Islander	0	0.5	< 0.1	0	0	0	0	2.4	0	1.3
White	0	37.9	54	58.6	0	0	77	42.2	0	72.2
Other	0	0	0	0	0	0	0	13.8	0	0
Unknown/Missing	100.0	43.7	6.5	17.3	100.0	100.0	7.6	7.1	100.0	6.1
Cardiovascular disease										
Cerebrovascular disease	2.5	6.6	1.8	5.2	12.6	6.7	2.8	2.1	3.5	3.1
Coronary arteriosclerosis	7.4	17.4	10.0	12.7	25.1	15.2	10.0	10.0	8.6	14.4
Heart failure	1.9	6.7	3.6	8.7	9.3	6.9	3.1	4.3	3.8	4.0
Hypertensive disorder	65.7	58.1	68.7	76.3	74.9	79.0	66.1	68.4	51.4	73.8
Ischemic heart disease	3.9	7.5	4.2	8.6	11.1	8.2	4.5	3.6	4.1	6.2
Peripheral vascular disease	3.2	4.8	4.9	8.5	12.8	10.4	4.2	3.5	4.4	4.3
Pulmonary embolism	0.4	0.8	1.0	1.1	0.9	0.7	0.5	< 0.1	0.5	0.6
Venous thrombosis	1.0	1.4	1.2	1.7	2.2	1.6	1.1	0.9	0.9	1.1
Diabetes-related complications										
Ketoacidosis	0.2	< 0.1	< 0.1	0.3	0.3	0.2	0.1	< 0.1	0.1	< 0.1
Peripheral neuropathy	1.9	1.4	5.4	8.4	4.9	6.8	4.2	3.7	2.8	3.5
Retinopathy	1.8	1.0	1.7	2.5	3.7	3.4	0.9	1.6	1.6	2.6
Endocrine disorders										
Goiter	3.1	4.3	4.4	3.5	3.8	3.7	2.9	4.3	2.1	1.8
Hyperthyroidism	0.9	1.0	1.4	1.3	1.1	1.2	0.8	1.7	0.6	0.5
Hypothyroidism	12.3	7.6	14.4	15.5	14.7	17.6	12.9	14.6	9.2	8.4
Gastrointestinal disorders										
Acute pancreatitis	0.3	< 0.1	< 0.1	0.8	0.4	0.4	0.3	< 0.1	0.3	0.2
Chronic liver disease	3.3	1.9	1.8	5.2	2.4	3.5	2.9	2.9	1.7	2.0
Crohn's disease	0.3	< 0.1	< 0.1	0.3	0.3	0.3	0.2	0	0.2	0.2
Ulcerative colitis	0.3	< 0.1	< 0.1	0.2	0.5	0.4	0.2	< 0.1	0.2	0.4
Metabolic	0	0	0	0	0	0	0	0	0	0
Hyperlipidemia	67.5	48.6	64.7	66.4	63.1	81.2	67.3	77.3	46.2	72.4
Hypoglycemia	0.4	0.3	< 0.1	0.9	0.4	0.5	0.3	< 0.1	0.2	< 0.1
Obesity	16.9	15.9	28.1	37.0	10.2	21.8	25.6	16.6	10.3	29.1
Musculoskeletal disorders										
Bone fracture	2.3	2.1	1.8	4.9	4.5	3.5	2.1	1.7	2.2	1.2
Osteoarthritis	17.1	14.2	17.1	36.5	30.4	26.8	16.3	13.0	15.2	20.9
Neoplasms										
Malignant neoplastic disease	5.9	11.3	8.4	6.0	19.0	10.4	6.6	8.7	6.3	8.9
Malignant breast tumor	1.3	2.7	2.9	1.7	2.9	1.8	1.4	1.5	1.3	0.2
Malignant urinary bladder tumor	0.2	0.5	< 0.1	0.1	1.2	0.5	0.3	0.7	0.3	0.6
Other										
Chronic obstructive lung disease	2.7	3.5	4.1	19.9	10.4	8.7	5.1	2.8	5.2	11.0
Dementia	0.2	1.6	0.8	2.1	2.8	2.3	0.9	1.1	0.9	1.6
Depressive disorder	9.1	7.1	12.2	33.7	8.0	13.9	13.7	11.0	7.0	22.1
Renal impairment	3.2	8.2	9.2	8.8	13.9	14.1	6.3	8.0	6.5	8.1
Urinary tract infectious disease	7.0	4.4	3.4	12.5	10.7	11.3	5.5	4.7	5.8	2.5
Visual system disorder	24.2	15.4	31.6	43.5	52.0	39.5	12.7	21.9	19.0	44.1

Abbreviations: CCAE: IBM MarketScan® Commercial Claims and Encounters Data (CCAE), CUIMC: Columbia University Irving Medical Center, JHM: Johns Hopkins Medicine, MDCD: IBM Health MarketScan® Multi-State Medicaid Database, MDCR: IBM Health MarketScan® Medicare Supplemental and Coordination of Benefits Database, OCEDM: Optum Clinformatics Extended Data Mart - Date of Death (DOD), OEHR: Optum© de-identified Electronic Health Record Dataset, STARR: Stanford Medicine, USOC: US Open Claims

Supplemental Table S7 | Baseline Characteristics and Clinical Covariates in Patients Using Sulfonylureas as Second-Line Antihyperglycemic Agents in US Databases

