

## 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  $\geq$  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  $\geq$  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	HxNorm	NO	YES	NO
40239216	linagliptin	1100699	HxNorm	NO	YES	NO
40166035	saxagliptin	857974	HxNorm	NO	YES	NO
1580/4/	sitagliptin	593411	HxNorm	NO	YES	NO
19122137	vildagliptin	596554	HxNorm	NO	YES	NO

### vi. Concept: GLP-1 receptor agonists

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
44816332	albiglutide	1534763	HxNorm	NO	YES	NO
45774435	dulaglutide	1551291	HxNorm	NO	YES	NO
1583/22	exenatide	60548	HxNorm	NO	YES	NO
401/0911	liraglutide	4/5968	HxNorm	NO	YES	NO
44506754	lixisenatide	1440051	HxNorm	NO	YES	NO
793143	semaglutide	1991302	HxNorm	NO	YES	NO

### vii. Concept: SGLT2 inhibitors

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
43526465	canagliflozin	13/3458	HxNorm	NO	YES	NO
44/85829	dapagliflozin	1488564	HxNorm	NO	YES	NO
45/14/51	empagliflozin	1545653	HxNorm	NO	YES	NO
793293	ertugliflozin	1992672	HxNorm	NO	YES	NO

## viii. Concept: Sulfonylureas

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
15949/3	chlorthalidone	2404	HxNorm	NO	YES	NO
1597756	glimepiride	25789	HxNorm	NO	YES	NO
1560171	glipizide	4821	HxNorm	NO	YES	NO
1909/821	glucagon	25793	HxNorm	NO	YES	NO
1559684	glyburide	4815	HxNorm	NO	YES	NO
1502809	tolazamide	10633	HxNorm	NO	YES	NO
1502855	tolbutamide	10635	HxNorm	NO	YES	NO

## ix. Concept: Other anti-diabetics

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
1529331	acarbose	16681	HxNorm	NO	YES	NO
1530014	acetohexamide	173	HxNorm	NO	YES	NO
730548	bromocriptine	1760	HxNorm	NO	YES	NO
19033498	carbutamide	2068	HxNorm	NO	YES	NO
19001409	glibornuride	102846	HxNorm	NO	YES	NO
19059/96	glucosamine	4816	HxNorm	NO	YES	NO
19001441	glymidine	102848	HxNorm	NO	YES	NO
1510202	miglitol	30009	HxNorm	NO	YES	NO
1502826	nateglinide	274332	HxNorm	NO	YES	NO
1525215	pioglitazone	33/38	HxNorm	NO	YES	NO
1516/66	repaglinide	/3044	HxNorm	NO	YES	NO
1547504	rosiglitazone	84108	HxNorm	NO	YES	NO
1515249	troglitazone	72610	HxNorm	NO	YES	NO

## x. Concept: Insulin

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
1596977	insulin, regular, human	253182	HxNorm	NO	YES	NO
1550023	insulin lispro	86009	HxNorm	NO	YES	NO
156/198	insulin aspart, human	51428	HxNorm	NO	YES	NO
1502905	insulin glargine	2/4/83	HxNorm	NO	YES	NO
1513876	insulin lispro protamine, human	314684	HxNorm	NO	YES	NO
1531601	insulin aspart protamine, human	352385	HxNorm	NO	YES	NO
1586346	insulin, regular, pork	221109	HxNorm	NO	YES	NO
1544838	insulin glulisine, human	400008	HxNorm	NO	YES	NO
1516976	insulin detemir	139825	HxNorm	NO	YES	NO
1590165	insulin, regular, beef-pork	235275	HxNorm	NO	YES	NO
1513849	lente insulin, human	314683	HxNorm	NO	YES	NO
1562586	lente insulin, pork	93108	HxNorm	NO	YES	NO
1588986	insulin human, rDNA origin	631657	HxNorm	NO	YES	NO
1513843	lente insulin, beef-pork	314682	HxNorm	NO	YES	NO
1586369	ultralente insulin, human	221110	HxNorm	NO	YES	NO
356056/0	insulin argine	1/40938	HxNorm	NO	YES	NO
356027/7	insulin degludec	1670007	HxNorm	NO	YES	NO
21600/13	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	HxNorm	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  $\geq 18$  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  $\geq$  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	HxNorm	NO	YES	NO

