

Sex and Race Differences in Type 2 Diabetes Drug Initiation After Metformin

Michelle Jin¹, Clair Blacketer^{2,3}, Fan Bu⁴, Talita Duarte-Salles^{3,5}, Wallis CY Lau⁶, Kenneth KC Man⁶, Evan Minty^{7,9}, Anna Ostropolets², Mui Van Zandt⁹, Can Yin⁹, George Hripcsak^{10,11}, Marc A Suchard^{12,13}

¹Computational Biology, University of California, Los Angeles

²Johnson and Johnson, Raritan, NJ

³Department of Medical Informatics, Erasmus University Medical Center

⁴Department of Biostatistics, University of Michigan

⁵Fundació Institut Universitari per a la recerca a l'Atenció Primària de Salut Jordi Gol i Gurina

⁶Research Department of Practice and Policy, UCL School of Pharmacy

⁷O'Brien Institute for Public Health, University of Calgary

⁸Department of Biomedical Informatics and Data Science, Johns Hopkins University

⁹Real World Solutions, IQVIA

¹⁰Department of Biomedical Informatics, Columbia University Medical Center

¹¹New York-Presbyterian Hospital

¹²Department of Biostatistics, Fielding School of Public Health, University of California, Los Angeles

¹³VA Informatics and Computing Infrastructure, US Department of Veterans Affairs

Background

Adoption of post-metformin therapies for type 2 diabetes mellitus (T2DM) varies across demographics and clinical groups, but evidence on treatment initiation patterns remains limited and inconsistent. Some studies suggest that women and racial minorities receive newer cardioprotective agents less frequently than their counterparts, while others find no substantial differences by ethnicity or socioeconomic status.¹⁻

³ Others show that patients with established cardiovascular disease initiate cardioprotective agents at lower rates than those without, despite guideline recommendations.⁴

To address this gap, we leveraged multinational real-world data from the Large-scale Evidence Generation and Evaluation across a Network of Databases for Type 2 Diabetes Mellitus (LEGEND-T2DM) initiative to characterize initiation of four major post-metformin antihyperglycaemic classes across demographic and clinical subgroups and healthcare settings.

Methods

We conducted a federated retrospective study within the LEGEND-T2DM initiative using 10 databases standardized to the Observational Medical Outcomes Partnership (OMOP) Common Data Model (v5.3.1).⁵ Databases included five administrative claims sources (CCAE, MDCD, MDCR, Optum's de-identified Clinformatics (R) Extended Data Mart Database, Date of Death (DOD) (OptumDod), IQVIA Longitudinal Prescription and Professional Medical Claims (LRx/Dx) (US Open Claims)) and five electronic health record sources (Optum's longitudinal EHR repository (OptumEHR), VA-OMOP, SIDIAP, IQVIA Germany Disease Analyzer (DA), UK IQVIA Medical Research Data (UKIMRD)).

We applied a new-user cohort design to identify adults with T2DM who initiated an antihyperglycaemic agent (AHA) after metformin monotherapy, requiring ≥ 365 days of prior observation and no prior exposure to other post-metformin AHAs or >30 days of prior insulin use.