*** The table reports clinical covariates within 365 days of treatment initiation.**

Characteristic	CCAE (%) (N = 176286)	CUIMC (%) (N = 1894)	JHM (%) (N = 1383)	MDCD (%) (N = 26761)	MDCR (%) (N = 44275)	OCEDM (%) (N = 131197)	OEHR (%) (N = 179287)	STARR (%) (N = 1726)	USOC (%) (N = 1883873)	VA (%) (N = 1762860)
Gender										
Female	44.6	52.8	53.4	63.0	46.6	46.0	46.5	45.0	48.8	4.9
Male	55.4	47.1	46.6	37.0	53.4	54.0	53.5	55.0	51.2	95.1
Age group										
< 45	16.9	8.0	12.0	30.1	0	8.9	14.0	11.5	11.8	5.0
45 - 64	80.8	44.8	51.9	60.6	2.2	40.5	53.4	45.6	48.9	49.1
65 - 84	2.2	42.2	33.2	8.8	90.4	48.0	31.8	40.2	39.1	43.7
> 85	0	4.6	2.5	0.5	7.3	2.5	0.8	2.7	0.2	2.1
Race										
American Indian Or Alaska Native	0	< 0.1	< 0.1	0	0	0	0	< 0.1	0	0.8
Asian	0	2	6.4	0	0	0	2.6	22	0	0.8
Black Or African American	0	13.7	33.6	28.1	0	0	11.1	8.4	0	15.1
Native Hawaiian Or Other Pacific Islander	0	0.3	< 0.1	0	0	0	0	2.8	0	1
White	0	31.2	48.3	53.2	0	0	78.1	43	0	73.6
Other	0	0	0	0	0	0	0	18.9	0	0
Unknown/Missing	100.0	52.8	11.7	18.7	100.0	100.0	8.2	4.9	100.0	8.7
Cardiovascular disease										
Cerebrovascular disease	2.5	6.9	2.0	5.3	12.0	6.7	2.8	2.5	3.3	4.4
Coronary arteriosclerosis	7.3	16.7	10.1	11.8	24.0	16.1	10.2	9.4	8.3	15.4
Heart failure	2.2	8.7	4.6	9.0	10.6	7.6	3.6	4.3	4.1	4.8
Hypertensive disorder	61.2	62.6	68.8	75.6	66.3	78.9	64.6	71.0	48.3	77.3
Ischemic heart disease	4.3	9.1	4.8	8.5	11.8	8.9	4.7	4.5	4.1	12.2
Peripheral vascular disease	2.7	5.8	4.6	7.7	10.8	10.5	4.2	4.8	4.3	4.9
Pulmonary embolism	0.4	0.5	0.7	1.1	0.9	0.8	0.6	0.6	0.5	0.5
Venous thrombosis	0.9	0.5	1.2	1.9	2.2	1.7	1.1	1.4	0.9	1.0
Diabetes-related complications										
Ketoacidosis	0.3	< 0.1	< 0.1	0.6	0.2	0.3	0.2	< 0.1	0.2	< 0.1
Peripheral neuropathy	2.0	1.5	5.1	7.3	4.1	7.7	4.9	4.3	3.0	3.5
Retinopathy	1.9	1.2	3.7	2.6	3.6	3.6	1.0	2.0	1.6	3.4
Endocrine disorders										
Goiter	2.0	2.6	3.2	2.5	2.0	2.5	1.9	2.8	1.4	0.9
Hyperthyroidism	0.7	0.4	0.9	1.2	0.7	1.0	0.6	1.3	0.4	0.4
Hypothyroidism	9.5	5.2	11.8	13.1	10.4	16.0	10.8	13.4	7.6	6.9
Gastrointestinal disorders										
Acute pancreatitis	0.5	0.9	0.4	1.4	0.6	0.7	0.4	0.9	0.5	0.4
Chronic liver disease	3.1	2.5	1.8	5.8	2.1	3.2	2.9	2.9	1.6	2.5
Crohn's disease	0.2	< 0.1	< 0.1	0.3	0.3	0.2	0.2	< 0.1	0.2	0.2
Ulcerative colitis	0.3	< 0.1	< 0.1	0.2	0.4	0.3	0.3	0.4	0.2	0.3
Metabolic	0	0	0	0	0	0	0	0	0	0
Hyperlipidemia	59.6	48.8	60.8	62.1	49.3	78.2	63.5	73.1	40.6	73.6
Hypoglycemia	0.3	0.6	< 0.1	0.7	0.3	0.4	0.3	< 0.1	0.2	0.1
Obesity	15.3	15.5	31.2	35.7	7.8	22.0	23.9	20.3	9.9	30.2
Musculoskeletal disorders										
Bone fracture	2.2	2.3	2.2	4.7	4.6	3.4	2.3	3.5	2.1	1.4
Osteoarthritis	15.3	16.2	16.9	33.2	26.3	26.2	15.9	14.2	13.9	22.3
Neoplasms										
Malignant neoplastic disease	5.5	10.6	8.2	6.1	17.9	10.8	6.6	11.3	6.1	9.3
Malignant breast tumor	1.1	2.2	2.2	1.5	2.7	1.8	1.2	2.8	1.1	0.1
Malignant urinary bladder tumor	0.2	0.5	< 0.1	0.2	1.1	0.5	0.3	< 0.1	0.3	0.6
Other										
Chronic obstructive lung disease	2.9	4.0	5.9	18.5	11.1	9.9	5.5	2.7	5.6	10.9
Dementia	0.2	1.7	1.4	1.6	2.9	2.2	0.9	1.0	0.8	1.0
Depressive disorder	8.7	10.3	14.8	32.5	7.0	14.0	13.7	12.2	6.9	21.2
Renal impairment	3.4	6.3	7.9	8.9	12.3	15.2	6.9	10.8	6.7	5.4
Urinary tract infectious disease	6.6	5.4	2.4	13.6	10.3	10.8	5.1	5.7	5.3	2.5
Visual system disorder	22.2	18.0	33.3	40.3	47.7	39.2	14.4	21.7	17.6	44.0

Abbreviations: CCAE: IBM MarketScan® Commercial Claims and Encounters Data (CCAE), CUIMC: Columbia University Irving Medical Center, JHM: Johns Hopkins Medicine, MDCD: IBM Health MarketScan® Multi-State Medicaid Database, MDCR: IBM Health MarketScan® Medicare Supplemental and Coordination of Benefits Database, OCEDM: Optum Clinformatics Extended Data Mart - Date of Death (DOD), OEHR: Optum© de-identified Electronic Health Record Dataset, STARR: Stanford Medicine, USOC: US Open Claims

Supplemental Table S8 | Baseline Characteristics and Clinical Covariates in Patients Using Glucagon-like Peptide-1 Receptor Agonists as Second-Line Antihyperglycemic Agents in non-United States Databases
*** The table reports clinical covariates within 365 days of treatment initiation.**

Characteristic	ALPD (%) (N = 34)	FLDP (%) (N = 493)	GDA (%) (N = 793)	HIC (%) (N = 56)	SIDIAP (%) (N = 1179)	IMRD (%) (N = 1212)
Gender						
Female	26.5	46.2	49.2	53.6	53.9	52.4
Male	23.5	53.1	50.6	46.4	46.1	47.6
Unknown/Missing	50.0	0.7	0.2	0	0	0
Age group						
< 45	0	9.1	17.7	0	14.0	22.8
45 - 64	41.2	56.9	54.4	23.2	61.5	62.0
65 - 84	0	31.9	26.2	16.1	24.4	15.1
> 85	0	1.2	1.0	0	0	0
Race						
White	0	0	0	71.4	0	25.5
Black	0	0	0	0	0	< 0.1
Asian	0	0	0	0	0	0
Other	0	0	0	0	0	NA
Unknown/Missing	100.0	100.0	100.0	28.6	100.0	74.5
Cardiovascular disease						
Cerebrovascular disease	< 0.1	3.2	2.9	0	0.4	0.9
Coronary arteriosclerosis	< 0.1	2.2	2.9	0	0	< 0.1
Heart failure	< 0.1	1.2	5.4	< 0.1	1.4	0.6
Hypertensive disorder	44.1	43.8	42.4	< 0.1	5.4	4.2
Ischemic heart disease	< 0.1	4.7	6.9	< 0.1	2.0	1.3
Peripheral vascular disease	0	< 0.1	6.4	0	0.5	0
Pulmonary embolism	0	< 0.1	0.6	0	< 0.1	< 0.1
Venous thrombosis	< 0.1	1.2	1.9	0	1.0	0.9
Diabetes-related complications						
Ketoacidosis	0	< 0.1	0	< 0.1	0	0
Retinopathy	0	0	-	0	-	4.6
Endocrine disorders						
Goiter	0	2.6	7.2	0	0.8	< 0.1
Hyperthyroidism	< 0.1	2.0	1.6	0	0.5	< 0.1
Hypothyroidism	< 0.1	8.3	7.9	0	1.7	0.6
Gastrointestinal disorders						
Acute pancreatitis	0	0	< 0.1	0	< 0.1	0
Chronic liver disease	0	< 0.1	< 0.1	0	< 0.1	0
Crohn's disease	0	0	0	0	0	0
Ulcerative colitis	0	< 0.1	0	0	< 0.1	0
Metabolic	0	0	0	0	0	0
Hyperlipidemia	< 0.1	16.0	23.2	< 0.1	3.6	1.6
Obesity	< 0.1	3.0	22.6	< 0.1	14.8	3.7
Musculoskeletal disorders						
Bone fracture	0	1.4	1.4	0	2.0	1.1
Osteoarthritis	17.6	8.3	11.3	0	5.5	3.0
Neoplasms						
Malignant neoplastic disease	0	1.6	3.5	< 0.1	1.7	0.5
Malignant breast tumor	0	< 0.1	< 0.1	0	0.5	0
Malignant urinary bladder tumor	0	0	0	0	< 0.1	< 0.1
Other						
Chronic obstructive lung disease	< 0.1	1.8	5.9	0	1.4	1.1
Dementia	0	< 0.1	0.6	< 0.1	0	< 0.1
Depressive disorder	< 0.1	9.9	12.5	0	4.2	3.6
Renal impairment	0	< 0.1	6.2	< 0.1	1.5	1.1
Urinary tract infectious disease	< 0.1	< 0.1	3.5	< 0.1	5.5	3.0
Visual system disorder	0	5.7	7.6	< 0.1	11.2	9.0
Peripheral neuropathy	-	< 0.1	-	< 0.1	< 0.1	0
Hypoglycemia	-	< 0.1	0.8	< 0.1	< 0.1	< 0.1

Abbreviations: ALPD: Australia Longitudinal Patient Database Practice Profile, FLPD: France Longitudinal Patient Database, GDA: Germany Disease Analyser, HIC: Health Informatics Centre at the University of Dundee, IMRD: United Kingdom-IQVIA Medical Research Data SIDIAP: Information System for Research in Primary Care