### vi. Concept: DPP4 inhibitors excluding alogliptin

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

#### IV. Heterogeneity 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  $\geq$  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  $\geq$  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 cardiovascular 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	2339/2005	SNOMED	YES	YES	NO
312337	Arterial embolus and thrombosis	266262004	SNOMED	NO	YES	NO
4278217	Arterial thrombosis	65198009	SNOMED	NO	YES	NO
4048416/	Arteriosclerosis of artery of extremity	4439/1004	SNOMED	NO	YES	NO
318443	Arteriosclerotic vascular disease	/2092001	SNOMED	NO	YES	NO
314659	Arteritis	52089001	SNOMED	NO	NO	NO
404/962b	Atherosclerosis of artery	4415/4008	SNOMED	NO	YES	NO
40484541	Atherosclerosis of autologous vein bypass graft of limb	442693003	SNOMED	YES	YES	NO
312902	Benign intracranial hypertension	6826/002	SNOMED	YES	YES	NO
4288310	Carotid artery obstruction	69/9800/	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
44/82819	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
31699b	Coronary occlusion	63/39005	SNOMED	NO	YES	NO
134057	Disorder of cardiovascular system	49601007	SNOMED	NO	NO	NO
40480453	Disorder of vein of lower extremity	441/39009	SNOMED	YES	YES	NO
46272492	Dissection of artery	710864009	SNOMED	YES	YES	NO
4324690	Fracture of skull	/1642004	SNOMED	YES	YES	NO
441246	Hemangioma of intracranial structure	93468003	SNOMED	YES	YES	NO
380113	Hemorrhage in optic nerve sheaths	1446000/	SNOMED	YES	YES	NO
192763	Injury of blood vessel	57662003	SNOMED	YES	YES	NO
42/5428	Injury of vein	64583005	SNOMED	YES	YES	NO
442/ /4	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	Lenche's syndrome	30/816004	SNOMED	NO	YES	NO
4329847	Myocardial infarction	22298006	SNOMED	NO	YES	NO
4296029	Penarteritis	/680500/	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	Pre-cerebral arterial occlusion	266253001	SNOMED	NO	YES	NO
44041/	Pulmonary embolism	59282003	SNOMED	YES	YES	NO
4318842	Renal vasculitis	95578000	SNOMED	NO	YES	NO
380943	Rupture of siphilic cerebral aneurysm	186893003	SNOMED	YES	YES	NO
432923	Subarachnoid hemorrhage	21454007	SNOMED	NO	YES	NO
439040	Subdural hemorrhage	35486000	SNOMED	NO	YES	NO
320/41	Thrombophlebitis	64156001	SNOMED	YES	YES	NO
4141106	Thrombosis of arteries of the extremities	33591000	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	3/340800/	SNOMED	NO	YES	NO
443752	Ventricular hemorrhage	23276006	SNOMED	YES	YES	NO
432346	Dissection of vertebral artery	230/30001	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	HxNorm	NO	YES	NO
43526465	canagliflozin	1373458	HxNorm	NO	YES	NO
1594973	chlorpropamide	2404	HxNorm	NO	YES	NO
44785829	dapagliflozin	1488564	HxNorm	NO	YES	NO
45774435	dulaglutide	1551291	HxNorm	NO	YES	NO
45774751	empagliflozin	1545653	HxNorm	NO	YES	NO
793293	ertugliflozin	1992672	HxNorm	NO	YES	NO
1583722	exenatide	60548	HxNorm	NO	YES	NO
1597756	glimepiride	25789	HxNorm	NO	YES	NO
1560171	glipizide	4821	HxNorm	NO	YES	NO
19097821	gliquidone	25793	HxNorm	NO	YES	NO
1559684	glyburide	4815	HxNorm	NO	YES	NO
40170911	liraglutide	475968	HxNorm	NO	YES	NO
44506754	lixisenatide	1440051	HxNorm	NO	YES	NO
793143	semaglutide	1991302	HxNorm	NO	YES	NO
1502809	tolazamide	10633	HxNorm	NO	YES	NO
1502855	tolbutamide	10635	HxNorm	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
<b>US National Databases</b>		
IBM MarketScan® Commercial Claims and Encounters Data	CCAЕ	IBM Health MarketScan® Commercial Claims and Encounters Database (CCAЕ) 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.
<b>US Health System Databases</b>		
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.
<b>Non-US Databases</b>		
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; <a href="http://www.sidiap.org">www.sidiap.org</a> ) 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**

