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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.

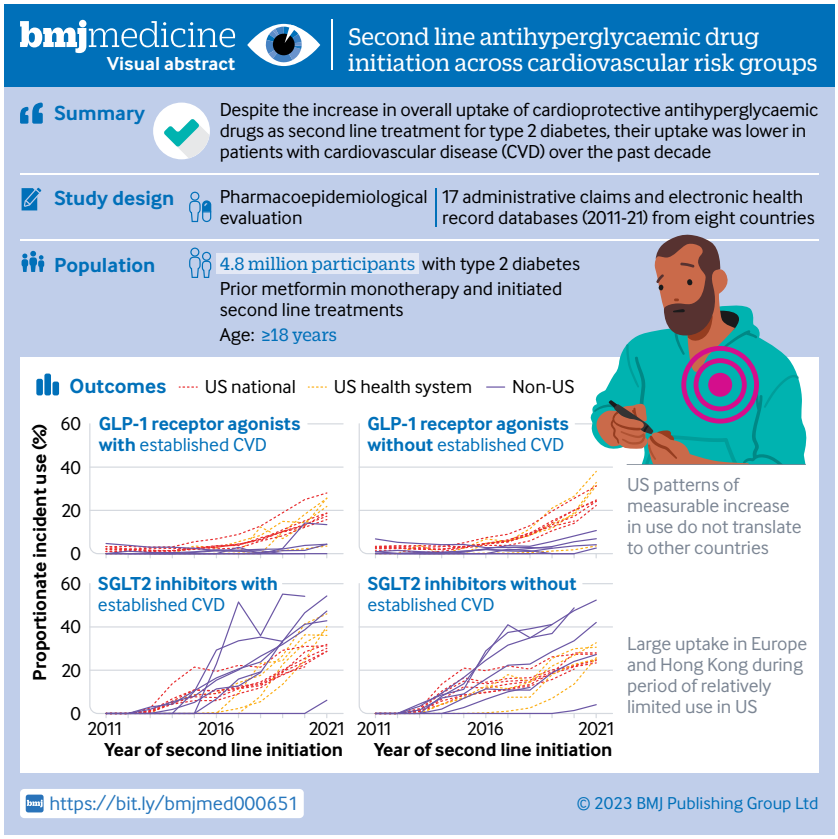

Figure 1 | Visual abstract

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

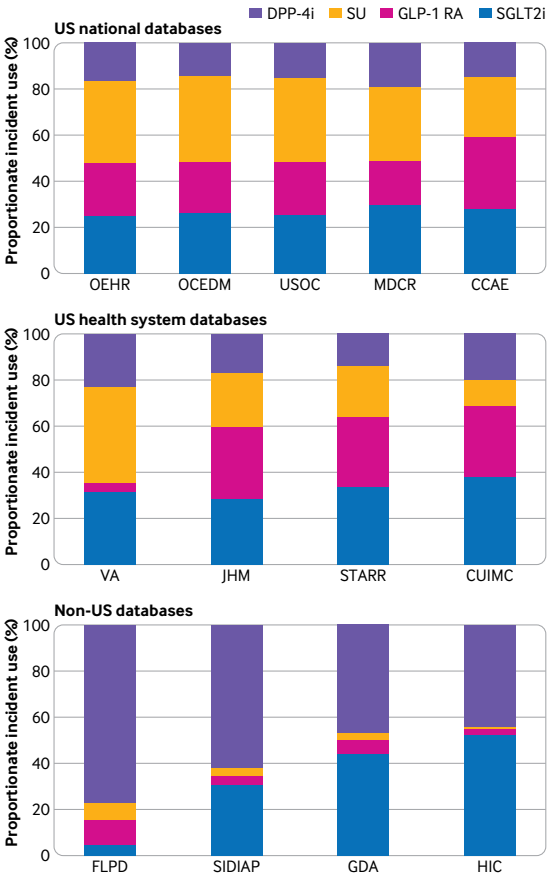

Figure 2 | Proportional incident use of second line antihyperglycaemic drugs in United States national databases, United States health system. CCAE=IBM MarketScan Commercial Claims and Encounters Data; CUIMC=Columbia University Irving Medical Centre; DPP-4i=dipeptidyl peptidase-4 inhibitors; FLPD=France 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