Supplemental Table S9 | Baseline Characteristics and Clinical Covariates in Patients Using Sodium-Glucose Cotransporter 2 Inhibitors as Second-Line Antihyperglycemic Agents in non-United States Databases
*** The table reports clinical covariates within 365 days of treatment initiation.**

Characteristic	ALPD (%) (N = 762)	FLDP (%) (N = 70)	GDA (%) (N = 6418)	HIC (%) (N = 1625)	SIDIAP (%) (N = 8124)	IMRD (%) (N = 4145)
Gender						
Female	16.8	45.7	36.4	40.4	36.4	42.4
Male	23.8	54.3	63.3	59.6	63.6	57.6
Unknown/Missing	59.4	0	0.3	0	0	0
Age group						
< 45	9.5	0	6.3	10.6	4.9	13.3
45 - 64	47.6	30.0	51.1	57.5	49.0	64.4
65 - 84	41.3	57.1	40.8	31.3	43.8	22.0
> 85	1.2	0	1.7	0	2.3	0.1
Race						
White	0	0	0	59.1	0	27.2
Black	0	0	0	0	0	0.3
Asian	0	0	0	0.5	0	1.1
Other	0	0	0	0	0	0.5
Unknown/Missing	100.0	100.0	100.0	40.4	100.0	70.9
Cardiovascular disease						
Cerebrovascular disease	1.6	< 0.1	3.7	0.6	0.8	0.4
Coronary arteriosclerosis	< 0.1	< 0.1	6.6	0.9	< 0.1	< 0.1
Heart failure	1.8	7.1	6.8	1.6	3.0	0.3
Hypertensive disorder	28.6	32.9	43.5	3.8	4.0	2.6
Ischemic heart disease	4.6	< 0.1	12.6	2.9	6.3	0.9
Peripheral vascular disease	0	< 0.1	5.7	< 0.1	1.0	0.2
Pulmonary embolism	1.0	0	0.5	< 0.1	0.1	0.1
Venous thrombosis	0.8	< 0.1	1.3	0	1.0	0.5
Diabetes-related complications						
Ketoacidosis	< 0.1	0	< 0.1	< 0.1	< 0.1	0
Retinopathy	< 0.1	0	-	0	-	5.5
Endocrine disorders						
Goiter	< 0.1	< 0.1	5.8	0	0.5	< 0.1
Hyperthyroidism	< 0.1	< 0.1	1.2	0	0.4	< 0.1
Hypothyroidism	3.3	15.7	5.8	< 0.1	1.0	0.6
Gastrointestinal disorders						
Acute pancreatitis	0	0	0.4	0	0.3	0.1
Chronic liver disease	< 0.1	< 0.1	0.5	0	0.2	< 0.1
Crohn's disease	< 0.1	0	< 0.1	0	< 0.1	< 0.1
Ulcerative colitis	< 0.1	0	0.2	< 0.1	0	< 0.1
Metabolic	0	0	0	0	0	0
Hyperlipidemia	19.7	17.1	23.8	< 0.1	2.8	1.0
Obesity	2.5	< 0.1	11.2	1.3	7.7	0.8
Musculoskeletal disorders						
Bone fracture	1.0	0	2.1	0	2.3	0.7
Osteoarthritis	7.2	< 0.1	10.4	0.5	3.6	1.6
Neoplasms						
Malignant neoplastic disease	2.4	0	3.6	1.1	1.8	0.9
Malignant breast tumor	< 0.1	0	0.5	< 0.1	0.2	0.2
Malignant urinary bladder tumor	0	0	0.1	0	0.1	< 0.1
Other						
Chronic obstructive lung disease	2.4	< 0.1	5.8	0.7	1.4	1.3
Dementia	0	0	0.9	< 0.1	0.2	< 0.1
Depressive disorder	7.1	< 0.1	8.5	0.4	1.5	1.8
Renal impairment	1.2	0	4.3	0.6	1.5	0.4
Urinary tract infectious disease	4.2	< 0.1	3.9	0.4	5.7	1.4
Visual system disorder	4.9	< 0.1	7.0	1.4	12.9	8.6
Peripheral neuropathy	-	0	-	0	0.4	< 0.1
Hypoglycemia	-	< 0.1	0.1	0	< 0.1	0.2

Abbreviations: ALPD: Australia Longitudinal Patient Database Practice Profile, FLPD: France Longitudinal Patient Database, GDA: Germany Disease Analyser, HIC: Health Informatics Centre at the University of Dundee, IMRD: United Kingdom-IQVIA Medical Research Data SIDIAP: Information System for Research in Primary Care

Supplemental Table S10 | Baseline Characteristics and Clinical Covariates in Patients Using Dipeptidyl Peptidase-4 Inhibitors as Second-Line Antihyperglycemic Agents in non-United States Databases
*** The table reports clinical covariates within 365 days of treatment initiation.**

Characteristic	ALPD (%) (N = 1672)	FLDP (%) (N = 11047)	GDA (%) (N = 23286)	HIC (%) (N = 3612)	SIDIAP (%) (N = 46535)	IMRD (%) (N = 20723)
Gender						
Female	24.3	39.4	43.5	41.6	42.2	41.2
Male	36.2	60.4	56.4	58.4	57.8	58.8
Unknown/Missing	39.5	0.2	0.1	0	0	0
Age group						
< 45	8.7	5.7	4.6	6.2	3.5	8.4
45 - 64	47.3	50.2	43.3	48.7	39.5	49.9
65 - 84	40.0	41.6	47.7	41.6	50.0	38.8
> 85	3.6	2.3	4.4	3.1	7.0	2.8
Race						
White	0	0	0	76	0	27.1
Black	0	0	0	0	0	0.3
Asian	0	0	0	1.6	0	1.5
Other	0	0	0	0	0	0.3
Unknown/Missing	100.0	100.0	100.0	22.4	100.0	70.8
Cardiovascular disease						
Cerebrovascular disease	1.5	2.8	4.3	0.8	1.2	0.7
Coronary arteriosclerosis	0.4	1.5	4.4	1.1	0	0.1
Heart failure	1.9	1.1	6.9	1.1	1.8	0.6
Hypertensive disorder	31.5	49.7	49.3	4.8	4.2	2.7
Ischemic heart disease	4.2	4.8	11.6	3.3	2.6	1.1
Peripheral vascular disease	0.5	0.9	5.6	0.6	0.9	0.1
Pulmonary embolism	< 0.1	0.4	0.6	0.2	0.2	0.1
Venous thrombosis	0.4	0.6	1.5	< 0.1	1.0	0.4
Diabetes-related complications						
Ketoacidosis	0	0	< 0.1	< 0.1	0	0
Retinopathy	0.4	0.1	-	< 0.1	-	5.7
Endocrine disorders						
Goiter	0.5	1.0	6.9	< 0.1	0.4	< 0.1
Hyperthyroidism	0.5	0.5	1.6	< 0.1	0.4	< 0.1
Hypothyroidism	2.2	5.9	5.9	0.4	1.3	0.7
Gastrointestinal disorders						
Acute pancreatitis	< 0.1	< 0.1	0.4	< 0.1	0.2	< 0.1
Chronic liver disease	0	0.1	0.5	< 0.1	0.4	< 0.1
Crohn's disease	< 0.1	< 0.1	0.1	< 0.1	< 0.1	< 0.1
Ulcerative colitis	< 0.1	< 0.1	0.2	< 0.1	< 0.1	< 0.1
Metabolic	0	0	0	0	0	0
Hyperlipidemia	22.4	21.8	24.5	0.9	3.6	1.2
Obesity	2.1	0.6	8.7	1.0	7.5	0.8
Musculoskeletal disorders						
Bone fracture	1.0	1.3	3.2	0.5	3.5	0.8
Osteoarthritis	4.2	7.9	12.0	0.6	4.8	2.1
Neoplasms						
Malignant neoplastic disease	2.9	2.2	5.2	2.1	3.0	1.2
Malignant breast tumor	0.7	0.5	0.6	< 0.1	0.3	0.1
Malignant urinary bladder tumor	< 0.1	< 0.1	0.2	< 0.1	0.3	< 0.1
Other						
Chronic obstructive lung disease	2.8	2.6	6.4	1.5	1.5	1.7
Dementia	0.7	0.2	2.0	0.4	0.6	0.3
Depressive disorder	7.5	8.6	9.1	0.5	2.4	1.7
Renal impairment	2.0	0.9	6.5	1.8	3.9	2.8
Urinary tract infectious disease	5.0	1.6	5.4	1.0	6.8	2.0
Visual system disorder	7.6	5.7	9.1	1.8	15.9	10.3
Peripheral neuropathy	-	0.4	-	< 0.1	0.3	0
Hypoglycemia	-	< 0.1	0.3	< 0.1	< 0.1	0.3