<b>GLP-1 RA</b>	<b>SGLT2i</b>	<b>DPP-4i</b>	<b>SU</b>
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
<b>US National Databases</b>											
CCAIE	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
<b>US Health System Databases</b>											
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
<b>Non-US Databases</b>											
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, CCAIE - IBM MarketScan® Commercial Claims and Encounters Data (CCAIE), 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)
<b>Gender</b>										
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
<b>Age group</b>										
< 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
<b>Race</b>										
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
<b>Cardiovascular disease</b>										
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
<b>Diabetes-related complications</b>										
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
<b>Endocrine disorders</b>										
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
<b>Gastrointestinal disorders</b>										
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
<b>Musculoskeletal disorders</b>										
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
<b>Neoplasms</b>										
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
<b>Other</b>										
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 (CCAЕ), 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)
<b>Gender</b>										
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
<b>Age group</b>										
< 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
<b>Race</b>										
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
<b>Cardiovascular disease</b>										
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
<b>Diabetes-related complications</b>										
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
<b>Endocrine disorders</b>										
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
<b>Gastrointestinal disorders</b>										
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
<b>Musculoskeletal disorders</b>										
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
<b>Neoplasms</b>										
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
<b>Other</b>										
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 (CCAЕ), 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)
<b>Gender</b>										
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
<b>Age group</b>										
< 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
<b>Race</b>										
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
<b>Cardiovascular disease</b>										
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
<b>Diabetes-related complications</b>										
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
<b>Endocrine disorders</b>										
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
<b>Gastrointestinal disorders</b>										
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
<b>Musculoskeletal disorders</b>										
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
<b>Neoplasms</b>										
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
<b>Other</b>										
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 (CCAЕ), 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)
<b>Gender</b>										
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
<b>Age group</b>										
< 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
<b>Race</b>										
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
<b>Cardiovascular disease</b>										
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
<b>Diabetes-related complications</b>										
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
<b>Endocrine disorders</b>										
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
<b>Gastrointestinal disorders</b>										
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
<b>Musculoskeletal disorders</b>										
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
<b>Neoplasms</b>										
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
<b>Other</b>										
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 (CCAЕ), 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)
<b>Gender</b>						
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
<b>Age group</b>						
< 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
<b>Race</b>						
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
<b>Cardiovascular disease</b>						
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
<b>Diabetes-related complications</b>						
Ketoacidosis	0	< 0.1	0	< 0.1	0	0
Retinopathy	0	0	-	0	-	4.6
<b>Endocrine disorders</b>						
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
<b>Gastrointestinal disorders</b>						
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
<b>Musculoskeletal disorders</b>						
Bone fracture	0	1.4	1.4	0	2.0	1.1
Osteoarthritis	17.6	8.3	11.3	0	5.5	3.0
<b>Neoplasms</b>						
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
<b>Other</b>						
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, FLDP: 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)
<b>Gender</b>						
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
<b>Age group</b>						
< 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
<b>Race</b>						
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
<b>Cardiovascular disease</b>						
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
<b>Diabetes-related complications</b>						
Ketoacidosis	< 0.1	0	< 0.1	< 0.1	< 0.1	0
Retinopathy	< 0.1	0	-	0	-	5.5
<b>Endocrine disorders</b>						
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
<b>Gastrointestinal disorders</b>						
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
<b>Musculoskeletal disorders</b>						
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
<b>Neoplasms</b>						
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
<b>Other</b>						
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, FLDP: 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)
<b>Gender</b>						
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
<b>Age group</b>						
< 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
<b>Race</b>						
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
<b>Cardiovascular disease</b>						
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
<b>Diabetes-related complications</b>						
Ketoacidosis	0	0	< 0.1	< 0.1	0	0
Retinopathy	0.4	0.1	-	< 0.1	-	5.7
<b>Endocrine disorders</b>						
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
<b>Gastrointestinal disorders</b>						
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
<b>Musculoskeletal disorders</b>						
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
<b>Neoplasms</b>						
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
<b>Other</b>						
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, FLDP: 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)
<b>Gender</b>						
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
<b>Age group</b>						
< 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
<b>Race</b>						
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
<b>Cardiovascular disease</b>						
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
<b>Diabetes-related complications</b>						
Ketoacidosis	0	0	< 0.1	0	0	< 0.1
Retinopathy	0	< 0.1	-	< 0.1	-	4.8
<b>Endocrine disorders</b>						
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
<b>Gastrointestinal disorders</b>						
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
<b>Musculoskeletal disorders</b>						
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
<b>Neoplasms</b>						
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
<b>Other</b>						
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, FLDP: 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
<b>US National Databases</b>			
CCAIE	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
<b>US Health System Databases</b>			
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
<b>Non-US Databases</b>			
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, CCAIE - IBM MarketScan® Commercial Claims and Encounters Data (CCAIE), 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
<b>US National Databases</b>			
CCAIE	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
<b>US Health System Databases</b>			
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
<b>Non-US Databases</b>			
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, CCAIE - IBM MarketScan® Commercial Claims and Encounters Data (CCAIE), 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
<b>US National Databases</b>			
CCAIE	-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
<b>US Health System Databases</b>			
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
<b>Non-US Databases</b>			
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, CCAIE - IBM MarketScan® Commercial Claims and Encounters Data (CCAIE), 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
<b>US National Databases</b>			
CCAЕ	-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
<b>US Health System Databases</b>			
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
<b>Non-US Databases</b>			
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 (CCAЕ), 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
<b>US National Databases</b>			
CCAIE	-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
<b>US Health System Databases</b>			
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
<b>Non-US Databases</b>			
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

