Multi-national Patterns of Individual Cardioprotective Agents as Second-line Treatments for Type 2 Diabetes Mellitus: a LEGEND-T2DM Study

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Background

Clinical guidelines in the United States and Europe for treating patients with Type 2 Diabetes Mellitus (T2DM) and pre-existing cardiovascular diseases recommend the use of glucagon-like peptide-1 receptor agonists (GLP1ra) or sodium-glucose cotransporter-2 inhibitors (SGLT2i) as second-line treatments after metformin [1, 2]. GLP1ra and SGLT2i have also been recommended as treatments irrespective of metformin since 2022 [3]. Since the approval of the first GLP1ra (exenatide) in 2005 [4] and first SGLTi (canagliflozin) in 2013 [5], there has been an increasing uptake of these newer agents in the US and internationally [6]. Previous investigation of drug utilization using large-scale observational data has predominantly focused on class-level characterization and comparison, and have found differential risks of clinical outcomes associated with treatments using different drug classes [7]. There is still an evidence gap in characterizing and comparing individual drugs. In this study, we focus on characterizing the trends and patterns at the individual drug level within GLP1ra and SGLT2i drug classes.

Methods

We perform drug-level utilization and characterization studies as part of the Large-scale Evidence Generation and Evaluation across a Network of Databases for Type 2 Diabetes Mellitus (LEGEND-T2DM) study [8]. Study protocol and open-source software package are publicly available at `https://ohdsi-studies.github.io/LegendT2dm/Protocol` and `https://github.com/ohdsi-studies/LegendT2dm`.

This OHDSI network study involves 10 US and 5 international observational healthcare databases including 9 administrative insurance claims and 6 electronic health records. The US databases are: Merative Marketscan® Commercial Claims and Encounters Data (**CCAE**), Columbia University Irving Medical Center (**CUIMC**), Johns Hopkins Medicine (**JHM**), Merative Marketscan® Multi-State Medicaid Database (**MDCD**), Merative Marketscan® Medicare Supplemental and Coordination of Benefits Database (**MDCR**), United States Open Claims (**Open Claims**), Optum© Clinformatics Extended Data Mart - Date of Death (**OptumDOD**), Optum© de-identified Electronic Health Record Dataset (**OptumEHR**), Stanford Research Repository (**STARR**), and Department of Veterans Affairs Healthcare System (**VA**). The international databases are: Australia Longitudinal Patient Database and Practice Profile (**ALPD**), China Wondersgroup (**ChinaWD**) France Longitudinal Patient Database (**FranceLPD**), Germany Disease Analyzer (**GermanyDA**), and Information System for Research in Primary Care (**SIDIAP**).

We use a new-user cohort design to capture T2DM patients who initiated a GLP1ra or SGLT2i with prior metformin exposure between years 2011 and 2022. We then measure the yearly incidence rate of initiation for each drug among all patients with T2DM and a subgroup of patients with T2DM and established cardiovascular diseases (CVD). We further examine between-sex differences (female vs male) among patients whose sex information is available. Since there is substantial variation in drug-level exposure cohort sizes with many patient cohorts having very few or near zero counts, we only report results for five most commonly used drugs: dulaglutide and semaglutide among GLP1ra's, and canagliflozin, dapagliflozin and empagliflozin among SGLT2i's. Comprehensive characterization and visualization of all drug-level new-user cohorts are provided on an interactive web-app at `https://data.ohdsi.org/LegendT2dmDrugCohortExplorer/`.

Results

1.26M patients with T2DM across all databases initiated one of the five agents of GLP1ra or SGLT2i, among whom 393,480 (31%) had established CVD. Among all new-users, 436,698 (35%) initiated empagliflozin, followed by semaglutide with 234,650 (19%) new-users. Among patients with established CVD, most were new-users of empagliflozin too (162,256, 41%), but the second most prescribed drug was dapagliflozin (218,874, 18%). Upon inspecting the cohort counts, we see some heterogeneity across data sources, especially among international databases. For instance, the Australian data source (ALPD) has no records of GLP1-ra initiators. On the contrary, in the French data source (FranceLPD), we observe disproportionately high usage of the GLP1-ra drugs but only a tiny fraction of empagliflozin new users. We present all drug-level cohort counts (when available) in Table 1.

For eight of the ten US data sources and two of the five international databases, we measured yearly initiation rates for each drug (Figure 1). Two US data sources and three international ones were excluded due to insufficient cohort sample sizes ($< 1,000$) or lack of longitudinal coverage. Overall we see increasing trends in the uptake of all drugs, except for canagliflozin. Across the ten databases examined here, initiation of canagliflozin had a small increase during 2013-2015 immediately after its approval in 2013 but quickly dropped after 2015. Empagliflozin has seen the most rapid uptake across almost all data sources, followed by semaglutide which was approved later (in 2017 by US FDA and 2018 by EMA). Across all five drugs presented, initiation rates among patients with T2DM and established CVD are overall lower than those in the general T2DM patient population, but with similar trends across new-users of the individual drugs.