Abbreviations: ALPD: Australia Longitudinal Patient Database Practice Profile, FLPD: France Longitudinal Patient Database, GDA: Germany Disease Analyser, HIC: Health Informatics Centre at the University of Dundee, IMRD: United Kingdom-IQVIA Medical Research Data SIDIAP: Information System for Research in Primary Care

Supplemental Table S11 | Baseline Characteristics and Clinical Covariates in Patients Using Sulfonylureas as Second-Line Antihyperglycemic Agents in non-United States Databases
*** The table reports clinical covariates within 365 days of treatment initiation.**

Characteristic	ALPD (%) (N = 71)	FLDP (%) (N = 1675)	GDA (%) (N = 7034)	HIC (%) (N = 913)	SIDIAP (%) (N = 17499)	IMRD (%) (N = 6648)
Gender						
Female	29.6	45.5	46.9	44.6	43.4	43.0
Male	43.7	54.4	53.0	55.4	56.6	57.0
Unknown/Missing	26.7	0.1	0.1	0	0	0
Age group						
< 45	0	7.0	3.6	5.9	4.6	8.2
45 - 64	33.8	52.3	37.5	43.1	45.8	46.4
65 - 84	52.2	38.0	55.5	47.9	45.8	42.6
> 85	0	2.3	3.5	2.8	3.7	2.6
Race						
White	0	0	0	72.8	0	31.9
Black	0	0	0	0	0	0.3
Asian	0	0	0	0	0	1.2
Other	0	0	0	0	0	0.3
Unknown/Missing	100.0	100.0	100.0	27.2	100.0	66.3
Cardiovascular disease						
Cerebrovascular disease	< 0.1	2.8	5.0	0.9	1.2	0.9
Coronary arteriosclerosis	0	1.5	3.5	1.4	< 0.1	0.2
Heart failure	< 0.1	0.9	8.8	1.2	1.6	1.1
Hypertensive disorder	29.6	48.2	57.9	6.7	6.3	5.4
Ischemic heart disease	< 0.1	4.7	15.5	4.0	2.8	2.7
Peripheral vascular disease	0	0.5	5.8	< 0.1	0.9	0.4
Pulmonary embolism	0	0.5	0.4	0	0.2	< 0.1
Venous thrombosis	0	0.5	1.4	< 0.1	1.0	0.4
Diabetes-related complications						
Ketoacidosis	0	0	< 0.1	0	0	< 0.1
Retinopathy	0	< 0.1	-	< 0.1	-	4.8
Endocrine disorders						
Goiter	0	1.3	7.4	0	0.3	< 0.1
Hyperthyroidism	0	1.0	1.6	< 0.1	0.3	< 0.1
Hypothyroidism	< 0.1	6.8	5.3	1.1	1.1	0.9
Gastrointestinal disorders						
Acute pancreatitis	< 0.1	< 0.1	0.4	< 0.1	0.3	0.1
Chronic liver disease	0	0.4	0.4	< 0.1	0.4	< 0.1
Crohn's disease	0	0	0.1	0	< 0.1	< 0.1
Ulcerative colitis	0	< 0.1	0.2	0	< 0.1	< 0.1
Metabolic	0	0	0	0	0	0
Hyperlipidemia	21.1	20.7	27.7	1.6	4.6	2.3
Obesity	0	0.5	7.7	1.1	8.4	1.2
Musculoskeletal disorders						
Bone fracture	0	1.4	2.8	< 0.1	3.9	1.0
Osteoarthritis	< 0.1	7.4	14.6	1.3	5.4	3.1
Neoplasms						
Malignant neoplastic disease	< 0.1	2.3	6.0	3.1	2.7	1.9
Malignant breast tumor	0	0.7	1.1	0	0.3	0.2
Malignant urinary bladder tumor	0	0	0.2	0	0.2	< 0.1
Other						
Chronic obstructive lung disease	< 0.1	2.9	6.9	2.0	1.5	1.4
Dementia	0	< 0.1	2.4	< 0.1	0.7	0.2
Depressive disorder	< 0.1	8.2	9.9	< 0.1	3.2	2.3
Renal impairment	0	0.4	4.8	1.5	1.7	3.1
Urinary tract infectious disease	7.0	1.3	5.6	1.1	3.7	2.2
Visual system disorder	11.3	5.0	10.2	1.6	15.6	9.9
Peripheral neuropathy	-	0.5	-	0	0.4	< 0.1
Hypoglycemia	-	< 0.1	0.1	0	< 0.1	0.2

Abbreviations: ALPD: Australia Longitudinal Patient Database Practice Profile, FLPD: France Longitudinal Patient Database, GDA: Germany Disease Analyser, HIC: Health Informatics Centre at the University of Dundee, IMRD: United Kingdom-IQVIA Medical Research Data SIDIAP: Information System for Research in Primary Care

Supplemental Table S12 | Annualized Change in the Age- and Sex-Standardized Incident Use of Glucagon-like Peptide-1 Receptor Agonists for Patients with Established Cardiovascular Disease and Patients without Established Cardiovascular Disease

Data Source	Age- and Sex-Standardized Slope for Patients with CVD	Age- and Sex-Standardized Slope for Patients without CVD	P-value for Slope Difference
US National Databases			
CCAE	1.53% (0.94 to 2.12)	4.78% (3.21 to 6.36)	0.001
MDCD	0.99% (0.58 to 1.41)	1.41% (1.19 to 1.62)	0.03
MDCR	0.71% (0.11 to 1.31)	0.39% (-1.46 to 2.24)	0.658
OCEDM	1.95% (1.19 to 2.71)	4.27% (3.25 to 5.3)	0.001
OEHR	1.55% (0.76 to 2.33)	6.86% (3.25 to 10.46)	0.004
USOC	1.3% (0.52 to 2.07)	4.56% (1.67 to 7.46)	0.016
US Health System Databases			
CUIMC	1.3% (0.79 to 1.81)	3.44% (1.34 to 5.53)	0.025
JHM	0.6% (0.1 to 1.1)	2.22% (1.01 to 3.43)	0.009
STARR	0.77% (0.37 to 1.18)	1.41% (-0.23 to 3.05)	0.328
VA	0.67% (0.17 to 1.17)	1.58% (0.37 to 2.78)	0.089
Non-US Databases			
ALPD	-0.36% (-0.93 to 0.22)	-0.52% (-1.03 to -0.01)	0.574
FLPD	0.35% (0.06 to 0.64)	1.07% (0.28 to 1.86)	0.045
GDA	0.45% (-0.05 to 0.96)	1.17% (0.04 to 2.29)	0.147
HIC	0.03% (-0.12 to 0.18)	0.62% (-0.08 to 1.32)	0.05
HKHA	NA	NA	NA
IMRD	0.28% (-0.2 to 0.76)	1.27% (-1.63 to 4.17)	0.22
SIDIAP	0.21% (-0.09 to 0.5)	0.83% (0.03 to 1.63)	0.075

Abbreviations: ALPD - Australia Longitudinal Patient Database Practice Profile, CCAE - IBM MarketScan® Commercial Claims and Encounters Data (CCAE), CUIMC - Columbia University Irving Medical Center, FLPD - France Longitudinal Patient Database, GDA - Germany Disease Analyser, HIC - Health Informatics Centre at the University of Dundee, HKHA - Hong Kong Hospital Authority, IMRD - UK-IQVIA Medical Research Data, JHM - Johns Hopkins Medicine, MDCD - IBM Health MarketScan® Multi-State Medicaid Database, MDCR - IBM Health MarketScan® Medicare Supplemental and Coordination of Benefits Database, OCEDM - Optum Clinformatics Extended Data Mart - Date of Death (DOD), OEHR - Optum© de-identified Electronic Health Record Dataset, SIDIAP - Information System for Research in Primary Care, STARR - Stanford Medicine, USOC - United States Open Claims, VA - Department of Veterans Affairs Healthcare System