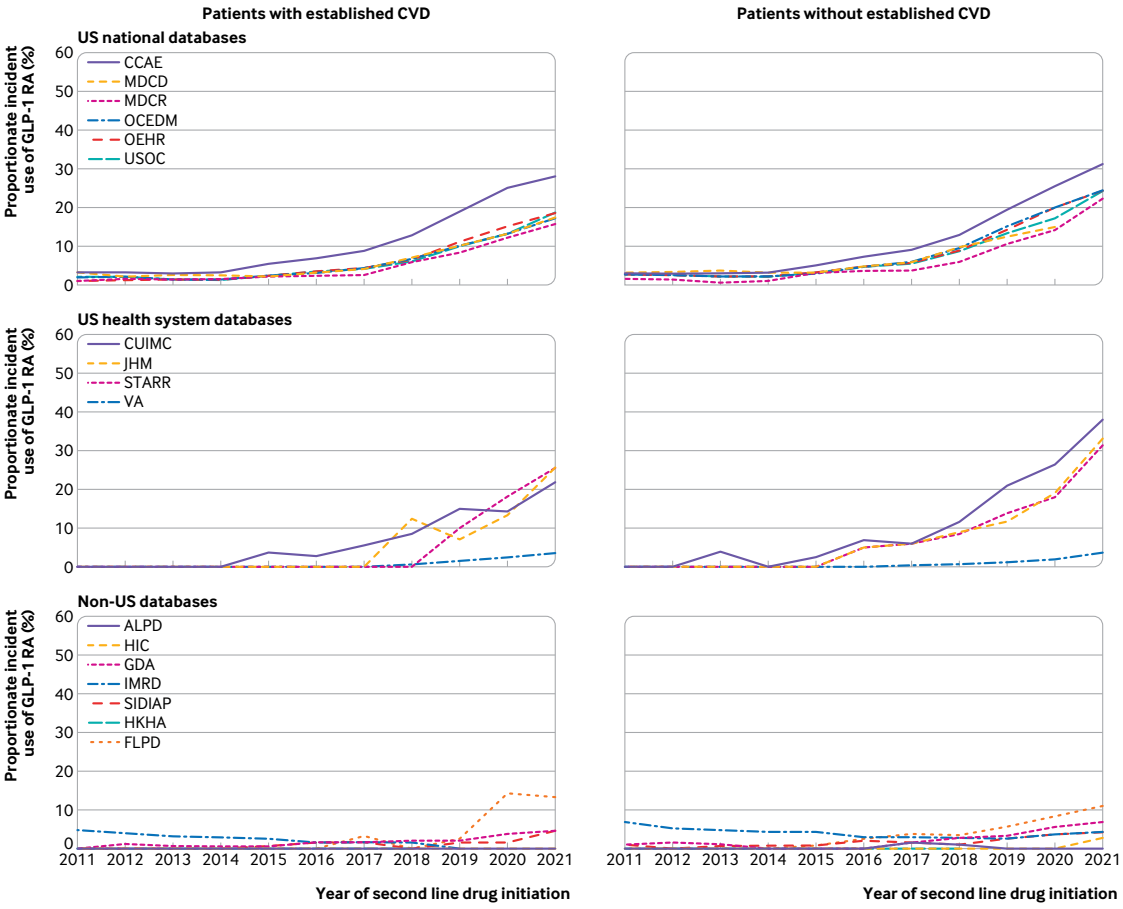

Figure 3 | Proportional first incident use of glucagon-like peptide-1 receptor agonists as second line therapy after metformin in patients with established cardiovascular disease, and patients without established cardiovascular disease. ALPD=Australia Longitudinal Patient Database Practice Profile; CCAE=IBM 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).