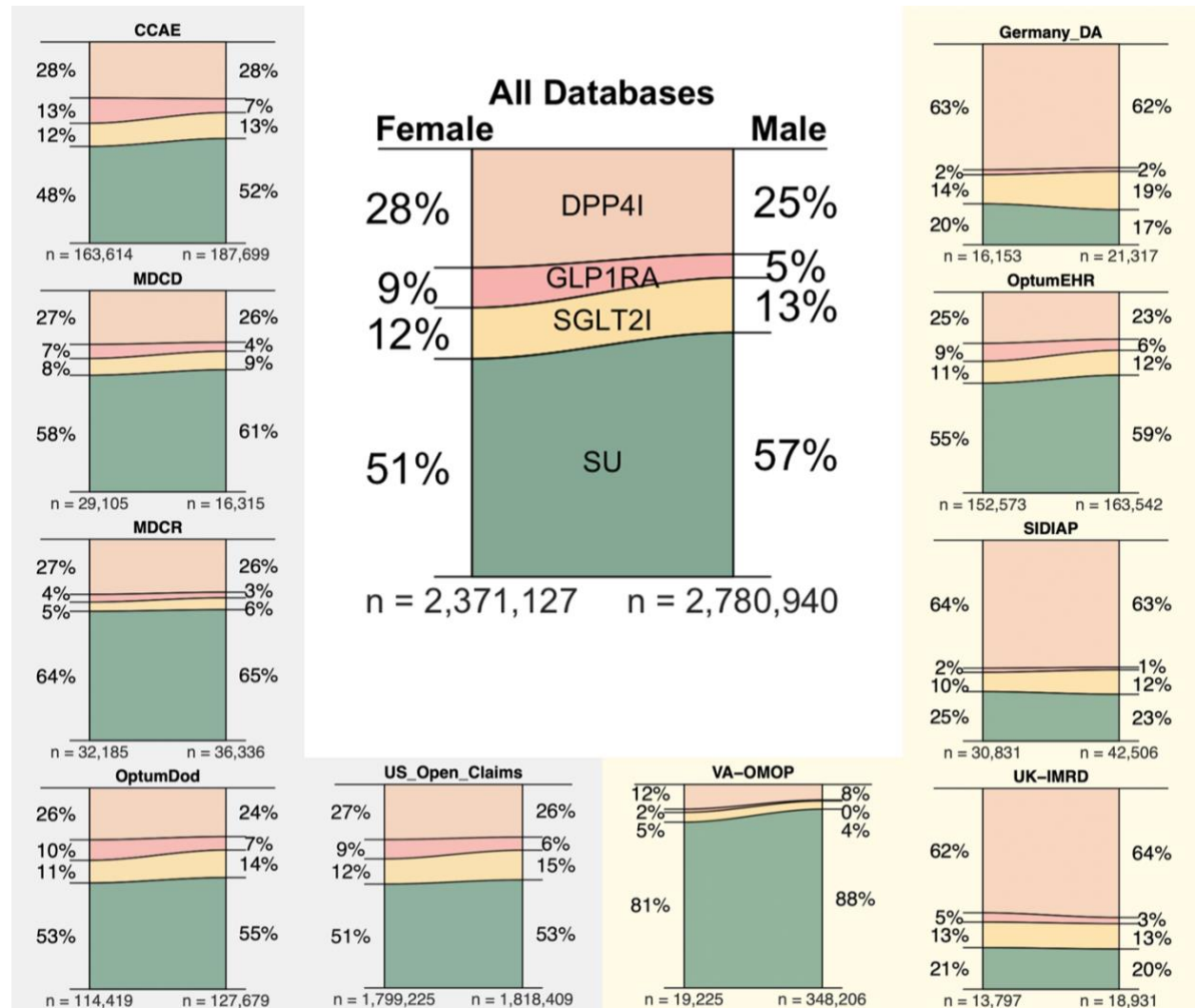
Initiation was assessed across four major drug classes: dipeptidyl peptidase-4 inhibitors (DPP4Is), glucagon-like peptide-1 receptor agonists (GLP1RAs), sodium-glucose cotransporter-2 inhibitors

(SGLT2Is), and sulfonylureas (SUs), stratified by sex, cardiovascular risk, and race (Black vs. all, where available) at three levels: pooled across databases, within each database, and by drug.

We assessed temporal trends from 2010–2021 by drug class and sex using two complementary approaches: absolute incidence rates per person-year (cohort counts divided by person-years) and proportional initiation (each drug class as a proportion of total initiations) pooled across databases. Log-linear regression was applied to estimate average annual percent change and 95% confidence intervals.