Supplemental Table S13 | Annualized Change in the Age- and Sex-Standardized Incident Use of Sodium-Glucose Cotransporter 2 Inhibitors for Patients with Established Cardiovascular Disease and Patients without Established Cardiovascular Disease

Data Source	Age- and Sex-Standardized Slope for Patients with CVD	Age- and Sex-Standardized Slope for Patients without CVD	P-value for Slope Difference
US National Databases			
CCAE	1.18% (0.52 to 1.83)	1.91% (0.24 to 3.58)	0.29
MDCD	1.58% (1.16 to 2)	1.38% (0.17 to 2.58)	0.633
MDCR	0.16% (-1.15 to 1.47)	-0.3% (-3.17 to 2.58)	0.7
OCEDM	2.15% (1.17 to 3.13)	2.74% (1.77 to 3.7)	0.275
OEHR	1.99% (1.16 to 2.81)	4.04% (2.8 to 5.28)	0.005
USOC	1.58% (0.73 to 2.43)	3.13% (1.07 to 5.19)	0.09
US Health System Databases			
CUIMC	1.76% (0.94 to 2.57)	2.26% (1.08 to 3.45)	0.357
JHM	0.83% (0.65 to 1.02)	1.86% (1.21 to 2.5)	0.003
STARR	0.74% (0.39 to 1.09)	1.68% (0.64 to 2.73)	0.044
VA	2.95% (1.56 to 4.33)	4.9% (2.79 to 7)	0.064
Non-US Databases			
ALPD	-1.92% (-6.25 to 2.41)	-4.68% (-14.23 to 4.87)	0.486
FLPD	0.11% (-0.03 to 0.26)	0.55% (-0.05 to 1.15)	0.082
GDA	2.56% (0.95 to 4.17)	4.05% (1.01 to 7.1)	0.264
HIC	0.71% (0.39 to 1.03)	2.58% (1.38 to 3.79)	0.003
HKHA	NA	NA	NA
IMRD	1.12% (0.08 to 2.16)	2.92% (-3.55 to 9.39)	0.303
SIDIAP	1.62% (0.97 to 2.28)	2.18% (0.6 to 3.76)	0.393

Abbreviations: ALPD - Australia Longitudinal Patient Database Practice Profile, CCAE - IBM MarketScan® Commercial Claims and Encounters Data (CCAE), CUIMC - Columbia University Irving Medical Center, FLPD - France Longitudinal Patient Database, GDA - Germany Disease Analyser, HIC - Health Informatics Centre at the University of Dundee, HKHA - Hong Kong Hospital Authority, IMRD - UK-IQVIA Medical Research Data, JHM - Johns Hopkins Medicine, MDCD - IBM Health MarketScan® Multi-State Medicaid Database, MDCR - IBM Health MarketScan® Medicare Supplemental and Coordination of Benefits Database, OCEDM - Optum Clinformatics Extended Data Mart - Date of Death (DOD), OEHR - Optum© de-identified Electronic Health Record Dataset, SIDIAP - Information System for Research in Primary Care, STARR - Stanford Medicine, USOC - United States Open Claims, VA - Department of Veterans Affairs Healthcare System

Supplemental Table S14 | Annualized Change in the Incident Use of Dipeptidyl Peptidase-4 Inhibitors for Patients with Established Cardiovascular Disease and Patients without Established Cardiovascular Disease

Data Source	Slope for Patients with CVD	Slope for Patients without CVD	P-value for Slope Difference
US National Databases			
CCAE	-0.75% (-1.17 to -0.33)	-1.9% (-2.99 to -0.82)	0.025
MDCD	-0.07% (-0.36 to 0.22)	-0.93% (-1.56 to -0.31)	0.007
MDCR	-3.92% (-11.75 to 3.92)	-3.92% (-8.49 to 0.65)	0.999
OCEDM	0.86% (0.43 to 1.3)	-0.69% (-1.56 to 0.19)	0.002
OEHR	1.16% (0.65 to 1.67)	2.21% (1.39 to 3.03)	0.016
USOC	0.07% (-0.45 to 0.6)	-0.32% (-1.35 to 0.71)	0.373
US Health System Databases			
CUIMC	-0.17% (-1.3 to 0.96)	-0.18% (-0.42 to 0.06)	0.993
JHM	0.23% (-0.37 to 0.82)	-0.31% (-3.97 to 3.35)	0.661
STARR	0.04% (-0.35 to 0.42)	0.12% (-0.41 to 0.66)	0.716
VA	6.93% (5.54 to 8.32)	12.65% (10.09 to 15.21)	0.001
Non-US Databases			
ALPD	-0.4% (-2.05 to 1.25)	9.02% (1.67 to 16.37)	0.007
FLPD	1.18% (0.53 to 1.83)	6.7% (3.08 to 10.33)	0.003
GDA	3.38% (1.62 to 5.14)	4.34% (2.1 to 6.58)	0.376
HIC	-0.35% (-0.99 to 0.28)	-0.19% (-1.64 to 1.25)	0.782
HKHA	7.26% (-23.68 to 38.2)	12% (-55.53 to 79.52)	0.503
IMRD	-0.12% (-0.46 to 0.23)	0.67% (-2.82 to 4.16)	0.39
SIDIAP	1.28% (-0.56 to 3.12)	6.72% (-2.29 to 15.73)	0.139

Abbreviations: ALPD - Australia Longitudinal Patient Database Practice Profile, CCAE - IBM MarketScan® Commercial Claims and Encounters Data (CCAE), CUIMC - Columbia University Irving Medical Center, FLPD - France Longitudinal Patient Database, GDA - Germany Disease Analyser, HIC - Health Informatics Centre at the University of Dundee, HKHA - Hong Kong Hospital Authority, IMRD - UK-IQVIA Medical Research Data, JHM - Johns Hopkins Medicine, MDCD - IBM Health MarketScan® Multi-State Medicaid Database, MDCR - IBM Health MarketScan® Medicare Supplemental and Coordination of Benefits Database, OCEDM - Optum Clinformatics Extended Data Mart - Date of Death (DOD), OEHR - Optum© de-identified Electronic Health Record Dataset, SIDIAP - Information System for Research in Primary Care, STARR - Stanford Medicine, USOC - United States Open Claims, VA - Department of Veterans Affairs Healthcare System

Supplemental Table S15 | Annualized Change in the Incident Use of Sulfonylureas for Patients with Established Cardiovascular Disease and Patients without Established Cardiovascular Disease

Data Source	Slope for Patients with CVD	Slope for Patients without CVD	P-value for Slope Difference
US National Databases			
CCAE	-0.29% (-0.97 to 0.39)	-1.58% (-3.21 to 0.05)	0.078
MDCD	-0.14% (-0.57 to 0.29)	-1.67% (-2.38 to -0.97)	0.001
MDCR	-5.75% (-15.17 to 3.66)	-3.94% (-11.27 to 3.39)	0.685
OCEDM	2.47% (1.54 to 3.4)	0.53% (-1.07 to 2.12)	0.019
OEHR	2.17% (1.36 to 2.99)	3.97% (1.46 to 6.49)	0.096
USOC	1.13% (-0.1 to 2.36)	1.63% (-1.15 to 4.41)	0.663
US Health System Databases			
CUIMC	-0.46% (-0.86 to -0.06)	-0.81% (-1.3 to -0.33)	0.159
JHM	-0.13% (-1.5 to 1.25)	-0.99% (-5.02 to 3.05)	0.544
STARR	-0.26% (-0.69 to 0.17)	-1.07% (-1.92 to -0.22)	0.046
VA	-3.07% (-8.1 to 1.96)	-3.09% (-9.49 to 3.3)	0.994
Non-US Databases			
ALPD	0	-0.05% (-1.24 to 1.13)	0.892
FLPD	0.07% (-0.07 to 0.2)	0.12% (-0.46 to 0.7)	0.797
GDA	-0.16% (-0.28 to -0.03)	-0.08% (-0.29 to 0.14)	0.389
HIC	-0.19% (-0.36 to -0.01)	-0.62% (-1 to -0.25)	0.019
HKHA	2.89% (-30.37 to 36.14)	0.63% (-58.28 to 59.53)	0.712
IMRD	-0.41% (-0.83 to 0)	-0.03% (-0.79 to 0.73)	0.13
SIDIAP	-0.21% (-0.48 to 0.06)	-1.32% (-2.4 to -0.25)	0.023