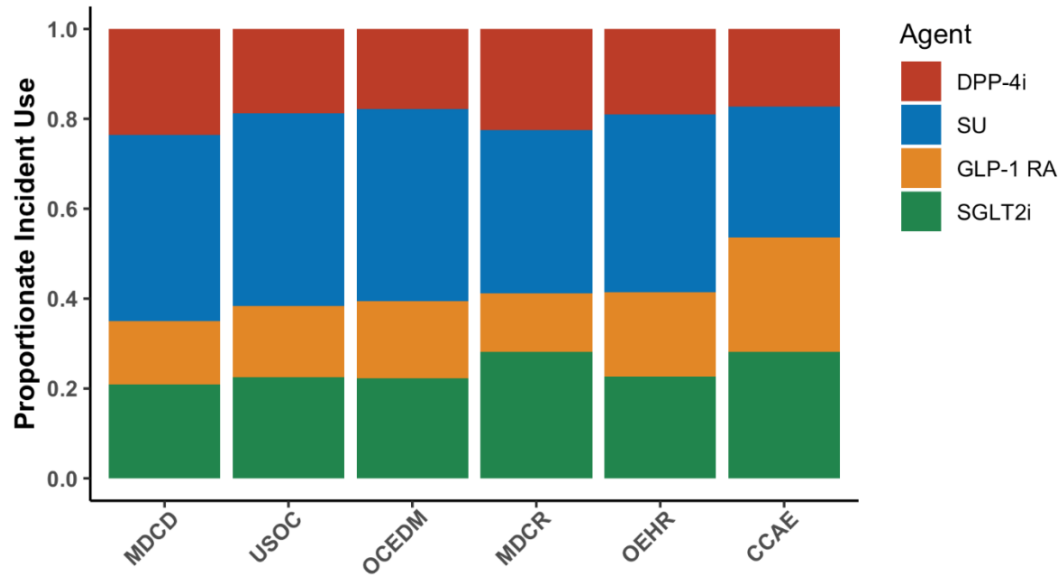
**Abbreviations:** ALPD - Australia Longitudinal Patient Database Practice Profile, CCAIE - IBM MarketScan® Commercial Claims and Encounters Data (CCAIE), CUIMC - Columbia University Irving Medical Center, FLPD - France Longitudinal Patient Database, GDA - Germany Disease Analyser, HIC - Health Informatics 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