Results

Figure 1. Sex-Based Differences in T2DM Drug Initiation Across Data Sources

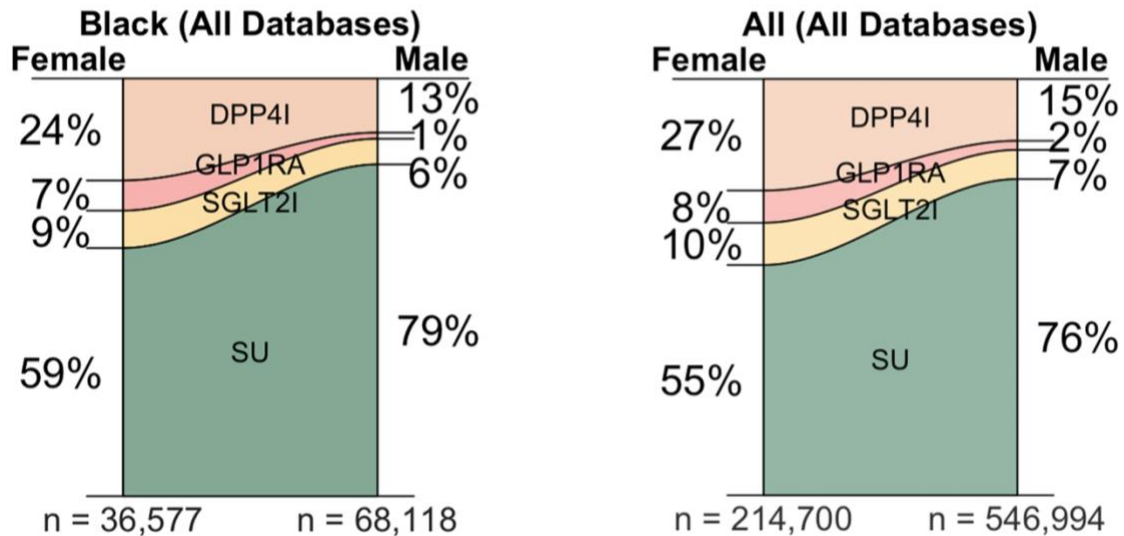


Alluvial diagrams depicting the proportional post-metformin T2DM drug class initiations stratified by sex across 10 data sources. Cohort counts are shown beneath each sex group. The central panel presents pooled proportions. Surrounding panels display database-specific patterns by data source type: claims (gray) and EHR (yellow).

Across the 10 databases, SUs and DPP4Is were the most initiated post-metformin therapies, reflecting their historical dominance over the study period. Sex-based differences were modest: males initiated SUs at a higher proportion (F:M 51% vs. 57%), while females initiated GLP1RAs at a higher proportion (9%

vs. 5%); SGLT2I and DPP4I initiation remained similar across sexes (Figure 1). These patterns were consistent across cardiovascular risk strata and individual databases, with sex differences generally not exceeding 5 percentage points. At the drug level, modest within-class variation was observed, most notably for SGLT2Is, where males more often initiated empagliflozin (52% vs. 68%), while females more often initiated canagliflozin (22% vs. 18%) and dapagliflozin (25% vs. 18%).

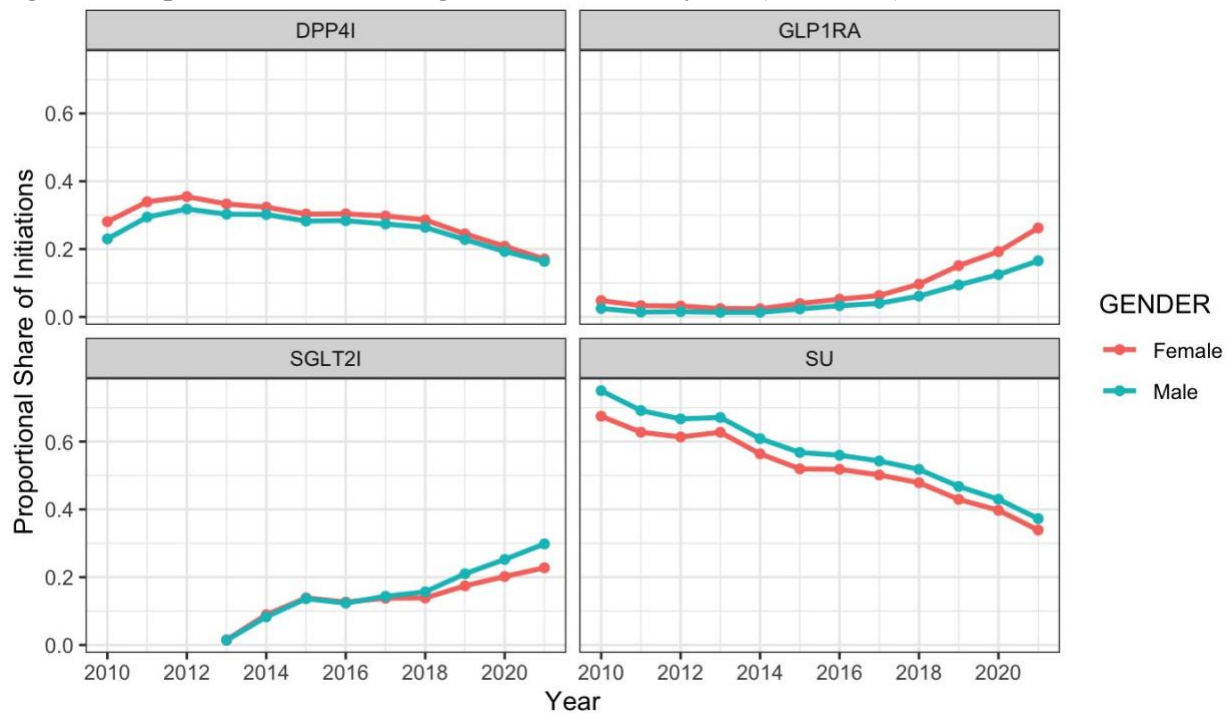
Figure 2. Sex-Based Differences in T2DM Drug Initiation by Race Group



Alluvial diagrams depicting the proportional distribution of post-metformin T2DM drug class initiation by sex between Black patients (left) and the overall population (right), pooled across four databases with available race data. Cohort counts are shown beneath each sex and race group.