Abbreviations: ALPD - Australia Longitudinal Patient Database Practice Profile, CCAE - IBM MarketScan® Commercial Claims and Encounters Data (CCAE), CUIMC - Columbia University Irving Medical Center, FLPD - France Longitudinal Patient Database, GDA - Germany Disease Analyser, HIC - Health Informatics Centre at the University of Dundee, HKHA - Hong Kong Hospital Authority, IMRD - UK-IQVIA Medical Research Data, JHM - Johns Hopkins Medicine, MDCD - IBM Health MarketScan® Multi-State Medicaid Database, MDCR - IBM Health MarketScan® Medicare Supplemental and Coordination of Benefits Database, OCEDM - Optum Clinformatics Extended Data Mart - Date of Death (DOD), OEHR - Optum© de-identified Electronic Health Record Dataset, SIDIAP - Information System for Research in Primary Care, STARR - Stanford Medicine, USOC - United States Open Claims, VA - Department of Veterans Affairs Healthcare System

Supplemental Table S16 | Annualized Change in the Age- and Sex-Standardized Incident Use of Dipeptidyl Peptidase-4 Inhibitors for Patients with Established Cardiovascular Disease and Patients without Established Cardiovascular Disease

Data Source	Age- and Sex-Standardized Slope for Patients with CVD	Age- and Sex-Standardized Slope for Patients without CVD	P-value for Slope Difference
US National Databases			
CCAE	-0.62% (-0.92 to -0.33)	-1.59% (-2.44 to -0.74)	0.017
MDCD	-0.38% (-0.75 to -0.01)	-1.86% (-2.86 to -0.86)	0.004
MDCR	-2.05% (-4.54 to 0.45)	-2.24% (-4.51 to 0.04)	0.881
OCEDM	-0.17% (-0.38 to 0.04)	-1.07% (-1.7 to -0.44)	0.005
OEHR	0.5% (0.24 to 0.75)	1.17% (0.8 to 1.54)	0.003
USOC	-0.33% (-0.5 to -0.16)	-0.73% (-1.38 to -0.09)	0.129
US Health System Databases			
CUIMC	0.1% (-0.26 to 0.45)	-0.39% (-1.14 to 0.37)	0.145
JHM	0.28% (-0.35 to 0.91)	1.02% (-1.89 to 3.93)	0.511
STARR	-0.03% (-0.29 to 0.23)	0.05% (-0.34 to 0.45)	0.629
VA	2.15% (1.6 to 2.71)	3.69% (2.03 to 5.35)	0.04
Non-US Databases			
ALPD	-2.67% (-5.9 to 0.56)	-5.13% (-10.68 to 0.42)	0.319
FLPD	0.62% (0.32 to 0.91)	1.02% (0.44 to 1.6)	0.121
GDA	1.5% (0.72 to 2.29)	3% (1.41 to 4.59)	0.047
HIC	-0.6% (-1.25 to 0.06)	-1.43% (-3.15 to 0.28)	0.243
HKHA	NA	NA	NA
IMRD	-0.11% (-0.61 to 0.4)	0.41% (-3.94 to 4.76)	0.64
SIDIAP	-0.06% (-0.43 to 0.3)	-0.06% (-0.97 to 0.84)	0.997

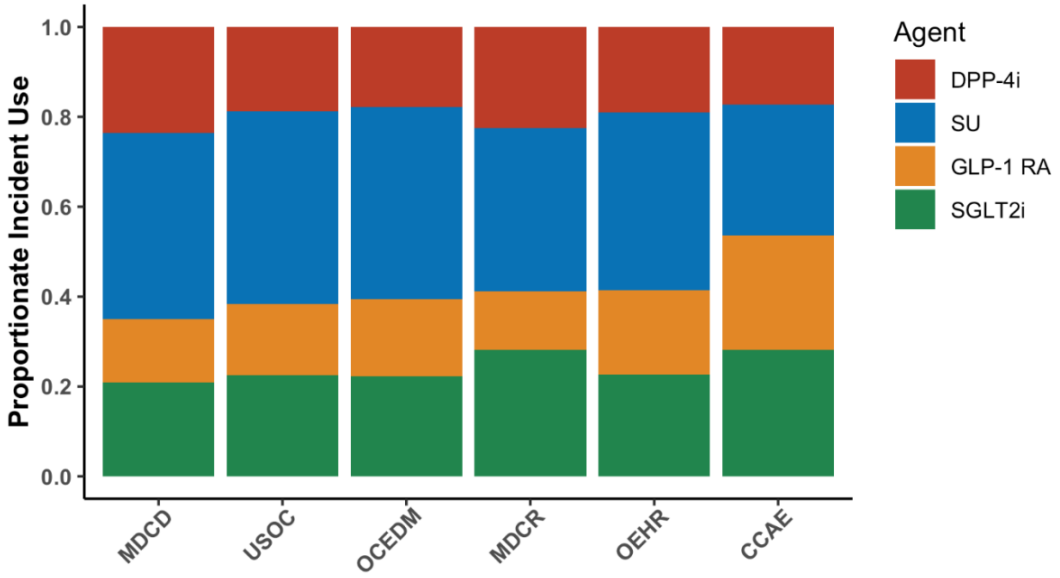
Abbreviations: ALPD - Australia Longitudinal Patient Database Practice Profile, CCAE - IBM MarketScan® Commercial Claims and Encounters Data (CCAE), CUIMC - Columbia University Irving Medical Center, FLPD - France Longitudinal Patient Database, GDA - Germany Disease Analyser, HIC - Health Informatics Centre at the University of Dundee, HKHA - Hong Kong Hospital Authority, IMRD - UK-IQVIA Medical Research Data, JHM - Johns Hopkins Medicine, MDCD - IBM Health MarketScan® Multi-State Medicaid Database, MDCR - IBM Health MarketScan® Medicare Supplemental and Coordination of Benefits Database, OCEDM - Optum Clinformatics Extended Data Mart - Date of Death (DOD), OEHR - Optum© de-identified Electronic Health Record Dataset, SIDIAP - Information System for Research in Primary Care, STARR - Stanford Medicine, USOC - United States Open Claims, VA - Department of Veterans Affairs Healthcare System

Supplemental Table S17 | Annualized Change in the Age- and Sex-Standardized Incident Use of Sulfonylureas for Patients with Established Cardiovascular Disease and Patients without Established Cardiovascular Disease

Data Source	Age- and Sex-Standardized Slope for Patients with CVD	Age- and Sex-Standardized Slope for Patients without CVD	P-value for Slope Difference
US National Databases			
CCAE	-0.25% (-0.77 to 0.28)	0.55% (-0.52 to 1.62)	0.099
MDCD	-0.53% (-1.17 to 0.1)	-3.12% (-4.08 to -2.15)	<0.001
MDCR	-1.21% (-2.79 to 0.38)	-1.08% (-3.44 to 1.28)	0.905
OCEDM	0.39% (-0.03 to 0.81)	-0.63% (-3.56 to 2.3)	0.368
OEHR	0.74% (0.52 to 0.95)	-0.81% (-3.04 to 1.42)	0.091
USOC	0.06% (-0.33 to 0.46)	-0.45% (-1.07 to 0.17)	0.09
US Health System Databases			
CUIMC	-0.22% (-0.71 to 0.28)	-0.68% (-1.41 to 0.06)	0.186
JHM	0.37% (-0.52 to 1.25)	1.17% (-3.14 to 5.49)	0.624
STARR	-0.18% (-0.66 to 0.31)	-0.86% (-1.73 to 0.02)	0.097
VA	-0.1% (-0.75 to 0.54)	0.16% (-3 to 3.31)	0.829
Non-US Databases			
ALPD	-0.38% (-1.15 to 0.38)	-1.27% (-2.54 to 0)	0.135
FLPD	0.03% (-0.12 to 0.18)	0.24% (-0.38 to 0.87)	0.384
GDA	0.09% (-0.25 to 0.43)	0.2% (-0.22 to 0.62)	0.578
HIC	-0.28% (-0.54 to -0.02)	-0.66% (-0.96 to -0.35)	0.031
HKHA	NA	NA	NA
IMRD	-0.15% (-0.37 to 0.06)	0.54% (-1.24 to 2.33)	0.169
SIDIAP	-0.1% (-0.31 to 0.11)	-1.1% (-1.87 to -0.33)	0.008