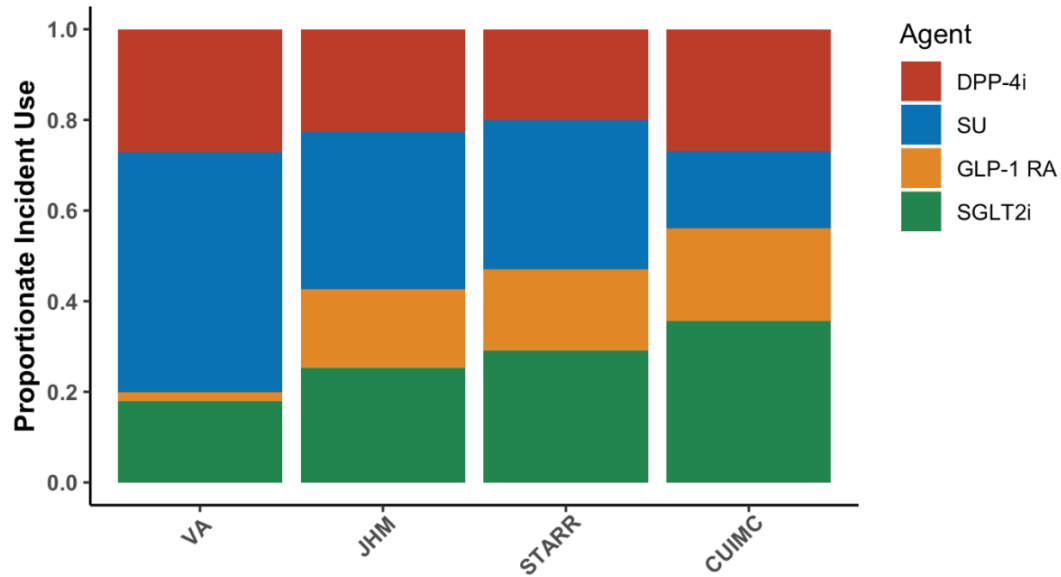
**Supplemental Table S17 | Annualized Change in the Age- and Sex-Standardized Incident Use of Sulfonylureas for Patients with Established Cardiovascular Disease and Patients without Established Cardiovascular Disease**

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
<b>US National Databases</b>			
CCAIE	-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
<b>US Health System Databases</b>			
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
<b>Non-US Databases</b>			
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