For the four drugs that have seen stable increase in uptake (dulaglutide, semaglutide, dapagliflozin, and empagliflozin) we also measured initiation rates stratified by sex (female vs male, Figure 2). The darker shades of orange and green show yearly initiation rates for female and male patients, respectively. The lighter shades show trends for patients with established CVD. Between the two GLP1ra drugs, there is substantially higher utilization of semaglutide among female patients, but that is not seen for dulaglutide. However, for both dapagliflozin and empagliflozin, uptake among male patients is noticeably higher and grows more rapidly compared to that among female patients. Between the two drug classes and across the US data sources (first 7 columns), there is a clear between-sex divide in initiation trends between semaglutide and empagliflozin: for female patients, the uptake rate for semaglutide is higher and grows more quickly than that for male patients, but for male patients there has been a higher uptake of empagliflozin. This sex difference persists in both the general T2DM patient population (darker-colored lines) and the subset with concomitant CVD (lighter-colored lines). We also see a similar pattern between semaglutide and dapagliflozin new-users with higher rates of uptake among male patients for dapagliflozin, though the difference is less substantial.

Conclusion

We identified over 1.2M T2DM patients who initiated on five GLP1ra and SGLT2i drugs after metformin during 2011 to 2022 across 15 US and international databases. As second line agents, empagliflozin has seen the most substantial increase in drug initiation since 2015, followed by semaglutide with similarly rapid uptake since 2017. We have found a between-sex difference in drug initiation trends, where female patients have a higher rate of initiating semaglutide and male patients empagliflozin.

Table 1: Sample sizes of antihyperglycemic drug new-user cohorts of GLP1ra and SGLT2i drugs across data sources. We report cohort counts for general patients ("Main") and patients with established cardiovascular diseases ("CVD"). Cohort counts below 10 are denoted by "<10".

	dulaglutide		semaglutide		canagliflozin		dapagliflozin		empagliflozin	
	Main	CVD	Main	CVD	Main	CVD	Main	CVD	Main	CVD
US:										
CCAE	15,697	3,372	21,179	4,592	10,964	2,481	17,889	4,084	24,019	6,235
CUIMC	358	130	1,250	415	143	58	330	203	1,262	668
JHM	378	74	329	70	32	10	118	37	638	207
MDCD	2,632	788	616	204	1,963	522	1,604	661	3,251	1,324
MDCR	1,160	574	1,290	621	1,142	580	1,133	626	3,415	2,048
Open Claims	161,536	43,543	174,295	47,373	124,509	33,471	167,848	52,432	302,829	107,208
OptumDOD	12,220	4,235	18,824	6,630	8,127	2,439	7,727	4,284	30,445	13,513
OptumEHR	14,107	3,017	14,064	3,255	10,952	2,157	11,877	2,930	24,011	7,351
STARR	362	70	524	84	206	42	194	64	836	224
VA	433	191	1,258	539	31	<10	58	33	37,612	19,772
International:										
ALPD							278	26	487	38
ChinaWD	47	18	53	21	90	38	778	440	20	14
FranceLPD	410	63	196	31			243	63	<10	
GermanyDA	757	296	336	128	<10	<10	4,855	2,103	4,152	2,325
SIDIAP	510	69	436	70	477	66	3,942	886	3,712	1,329
TOTAL:	210,607	56,440	234,650	64,033	158,641	41,879	218,874	68,872	436,698	162,256