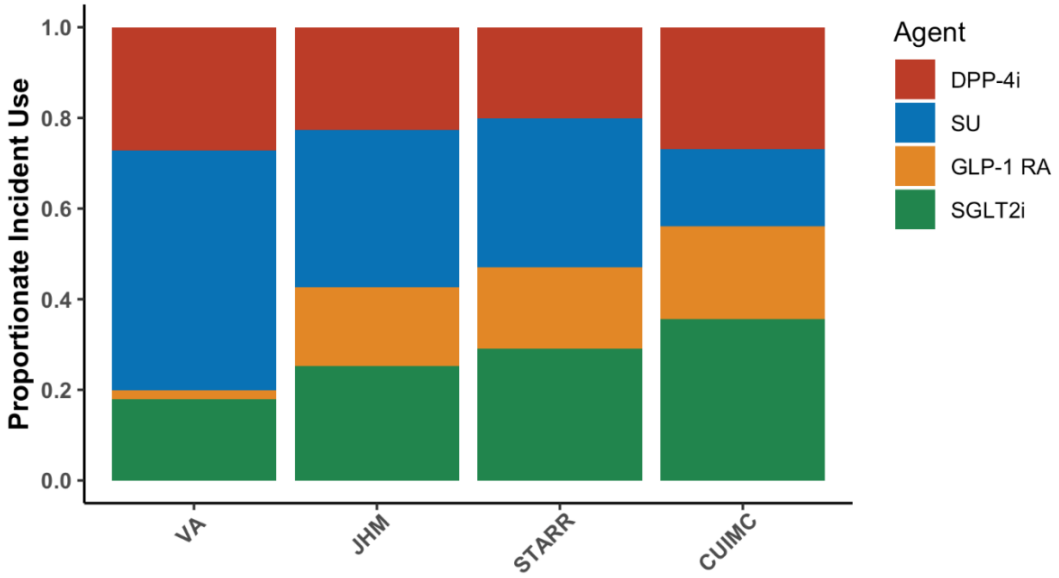
Abbreviations: ALPD - Australia Longitudinal Patient Database Practice Profile, CCAE - IBM MarketScan® Commercial Claims and Encounters Data (CCAE), CUIMC - Columbia University Irving Medical Center, FLPD - France Longitudinal Patient Database, GDA - Germany Disease Analyser, HIC - Health Informatics Centre at the University of Dundee, HKHA - Hong Kong Hospital Authority, IMRD - UK-IQVIA Medical Research Data, JHM - Johns Hopkins Medicine, MDCD - IBM Health MarketScan® Multi-State Medicaid Database, MDCR - IBM Health MarketScan® Medicare Supplemental and Coordination of Benefits Database, OCEDM - Optum Clinformatics Extended Data Mart - Date of Death (DOD), OEHR - Optum© de-identified Electronic Health Record Dataset, SIDIAP - Information System for Research in Primary Care, STARR - Stanford Medicine, USOC - United States Open Claims, VA - Department of Veterans Affairs Healthcare System

Supplemental Figure S1 | Proportional Incident Use of Second-Line Antihyperglycemic Agents in United States National Databases in 2020



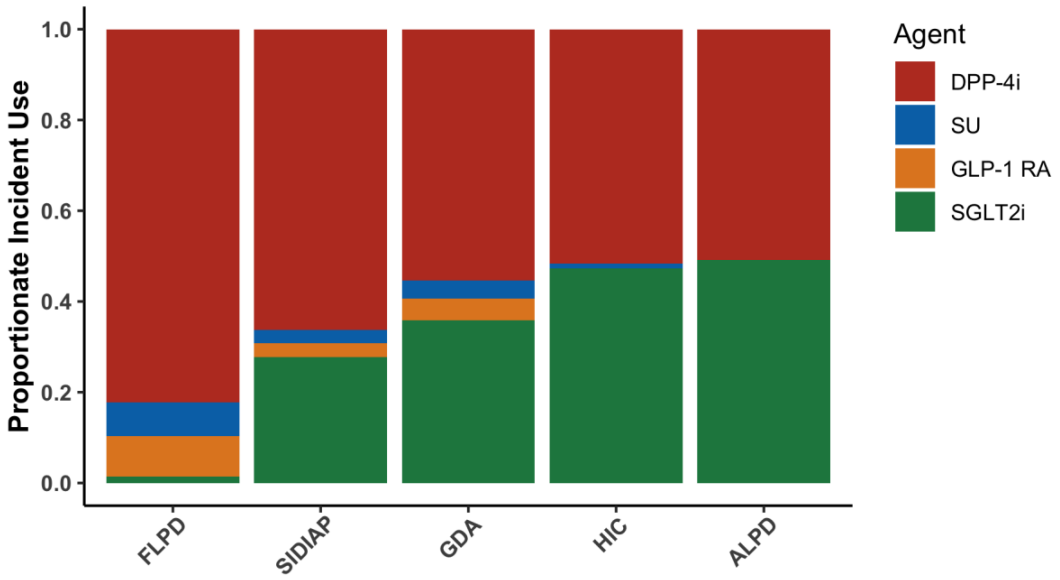
Abbreviations: CCAE - IBM MarketScan® Commercial Claims and Encounters Data (CCAE), DPP-4i - Dipeptidyl Peptidase-4 Inhibitors, GLP-1 RA - Glucagon-like Peptide-1 Receptor Agonist, MDCD - IBM Health MarketScan® Multi-State Medicaid Database, MDCR - IBM Health MarketScan® Medicare Supplemental and Coordination of Benefits Database, OCEDM - Optum Clinformatics Extended Data Mart - Date of Death (DOD), OEHR - Optum© de-identified Electronic Health Record Dataset, SGLT2i - Sodium-Glucose Cotransporter 2 Inhibitor, SU - Sulfonylurea, USOC - United States Open Claims

Supplemental Figure S2 | Proportional Incident Use of Second-Line Antihyperglycemic Agents in United States Health System Databases in 2020



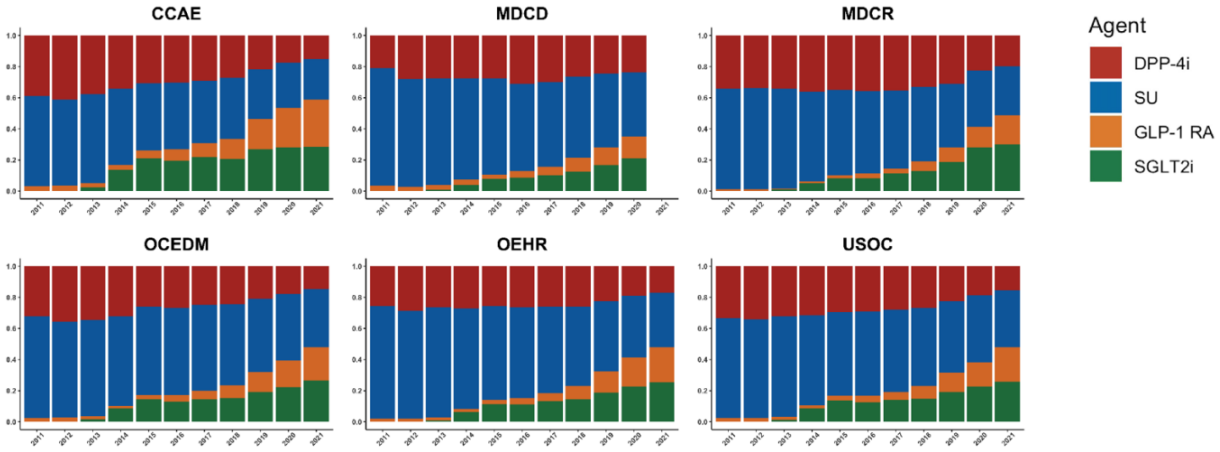
Abbreviations: CUIMC - Columbia University Irving Medical Center, DPP-4i - Dipeptidyl Peptidase-4 Inhibitors, GLP-1 RA - Glucagon-like Peptide-1 Receptor Agonist, JHM - Johns Hopkins Medicine, SGLT2i - Sodium-Glucose Cotransporter 2 Inhibitor, STARR - Stanford Medicine, SU - Sulfonylurea, VA - Department of Veterans Affairs Healthcare System