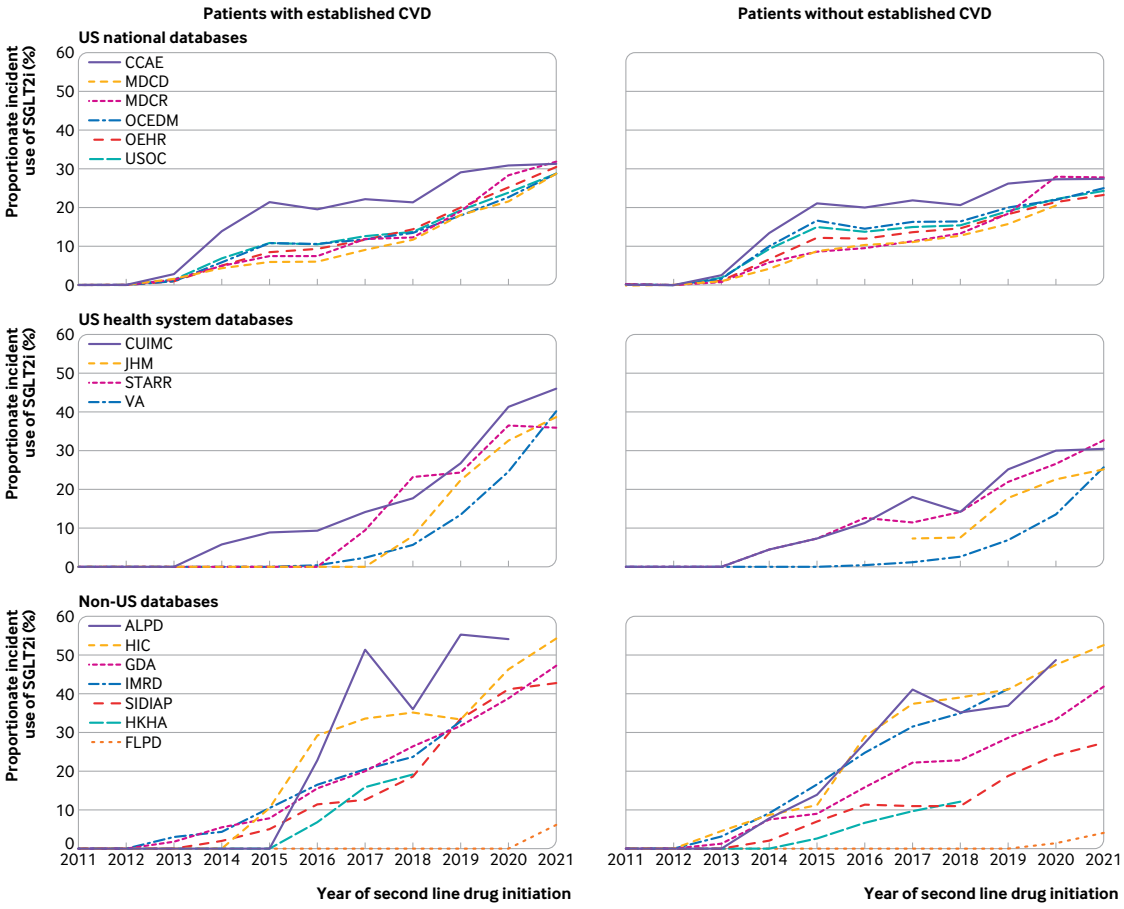

Figure 4 | Proportional first incident use of sodium-glucose Cctransporter 2 inhibitors as second line therapy after metformin in (A) patients with established cardiovascular disease, and (B) patients without established cardiovascular disease. ALPD=Australia Longitudinal Patient Database Practice Profile; 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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