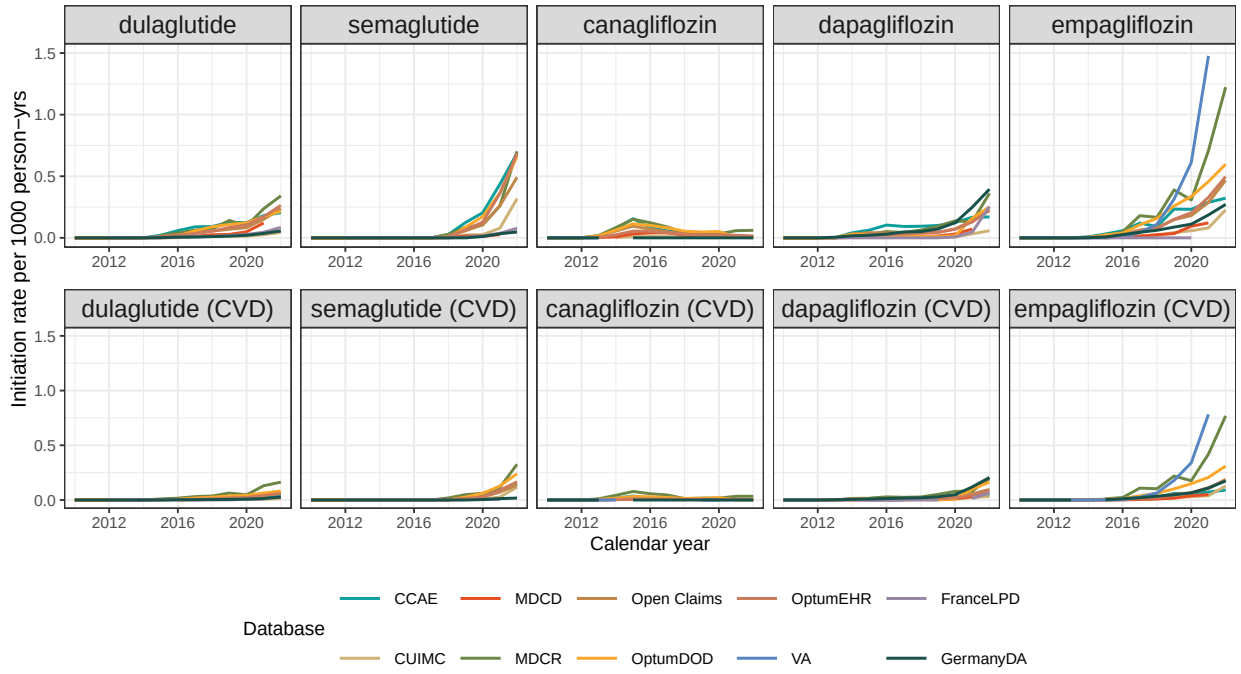

Figure 1: **Overall trends in GLP1ra and SGLT2i drug initiation from 2011 to 2022.** Initiation rates (per 1000 person-years) by calendar year of drug initiation for each commonly used SGLT2 and GLP1 agent (dulaglutide, semaglutide, canagliflozin, dapagliflozin, and empagliflozin) for general patients and patients with established CVD.

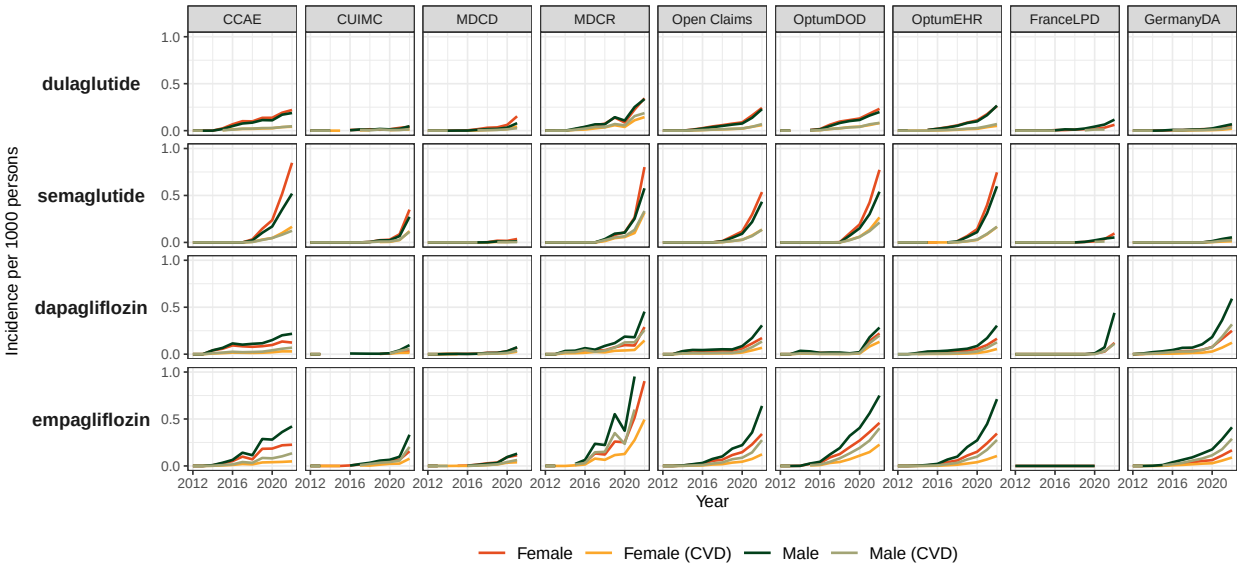

Figure 2: **Female vs male differences in drug initiation trends, 2011-2022.** Initiation rates (per 1000 persons) of drug initiation by calendar year for each commonly used GLP1ra and SGLT2i (dulaglutide, semaglutide, dapagliflozin, and empagliflozin) for general patients and patients with established CVD.

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