Supplemental Figure S3 | Proportional Incident Use of Second-Line Antihyperglycemic Agents in non-United States Databases in 2020



Abbreviations: ALPD - Australia Longitudinal Patient Database Practice Profile, DPP-4i - Dipeptidyl Peptidase-4 Inhibitors, FLPD - France Longitudinal Patient Database, GDA - Germany Disease Analyser, GLP-1 RA - Glucagon-like Peptide-1 Receptor Agonist, HIC - Health Informatics Centre at the University of Dundee, HKHA - Hong Kong Hospital Authority, SGLT2i - Sodium-Glucose Cotransporter 2 Inhibitor, SIDIAP - Information System for Research in Primary Care, SU - Sulfonylurea

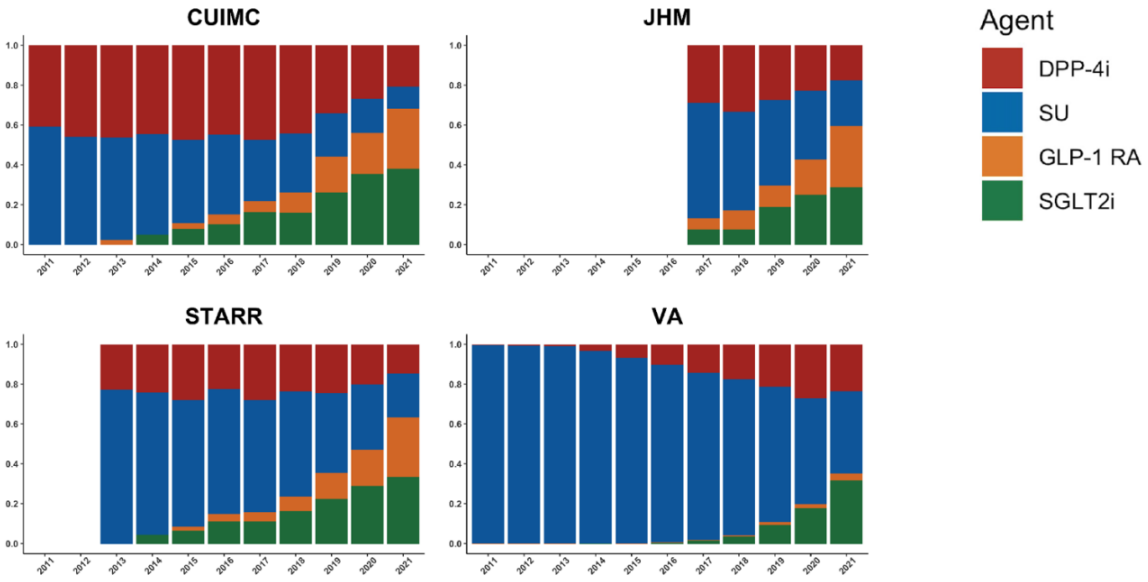
Supplemental Figure S4 | Yearly Trends in Proportional Incident Use of Second-Line Antihyperglycemic Agents in US National Databases



Y-axes are the proportion of each drug used among those initiating a second-line T2DM drug in a calendar year, and X-axes represent calendar years.

Abbreviations: Abbreviations: CCAE - IBM MarketScan® Commercial Claims and Encounters Data (CCAE), DPP-4i - Dipeptidyl Peptidase-4 Inhibitors, GLP-1 RA - Glucagon-like Peptide-1 Receptor Agonist, MDCD - IBM Health MarketScan® Multi-State Medicaid Database, MDCR - IBM Health MarketScan® Medicare Supplemental and Coordination of Benefits Database, OCEDM - Optum Clinformatics Extended Data Mart - Date of Death (DOD), OEHR - Optum© de-identified Electronic Health Record Dataset, SGLT2i - Sodium-Glucose Cotransporter 2 Inhibitor, SU - Sulfonylurea, USOC - United States Open Claims

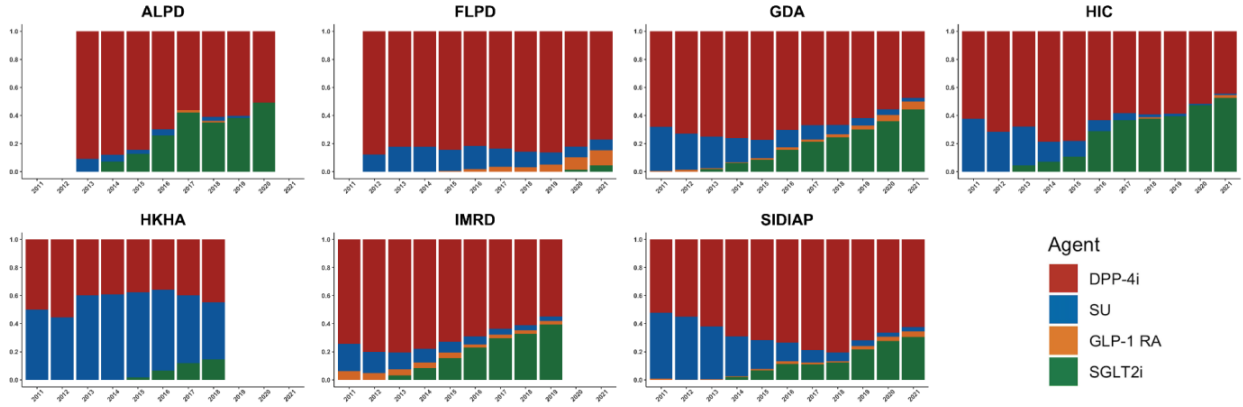
Supplemental Figure S5 | Yearly Trends in Proportional Incident Use of Second-Line Antihyperglycemic Agents in US Health System Databases



Y-axes are the proportion of each drug used among those initiating a second-line T2DM drug in a calendar year, and X-axes represent calendar years.

Abbreviations: Abbreviations: CUIMC - Columbia University Irving Medical Center, DPP-4i - Dipeptidyl Peptidase-4 Inhibitors, GLP-1 RA - Glucagon-like Peptide-1 Receptor Agonist, JHM - Johns Hopkins Medicine, SGLT2i - Sodium-Glucose Cotransporter 2 Inhibitor, STARR - Stanford Medicine, SU - Sulfonylurea, VA - Department of Veterans Affairs Healthcare System

Supplemental Figure S6 | Yearly Trends in Proportional Incident Use of Second Line Antihyperglycemic Agents in non-United States Databases



Y-axes are the proportion of each drug used among those initiating a second-line T2DM drug in a calendar year, and X-axes represent calendar years.

Abbreviations: ALPD - Australia Longitudinal Patient Database Practice Profile, DPP-4i - Dipeptidyl Peptidase-4 Inhibitors, FLPD - France Longitudinal Patient Database, GDA - Germany Disease Analyser, GLP-1 RA - Glucagon-like Peptide-1 Receptor Agonist, HIC - Health Informatics Centre at the University of Dundee, HKHA - Hong Kong Hospital Authority, IMRD - UK-IQVIA Medical Research Data, SGLT2i - Sodium-Glucose Cotransporter 2 Inhibitor, SIDIAP - Information System for Research in Primary Care, SU - Sulfonylurea