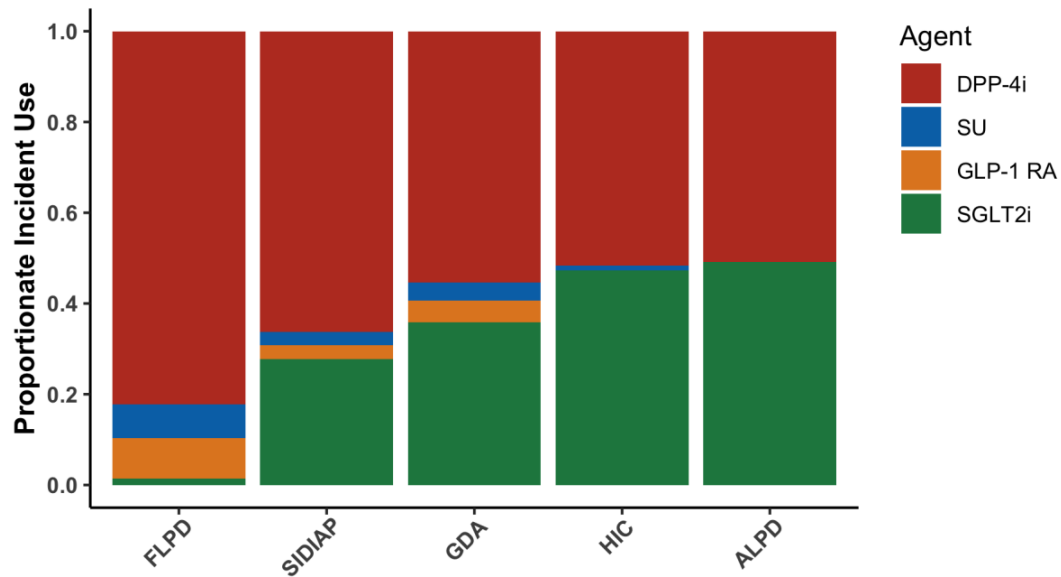
**Abbreviations:** ALPD - Australia Longitudinal Patient Database Practice Profile, CCAIE - IBM MarketScan® Commercial Claims and Encounters Data (CCAIE), CUIMC - Columbia University Irving Medical Center, FLPD - France Longitudinal Patient Database, GDA - Germany Disease Analyser, HIC - Health Informatics 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 | Proportionate Incident Use of Second-Line Antihyperglycemic Agents in United States National Databases in 2020**

**Abbreviations:** CCAE - IBM MarketScan® Commercial Claims and Encounters Data (CCA), 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

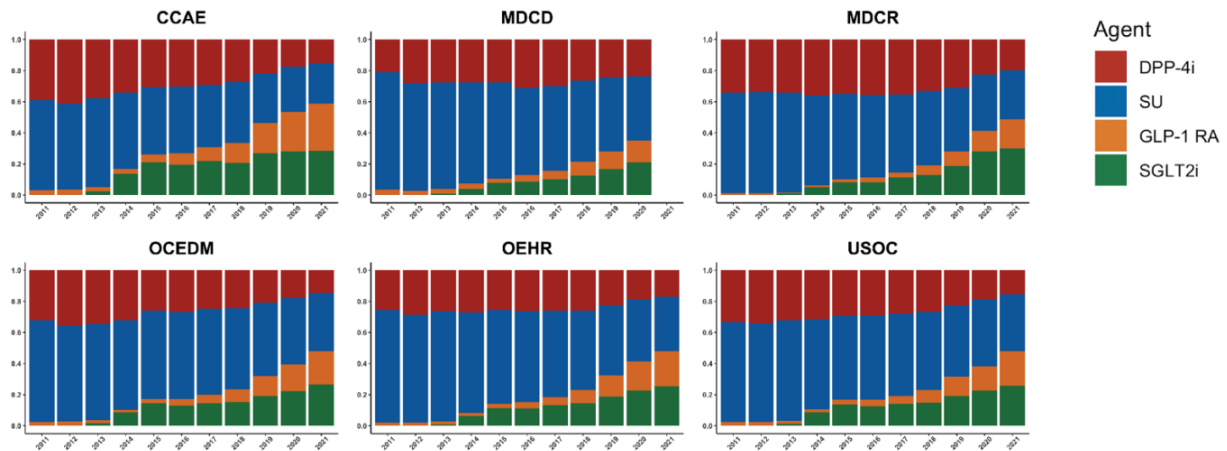
**Supplemental Figure S2 | Proportionate Incident Use of Second-Line Antihyperglycemic Agents in United States Health System Databases in 2020**

**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 | Proportionate 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