Among the four databases with available race data (OptumEHR, MDCD, IQVIA Medical Research Data (IMRD), VA-OMOP), initiation proportions were similar between Black patients and the entire population, with differences of $\leq 2\%$ across drug classes. However, sex differences were more pronounced within these databases than in the full 10-database analysis, with males initiating SUs at higher proportions (F:M Black: 59% vs. 79%; overall: 55% vs. 76%) and females initiating GLP1RAs at higher proportions (Black: 7% vs. 1%; overall: 8% vs. 2%) (Figure 2). The greater magnitude of sex differences in these databases may reflect database composition or race-associated variation in initiation, though it may also reflect unmeasured confounding, and should be interpreted cautiously given the descriptive, unadjusted nature of the analysis.

Figure 3. Proportion of T2DM Drug Class Initiations by Sex (2010-2021)



Proportion of post-metformin T2DM initiations by drug class and sex over time. Each panel represents one drug class, lines stratified by sex.

Longitudinal analyses from 2010–2021 showed significant increases in absolute initiation rates across all four drug classes (all $p < 0.01$). GLP1RA and SGLT2I demonstrated the steepest average annual growth: females at 34.4% (95% CI: 26.1–43.2%) and 37.3% (20.0–57.1%), and males at 38.9% (31.1–47.3%) and 46.1% (28.5–66.1%), respectively, compared to DPP4I and SU at 5–7%. Despite absolute increases, proportional analyses showed declining shares of DPP4I and SU and increasing shares of GLP1RA and SGLT2I, reflecting a shift toward newer cardioprotective agents relative to older classes (Figure 3). Sex differences were consistent across both analyses, with males showing faster SGLT2I growth and females faster GLP1RA adoption in later study years, suggesting sex-based uptake trajectories diverged and widened over time.

Conclusion

This multinational real-world analysis found that overall, demographic differences in post-metformin AHA initiation were modest at the population level. Modest but consistent sex-based differences were observed across 10 databases, while differences by recorded race were limited. However, within the subset of databases with race data, sex differences were more pronounced, suggesting greater heterogeneity in sex-based treatment patterns within more granular data sources, although these findings should be interpreted cautiously given incomplete race capture across data sources.

Initiation patterns also evolved over time, reflecting increasing uptake of newer cardioprotective therapies, with evidence of diverging sex-specific trajectories in the adoption of GLP1RAs and SGLT2Is. Heterogeneity in initiation patterns persisted across databases and patient subgroups, suggesting that local population characteristics, data source composition, and healthcare systems may contribute to observed variation. These findings highlight the value of federated OMOP standardized networks for characterizing

real-world treatment variation and underscore the need for richer clinical and socioeconomic data to better understand factors influencing therapy selection.

References

1. RG McCoy, HK Van Houten, SM Dunlay, X Yao, T Dempsey, PA Noseworthy, LR Sangaralingham, AH Limper, ND Shah. Race and sex differences in the initiation of diabetes drugs by privately insured US adults. *Endocrine*. 2021;73:480–4. PubMed PMID: [33830439](#).
2. LA Rodriguez, H Finertie, RS Neugebauer, B Gosiker, TW Thomas, AJ Karter, LK Gilliam, C Oshiro, J An, G Simonson, AE Cassidy-Bushrow, S Dombrowski, M Nolan, PJ O'Connor, JA Schmittiel. Race and ethnicity and pharmacy dispensing of SGLT2 inhibitors and GLP-1 receptor agonists in type 2 diabetes. *Lancet Regional Health–Americas*. 2024;100759. PubMed PMID: [38745886](#).
3. P Bidulka, R Mathur, DG Lugo-Palacios, S O'Neill, A Basu, RJ Silverwood, P Charlton, A Briggs, L Smeeth, AI Adler, IJ Douglas, K Khunti, R Grieve. Ethnic and socioeconomic disparities in initiation of second-line antidiabetic treatment for people with type 2 diabetes in england: A crosssectional study. *Diabetic Medicine*. 2022;39:e14874. PubMed PMID: [36134467](#).
4. R Khera, LS Dhingra, A Aminorroaya, K Li, JJ Zhou, F Arshad, others. Multinational patterns of second-line antihyperglycaemic drug initiation across cardiovascular risk groups: Federated pharmacoepidemiological evaluation in LEGEND-T2DM. *BMJ Medicine*. 2023;2:e000651. PubMed PMID: [37829182](#).
5. Observational Health Data Sciences and Informatics (OHDSI). The OMOP common data model. <https://www.ohdsi.org/data-standardization/the-common-data-model/>.