Multinational Patterns of Second-line Anti-hyperglycemic Drug Initiation: A LEGEND-T2DM Study

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BACKGROUND

The management of type 2 diabetes mellitus (T2DM) has evolved over the last decade. Pharmacological agents in the sodium-glucose co-transporter-2 inhibitors (SGLT2i) and glucagon-like peptide-1 receptor agonists (GLP1-RA) improving cardiovascular outcomes, with the effect demonstrated in several randomized control trials.(1–5) In addition, SGLT2i reduce progression of renal disease.(1,2,5) While international guidelines strongly recommend the use of SGLT2i in over half and GLP1-RAs in over a third of all patients with T2DM,(6,7) the real-world uptake of these drugs continues to be limited.(8–12) However, the patterns of use have exclusively focused on prevalent use, and US-based studies focused on single-payers or national surveys. These assessments do not accurately capture the uptake patterns for novel therapies, for whom both the uptake and the use are likely to grow over time. An international appraisal of the uptake of these agents as second-line therapy among those escalated from metformin monotherapy is critical. This is particularly relevant as an assessment of their utilization relative to other agents,

namely, dipeptidyl peptidase-4 inhibitors (DPP-4i) and sulfonylureas (SU) that have been available for longer, but either have neutral effects on cardiovascular and renal risk or lack any known cardioprotective or renoprotective effects altogether.

In a large, multinational study, LEGEND-T2DM, we describe patterns of uptake of four key second-line agents - GLP1RA, SGLT2i, DPP4i, and SU - during escalation from metformin monotherapy and across clinical subgroups.

METHODS

Study Overview

The study leverages federated learning on international data all mapped to the Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM). Using a consistent strategy of identifying patients with T2DM receiving metformin monotherapy, who were initiated on second-line anti-hyperglycemic agents, we evaluated patterns of uptake of agents with and without known cardioprotective effects across patients spanning the cardiovascular risk spectrum.

Data Sources

We identified participating data sources in the LEGEND-T2DM initiative,(13) a large-scale observational study of real-world characterization of second-line anti-hyperglycemic agents. The study is based on 17 real-world data sources, spanning claims databases and electronic health record (EHR) 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.

Study Population

For each data source, we included all patients with T2DM receiving metformin monotherapy, who initiated treatment with one of the 22 drug ingredients that comprise the GLP1RA, SGLT2i, DPP4i, and SU drug classes. We excluded those who initiated thiazolidinediones given their known association with a risk of heart failure and bladder cancer.(14,15)

A high cardiovascular (CV) risk cohort represented those at elevated risk defined as having an established cardiovascular disease or a cardiovascular disease-defining procedure. The low CV risk cohort was defined as the absence of prior disease diagnosis and absent history of CV procedures.

Study Exposures and Outcomes

The study used calendar years as the exposure with the initiation of one of 4 second-line antihyperglycemic agents the outcome.

Statistical Analysis

We evaluated the trend of yearly proportional incidence of all four second-line antihyperglycemic drug classes across the 17 databases. Proportional incidence was defined as the ratio of the number of patients who started using an antihyperglycemic agent from a particular drug class to the total number of patients initiating second-line agents in that year.

Given the known cardioprotective effects of GLP-1 RAs and SGLT2is, we

performed stratified analysis among high and low CV risk subpopulations. In linear regression we evaluated proportionate uptake of second-line drugs as the dependent variable and the year as the continuous independent variable. We evaluated differences in uptake of cardioprotective agents across high versus low CV risk, through quantitative interaction in linear regression, between cohorts specific CV risk category and calendar year. In sensitivity analysis, given predominant increase in use after 2016, a piecewise linear trend assessment with a node in 2016 was also evaluated.