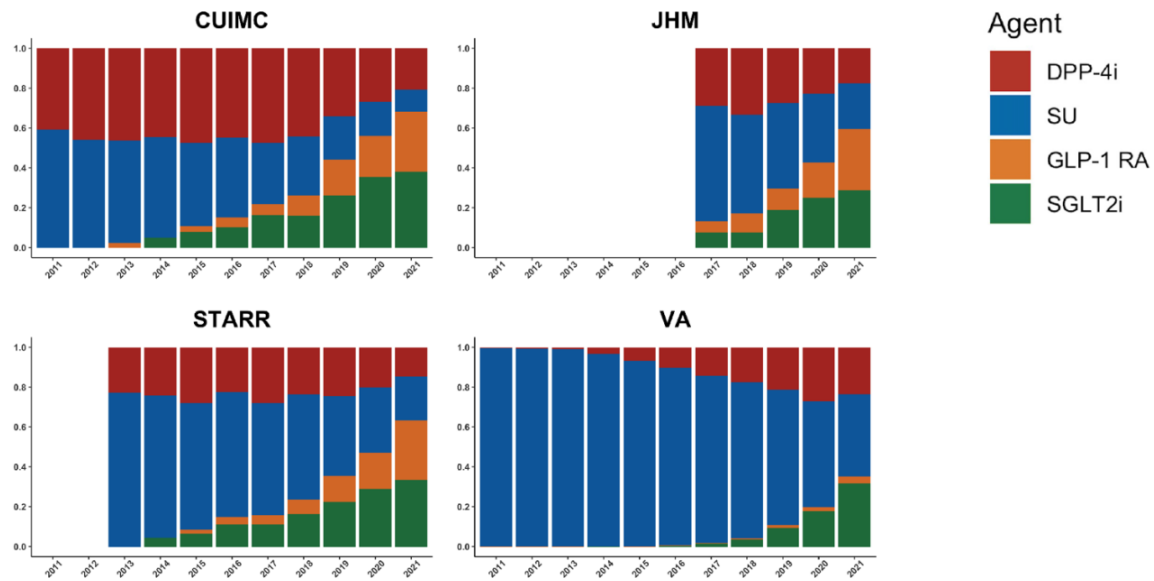
### Supplemental Figure S4 | Yearly Trends in Proportional Incident Use of Second-Line Antihyperglycemic Agents in US National Databases



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 (CCAIE), 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

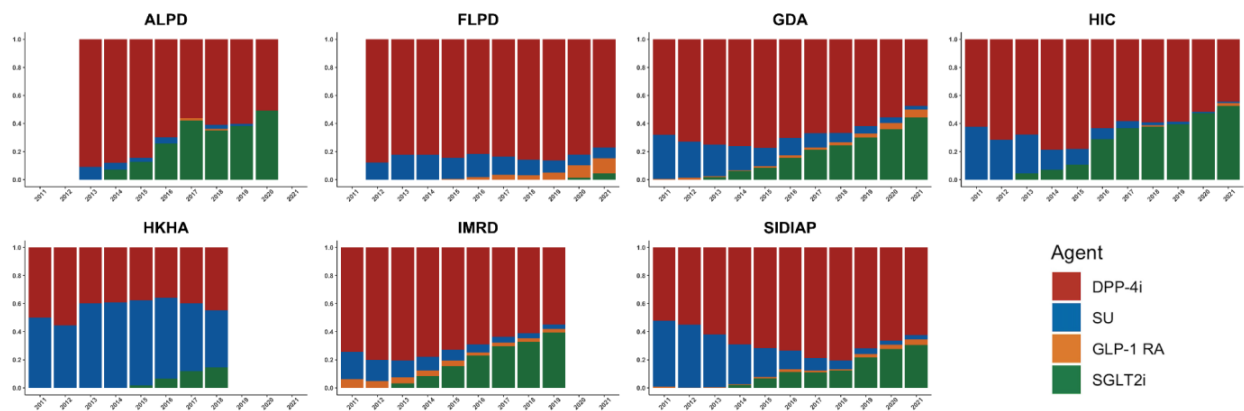
### Supplemental Figure S5 | Yearly Trends in Proportional Incident Use of Second-Line Antihyperglycemic Agents in US Health System Databases



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