RESULTS

Cohort Characteristics

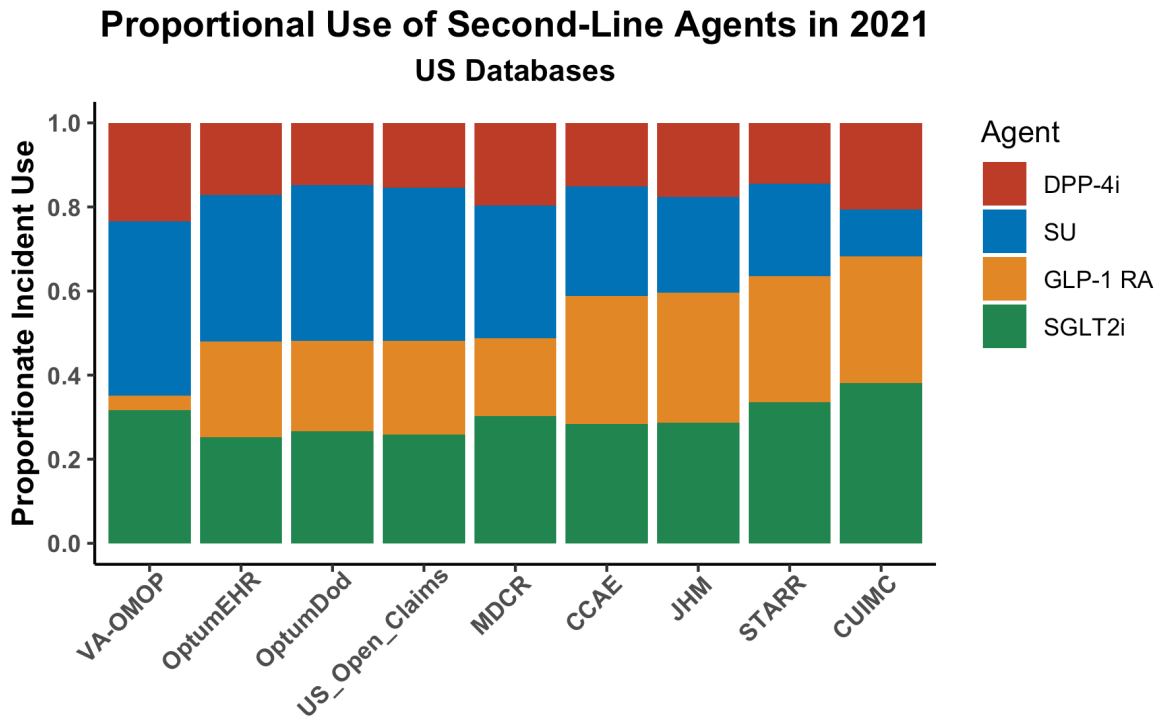
There were a total of 10,384,267 individuals with T2DM included across cohorts, representing individuals initiating one of the four second-line anti-hyperglycemic agents between 2011-2021. This includes 10,041,887 individuals across US-based databases and 342,380 from international databases. The latter includes 146,611 from Spain, 74,986 from Germany, 65,415 from the UK, 26,512 from France, 12,271 from Scotland, 11,744 from Hong Kong, and 4,841 from Australia.

Trends in the Uptake of Second-Line Cardioprotective Agents Across Cohorts

The proportion of second-line antihyperglycemic drug uptake varied across cohorts. Between 2011 and 2021, the use of GLP-1 RA as the second-line antihyperglycemic agent increased across all US national data sources, without any use in 2011 to 18.5% in 2021 in the IBM Health MarketScan® Medicare (MDCR) population, and 30.5% in the Commercial Claims and Encounters Database (CCAE).

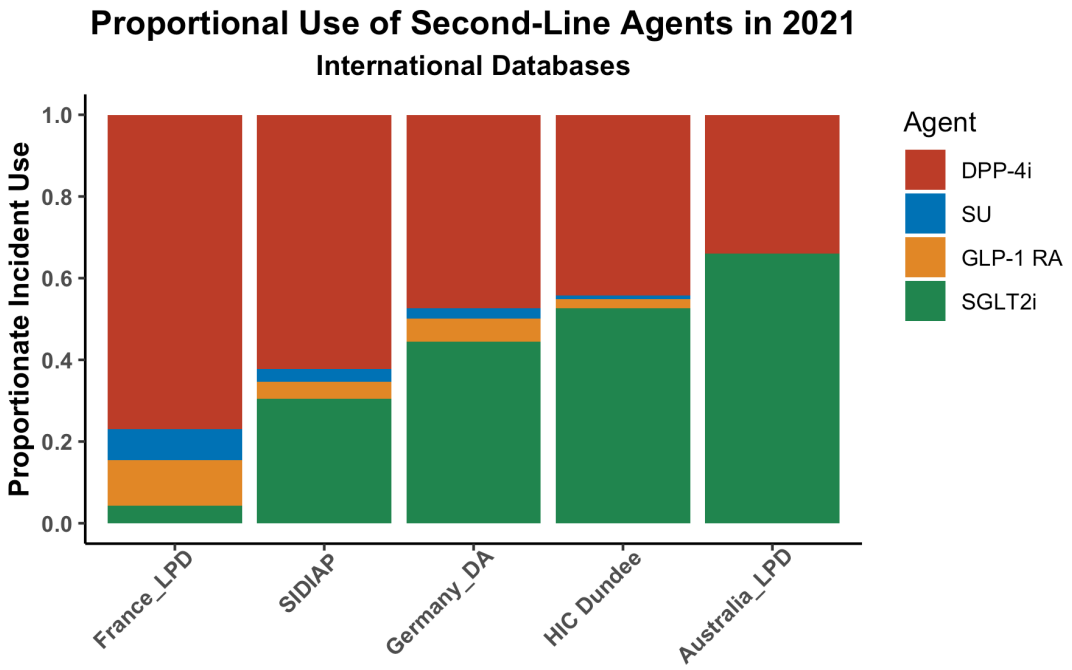
Similarly, the use of SGLT2i in the US national databases increased from no use in 2011 across data sources to 25.2% in 2021 in the Optum© de-identified Electronic Health Record Dataset (OptumEHR) and 30.2% in the Medicare population. The Veterans Affairs Health System in the US (VA-OMOP) had the lowest proportionate utilization of the cardioprotective antihyperglycemic agents in the US, driven predominantly by the low use of GLP1-RAs.

Figure 1: Proportional Use of Second-Line Antihyperglycemic Agents in US Databases in 2021



The use of SGLT2i in the international databases increased from no use in 2011 to 4.4% in France and up to 66.1% in Australia by 2021. Throughout the study period, there was limited use of GLP-1 RA in Australia. However, among the international databases available, the use of GLP-1 RA increased most in France, increasing to 15.4% in 2021.

Figure 2: Proportional Use of Second-Line Antihyperglycemic Agents in International Databases in 2021



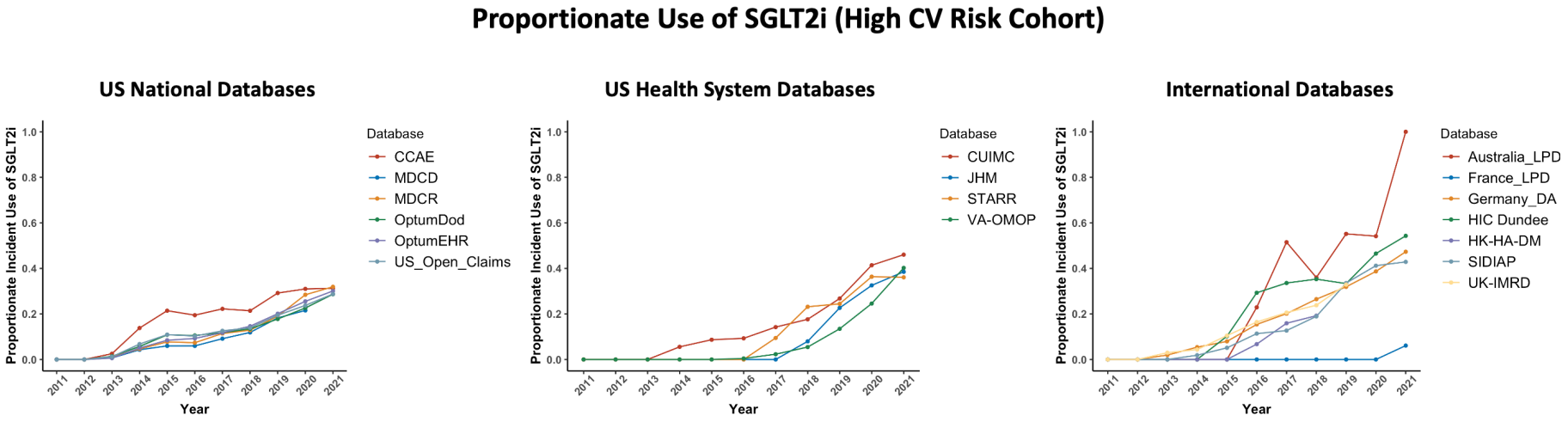
Second-Line Antihyperglycemic Drug Use Across Cardiovascular Risk Groups

The use of GLP-1 RA in the high CV risk cohort in US national databases increased consistently from no use in 2011 to 15.7% in Medicare (MDCR) patients and up to 28.0% in the Commercial Claims and Encounters Database (CCAE) population. Meanwhile, the use of SGLT2i in the high CV risk cohort, in the same period, reached 28.7% in Optum Clinformatics Extended DataMart (OptumDod) and 31.9% in the Medicare population.

The use of GLP-1 RA increased from no use in 2011 to 13.4% in France. While SGLT2i were not in use as second-line antihyperglycemic agents in 2011 in any of the international databases, their use grew to include 6.1% of the high CV risk population in France, and 100% of the high CV risk cohort in Australia.

Since 2016, when the uptake of cardioprotective agents started increasing among patients, the proportional use of SGLT2i was more rapid in the patients with established CV disease, compared to patients without CV disease (p-interaction < 0.05 for all).

Figure 3: Proportional Use of SGLT2i in Patients with Established Cardiovascular Disease



Abbreviations:
CCAE: Commercial Claims and Encounters Database, CUIMC: Columbia University Irving Medical Center, HIC Dundee: Health Informatics Centre at the University of Dundee, HK-HA-DM: Hong Kong University, JHM: Johns Hopkins Medicine, MDCD: IBM Health MarketScan® Multi-State Medicaid Database, MDCR: IBM Health MarketScan Medicare, OptumDod: Optum Clinformatics Extended Data Mart - Date of Death, OptumEHR: Optum© de-identified Electronic Health Record Dataset, SIDIAP: Information System for Research in Primary Care, STARR: Stanford, UK-IMRD: United Kingdom IQVIA Medical Research Data, VA-OMOP: Department of Veterans Affairs

CONCLUSION

Cardioprotective agents are increasingly used as second-line antihyperglycemic agents. However, they represent a minority among the second-line agents used in the US, even among patients with elevated cardiovascular risk. In contrast, the international uptake of these agents is higher than the US, particularly among the population with elevated risk of cardiovascular events.

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